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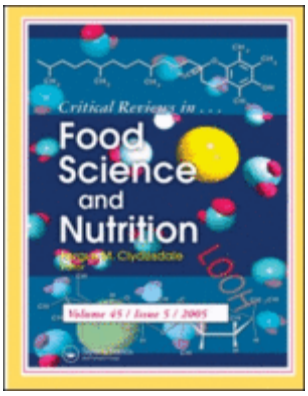

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Plant-Based Foods As a Source of Lipotropes for Human Nutrition: a Survey of *In Vivo* Studies

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Abstract

Increased consumption of plant products is associated with lower chronic disease prevalence. This is attributed to the great diversity of their phytochemicals and to their numerous positive physiological effects. The most investigated have been their antioxidant, anti-carcinogenic, hypolipidemic and hypoglycemic properties. Yet, some compounds have been very early shown to be lipotropic in animals. This property is defined as the capacity of a compound to hasten the removal of fat from liver and/or to reduce hepatic lipid synthesis through several mechanisms, mainly involving increased phospholipid synthesis *via* the transmethylation pathway for triglyceride-rich lipoprotein exportation from liver, increased fatty acid β-oxidation and/or down- and up-regulation of genes involved in respectively lipogenic and fatty acid oxidation enzyme synthesis. Main plant lipotropes are choline, betaine, *myo*-inositol, methionine and carnitine. Magnesium, niacin, pantothenate and folates also indirectly support the overall lipotropic effect. The exhaustive reviewing of animal studies investigating the effect of phytochemicals on hepatic lipid metabolism suggest that some unsaturated fatty acids, acetic acid, melatonin, phytic acid, some fiber, oligofructose, flavonoids, lignans, stilbenes, curcumin and saponins may be also considered as having lipotropic effects. However, this will have to be confirmed in humans for which intervention studies are practically non-existent.

Keywords: Phytochemicals, lipotrope, hepatic steatosis, humans, rats

PLANT-BASED FOOD CONSUMPTION, CHRONIC DISEASE RISK AND PHYTOCHEMICALS

Epidemiological and observational studies

Increased consumption of plant-based foods (PBF), mainly whole-grain cereals, legumes, vegetables and fruits, is generally associated with a lower prevalence of all-cause mortality and of the major chronic diseases that are cardiovascular diseases (CVD), obesity, diabetes and cancers. However, more specifically, the effects seem to vary according to the botanical origin of the PBF with more or less conclusive results from prospective studies. Thus, while whole-grain cereals have been convincingly shown to be protective against all main chronic diseases or disorders (Chan et al., 2007; Chatenoud et al., 1998; De Munter et al., 2007; Flight and Clifton, 2006; Jacobs et al., 2007; Jacobs et al., 1998; Koh-Banerjee et al., 2004; Koh-Banerjee and Rimm, 2003; Larsson et al., 2005; Mellen et al., 2008; Murtaugh et al., 2007; Sahyoun et al., 2006; Schatzkin et al., 2008; Van De Vijver et al., 2009; Venn and Mann, 2004; Williams et al., 2008), the effects of legumes, fruits and/or vegetables are less obvious with both either no or positive effects reported that depends on the variety used, the population studied, the targeted disease or the age of the subjects. For example, the protective role of PBF and plant-based diets against childhood obesity has been recently reviewed: it clearly appears that, except for ready-to-eat cereals, there is a lack of evidence to conclude for an association between PBF and childhood obesity in relation with fruit and vegetable, grain other than cereal, and legume intake (Newby, 2009).

To summarize, the most conclusive associations are observed with whole-grain cereals for all diseases, with legumes on mortality risk (all-cause, CVD or cancers) (Nagura et al., 2009; Noethlings et al., 2008), with fruits on CVD (Hung et al., 2004; Nagura et al., 2009) and weight gain/obesity (Buijsse et al., 2009; He et al., 2004), with vegetables on CVD (Hung et al., 2004; Nagura et al., 2009), weight gain/obesity (Buijsse et al., 2009; He et al., 2004) and type 2 diabetes (Bazzano et al., 2008; Villegas et al., 2008), and with both fruits and vegetables on all-cause mortality (Rissanen et al., 2003; Steffen et al., 2003) and cancers (Pavia et al., 2006; Van

Duijnhoven et al., 2009) (Table 1). Moreover, some authors have observed a significant association between diseases risk and mortality with specific vegetable or fruit sub-family consumption such as cruciferous, *Alliaceae*, green leafy and yellow-orange vegetables, root vegetables, citrus or fruit-berry. This is underlined for cancer (Kolonel et al., 2000; Wu et al., 2009), diabetes (Bazzano et al., 2008), cerebrovascular disease (Mizrahi et al., 2009) and all-cause mortality (Nagura et al., 2009; Noethlings et al., 2008) risks. More specifically, the inverse association between green tea consumption and psychological distress in a Japanese cohort has been recently reported (Hozawa et al., 2009). Studies reporting increased prevalence of chronic diseases with increased consumption of PBF are practically non-existent except one Chinese study that reported increased prevalence of obesity among high consumers of vegetables but the culinary habits involved the cooking of vegetables with important amount of oil for stir-frying (Shi et al., 2008). Despite some contradictory reported results, or at least the absence of significant effect, PBF consumption does not appear negative for health on a long term, provided they are not systematically accompanied with sausages or other energy-dense seasonings and snack foods. It is therefore certain that increasing its PBF consumption is not unhealthy, if not always reflected in a significant health benefit.

A whole set of phytochemicals with numerous physiological effects

The overall potential positive effect of PBF on chronic diseases would be associated with the presence, especially in unrefined and/or minimally-processed PBF, of a great variety of phytochemicals (vitamins, minerals, trace elements, carotenoids, polyphenols, phytosterols,…) together with the fibre fraction of PBF which would act synergistically to favour various positive physiological effects (Slavin, 2003). The mechanisms may involve (1) the chelation, reduction and/or trapping of free oxidative radicals (*i.e.* the antioxidant capacity) (Fang et al., 2002; Pellegrini

et al., 2003; Wu et al., 2004a), (2) the stimulation/modulation of the immune function (Barr et al., 1998; Mantovani et al., 2008), (3) the regulation of glucose homeostasis (*e.g.* magnesium stimulates the glucose uptake by insulin) (Venn and Mann, 2004), (4) the lowering of circulating or liver damaging lipid fractions (*e.g.* LDL-cholesterol) (Lee et al., 2005; Okazaki and Katayama, 2008), (5) the reduction of hyperhomocysteinemia recognized as a risk factor for CVD (Graham et al., 1997; Samman et al., 2002) and for carcinogenesis (Wu and Wu, 2002), (6) the anti-carcinogenicity or the capacity to induce apoptosis (Azzi and Stocker, 2000; Rubis et al., 2008; Shamsuddin, 2002), and/or (7) the anti-aggregability (Shechter et al., 1999) and anti-inflammatory (Liu et al., 2004; Rahman et al., 2006) properties of polyphenols and other micronutrients richly contained in the bran and germ fractions of cereals but also in whole-grain legumes, fruits and vegetables (Azzi and Stocker, 2000; Eastwood, 1999; Fardet, 2009; Lotito and Frei, 2006; Prior, 2003; Thompson et al., 2005). As demonstrated more recently, the up- or down-regulation of cell redox status *via* signalling-related mechanisms, of glutathione synthesis and/or of genes involved in the development of chronic diseases (Azzi and Stocker, 2000; Moskaug et al., 2005; Rahman et al., 2006), notably through the action of polyphenols and/or their metabolites (Horev-Azaria et al., 2009; Hsu and Yen, 2008), would also be involved. Today, one agrees to advance that several phytochemicals are involved in each of these physiological mechanisms through a synergetic effect. For example, the antioxidant capacity of fruits, vegetables and whole-grain cereals is attributed to very different compounds such as polyphenols, vitamins E and C, selenium, phytic acid... In other words, one compound may exert several protective functions and several phytochemicals may act synergistically to counteract the development of one damaging physiological process as we have recently reviewed it for the protective mechanisms associated with whole-grain cereal consumption (Fardet, 2009).

It is therefore more and more admitted that a small amount of a cocktail of phytomicronutrients would be more beneficial than only one or two phytomicronutrients at high doses as recently demonstrated in healthy women consuming either 18 botanical families of

vegetables and fruits with a modest antioxidant effect or 5 botanical families with a high reported *in vivo* antioxidant activity (Thompson et al., 2006). Moreover, similarly to the increased oxidative stress that has been shown to be involved in most of the previously cited chronic diseases (Bartsch and Nair, 2006,Castelao and Gago-Dominguez, 2008; Keaney et al., 2002; Maiese et al., 2007), other impaired physiological mechanisms may be common to different metabolic disorders, such as increased inflammation, immuno- or glucose homeostasis dysregulation, and/or hyperlipidemia in plasma or liver. However, the number of different phytochemicals contained in PBF is so high that the elucidation of all the mechanisms involved will be a long lasting and difficult task.

PLANT-BASED FOODS AS DIETARY SOURCES OF LIPOTROPES

The main lipotropes: betaine, choline, myo-inositol and methionine

Betaine, choline, myo-inositol and methionine in plants

Although discovered a very long time ago in plants, some of them have been rather neglected when compared to studies related to health potential of minerals, trace elements, vitamins and more recently polyphenols. These compounds are choline, betaine and *myo*-inositol, this latter being a natural isomer of glucose that belongs to the cyclitol family (Figure 1). They have been mostly studied as isolated compounds and often at non-nutritional doses. In plants, betaine has choline as precursor. Betaine and choline are water soluble cytoplasmic osmolytes and thermoprotectants that play a regulatory role in situation of stress for the plant, notably in water-depressed (drought), saline and temperature-stressed environments (Caldas et al., 1999; Hanson and Hitz, 1982; Hanson and Wyse, 1982; Hitz et al., 1982; Ladyman et al., 1980; Nolte et al., 1997; Summers and Weretilnyk, 1993). Among PBF, beetroot (*Beta vulgaris*), *Chenopodiaceae*- (*e.g.* spinach, lambsquarters and whole-grain pseudocereals such as amaranth and quinoa) and *Gramineae*- (*i.e.* whole-grain cereals)

derived plants are well recognized for their high betaine content, as a result of an adaptation to environmental stress (Craig, 2004; Hanson and Hitz, 1982; Hanson et al., 1985; Hanson and Wyse, 1982; Hitz et al., 1982; Yokoishi and Tanimoto, 1994). The database recently released by USDA for betaine and choline contents confirmed these observations (USDA, 2008). Except fruits, PBF are generally a good source of choline, particularly whole-grain cereals, wheat bran and germ, leafy vegetables and soybean (USDA, 2008).

Otherwise, choline and *myo*-inositol are important constituents of cell membranes as precursors of phosphatidylcholine and phosphatidylinositol. In many plants, *myo*-inositol is also the basic constituent of *myo*-inositol phosphate or phytate (IP6) that plays a role as phosphorus and *myo*-inositol stores used for future seed development, but also as regulator of inorganic phosphate levels (Lott et al., 2000). Among PBF, whole-grain cereals, legumes, nuts and seeds contain the highest levels of phytate (Harland and Oberleas, 1987; Lott et al., 2000; Reddy et al., 1982). On the other hand, *myo*-inositol may be also present as free or conjugated (*e.g.* glycosylated *myo*-inositol or galactinol) soluble compound, as in citrus fruits where free *myo*-inositol content may reach up to nearly 7% of total sugars in lemon (Masuda et al., 2003) and concentrations up to 153 mg/100 mL in fresh juice from kiwifruit (Sanz et al., 2004). Although literature data are scarce, the richest sources of free or conjugated *myo*-inositol appear to be legumes (Schweizer et al., 1978; Sosulski et al., 1982), wheat germ (Horbowicz and Obendorf, 1994), pseudo-cereals (Becker et al., 1981; Koziol, 1992) and fruits (Clements and Darnell, 1980), especially citrus (Masuda et al., 2003; Sanz et al., 2004).

Concerning methionine, it is an essential aminoacid especially found in high amounts in cereals, legumes, nuts and seeds (USDA, 2005b, 2005c, 2005d).

The lipotropic effect of betaine, choline, myo-inositol and methionine

In humans, betaine (Craig, 2004), choline (Zeisel and Costa, 2009) and *myo*-inositol (Clements and Reynertson, 1977; Fux et al., 1996; Sundkvist et al., 2000) have been shown to exert multi-factorial

physiological effects. Being essential nutrients for human organism, they were cited as vitamins (vitamin I for *myo*-inositol, vitamin B10 for betaine and vitamin J for choline) for a quite long time in some scientific articles, especially *myo*/*meso*-inositol and choline (Calhoun et al., 1958; Calhoun et al., 1960; Ournac, 1970; Scriban, 1970; Seifert, 1972). Yet, the vitaminic status of choline has been very early debated and it was concluded in 1944 that "it would appear to be more satisfactory to leave choline unclassified" due to the lack of scientific evidences (Mchenry and Patterson, 1944). These compounds, notably betaine, are yet still today presented as vitamins on some web sites, but not in scientific literature. Betaine and choline are first well-known as methyl donors able to stabilize the plasma homocysteine level (Craig, 2004; Olthof and Verhoef, 2005; Sanders and Zeisel, 2007), hyperhomocysteinemy being a risk factor for CVD (Eikelboom et al., 1999; Graham et al., 1997).

Betaine, choline and *myo*-inositol have been first very early shown to have the particularity to exert lipotropic effect within animal liver (Best, 1934; Best and Huntsman, 1932; Best and Huntsman, 1935; Gavin and Mchenry, 1941a; Owens, 1942; Perrault and Dormard, 1966; Thuillier, 1956) (Supplemental Table 1). Although betaine and choline were discovered during the 19th century in respectively beet juice and ox bile (1862) - *chole* is bile in greek (Li and Vance, 2008), the term "lipotropic" was first used only in 1935 by Best et al. who showed that choline is able to prevent and cure fatty livers in rats and that increased liver fat infiltration and accumulation was primarily due to deficiency in some essentials factors whose the principal role is to assure lipid transport and turnover (Best, 1935). Today, one defines lipotropes as compounds that act on lipid metabolism by preventing fat accumulation within the liver through hastening fat removal or by preventing excessive fat deposits (*e.g.* accumulation of cholesterol).

The prevalence of NAFL and NASH in the general population of the United States is estimated at 20% and 3% respectively and can be as high as 95% in high-risk subgroups with abnormal liver enzymes,type 2 diabetes mellitus, or morbid obesity {Falck-Ytter, 2001 #20830}.

Excessive hepatic fat deposits indeed leads to fatty liver or steatosis, a metabolic dysregulation generally observed in situations of alcohol excess (Lieber, 1997), obesity, overweight and diabetes

(James and Day, 1998; Patrick, 2002; Sharabi and Eldad, 2000; Shimada et al., 2002; Silverman et al., 1990; Silverman et al., 1989). A fatty liver is vulnerable and steatosis may lead to steatohepatitis (hepatocellular inflammation), fibrosis or cirrhosis, but not systematically (Adams et al., 2005; Angulo and Lindor, 2001; Day and James, 1998a; James and Day, 1998). Moreover, patients with hepatic steatosis present an increased risk of developing CVD (Mannarino et al., 2009). In addition, fatty liver is often associated with a cluster of several impaired physiological mechanisms including insulin resistance (Gastaldelli et al., 2009; Mamone et al., 2009; Marchesini et al., 1999; Patrick, 2002; Seppala-Lindroos et al., 2002; Valtuena et al., 2006), increased oxidative stress (Day and James, 1998a; Day and James, 1998b; Kwon et al., 2009a; Reid, 2001), hyperlipidemia (Brouwers et al., 2005; James and Day, 1998; Sharabi and Eldad, 2000; Shimada et al., 2002; Vuppalanchi and Chalasani, 2009), metabolic syndrome symptoms (Cortez-Pinto et al., 1999; Mannarino et al., 2009; Patrick, 2002; York et al., 2009), endothelial dysfunction and arterial stiffness (Mannarino et al., 2009), and hepatocarcinogenesis (Shimada et al., 2002; Yatsuji et al., 2006). A minimum of 5-10% hepatic steatosis or fat accumulation by weight is generally considered to diagnose non-alcoholic fatty liver (NAFL) (Neuschwander-Tetri and Caldwell, 2003). And steatosis is considered mild (grade 1), moderate (grade 2) or severe (grade 3) when respectively <33%, 33-66% or >66% of hepatocytes are affected (Angulo, 2002; Brunt et al., 1999).

The development of fatty liver mainly results from the following metabolic dysfunctions: 1) enhancement of fatty acid (FA) synthesis, 2) increased mobilization of FA from adipose tissues, 3) inhibition or impairment of mitochondrial FA β-oxidation (Fromenty and Pessayre, 1995), 4) increased transformation of FA into triglycerides (TG) by esterification, and 5) decreased release of TG from liver (that notably naturally occurs *via* VLDL in a healthy liver) that can result from decreased ApoB or microsomal TG transfert protein (MTP) syntheses (Jamil et al., 1998). All of these mechanisms are particularly involved in situation of insulin resistance or hyperinsulinaemia (Adams et al., 2005).

Ajouter comme mécanisme:
- import of lipoprotein TG by the LDL receptor
- de novo lipogenesis from fructose and carbohydrates ({Lim, 2010 #18755}: page 3, Figure 1)

Otherwise, in humans with non-alcoholic fatty liver diseases (NAFLD), increased long-chain poly-unsaturated FA (PUFA) n-6/n-3 ratio was also observed and authors concluded that such "condition may favour lipid synthesis over oxidation and secretion" (Araya et al., 2004). Indeed, imbalanced diets generally lead to increased PUFA n-6/n-3 ratio that reduces PPARα activation and increases SREBP-1 (sterol regulatory element binding protein) expression, both mechanisms leading to respectively decreased peroxisomal/mitochondrial β-oxidation and increased ApoB-100 degradation (that means a reduction of TG exportation from liver *via* VLDL), and to enhanced FA and TG synthesis (Araya et al., 2004). The depletion in long-chain PUFA of the n-3 and n-6 series might notably result from both their increased peroxidation in situation of increased oxidative stress and inadequate intake (Araya et al., 2004). In obese patients, higher hepatic mRNA levels of SREBP-1c (+33%) and fatty acid synthase (FAS) (+70%), higher SREBP-1c/PPARα ratio (+62%) with a concomitant reduced level of hepatic long-chain PUFA n-3 (-53%) and insulino-resistance, as compared to non-obese subjects, were reported and proposed as conditions that would favour lipogenesis to the detriment of FA oxidation (Pettinelli et al., 2009).

In the case of NAFL associated with insulin resistance, the increased hepatic free fatty acid (FFA) synthesis from glucose not uptook by peripheral adipocytes is also involved; while, in the case of obesity, increased amounts of FFA simply enter the liver (Patrick, 2002). In presence of excess FA, the mitochondrial β-oxidation pathway thus becomes an insufficient way of degrading excess fat that accumulates in TG stored within cytoplasm. Excess TG may be also secreted in plasma *via* VLDL leading to hypertriglyceridemia (Pagano et al., 2002). In the end, the increased level of lipid peroxidation in hepatosteatosis generates more free radicals that may lead to mitochondrial DNA damages and inhibit further lipid β-oxydation (Patrick, 2002). Thus, in a rat nutritional model of hepatic steatosis with inflammation (following a 4-week methionine-choline-deficient diet) - that is morphologically similar to non-alcoholic steatohepatitis in humans - significant increased in hepatic microsomal CYP2E1 (cytochrome P450 2E1**)** content was reported,

this effect generating more reactive oxygen species that may damage liver cells (Weltman et al., 1996).

In the case of high-cholesterol diet, it has been shown in rats that cholesterol lead to specific depressed activities of mitochondrial phosphatidylcholine and phosphatidylethanolamine 24 hours after i.p. injection of [1-^{14}C]acetate (respectively around -84% and -64%) (Morin, 1967), both compounds being essential for PL synthesis, then LDL exportation from liver. Authors suggested that cholesterol may have selectively decreased rate of synthesis and turnover from acetate for these compounds to the benefits of other phospholipids (PL) containing linoleic, eicosatrienoic acid, and arachidonic acids (Morin, 1967).

In the case of alcohol-induced fatty liver, excess ethanol consumption lead to increased hepatic lipogenesis from excess acetyl-CoA generated by ethanol metabolism. More specifically, the down-regulation of the PPARα (peroxisome proliferator-activated receptor) - as shown *in vitro* on hepatocytes in presence of ethanol (Galli et al., 2001) - appear to be specifically involved; and mitochondrial DNA deletions have been observed in patients with microvesicular alcoholic fatty liver (Fromenty et al., 1995). In addition, increased oxidative stress is also particularly involved: thus, by measuring ethane exhalation in high-alcohol consumers, hepatic fat deposits were suggested to be the factor leading to increased lipid peroxidation *via* increased production of oxygen radicals following mitochondrial changes in the respiratory chain (Lettéron et al., 1993). Other mechanisms have been unravelled in rats and minipigs chronically fed alcohol. They involve: alteration of hepatic methylation *via* inhibition of methionione synthase that allows methionine synthesis from homocysteine (Barak et al., 1997; Barak et al., 1987), decreased levels of *S*-adenosyl methionine (*i.e.* abnormal/altered methionine metabolism) that leads to depressed phosphatidylcholine synthesis (Figure 2A) (Esfandiari et al., 2007), increased SREBP-1C expression that has acetyl-CoA carboxylase (ACC), FAS and glycerol-3-phosphate acyltransferase as target genes (Esfandiari et al., 2007), decreased methionine synthase activity (MS, Figure 2A) (Halsted et al., 2002), and a suppressive effect on the phosphatidylethanolamine-*N*-

methyltransferase pathway (PEMT, Figure 2A) (Zivkovic et al., 2009). However, upon prolonged period of alcohol consumption, concomitant increased hepatic betaine homocysteine *s*-methyltransferase (BHMT) activity and decreased betaine levels were also observed, resulting from an adaptation to methionine synthetase deficiency in order to yield sufficient amount of methionine for *S*-adenosylmethionine synthesis (Figure 2A) (Barak et al., 1987). Both significant decreases in methionine synthase and increase in BHMT have been also observed in micropigs chronically fed alcohol upon 14 weeks, but, in this case, only when ethanol feeding was accompanied by folate deficiency (Halsted et al., 2002).

Fatty liver or hepatic steatosis models

In animals - mainly rats and mice, fatty liver is generally provoked by using lipotrope-deficient diets (Lombardi et al., 1968; Olson et al., 1958a), high-fat diet (≈ 20-40%) (Borgschulte et al., 2008; Olson et al., 1958a; Ryu and Cha, 2003; Singal and Eckstein, 1939), high-cholesterol diet (Felmlee et al., 2009), high-fructose/glucose/sucrose diet (≈ 60%) (Hammond et al., 2003; Olson et al., 1958a; Rosenfeld, 1973; Ryu and Cha, 2003; Sanchez-Lozada et al., 2010), low-PUFA diet (Goheen et al., 1983; Keim and Mares-Perlman, 1984), orotic acid-supplemented diet (fatty liver resulting from ApoB synthesis impairment) (Fukuwatari et al., 2002; Nagiel-Ostaszewski and Lau-Cam, 1990; Vaishwanar et al., 1972) or ethanol-rich diet (Balkan et al., 2004; Barak et al., 1997; Song et al., 2008). Fatty liver may be also provoked by single ethanol (Baker et al., 1973), carbone tetrachloride (CCl_4) (Vaishwanar et al., 1972) or DDT (1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethane) (Okazaki et al., 2006) injections, *via* depleting hepatic carnitine levels by using chemicals such as mildronate or THP (trimethylhydraziniumpropionate) (Degrace et al., 2007; Spaniol et al., 2003) or *via* hypercaloric and fat-free parenteral nutrition (Keim and Mares-Perlman, 1984). The use of specific mice strains that mimic choline-deficient diet has also been reported (Dumas et al., 2006). There are still other animal models of steatosis, notably in relation with naturally occuring mutations in rats (*e.g.* obese fa/fa Zucker rats) and mice (*db*/*db* mice - diabetic dyslipidemia - or

ob/*ob* mice - leptin-deficient), genetically modified mice or rats and mice treated with environmental inhibitors of hepatic FA oxidation (*e.g.* glucocorticoids, estrogen antagonists, tamoxifen, valproic acid or etomoxir - a CPT-1 inhibitor) (Angulo, 2002; Koteish and Diehl, 2001). Conversely, KO mice for specific enzymes involved in lipogenesis may be used to limit the development of fatty liver, *e.g.* mitochondrial glycerol-3-phosphate acyltransferase (mtGPAT) -/- mice, mtGPAT catalysing the rate-limiting step in TG synthesis (Hammond et al., 2003).

In humans, as presented previously, hepatic steatosis is observed in situations of overweight, obesity, diabetes, hyperlipidemia or alcohol excess. Otherwise, humans in situation of total parenteral nutrition may exhibit choline deficiencies with a resulting hepatic steatosis (Buchman et al., 2001; Buchman et al., 1995), but the high content in dextrose and glucose of parenteral solutions might be also involved (Liang et al., 1999).

In the end, protein-calorie malnutrition, rapid weight loss or chronic starvation/food deprivation may also lead to NAFLD in both humans (Adams et al., 2005; Angulo, 2002; Doherty et al., 1992; Neuschwander-Tetri and Caldwell, 2003) and animals (Ginneken et al., 2007; Nieminen et al., 2009; Yasuhara et al., 1991). Possible involved mechanisms may be in relation with lipotrope depletion, and also n-3 PUFA depletion. Indeed, n-3 PUFA contribute to the regulation of lipid metabolism, notably by inhibiting transcription of lipogenic genes and inducing gene in relation with FA β-oxidation. In addition, starving lead specific hormonal profiles that can promote TG hydrolysis into adipose tissues, FA products being thereafter taken up by the liver where they may be newly synthesized into TG (Kersten et al., 1999).

Betaine, choline, myo-inositol, methionine and *in vivo* lipotrope-related studies

The lipotropic efficiency of betaine, choline and *myo*-inositol towards fatty liver has thus been demonstrated since a long time by using lipotrope-deficient, high-fat/high-sucrose or ethanol-enriched diets in rats as exhaustively reviewed in Supplemental Table 1 (Barak et al., 1997; Barak et al., 1996a; Barak et al., 1996b; Best et al., 1950; Carroll and Williams, 1982; Chahl and Kratzing,

1966a; Gavin and Mchenry, 1940; Halliday, 1938; Hayashi et al., 1974a). The efficiency was notably determined through dose-response curves, choline being 3-fold the potency of betaine and methionine and betaine being more efficient than *myo*-inositol (Best et al., 1950; Young et al., 1965). Microscopical observations confirmed the lower lipotropic potential of betaine compared to choline (Ball, 1964). However, Andersen and Holub showed that, on a same molar basis of 5.4 mmol/kg of diet, choline and *myo*-inositol had the same lipotropic effect towards hepatic TG accumulation in rats fed a basal diet not supplemented with choline or *myo*-inositol suggesting that previously reported efficiency ratios would differ according to the experimental scheme (Andersen and Holub, 1980).

In humans, published results were scarcer. The first results reported in a scientific journal, to our knowledge, were those of Broun and Muether in 1942: authors apparently based on the results of Griffith and Mulford - obtained in rats and released one year before (Griffith and Mulford, 1941b) - to test choline chloride for more than 2 years in humans (1 g daily) with hepatic cirrhosis (Broun and Meuther, 1942). They notably observed decreases in blood bilirubin and cholesterol, elimination of ascites – *i.e.* accumulation of fluid into peritoneal cavity that may be TG-rich - and decreased liver size (Broun and Meuther, 1942). Three years latter, Barclay and Cooke reported the case of a 27 years-old man who had developed severe liver dysfunction (and renal failure) after receiving large doses of barbiturates for anxiety state; and who was treated both orally (2-5 g for one day) and intravenously (6-8 g) with high doses of choline chloride, then methionine (6 g) and choline chloride during more than one month: recovery of the patient was noted despite important side-effects related to the choline treatment (*i.e.* fall in red cells - anemia, severe sweating, bronchial secretion and painful abdominal cramps,…), probably due to the high doses used (Barclay and Cooke, 1945). In 1946-1948, improvement of liver functions, notably ascite clearance and decreased liver size, were reported in patient with cirrhosis of the liver with ascites and that were administered a low fat, high-protein/carbohydrate diet supplemented with choline (1 g daily) (Broun, 1948) or a combination of choline and cystine (1-3 g daily each) (Beams, 1946). In the

latter study, hepatic fatty changes were suspected based on the agreement that such treatment is more effective "when there are fatty changes in the liver" and when there is an enlarged liver rather than when livers are small and probably contracted by fibrous tissue: a lipotropic action of choline and cystine was therefore proposed (Beams, 1946). Prolonged hepatic fatty infiltration was indeed emphasized in the development of cirrhosis associated with diabetes and chronic alcoholism (Russakoff and Blumberg, 1944). Latter, the positive effects of a lipotropic therapy were reported in humans exhibiting various hepatic dysfunctions and/or atherosclerosis (Colson and Gallay, 1964; Nadeau et al., 1954; Navarranne et al., 1964; Warembourg and Bertrand, 1964). Thus, in 1954, Nadeau et al. suggested that fatty liver in alcoholic patients may result from a dietary carence that has lead to choline deficiency, and they observed that the administration of lipotrope tablets lead to rapid improvement of hepatic function - by decreasing values of the bromosulphalein test, this latter being notably shown in dogs to be tightly related to hepatic fatty overload (Hough et al., 1943; Popper and Schaffner, 1952) - and might be a significant supplement to an adequate diet (Nadeau et al., 1954). In 1964, several authors reported improvements of hepatic function and atherosclerotic markers in humans with hepatic and/or cardiovascular dysfunctions following admisnitration of Ornitaine® (10.045 formula, Jacques Logeais laboratory, Issy-Les-Moulineaux), a cocktail containing ornithine chlorhydrate and other associated substances such as pyridoxine chlorhydrate, sorbitol and 2 lipotropes that are betaine and magnesium citrate (Navarranne et al., 1964; Warembourg and Bertrand, 1964). In 1991, Zeisel et al. reported that choline-deficient subjects developed upon 3 weeks symptoms of incipient liver dysfunction, notably an increased in serum alanin aminotransferase (ALT) and a decrease in plasma phosphatidylcholine (Zeisel et al., 1991). More recently, it was shown (*via* the use of computed tomography, a non-invasive method for estimating hepatic fat content) in patients receiving parenteral nutrition that dietary choline deficiency lead to the development of hepatosteatosis, as it was reported in animal models (Buchman et al., 2001; Zeisel et al., 1991). However, it was also shown that plasma level of free choline and PL-bound choline were not different between patients with and without severe liver

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fibrosis, and was not correlated with the degree of fat infiltration within liver (Nehra et al., 2001). More recently, men (40% of the 20 tested) and postmenopausal women (80% of the 15 tested) deprived of dietary choline have been reported to develop hepatic steatosis, the most common sign of choline deficiency (Fischer et al., 2007).

Betaine has above all been used in human for treating homocystinuria that notably results from a deficit in cystathionine synthase (Berlow et al., 1989). Its use in the treatment of non-alcoholic steatohepatitis has been however shown in humans to lead to significant improvement of liver functions such as a decreased in level of serum ALT during treatment and a lower degree of steatosis, necroinflammatory grade and stage of fibrosis (observed *via* biopsies) after one year of betaine treatment (Abdelmalek et al., 2001); and the use during 8 weeks of oral betaine glucuronate combined with diethanolamine glucuronate (used for PL synthesis) and nicotinamide ascorbate significantly reduces hepatic steatosis scores and liver enlargement in patients with non-alcoholic steatohepatitis as compared to a placebo without adverse effects (Miglio et al., 2000).

Methionine has been also early recognized as a lipotrope compound (Best and Ridout, 1940; Caballero et al., 2008; Chahl and Kratzing, 1966b; Shils and Stewart, 1954; Tucker and Eckstein, 1937) and would directly account for the lipotropic effect of proteins (Eckstein, 1952). The lipotropic effect of methionine was demonstrated to be notably based on methyl supply for choline synthesis (see Figure 2A) (Du Vigneaud et al., 1940; Du Vigneaud et al., 1941). This was latter confirmed that methionine does not directly act upon lipid metabolism but as a precursor of choline through methyl donation to phosphatidylethanolamine (Figure 2A) (Labadie, 1974). Its lipotropic potency would be weaker than that of choline at equivalent quantities (Chahl and Kratzing, 1966b), up to 3-fold lower as shown in weanling rats (Griffith and Mulford, 1941a). Methionine is also the product of homocysteine methylation by betaine (Figure 2A). Although partial deficiencies of some amino-acid (*e.g.* threonine) may lead to fat accumulation into rat liver (Harper et al., 1954a) and although protein play a role in controlling liver fat content (Channon and Wilkinson, 1935), only methionine among the essential amino-acids appears to exert a direct lipotropic effect (Eckstein,

1952). However, high doses of methionine (2.5% of the diet) were shown to increase incorporation of acetate into liver lipids (+118%) after 7 days of treatment in rats fed a standard 9% casein-based diet (Supplemental Table 1) (Yokota et al., 1974).

More generally, this tends to emphasize that lipotropic effect seems to depend on the lipotrope dose used whatever the compound considered and that a balanced amount of various lipotropes at moderate dose might be the best equilibrium to reach - as we will discuss later.

Detailed physiological mechanisms associated with the lipotropic effect of betaine, choline, methionine and myo-inositol

The mechanisms by which betaine, choline, *myo*-inositol and methionine prevent development of fatty liver is mainly in relation with a facilitated transfer of FA from liver to bloodstream (Arvidson and Borgström, 1963; Yagi and Kotaki, 1969), a decreased neutral lipid content in the liver (Leclerc and Miller, 1989), an improvement of TG-rich lipoprotein formation (VLDL and LDL that include PL) and their increased secretion from the liver (Burton and Wells, 1977; Kotaki et al., 1968; Lombardi, 1971; Mookerjea, 1971; Yao and Vance, 1990; Zilversmit and Diluzio, 1958), a reduced rate of FA mobilization from adipose tissue to the liver (Hayashi et al., 1974b), and/or a reduced lipid synthesis in the liver by a reduced FAS and/or ACC activities (Beach and Flick, 1982; Ikeda et al., 1992; Katayama, 1997b).

More generally, lipotropic effect is related to the ability for betaine, choline and methionine to transfer their labile methyl groups, thus participating in a chain reaction that finally yields compounds in charge of regulating fat transit outside the liver (Figure 2A) or towards mitochondria where they are β-oxidized (Figure 2B) (Labadie, 1974). *Myo*-inositol being not a methyl donor, its lipotropic effect is mainly based on its ability to favour phosphatidylinositol synthesis that is thereafter used for lipoprotein formation in reticulum endoplasmic or for lipoprotein transport from liver to bloodstream (Figure 2A) (Yagi and Kotaki, 1969).

Thus, choline participates in and accelerates the synthesis of fat into PL from phosphatidylethanolamine - notably of lecithin type like phosphatidylcholine (Figure 2A) (Mchenry and Patterson, 1944; Mookerjea, 1971; Nadeau et al., 1954; Tokmakjian and Haines, 1979), this latter being indispensable to export fat outside hepatocytes and methionine indirectly contribute to fat exportation from liver by allowing formation of choline. Accordingly, phosphatidylcholine has been shown to limit excess TG in cultured rat hepatocytes by favouring their exportation *via* lipoproteins (Yao and Vance, 1988, 1989). As choline, betaine was early shown to accelerate PL turnover but the effect would be less than choline in doses up to 50 mg per rat and the increase not directly proportional to doses ingested (Perlman and Chaikoff, 1939).

In culture hepatocytes from rats fed a choline-deficient diet, Yao and Vance unravelled important mechanisms that are involved in the lipotropic effect of choline, betaine and methionine, *i.e.*: normal hepatic secretion of VLDL (a TG-rich lipoprotein) requires phosphatidylcholine synthesis - *i.e.* a choline head group moiety -, choline and methionine stimulate the synthesis of phosphatidylcholine, choline favours TG excretion from hepatocytes and betaine may correct VLDL secretion inhibition initiated by choline deficiency (Yao and Vance, 1988, 1989). Accordingly, the impairment of lipoprotein and TG secretions from liver, the subsequent increase in hepatic TG synthesis - *i.e.* increased activity of FAS (Rosenfeld, 1973) - and the decreased plasma PL levels (lecithins and sphingomyelins) of chilomicrons, VLDL and LDL have been reported in rats deprived of choline (Lombardi et al., 1968; Mookerjea, 1971; Mookerjea et al., 1975; Olson et al., 1958a), TG being characterized by increased palmitic acid (16:0) content (Rosenfeld, 1973) - this latter being the first FA produced during lipogenesis and from which longer FA are generated. In the absence of adequate phosphatidylcholine, cholesterol and TG are likely to move towards cytosol, leading to fatty liver as shown in choline-deficient rats (Da Costa et al., 1995). Latter, in choline-deficient rats, Yao and Vance observed hepatic TG accumulation, plasmatic TG and VLDL reduction, decrease in phosphatidylcholine and TG content of VLDL but no change in plasmatic

HDL level (Yao and Vance, 1990). Choline may also prevent from an increased phospholipases A_2 and C activity, the enzymes that releases FFA from membrane PL (Singh et al., 1990).

To go further, KO mice for the hepatic enzyme that allow transformation of phosphatidylethanolamine into phosphatidylcholine (*i.e.* phosphatidylethanolamine *N*-methyltransferase: *Pemt*$^{-/-}$ mice) and/or for the hepatic enzyme that allow phosphatidylcholine to be secreted within bile (*i.e.* phosphatidylcholine-specific flippase, multiple drug-resistant protein 2: *Mdr2*$^{-/-}$/*Pemt*$^{-/-}$ mice) were produced by breeding (Li et al., 2005). It was clearly shown that choline-deficient *Pemt*$^{-/-}$ mice died within 5 days after an hepatic phosphatidyl depletion of 50% but that choline-deficient *Mdr2*$^{-/-}$/*Pemt*$^{-/-}$ mice survived until more than 90 days with the same 50% phosphatidylcholine depletion, effect being attributed to an important adaptation of the phosphatidylcholine homeostasis that is activation of various hepatic choline recycling pathway (*e.g.* up regulation of phospholipase A_2, choline kinase and phosphocholine cytidyltransferase activities and decreased expression of choline oxidase) and the lack of phosphatidylcholine depletion *via* biliary secretion (Li et al., 2005).

Choline deficiency therefore does not allow supplying the adequate amount of PL for lipoprotein synthesis and leads to impaired released of hepatic TG into plasma, to reduced levels of plasma and hepatic PL and consequently to reduced lipoprotein secretion from liver (Haines and Mookerje.S, 1965; Recknagel, 1967). Lipoproteins indeed include a membrane that contains PL such as phosphatidylcholine (*i.e.* lecithin) to the formation of which participate choline, but also *myo*-inositol (Mchenry and Patterson, 1944; Yagi and Kotaki, 1969). However, by using germ-free and inositol-deficient mice, it was demonstrated that inositol synthetized by intestinal microflora do not contribute to reduce the extent of fatty liver (Ikeda et al., 1992). Same authors showed that inositol may also depress the activity of several enzymes involved in hepatic lipogenesis, *i.e.* FAS, G6PDH (Glucose-6-phosphate dehydrogenase) and ACC (Ikeda et al., 1992). Since the effect of inositol supplementation on decreasing these enzyme activities was less marked, their results would

also suggested that a fraction of dietary inositol may be degraded or used for fuel by microbiota at the intestinal level (Ikeda et al., 1992).

In the end, another unexpected cellular mechanism might be involved in the lipotropic effect of betaine, choline and *myo*-insoitol. Indeed, as small hydrosoluble molecules that do not interfere with cellular protein functions - even at high concentrations -, betaine, choline and *myo*-inositol are all osmolytes and may participate in cell volume regulation, the level of cellular hydration affecting cellular metabolism *via* gene expression modifications (Häussinger, 1996). Thus, increased cell swelling in rat hepatocytes was shown to increase lipogenesis and to activate ACC (Baquet et al., 1991; Hue, 1994), this enzyme allowing formation of the metabolic intermediate malonyl-CoA that plays a major role in FA synthesis. In the same way, hypo-osmotic incubation of hepatocytes - *i.e.* that increases their volume - was shown to inhibits CPT-1 (carnitine palmitoyltransferase-1) (allows lipid transfer within mitochondria) whose deficit lead to defective FA oxidation (Figure 2B) (Guzmán et al., 1994). Conversely, transfert of osmolytes into cell will lead to cell shrinkage and inverse effects (Häussinger, 1996). We may therefore hypothesized that increased cellular content of betaine, choline and *myo*-inositol might contribute to cell shrinkage with possible potential positive effects upon lipid metabolism and fat liver content (Figure 2A).

Lipotropes or methyl donors?

It has been reported that lipotrope-deficient diets may be carcinogenic in the absence of carcinogens (Henning and Swendseid, 1996,Moon et al., 1998,Poirier and Whitehead, 1973): this is why lipotrope-deficient diets have often been used to favour carcinogenesis in rats (Rogers, 1975), more specifically in liver (Christman et al., 1993). This is based on the property of some lipotropes to transfer their methyl groups (labile methyls) and on the association between an increased level of DNA hypomethylation and cancers (Goelz et al., 1985; Van Den Veyver, 2002) as it was shown in rats consuming lipotrope-deficient diets (Christman et al., 1993; Locker et al., 1986). For exemple, female rats fed a methyl-deficient diet and in which mammary carcinogenesis was induced were

also characterized by DNA hypomethylation in mammary tissues that was associated with the highest number of tumors (Moon et al., 1998). More generally, a decrease in the amount of methyl groups within organism would favour an increased sensibility towards cancers by altering immune function and xenobiotic (*e.g.* carcinogens) metabolism (Nauss et al., 1982; Newberne and Rogers, 1986).

The lipotrope/methyl donor-deficient diet is therefore the only dietary deficiency to be carcinogenic (Ghoshal and Farber, 1984; Locker et al., 1986; Wu et al., 1998). Maybe this is one of the reasons why both lipotrope- and methyl donor-deficiencies have been, purposely or not, often confounded until now (Wu et al., 1998). The term *methyl donor-deficient diet* is today most often used than *lipotrope-deficient diet*. Yet, while all lipotropes are not methyl donors (*e.g. myo*-inositol), all methyl donors have not been shown to be lipotropic (*e.g. S*-adenosyl-methionine).

Are proteins lipotropic? {Zhang, 1993 #26561}: fish proteins and cholesterol in rats

The lipotropic effect of proteins has been very early discussed and reviewed (McHenry and Patterson, 1944). In 1935, it has been notably suggested that hepatic fat deposits was influenced by and linked to protein metabolism (Best and Huntsman, 1935). Thus, the same year, it was shown that increasing the protein content (caseinogen, from 0 to 50%) of a high-fat diet (40%) containing 17.5 mg choline/100 g at the expense of carbohydrates (glucose hydrate, from 50 to 0%) counteracted the development of fatty liver in rats, and the effect was apparently dose-dependent (Channon and Wilkinson, 1935). In the same study, authors also showed that the quality of liver lipids was altered upon high-protein diet with phosphatide and free cholesterol percentage increasing while TG percentage decreasing; and they finally suggested that some aminoacids of caseinogen may be converted within choline and betaine (Channon and Wilkinson, 1935). Their results were further criticized by Best et al. that found higher liver fat percentages in rats within

similar conditions of diet and they argued that their diet would contain other non-protein "lipotropic factor" (Best, 1935). The lack of an adequate amount of protein in the diet was however latter shown to cause hepatic fat accumulation in rats by these same authors (Best et al., 1955); however, re-feeding rats with an adequate diet containing 18% casein lead to the development of a "transient" increased fatty liver that return to normality after 3 weeks of the diet (Best et al., 1955).

Based on the previously demonstrated lipotropic effect of betaine and choline (Best and Huntsman, 1932), it was hypothesized that amino-acids from casein were converted into betaine and choline in the liver (Channon and Wilkinson, 1935). One thereafter wondered which amino-acid was more particularly involved in the lipotropic effect of proteins. Methionine was thus rapidly shown to be lipotropic while cystine supplementation by 0.5% in the diet increased fat liver content in rats (Beeston and Channon, 1936; Tucker and Eckstein, 1937) and lysine had no effect (Tucker and Eckstein, 1938). In addition to the lipotropic effect of methionine from casein, that of threonine was also suggested (Beveridge et al., 1945) then confirmed (Harper et al., 1953) but partly depending on the amount of tryptophane, glycine or protein in the diet (Harper et al., 1954b,Singal et al., 1953). A small lipotropic effect of tryptophane and of glutamic acid - but only with high-cholesterol-liver, not with high-FA-liver - was otherwise reported (Channon et al., 1943). However, except methionine, it was also observed in rats a lack of lipotropic effect for all essential amino-acids including threonine (Eckstein, 1952).

A series of proteins was also tested for their lipotropic activity and the following ranking was obtained by deceasing intensity: gromax and whale muscle protein > caseinogen > albumin > beef muscle protein and edestin > fibrin and gliadin > gelatine and zein (Channon et al., 1938); and it was noted that the lipotropic effect of these proteins correlated with their methionine content (Tucker and Eckstein, 1938). Thus, arachin, a protein of low methionine content had no lipotropic activity (Singal and Eckstein, 1939).

In 1969, it was simply demonstrated that rats fed a low-protein diet (5% casein only) had a higher hepatic total FA content compared to normal diet - together with a lower level of liver PL of

27% after 6 weeks (Osumi et al., 1969). The lipotropic action of proteins was further underlined in rats and woodchucks for which the effect of lipotropic factors (choline, methionine, folic acid and vitamin B12) varied according to the amount of soy protein isolate in the diet (*i.e.* 10 *vs* 20%) (Boyd et al., 1986). Lipotropic effect of proteins has also been emphasized in rats fed a high-fat plus cholesterol *vs* high-fat and fish proteins plus cholesterol diet, results showing a significantly lower level of hepatic total cholesterol and TG with the fish protein-containing diet (Hosomi et al., 2009). Both an increased expression of hepatic CYP7A1 (cholesterol 7α-hydroxylase) - *via* activation of the transcription factor liver receptor homologue-1 - and an inhibition of cholesterol and bile acid absorption within small intestine are notably involved (Hosomi et al., 2009). Similarly, compared to casein, rats fed pork protein had lower hepatic levels of TG (-46%) *via* decreased mRNA SREBP-1c (sterol regulatory element binding protein) and G6PDH concentrations, *i.e. via* a reduced FA synthesis (Brandsch et al., 2006). In rats receiving cholesterol intravenously and intragastrically, soy protein compared to casein was shown to be antihypercholesterolemic *via* stimulation of hepatic cholesterol synthesis in response to increased faecal steroid excretion (Nagata et al., 1982). Such an effect may be attributable to the lower digestibility of soybean protein compared to casein, hydrophobic peptides of soybean protein binding bile acids and consequently stimulating hepatic cholesterol turnover (Iwami et al., 1986). Moreover, it was shown in rats that highly purified soybean proteins affect enzymes involved in cholesterol metabolism (Madani et al., 1998). Compared to casein, rice and soy proteins were also shown to exert lipotropic effect in both growing and adults rats fed or not with high-cholesterol diet, protective mechanisms involving a reduced secretion of hepatic cholesterol into circulation, an increased excretion of biliary bile acids and reduced hepatic TG accumulation (Yang and Kadowaki, 2009; Yang et al., 2007). Compared to casein, soybean proteins were also shown to significantly reduce cholesterol, TG and ApoA-1 (apolipoprotein A-1) secretion from isolated rat liver, and cholesterol and TG contents in liver; difference in secretion being not observed with corresponding equivalent amino acid mixtures (Sugano et al., 1982).

Study by Iritani et al. (1986): lipotropic effect of gluten and soybean protein vs casein and fish protein towards TG content in liver

Lipotropic effect of proteins seems therefore to depend on protein origin - and probably also methionine content. Thus, in rats fed 25% either casein or proteins from lactalbumin, whole egg, egg albumin, sardine, soybean and wheat gluten, its has been shown significant variations in hepatic cholesterol, TG and PL concentrations, wheat gluten proteins leading to the highest lipid accumulation while soybean proteins leading to the lowest TG accumulation (Sugiyama et al., 1996). In addition, authors reported that lactalbumine and whole egg proteins lead to the highest methionine concentration in rat liver, that casein lead to around 10% more phosphatidylcholine relative to total PL than soybean proteins, and that methionine content of dietary proteins was correlated with the liver microsomal phosphatidylcholine/phosphatidylethanolamine ratio (Sugiyama et al., 1996).

In humans, the lipotropic effect of proteins was apparently very little studied. A report was made with a mildly hypercholeterolemic and healthy middle-aged alcoholic woman upon either a normal diet containing 100 g protein or a low-protein diet of 25 g: liver biopsies did not reveal any fatty material accumulation upon the low-protein diet but it was observed in serum important decreases in lipid (cholesterol, PL and TG) and lipoprotein concentrations suggesting impairment of lipid metabolism within liver, notably for cholesterol (Olson et al., 1958b). Then the administration of a supplement of lipotropic factors (choline, methionine, inositol, vitamin B12 and liver concentrate) restaured serum cholesterol to its normal level (Olson et al., 1958b). The lipotropic effect of proteins has been recently confirmed in healthy humans fed a high-fat *vs* a high-fat and high-animal protein diet by measuring the intrahepatocellular lipids by ^{1}H-magnetic resonance spectroscopy: a blunting effect of proteins upon liver lipids (≈ -22%) was observed (Bortolotti et al., 2009)

The lipotropic effect of caloric restriction (30%) in humans {Elias, 2010 #25149} {Lazo, 2010 #22481}: Reduced steatosis through better lifestyle (moderate caloric restriction + exercise) is also possible : another alternative to lipotropes or a combination of both.

The lipotropic effect of inositol isomers and phytate

Besides *myo*-inositol, inositol possess 8 other isomers, notably *chiro*- and *scyllo*-inositol that are also present in PBF, but at a largely lower levels than *myo*-inositol (Kim et al., 2005; Sanz et al., 2004). However, to our knowledge, only *myo*-inositol was shown to have lipotropic properties (Andersen and Holub, 1980; Beach and Flick, 1982; Okazaki et al., 2006; Yagi and Kotaki, 1969). Conversely, *chiro*-inositol consumption has been reported to increase fat deposits in rat liver (Okazaki et al., 2006). Actually, *chiro*-inositol is recognized for its ability to improve insulin regulation and is used in diabetes management (Kim et al., 2005).

Myo-inositol is present in PBF mainly as free or conjugated forms such as galactinol (*i.e.* monoglycosylated *myo*-inositol), di-glycosylated *myo*-inositol (Horbowicz et al., 1998,Obendorf et al., 1982,Steadman et al., 2000) or *myo*-inositol phosphates such as *myo*-inositol hexakisphosphate (*i.e.* IP6) or phytic acid that is generally the most abundant *myo*-inositol phosphate followed by IP5, IP4, etc. (Chen, 2004; Helfrich and Bettmer, 2004). However, as regards with high phytic acid content in numerous PBF, especially grain products - *i.e.* whole-grain cereals, legumes, nuts and seeds -, the question whether or not phytic acid has to be considered as a source of lipotropes is an important issue.

Phytic acid has been reported to reduce hepatic and serum lipid levels in diabetic and aged ICR mice (Lee et al., 2005; Lee et al., 2007b), in high-sucrose fed rats (Katayama, 1995; Onomi et al., 2004) and in DDT-fed rats (Okazaki et al., 2003) *via* notably a significant increase in fecal triacylglycerols, cholesterol and bile acid contents (Lee et al., 2007b) (Supplemental Table 3). A decreased dose-dependent effect on several hepatic lipid parameters (total lipids and TG contents, and G6PDH, malic enzyme - ME - and FAS activities) was otherwise shown in high-sucrose fed rats with increasing level of phytae from 0.1 to 2.5% of the diet (Katayama, 1997a). Mechanisms involve a depressed activity of lipogenic enzymes such as FAS and NADPH-generating enzymes - NADPH being importantly used for FA synthesis - like ME, G6PDH and 6-phosphogluconate dehydrogenase (Katayama, 1995,Okazaki et al., 2003,Onomi et al., 2004). Phytic acid was also shown to have a similar lipotropic action than free *myo*-inositol in sucrose-fed rats in relation with a

decreased hepatic lipogenesis (Katayama, 1997b). Interestingly, hepatic free *myo*-inositol content was identical for rats fed either phytic acid or free *myo*-inositol (Okazaki and Katayama, 2008), suggesting a metabolisation of phytic acid in rats and mice. This is probably the result of phytate hydrolysis into free *myo*-inositol by small intestine phytases through an adaptative response before phytic acid be fermented within the colon (Lopez et al., 2002; Lopez et al., 2000). Accordingly, it has been previously shown that phytic acid is rapidly absorbed in stomach and small intestine of rats, and then metabolized and distributed to various tissues, probably mainly under the form of *myo*-inositol and/or IP1 (Sakamoto et al., 1993). However, no studies reported lipotropic effect of phytate in humans. This has probably to be related to the weaker phytase activity in humans which is reported to be 30-fold less than in rat duodenum (Iqbal et al., 1994).

Yet, phytate was shown very early to be degraded in humans based on a 20-60% recovery of ingested phytin (calcium-magnesium salt of phytate) in faeces (McCance and Widdowson, 1935). A 60% degradation of wheat bran phytate into *myo*-inositol penta-, tetra- and triphosphates has also been reported in ileostomates (Sandberg et al., 1987). Although mucosal phytases and alkaline phosphatases are present in humans (Bitar and Reinhold, 1972), the degradation of phytate appears to be mainly due to dietary phytases of plant and/or microbial origins that could be activated at the low pH encountered in the stomach (as *e.g.* for cereal phytases), as shown in healthy ileostomates with phytase-deactivated wheat bran (Sandberg and Andersson, 1988), but also due to endogenous microbial phytases within the colon (Sandberg and Andlid, 2002). Another *in vitro* study lead within 3 cell lines (*i.e.* mouse T cell leukemia, human erythroleukemia and human colon adenocarcinoma) showed that phytic acid may be uptook as such and/or partly dephosphorylated (Vucenik and Shamsuddin, 1994). However, no human studies have reported increased hepatic free *myo*-inositol content or improved liver FA metabolism following high-phytate consumption. Up today, results are therefore not sufficiently convincing to consider *myo*-inositol phosphates as a source of lipotropes in humans; and the extrapolation of the lipotropic effect of *myo*-inositol phosphates from rats to human remains highly uncertain or prematured.

The lipotropic effect of carnitine

Study in humans with carnitine: no effect {Uygun, 2000 #17953}
Home parenteral nutrition and carnitine deficiency: a probable cause for steatosis {Bowyer, 1985 #17975}

As betaine and choline, carnitine is a trimethylated molecule that has been shown to have a lipotropic effect in rats fed choline-methionine-deficient and high-fat (30%) diet (Khairallah and Wolf, 1965), or in rats submitted to protein and/or methionine/lysine (carnitine precursors) restrictions (Hu, 1975,Ortega, 1989). The effect is dose-dependent between 0.1 and 0.8% of the diet and apparently more marked with TG than with other classes of lipids that are PL, cholesterol and nonesterified FA (Supplemental Table 2) (Rhew and Sachan, 1986). Indeed, carnitine was shown to increase hepatic cholesterol content in sedentary *vs* excersized rats fed high-fat diet rich in either saturated or monounsaturated FA, probably as a result of an increased cholesterol turnover (Karanth and Jeevaratnam, 2009); and in obese cats, high level of carnitine in the diet (1000 mg/kg) did not reduce liver lipid (TG, PL and cholesterol) contents compared to low level (40 mg/kg) (Blanchard et al., 2002).

As choline, betaine and *myo*-inositol, the lipotropic effect of carnitine can be also simply unravelled in carnitine-deficient rats that notably develop an important increase in hepatic TG content (> +250%) and a significant decrease in PL content (-22 and -36%; Supplemental Table 2) (Degrace et al., 2007). However, at equimolar amounts, lipotropic effect of carnitine was demonstrated to be significantly lower in rat than that of choline (Hu, 1975; Khairallah and Wolf, 1965). In addition, in rats fed a 20%-protein and choline deficient diet, carnitine surprisingly did not allow preventing fatty liver whereas choline did, probably since methyl group of carnitine is not labile and cannot be transferred to form methionine from homocysteine (Fritz and Dupont, 1957). Such apparent contradictory results have probably to be attributed to experimental conditions, notably diet composition.

Carnitine is mandatory for the uptake of long-chain FA acyl-CoA from the cytosol to mitochondria where they are β-oxidized to produce energy (Figure 2B). Accordingly, carnitine acyltransferase, the rate-limiting enzyme in FA β-oxidation is activated by exogenous carnitine (Mccarty, 1994). In humans, it is proposed as commercial *fat burners* to help loose weight through increased fat oxidation rate as shown in overweight subjects (Wutzke and Lorenz, 2004), but also to increase exercise performances (Decombaz et al., 1992; Lennon et al., 1983). The lipotropic effect of carnitine is therefore to stimulate FA oxidation (Hu, 1975).

Body carnitine results from both synthesis from dietary lysine and methionine contents (Figure 2C) and from natural carnitine found in low amount in PBF such as avocado, *tempeh* (fermented soya), some nuts, seeds, legumes, vegetables, fruits et cereals (*e.g.* pumpkin, sunflower, sesame, cabbage, common bean, apricots and banana). Compared to animal tissues, the carnitine and acylcarnitine (2% of the total carnitine pool) contents in plant tissues is around a hundred and thousand times lower (Bourdin et al., 2007) and best sources are of animal origin such as red meat and, to a lesser extent, milk products (Seline and Johein, 2007). Values of respectively 0.32, 0.51 and 0.27 mg/100 g dry weight (dw) have been reported for rapessed, flax and tobacco (Bourdin et al., 2007), values that are closer to ranges found for B vitamins in PBF than those found for betaine, choline, *myo*-inositol and methionine. More generally, Seline and Johein determined total carnitine contents of 74 food products and obtained the following ranges on a fresh weight-basis: 3.2 (breast pheasant) – 166.0 (kangaroo steak) mg/100 g for 20 animal products, 0.64 (Babybel®) - 14.9 (Norwegian goat cheese) mg/100 g for 20 cheeses, 2.2 (yogurt) - 42.8 (condensed milk) mg/100 g for 17 liquid dairy products, and 0.014 (orange) - 4.98 (oyster mushroom) mg/100 g for 13 plant-based foods (Seline and Johein, 2007), thus confirming conclusions of Bourdin et al. when comparing animal- and plant-based foods (Bourdin et al., 2007). Among PBF, mushrooms (1.32, 2.62 and 4.98 mg/100 g for respectively chanterelle, mushroom and oyster mushroom) appears as the best source of carnitine both on a 100 g fresh food- and dry weight-basis followed by avocado

(0.43 mg/100 g), carrot (0.40 mg/100 g), cauliflower (0.36 mg/100 g), cucumber (0.19 mg/100 g), banana (0.10 mg/100 g) and apple (0.05 mg/100 g) (Seline and Johein, 2007)

The contribution of magnesium and vitamins B to the overall lipotropic effect

Magnesium and B vitamins

In addition to the well-recognized lipotrope compounds that are choline, *myo*-inositol, methionine and betaine, the contribution of micronutrients such as niacin (vitamin B3) (Perry, 1960,Van Der Hoorn et al., 2008), pantothenic acid (vitamin B5) (Catolla Cavalcanti and Levis, 1950; Turchetto et al., 1955), folates (vitamin B9) (Kelley et al., 1950; Laird and Drill, 1971) and magnesium (Colson and Gallay, 1964; Navarranne et al., 1964; Warembourg and Bertrand, 1964) to the overall lipotropic effect of PBF has been also emphasized (Supplemental Table 1). Although very early shown to exert a lipotrope effect in rats (Halliday, 1938), pyridoxin (vitamin B6) was no longer considered as a lipotrope (Carter and Phizackerley, 1951) due to further contradictory results (Audet and Lupien, 1974; Gavin and Mchenry, 1940; Johnston et al., 1961; Mchenry and Gavin, 1941; Saheb and Demers, 1972); and the lipotropic effect of pyridoxin has not been convincingly confirmed until today despite several studies showing the development of fatty liver in rats fed a high protein diet without pyridoxin (Abe and Kishino, 1982; Okada and Ochi, 1971; Okada and Suzuki, 1974; Suzuki et al., 1976). Therefore, although some have considered it as a lipotrope and although it is used within the composition of commercial lipotrope supplements, one believes that literature is not enough convincing to validate it as a lipotrope, especially in humans.

Lipotrope effect has also been reported for vitamin B12 (cobalamine) either alone (Drill, 1954; Quan and Le Breton, 1973; St. Greif and Wenning, 1954; Shils and Stewart, 1954) or in combination with choline and folates (Laird and Drill, 1971), this B vitamin being only present in animal-based food (ABF) products, and to a lesser extent in some fermented cereals (*e.g.* beer)

where it is supplied by yeast. It is notably involved within the process of transmethylation that corresponds to the transfert of a methyl group from 5-methyl tetrahydrofolates to homocysteine allowing methionine formation in a way similar to the action of betaine with homocysteine (Figure 2A) (Gillis and Norris, 1951; Jaenicke and Rudiger, 1971; Newberne and Rogers, 1986). Accordingly, carcinogenic lipotrope-deficient or methyl donor-deficient diets generally include vitamin B12 deficiency (Christman et al., 1993; Moon et al., 1998; Newberne et al., 1971; Rogers and Newberne, 1969; Wu et al., 1998).

Physiological mechanisms associated with the lipotropic effect of B vitamins and magnesium

The mechanisms by which magnesium and B vitamins may limit fat deposits are multi-factorial, especially for niacin.

Folates (vitamin B9)

For folates (or folic acid), the mechanism involved in its contribution to the overall lipotropic effect is its action as precursor of the methyl donor 5-methyl tetrahydrofolate that leads to methionine formation from homocysteine *via* methyl donation, and latter to choline regeneration (Figure 2A) (Zeisel, 1981), thus importantly participating in the lipotropic effect. Thus, it has been shown in chronically ethanol fed micropigs that folate deficiency accelerated alcoholic steatosis as shown by liver histopathology and by accentuation of abnormal methionine metabolism (*i.e.* hepatic methionine depletion were of -39 and -68% for respectively folates-sufficient and folate-depleted *vs* nopn-alcoholic and folate-sufficient micropigs; Supplemental Table 1) (Halsted et al., 2002). Latter, the same research team showed that folate deficiency was also accompanied by significant effects on gene expression in relation with lipid metabolism, notably an increased mRNA expression of SREBP-1c and ACC (key compounds in lipogenesis) - but no effect on FAS mRNA expression – in chronically ethanol or not fed micropigs (Supplemental Table 1) (Esfandiari et al., 2005). The lipotropic effect of folic acid has been also emphasized in rats (Drill, 1954; Kelley et al., 1950), but

it appears to be effective only when adequate amounts of other lipotropes, notably choline, are initially present in the diet (Laird et al., 1965). This supportive lipotropic effect of folates is concomitant with their ability to reduce hyperhomocysteinemia (Brouwer et al., 1999; Moat et al., 2003), a CVD risk factor.

Niacin (vitamin B3)

Although we chose to consider niacin (vitamin B3 or vitamin PP or nicotinic acid) as contributing to the overall lipotropic effect of PBF, first reported results were quite contradictory as regards with effect of this vitamin B on hepatic lipid metabolism (Baker et al., 1977; Baker et al., 1973; Gaylor et al., 1960; Griffith and Mulford, 1941b; Merrill and Lemley-Stone, 1957; Orbetsova et al., 1977; Rikans et al., 1965): for example, Griffith and Mulford observed an increased liver fat percentage of around 4% in rats fed during 8 days a niacin-supplemented diet (22.3% fat) as compared to basal diet (18% fat), the increased range being more marked in the presence of 0.04% choline chloride - *i.e.* from 12.5 to 19.9% (Griffith and Mulford, 1941b); in addition, a 2%-supplementation nicotinic acid was shown to induce fatty liver in rats, the effect being counteracted when adding 0.4% choline chloride (Handler and Dann, 1942); and a daily injection during one month of a high dose of nicotinic acid (250 mg/kg b.w.) in spontaneously hypertensive rats fed either normal diet or atherogenic diet (2% cholesterol) increased hepatic cholesterol, TG, total lipid, and esterified and FFA contents (Orbetsova et al., 1977). Conversely, Merrill and Lemley-Stone latter showed that the addition of 0.4% nicotinic acid to an initial 2%-cholesterol diet largely lowered average liver cholesterol content in rabbits from 6.55 to 1.51% (Merrill and Lemley-Stone, 1957). In 1958, Schön showed that incorporation of 3-4% nicotinic acid in a hypolipotropic diet free from cholesterol partly reversed increased hepatic cholesterol concentration by around 42-46% in rats, advancing that a relative lack of Coenzyme A (CoA) may be responsible for the effect of the hypolipotropic diet (Schön, 1958). Then, Baker et al. showed that nicotinic acid may prevent hepatic steatosis (decreased total fat, neutral fat and non-esterified FA levels to the normality) in ethanol-treated rats

and hypothesized that nicotinic acid may have depress the mobilization of non-esterified FA from adipose tissue that was induced by ethanol (Baker et al., 1973). Nicotinic acid was also shown to importantly reduce different lipid fractions (total lipids, cholesterol, lipid phosphorus and TG) in rat fatty livers induced with CCl_4 and orotic acid: competitiveness with CoA synthesis (involved in lipogenesis) and a possible inhibition of fat depot mobilization and TG/FFA availability for lipid synthesis have been hypothesized in this study (Vaishwanar et al., 1972). And in laying hens supplemented with niacin, 50 mg niacin/kg reduced fat infiltration in liver by around 29%, but effect was not significant due to a high variability in data (Hartfiel and Kirchner, 1973). Conversely, excess fat deposits in high-fat- or normal-diet-fed rats supplemented with niacin at a high level of 0.1% have been observed despite the presence of choline (Baker et al., 1977; Rikans et al., 1965). In the study of Baker et al., the 0.1% niacin-supplementation of rats fed a choline-deficient diet lead to -40, +94, -14, +116 and +33% changes in respectively hepatic PL, TG, free cholesterol, cholesterol esters and non-esterified FA contents but effects were not significant (Baker et al., 1977). Adding 0.5% choline dihydrogen citrate to the 0.1% nicotinic acid lead to reduction for all lipid classes, effect becoming significant for TG (-26%) and cholesterol ester (-7%) contents, but surprisingly also for PL content (-52%), also indicating "that niacin interferes with choline-induced lipotropism" (Baker et al., 1977). Although 0.1% niacin-supplementation was not nutritionally realistic, Baker et al. interestingly showed by using the *in vitro* models *Escherichia coli* (requiring vitamin B12 or methionine) and thermophilic yeast *Torulopsis pintolopessi* (requiring choline or methionine) that the potentiated hepatic steatosis induced by high doses of nicotinic acid (Sorrell et al., 1976) - although plasma TG level is generally decreased - may be ascribed to its interference in the transmethylation process by preventing methionine to provide methyl groups for choline synthesis and by blocking vitamin B12 from acting as a co-factor in the methylation of homocysteine in methionine (Baker et al., 1977; Rikans et al., 1964). Accordingly, it had been previously hypothesized that the antilipotropic effect of nicotinic acid at high doses (from 1 to 4%) might be due to the important need in methyl groups of its detoxification products (Schön, 1958) - notably

nicotinamide that requires more methyl groups for excretion than nicotinic acid (Miller et al., 1960), excess niacin being methylated in the liver to *N*-methyl-nicotinamide then excreted in urine (Institute of Medicine, 1998); which lead to assimilate nicotinic acid to a "methyl trap that drains off methyl groups from choline and/or methionine synthesis leading to a functional choline deficiency" and leading to impaired secretion of lipids from the liver (Baker et al., 1977; Cantoni, 1951,Handler, 1944; Perlzweig et al., 1943). Indeed, addition of choline generally reverses the fatty liver induced by excess niacin (Baker et al., 1977; Rikans et al., 1965).

More specifically, concerning liver cholesterol, nicotinic acid has been shown by different authors to significantly reduce its content and its rate of biosynthesis (Merrill and Lemley-Stone, 1957; Perry, 1960; Schade and Saltman, 1959; Schön, 1958), an effect attributed to a lack of acetyl-CoA needed for cholesterol synthesis, CoA competing with detoxication systems - notably towards nicotinuric acid at high doses of nicotinic acid - and lipid synthesis (Schade and Saltman, 1959). Other advanced that nicotinic acid would divert cholesterol precursors towards oxidation rather than in the cholesterol synthesis pathway, as for FA formation (Perry, 1960). In another study, different rate of acetate incorporation into cholesterol synthesis were obtained with rat liver slices incubated in 2-C^{14} sodium acetate according to the mode of administration of nicotinic acid, either chronically injected in rats during 21 days before killing at a level of 20 mg/kg b.w. or directly added to incubation medium of liver slices at a concentration of 10^{-3} M (Orbetsova et al., 1976). In the former case no changes were observed while a stimulation of acetate incorporation was reported in the latter case. Authors suggested that chronic administration of nicotinic acid *vs* direct incubation or single injection would not influence cholesterol synthesis at the same level of the metabolic chain (Orbetsova et al., 1976). Accordingly, they observed in rats injected with nicotinic acid (250 mg/kg b.w.) a decreased hepatic cholesterol and TG content after 6 hours with increase after 3 hours (Orbetsova, 1977). In humans, nicotinic acid administration - from 1 to 2 g 3 times daily - lead to lowered serum cholesterol levels (Miller et al., 1960; Parsons, 1961b), such reduction being likely to partly result from marked reduction in hepatic cholesterol synthesis (Parsons, 1961b). Thus, from

these studies, it seems that nicotinic acid induces fatty liver only at high doses and in absence of one or more other lipotropes with variations according to animal species and modes of administration, *i.e.* single injection *vs* chronic administration. That would partly explain apparent contradictory results between studies.

Other mechanisms might be involved in the positive effect of niacin on hepatic lipid metabolism. *In vitro*, nicotinic acid has been thus shown to importantly inhibit at various doses (from 19 to 100% for respectively 10 to 100 mkmoles of nicotinic acid) ACC activity, the main enzyme involved in FA synthesis (Fomenko et al., 1979). Yet, with the objective of unravelling mechanisms by which nicotinic acid inhibits ketogenesis, when incubating *in vitro* mitochondria with palmitic acid, CoA, carnitine and nicotinic acid, this latter had no influence on the rate of β-oxidation, suggesting that enzymes required for palmitate β-oxidation and the production of acetyl CoA are not affected by nicotinic acid (Yeh, 1976). This would confirm previous results showing lack of effect of nicotinic acid on hepatic acetyl-CoA concentration at an injection level of 50 mg/kg body weight (Mayor et al., 1967). Based on the antioxidant property of copper (Cu) and of the hypolipidemic capacity of niacin, Salama et al. interestingly demonstrated in high-carbohydrate fed rats that a copper nicotinic acid complex (a therapeutic drug), administered by stomach tubing at apparently nutritional doses - *i.e.* 400 mg/kg -, is able to correct fatty liver by notably significantly decreasing total lipid content and increasing antioxidant status (Salama et al., 2007), increased oxidative stress *via* accumulation of free radicals being a cause that may lead to fatty liver. Indeed, a decreased expression of superoxide dismutase has been observed in patients with cirrhotic stage non-alcoholic steatohepatitis (Sreekumar et al., 2001). Such a decrease generally lead to increased levels of reactive oxygen species (ROS) that may yield mutation in mitochondrial DNA, mitochondria being the site of FA β-oxidation (Sreekumar et al., 2001). Finally, niacin, together with pyridoxin, vitamin C, iron and other enzymes, participates in the synthesis of the lipotrope carnitine (Figure 2C).

Recent studies allowed unravelling new mechanisms that may contribute to the overall positive effect of niacin on hepatic lipid metabolism (Figure 2C). Thus, results obtained with HepG2 cells showed that niacin may: 1°) inhibit TG production and FA synthesis combined with accelerated ApoB (a TG-rich lipoprotein) degradation (Jin et al., 1999; Jin et al., 1996; Kashyap et al., 1997; Van Der Hoorn et al., 2008); 2°) increase efflux of HDL ApoA-1 (Jin et al., 1997); 3°) reduce intracellular cholesterol (total, free and esters); 4°) induce expression of PPARα mRNA (PPARα regulates FA oxidation and stimulates peroxysome proliferation) (Siripurkpong and Na-Bangehang, 2009); 5°) up-regulate ABCA1 (ATP-Binding Cassette Transporter 1) mRNA expression (Siripurkpong and Na-Bangehang, 2009) - ABCA1 effluxes excess cellular cholesterol to ApoA-1 to form nascent HDL; 6°) reduce expression of CETP (Cholesteryl Ester Transfer Protein) mRNA (Van Der Hoorn et al., 2008) - CETP mediates the transfer of cholesteryl esters from HDL to pro-atherogenic apoB-lipoproteins; 7°) inhibit hepatocyte DGAT (diacylglycerol acyltransferase), the key enzyme for the synthesis of triglycerides, finally resulting in a potential reduction of hepatic atherogenic lipoprotein secretion (Ganji et al., 2002); and 8°) inhibit surface expression of ATP synthase β chain - this latter mediating hepatic HDL endocytose (Martinez et al., 2003); and consequently 9°) reduce HDL uptake by HepG2 cell (Zhang et al., 2008).

In the fifties, Niacin was otherwise reported to be hypolipidemic in humans, notably hypocholesterolemic (Altschul et al., 1955,Parsons and Flinn, 1959), and is today widely used clinically as a drug at high doses (generally 3-6 g daily) in the treatment of lipid disorders such as hyperlipidemia (Figge et al., 1988; Grundy et al., 1981) by notably reducing plasma TG and cholesterol levels and raising plasma HDL cholesterol level (Chapman et al., 2010; Shepherd et al., 1979). The effect of nicotinic acid was also tested in healthy women at the high dose of 2 g/day and was shown to decrease both acutely and chronically VLDL-TG production rate from liver (Wang et al., 2001). A similar reduction was observed with hyperlipidemic patients given 1 g three time daily of niacin (Grundy et al., 1981). However, within clinical therapy context, such high-dose of niacin (around 1-3 g daily) may be hepatotoxic - and also lead to various undesirable, but generally

reversible, side-effects like blushing/flushing, itching, gastrointestinal irritation,… -, notably with slow/sustained-release niacin as compared to immediate-release niacin (Dalton and Berry, 1992; Etchason et al., 1991; Lawrence, 1993; Pardue, 1961; Rader et al., 1992; Reimund and Ramos, 1994; Schwenk and Fisher, 1994; Stern, 2007); but the co-administration of betaine (Mccarty, 2000) or methionine (Aronov et al., 1999) decreased hepatotoxic risk. Others reported the beneficial use of *myo*-inositol hexanicotinate instead of niacin alone, *myo*-inositol hexanicotinate being free from side effects (Welsh and Ede, 1961); and Baggenstos et al. (1967), *via* liver biopsies in hypercholesterolemic humans chronically administered 1.5 to 6 g nicotinic acid, observed minor histological alterations that were also reported in healthy patients, and concluded that the use of nicotinic acid is not contraindicated in carefully supervised patients. Similarly, after one year of nicotinic acid therapy in 17 patients, no significant hepatic alteration was found *via* the use of several liver tests, and needle biopsies did not show any fatty changes or abnormalities (Parsons and Flinn, 1959) although significant alterations in hepatic function tests were reported in another studies 2 years later in 10 hypercholesterolemic patients among 36 (Parsons, 1961a). Recently, lower doses of niacin up to 50.1 mg daily have been tested in healthy volunteers and it has been observed that a 16.7 mg-dose niacin does not cause flushing symptoms, that are sporadic at a 50.1 mg-dose (Schweikart et al., 2009). In addition, no change occurs concerning blood pressure, pulse and skin temperature (Schweikart et al., 2009). In addition, niacin may reduce the release of FFA in plasma through inhibition of catecholamine stimulation of TG lipolysis in adipose tissue (Arner, 1999), as notably shown *in vitro* (Carlson, 1963), leading to reduction of hepatic VLDL-TG production (Chapman et al., 2010; Figge et al., 1988) and resulting in decreased plasma VLDL-TG concentrations (Grundy et al., 1981). This may occur *via* either a reduced transport of FFA to the liver or a direct inhibition of hepatic secretion/synthesis of ApoB-containing lipoproteins (Tato et al., 1998). Others have shown in nondiabetic patients that the administration of 2 g daily of nicotinic acid during 2 weeks reduces cholesterol synthesis by around 50% (Nunn et al., 1961). And a study in hyperlipidemic subjects that were administered 1 to 2 g daily nicotinic acid has lead to

suggest that serum cholesterol reduction has to be attributed to reduction of cholesterol synthesis at the hepatic level (Parsons, 1961a).

Compared to other lipotropes, physiological mechanisms involved in the lipotropic effect of niacin therefore appear multifactorial as we have tentatively summarized and illustrated it in Figure 2C based on references cited previously and on those from Supplemental Table 1.

Pantothenic acid (vitamin B5)

As for niacin, apparent contradictory results have been also reported for pantothenic acid (Carter and Hockaday, 1962; Griffith and Mulford, 1941b; Morgan and Lewis, 1953; Schaefer et al., 1942). First, is was found that feeding rats with a B vitamin- (including thiamine, riboflavin, pantothenic acid and pyridoxine) or a pantothenic acid-deficient diet prevented the development of fatty liver (Engel, 1942; Morgan and Lewis, 1953), notably an increased cholesterol content in high-cholesterol fed rats (Guehring et al., 1952), pantothenic acid being indirectly involved in the transformation of acetate into cholesterol (Bloch and Rittenberg, 1942) *via* acetyl-CoA action and being constitutive of the coenzyme. A 2-fold decreased food intake has been notably proposed as an explanation for the observed reduced liver fat content of pantothenic acid-deficient rats (Guggenheim and Olson, 1952). Others suggested that adrenal hormone production is reduced and fat metabolism seriously impaired in pantothenic acid-deficient rats, adrenal hormone being synthetized from cholesterol and pantothenic acid being involved in cholesterol synthesis (Morgan and Lewis, 1953). However, fatty liver was reduced to normal level in rats when adding adequate amounts of both inositol and choline to diets containing B vitamins thus moderating and relativising the role that pantothenic acid may play in fatty liver development (Engel, 1942). The same year, it was shown that pantothenic acid deficiency may lead to fatty liver in dogs (Schaefer et al., 1942) and progressive increase in lipid globules in rat liver (Wirtschafter and Walsh, 1962). It was also observed in pantothenic acid-deficient and high-fat fed rats a reduced hepatic neutral fat content compared to pantothenic acid-supplemented and high-fat fed rats, with no difference for hepatic

total cholesterol, free cholesterol and PL contents (Carter and Hockaday, 1962). The same tendencies were reported with low-fat diets (Carter and Hockaday, 1962). Conversely, in the fifties, Italian research teams reported lipotropic action of pantothenic acid in rats (Catolla Cavalcanti and Levis, 1950,Turchetto et al., 1955). In pantothenic acid-deficient cats (only 0 to 3 mg/kg diet), some hepatic fatty metamorphosis and fine and coarse vacuolar formation with lipids evenly deposited were reported, no histological changes being observed when increasing pantothenic acid content of the diet from 5 to 20 mg despite a largely higher weight gain (Gershoff and Gottlieb, 1964). In 1968, Williams et al. showed that supplementing low-fat or high-fat fed rats with pantothenic acid increased liver weight and FA contents but not that of PL with variations according to the FA considered, *e.g.* higher levels of stearate and arachidonate in PL and higher proportion of linoleate in TG (Williams et al., 1968). In 1969, Osumi et al. showed in rats that Ca-pantothenate partly reduced the high hepatic TG content initially developed through a low-protein diet (Osumi et al., 1969) while no change in hepatic lipid content was observed with pantothenic-deficient- *vs* normal-fed rats (Fidanza et al., 1970). Latter, pantothenic acid carence has been shown to increase, but not significantly, the total lipid content of liver in ducklings (Saheb and Demers, 1972). In pantothenic acid-deficient rats kept on diet for more than 75 days, significantly lower phosphatidylcholine content of 40% compared to non-deficient rats was also observed (Mahboob, 1975). In mice with hypothalamic obesity induced by aurothioglucose, pantothenic acid derivatives (phosphopantothenate, pantethine and panthenol) importantly and significantly reduced hepatic TG content with no effect on total PL and free cholesterol, and significant effect upon total cholesterol and cholesterol ester reduction by panthenol, reduced resistance to insulin and lipolysis activation being hypothesized as possible mechanisms (Naruta and Buko, 2001).

More generally, pantothenic acid is recognized as maintaining normal hepatic functions (Ueshima et al., 1956,Ueshima et al., 1958), and pantothenic acid deficiency lead to lower weight gain in rats with probable hepatic mitochondrial dysfunctions like a slower rate of the oxidation process (Mahboob and Estes, 1978).

Pantothenic acid is otherwise both precursor and constitutive of CoA (*i.e.* the pantothenic acid active form)(Kaplan and Lipmann, 1948; Lipmann et al., 1947; Novelli et al., 1949; Smith and Song, 1996) that is active in β-oxidation, the main pathway to FA degradation (Figure 2B). Accordingly, an increased in pantothenic acid consumption (5 mg daily) was shown to enhance CoA activity in rat liver for the first 2 days compared to a control group (Causi et al., 1958). And the hepatic CoA content (total, acid-soluble and long-chain acyl) was increased following pantothenic acid supplementation for both low- and high-fat diets in rats while the CoA values were always lower with the high-fat diet (18%) than with the low-fat diet (6%) (Williams et al., 1968). The liver acyl-CoA content was otherwise increased by Ca-pantothenate after being decreased by a low-protein diet (Osumi et al., 1969). Similarly to these results, it has been shown that the hepatic total CoA content was significantly reduced in pantothenic acid-deficient weanling rats (Moiseenok et al., 1987). Latter, the hepatic free CoA content reduction of developping mice treated with valproate – that inhibits FA oxidation - was shown to be partly reversed when supplemented with pantothenate plus L-carnitine and L-cysteine with no effect when L-carnitine was administered alone, the increase in CoA content being also observed in absence of valproate (Thurston and Hauhart, 1992). In addition, pantothenic acid-deficient rats exhibited a lower level of hepatic peroxisomal β-oxidation that was restaured to normal level following supplementation: this down-regulation of peroxisomal β-oxidation was paralleled with a reduced activity of the hepatic long-chain acyl-CoA synthetase that activates FA degradation (Youssef et al., 1994). Authors suggested that such an effect may result from an "adaptation to the reduced ability of the liver to activate FA to their acyl-CoA thioesters" (Youssef et al., 1994).

Such results emphasized different pantothenic acid effects on hepatic lipid metabolism (see Supplemental Table 1 that reports most relevant studies). We believe that the contradictarory results obtained with both niacin and pantothenic acid probably depends on the presence or not of the other main lipotropes - choline, betaine, methionine and *myo*-inositol - or other B vitamins, but also on

doses and animal species used, and on experimental scheme. In other words, the lipotropic action of B-vitamins, notably niacin and pantothenic acid - probably exerts in synergy with other lipotropes. This is the reason why in the end we have considered that niacin and pantothenic acid may be considered as contributing to the overall lipotropic effect of PBF in normal dietary conditions, *i.e.* at normal doses and including the presence of other lipotropes. Nowadays, it is otherwise commonly used in lipotropic supplements.

Magnesium

Concerning magnesium, its depletion has been associated with cirrhosis (Koivisto et al., 2002), and hypomagnesemia associated with NAFLD and non-alcoholic steatohepatitis (Hanje et al., 2006). A low plasma level of magnesium has also been associated with insulin resistance (Rosolova et al., 1997), and a low magnesium diet was otherwise shown to decrease insulin sensitivity (Nadler et al., 1993). Magnesium has been also shown to reduce hyperlipidemia (Kisters et al., 1993).

More specifically, magnesium is well known as antioxidant (Freedman et al., 1992). It is also particularly involved in the reaction of CoA with ATP (Mg-ATP complex) and FFA to yield acyl-CoA (Figure 2B), and it activates CoA synthesis from pantothenic acid proportionally to the presence of ATP. It is also required by mitochondria for oxidative phosphorylations that produce ATP. All of these properties of magnesium play a role in the overall FA β-oxidation process (Figure 2B) (Andrieux-Domont and Le Van, 1970; Berg, 1959; Garfinkel and Garfinkel, 1985; Ingraham and Green, 1958). The role of magnesium on FA oxidation was well illustrated by the dramatic increase of palmitate oxidation reached in heart muscle mitochondria when increasing magnesium concentration from 0.01 to 5 mM in presence of carnitine (≈ +800%) or acetylcarnitine (≈ +950%; Supplemental Table 1) (Fritz, 1959).

As regards with these specific properties of magnesium and since increased oxidative stress and insulin resistance may be associated with fatty liver, magnesium may be considered as contributing to the overall lipotropic effect of PBF. It has moreover been cited as lipotrope in the

clinical report of Colson and Gallay (Colson and Gallay, 1964) and is commonly used as such in current commercial lipotrope complexes. There are however no human studies investigating the effects of a magnesium therapy in patients with fatty liver.

Other phytochemicals and plant extracts

Lipotropic effect of choline, betaine, methionine and *myo*-inositol has been unravelled in rats quite early between 1932 and 1941 (Best and Huntsman, 1932; Gavin and Mchenry, 1941b; Tucker and Eckstein, 1937); then, always in rats, the lipotropic potential of vitamins B was apparently first emphasized around 1950 (Catolla Cavalcanti and Levis, 1950; Kelley et al., 1950; Tyner et al., 1950). The effect of carnitine on FA oxidation was reported in rat liver slice in 1959 (Fritz, 1959) and carnitine was shown to importantly reduce hepatic TG content in choline-methionine-deficient and high-fat (30%) fed rats (see Supplemental Tables 1 and 2) (Khairallah and Wolf, 1965).

From the survey and analysis of studies dealing with effect of plant compounds on hepatic lipid metabolism, it appears that this is not before the end of the sixties that research focused on other phytochemicals, notably hydroxycitric acid (HCA), organosulfur compounds, fiber, polyphenols, saponins, unsaturated and short-chain FA or melatonin (Supplemental Tables 2, 3 and 4). The exception was β-sitosterol that was reported in 1955 to reduce hepatic cholesterol content in high-cholesterol fed mice (Beher and Anthony, 1955). Around 1970, HCA was shown to decrease rate of lipogenesis and FA synthesis in rat liver (Lowenstein, 1971; Sullivan et al., 1972); and in the seventies, great interest was brought to fiber and derived compounds (Supplemental Table 3). Interest for the effect of polyphenols and derived compounds on hepatic lipid metabolism really begins in the nineties. Finally, concerning unsaturated FA, organosulfur compounds, short-chain FA and melatonin, their positive effect on hepatic lipid metabolism appear to have been put forward around respectively 1965, 1970, 1990 and 1995 (Supplemental Table 2).

Now, we therefore considere all phytochemicals - other than betaine, choline, methionine, *myo*-inositol, vitamins B, magnesium, carnitine and phytate - for which at least one significant positive effect on lipid metabolism has been reported, be on total lipid, TG or cholesterol contents, on lipogenic enzyme activities, FA oxidation enzyme activities, gene expression of PPARα and SREBP, or rate of lipogenesis (Supplemental Tables 1-4). However, in the following section will be considered as lipotropic compounds *sensu stricto* only those that significantly reduce hepatic total lipid or TG contents. Those decreasing only hepatic cholesterol content may not be considered as lipotrope since steatosis is mostly concerned by TG accumulation or retention within hepatocytes (Adams et al., 2005).

Specific plant compounds: hydroxycitric acid and organosulfur compounds

Besides the 8 previously defined lipotropes that are betaine, choline, *myo*-inositol, methionine, magnesium, niacin, pantothenic acid and folates and that are quite ubiquitous in plants, other phytochemicals that come from specific botanical families have been cited as having positive effects on hepatic lipid metabolism: they were HCA (Lowenstein, 1971; Sullivan et al., 1972) mainly isolated from fruits of the *Garcinia* family, notably *Garcinia cambogia* (Heymsfield et al., 1998; Lewis and Neelakantan, 1965) and used in commercial nutritional supplements that aim at loosing weight, and cysteine-containing compounds as the organosulfured compounds found in *Allium* species (*e.g.* s-ethyl cysteine and s-methyl cysteine in onion or garlic) (Supplemental Table 2).

Hydroxycitric acid

The lipotropic effect of HCA may however appear controversial as illustrated by the apparent contradictory results obtained, as the increased post-prandial hepatic lipid content of chronically high-fructose fed rat supplemented with HCA (Brandt et al., 2006), the decreased rate of lipogenesis in rat liver following either i.v./i.p. HCA injection or orally ingested HCA (Lowenstein,

1971,Sullivan et al., 1974b,Sullivan et al., 1972), the absence of effect on liver lipid content following HCA supplementation in normal rats (Sullivan et al., 1974a) or in rats with experimentally induced obesity (Sullivan and Triscari, 1977), the important increase in hepatic post-prandial lipid content (≈ +67%) in high-fructose fed rats (Brandt et al., 2006) or the significant reduction of hepatic FA synthesis rate by HCA in high-fructose and high-glucose fed rats (Sullivan et al., 1974b; Sullivan et al., 1977) (Table 2 and Supplemental Table 2). In addition, HCA was shown *in vitro* to inhibit ATPCL/CCE (ATP-citrate lyase/citrate cleavage enzyme) activity, the enzyme that catalyzes the split of citrate to oxaloacetate and acetyl CoA, the construction material for FA: this inhibition of the conversion of carbohydrate metabolites into fat favours glycogen accumulation within muscles and liver (Supplemental Table 2) (Watson et al., 1969).

Conversely, HCA was convincingly shown to significantly reduce weight gain or regain in rats (Brandt et al., 2006; Greenwood et al., 1981; Kang et al., 2007; Leonhardt and Langhans, 2002; Nageswara Rao and Sakariah, 1988; Shara et al., 2004; Shara et al., 2003). This effect might be notably attributed to the anorectic property of HCA in relation with an increased FA β-oxidation (Leonhardt and Langhans, 2002) that would result from reduction in malonyl CoA production (*via* inhibition of ATPCL) (McCarty, 1994), an inhibitor of CPT-1 (Figure 1b), and to the role that plays FA oxidation in the metabolic control of food intake at high fat dose (Scharrer and Langhans, 1986).

The rare study lead in human failed to show any significant decreased hepatic *de novo* lipogenesis following high-dose HCA consumption (6 g daily), either after fasting or fructose infusion (Supplemental Table 2) (Schwarz et al., 1999). Yet, HCA was reported to significantly reduce weight gain and BMI in obese subjects after 8 weeks HCA treatment (-5%, 2800 mg daily) (Preuss et al., 2004a), in normal/overweight subjects upon 2 weeks of daily 500 mg-HCA supplementation (-0.5 to -1.5 kg) (Kovacs et al., 2001a,Kovacs et al., 2001b) and in overweight subjects after a 8 week-HCA treatment (750 mg daily, ≈ -4.5 kg)(Badmaev et al., 2002), while no effect were observed in overweight subjects that were given 1500 mg HCA daily for 12 weeks

(Heymsfield et al., 1998). In addition, HCA supplementation does not increase satiety in humans (Kovacs et al., 2001a; Kovacs et al., 2001b) but may decrease blood levels in TG, LDL and cholesterol (Badmaev et al., 2002; Preuss et al., 2004b). The effect on body weight loss might be in relation with an increased short-term rate of fat oxidation as demonstrated in either athletes (Lim et al., 2002) or untrained men (Tomita et al., 2003) although others have reported no significant effect in sedentary adults at rest or during moderately intense exercise (Kriketos et al., 1999); and no significant increased total fat oxidation was registered in enduranced-trained humans that were given HCA solution of 19 g/L at a level of 3.1 mL/kg b.w. before and after exercise (Van Loon et al., 2000). In mice, while a single HCA treatment of 10-30 mg had no effect on respiratory exchange ratio, chronic HCA administration (10 mg HCA twice a day for 25 days) promote lipid oxidation, either at rest or upon exercising conditions (Ishihara et al., 2000).

The lack of effect or the increase post-prandial content of hepatic lipid contents following HCA supplementation in rats appears contradictory to the ability of HCA to importantly inhibit hepatic rate of lipogenesis in chronically fed rats. This means that if, *in vivo*, HCA really inhibits CCE activity, this does not reflect in lower total lipid content upon a long period of time. However, to our knowledge, no study has investigated the specific effect of HCA on hepatic TG content. Further studies are therefore needed before concluding or not HCA is a lipotrope *sensu stricto*.

Cysteine-containing compounds

Concerning water-soluble (*e.g. s*-allyl cysteine, *s*-ethyl cysteine, *n*-acetyl cysteine, *s*-propyl cysteine) and lipid-soluble (*e.g.* diallyl sulphide and dipropyl sulphide) organosulfur compounds, they have been shown in mice or rats fed a methionine-choline deficient (Lin et al., 2008), high-fat (Lin and Yin, 2008) or high-cholesterol (Kumari and Augusti, 2007) diet to alleviate and/or to protect liver from induced hepatotoxicity and from high saturated fat-associated oxidative damages, but also to reduce hepatic biosynthesis of TG and cholesterol (Supplemental Table 2) (Kumari and Augusti, 2007; Lin et al., 2004). Similar results were reported in diabetic mice (Hsu et al., 2004).

Some of the mechanisms involved - notably as unravelled by using rat hepatocytes - are probably in relation with a decreased activity of two lipogenic enzymes that are ME and FAS, a decreased activity of HMG-CoA reductase and a reduced rate of acetate or mevalonate incorporation into lipids (Supplemental Table 2) (Gebhardt and Beck, 1996; Kumari and Augusti, 2007; Kumari et al., 1995; Lin et al., 2008; Lin and Yin, 2008; Lin et al., 2004; Liu and Yeh, 2000; Yeh and Yeh, 1994). This has been linked to significant depressed mRNA expressions for ME, FAS, HMG-CoA reductase and SREBP-2 (Supplemental Table 2) (Lin and Yin, 2008). In addition, studies lead in HepG2 cells suggest that the concerted action of several organosulfur compounds would allow reaching a higher inhibition of acetate incorporation into cholesterol as compared to isolated organosulfur compounds (*i.e. s*-allyl or *s*-propyl cysteine) (Lee and Yeh, 2003) and that inhibition of hepatic cholesterol synthesis would mainly result from water-soluble organosulfur compounds not lipid-soluble compounds that may become toxic at high doses (*i.e.* 1-4 mM) (Yeh and Liu, 2001). One may therefore conclude that results convincingly support lipotropic effect of organosulfur compounds.

Unsaturated and short-chain fatty acids, melatonin and para-aminobenzoic acid

Mono-unsaturated and poly-unsaturated fatty acids

Unsaturated FA are common to both PBF and ABF. Results from studies lead with unsaturated FA and oils specific to animal products (*e.g.* fish) have been therefore also presented in Supplemental Table 2 to allow comparisons.

Most of studies were lead in rats or mice (Supplemental Table 2). The only human studies concerns patient with NAFLD who were administered 1-2 g daily of PUFA for 6-12 months (Capanni et al., 2006; Spadaro et al., 2008). Results clearly showed a significant decrease in the degree of steatosis with 24-30% of subjects having no more steatosis diagnosed (Capanni et al., 2006; Spadaro et al., 2008). However, PUFA were either of animal origin (Capanni et al., 2006) or no precision were given (Spadaro et al., 2008). Accordingly, n-3 PUFA have been recently

proposed as a therapeutic liver drug to treat patients with NAFLD (Xin et al., 2008). It has been otherwise observed in liver of NAFLD patients a marked enhancement in long-chain PUFA *n*−6/*n*−3 ratio, such a condition being likely to "favour lipid synthesis over oxidation and secretion", thereby leading to steatosis (Araya et al., 2004).

Among mechanisms involved, PUFA are known to inhibit the expression of FAS (Moon et al., 2002) as shown with conjugated linoleic acid (CLA) in high-fat-fed rats (Choi et al., 2007), with dietary long-chain n-3 FA-containing krill oil in high-fat-fed mice (Tandy et al., 2009), with PUFA from safflower oil in high-fructose/glucose fed rats (Toussant et al., 1981), with methyl esters of polyunsaturated *vs* long-chain saturated FA given to rats fed fat-free diet for 7 days (Clarke et al., 1977) and with α-linolenic acid (18:3 n-3)-rich diet in both wild type and PPARα-null (KO) mice (Supplemental Table 2) (Morise et al., 2009). And several authors have described n-3 PUFA as "negative regulator of hepatic lipogenesis" (Alwayn et al., 2005; Sekiya et al., 2003; Spadaro et al., 2008). PUFA were also shown to increase PPARα mRNA expression (Choi et al., 2007; Morise et al., 2009) and to decrease SREBP mRNA expression (Sekiya et al., 2003) or activity (Di Nunzio et al., 2010), to inhibit activities of several lipogenic (TG and cholesterol) enzymes that are ACC, G6PDH, HMG-CoA reductase and ME and to increase activities of FA oxidation enzymes that are CPT and acyl-CoA oxidase (ACO) (Supplemental Table 2). Cellular and nuclear mechanisms by which PUFA may favour peroxisomal and mitochondrial FA β-oxidation *via* PPAR up-regulation and inhibit TG and FA synthesis *via* SREBP1 down-regulation have been described and reviewed by Clarke (Clarke, 2001). However, concerning SREBP, results are not always consistent since some studies reported no effect or increased expression of SREBP (Gotoh et al., 2009; Morise et al., 2009) but this may be explained by the specific strains of mice used in these studies, *i.e. db*/*db* mice (with hyperlipidemic, diabetic and obese symptoms) (Gotoh et al., 2009) and PPARα-null (KO) mice (Morise et al., 2009). In addition to these mechanisms, it was shown in ethanol-fed rats that DHA and AA prevent from fatty liver development, and that protection of some mitochondrial enzymes (aldehyde dehydrogenase, ATP synthase, and 3-ketoacyl-CoA thiolase) from oxidation by

PUFA might be involved (Song et al., 2008). And in rats submitted to hypercaloric and fat-free parenteral nutrition, it has been suggested that a lack of PUFA may lead to impaired lipid transport (*i.e.* impaired formation of lipoproteins that exports lipids outside liver) and enhanced lipogenesis (Goheen et al., 1983,Keim and Mares-Perlman, 1984).

As shown recently in mice fed synthetic diet containing lard (low in PUFA and highly unsaturated FA, HUFA), canola oil (high in PUFA, *i.e.* linoleic and linolenic acids) or a mixture of menhaden and fish/fungal oils (high in HUFA, *i.e.* AA, EPA and DHA), it seems that HUFA from animal origin (menhaden/fish/fungal oil) are more efficient in preventing from steatosis than PUFA from plant origin (canola oil) although linoleic and linolenic acids are both precursors *in vivo* of HUFA (Sealls et al., 2008). Yet, MUFA-rich olive oil was shown to be more efficient in reducing degree of steatosis in methionine-choline-deficient rats than PUFA-rich fish oil; and while olive oil consumption significantly reduced hepatic TG content by around 29%, fish oil failed to (Supplemental Table 5) (Hussein et al., 2007). Accordingly, the role of oleic acid in olive oil to prevent steatosis in NAFLD patients has been latter discussed (Assy et al., 2009). Indeed, oleic acid is able to decrease NF-κB activation and LDL oxidation while increasing insulin resistance that in the end lead to dow- and up-regulation of respectively SREBP and PPARα and PPARγ and increased hepatic FA oxidation (Assy et al., 2009). However, several other phytochemicals would also contribute to the overall lipotropic effect of olive oil, such as phenolic compounds, squalene, lignans and hydroxytyrosol, which prompted Assy et al. to suggest that olive oil and, more generally MUFA-rich foods, is a main contributor of the beneficial effect of the Mediterranean diet in the primary prevention of NAFLD (Assy et al., 2009). Besides olive oil, PUFA/n-3 rich/low-*trans* structured fat synthesized from flaxseed oil, butter fat and palm stearin was alo shown to exert significant lipotropic effects, among which a decreased hepatic TG content of 16%, an increased β-oxidation of 96% and an increased CPT activity of 88% in ApoE$^{-/-}$ mice compared to ApoE$^{-/-}$ mice fed a 10%-fat (commercial shortening, 53.4% *trans* FA) diet (Supplemental Table 5) (Cho et al., 2009). However, results do not appear always consistent. Thus, the respective efficacity of different

oils in improving various markers of hepatic lipid metabolism has been tested in rats fed initially a 10%-fat diet rich in saturated lipids: while sunflower (n-6 PUFA-rich), linseed (enriched with α-linolenic acid) or sardine (n-3 PUFA-rich) oils importantly decreased TG content, and ACC and G6PDH activities, olive oil (oleic acid-rich) failed to (Supplemental Table 5) (Takeuchi et al., 2001). However, all oils importantly and significantly increased β-oxidation and CPT activity (at least +100%), olive oil remaining the less efficient (Takeuchi et al., 2001). These results appear somewhat contradictory with those of Hussein et al. reported above with olive and fish oils (Hussein et al., 2007). Discrepencies may be ascribed to the different models tested, *i.e.* methionine-choline deficient *vs* 10%-fat fed rats.

As for fiber and polyphenols, unsaturated FA are composed of numerous compounds and it is difficult to test each one as regards with hepatic steatosis improvement. However, results tends to show a lipotropic effect of unsaturated FA, with notably important TG reductions of -83% with arachidonic acid in ethanol fed rats (Goheen et al., 1983) and of around -49% with linseed oil (rich in α-linolenic acid) in PPARα-null (KO) female mice fed high-fat diet (Morise et al., 2009) (Supplemental Table 2). Although FA are not from natural origin, important reduction in lipogenic enzyme activities were also reported with ethyl linoleate and methyl linolenate/linoleate/oleate (Clarke et al., 1977; Toussant et al., 1981). In addition, decreased SREBP and increased PPAR were also observed, which is also supportive and indicative of a decreased lipogenic activity (Supplemental Table 2).

In the end, one may first wonder whether all unsaturated FA of plant origin are lipotropic or not: if results appear still insufficient to definitively conclude, those reported in Supplemental Table 2 in both animals and humans tend to support a lipotropic effect whose significance vary according to models and FA chosen. Secondly, one may wonder whether n-6 (*e.g.* arachidonic acid, C20:4 n-6) and n-3 (*e.g.* α-linolenic acid, C18:3 n-3) would have the same lipotropic potential. In humans, only n-3 PUFA have been proposed to treat patients with NAFLD (Xin et al., 2008), excess n-6 consumption being pro-inflammatory (Lee et al., 2007a) and being likely to be involved in the

promotion of hepatic necro-inflammation (Cortez-Pinto et al., 2006) that may transform NAFLD into non-alcoholic steatohepatitis.

Short-chain fatty acids

Short-chain fatty acids (SCFA) mainly result in humans and animals from fiber fermentation and the most important are acetate, propionate and butyrate. As for the previously PBF compounds, they have been shown, either as isolated compound or in mixture, to exert positive and significant effects on hepatic lipid metabolism (Supplemental Table 2). But only one study reported a significant decrease in hepatic TG content (around 16%) with acetic acid in high-fat fed mice (Kondo et al., 2009). Among mechanisms involved, up-regulation of PPARα, ACO and CPT-1, and down-regulation of FAS gene expression were demonstrated (Kondo et al., 2009). Consequently, SCFA being produced *via* fiber fermentation within colon, fiber may be considered as possibly indirectly playing a role in these mechanisms.

Other studies mainly reported the inhibition effect of SCFA upon rate of cholesterol synthesis as shown in isolated hepatocytes with propionic acid (Wright et al., 1990) or in liver slices with SCFA mixture of acetic, propionic and butyric acids (Hara et al., 1999) (Supplemental Table 2). And hepatic acetate and propionate concentrations were shown to be negatively correlated with hepatic cholesterol content in rats (Koseki et al., 1991).

Melatonin

In human, melatonin is synthesized from serotonin in pineal gland and is before all known as being the central hormone that regulates chronobiological rhythms, notably sleeping. In plants, melatonin is a strong antioxidant and also plays a role in its growth. To our knowledge, there is no database for the melatonin content of PBF, and melatonin content of some PBF still remains unknown. However, hazelnuts and walnuts are considered as good vegetable sources of melatonin; and

melatonin is also found in algae, ginger, grape, cocoa, cereals (*e.g.* maize, rice and wheat), tomatoes, potatoes and green vegetables.

Several studies have reported a protective effect of melatonin against liver injury in relation with its antoxidant property and its effect on gene expression in relation with antioxidant status (Catala et al., 2007; Leon et al., 2004; Sener et al., 2004; Subramanian et al., 2007; Taysi et al., 2003). More specifically, altough studies are scarce, melatonin has been reported in rats, mice and minks to importantly reduce hepatic TG contents and to improve grade for steatosis (Supplemental Table 2) (Kuzu et al., 2007; Nieminen et al., 2001; Pan et al., 2006; Sener et al., 2004; Shieh et al., 2009; Subramanian et al., 2007). However, doses used in rat and mice studies were high and un-physiological (*i.e.* from 0.5-10 mg/kg b.w. injected i.p. and 10 mg/L of drinking water) (Pan et al., 2006; Sener et al., 2004). The study lead in minks used more physiological doses around 10 μg daily (Nieminen et al., 2001).

Mechanims involved in this lipotrope effect might notably include a reduced oxidative stress - increased oxidative stress and lipid peroxidation being associated with steatosis - and decreased insulin resistance (Kuzu et al., 2007; Sener et al., 2004). Increased insuline resistance is an important parameter in the ethiology of fatty liver. Indeed, such decreased insulin sensitivity may accelerate TG hydrolysis within adipose tissues releasing FFA within bloodstream, this latter being then uptook in great amount by the liver and re-synthesized in TG forming excess fat deposits. Deficiency in MTP and decreased synthesis of ApoB that are involved in VLDL assembly to export TG from liver are notably mainly involved in such an impaired metabolic context (Adams et al., 2005).

<u>*Para*-aminobenzoic acid</u>

Para-aminobenzoic acid (PABA) is also cited as a lipotrope within some web sites based on its ability to stimulate production of folic acid by bacteria within intestine, a condition that in the end would help in the production of pantothenic acid, this latter contributing as CoA precursor to the

lipotropic effect. Indeed, PABA has been shown to decrease serum cholesterol level in men (Failey and Childress, 1962), to play a role in folate formation (Barbieri et al., 1995), notably as intermediate in the bacterial synthesis of folates (Wegkamp et al., 2007) and has been recognized as stimulating bacteria growth (Briggs and Daft, 1955; Pfiffner and Bird, 1956). In addition, bacteria are found in human intestine, folates are lipotropes, and PABA omission in the diet of guinea pig was shown to lead to folic acid deficiency (Woodruff et al., 1953). Yet, although used in commercial lipotropic complexes, the lipotropic effect of PABA, notably a reduced hepatic TG or lipid content, has never been demonstrated, neither in animals nor in humans. It has only been shown in rats that steatosis was associated with an increased level of acetylation due to inhibition of FA oxidation, this being reflected with increased level of acetylated PABA in rat urine (Van Hung, 1953).

Fiber-type and polyphenol-type compounds

Plant-based foods are also well-known sources of fiber (soluble and insoluble), oligosaccharides, polyphenols and phenolic-derived compounds that cannot be found in ABF. All of these compounds have been shown to positively affect lipid metabolism in both humans and animals according to various mechanisms. However, they have never been cited as lipotropes.

Soluble and insoluble fiber

Both soluble (*e.g.* pectin from sugarbeet fiber) and insoluble fiber (*e.g.* cellulose and insoluble hemicellulose from wheat bran) have been convincingly reported to reduce hepatic TG and/or total lipid/fat contents in rats fed various steatogen diets (Supplemental Table 3). For example, 85% hepatic TG content reduction has been reached by supplementing diet with 5% lignin in high-cholesterol (1%) fed rats (Story et al., 1981). However, in rats fed normal diet, lipotropic effect of fiber would be less conclusive (Schneeman and Richter, 1993).

Concerning cholesterol, apparent contradictory results - *i.e.* lower hepatic content together with higher HMG-CoA reductase activity and higher rate of synthesis - were also reported (Thomas et al., 1983). This may be attributed to an adaptation resulting from the higher release of cholesterol and its precursors (*i.e.* bile acids) within intestine *via* hydrophobic binding to insoluble fiber or trapping within soluble and viscous fiber. Consequently, the liver compensates losses in cholesterol by increasing its synthesis and turnover through an enhanced HMG-CoA reductase activity and rate of cholesterol synthesis (Figure 2D). Thus, Thomas et al. have notably shown on liver slices of rats fed for 1 month a 11%-fat diet supplemented with 30% of neutral detergent fiber from blackgram that incorporation of [U-^{14}C]glucose or [1,2-^{14}C]Na-acetate into cholesterol was increased by respectively 80 and 258% (Thomas et al., 1983).

Physico-chemical properties of fiber have therefore to be considered to explain their hepatic lipid-lowering effect. For exemple, fiber, especially hydrophobic lignin (including in the fiber definition), have been early shown to adsorb and/or sequestrate bile acid conjugates *via* hydrophobic bounds (Eastwood and Mowbray, 1976; Eastwood, 1975; Eastwood and Girdwood, 1968; Eastwood and Hamilton, 1968) thus potentially stimulating cholesterol efflux from liver. Latter, Mongeau and Brassard evaluated the bile salt binding capacity of various cereal products ranging from 16.2 μmol glycocholate/0.2 g of neutral detergent fiber (NDF) for wheat germ to 34.2 μmol glycocholate/0.2 g NDF for spoon-size shredded wheat (Mongeau and Brassard, 1982).

Thanks to new technical tools, the effect of fiber on hepatic gene expression can be now studied. Thus, recently, it has been shown in mice fed a 10% husk diet that genes encoding for FA oxidation and lipogenesis were respectively up- and down-regulated after 3 weeks but the inverse was observed after 10 weeks suggesting a "regulatory mechanism to restore the lowered plasma cholesterol and TG levels" (Chan and Heng, 2008). However, at the hepatic cellular level, it is unlikely that fiber compounds act directly on gene and explanations have probably to be found in fiber-associated compounds like polyphenols and their resulting conjugated and metabolized forms

and/or fiber fermentation products that are SCFA, especially propionic acid, all of them being able to reach liver and directly impact cellular metabolism and gene expression.

Oligosacharides

Oligosaccharides from PBF are considered as fiber-type compounds that are completely fermented within colon and that include oligofructoses and galactosides like verbascose, stachyose and raffinose; but, to our knowledge, hepatic lipid-lowering effect has been mainly reported for oligofructoses like fructans (*e.g.* inulin) in rats fed standard, high-sucrose or high-fructose diet and in obese Zucker rats (Supplemental Table 3) (Busserolles et al., 2003; Daubioul et al., 2002; Daubioul et al., 2000; Kok et al., 1996a; Kok et al., 1996b; Sugatani et al., 2006). The action of inulin-type fructans on TG and cholesterol metabolism has been recently reviewed by Beylot (Beylot, 2005). Among mechanisms involved, fructans have been notably shown to decrease gene expression and/or resulting activities of lipogenic enzymes that are ME, FAS, ACC, ATPCL/CCE and G6PDH (Figure 2D, Table 3 and Supplemental Table 3) (Aghelli et al., 1998; Delzenne and Kok, 1999). Such data tend to explain that the reduction of TG-rich lipoproteins (*i.e.* VLDL) secretion observed in rats would be in relation with a decreased hepatic lipogenesis (Delzenne and Daubioul, 2000). Other mechanism possibly include the production of proprionate - through colonic fermentation of fructans - that was shown to inhibit lipogenesis in rat hepatocytes *in vitro* (Supplemental Table 2) (Demigné et al., 1995,Wright et al., 1990). Beylot otherwise suggests that "hypotriglyceridaemic action of fructans results rather from a decrease in the hepatic TG synthesis than from a higher clearance of TG-rich lipoproteins" (Beylot, 2005). In their review, Delzenne and Daubioul also proposed that 1°) fructans, by affecting glycemic and insulinemic responses, indirectly modulate TG levels, insulin participating in the regulation of TG synthesis; and/or that 2°) since oligofructose may increase GLP-1 caecal concentration in rats fed oligofructose (Kok et al., 1998) and since GLP-1 may increase insulin sensitivity, this hormone is likely to be a modulator of lipid metabolism as well (Delzenne and Daubioul, 2000). This last hypothesis is supported by a

recent study showing in hyperinsulinaemic subjects fed +20 g/d of wheat fiber a significant increase in plasma GLP-1 concentration upon 12 months (Freeland et al., 2010).

Resistant starch? Not really a phytochemical? Specific of processed PBF except banana. Depends on process conditions (difficult to select as lipotrope from RS databases)
- Shimotoyodome (2010): high-fat mice
- Han (2005): high-cholesterol fed rats (no effect on cholesterol content)
- Han (2003): cholesterol-free diet fed rats
- Shao (2002): cholesterol (0.2 g/day : environ 1% diet?) fed rats
- Lopez (2001): normal rats (TG decrease)
- Cheng and Lai (2000): high-cholesterol rats (effect on TG)
- Fernandez (2000): hypercholesterolemic guinea pigs
- Levrat (1996): 0.4%-cholesterol fed rats
- Ranhotra (1996): 10%-fat hamsters (no decrease in liver lipid)
- Morand (1994): normal rats

{Perera, 2010 #25021}: revue de synthèse sur food contents

Polyphenols

Polyphenols i

compounds), li

positive effects

quite recent and

specific hepatic lipid metabolism, to our knowledge, no study has reported a lipotropic effect of polyphenols in humans.

In animal models, hepatic lipid metabolism improvement has been observed for the 4 four classes of polyphenols, especially flavonoids and lignans (Supplemental Table 4). However, significant hepatic TG reductions were reported only for lignans, and in lesser extent for flavonoids (Supplemental Table 4). From studies reviewed in Supplemental Table 4, one can observe that for the few one that investigated effect of polyphenols in non-steatosis models (*i.e.* with standard diets), no significant effect on hepatic cholesterol and TG contents were observed (Nakamura et al., 2001; Nakamura and Tonogai, 2002). In addition, most of studies are concerned with flavonoids and lignans, and secondarily with phenolic acid and stilbenes (only one study) (Supplemental Table 4).

Compared to flavonoids and lignans, the few studies lead with phenolic acids, mainly ferulic acid, did not support a conving lipotropic effect (Supplemental Table 4). For exemple, gallic acid was shown to have no effect on FAS activity *in vitro* (Wang et al., 2003). The most significant effect was the inhibition of HMG-CoA reductase by ferulic acid in high-cholesterol fed rats (Kim et al., 2003). In this study, ferulic acid was also shown to significantly reduce acyl-CoA:cholesterol acyltransferase (that forms cholesteryl esters from cholesterol) activity (Kim et al., 2003). However, this is not sufficient to considere phenolic acids as having a lipotropic effect.

Concerning flavonoids and lignans, sesamin (a lignan) has been reported to be a potent inducer of hepatic FA oxidation in 10-15%-fat fed rat (Ashakumary et al., 1999; Ide et al., 2001), and the flaxseed lignan secoisolariciresinol (SECO) was recently shown to dose-dependently reduce hepatic lipid accumulation in high-cholesterol fed rats (Felmlee et al., 2009). Major green tea polyphenols (*e.g.* (-)-epigallocatechin-3-gallate) may prevent fatty liver disease in high-fat fed mice (Bose et al., 2008); and various types of flavonoïds have been shown to prevent liver steatosis (Dulloo et al., 1999; Klaus et al., 2005; Rumpler et al., 2001; Sachan and Hongu, 2000; Shimotoyodome et al., 2005; Venables et al., 2008). Mechanisms involved would be notably the ability of polyphenols to down-regulate and up-regulate gene expression of respectively lipogenic and FA oxidation enzymes, and their resulting activities, but also to increase PPARα and decrease SREBP gene expression (Figure 2D and Supplemental Table 2). Flavonoids were notably shown to strongly inhibit *in vitro* FAS activity (Wang et al., 2003; Wang and Tian, 2001). In a recent review, the modulation of lipid homeostasis by flavonoids within liver was described (Peluso, 2006). Briefly, flavonoids, *via* phosphodiesterase inhibition (Ko et al., 2004; Nichols and Morimoto, 1999, 2000), would notably stimulate lipolysis products from TG and cholesteryl esters (Peluso, 2006). Indeed, phosphodiesterase inhibition would favour increase of cyclic adenosine monophosphate (cAMP) level, activation of proteine kinase A, subsequent increase in hepatic triacylglycerol hydrolase activity and β-oxidation of lipidic hydrolysis products (Peluso, 2006).

Concerning the fourth class of polyphebnols that are stilbenes, despite rarity of studies, the only one reported in Supplemental Table 4 brought interesting results for leading future studies. Stilbenes (*i.e.* cajanin, and longistylin C and A) containing extract/fraction from *Cajanus cajan* supplemented at a level of 200 mg/kg b.w. allowed significantly reducing TG and total cholesterol contents in hypercholesterolemic mice by respectively 14 and 23% (Luo et al., 2008).

However, polyphenols are a huge phytochemical family, composed of several hundreds of different compounds with probable different effects on hepatic lipid metabolism: all have probably not a lipotropic effect *sensu stricto*. In literature, polyphenol content of PBF is mostly expressed by

the Total Phenolic Compound (TPC) content (estimated *via* the Folin Ciocalteu's colorimetric method). The TPC content corresponds to the easily extractable fraction and obviously does not include only one type of polyphenol. However, this is among this polyphenol fraction that are to be found those the most likely to be absorbed within small intestine and, consequently, the most likely to exert a potential lipotropic action. One may therefore consider TPC content as a *whole compound* with a potential lipotropic effect.

Accordingly, rather than to focuse on an isolated compound, more and more studies now investigate the effect of ethanol- and/or water-extractable polyphenols from plants on hepatic lipid metabolism in various animal models (Supplemental Table 4). For example, sylimarin and green tea polyphenol extracts significantly reduced degree of steatosis and hepatic TG contents in respectively hamsters fed a 10%-fat and 0.2%-cholesterol diet (Lin et al., 2009) and in leptin-deficient (*ob*/*ob*) mice (Bruno et al., 2008).

Curcumin

Curcumin is not classified as a polyphenol *sensu stricto* but may be considered as a polyphenol-derived compound (Figure 1). Among the two studies reported in Supplemental Table 4, curcumin was interestingly shown to significantly decrease hepatic TG content by 22% in high-cholesterol fed rats (Seetharamaiah and Chandrasekhara, 1993).

Saponins

As curcumin, saponins are not *sensu stricto* polyphenols but possess a polyphenol-like chemical structure (Figure 1). They are generally included in the fiber fraction. Studies are less recent than with polyphenols (Supplemental Table 4). Their consumption or injection may lead to reduced hepatic fat deposits or lipid contents (TG and cholesterol) (Khanal et al., 2009; Onning and Asp, 1995). For example, plant saponins from *Aralia mandshurica* and commercial white saponins reduced hepatic TG contents by respectively -40/-35% and -39/-20% in high-fat (Wojcicki et al.,

1977) and high-cholesterol (Oakenfull et al., 1979) fed rats (Supplemental Table 4). Paradoxically, saponin supplementation also lead to an increased rate of liver cholesterol synthesis as shown with ginsenosides purified from ginseng in rats (Supplemental Table 4) (Sakakibara et al., 1975). This has probably to be attributed to the same effect as for fiber, *i.e.* the adsorption of bile salts by saponins within digestive tract that thereafter stimulates cholesterol turnover and hepatic synthesis (Figure 2D). Indeed, saponins are most of the time associated with fiber within food matrix.

Coumarin: Auraptene in fatty long Evans rats {Nagao, 2010 #22917}

Alkylresorcinols

Alkylresorcinols are mainly found in wheat and rye in a range of around 30-150 mg/100 g and also exhibit a polyphenol-like chemical structure (Ross et al., 2004b). Although not demonstrated directly *in vivo*, alkylresorcinols were shown *in vitro* to importantly inhibit GPDH activity, the key enzyme in TG synthesis and to reduce TG accumulation within 3T3-L1 cells (Rejman and Kozubek, 2003), suggesting that alkylresorcinols might exert *in vivo* a potential lipotropic effect. In addition, they were reported to significantly decrease total hepatic cholesterol content in rats (Ross et al., 2004a). But further studies are needed to test in animal models of fatty liver the effect of alkylresorcinol on TG or total lipid content.

Cholesterol-lowering phytochemicals

Several phytochemicals are generally tested for their cholesterol-lowering properties, notably at the plasma level. They are γ-oryzanol, tocotrienols, policosanol and phystosterols.

Gamma-oryzanol

Gamma-oryzanol is a mixture of ferulic acid esters of triterpene alcohols and sterols (Figure 1) extracted from rice bran oil. Among the four studies we reported in Supplemental Table 4, γ-oryzanol was shown to reduce hepatic TG contents in high-cholesterol fed rats, but effect was significant only ~~at the high level of 1.2% supplementation~~ (~~-33%~~ -37%) (Seetharamaiah and

Chandrasekhara, 1988, 1993). In the two other studies, γ-oryzanol was reported to signficantly reduce hepatic cholesterol content by 19% but failed to significantly inhibit HMG-CoA reductase activity in respectively hypercholesterolemic rats (Suh et al., 2005) and hamsters (Rong et al., 1997). Further studies would be necessary to definitively conclude on the lipotrope status of γ-oryzanol.

Tocotrienols

Tocotrienols (α, β, γ and δ) are mainly found in whole-grain cereals (especially in wheat germ) and unrefined vegetable oils, and belong to the vitamin E family together with tocopherols (α, β, γ and δ). Tocotrienols are recognized as hypocholesterolemic compounds in both humans and animals (Cicero and Gaddi, 2001; Minhajuddin et al., 2005; Qureshi et al., 1997). At the hepatic level, its main reported effect on lipid metabolism is its ability to inhibit HMG-CoA reductase as shown in cockerels (Qureshi et al., 1986) and guinea pigs (Khor et al., 1995), and to reduce subsequent rate of cholesterol biosynthesis as shown in human HepG2 cells (Parker et al., 1993). More specifically, both δ- and γ-tocotrienols have been shown *in vitro* to stimulate ubiquitination and degradation of HMG-CoA reductase, and only δ-tocotrienols has been shown to completely block SREBP-2 processing (Song and Debose-Boyd, 2006). In the end, γ-tocotrienol importantly increases LDL receptor protein level in HepG2 cells (Parker et al., 1993). However, in the same time, FAS activity was significantly increased by around 40% in cockerels upon tocotrienol supplementation at a 0.002% level (Supplemental Table 2) (Qureshi et al., 1986). Such results do not support a lipotropic effect of tocotrieneols.

Policosanol

Policosanol is a mixture of high-molecular-mass aliphated alcohols initially isolated and purified from sugar cane wax. It is mainly composed of octacosanol followed by triacontanol and hexacosanol; other alcohols - tetracosanol, heptacosanol, nonacosanol, dodriacontanol and

tetratriacontanol - are minor components. As tocotrienols, it is first recognized as a serum lipid-lowering agent able to protect from cardiovascular diseases (Gouni-Berthold and Berthold, 2002; McCarty, 2002; Varady et al., 2003). And, as tocotrienols, it may inhibit HMG-CoA reductase activity (Mccarty, 2002) and increase LDL receptor protein level as shown *via* an increased hepatic LDL-binding activity (Menendez et al., 1996,Menendez et al., 1997). Studies are scarce but it has also been shown in hypercholeterolemic rabbits to significantly decrease hepatic cholesterol synthesis (Menendez et al., 1997). Similar results were obtained in cultured human fibroblasts (Menendez et al., 1994). But, to our knowledge, no effect on hepatic TG content has been reported (Supplemental Table 2). As tocotrienols, policosanol cannot be therefore considered as having a lipotropic effect *sensu stricto*.

Phytosterols

As early as 1956, it was shown that β-sitosterol (20 to 25 g daily) could reduce serum cholesterol in patients with hypothyroidism by around 20% (Best and Duncan, 1956). But, to our knowledge, there is no studies lead in humans to investigate the effect of phytosterol consumption on steatosis. In animal models, phytosterols have no significant effects on hepatic TG content contrary to cholesterol content (Supplemental Table 4). Yet, phytosterols were shown to increase HMG-CoA reductase, CYP7A1 and sterol 27-hydroxylase activities: such enhanced activities may be explained by the increased cholesterol release within small intestine under the action of phytosterols, which in turn stimulates cholesterol synthesis to compensate such intestinal losses (Moghadasian et al., 2001), similarly to what occurs with fiber or saponins. Mechanisms underlying the cholesterol-lowering properties of phytosterols have been otherwise thoroughly described by Brufau et al. (Brufau et al., 2008). Besides, phytosterols were shown to importantly decrease hepatic ACC, ME and G6PDH activities in high-cholesterol fed rats (Figure 2D) (Laraki et al., 1993). Although these enzymes are directly involved in FA synthesis, we lack studies demonstrating a significant reduced hepatic TG and/or lipid contents to conclude that phytosterols are lipotropic.

Comment citer ce document :
Fardet, A., Chardigny, J.-M. (2013). Plant-Based Foods as a Source of Lipotropes for Human Nutrition: A Survey of In Vivo Studies. Critical Reviews in Food Science and Nutrition, 53 (6), 535-590. DOI : 10.1080/10408398.2010.549596

Plant or plant-based food extracts

Plant-based foods may contain a whole set of lipotropes. Thus, the effect of foods or of their extracts on steatosis is particularly relevant to study and closer to the *nutritional reality* than the study of isolated compounds, often used at doses higher than that really consumed by humans.

Thus, some authors focused on various plant extracts rather than on a particular compound. Studies are numerous and all could not have been cited in Supplemental Table 5. It is interesting to note that complex foods or food extracts may lead to similar or enhanced lipotrope-like effects than isolated compounds, *i.e.* mainly decreased hepatic TG and TC contents, increased activities of enzymes involved in FA oxidation, decreased activities of enzymes involved in FA and cholesterol synthesis. For exemple, plant extract from *Platycodi radix* was more efficient in reducing TG (-44%) than crude saponins (-17%, NS) from the food extract (Supplemental Table 5) (Kwon et al., 2009b); and while tomato powder significantly reduced by 22% hepatic TG content in rats fed standard diet, lycopene alone in the same amount than in tomato powder had no effect (Alshatwi et al., 2010). Literature survey also unravels that foods tested cover a large range of PBF that are cereal products, vegetable oils, fruits, seeds, vegetables, beverages or leaf extracts (Supplemental Table 5).

However, the whole *food package* is not always more efficient towards liver steatosis or associated lipid metabolism parameters than the isolated compound. For example, purified polyphenols from *Hibiscus sabdariffa* (74% content) had more marked effect on hepatic cholesterol and TG contents than the corresponding plant-extract containing 2% polyphenols (Yang et al., 2010). Some antinutrients from leaf extracts like tannins and saponins may be involved in impaired hepatic functions as suggested by de Melo et al. who observed in rat liver higher levels of lipids and cholesterol following cassava leaves flour consumption compared to control (De Melo et al., 2008). Otherwise, it was shown with *Ziziphus Mauritania* leaf extract that pre-treatment (30 min before alcohol administration) was more efficient than co- or post-administration in reducing hepatic

cholesterol and TG contents of chronic alcohol administered rats (Dahiru and Obidoa, 2009). Finally, the importance of interactions that exist between phytochemicals and micronutrients within PBF is well illustrated by a study investigating the effect of rice bran, defatted rice bran and rice bran oils with or without gum and wax on hepatic cholesterol and TG contents in hypercholesterolemic hamsters (Kahlon et al., 1992). Results showed various ranges of TG and cholesterol reductions according to bran fraction tested, *e.g.* ranking from -14% hepatic TG content (non significant) for defatted rice bran + rice bran oil to -33% (significant) for whole rice bran (Kahlon et al., 1992).

COMPARISON OF THE POTENTIAL LIPOTROPIC EFFECT OF THE DIFFERENT CLASSES OF PLANT COMPOUNDS AS UNRAVELLED FROM RAT STUDIES

Study selection

The lipotropic potential of each plant compound have been evaluated by selecting studies from supplemental Tables 1-4. To allow relevant comparisons, only studies lead in rats fed steatogen diet supplemented with phytochemicals have been considered. Selected steatogen diets are those involving excess fat, sucrose, glucose and fructose percentages, alcohol and lipotrope deficiencies. We therefore chose to select only steatogenic diets of nutritional origin; fatty liver provoked by chemicals or drugs like CCl_4 or DDT were not considered. Finally, 3 studies using obese *fa*/*fa* Zucker rats were also selected since these rats developed fatty liver (Daubioul et al., 2002) and since many of its metabolic abnormalities, including leptin and insuline resistance and hyperlipidemia, are observed in human obesity (Kurtz et al., 1989; Marchesini et al., 1999; Sharabi

and Eldad, 2000; Shimizu et al., 2007; Silverman et al., 1989). One study is concerned with HCA (Sullivan et al., 1977) and two with oligofructose (Daubioul et al., 2002; Daubioul et al., 2000). However, in order to obtain a sufficient number of data, all the durations for feeding periods and all the percentages for phytochemical supplementation have been selected. Markers of lipid metabolism chosen were those the most common to a maximum of phytochemicals, *i.e.* hepatic total lipid/fat, TG and cholesterol contents, activity of main lipogenic enzymes (FAS, ME, G6PDH, ACC/CBX and ATPCL/CCE), and mRNA levels of 2 transcription factors that are PPARα and SREBP; PPARα up-regulating peroxisome proliferation involved in FA β-oxidation and SREBP up-regulating synthesis of enzymes involved in sterol biosynthesis. As a result, 4, 12, 10, 7, 3, 2 and 3 studies have been selected for respectively betaine, choline, *myo*-inositol, methionine, niacin, pantothenic acid and folates; 8, 3, 2, 3 and 2 studies for respectively carnitine, HCA, organosulfur compounds, MUFA/PUFA and melatonin; 14, 5 and 7 studies for respectively soluble/insoluble fiber, phytic acid and oligosaccharides; 2, 4, 8, 2, 4, 4, 3 and 3 studies for respectively phenolic acids, flavonoids, lignans, curcumin, saponins, phytosterols, γ-oryzanol and polyphenol-rich plant extracts, *i.e.* a total of 115 studies which corresponds to around 30% of studies reported in Supplemental Tables. The highest numbers of studies were therefore found in the order fiber > choline > *myo*-inositol > carnitine = lignans. The collected data are synthesized within Tables 2 and 3. Percentage changes for hepatic total lipids/fat, TG and cholesterol contents are presented in Figure 3 A-C while percentage changes for lipogenic enzyme activity are presented in Figures 4 A-E. Considering all compounds, feeding periods cover a range of 1 to 182 days while supplementation percentages cover a range from around 1 ppm for folates to 30% for fiber (Tables 2 and 3).

Influence of phytochemicals on hepatic total lipid, TG and cholesterol contents following steatogen diet consumption by rats

First, concerning hepatic lipid contents, the most striking reductions, *i.e.* > 80%, are reached for total lipid and TG contents with choline, methionine, *myo*-inositol, fiber (lignin) and phytic acid. Although only one study could have been selected, unsaturated FA (*i.e.* arachidonic acid in the study concerned) may also lead to important reduction in total lipid/fat (-63%) and TG contents (-83%) (Goheen et al., 1983). Conversely, increases in hepatic lipid percentages ranged between +1% for cholesterol content with phenolic acids and +136% for TG content with lignans with significant effects reached only for fiber and lignans on cholesterol content (resp. +17 and +21%), and lignans on TG content (+136%). (Table 3).

If increased cholesterol contents are not unexpected with fiber since they may stimulate hepatic cholesterol turnover consequently to an increase faecal excretion, that of TG content with lignans is very surprising. However, the effect has been reported for fish oil only (at a level of 8%) not with palm and safflower oils (resp. -68 and -23% TG content reduction, $p < 0.05$) (Ide et al., 2004). As an explanation, authors suggested that the interaction of sesamin with fish oil may have change expression of genes involved in VLDL assembly and production, impairing hepatic TG excretion (Ide et al., 2004). Concerning other studies with lignans, TG content modifications were all ≤ 0 within the range [≈ 0/-68%] (Figure 3B and Supplemental Table 4). It is interesting to note that the sole increase was obtained with the only oil rich in HUFA (10% of 20:5n-3 and 32.6% of 22:6n-3) that is fish oil, oils used in other studies being all vegetable oils (safflower, palm and coconut oil) with largely less HUFA contents: indeed, palm oil is characterized by a high level of 16:0 (≈ 45%) and 18:1n-9 (≈ 39%) (Ide et al., 2004), safflower oil by a high level of 18:2n-6 (≈ 78%) and 18:1n-9 (≈ 13%) (Ide et al., 2004) and coconut oil by a high level of saturated FA (≈ 87%) (USDA, 2005e). Another explanation for the high increased TG content of +136% might therefore rely on the fact that fish oil is a n-3 PUFA-rich oil contrary to palm (saturated and MUFA-rich) and safflower (n-6 PUFA-rich) oils. Indeed, PUFA are known to be lipotropic (see above) which may have lead to the absence of TG reduction effect by sesamin: otherwise, in this study, palm and

safflower oils alone lead to respectively 5.8- and 3.2-fold more hepatic TG accumulation than fish oil for which level of hepatic TG is quite low (14 μmol/g liver) (Ide et al., 2004). This means that the 10%-fish oil diet was not steatogen.

Besides, although no level of significance was given, a surprising +47% increase in hepatic TG content has been found in rats (Table 3) when increasing the neutral detergent fiber content (from wheat bran) of the diet from 2.83 to 11.17% at the expense of the protein content (from 19.01 to 9.31%) (Supplemental Table 3) (Stewart et al., 1987). One explanation may be found in that low-protein diet may be steatogen (Best et al., 1955) and that normal protein levels recommended are generally 20% of the diet for growing rats and 14% for adult rats (Reeves et al., 1993). In addition, in the study by Stewart et al., at a constant fiber and fat levels of respectively 7 and 17.5%, the increase in protein level from 21.93 to 35.93% lead to +82% TG content (Stewart et al., 1987). It may be hypothesized that a too important distance from standard protein level remains steatogen whatever the level of fiber.

Concerning hepatic cholesterol content reduction, it tends to be less important than TG content reduction with choline, *myo*-inositol, carnitine, phytic acid and oligofructose, while opposite tendency may be observed with phytosterols (Tables 2 and 3). Finally, maximal hepatic cholesterol content reduction reached are quite high for choline (-56%), folates (-51%), carnitine (-60%), fiber (-75%), saponins (-52%) and phytosterols (-76%) (Tables 2 and 3).

Influence of phytochemicals on hepatic lipogenic enzyme activities following steatogen diet consumption by rats

Myo-inositol, unsaturated FA, phytic acid, oligofructose and lignans were the compounds the most often tested for their ability to reduce lipogenic enzyme activities in rats, and results showed that these compounds may be all efficient depressors of them (Figures 4 A-E). The most important

reductions (≥ 50%) are obtained with unsaturated FA and lignans on FAS, ME, G6PDH, ACC/CBX and/or ATPCL/CCE activities (Tables 2 and 3; Figures 4 A-E). However, unsaturated FA tested here were all either methylated or ethylated, and therefore they did not correspond to the natural form found in PBF (Supplemental Table 2) (Clarke et al., 1977; Toussant et al., 1981). A 65%-decrease has been also obtained with phytic acid on FAS (Figures 4A) activity (Katayama, 1997a). One unexpected result as regards with effect on other lipogenic enzymes is the tendency of lignans to increase ME activity (up to +125%, Table 3). However, in the study reporting this result, *i.e.* by Ashakumary et al., ME activity was first reduced by 50% at 0.1% sesamin level then increased by 25 and 125% at respectively 0.2 and 0.5% level of the diet, and this was paralleled by increasing mRNA levels for the enzyme (Ashakumary et al., 1999). These results were later confirmed in rats with quite the same conditions (Supplemental Table 4) (Ide et al., 2001). One explanation may be based on the PPAR-dependent regulation of ME gene expression unlike other other lipogenic enzymes like FAS or G6PDH (Castelein et al., 1994). Thus, lipotropes, by inducing increased PPAR mRNA expression may increase in the same time ME activity: this underlined the dual role played by the transcription factor PPAR that both favour FA β-oxidation and ME activity (Castelein et al., 1994).

Influence of phytochemicals on hepatic PPAR and SREBP mRNA expression following steatogen diet consumption by rats

Concerning changes in the levels of both transcription factors PPARα and SREBP, data collected are scarce, but they indicate that flavonoids importantly increase PPARα mRNA levels, and that lignan importantly reduce that of SREBP, both results being in agreement with a lipotropic effect, *i.e.* a reduction of hepatic lipid content (Tables 2 and 3).

THE WHOLE LIPOTROPE VS ANTIXODANT "PACKAGE"

The antioxidant "package"

The lipotropic potential of PBF has quite interesting similarities with the concept of antioxidant capacity of PBF. Indeed, lipotropes and antioxidants both include several phytochemicals with different physiological modes of action dedicated to reach a same physiological effect: either a decreased fatty liver or a decreased oxidative stress. Indeed, it is today more and more assumed that it is preferable to consume several antioxidants in a limited amount than only one at high dose (Murakami et al., 2003,Stanner et al., 2004), as the ATBC (Alpha-Tocopherol, Beta-Carotene Cancer) study has dramatically showed it, with a 8% increased mortality and 18% increase in lung cancer registered in the group of male smokers consuming a supplemented dose of 20 mg/day β-carotene (The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994). This underlines that high dose of only one substance may be pro-oxidative and harmful. As stated by Stanner et al., "The most prudent public health advice remains to increase the consumption of plant foods, as such dietary patterns are associated with reduced risk of chronic diseases" (Stanner et al., 2004). The synergy between antioxidants appears therefore essential since one antioxidant may regenerate the other after being oxidized. This is well illustrated by vitamin C that regenerates oxidized vitamin E and glutathione that regenerates oxidized vitamin C. This has also been demonstrated with various combinations of antioxidants, *e.g.* green tea extract, quercetin and folic acid protect better against H_2O_2-induced cellular damages than compound alone (Jeong et al., 2005), combinations of various antioxidants (*i.e.* ascorbic acid, caffeic acid, quercetin and urate) have been shown *in vitro* to have a higher antioxidant potential than the sum of their components (Parker et al., 2010), and tomato powder is more protective against elevated serum MDA levels in rats receiving H_2O_2 than isolated lycopene (Alshatwi et al., 2010). Thus, at least 30 phytochemicals

or group of compounds in whole-grain cereals have been reported to have an antioxidant effect *in vivo*, direct or indirect (Fardet, 2009); and their physiological mode of action may express very differently by trapping reactive oxygen species (ROS), breaking oxidative chain reactions, detoxifying potentially oxidative compounds, regulating glutathione synthesis or being co-factors of enzymes involved in the antioxidant defense (Fardet et al., 2008). More generally, it has been reviewed that optimal health - notably as regards with CVD and cancer prevention - requires the combined actions of vitamins E, C and A, and of carotenoids and other "conutrients" contained in fruits and vegetables (Gey, 1998).

The lipotropic "package"

We believe that the same is true for lipotropes, *i.e.* it is preferable to consume complex PBF containing several lipotropes than only one lipotrope at high dose, notably due to their different mode of action towards lipid metabolism in liver that can complete between each others. The issue of synergism for lipotropes might be well illustrated by the example of niacin that may be hepatotoxic and produce other harmful side-effects (*e.g.* flushing and nausea) at high doses within a therapeutic context (McKenney et al., 1994), but may be beneficial at lower dose and/or accompanied with other lipotropes such as betaine (McCarty, 2000), choline (Wenru et al., 1994), folates (Mccarty, 2000), methionine (Aronov et al., 1999) or *myo*-inositol in the form of *myo*-inositol hexanicotinate (or hexanicite) that produces a sustained-release of nicotinic acid together with absence of the side effects observed when niacin is administered alone (El-Enein et al., 1983; Mercier et al., 1967; Welsh and Ede, 1961). There are several other examples of the lipotropic effect in rats of one compound reinforced and improved by the addition of another lipotrope as it was shown with pantothenic acid and *myo*-inositol (Catolla Cavalcanti and Levis, 1950), with choline and folates (Laird et al., 1965), with choline and carnitine (Ball, 1964) and with choline

and *myo*-inositol (Andersen and Holub, 1980; Engel, 1942; Kotaki et al., 1968). For exemple, in the study of Kotaki et al., while the use of only choline or *myo*-inositol only partly cures fatty liver in rats, the use of both compounds almost completely cured rats (Kotaki et al., 1968). Similarly, the lipotropic effect in rats fed either a high-fat or a B vitamin-deficient diet has been shown to be at its optimum when combining respectively the consumption of choline, folic acid, inositol and cobalamine (Drill, 1954) and the consumption of B vitamins, choline and *myo*-inositol, the only consumption of B vitamin in this latter study unexpectedly aggravating fatty liver (Shils and Stewart, 1954). It was also shown in rats fed choline-deficient diet that 0.5%-methionine supplementation lead to increased total hepatic lipid content, probably as a result of dietary amino acid imbalance (Arvidson and Asp, 1982). These examples illustrated well the interactions or the interferences that may exist between lipotropes, some B vitamins being for exemple able to potentiate and/or to catalize the lipotrope action of other lipotropes such as choline. Similarly to niacin when used at clinical doses, some phenolic compounds that are antioxidant at low doses may have pro-oxidative effect at higher doses as shown with quinones (menadione and hydroxyquinone) in cultured HepG2 cells (Rushmore et al., 1991) and isolated rat hepatocytes (Thor et al., 1982).

This raises the issue that a single agent at high dose may have physiological side-effects that would be masked by combining several agents at lower doses with complementary physiological mechanisms of action. Such an issue has been notably emphasized for the carcinogenic process that involves several stages with different impaired physiological mechanisms and that might be best prevented by combining multiple agents with distinct molecular mechanisms than only one agent at high dose with side-effect (Ohigashi and Murakami, 2004). Accordingly, same authors previously showed synergistic effects of epigallocatechin gallate (0.04 μM) and genistein (2 μM) at low doses towards suppression of NO generation while both compounds were antagonistic at high doses (50 μM) and had no effect when tested alone

(Murakami et al., 2003). In addition, choice of compounds with different mechanisms of action should be "a prerequisite" to test synergicity (Ohigashi and Murakami, 2004).

Finally, besides the 4 main lipotropes that are choline, betaine, *myo*-inositol and metionine, magnesium and B vitamins, we have showed that at least 14 other phytochemicals or groups of phytochemicals may be considered as having a direct lipotropic effect (*i.e.* decreased hepatic TG and/or lipid/fat contents) and/or as indirectly contributing to the overall lipotrope effect (*e.g.* decreased lipogenic enzyme activities) (See Supplemental Tables 1-4). It seems, therefore, that as for antioxidant phytomicronutrients, it would also exist within PBF a whole food *package* of lipotropic phytomicronutrients for which the synergic action would be better than the action of only one or two compounds; and for which physiological modes of action appear very diversified such as the down- or up-regulation of gene expression, the inhibition of lipogenic enzymes and the stimulation of FA oxidation enzymes, methyl donation for the synthesis of PL involved in VLDL/LDL exportation from liver, and/or action of enzyme co-factors.

Several phytochemical properties to improve fatty liver

In addition, since increased oxidative stress is also generally associated with fatty liver, both lipotropes and antioxidants may synergistically contribute to alleviate hepatic steatosis. This is well illustrated by the unrefined/virgin olive oil phytochemical *package* that is composed of several compounds with complementary properties that all may contribute to protect from impaired physiological functions associated with fatty liver: thus, Assy et al. proposed that the potential proptective role of olive oil towards NAFLD may be attributed to the combined actions of phenolic compounds (hydroxytyrosol, oleuropein, caffeic acid, o-coumaric acid, vanillic acid and 3,4-dihydroxyphenylethanol), oleic acid and squalene that exert anti-inflammatory, antioxidant and immunomodulatory actions, that modulate transduction pathways, that regulate gene expression in

liver regeneration, that inhibit HMG-CoA reductase and lipooxigenase, that change membrane fluidity and/or that decrease RAS (belongs to GTPases, involved in receptor-mediated signal transduction pathways) activation, all of them being involved in fatty liver development (Assy et al., 2009).

CONCLUSIONS AND PERSPECTIVES

What compound should be considered as lipotropes?

If the lipotropic effect of some phytonutrients has been well studied in rats, paradoxically no studies have defined the lipotrope content and lipotrope density of PBF, raw or processed. It is true that the interest in betaine, choline and *myo*-inositol contents of PBF seems rather recent and databases remain insufficient, especially for free *myo*-inositol.

Defining the lipotropic capacity of PBF involves defining what compounds should be considered as a lipotrope. *Sensu stricto*, it is a compound that decreased hepatic fat content, mainly TG content since TG are main constituent of excess fat deposits in steatosis (Adams et al., 2005; Araya et al., 2004). On such a basis, most of compounds cited in Supplemental Tables 1-4 are potential lipotropes for human nutrition, some being ubiquitous in PBF like betaine, choline, *myo*-inositol, magnesium, B vitamins and polyphenols while other being specific of plant species like cysteine-containing compounds. Studies in rats have clearly demonstrated that betaine, choline, *myo*-inositol, methionine and carnitine have lipotropic effects and that physiological mechanisms of action differ from one compound to another (Figure 1 A-D). Then, results of Supplemental Tables clearly showed that niacin, pantothenic acid, folates may be considered as significantly contributing to the overall lipotropic effect. All these compounds have been cited as lipotrope in literature. Despite the absence of study, magnesium can be reasonably also considered as having a

lipotropic action since indispensable as CoA cofactor allowing transformation of FA into acyl-CoA. Otherwise, cobalamine (vitamin B12), cited as lipotrope in some studies, is the only compound to be found exclusively in animal-based foods.

Concerning the other phytochemicals, to our knowledge, they have never been cited as lipotropes in literature. From studies reported in Supplemental Tables and Tables 2 and 3 and based on significant hepatic TG content reduction, one has considered that organosulfur compounds, unsaturated FA (probably mainly n-3 PUFA such as α-linolenic and/or n-9 MUFA like oleic acid), acetic acid, melatonin, deoxynojirimycin, phytic acid, fiber, oligofructose, flavonoids, lignans, stilbenes, curcumin and saponins may be considered as having a lipotropic effect. However, except for phytic acid and lignans, further studies are undoubtedly necessary to confim these first results, first in animal models, then in humans. For the remaining phytochemicals that are ~~phenolic acids, γ-oryzanol~~, propionic acid, phytosterols, alkylresorcinol, policosanol and tocotrienols, their ability to significantly reduce steatosis, hepatic TG and/or total lipid contents remains to be demonstrated in both rats and humans. Their effect on hepatic cholesterol metabolism and their ability to reduce its hepatic synthesis are more relevant than with TG.

Resistant starch + ferulic acid + oryzanol

While the antioxidant and hypolipidemic capacities of PBF have been extensively investigated, the lipotropic capacity of PBF would therefore deserve more attention. Indeed, similarly to increased oxidative stress and/or hyperlipidemia that have been shown to be involved in the development of numerous metabolic and/or chronic diseases, fatty liver is also a common symptom to several chronic diseases, especially in the first stage of pathology development.

The lack of human studies

Although numerous studies - mainly interventional - have underlined the ability of PBF to positively affect some metabolic biomarkers, there is undoubtedly a lack of studies in humans that

have investigated the lipotropic effect of complex PBF or of their phytonutrients as free compounds. Thus, apart the few medical/clinical reports published in 1954 and 1964 concerning patients that were administered lipotropic formula or tablets (Colson and Gallay, 1964; Nadeau et al., 1954; ~~Navarranne et al., 1964;~~ Warembourg and Bertrand, 1964) and the few reported studies in choline-deficient subjects (Fischer et al., 2007,Zeisel et al., 1991) - notably as a result of total parenteral nutrition (Buchman et al., 2001), in NAFLD patients administered either betaine (Abdelmalek et al., 2001) or PUFA (Capanni et al., 2006; Spadaro et al., 2008), to our knowledge, there is no intervention studies directly investigating the effect of complex PBF consumption on the prevention of fatty liver development in humans. The first step might be to lead observational studies and to search for associations between consumption of ~~some foods,~~ phytochemicals and/or class of phytochemicals with NAFLD risk or prevalence.

of PBF like whole-grain cereals, fruits, vegetables and/or legumes

The reasons for the rarity of human studies are unclear. One explanation may be linked to the nature of technics that has to be used to diagnose hepatic stetaosis. Generally, the biomarker used in routine for evaluating liver injury in humans is the serum level of ALT. This level is then compared to those of alkaline phosphatase (ALP) and aspartate aminotransferase (AST) to help determine which form of liver disease is present, notably for hepatitis. But this test is not sufficiently specific to diagnose fatty liver. The most reliable test is biopsy, considered as the *gold standard* to best characterizing steatosis, but it is invasive. It is therefore generally performed only when more serious liver diseases are diagnosed. Alternatively, non-invasive technics like magnetic resonance imaging scanning, computerized tomography (density measurements obtained *via* two-dimensional X-ray images) (Buchman et al., 1995) or ultrasonography (Capanni et al., 2006; Spadaro et al., 2008) that allows estimating hepatic fat storage.

Other explanations for the lack of human studies may be based on the costliness of intervention studies, or simply on the fact that the lipotropic property of phytochemicals has been neglected or under-estimated to the benefit of their antioxidant and/or anticarcinogenic properties.

Yet, the lipotrope supplements or complexes apparently constitute a large and lucrative market targeted for people aiming at loosing weight *via* "fat burning" as indicated by manufacturers. One may therefore reasonably suppose that it is very likely that intervention studies have been performed in humans but that their results have not been published, since being perhaps essentially lead by private industry.

{Manna, 2010 #20033}: "Identification of Noninvasive Biomarkers for Alcohol-Induced Liver Disease Using Urinary Metabolomics and the Ppara-null Mouse"
{Cheng, 2010 #22506}: "Metabolomic study of the LDL receptor null mouse fed a high-fat diet reveals profound perturbations in choline metabolism that are shared with ApoE null mice"
{Barr, 2010 #22914}
{Griffin, 2006 #10348}: metabonomics for studying steatosis of liver
{Griffin, 2004 #25160}: metabonomics and fatty liver metabolism
{Lazo, 2010 #22481}: Reduced steatosis through better lifestyle (moderate caloric restriction + exercise) is also possible : another alternative to lipotropes or a combination of both.
{Loftus, 2010 #25931}: liver and metabonomics
The lipotropic effect of caloric restriction (30%) in humans {Elias, 2010 #25149}
{Kim, 2010 #26157}: metabonomics of high-fat fed mice

The contribution of metabolomics

Metabolomics is a quite recent set o

biological fluids like urine, plasma

soluble, like from liver homogenat

molecules (< 1500 Da) such as metabolic intermediates, secondary metabolites, hormones and other signalling molecules, that can be found within a biological samples, *i.e.* a specific cell, organ or organism (Wishart et al., 2007). By allowing characterizing simultaneously several hundreds of metabolites (*i.e.* a metabolic fingerprint), this high-troughput technic, generally based on mass spectrometry or ^{1}H NMR, brings new information on the modified metabolic pathways following nutritional interventions (Fardet et al., 2007; Stella et al., 2006; Walsh et al., 2007) or the development of chronic diseases such as diabetes (Griffin and Vidal-Puig, 2008), cardiovascular diseases (Brindle et al., 2002) and cancer (Yang et al., 2004), especially in the initial stages when prevention remains possible as, *e.g.* in terms of nutritional choices. In addition, for human studies, it has the advantage of non-invasiveness, notably by simply collecting urine or saliva.

From the few studies carried out in both humans with steatosis and animal models of fatty liver, and by notably focusing on the lipidome, one have collected promising results that would be helpful for future human intervention studies. Subramanian et al. have notably shown that NAFLD patients may be separated from controls by a significant increase in the level of serum β-anomer

glucose level and that serum lactate level tended to be lower at the limit of significance (Subramanian et al., 2008). Based on these two markers, they have accurately classified 118/120 patients as control or NAFLD subjects (Subramanian et al., 2008). One may understand that by unravelling new biomarkers in serum or urine through metabolomics, it will become quite effective, easy and rapid to diagnose hepatic steatosis with a 100%-reliability.

Otherwise, the few studies lead in animal models have allowed better understanding how hepatic lipid metabolic pathways are involved in steatosis, which one are activated or depressed and how lipidome or lipid profiles are modified compared to controls (Ginneken et al., 2007; Griffin et al., 2007; Pilvi et al., 2008; Zivkovic et al., 2009). In these four studies, steatosis has been provocked by starvation, high-fat diet, 1% orotic acid supplementation and alcohol excess in respectively mice (Ginneken et al., 2007; Pilvi et al., 2008), rats (Griffin et al., 2007) and minipigs (Zivkovic et al., 2009). For example, in mice, while hepatic phosphatidylcholine content was importantly reduced after 24 hours starvation, the appearance of a new putative biomarker of steatosis was also observed; and it was identified as a 49:4-TG with an odd number of C atoms, such odd TG being rare compounds (Ginneken et al., 2007). In the study with minipigs, Zivkovic et al. showed that alcoholic steatosis is likely to notably result from alcohol suppressive efefct on the phosphatidylethanolamine-*N*-methyltransferase pathway (Figure 2A) (Zivkovic et al., 2009).

and also how liver metabolite profiling changes upon high-cholesterol diet from simple steatosisi to steatohepatitis (Vinaixa et al (2010)

Metabolomics appears therefore as a suitable complementary technic for studying effect of phytochemicals on hepatic steatosis development or finding associations between levels of phytochemical consumption and risk/prevalence or degree of NAFLD. That should allow leading more human studies based on the simple measurement of new serum and/or urinary NAFLD biomarkers.

Databases for the lipotrope contents of plant-based foods

Last but not least issue is the absence of official database available for some of the lipotropic compounds found PBF, notably free *myo*-inositol, carnitine, melatonin, organosulfur compounds, acetic acid, oligofructose, curcumin and saponins. Data has to be found article by article - when they exist! Concerning *myo*-inositol, the sole database is that of Clements and Darnell for total *myo*-inositol (Clements and Darnell, 1980); however, it includes *myo*-inositol moieties from all *myo*-inositol-derived compounds, notably phytic acid (*myo*-inositol hexakisphosphates) for which the lipotropic effect has not been demonstrated in humans.

Concerning choline and betaine contents of foods, databases have been released only recently between 2002 and 2008 (De Zwart et al., 2003; Sakamoto et al., 2002; Slow et al., 2005; Zeisel et al., 2003), the most exhaustive and involving foods of different countries being that of USDA released in 2008 (USDA, 2008).

Data for the methionine, magnesium, and B vitamin contents of PBF are obviously easily available *via* notably the Souci et al. (Souci et al., 2008) and USDA (USDA, 2005a) databases by food group.

Concerning polyphenols, databases and literature data become more and more numerous and accessible (Neveu et al., 2010; USDA, 2004, 2007, 2008; Wu et al., 2004b). The problem for polyphenols is that all polyphenols are probably not lipotropic: for example, as can be seen from Supplemental Table 4, most striking effects have been obtained with catechins (a flavonoid) and sesamin (a lignan) while no significant lipotropic effect has been reported for ferulic acid (phenolic acid). This means that, ideally, one should determine the content in specific polyphenol food by food. However, now, the recent Phenol-Explorer (Neveu et al. 2010) and USDA databases for the flavonoid (USDA, 2007), proanthocyanidin (USDA, 2004) and isoflavone (USDA, 2008) contents give such information for numerous PBF. In the end, as we discussed previously, one may also make the approximation that the TPC content of PBF - that is generally measured in literature - corresponds to *one compound* with a potential lipotropic effect.

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ABBREVIATIONS

ABCA: ATP-Binding Cassette transporter

ACC: Acetyl-CoA Carboxylase

ACO: Acyl-CoA Oxidase

ALT: Alanin aminotransferase

ApoA/ApoB: Apolipoprotein A or B

ATP: Adenosine Triphosphate

ATPCL/CCE: ATP-Citrate Lyase or Citrate Cleavage Enzyme

BHMT: Betaine Homocysteine S-Methyltransferase

CETP: Cholesteryl Ester Transfer Protein

CoA: Coenzyme A

CPT: Carnitine Palmitoyltransferase

CVD: Cardiovascular Diseases

CYP2E1: Cytochrome P450 2E1

CYP7A1: CYtochrome P450, family 7, subfamily A, polypeptide 1 or cholesterol 7 α-hydroxylase

DGAT: Diacylglycerol Acyltransferase

DNA: Deoxyribonucleic Acid

FA: Fatty Acid

FAS: Fatty Acid Synthase/Synthetase

FFA: Free Fatty Acid

G6PDH: Glucose-6-Phosphate Dehydrogenase

HDL: High-Density Lipoprotein

HUFA: Highly Unsaturated Fatty Acid

i.p.: intraperitoneally

LDL: Low Density Lipoprotein

ME: Malic Enzyme

1 mRNA: Messenger Ribonucleic Acid

2 mtGPAT: mitochondrial Glycerol-3-Phosphate Acyltransferase

3 MTP: Microsomal triglyceride Transfert Protein

4 NAFL: Non-Alcoholic Fatty Liver

5 NAFLD: Non-Alcoholic Fatty Liver Disease

6 PABA: Para-Aminobenzoic Acid

7 PBF: Plant Based Foods

8 PL: Phospholipid

9 PPAR: Peroxisome Proliferator Activated Receptor

10 PUFA: Poly-Unsaturated Fatty Acid

RS: Resistant Starch

11 SREBP: Sterol Regulatory Element Binding Protein

12 TG: Triglyceride

13 USDA: United States Department of Agriculture

14 VLDL: Very Low Density Lipoprotein

REFERENCES

Abdelmalek, M. F., Angulo, P., Jorgensen, R. A., Sylvestre, P. B. and Lindor, K. D. (2001). Betaine, a promising new agent for patients with nonalcoholic steatohepatitis: Results of a pilot study. *American Journal of Gastroenterology* **96**: 2711-2717.

Abe, M. and Kishino, Y. (1982). Pathogenesis of fatty liver in rats fed a high protein diet without pyridoxine. *Journal of Nutrition* **112**: 205-210.

Adams, L. A., Angulo, P. and Lindor, K. D. (2005). Nonalcoholic fatty liver disease. *Canadian Medical Association Journal* **172**: 899-905.

Aghelli, N., Kabir, M., Berni-Canani, S., Petitjean, E., Boussairi, A., Luo, J., Bornet, F., Slama, G. and Rizkalla, S. W. (1998). Plasma lipids and fatty acid synthase activity are regulated by short-chain fructo-oligosaccharides in sucrose-fed insulin-resistant rats. *Journal of Nutrition* **128**: 1283-1288.

Alshatwi, A. A., Al Obaaid, M. A., Al Sedairy, S. A., Al-Assaf, A. H., Zhang, J. J. and Lei, K. Y. (2010). Tomato powder is more protective than lycopene supplement against lipid peroxidation in rats. *Nutrition Research* **30**: 66-73.

Altschul, R., Hoffer, A. and Stephen, J. D. (1955). Influence of nicotinic acid on serum cholesterol in man. *Archives of Biochemistry and Biophysics* **54**: 558-559.

Alwayn, I. P. J., Gura, K., Nosé, V., Zaosche, B., Javid, P., Garza, J., Verbesey, J., Voss, S., Ollero, M. andersson, C., Bistrian, B., Folkman, J. and Puder, M. (2005). Omega-3 fatty acid supplementation prevents hepatic steatosis in a murine model of nonalcoholic fatty liver disease. *Pediatric Research* **57**: 445-452.

Andersen, D. B. and Holub, B. J. (1980). The relative response of hepatic lipids in the rat to graded levels of dietary *myo*-inositol and other lipotropes. *Journal of Nutrition* **110**: 496-504.

Andrieux-Domont, C. and Le van, H. (1970). Influence of magnesium on enzymatic synthesis of coenzyme a. *Comptes Rendus des Séances de la Société de Biologie et de ses Filiales* **164**: 292-296.

Angulo, P. (2002). Nonalcoholic fatty liver disease. *New England Journal of Medicine* **346**: 1221-1231.

Angulo, P. and Lindor, K. D. (2001). Treatment of nonalcoholic fatty liver: present and emerging therapies. *Seminars in Liver Disease* **21**: 81-88.

Araya, J., Rodrigo, R., Videla, L. A., Thielemann, L., Orellana, M., Pettinelli, P. and Poniachik, J. (2004). Increase in long-chain polyunsaturated fatty acid n - 6/n - 3 ratio in relation to hepatic steatosis in patients with non-alcoholic fatty liver disease. *Clinical Science* **106**: 635-643.

Arner, P. (1999). Catecholamine-induced lipolysis in obesity. *International Journal of Obesity* **23**: 10-13.

Aronov, D. M., Keenan, J. M., Akhmedzhanov, N. M., Tikhomirova, E. A., Perova, N. V., Olferiev, A. M. and Golubev, M. A. (1999). Methionine, reduces hepatotoxic side effects of long acting niacin. *Circulation* **100**: 469.

Arvidson, G. and Borgström, B. (1963). Studies in choline deficiency. Fate of injected 1-^{14}C-palmitic acid and fatty acid spectra in fasting and refed rats. *Proceedings of the Society for Experimental* Biology *and Medicine* **112**: 676-679.

Arvidson, G. A. E. and Asp, N.-G. (1982). Hepatic free choline and betaine and the utilization of dietary protein in the choline-deficient rat. *Annals of Nutrition and Metabolism* **26**: 12-17.

Ashakumary, L., Rouyer, I., Takahashi, Y., Ide, T., Fukuda, N., Aoyama, T., Hashimoto, T., Mizugaki, M. and Sugano, M. (1999). Sesamin, a sesame lignan, is a potent inducer of hepatic fatty acid oxidation in the rat. *Metabolism* **48**: 1303-1313.

Assy, N., Nassar, F., Nasser, G. and Grosovski, M. (2009). Olive oil consumption and non-alcoholic fatty liver disease. *World Journal of Gastroenterology* **15**: 1809-1815.

Audet, A. and Lupien, P. J. (1974). Triglyceride metabolism in pyridoxine-deficient rats. *Journal of Nutrition* **104**: 91-100.

Azzi, A. and Stocker, A. (2000). Vitamin e: Non-antioxidant roles. *Progress in Lipid Research* **39**: 231-255.

Badmaev, V., Majeed, M. and Conte, A. A. (2002). Open field, physician controlled clinical evaluation of a botanical weight loss formula based on garcinia cambogia derived (-)hydroxycitric acid. *NutraCos* **1**: 10-14.

Baggenstoss, A., Christensen, N., Berge, K. G., Baldus, W. P., Spiekerman, R. and Ellefson, R. D. (1967). Fine structural changes in liver in hypercholesteremic patients receiving long-term nicotinic acid therapy. *Mayo Clinic Proceedings* **42**: 385-399.

Baker, H., Frank, O., Zetterman, R. and Hutner, S. H. (1977). Possible explanation of potentiation of hepatic steatosis induced by high nicotinic-acid, choline and ethionine. *Nutrition Reports International* **15**: 607-618.

Baker, H., Luisada-Opper, A., Sorrell, M. F., Thomson, A. D. and Frank, O. (1973). Inhibition by nicotinic acid of hepatic steatosis and alcohol dehydrogenase in ethanol-treated rats. *Experimental and Molecular* Pathology **19**: 106-112.

Balkan, J., Oztezcan, S., Kucuk, M., Cevikbas, U., Kocak-Toker, N. and Uysal, M. (2004). The effect of betaine treatment on triglyceride levels and oxidative stress in the liver of ethanol-treated guinea pigs. *Experimental and Toxicologic Pathology* **55**: 505-509.

Ball, C. R. (1964). Actions of betaine, carnitine and choline on pattern of hepatic liposis in mice fed high-fat low-protein diet. *Anatomical Record* **149**: 677-689.

Baquet, A., Maisin, L. and Hue, L. (1991). Swelling of rat hepatocytes activates acetyl-CoA carboxylase in parallel to glycogen synthase. *Biochemical Journal* **278**: 887-890.

Barak, A. J., Beckenhauer, H. C., Badakhsh, S. and Tuma, D. J. (1997). The effect of betaine in reversing alcoholic steatosis. *Alcoholism: Clinical and Experimental Research* **21**: 1100-1102.

Barak, A. J., Beckenhauer, H. C. and Tuma, D. J. (1996a). Betaine effects on hepatic methionine metabolism elicited by short-term ethanol feeding. *Alcohol* **13**: 483-486.

Barak, A. J., Beckenhauer, H. C. and Tuma, D. J. (1996b). Betaine, ethanol and the liver: A review. *Alcohol* **13**: 395-398.

Barak, A. J., Beckenhauer, H. C., Tuma, D. J. and Badakhsh, S. (1987). Effects of prolonged ethanol feeding on methionine metabolism in rat-liver. *Biochemistry and Cell Biology-Biochimie Et Biologie Cellulaire* **65**: 230-233.

Barbieri, B., Papadogiannakis, N., Eneroth, P. and Olding, L. B. (1995). Arachidonic-acid is a preferred acetyl donor among fatty-acids in the acetylation of p-aminobenzoic acid by human lymphoid-cells. *Biochimica Et Biophysica Acta-Lipids and Lipid Metabolism* **1257**: 157-166.

Barclay, J. A. and Cooke, W. T. (1945). Hepatorenal syndrome treated with choline chloride. *The Lancet* **246**: 458-460.

Barr, I. G., Sjölander, A. and Cox, J. C. (1998). Iscoms and other saponin based adjuvants. *Advanced Drug Delivery Reviews* **32**: 247-271.

Bartsch, H. and Nair, J. (2006). Chronic inflammation and oxidative stress in the genesis and perpetuation of cancer: Role of lipid peroxidation, DNA damage and repair. *Langenbeck's Archives of Surgery* **391**: 499-510.

Bazzano, L. A., Li, T. Y., Joshipura, K. J. and Hu, F. B. (2008). Intake of fruit, vegetables and fruit juices and risk of diabetes in women. *Diabetes Care* **31**: 1311-1317.

Beach, D. C. and Flick, P. K. (1982). Early effect of myoinositol deficiency on fatty-acid synthetic enzymes of rat-liver. *Biochimica Et Biophysica Acta* **711**: 452-459.

Beams, A. J. (1946). The treatment of cirrhosis of the liver with choline and cystine. *Journal of the American Medical Association* **130**: 190-194.

Becker, R., Wheeler, E. L., Lorenz, K., Stafford, A. E., Grosjean, O. K., Betschart, A. A. and Saunders, R. M. (1981). A compositional study of amaranth grain. *Journal of Food Science* **46**: 1175-1180.

Beeston, A. W. and Channon, H. J. (1936). Cystine and the dietary production of fatty livers. *Biochemical Journal* **30**: 280-284.

Beher, W. T. and Anthony, W. L. (1955). Effects of beta-sitosterol and ferric chloride on accumulation of cholesterol in mouse liver. *Proceedings of the Society for Experimental Biology and Medicine* **90**: 223-225.

Berg, P. (1959). Role of magnesium in acetyl coenzyme a formation by acetothiokinase. *Science* **129**: 895-896.

Berlow, S., Bachman, P. and Berry, G. (1989). Betaine therapy in homocystinemia. *Brain Dysfunction* **2**: 10-24.

Best, C. H. (1935). The lipotropic effect of protein. *Nature* **135**: 821-822.

Best, C. H. (1934). The role of the liver in the metabolism of carbohydrate and fat. III - the deposition of liver fat. *The Lancet* **223**: 1274-1277.

Best, C. H., Hartroft, W. S., Lucas, C. C. and Ridout, J. H. (1955). Effects of dietary protein, lipotropic factors and re-alimentation on total hepatic lipids and their distribution. *British Medical Journal* **1**: 1439-1444.

Best, C. H. and Huntsman, M. E. (1932). The effects of the components of lecithine upon deposition of fat in the liver. *Journal of Physiology* **75**: 405-412.

Best, C. H. and Huntsman, M. E. (1935). The effect of choline on the liver fat of rats in various states of nutrition. *Journal of Physiology* **83**: 255-274.

Best, C. H., Lucas, C. C., Ridout, J. H. and Patterson, J. M. (1950). Dose-response curves in the estimation of potency of lipotropic agents. *Journal of Biological Chemistry* **186**: 317-329.

Best, C. H. and Ridout, J. H. (1940). The lipotropic action of methionine. *Journal of Physiology* **97**: 489-494.

Best, M. M. and Duncan, C. H. (1956). Effects of sitosterol on the cholesterol concentration in serum and liver in hypothyroidism. *Circulation* **14**: 344-348.

Beveridge, J. M. R., Lucas, C. C. and O'Grady, M. K. (1945). The effect of dietary proteins and amino acids on liver fat. *Journal of Biological Chemistry* **160**: 505-518.

Beylot, M. (2005). Effects of inulin-type fructans on lipid metabolism in man and in animal models. *British Journal of Nutrition* **93**: S163-S168.

Bitar, K. and Reinhold, J. G. (1972). Phytase and alkaline phosphatase activities in intestinal mucosae of rat, chicken, calf and man. *Biochimica et Biophysica Acta* **268**: 442-452.

Blanchard, G., Paragon, B. M., Milliat, F. and Lutton, C. (2002). Dietary l-carnitine supplementation in obese cats alters carnitine metabolism and decreases ketosis during fasting and induced hepatic lipidosis. *Journal of Nutrition* **132**: 204-210.

Bloch, K. and Rittenberg, D. (1942). On the utilization of acetic acid for cholesterol formation. *Journal of Biological Chemistry* **145**: 625-636.

Borgschulte, G., Kathirvel, E., Herrera, M., French, S. W., Morgan, T. R., Morgan, K. and Bottiglieri, T. (2008). Betaine treatment reverses insulin resistance and fatty liver disease without reducing oxidative stress or endoplasmic reticulum stress in an animal model of nafld. *Gastroenterology* **134**: A414-A415.

Bortolotti, M., Kreis, R., Debard, C., Cariou, B., Faeh, D., Chetiveaux, M., Ith, M., Vermathen, P., Stefanoni, N., Le, K.-A., Schneiter, P., Krempf, M., Vidal, H., Boesch, C. and Tappy, L. (2009). High protein intake reduces intrahepatocellular lipid deposition in humans. *American Journal of Clinical Nutrition* **90**: 1002-1010.

Bose, M., Lambert, J. D., Ju, J., Reuhl, K. R., Shapses, S. A. and Yang, C. S. (2008). The major green tea polyphenol, (-)-epigallocatechin-3-gallate, inhibits obesity, metabolic syndrome and fatty liver disease in high-fat-fed mice. *Journal of Nutrition* **138**: 1677-1683.

Bourdin, B., Adenier, H. and Perrin, Y. (2007). Camitine is associated with fatty acid metabolism in plants. *Plant Physiology and Biochemistry* **45**: 926-931.

Boyd, J. N., Sherman, W. K., Graham, E. S., Graham, T. C. and Tennant, B. C. (1986). A comparison of the response of woodchucks and rats to variations in dietary lipotrope and protein content. *Journal of Nutrition* **116**: 2044-2054.

Brandsch, C., Shukla, A., Hirche, F., Stangl, G. I. and Eder, K. (2006). Effect of proteins from beef, pork and turkey meat on plasma and liver lipids of rats compared with casein and soy protein. *Nutrition* **22**: 1162-1170.

Brandt, K., Langhans, W., Geary, N. and Leonhardt, M. (2006). Beneficial and deleterious effects of hydroxycitrate in rats fed a high-fructose diet. *Nutrition* **22**: 905-912.

Briggs, G. M. and Daft, F. S. (1955). Water-soluble vitamins. I. Vitamin B12, folic acid, choline and para-aminobenzoic acid. *Annual Review of Biochemistry* **24**: 339-392.

Brindle, J. T., Antti, H., Holmes, E., Tranter, G., Nicholson, J. K., Bethell, H. W. L., Clarke, S., Schofield, P. M., McKilligin, E., Mosedale, D. E. and Grainger, D. J. (2002). Rapid and noninvasive diagnosis of the presence and severity of coronary heart disease using H-1-NMR-based metabonomics. *Nature Medicine* **8**: 1439-1444.

Broun, G. O. (1948). Treatment of hepatic cirrhosis. *Postgraduate Medicine* **4**: 203.

Broun, G. O. and Meuther, R. O. (1942). The treatment of hepatic cirrhosis with choline chloride and a diet low in fat and cholesterol. *Journal of the American Medical Association* **118**: 1403.

Brouwer, I. A., van Dusseldorp, M., West, C. E., Meyboom, S., Thomas, C. M. G., Duran, M., Hof, K. H. V., Eskes, T., Hautvast, J. and Steegers-Theunissen, R. P. M. (1999). Dietary folate from vegetables and citrus fruit decreases plasma homocysteine concentrations in humans in a dietary controlled trial. *Journal of Nutrition* **129**: 1135-1139.

Brouwers, M., Bilderbeek-Beckers, M. A. L., Georgieva, A. M., van der Kallen, C. J. H., van Greevenbroek, M. M. J. and de Bruin, T. W. A. (2005). Fatty liver in hypertriglyceridemic subjects with familial combined hyperlipidemia: Importance of visceral fat. *Atherosclerosis Supplements* **6**: 30-30.

Brufau, G., Canela, M. A. and Rafecas, M. (2008). Phytosterols: Physiologic and metabolic aspects related to cholesterol-lowering properties. *Nutrition Research* **28**: 217-225.

Bruno, R. S., Dugan, C. E., Smyth, J. A., DiNatale, D. A. and Koo, S. I. (2008). Green tea extract protects leptin-deficient, spontaneously obese mice from hepatic steatosis and injury. *Journal of Nutrition* **138**: 323-331.

Brunt, E. M., Janney, C. G., Di Bisceglie, A. M., Neuschwander-Tetri, B. A. and Bacon, B. R. (1999). Nonalcoholic steatohepatitis: A proposal for grading and staging the histological lesions. *American College of Gastroenterology* **94**: 2467-2474.

Buchman, A. L., Ament, M. E., Sohel, M., Dubin, M., Jenden, D. J., Roch, M., Pownall, H., Farley, W., Awal, M. and Ahn, C. (2001). Choline deficiency causes reversible hepatic abnormalities in patients receiving parenteral nutrition: Proof of a human choline requirement: A placebo-controlled trial. *Journal of Parenteral and Enteral Nutrition* **25**: 260-268.

Buchman, A. L., Dubin, M. D., Moukarzel, A. A., Jenden, D. J., Roch, M., Rice, K. M., Gornbein, J. and Ament, M. E. (1995). Choline deficiency: A cause of hepatic steatosis during parenteral nutrition that can be reversed with intravenous choline supplementation. *Hepatology* **22**: 1399-1403.

Buijsse, B., Feskens, E. J. M., Schulze, M. B., Forouhi, N. G., Wareham, N. J., Sharp, S., Palli, D., Tognon, G., Halkjaer, J., Tjonneland, A., Jakobsen, M. U., Overvad, K., van der A, D. L., Du, H. D., Sorensen, T. I. A. and Boeing, H. (2009). Fruit and vegetable intakes and subsequent changes in body weight in european populations: Results from the project on diet, obesity and genes (diogenes). *American Journal of Clinical Nutrition* **90**: 202-209.

Burton, L. E. and Wells, W. W. (1977). Characterization of the lactation-dependent fatty liver in *myo*-inositol deficient rats. *Journal of Nutrition* **107**: 1871-1883.

Busserolles, J., Gueux, E., Rock, E., Demigne, C., Mazur, A. and Rayssiguier, Y. (2003). Oligofructose protects against the hypertriglyceridemic and pro-oxidative effects of a high fructose diet in rats. *Journal of Nutrition* **133**: 1903-1908.

Caballero, F., Fernandez, A., Fernandez-Checa, J. C. and Garcia-Ruiz, C. (2008). Methionine deficiency accounts for the liver damage observed in a nutritional model of nonalcoholic steatohepatitis. *Journal of Hepatology* **48**: 917.

Caldas, T., Demont-Caulet, N., Ghazi, A. and Richarme, G. (1999). Thermoprotection by glycine betaine and choline. *Microbiology* **145**: 2543-2548.

Calhoun, W. K., Bechtel, W. G. and Bradley, W. B. (1958). The vitamin content of wheat, flour and bread. *Cereal Chemistry* **35**: 350-359.

Calhoun, W. K., Hepburn, F. N. and Bradley, W. B. (1960). The distribution of the vitamins of wheat in commercial mill products. *Cereal Chemistry* **37**: 755 - 761.

Cantoni, G. L. (1951). Methylation of nicotinamide with a soluble enzyme system from rat liver. *Journal of Biological Chemistry* **189**: 203-216.

Capanni, M., Calella, F., Biagini, M. R., Genise, S., Raimondi, L., Bedogni, G., Svegliati-Baroni, G., Sofi, F., Milani, S., Abbate, R., Surrenti, C. and Casini, A. (2006). Prolonged n-3 polyunsaturated fatty acid supplementation ameliorates hepatic steatosis in patients with non-alcoholic fatty liver disease: A pilot study. *Alimentary Pharmacology and Therapeutics* **23**: 1143-1151.

Carlson, L. A. (1963). Studies on effect of nicotinic acid on catecholamine stimulated lipolysis in adipose tissue *in vitro*. *Acta Medica Scandinavica* **173**: 719-722.

Carroll, C. and Williams, L. (1982). Choline deficiency in rats as influenced by dietary energy-sources. *Nutrition Reports International* **25**: 773-782.

Carter, C. W. and Hockaday, T. D. (1962). Liver lipids and ketone-body formation in rats deficient in pantothenate. *Biochemical Journal* **84**: 275-280.

Carter, C. W. and Phizackerley, P. J. R. (1951). The influence of pyridoxine on fat metabolism in the rat. *Biochemical Journal* **49**: 227-232.

Castelao, J. E. and Gago-Dominguez, M. (2008). Risk factors for cardiovascular disease in women: Relationship to lipid peroxidation and oxidative stress. *Medical Hypotheses* **71**: 39-44.

Castelein, H., Gulick, T., Declercq, P. E., Mannaerts, G. P., Moore, D. D. and Baes, M. I. (1994). The peroxisome proliferator activated receptor regulates malic enzyme gene expression. *Journal of Biological Chemistry* **269**: 26754-26758.

Catala, A., Zvara, A., Puskas, L. G. and Kitajka, K. (2007). Melatonin-induced gene expression changes and its preventive effects on adriamycin-induced lipid peroxidation in rat liver. *Journal of Pineal Research* **42**: 43-49.

Catolla Cavalcanti, A. and Levis, F. (1950). Steatosis of the liver due to phosphorus. I. Lipotropic action of pantothenic acid and of its combination with meso-inositol. *Archivio per le Scienze Mediche (Torino)* **90**: 529-541.

Causi, N., Romano, A. and Galfano, G. (1958). Coenzyme a in rat liver during administration of pantothenic acid and nicotinamide. *Bollettino-Societa Italiana Biologia Sperimentale (Napoli)* **34**: 163-164.

Chahl, J. S. and Kratzing, C. C. (1966a). Environmental temperature and choline requirement in rats .I. Choline deficiency in rats at various temperatures. *Journal of Lipid Research* **7**: 17-21.

Chahl, J. S. and Kratzing, C. C. (1966b). Environmental temperature and choline requirements in rats .2. Choline and methionine requirements for lipotropic activity. *Journal of Lipid Research* **7**: 22-26.

Chan, J. M., Wang, F. and Holly, E. A. (2007). Whole grains and risk of pancreatic cancer in a large population-based case-control study in the san francisco bay area, california. *American Journal of Epidemiology* **166**: 1174-1185.

Chan, M. Y. and Heng, C. K. (2008). Sequential effects of a high-fiber diet with psyllium husks on the expression levels of hepatic genes and plasma lipids. *Nutrition* **24**: 57-66.

Channon, H. J., Loach, J. V., Loizides, P. A., Manifold, M. C. and Soliman, G. (1938). The effect of proteins in the prevention of dietary fatty livers. *Biochemical Journal* **32**: 976-985.

Channon, H. J., Mills, G. T. and Platt, A. P. (1943). The action of amino-acids and proteins on liver-fat deposition. *Biochemical Journal* **37**: 483-492.

Channon, H. J. and Wilkinson, H. (1935). Protein and the dietary production of fatty livers. *Biochemical Journal* **29**: 350-356.

Chapman, M. J., Le Goff, W., Guerin, M. and Kontush, A. (2010). Cholesteryl ester transfer protein: At the heart of the action of lipid-modulating therapy with statins, fibrates, niacin and cholesteryl ester transfer protein inhibitors. *European Heart Journal* **31**: 149-164.

Chatenoud, L., Tavani, A., La Vecchia, C., Jacobs, D. R., Jr., Negri, E., Levi, F. and Franceschi, S. (1998). Whole grain food intake and cancer risk. *International Journal of Cancer* **77**: 24-28.

Chen, Q. (2004). Determination of phytic acid and inositol pentakisphosphates in foods by high-performance ion chromatography. *Journal of Agricultural and Food Chemistry* **52**: 4604-4613.

Cho, Y. Y., Kwon, E. Y., Kim, H. J., Park, Y. B., Lee, K. T., Park, T. and Choi, M. S. (2009). Low trans structured fat from flaxseed oil improves plasma and hepatic lipid metabolism in apo e-/- mice. *Food and Chemical Toxicology* **47**: 1550-1555.

Choi, J. S., Koh, I. U., Jung, M. H. and Song, J. (2007). Effects of three different conjugated linoleic acid preparations on insulin signalling, fat oxidation and mitochondrial function in rats fed a high-fat diet. *British Journal of Nutrition* **98**: 264-275.

Christman, J. K., Chen, M.-L., Sheikhnejad, G., Dizik, M., Abileah, S. and Wainfan, E. (1993). Methyl deficiency, DNA methylation and cancer: Studies on the reversibility of the effects of a lipotrope-deficient diet. *Journal of Nutritional Biochemistry* **4**: 672-680.

Cicero, A. F. G. and Gaddi, A. (2001). Rice bran oil and gamma-oryzanol in the treatment of hyperlipoproteinaemias and other conditions. *Phytotherapy Research* **15**: 277-289.

Clarke, S. D. (2001). Nonalcoholic steatosis and steatohepatitis.: I. Molecular mechanism for polyunsaturated fatty acid regulation of gene transcription. *American Journal of Physiology-Gastrointestinal and Liver Physiology* **281**: G865-869.

Clarke, S. D., Romsos, D. R. and Leveille, G. A. (1977). Differential effects of dietary methyl esters of long-chain saturated and polyunsaturated fatty acids on rat liver and adipose tissue lipogenesis. *Journal of Nutrition* **107**: 1170-1181.

Clements, R., Jr and Darnell, B. (1980). *Myo*-inositol content of common foods: Development of a high-*myo*- inositol diet. *American Journal of Clinical Nutrition* **33**: 1954-1967.

Clements, R. and Reynertson, R. (1977). Myoinositol metabolism in diabetes mellitus. Effect of insulin treatment. *Diabetes* **26**: 215-221.

Colson, J. A. and Gallay, C. (1964). Trial treatment of hepatic metabolic disorders by an original formula containing mainly ornithine combined with various classical lipotropic substances. *Toulouse Med* **65**: 207-229.

Cortez-Pinto, H., Camilo, M. E., Baptista, A., De Oliveira, A. G. and De Moura, M. C. (1999). Non-alcoholic fatty liver: Another feature of the metabolicsyndrome? *Clinical Nutrition* **18**: 353-358.

Cortez-Pinto, H., Jesus, L., Barros, H., Lopes, C., Moura, M. C. and Camilo, M. E. (2006). How different is the dietary pattern in non-alcoholic steatohepatitis patients? *Clinical Nutrition* **25**: 816-823.

Craig, S. A. S. (2004). Betaine in human nutrition. *American Journal of Clinical Nutrition* **80**: 539-549.

da Costa, K.-A., Garner, S. C., Chang, J. and Zeisel, S. H. (1995). Effects of prolonged (1 year) choline deficiency and subsequent re-feeding of choline on 1,2-sn-diradylglycerol, fatty acids and protein kinase c in rat liver. *Carcinogenesis* **16**: 327-334.

Dahiru, D. and Obidoa, O. (2009). Effect of aqueous extract of ziziphus mauritiana leaf on cholesterol and triglyceride levels in serum and liver of rats administered alcohol. *Pakistan Journal of Nutrition* **8**: 1884-1888.

Dalton, T. A. and Berry, R. S. (1992). Hepatotoxicity associated with sustained-release niacin. *American Journal of Medicine* **93**: 102-104.

Daubioul, C., Rousseau, N., Demeure, R., Gallez, B., Taper, H., Declerck, B. and Delzenne, N. (2002). Dietary fructans, but not cellulose, decrease triglyceride accumulation in the liver of obese zucker fa/fa rats. *Journal of Nutrition* **132**: 967-973.

Daubioul, C. A., Taper, H. S., De Wispelaere, L. D. and Delzenne, N. M. (2000). Dietary oligofructose lessens hepatic steatosis, but does not prevent hypertriglyceridemia in obese zucker rats. *Journal of Nutrition* **130**: 1314-1319.

Day, C. P. and James, O. F. W. (1998a). Hepatic steatosis: Innocent bystander or guilty party? *Hepatology* **27**: 1463-1466.

Day, C. P. and James, O. F. W. (1998b). Steatohepatitis: A tale of two "hits"? *Gastroenterology* **114**: 842-845.

de Melo, D. S., Correa, A. D., Marcos, F. C. A., de Sousa, R. V., de Abreu, C. M. P. and dos Santos, C. D. (2008). Effects of cassava leaves flour on the ast, alt, alp enzymes activity and hepatic lipids of wistar rats. *Ciencia e Tecnologia de Alimentos* **28**: 32-37.

de Munter, J. S., Hu, F. B., Spiegelman, D., Franz, M. and van Dam, R. M. (2007). Whole grain, bran and germ intake and risk of type 2 diabetes: A prospective cohort study and systematic review. *PLoS Medicine* **4**: e261.

de Zwart, F. J., Slow, S., Payne, R. J., Lever, M., George, P. M., Gerrard, J. A. and Chambers, S. T. (2003). Glycine betaine and glycine betaine analogues in common foods. *Food Chemistry* **83**: 197-204.

Decombaz, J., Gmuender, B., Sierro, G. and Cerretelli, P. (1992). Muscle carnitine after strenuous endurance exercise. *Journal of Applied Physiology* **72**: 423-427.

Degrace, P., Demizieux, L., Du, Z. Y., Gresti, J., Caverot, L., Djaouti, L., Jourdan, T., Moindrot, B., Guilland, J. C., Hocquette, J. F. and Clouet, P. (2007). Regulation of lipid flux between liver and adipose tissue during transient hepatic steatosis in carnitine-depleted rats. *Journal of Biological Chemistry* **282**: 20816-20826.

Delzenne, N. M. and Daubioul, C. (2000). Dietary fructans and lipid metabolism: Building a bridge from the colon to the liver. *Recent Research Developments in Nutrition* **3**: 227-238.

Delzenne, N. M. and Kok, N. N. (1999). Biochemical basis of oligofructose-induced hypolipidemia in animal models. *Journal of Nutrition* **129**: 1467-.

Demigné, C., Morand, C., Levrat, M.-A., Besson, C., Moundras, C. and Rémésy, C. (1995). Effect of propionate on fatty acid and cholesterol synthesis and on acetate metabolism in isolated rat hepatocytes. *British Journal of Nutrition* **74**: 209-219.

Di Nunzio, M., van Deursen, D., Verhoeven, A. J. M. and Bordoni, A. (2010). N-3 and n-6 polyunsaturated fatty acids suppress sterol regulatory element binding protein activity and increase flow of non-esterified cholesterol in HepG2 cells. *British Journal of Nutrition* **103**: 161-167.

Doherty, J. F., Adam, E. J., Griffin, G. E. and Golden, M. H. (1992). Ultrasonographic assessment of the extent of hepatic steatosis in severe malnutrition. *Archives of Disease in Childhood* **67**: 1348-1352.

Drill, V. A. (1954). Lipotropic effects of vitamin-b12 and other factors. *Annals of the New York Academy of Sciences* **57**: 654-663.

du Vigneaud, V., Chandler, J. P., Cohn, M. and Brown, G. B. (1940). The transfer of the methyl group from methionine to choline and creatine. *Journal of Biological Chemistry* **134**: 787-788.

du Vigneaud, V., Cohn, M., Chandler, J. P., Schenck, J. R. and Simmonds, S. (1941). The utilization of the methyl group of methionine in the biological synthesis of choline and creatine. *Journal of Biological Chemistry* **140**: 625-641.

Dulloo, A. G., Duret, C., Rohrer, D., Girardier, L., Mensi, N., Fathi, M., Chantre, P. and Vandermander, J. (1999). Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *American journal of Clinical Nutrition* **70**: 1040-1045.

Dumas, M. E., Barton, R. H., Toye, A., Cloarec, O., Blancher, C., Rothwell, A., Fearnside, J., Tatoud, R., Blanc, V., Lindon, J. C., Mitchell, S. C., Holmes, E., McCarthy, M. I., Scott, J., Gauguier, D. and Nicholson, J. K. (2006). Metabolic profiling reveals a contribution of gut microbiota to fatty liver phenotype in insulin-resistant mice. *Proceedings of the National Academy of Sciences of the United States of America* **103**: 12511-12516.

Eastwood, M. and Mowbray, L. (1976). The binding of the components of mixed micelle to dietary fiber. *American journal of Clinical Nutrition* **29**: 1461-1467.

Eastwood, M. A. (1975). Vegetable dietary fiber - potent pith. *Royal Society of Health Journal* **95**: 188-190.

Eastwood, M. A. (1999). Interaction of dietary antioxidants *in vivo*: How fruit and vegetables prevent disease? *Qjm-an International Journal of Medicine* **92**: 527-530.

Eastwood, M. A. and Girdwood, R. H. (1968). Lignin - a bile-salt sequestrating agent. *Lancet* **2**: 1170-1172.

Eastwood, M. A. and Hamilton, D. (1968). Studies on adsorption of bile salts to non-absorbed components of diet. *Biochimica et Biophysica Acta* **152**: 165-173.

Eckstein, H. C. (1952). Dietary essential amino acids and the liver lipide content of young white rats. *Journal of Biological Chemistry* **195**: 167-174.

Eikelboom, J. W., Lonn, E., Genest, J., Hankey, G. and Yusuf, S. (1999). Homocyst(e)ine and cardiovascular disease: A critical review of the epidemiologic evidence. *Annals of Internal Medicine* **131**: 363-375.

El-Enein, A. M. A., Hafez, Y. S., Salem, H. and Abdel, M. (1983). Role of nicotinic-acid and inositol hexa nicotinate as anti cholesterolemic and anti lipemic agents. *Nutrition Reports International* **28**: 899-912.

Engel, R. W. (1942). The relation of b-vitamins and dietary fat to the lipotropic action of choline. *Journal of Nutrition* **24**: 175-185.

Esfandiari, F., Villanueva, J. A., Wong, D. H., French, S. W. and Halsted, C. H. (2005). Chronic ethanol feeding and folate deficiency activate hepatic endoplasmic reticulum stress pathway in micropigs. *American Journal of Physiology-Gastrointestinal and Liver Physiology* **289**: G54-63.

Esfandiari, F., You, M., Villanueva, J. A., Wong, D. H., French, S. W. and Halsted, C. H. (2007). *S*-adenosylmethionine attenuates hepatic lipid synthesis in micropigs fed ethanol with a folate-deficient diet. *Alcoholism: Clinical and Experimental Research* **31**: 1231-1239.

Etchason, J. A., Miller, T. D., Squires, R. W., Allison, T. G., Gau, G. T., Marttila, J. K. and Kottke, B. A. (1991). Niacin-induced hepatitis - a potential side-effect with low-dose time-release niacin. *Mayo Clinic Proceedings* **66**: 23-28.

Failey, R. B. and Childress, R. H. (1962). The effect of para-aminobenzoic acid on the serum cholesterol level in man. *American Journal of Clinical Nutrition* **10**: 158-162.

Fang, Y. Z., Yang, S. and Wu, G. Y. (2002). Free radicals, antioxidants and nutrition. *Nutrition* **18**: 872-879.

Fardet, A. (2009). New hypotheses for the health protective mechanisms of whole-grain cereals: What is beyond fibre? *Nutrition research Reviews* In press.

Fardet, A., Canlet, C., Gottardi, G., Lyan, B., Remesy, C., Mazur, A., Paris, A. and A., S. (2007). Whole grain and refined wheat flours show distinct metabolic profiles in rats as assessed by a ^{1}H-NMR-based metabonomic approach. *Journal of Nutrition* **4**: 923-929.

Fardet, A., Rock, E. and Rémésy, C. (2008). Is the *in vitro* antioxidant potential of whole-grain cereals and cereal products well reflected *in vivo*? *Journal of Cereal Science* **48**: 258-276.

Felmlee, M. A., Woo, G., Simko, E., Krol, E. S., Muir, A. D. and Alcorn, J. (2009). Effects of the flaxseed lignans secoisolariciresinol diglucoside and its aglycone on serum and hepatic lipids in hyperlipidaemic rats. *British Journal of Nutrition* **102**: 361-369.

Fidanza, A., Decicco, A., Fiorilli, G. and Bruno, C. (1970). Liver lipids of pantothenic acid and polynsaturated fatty acids deficient rats. *Bollettino Della Societa Italiana Di Biologia Sperimentale* **46**: 684-686.

Figge, H. L., Figge, J., Souney, P. F., Mutnick, A. H. and Sacks, F. (1988). Nicotinic-acid - a review of its clinical use in the treatment of lipid disorders. *Pharmacotherapy* **8**: 287-294.

Fischer, L. M., daCosta, K. A., Kwock, L., Stewart, P. W., Lu, T.-S., Stabler, S. P., Allen, R. H. and Zeisel, S. H. (2007). Sex and menopausal status influence human dietary requirements for the nutrient choline. *American journal of Clinical Nutrition* **85**: 1275-1285.

Flight, I. and Clifton, P. (2006). Cereal grains and legumes in the prevention of coronary heart disease and stroke: A review of the literature. *European Journal of Clinical Nutrition* **60**: 1145-1159.

Fomenko, A. I., Shushevich, S. I. and Khalmuradov, A. G. (1979). Inhibition of activity of acetyl coenzyme a carboxylase from chicken liver by nicotinic-acid and its derivatives. *Biokhimiya* **44**: 1005-1009.

Freedman, A. M., Mak, I. T., Stafford, R. E., Dickens, B. F., Cassidy, M. M., Muesing, R. A. and Weglicki, W. B. (1992). Erythrocytes from magnesium-deficient hamsters display an enhanced susceptibility to oxidative stress. *American Journal of Physiology* **262**: C1371-C1375.

Freeland, K. R., Wilson, C. and Wolever, T. M. S. (2010). Adaptation of colonic fermentation and glucagon-like peptide-1 secretion with increased wheat fibre intake for 1 year in hyperinsulinaemic human subjects. *British Journal of Nutrition* **103**: 82-90.

Fritz, I. B. (1959). Action of carnitine on long chain fatty acid oxidation by liver. *American Journal of Physiology*- **197**: 297-304.

Fritz, I. B. and Dupont, P. (1957). Ineffectiveness of carnitine as a choline substitute in the prevention of fatty livers of rats maintained on a choline-deficient diet. *American Journal of Physiology-Gastrointestinal and Liver Physiology* **190**: 453-454.

Fromenty, B., Grimbert, S., Mansouri, A., Beaugrand, M., Erlinger, S., Rötig, A. and Pessayre, D. (1995). Hepatic mitochondrial DNA deletion in alcoholics: Association with microvesicular steatosis. *Gastroenterology* **108**: 193-200.

Fromenty, B. and Pessayre, D. (1995). Inhibition of mitochondrial beta-oxidation as a mechanism of hepatotoxicity. *Pharmacology and Therapeutics* **67**: 101-154.

Fukuwatari, T., Morikawa, Y., Sugimoto, E. and Shibata, K. (2002). Effects of fatty liver induced by niacin-free diet with orotic acid on the metabolism of tryptophan to niacin in rats. *Bioscience, Biotechnology, and Biochemistry* **66**: 1196-1204.

Fux, M., Levine, J., Aviv, A. and Belmaker, R. (1996). Inositol treatment of obsessive-compulsive disorder. *American Journal of Psychiatry* **153**: 1219-1221.

Galli, A., Pinaire, J., Fischer, M., Dorris, R. and Crabb, D. W. (2001). The transcriptional and DNA binding activity of peroxisome proliferator-activated receptor î± is inhibited by ethanol metabolism. *Journal of Biological Chemistry* **276**: 68-75.

Ganji, S. H., Tavintharan, S., Zhu, D. M., Kamanna, V. S. and Kashyap, M. L. (2002). Niacin non-competitively inhibits hepatocyte diacylglycerol acyltransferase, a key enzyme for triglyceride synthesis. *Arteriosclerosis Thrombosis and Vascular Biology* **22**: P238.

Garfinkel, L. and Garfinkel, D. (1985). Magnesium regulation of the glycolytic pathway and the enzymes involved. *Magnesium* **4**: 60-72.

Gastaldelli, A., Kozakova, M., Hojlund, K., Flyvbjerg, A., Favuzzi, A., Mitrakou, A. and Balkau, B. (2009). Fatty liver is associated with insulin resistance, risk of coronary heart disease and early atherosclerosis in a large european population. *Hepatology* **49**: 1537-1544.

Gavin, G. and McHenry, E. W. (1940). The b vitamins and fat metabolism. Iii. The effects of vitamin B6 upon liver and body fat. *Journal of Biological Chemistry* **132**: 41-46.

Gavin, G. and McHenry, E. W. (1941a). Inositol: A lipotropic factor. *Journal of Biological Chemistry* **139**: 485.

Gavin, G. and McHenry, E. W. (1941b). The effect of biotin upon fat synthesis and metabolism. *Journal of Biological Chemistry* **141**: 619-625.

Gaylor, J. L., Hardy, R. W. F. and Baumann, C. A. (1960). Effects of nicotinic acid and related compounds on sterol metabolism in the chick and rat. *Journal of Nutrition* **70**: 293-301.

Gebhardt, R. and Beck, H. (1996). Differential inhibitory effects of garlic-derived organosulfur compounds on cholesterol biosynthesis in primary rat hepatocyte cultures. *Lipids* **31**: 1269-1276.

Gershoff, S. N. and Gottlieb, L. S. (1964). Pantothenic acid deficiency in cats. *Journal of Nutrition* **82**: 135-138.

Gey, K. F. (1998). Vitamins e plus c and interacting conutrients required for optimal health: A critical and constructive review of epidemiology and supplementation data regarding cardiovascular disease and cancer. *Biofactors* **7**: 113-174.

Ghoshal, A. K. and Farber, E. (1984). The induction of liver cancer by dietary deficiency of choline and methionine without added carcinogens. *Carcinogenesis* **5**: 1367-1370.

Gillis, M. B. and Norris, L. C. (1951). The effect of vitamin B12 on the response of chicks to betaine and choline. *Journal of Nutrition* **43**: 295-302.

Ginneken, V. v., Verhey, E., Poelmann, R., Ramakers, R., Dijk, K. W. v., Ham, L., Voshol, P., Havekes, L., Eck, M. v. and Greef, J. v. d. (2007). Metabolomics (liver and blood profiling) in a mouse model in response to fasting: A study of hepatic steatosis. *Biochimica et Biophysica Acta, Molecular and Cell Biology of Lipids* **1771**: 1263-1270.

Goelz, S., Vogelstein, B., Hamilton, SR and Feinberg, A. (1985). Hypomethylation of DNA from benign and malignant human colon neoplasms. *Science* **228**: 187-190.

Goheen, S., Larkin, E. and Rao, G. (1983). Severe fatty liver in rats fed a fat-free ethanol diet and its prevention by small amounts of dietary arachidonate. *Lipids* **18**: 285-290.

Gotoh, N., Nagao, K., Onoda, S., Shirouchi, B., Furuya, K., Nagai, T., Mizobe, H., Ichioka, K., Watanabe, H., Yanagita, T. and Wada, S. (2009). Effects of three different highly purified n-3 series highly unsaturated fatty acids on lipid metabolism in c57bl/ksj-db/db mice. *Journal of Agricultural and Food Chemistry* **57**: 11047-11054.

Gouni-Berthold, I. and Berthold, H. K. (2002). Policosanol: Clinical pharmacology and therapeutic significance of a new lipid-lowering agent. *American Heart Journal* **143**: 356-365.

Graham, I. M., Daly, L. E., Refsum, H. M., Robinson, K., Brattstrom, L. E., Ueland, P. M., Palma-Reis, R. J., Boers, G. H., Sheahan, R. G., Israelsson, B., Uiterwaal, C. S., Meleady, R., McMaster, D., Verhoef, P., Witteman, J., Rubba, P., Bellet, H., Wautrecht, J. C., de Valk, H. W., Sales Luis, A. C., Parrot-Rouland, F. M., Tan, K. S., Higgins, I., Garcon, D., Medrano, M. J., Candito, M., Evans, A. E. and Andria, G. (1997). Plasma homocysteine as a risk factor for vascular disease.

The european concerted action project. *Journal Of the American Medical Association* **277**: 1775-1781.

Greenwood, M. R. C., Cleary, M. P., Gruen, R., Blase, D., Stern, J. S., Triscari, J. and Sullivan, A. C. (1981). Effect of (-)-hydroxycitrate on development of obesity in the zucker obese rat. *American Journal of Physiology* **240**: E72-E78.

Griffin, J. L., Scott, J. and Nicholson, J. K. (2007). The influence of pharmacogenetics on fatty liver disease in the wistar and kyoto rats: A combined transcriptomic and metabonomic study. *Journal of Proteome Research* **6**: 54-61.

Griffin, J. L. and Vidal-Puig, A. (2008). Current challenges in metabolomics for diabetes research: A vital functional genomic tool or just a ploy for gaining funding? *Physiological Genomics* **34**: 1-5.

Griffith, W. H. and Mulford, D. J. (1941a). Choline metabolism. Vi. Hemorrhagic degeneration and the labile methyl supply. *Journal of the American Chemical Society* **63**: 929-932.

Griffith, W. H. and Mulford, D. J. (1941b). Choline metabolism: Vii. Some dietary factors affecting the incidence and severity of hemorrhagic degeneration in young rats. *Journal of Nutrition* **21**: 633-646.

Grundy, S., Mok, H., Zech, L. and Berman, M. (1981). Influence of nicotinic acid on metabolism of cholesterol and triglycerides in man. *Journal of Lipid Research* **22**: 24-36.

Guehring, R. R., Hurley, L. S. and Morgan, A. F. (1952). Cholesterol metabolism in pantothenic acid deficiency. *Journal of Biological Chemistry* **197**: 485-493.

Guggenheim, K. and Olson, R. E. (1952). Studies of lipogenesis in certain b-vitamin deficiencies. *Journal of Nutrition* **48**: 345-358.

Guzmán, M., Velasco, G., Castro, J. and Zammit, V. A. (1994). Inhibition of carnitine palmitoyltransferase i by hepatocyte swelling. *FEBS Letters* **344**: 239-241.

Haines, D. S. M. and Mookerjea, S. (1965). Impairment of triglyceride transport from liver in choline deficiency. *Canadian Journal of Biochemistry* **43**: 507-520.

Halliday, N. (1938). Fatty livers in vitamin B6 deficient rats. *Journal of Nutrition* **16**: 285-290.

Halsted, C. H., Villanueva, J. A., Devlin, A. M., Niemelä, O., Parkkila, S., Garrow, T. A., Wallock, L. M., Shigenaga, M. K., Melnyk, S. and James, S. J. (2002). Folate deficiency disturbs hepatic methionine metabolism and promotes liver injury in the ethanol-fed micropig. *Proceedings of the National Academy of Sciences of the United States of America* **99**: 10072-10077.

Hammond, L. E., Lewin, T. M., Schwerbrock, N. M. J., Maeda, N. and Coleman, R. A. (2003). Reduced liver and heart triacylglycerol content in mitochondrial glycerol-3-phosphate acyltransferase -/- mice following high-sucrose feeding. *FASEB Journal* **17**: A1315-A1315.

Handler, P. (1944). The effect of excessive nicotinamide feeding on rabbits and guinea pigs. *Journal of Biological Chemistry* **154**: 203-206.

Handler, P. and Dann, W. J. (1942). The inhibition of rat growth by nicotinamide. *Journal of Biological Chemistry* **146**: 357-368.

Hanje, A. J., Fortune, B., Song, M., Hill, D. and McClain, C. (2006). The use of selected nutrition supplements and complementary and alternative medicine in liver disease. *Nutrition in Clinical Practice* **21**: 255-272.

Hanson, A. D. and Hitz, W. D. (1982). Metabolic responses of mesophytes to plant water deficits. *Annual Review of Plant Physiology* **33**: 163-203.

Hanson, A. D., May, A. M., Grumet, R., Bode, J., Jamieson, G. C. and Rhodes, D. (1985). Betaine synthesis in chenopods - localization in chloroplasts. *Proceedings of the National Academy of Sciences of the United States of America* **82**: 3678-3682.

Hanson, A. D. and Wyse, R. (1982). Biosynthesis, translocation and accumulation of betaine in sugar beet and its progenitors in relation to salinity. *Plant Physiology* **70**: 1191-1198.

Hara, H., Haga, S., Aoyama, Y. and Kiriyama, S. (1999). Short-chain fatty acids suppress cholesterol synthesis in rat liver and intestine. *Journal of Nutrition* **129**: 942-948.

Harland, B. F. and Oberleas, D. (1987). Phytate in foods. *World Review of Nutrition and Dietetics* **52**: 235-259.

Harper, A. E., Benton, D. A., Winje, M. E. and Elvehjem, C. A. (1954a). On the lipotropic action of protein. *Journal of Biological Chemistry* **209**: 171-177.

Harper, A. E., Monson, W. J., Benton, D. A., Winje, M. E. and Elvehjem, C. A. (1954b). Factors other than choline which affect the deposition of liver fat. *Journal of Biological Chemistry* **206**: 151-158.

Harper, A. E., Monson, W. J., Benton, D. A. and Elvehjem, C. A. (1953). The influence of protein and certain amino acids, particularly threonine, on the deposition of fat in the liver of the rat. *Journal of Nutrition* **50**: 383-393.

Hartfiel, W. and Kirchner, I. (1973). The importance of nicotinic acid and its effect on the liver fat content of laying hens. *Archiv fur Geflugelkunde* **37**: 114-117.

Häussinger, D. (1996). The role of cellular hydration in the regulation of cell function. *Biochemical Journal* **313**: 697-710.

Hayashi, E., Maeda, T. and Tomita, T. (1974a). Effect of myoinositol deficiency on lipid-metabolism in rats .1. Alteration of lipid-metabolism in myoinositol deficient rats. *Biochimica et Biophysica Acta* **360**: 134-145.

Hayashi, E., Maeda, T. and Tomita, T. (1974b). Effect of myoinositol deficiency on lipid-metabolism in rats .2. Mechanism of triacylglycerol accumulation in liver of myoinositol-deficient rats. *Biochimica Et Biophysica Acta* **360**: 146-155.

He, K., Hu, F. B., Colditz, G. A., Manson, J. E., Willett, W. C. and Liu, S. (2004). Changes in intake of fruits and vegetables in relation to risk of obesity and weight gain among middle-aged women. *International Journal of Obesity* **28**: 1569-1574.

Helfrich, A. and Bettmer, J. (2004). Determination of phytic acid and its degradation products by ion-pair chromatography (IPC) coupled to inductively coupled plasma-sector field-mass spectrometry (ICP-SF-MS). *Journal of Analytical Atomic Spectrometry* **19**: 1330-1334.

Henning, S. M. and Swendseid, M. E. (1996). The role of folate, choline and methionine in carcinogenesis induced by methyl-deficient diets. In: *Dietary fats, lipids, hormones and*

tumorigenesis: new horizons in basic research. pp. 143-155. Heber, D. and Kritchevsky, D., Eds., Plenum Press, New York.

Heymsfield, S. B., Allison, D. B., Vasselli, J. R., Pietrobelli, A., Greenfield, D. and Nunez, C. (1998). Garcinia cambogia (hydroxycitric acid) as a potential antiobesity agent: A randomized controlled trial. *Journal of the American Medical Association* **280**: 1596-1600.

Hitz, W. D., Ladyman, J. A. R. and Hanson, A. D. (1982). Betaine synthesis and accumulation in barley during field water-stress. *Crop Science* **22**: 47-54.

Horbowicz, M., Brenac, P. and Obendorf, R. L. (1998). Fagopyritol B1, O-α-D-galactopyranosyl-(1->-2)-D-*chiro*-inositol, a galactosyl cyclitol in maturing buckwheat seeds associated with desiccation tolerance. *Planta* **205**: 1-11.

Horbowicz, M. and Obendorf, R. L. (1994). Seed desiccation tolerance and storability: Dependence on flatulence-producing oligosaccharides and cyclitols? - review and survey. *Seed Science Research* **4**: 385-405.

Horev-Azaria, L., Eliav, S., Izigov, N., Pri-Chen, S., Mirelman, D., Miron, T., Rabinkov, A., Wilchek, M., Jacob-Hirsch, J., Amariglio, N. and Savion, N. (2009). Allicin up-regulates cellular glutathione level in vascular endothelial cells. *European Journal of Nutrition* **48**: 67-74.

Hosomi, R., Fukunaga, K., Arai, H., Nishiyama, T. and Yoshida, M. (2009). Effects of dietary fish protein on serum and liver lipid concentrations in rats and the expression of hepatic genes involved in lipid metabolism. *Journal of Agricultural and Food Chemistry* **57**: 9256-9262.

Hough, V. H., Monahan, E. P., Li, T. W. and Freeman, J. (1943). The effect of choline and cystine on the serum phosphatase and hepatic dye clearance of dogs maintained on deficient diets. *American Journal of Physiology* **642**: 642-651.

Hozawa, A., Kuriyama, S., Nakaya, N., Ohmori-Matsuda, K., Kakizaki, M., Sone, T., Nagai, M., Sugawara, Y., Nitta, A., Tomata, Y., Niu, K. and Tsuji, I. (2009). Green tea consumption is associated with lower psychological distress in a general population: The Ohsaki Cohort 2006 Study. *American Journal of Clinical Nutrition* **90**: 1390-1396.

Hsu, C.-C., Yen, H.-f., Yin, M.-C., Tsai, C.-M. and Hsieh, C.-H. (2004). Five cysteine-containing compounds delay diabetic deterioration in balb/ca mice. *Journal of Nutrition* **134**: 3245-3249.

Hsu, C.-L. and Yen, G.-C. (2008). Phenolic compounds: Evidence for inhibitory effects against obesity and their underlying molecular signaling mechanisms. *Molecular Nutrition and Food Research* **52**: 53-61.

Hu, M. C. C. (1975). Lipotropic action of carnitine in a low protein diet from plant sources. *Dissertation Abstracts International, B* **36**: 655.

Hue, L. (1994). Control of liver carbohydrate and fatty-acid metabolism by cell-volume. *Biochemical Society Transactions* **22**: 505-508.

Hung, H. C., Joshipura, K. J., Jiang, R., Hu, F. B., Hunter, D., Smith-Warner, S. A., Colditz, G. A., Rosner, B., Spiegelman, D. and Willett, W. C. (2004). Fruit and vegetable intake and risk of major chronic disease. *Journal of the National Cancer Institute* **96**: 1577-1584.

Hussein, O., Grosovski, M., Lasri, E., Svalb, S., Ravid, U. and Assy, N. (2007). Monounsaturated fat decreases hepatic lipid content in non-alcoholic fatty liver disease in rats. *World Journal of Gastroenterology* **13**: 361-368.

Ide, T., Ashakumary, L., Takahashi, Y., Kushiro, M., Fukuda, N. and Sugano, M. (2001). Sesamin, a sesame lignan, decreases fatty acid synthesis in rat liver accompanying the down-regulation of sterol regulatory element binding protein-1. *Biochimica et Biophysica Acta-Molecular and Cell Biology of Lipids* **1534**: 1-13.

Ide, T., Hong, D. D., Ranasinghe, P., Takahashi, Y., Kushiro, M. and Sugano, M. (2004). Interaction of dietary fat types and sesamin on hepatic fatty acid oxidation in rats. *Biochimica et Biophysica Acta-Molecular and Cell Biology of Lipids* **1682**: 80-91.

Ikeda, M., Uno, Y., Iwai, M., Sato, H., Kawabe, H. and Sakakibara, B. (1992). Effects of the inositol-deficient diet on the development of fatty liver lipogenic enzyme activities and plasma lipid levels in germ-free and conventional mice. *Vitamins (Kyoto)* **66**: 43-49.

Ingraham, L. L. and Green, D. E. (1958). Role of magnesium in enzyme-catalyzed syntheses involving adenosine triphosphate. *Science* **128**: 310-312.

Institute of Medicine and Food and Nutrition Board (1998). Niacin. In: *Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin and choline*, pp. 123-149. National Academy Press, Washington DC.

Iqbal, T. H., Lewis, K. O. and Cooper, B. T. (1994). Phytase activity in the human and rat small-intestine. *Gut* **35**: 1233-1236.

Ishihara, K., Oyaizu, S., Onuki, K., Lim, K. and Fushiki, T. (2000). Chronic (-)-hydroxycitrate administration spares carbohydrate utilization and promotes lipid oxidation during exercise in mice. *Journal of Nutrition* **130**: 2990-2995.

Iwami, K., Sakakibara, K. and Ibuki, F. (1986). Involvement of post-digestion hydrophobic peptides in plasma cholesterol-lowering effect of dietary plant-proteins. *Agricultural and Biological Chemistry* **50**: 1217-1222.

Jacobs, D. R., Jr andersen, L. F. and Blomhoff, R. (2007). Whole-grain consumption is associated with a reduced risk of noncardiovascular, noncancer death attributed to inflammatory diseases in the iowa women's health study. *American Journal of Clinical Nutrition* **85**: 1606-1614.

Jacobs, D. R., Jr., Marquart, L., Slavin, J. and Kushi, L. H. (1998). Whole-grain intake and cancer: An expanded review and meta-analysis. *Nutrition and Cancer* **30**: 85-96.

Jaenicke, L. and Rudiger, H. (1971). Formation of methionine methyl groups. *Federation Proceedings* **30**: 160-166.

James, O. F. W. and Day, C. P. (1998). Non-alcoholic steatohepatitis (nash): A disease of emerging identity and importance. *Journal of Hepatology* **29**: 495-501.

Jamil, H., Chu, C.-H., K . Dickson, J., , Jr., Chen, Y., Yan, M., Biller, S. A., Gregg, R. E., Wetterau, J. R. and Gordon, D. A. (1998). Evidence that microsomal triglyceride transfer protein is limiting in the production of apolipoprotein b-containing lipoproteins in hepatic cells. *Journal of Lipid Research* **39**: 1448-1454.

Jeong, Y., Choi, Y., Kim, D., Park, S., Yoon, J., Kwon, S., Park, E. and Park, K. (2005). Cytoprotective effect of green tea extract and quercetin against hydrogen peroxide-induced oxidative stress. *Archives of Pharmacal Research* **28**: 1251-1256.

Jin, F. Y., Kamanna, V. S. and Kashyap, M. L. (1999). Niacin accelerates intracellular apob degradation by inhibiting triacylglycerol synthesis in human hepatoblastoma (HepG2) cells. *Arteriosclerosis Thrombosis and Vascular Biology* **19**: 1051-1059.

Jin, F.-Y., Kamanna, V. S. and Kashyap, M. L. (1996). Niacin accelerates intracellular post-translational apolipoprotein b translocation/degradation by inhibiting triacylglycerol synthesis in human hepatoblastoma (hep g2) cells. *Circulation* **94**: I149.

Jin, F.-Y., Kamanna, V. S. and Kashyap, M. L. (1997). Niacin decreases removal of high-density lipoprotein apolipoprotein A-I but not cholesterol ester by Hep G2 cells : Implication for reverse cholesterol transport. *Arteriosclerosis, Thrombosis, and Vascular Biology* **17**: 2020-2028.

Johnston, P. V., Kopaczyk, K. C. and Kummerow, F. A. (1961). Effect of pyridoxine deficiency on fatty acid composition of carcass and brain lipids in the rat. *Journal of Nutrition* **74**: 96-102.

Kahlon, T. S., Saunders, R. M., Sayre, R. N., Chow, F. I., Chiu, M. M. and Betschart, A. A. (1992). Cholesterol-lowering effects of rice bran and rice bran oil fractions in hypercholesterolemic hamsters. *Cereal Chemistry* **69**: 485-489.

Kang, D. H., Jung, E. Y., Chang, U. J., Bae, S. H. and Suh, H. J. (2007). Psyllium husk combined with hydroxycitrate reduces body weight gain and body fat in diet-induced obese rats. *Nutrition Research* **27**: 349-355.

Kaplan, N. O. and Lipmann, F. (1948). The assay and distribution of coenzyme a. *Journal of Biological Chemistry* **174**: 37-44.

Karanth, J. and Jeevaratnam, K. (2009). Effect of dietary lipid, carnitine and exercise on lipid profile in rat blood, liver and muscle. *Indian Journal of Experimental Biology* **47**: 748-753.

Kashyap, M. L., Jin, F. Y. and Kamanna, V. S. (1997). Niacin, by inhibiting both fatty acid synthesis and triacylglycerol formation, augments apo b degradation in Hep G2 cells. *Atherosclerosis* **134**: 127-127.

Katayama, T. (1995). Effect of dietary-sodium phytate on the hepatic and serum levels of lipids and on the hepatic activities of nadph-generating enzymes in rats fed on sucrose. *Bioscience Biotechnology and Biochemistry* **59**: 1159-1160.

Katayama, T. (1997a). Dietary phytic acid acts on hepatic lipid metabolism in a similar manner as dietary *myo*-inositol: is phytic acid a vitamin-like substance? *Recent Research Developments in Agricultural and Biological Chemistry* **1**: 321-330.

Katayama, T. (1997b). Effects of dietary *myo*-inositol or phytic acid on hepatic concentrations of lipids and hepatic activities of lipogenic enzymes in rats fed on corn starch or sucrose. *Nutrition Research* **17**: 721-728.

Keaney, J. F., Larson, M. G., Vasan, R. S., Wilson, P. W. F., Lipinska, I., Corey, D., Massaro, J. M., Sutherland, P., Vita, J. A. and Benjamin, E. J. (2002). Obesity as a source of systemic oxidative stress: Clinical correlates of oxidative stress in the framingham study. *Circulation* **106**: 467-467.

Keim, N. L. and Mares-Perlman, J. A. (1984). Development of hepatic steatosis and essential fatty acid deficiency in rats with hypercaloric, fat-free parenteral nutrition. *Journal of Nutrition* **114**: 1807-1815.

Kelley, B., Totter, J. R. and Day, P. L. (1950). The lipotropic effect of folic acid on rats receiving various purified diets. *Journal of Biological Chemistry* **187**: 529-535.

Kersten, S., Seydoux, J., Peters, J. M., Gonzalez, F. J., Desvergne, B. a. and Wahli, W. (1999). Peroxisome proliferator-activated receptor α mediates the adaptive response to fasting. *Journal of Clinical Investigation* **103**: 1489-1498.

Khairallah, E. A. and Wolf, G. (1965). Growth-promoting and lipotropic effect of carnitine in rats fed diets limited in protein and methionine. *Journal of Nutrition* **87**: 469-476.

Khanal, T., Choi, J. H., Hwang, Y. P., Chung, Y. C. and Jeong, H. G. (2009). Protective effects of saponins from the root of platycodon grandiflorum against fatty liver in chronic ethanol feeding via the activation of amp-dependent protein kinase. *Food and Chemical Toxicology* **47**: 2749-2754.

Khor, H. T., Chieng, D. Y. and Ong, K. K. (1995). Tocotrienols inhibit liver HMG CoA reductase activity in the guinea pig. *Nutrition Research* **15**: 537-544.

Kim, H. K., Jeong, T. S., Lee, M. K., Park, Y. B. and Choi, M. S. (2003). Lipid-lowering efficacy of hesperetin metabolites in high-cholesterol fed rats. *Clinica Chimica Acta* **327**: 129-137.

Kim, J. I., Kim, J. C., Joo, H. J., Jung, S. H. and Kim, J. J. (2005). Determination of total *chiro*-inositol content in selected natural materials and evaluation of the antihyperglycemic effect of pinitol isolated from soybean and carob. *Food Science and Biotechnology* **14**: 441-445.

Kisters, K., Spieker, C., Tepel, M. and Zidek, W. (1993). New data about the effects of oral physiological magnesium supplementation on several cardiovascular risk factors (lipids and blood pressure). *Magnesium Research* **6**: 355-360.

Klaus, S., Pultz, S., Thone-Reineke, C. and Wolfram, S. (2005). Epigallocatechin gallate attenuates diet-induced obesity in mice by decreasing energy absorption and increasing fat oxidation. *International Journal of Obesity* **29**: 615-623.

Ko, W.-C., Shih, C.-M., Lai, Y.-H., Chen, J.-H. and Huang, H.-L. (2004). Inhibitory effects of flavonoids on phosphodiesterase isozymes from guinea pig and their structure-activity relationships. *Biochemical Pharmacology* **68**: 2087-2094.

Koh-Banerjee, P., Franz, M., Sampson, L., Liu, S., Jacobs, D. R., Jr., Spiegelman, D., Willett, W. and Rimm, E. (2004). Changes in whole-grain, bran and cereal fiber consumption in relation to 8-y weight gain among men. *American Journal of Clinical Nutrition* **80**: 1237-1245.

Koh-Banerjee, P. and Rimm, E. B. (2003). Whole grain consumption and weight gain: a review of the epidemiological evidence, potential mechanisms and opportunities for future research. *Proceedings of the Nutrition Society* **62**: 25-29.

Koivisto, M., Valta, P., Höckerstedt, K. and Lindgren, L. (2002). Magnesium depletion in chronic terminal liver cirrhosis. *Clinical Transplantation* **16**: 325-328.

Kok, N., Roberfroid, M. and Delzenne, N. (1996a). Dietary oligofructose modifies the impact of fructose on hepatic triacylglycerol metabolism. *Metabolism* **45**: 1547-1550.

Kok, N., Roberfroid, M., Robert, A. and Delzenne, N. (1996b). Involvement of lipogenesis in the lower VLDL secretion induced by oligofructose in rats. *British Journal of Nutrition* **76**: 881-890.

Kok, N. N., Morgan, L. M., Williams, C. M., Roberfroid, M. B., Thissen, J.-P. and Delzenne, N. M. (1998). Insulin, glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide and insulin-like growth factor i as putative mediators of the hypolipidemic effect of oligofructose in rats. *Journal of Nutrition* **128**: 1099-1103.

Kolonel, L. N., Hankin, J. H., Whittemore, A. S., Wu, A. H., Gallagher, R. P., Wilkens, L. R., John, E. M., Howe, G. R., Dreon, D. M., West, D. W. and Paffenbarger, R. S., Jr. (2000). Vegetables, fruits, legumes and prostate cancer: A multiethnic case-control study. *Cancer Epidemiology, Biomarkers and Prevention* **9**: 795-804.

Kondo, T., Kishi, M., Fushimi, T. and Kaga, T. (2009). Acetic acid upregulates the expression of genes for fatty acid oxidation enzymes in liver to suppress body fat accumulation. *Journal of Agricultural and Food Chemistry* **57**: 5982-5986.

Koseki, M., Seki, H., Kazama, M., Kitabatake, N. and Tochikura, T. (1991). Effects of pectin and lard on the production of short-chain fatty-acids in the cecum, on the growth of colonic bacteria and on the liver cholesterol level in rats. *Agricultural and Biological Chemistry* **55**: 1441-1448.

Kotaki, A., Sakurai, T., Kobayashi, M. and Yagi, K. (1968). Studies on myoinositol. IV. Effect of myoinositol on the cholesterol metabolism of rats suffering from experimental fatty liver. *Journal of Vitaminology (Kyoto)* **14**.

Koteish, A. and Diehl, A. M. (2001). Animal models of steatosis. *Seminars in Liver Disease* **21**: 89-104.

Kovacs, E. M. R., Westerterp-Plantenga, M. S., de Vries, M., Brouns, F. and Saris, W. H. M. (2001a). Effects of 2-week ingestion of (-)-hydroxycitrate and (-)-hydroxycitrate combined with medium-chain triglycerides on satiety and food intake. *Physiology and Behavior* **74**: 543-549.

Kovacs, E. M. R., Westerterp-Plantenga, M. S. and Saris, W. H. M. (2001b). The effects of 2-week ingestion of (-)-hydroxycitrate and (-)-hydroxycitrate combined with medium-chain triglycerides on satiety, fat oxidation, energy expenditure and body weight. *International Journal of Obesity* **25**: 1087-1094.

Koziol, M. J. (1992). Chemical composition and nutritional evaluation of quinoa (*Chenopodium quinoa* willd.). *Journal of Food Composition and Analysis* **5**: 35-68.

Kriketos, A. D., Thompson, H. R., Greene, H. and Hill, J. O. (1999). (-)-hydroxycitric acid does not affect energy expenditure and substrate oxidation in adult males in a post-absorptive state. *International Journal of Obesity* **23**: 867-873.

Kumari, K. and Augusti, K. T. (2007). Lipid lowering effect of s-methyl cysteine sulfoxide from allium cepa linn in high cholesterol diet fed rats. *Journal of Ethnopharmacology* **109**: 367-371.

Kumari, K., Mathew, B. C. and Augusti, K. T. (1995). Antidiabetic and hypolipidemic effects of s-methyl cysteine sulfoxide isolated from *Allium cepa* Linn. *Indian Journal of Biochemistry and Biophysics* **32**: 49-54.

Kurtz, T., Morris, R. and Pershadsingh, H. (1989). The Zucker fatty rat as a genetic model of obesity and hypertension. *Hypertension* **13**: 896-901.

Kuzu, N., Bahcecioglu, I. H., Metin, K., Ozercan, I. H., Tuzcu, M., Yalniz, M., Ustundag, B. and Sahin, K. (2007). Role of melatonin in treatment of nonalcoholic steatohepatitis in rats induced bu high fat diet. *Journal of Hepatology* **46**: S263.

Kwon, D. Y., Jung, Y. S., Kim, S. J., Park, H. K., Park, J. H. and Kim, Y. C. (2009a). Impaired sulfur-amino acid metabolism and oxidative stress in nonalcoholic fatty liver are alleviated by betaine supplementation in Rats. *Journal of Nutrition* **139**: 63-68.

Kwon, D. Y., Kim, Y. S., Hong, S. M. and Park, S. (2009b). Long-term consumption of saponins derived from Platycodi radix (22 years old) enhances hepatic insulin sensitivity and glucose-stimulated insulin secretion in 90 % pancreatectomized diabetic rats fed a high-fat diet. *British Journal of Nutrition* **101**: 358-366.

Labadie, P. (1974). Labile Methyls and Lipotropic Effect. *Revue du Praticien* **24**: 4839-4854.

Ladyman, J. A. R., Hitz, W. D. and Hanson, A. D. (1980). Translocation and metabolism of glycine betaine by barley plants in relation to water-stress. *Planta* **150**: 191-196.

Laird, R. D. and Drill, V. A. (1971). Lipotropic activity of inositol and chlortetracycline alone and in various combinations of choline, vitamin B12 and folic acid - Activity of 3 liver extracts with assays for these substances. *Archives Internationales de Pharmacodynamie et de Thérapie* **194**: 103-116.

Laird, R. D., McCormick, H. M. and Drill, V. A. (1965). Lipotropic activity of combinations of choline, vitamins B_{12} and B_{12b}, folic acid, and citrovorum factor. *Toxicology and Applied Pharmacology* **7**: 247-256.

Laraki, L., Pelletier, X., Mourot, J. and Debry, G. (1993). Effects of dietary phytosterols on liver lipids and lipid metabolism enzymes. *Annals of Nutrition and Metabolism* **37**: 129-133.

Larsson, S. C., Giovannucci, E., Bergkvist, L. and Wolk, A. (2005). Whole grain consumption and risk of colorectal cancer: a population-based cohort of 60 000 women. *British Journal of Cancer* **92**: 1803-1807.

Lawrence, S. P. (1993). Transient focal hepatic defects related to sustained-selease niacin. *Journal of Clinical Gastroenterology* **16**: 234-236.

Leclerc, J. and Miller, M. L. (1989). Inositol and choline levels in the diet and neutral lipid hepatic content of lactating rat. *International Journal for Vitamin and Nutrition Research* **59**: 180-183.

Lee, S., Gura, K. M. and Puder, M. (2007a). Omega-3 fatty acids and liver disease. *Hepatology* **45**: 841-845.

Lee, S. H., Park, H. J., Cho, S. Y., Jung, H. J., Cho, S. M., Cho, Y. S. and Lillehoj, H. S. (2005). Effects of dietary phytic acid on serum and hepatic lipid levels in diabetic KK mice. *Nutrition Research* **25**: 869-876.

Lee, S.-H., Park, H.-J., Chun, H.-K., Cho, S.-Y., Jung, H.-J., Cho, S.-M., Kim, D.-Y., Kang, M.-S. and Lillehoj, H. S. (2007b). Dietary phytic acid improves serum and hepatic lipid levels in aged ICR mice fed a high-cholesterol diet. *Nutrition Research* **27**: 505-510.

Lee, Y. H. and Yeh, Y. Y. (2003). Inhibitory effects of garlic extract and water-soluble organosulfur compounds of garlic on cholestergenesis in HepG-2 cells. *FASEB Journal* **17**: A752-A752.

Lennon, D. L., Stratman, F. W., Shrago, E., Nagle, F. J., Madden, M., Hanson, P. and Carter, A. L. (1983). Effects of acute moderate-intensity exercise on carnitine metabolism in men and women. *Journal of Applied Physiology* **55**: 489-495.

Leon, J., Acuña-Castroviejo, D., Sainz, R. M., Mayo, J. C., Tan, D.-X. and Reiter, R. J. (2004). Melatonin and mitochondrial function. *Life Sciences* **75**: 765-790.

Leonhardt, M. and Langhans, W. (2002). Hydroxycitrate has long-term effects on feeding behavior, body weight regain and metabolism after body weight loss in male rats. *Journal of Nutrition* **132**: 1977-1982.

Lettéron, P., Duchatelle, V., Berson, A., Fromenty, B., Fisch, C., Degott, C., Benhamou, J. P. and Pessayre, D. (1993). Increased ethane exhalation, an *in vivo* index of lipid peroxidation, in alcohol-abusers. *Gut* **34**: 409-414.

Lewis, Y. S. and Neelakantan, S. (1965). (-)-Hydroxycitric acid - the principal acid in the fruits of *Garcinia cambogia* desr. *Phytochemistry* **4**: 619-625.

Li, Z., Agellon, L. B. and Vance, D. E. (2005). Phosphatidylcholine homeostasis and liver failure. *Journal of Biological Chemistry* **280**: 37798-37802.

Li, Z. and Vance, D. E. (2008). Phosphatidylcholine and choline homeostasis. *Journal of Lipid Research* **49**: 1187-1194.

Liang, L. J., Yin, X. Y., Luo, S. M., Zheng, J. F., Lu, M. D. and Huang, J. F. (1999). A study of the ameliorating effects of carnitine on hepatic steatosis induced by total parenteral nutrition in rats. *World Journal of Gastroenterology* **5**: 312-315.

Lieber, C. S. (1997). Ethanol metabolism, cirrhosis and alcoholism. *Clinica Chimica Acta* **257**: 59-84.

Lim, K., Ryu, S., Ohishi, Y., Watanabe, I., Tomi, H., Suh, H., Lee, W. K. and Kwon, T. (2002). Short-term (-)-hydroxycitrate ingestion increases fat oxidation during exercise in athletes. *Journal of Nutritional Science and Vitaminology* **48**: 128-133.

Lin, C.-C. and Yin, M.-C. (2008). Effects of cysteine-containing compounds on biosynthesis of triacylglycerol and cholesterol and anti-oxidative protection in liver from mice consuming a high-fat diet. *British Journal of Nutrition* **99**: 37-43.

Lin, C.-C., Yin, M.-C., Hsu, C.-C. and Lin, M.-P. (2004). Effect of five cysteine-containing compounds on three lipogenic enzymes in Balb/cA mice consuming a high saturated fat diet. *Lipids* **39**: 843-848.

Lin, C.-C., Yin, M.-C. and Liu, W.-H. (2008). Alleviative effects of s-allyl cysteine and s-ethyl cysteine on MCD diet-induced hepatotoxicity in mice. *Food and Chemical Toxicology* **46**: 3401-3406.

Lin, M., Kao, S., Chung, P., Chan, K., Yang, M. and Wang, C. (2009). Improvement for high fat diet-induced hepatic injuries and oxidative stress by flavonoid-enriched extract from *Nelumbo nucifera* leaf. *Journal of Agricultural and Food Chemistry* **57**: 5925-5932.

Lipmann, F., Kaplan, N. O., Novelli, G. D., Tuttle, L. C. and Guirard, B. M. (1947). Coenzyme for acetylation, a pantothenic acid derivative. *Journal of Biological Chemistry* **167**: 869-870.

Liu, L. and Yeh, Y.-Y. (2000). Inhibition of cholesterol biosynthesis by organosulfur compounds derived from garlic. *Lipids* **35**: 197-203.

Liu, L., Zubik, L., Collins, F. W., Marko, M. and Meydani, M. (2004). The antiatherogenic potential of oat phenolic compounds. *Atherosclerosis* **175**: 39-49.

Locker, J., Reddy, T. V. and Lombardi, B. (1986). DNA methylation and hepatocarcinogenesis in rats fed a choline-devoid diet. *Carcinogenesis* **7**: 1309-1312.

Lombardi, B. (1971). Effects of choline deficiency on rat hepatocytes. *Federation Proceedings* **30**: 139-142.

Lombardi, B., Pani, P. and Schlunk, F. F. (1968). Choline-deficiency fatty liver: impaired release of hepatic triglycerides. *Journal of Lipid Research* **9**: 437-446.

Lopez, H. W., Leenhardt, F., Coudray, C. and Remesy, C. (2002). Minerals and phytic acid interactions: is it a real problem for human nutrition? *International Journal of Food Science and Technology* **37**: 727-739.

Lopez, H. W., Vallery, F., Levrat-Verny, M. A., Coudray, C., Demigne, C. and Remesy, C. (2000). Dietary phytic acid and wheat bran enhance mucosal phytase activity in rat small intestine. *Journal of Nutrition* **130**: 2020-2025.

Lotito, S. B. and Frei, B. (2006). Consumption of flavonoid-rich foods and increased plasma antioxidant capacity in humans: Cause, consequence, or epiphenomenon? *Free Radical Biology and Medicine* **41**: 1727-1746.

Lott, J. N. A., Ockenden, I., Raboy, V. and Batten, G. D. (2000). Phytic acid and phosphorus in crop seeds and fruits: a global estimate. *Seed Science Research* **10**: 11-33.

Lowenstein, J. M. (1971). Effect of (-)-hydroxycitrate on fatty acid synthesis by rat liver *in vivo*. *Journal of Biological Chemistry* **246**: 629-632.

Luo, Q.-F., Sun, L., Si, J.-Y. and Chen, D.-H. (2008). Hypocholesterolemic effect of stilbenes containing extract-fraction from *Cajanus cajan* L. on diet-induced hypercholesterolemia in mice. *Phytomedicine* **15**: 932-939.

Madani, S., Lopez, S., Blond, J. P., Prost, J. and Belleville, J. (1998). Highly purified soybean protein is not hypocholesterolemic in rats but stimulates cholesterol synthesis and excretion and reduces polyunsaturated fatty acid biosynthesis. *Journal of Nutrition* **128**: 1084-1091.

Mahboob, S. (1975). Effect of pantothenic-acid deficiency on microsomal lipids of rat-liver. *Annals of Nutrition and Metabolism* **19**: 91-95.

Mahboob, S. and Estes, L. W. (1978). Effect of pantothenic-acid deficiency on rat hepatocytes. *Annals of Nutrition and Metabolism* **22**: 177-180.

Maiese, K., Morhan, S. D. and Chong, Z. Z. (2007). Oxidative stress biology and cell injury during type 1 and type 2 diabetes Mellitus. *Current Neurovascular Research* **4**: 63-71.

Mamone, F., Riggio, S., Mandraffino, G., Maimone, S., La Scala, M., Sardo, M. A. and Saitta, A. (2009). Assessment of liver stiffness values in subjects affected by familial combined hyperlipidemia with different degree of hepatic steatosis. *Nutrition, Metabolism and Cardiovascular Diseases* **19**: S15.

Mannarino, M. R., Pirro, M., Helou, R., Covelli, D., Pucci, G., Schillaci, G. and Mannarino, E. (2009). Liver steatosis: an independent predictor of arterial stiffness in dyslipidemic patients. *Nutrition, Metabolism and Cardiovascular Diseases* **19**: S15-S16.

Mantovani, M. S., Bellini, M. F., Angeli, J. P. F., Oliveira, R. J., Silva, A. F. and Ribeiro, L. R. (2008). Beta-glucans in promoting health: Prevention against mutation and cancer. *Mutation Research-Reviews in Mutation Research* **658**: 154-161.

Marchesini, G., Brizi, M., Morselli-Labate, A. M., Bianchi, G., Bugianesi, E., McCullough, A. J., Forlani, G. and Melchionda, N. (1999). Association of nonalcoholic fatty liver disease with insulin resistance. *American Journal of Medicine* **107**: 450-455.

Martinez, L. O., Jacquet, S., Esteve, J.-P., Rolland, C., Cabezon, E., Champagne, E., Pineau, T., Georgeaud, V., Walker, J. E., Terce, F., Collet, X., Perret, B. and Barbaras, R. (2003). Ectopic [beta]-chain of ATP synthase is an apolipoprotein A-I receptor in hepatic HDL endocytosis. **421**: *Nature* 75-79.

Masuda, T., Kawano, A., Kitahara, K., Nagashima, K., Aikawa, Y. and Arai, S. (2003). Quantitative determination of sugars and *myo*-inositol in citrus fruits grown in Japan using high-

performance anion-exchange chromatography. *Journal of Nutritional Science and Vitaminology* **49**: 64-68.

Mayor, F., Veloso, D. and Williams.Dh (1967). Effects of nicotinic acid on acetoacetate and 3-hydroxybutyrate concentrations of rat blood and liver. *Biochemical Journal* **104**: 57a-57P.

McCance, R. A. and Widdowson, E. M. (1935). Phytin in human nutrition. *Biochemical Journal* **29**: 2694-2699.

McCarty, M. F. (1994). Promotion of hepatic lipid oxidation and gluconeogenesis as a strategy for appetite control. *Medical Hypotheses* **42**: 215-225.

McCarty, M. F. (2000). Co-administration of equimolar doses of betaine may alleviate the hepatotoxic risk associated with niacin therapy. *Medical Hypotheses* **55**: 189-194.

McCarty, M. F. (2002). Policosanol safely down-regulates HMG-CoA reductase - potential as a component of the Esselstyn regimen. *Medical Hypotheses* **59**: 268-279.

McHenry, E. W. and Gavin, G. (1941). The B vitamins and fat metabolism. IV. The synthesis of fat from protein. *Journal of Biological Chemistry* **138**: 471-475.

McHenry, E. W. and Patterson, J. M. (1944). Lipotropic factors. *Physiological reviews* **24**: 128-167.

McKenney, J. M., Proctor, J. D., Harris, S. and Chinchili, V. M. (1994). A comparison of the efficacy and toxic effects of sustained- *vs* immediate-release niacin in hypercholesterolemic patients. *Journal of the American Medical Association* **271**: 672-677.

Mellen, P. B., Walsh, T. F. and Herrington, D. M. (2008). Whole grain intake and cardiovascular disease: A meta-analysis. *Nutrition Metabolism and Cardiovascular Diseases* **18**: 283-290.

Menendez, R., Amor, A. M., Gonzalez, R. M., Fraga, V. and Mas, R. (1996). Effect of policosanol on the hepatic cholesterol biosynthesis of normocholesterolemic rats. *Biological Research* **29**: 253-257.

Menendez, R., Arruzazabala, L., Mas, R., DelRio, A., Amor, A. M., Gonzalez, R. M., Carbajal, D., Fraga, V., Molina, V. and Illnait, J. (1997). Cholesterol-lowering effect of policosanol on rabbits

with hypercholesterolaemia induced by a wheat starch-casein diet. *British Journal of Nutrition* **77**: 923-932.

Menendez, R., Fernandez, S. I., Del Rio, A., Gonzalez, R. M., Fraga, V., Amor, A. M. and Mas, R. M. (1994). Policosanol inhibits cholesterol biosynthesis and enhances low density lipoprotein processing in cultured human fibroblasts. *Biological Research* **27**.

Mercier, J., Lumbroso, A., Vovan, L. and Dessaigne, S. (1967). On the hepatoprotective lipotropic proprieties of hexanicit. *Thérapie* **22**: 1153-1158.

Merrill, J. M. and Lemley-Stone, J. (1957). Effects of nicotinic acid on serum and tissue cholesterol in rabbits. *Circulation Research* **5**: 617-619.

Miglio, F., Rovati, L. C., Santoro, A. and Setnikar, I. (2000). Efficacy and safety of oral betaine glucuronate in non-alcoholic steatohepatitis - A double-blind, randomized, parallel-group, placebo-controlled prospective clinical study. *Arzneimittel Forschung-Drug Research* **50**: 722-727.

Miller, O. N., Hamilton, J. G. and Goldsmith, G. A. (1960). Investigation of the Mechanism of Action of Nicotinic Acid on Serum Lipid Levels in Man. *American Journal of Clinical Nutrition* **8**: 480-490.

Minhajuddin, M., Beg, Z. H. and Iqbal, J. (2005). Hypolipidemic and antioxidant properties of tocotrienol rich fraction isolated from rice bran oil in experimentally induced hyperlipidemic rats. *Food and Chemical Toxicology* **43**: 747-753.

Mizrahi, A., Knekt, P., Montonen, J., Laaksonen, M. A., Heli?vaara, M. and J?rvinen, R. (2009). Plant foods and the risk of cerebrovascular diseases: a potential protection of fruit consumption. *British Journal of Nutrition* **102**: 1075-1083.

Moat, S. J., Hill, M. H., McDowell, I. F. W., Pullin, C. H., Ashfield-Watt, P. A. L., Clark, Z. E., Whiting, J. M., Newcombe, R. G., Lewis, M. J. and Powers, H. J. (2003). Reduction in plasma total homocysteine through increasing folate intake in healthy individuals is not associated with

changes in measures of antioxidant activity or oxidant damage. *European Journal of Clinical Nutrition* **57**: 483-489.

Moghadasian, M. H., Nguyen, L. B., Shefer, S., Salen, G., Batta, A. K. and Frohlich, J. J. (2001). Hepatic cholesterol and bile acid synthesis, low-density lipoprotein receptor function, and plasma and fecal sterol levels in mice: effects of apolipoprotein E deficiency and probucol or phytosterol treatment. *Metabolism-Clinical and Experimental* **50**: 708-714.

Moiseenok, A. G., Sheibak, V. M. and Gurinovich, V. A. (1987). Hepatic CoA, S-Acyl-CoA, biosynthetic precursors of the coenzyme and pantothenate-protein complexes in dietary pantothenic-acid deficiency. *International Journal for Vitamin and Nutrition Research* **57**: 71-77.

Mongeau, R. and Brassard, R. (1982). Insoluble dietary fiber from breakfast cereals and brans: bile salt binding and water-holding capacity in relation to particle size. *Cereal Chemistry* **59**: 413-417.

Mookerjea, S. (1971). Action of choline in lipoprotein metabolism. *Federation Proceedings* **30**: 143-150.

Mookerjea, S., Park, C. and Kuksis, A. (1975). Lipid profiles of plasma lipoproteins of fasted and fed normal and choline-deficient rats. *Lipids* **10**: 374-382.

Moon, Y. S., Keller, W. L. and Park, C. S. (1998). Dietary lipotrope-mediated mammary carcinogenesis in female rats. *Nutrition Research* **18**: 1605-1614.

Moon, Y. S., Latasa, M. J., Griffin, M. J. and Sul, H. S. (2002). Suppression of fatty acid synthase promoter by polyunsaturated fatty acids. *Journal of Lipid Research* **43**: 691-698.

Morgan, A. F. and Lewis, E. M. (1953). The modification of choline deficiency by simultaneous pantothenic acid deficiency. *Journal of Biological Chemistry* **200**: 839-850.

Morin, R. J. (1967). The influence of cholesterol on incorporation of (I-^{14}C)acetate into phosphatidyl choline and phosphatidyl ethanolamine of rat-liver Mitochondria. *Biochimica et Biophysica Acta* **144**: 594-604.

Morise, A., Thomas, C., Landrier, J.-F., Besnard, P. and Hermier, D. (2009). Hepatic lipid metabolism response to dietary fatty acids is differently modulated by PPARα in male and female mice. *European Journal of Nutrition* **48**: 465-473.

Moskaug, J. O., Carlsen, H., Myhrstad, M. C. and Blomhoff, R. (2005). Polyphenols and glutathione synthesis regulation. *American Journal of Clinical Nutrition* **81**: 277S-283S.

Murakami, A., Takahashi, D., Koshimizu, K. and Ohigashi, H. (2003). Synergistic suppression of superoxide and nitric oxide generation from inflammatory cells by combined food factors. *Mutation Research-Fundamental and Molecular Mechanisms of Mutagenesis* **523-524**: 151-161.

Murtaugh, M. A., Jacobs, D. R., Jacob, B., Steffen, L. M. and Marquart, L. (2007). Epidemiological support for the protection of whole grains against diabetes. *Proceedings of the Nutrition Society* **62**: 143-149.

Nadeau, G., Rouleau, Y. and Delage, J. (1954). The fate of the liver in alcoholics. II. Use of lipotropic factors in the treatment of hepatic dysfunction. *Laval Med* **19**: 52-58.

Nadler, J., Buchanan, T., Natarajan, R., Antonipillai, I., Bergman, R. and Rude, R. (1993). Magnesium deficiency produces insulin resistance and increased thromboxane synthesis. *Hypertension* **21**: 1024-1029.

Nagata, Y., Ishiwaki, N. and Sugano, M. (1982). Studies on the mechanism of antihypercholesterolemic action of soy protein and soy protein-type amino acid mixtures in relation to the casein counterparts in rats. *Journal of Nutrition* **112**: 1614-1625.

Nageswara Rao, R. and Sakariah, K. K. (1988). Lipid-lowering and antiobesity effect of (-)hydroxycitric acid. *Nutrition Research* **8**: 209-212.

Nagiel-Ostaszewski, I. and Lau-Cam, C. A. (1990). Protection by pantethine, pantothenic-acid and cystamine against carbon tetrachloride-induced hepatotoxicity in the rat. *Research Communications in Chemical Pathology and Pharmacology* **67**: 289-292.

Nagura, J., Iso, H., Watanabe, Y., Maruyama, K., Date, C., Toyoshima, H., Yamamoto, A., Kikuchi, S., Koizumi, A., Kondo, T., Wada, Y., Inaba, Y., Tamakoshi, A. and null, t. J. S. g.

(2009). Fruit, vegetable and bean intake and mortality from cardiovascular disease among Japanese men and women: the JACC Study. *British Journal of Nutrition* **102**: 285-292.

Nakamura, Y., Kaihara, A., Yoshii, K., Tsumura, Y., Ishimitsu, S. and Tonogai, Y. (2001). Effects of the oral administration of green tea polyphenol and tannic acid on serum and hepatic lipid contents and fecal steroid excretion in rats. *Journal of Health Science* **47**: 107-117.

Nakamura, Y. and Tonogai, Y. (2002). Effects of grape seed polyphenols on serum and hepatic lipid contents and fecal steroid excretion in normal and hypercholesterolemic rats. *Journal of Health Science* **48**: 570-578.

Naruta, E. and Buko, V. (2001). Hypolipidemic effect of pantothenic acid derivatives in mice with hypothalamic obesity induced by aurothioglucose. *Experimental and Toxicologic Pathology* **53**: 393-398.

Nauss, K. M., Connor, A. M., Kavanaugh, A. and Newberne, P. M. (1982). Alterations in immune function in rats caused by dietary lipotrope deficiency - effect of age. *Journal of Nutrition* **112**: 2333-2341.

Navarranne, Fritz, Tanguy, Meriaux and Marion (1964). First biological results of a new lipotropic formula. *La Clinique (Paris)* **59**: 443-445.

Nehra, V., Angulo, P., Buchman, A. L. and Lindor, K. D. (2001). Nutritional and metabolic considerations in the etiology of nonalcoholic steatohepatitis. *Digestive Diseases and Sciences* **46**: 2347-2352.

Neuschwander-Tetri, B. A. and Caldwell, S. H. (2003). Nonalcoholic steatohepatitis: Summary of an AASLD Single Topic Conference. *Hepatology* **37**: 1202-1219.

Neveu, V., Perez-Jimenez, J., Vos, F., Crespy, V., du Chaffaut, L., Mennen, L., Knox, C., Eisner, R., Cruz, J., Wishart, D. and Scalbert, A. (2010). Phenol-explorer: an online comprehensive database on polyphenol contents in foods. *Database* **2010**: bap024-.

Newberne, P. M. and Rogers, A. E. (1986). Labile methyl groups and the promotion of cancer. *Annual Review of Nutrition* **6**: 407-432.

Newberne, P. M., Wilson, R. and Rogers, A. E. (1971). Effects of a low-lipotrope diet on response of young male rats to pyrrolizidine alkaloid, monocrotaline. *Toxicology and Applied Pharmacology* **18**: 387-397.

Newby, P. (2009). Plant foods and plant-based diets: protective against childhood obesity? *American Journal of Clinical Nutrition* **89**: 1572S-1587.

Nichols, M. R. and Morimoto, B. H. (1999). Tyrosine kinase-independent inhibition of cyclic-AMP phosphodiesterase by genistein and tyrphostin 51. *Archives of Biochemistry and Biophysics* **366**: 224-230.

Nichols, M. R. and Morimoto, B. H. (2000). Differential inhibition of multiple cAMP phosphodiesterase isozymes by isoflavones and tyrphostins. *Molecular Pharmacology* **57**: 738-745.

Nieminen, P., Kakela, R., Mustonen, A. M., Hyvarinen, H. and Asikainen, J. (2001). Exogenous melatonin affects lipids and enzyme activities in mink (*Mustela vison*) liver. *Comparative Biochemistry and Physiology C-Toxicology and Pharmacology* **128**: 203-211.

Nieminen, P., Mustonen, A. M., Karja, V., Asikainen, J. and Rouvinen-Watt, K. (2009). Fatty acid composition and development of hepatic lipidosis during food deprivation-mustelids as a potential Animal model for liver steatosis. *Experimental Biology and Medicine* **234**: 278-286.

Noethlings, U., Schulze, M. B., Weikert, C., Boeing, H., van der Schouw, Y. T., Bamia, C., Benetou, V., Lagiou, P., Krogh, V., Beulens, J. W. J., Peeters, P. H. M., Halkjaer, J., Tjonneland, A., Tumino, R., Panico, S., Masala, G., Clavel-Chapelon, F., de Lauzon, B., Boutron-Ruault, M.-C., Vercambre, M.-N., Kaaks, R., Linseisen, J., Overvad, K., Arriola, L., Ardanaz, E., Gonzalez, C. A., Tormo, M.-J., Bingham, S., Khaw, K.-T., Key, T. J. A., Vineis, P., Riboli, E., Ferrari, P., Boffetta, P., Bueno-de-Mesquita, H. B., van der A, D. L., Berglund, G., Wirfalt, E., Hallmans, G., Johansson, I., Lund, E. and Trichopoulo, A. (2008). Intake of vegetables, legumes, and fruit, and risk for all-cause, cardiovascular, and cancer mortality in a European diabetic population. *Journal of Nutrition* **138**: 775-781.

Nolte, K. D., Hanson, A. D. and Gage, D. A. (1997). Proline accumulation and methylation to proline betaine in citrus: Implications for genetic engineering of stress resistance. *Journal of American Society for Horticultural science* **122**: 8-13.

Novelli, G. D., Kaplan, N. O. and Lipmann, F. (1949). The liberation of pantothenic acid from coenzyme A. *Journal of Biological Chemistry* **177**: 97-107.

Nunn, S. L., Tauxe, W. N. and Juergens, J. L. (1961). Effect of nicotinic acid on human cholesterol biosynthesis. *Circulation* **24**: 1099.

Oakenfull, D. G., Fenwick, D. E., Hood, R. L., Topping, D. L., Illman, R. L. and Storer, G. B. (1979). Effects of saponins on bile-acids and plasma-lipids in the rat. *British Journal of Nutrition* **42**: 209-216.

Ohigashi, H. and Murakami, A. (2004). Cancer prevention with food factors: alone and in combination. *Biofactors* **22**: 49-55.

Okada, M. and Ochi, A. (1971). The effect of dietary protein level on transaminase activities and fat deposition in vitamin B6-depleted rat liver. *Journal of Biochemistry* **70**: 581-585.

Okada, M. and Suzuki, K. (1974). Amino acid metabolism in rats fed a high protein diet without pyridoxine. *Journal of Nutrition* **104**: 287-293.

Okazaki, Y. and Katayama, T. (2008). Dietary myositol hexakisphosphate, but not *myo*-inositol, clearly improves hypercholesterolemia in rats fed casein-type amino acid mixtures and 1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethane. *Nutrition Research* **28**: 714-721.

Okazaki, Y., Kayashima, T. and Katayama, T. (2003). Effect of dietary phytic acid on hepatic activities of lipogenic and drug-metabolizing enzymes in rats fed 1,1,1-trichloro-2,2-bis (P-chlorophenyl) ethane (DDT). *Nutrition Research* **23**: 1089-1096.

Okazaki, Y., Setoguchi, T. and Katayama, T. (2006). Effects of dietary *myo*-inositol, D-*chiro*-inositol and L-*chiro*-inositol on hepatic lipids with reference to the hepatic *myo*-inositol status in rats fed on 1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethane. *Bioscience, Biotechnology, and Biochemistry* **70**: 2766-2770.

Olson, R. E., Jablonski, J. R. and Taylor, E. (1958a). The Effect of Dietary Protein, Fat, and Choline upon the Serum Lipids and Lipoproteins of the Rat. *American Journal of Clinical Nutrition* **6**: 111-118.

Olson, R. E., Vester, J. W., Gursey, D., Davis, N. and Longman, D. (1958b). The effect of low-protein diets upon serum cholesterol in man. *American Journal of Clinical Nutrition* **6**: 310-324.

Olthof, M. R. and Verhoef, P. (2005). Effects of betaine intake on plasma homocysteine concentrations and consequences for health. *Current Drug Metabolism* **6**: 15-22.

Onning, G. and Asp, N. G. (1995). Effect of oat saponins on plasma and liver lipids in gerbils (*Meriones unguiculatus*) and rats. *British Journal of Nutrition* **73**: 275-286.

Onomi, S., Okazaki, Y. and Katayama, T. (2004). Effect of dietary level of phytic acid on hepatic and serum lipid status in rats fed a high-sucrose diet. *Bioscience, Biotechnology and Biochemistry* **68**: 1379-1381.

Orbetsova, V. T. (1977). Changes in levels of serum and liver lipids after a single injection of nicotinic-acid. *Dokladi Na Bolgarskata Akademiya Na Naukite* **30**: 613-616.

Orbetsova, V. T., Kiprov, D. I. and Vucheva, N. V. (1977). Effect of nicotinic-acid on level of serum and liver lipids in spontaneously hypertensive rats fed an atherogenic diet. *Dokladi Na Bolgarskata Akademiya Na Naukite* **30**: 465-468.

Orbetsova, V. T., Polyakova, E. D., Klimova, T. A. and Dizhe, E. B. (1976). Influence of nicotinic-acid on the synthesis of cholesterol and fatty-acids in liver of albino-rats. *Dokladi Na Bolgarskata Akademiya Na Naukite* **29**: 137-140.

Ortega, M. F. (1989). Effect of dietary lysine level and protein restriction on the lipids and carnitine levels in the liver of pregnant rats. *Annals of Nutrition and Metabolism* **33**: 162-169.

Osumi, Y., Nagasaka, Y. and Shimamot.K (1969). Lipid metabolism in rats with fatty liver caused by low protein diet and effects of oral administration of L-methionine L-cysteine pantethine and calcium pantothenate upon it. *Japanese Journal of Pharmacology* **19**: 74-88.

Ournac, A. (1970). Vitamins of wine. *Annales de la Nutrition et de l'Alimentation* **24**: B333-B365.

Owens (1942). The comparative effects of inositol and lipocaic in depancreatized dogs. *Federation Proceedings* **1**: 65.

Pagano, G., Pacini, G., Musso, G., Gambino, R., Mecca, F., Depetris, N., Cassader, M., David, E., Cavallo-Perin, P. and Rizzetto, M. (2002). Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: Further evidence for an etiologic association. *Hepatology* **35**: 367-372.

Pan, M., Song, Y.-L., Xu, J.-M. and Gan, H.-Z. (2006). Melatonin ameliorates nonalcoholic fatty liver induced by high-fat diet in rats. *Journal of Pineal Research* **41**: 79-84.

Pardue, W. O. (1961). Severe liver dysfunction during nicotinic acid therapy. *Journal of the American Medical Association* **175**: 137-138.

Parker, R. A., Pearce, B. C., Clark, R. W., Gordon, D. A. and Wright, J. J. (1993). Tocotrienols regulate cholesterol production in mammalian cells by post-transcriptional suppression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. *Journal of Biological Chemistry* **268**: 11230-11238.

Parker, T. L., Miller, S. A., Myers, L. E., Miguez, F. E. and Engeseth, N. J. (2010). Evaluation of synergistic antioxidant potential of complex mixtures using oxygen radical absorbance capacity (ORAC) and electron paramagnetic resonance (EPR). *Journal of Agricultural and Food Chemistry* **58**: 209-217.

Parsons, W. B. (1961a). Studies of nicotinic acid use in hypercholesteremia: changes in hepatic function, carbohydrate tolerance, and uric acid metabolism. *Archives of Internal Medicine* **107**: 85-99.

Parsons, W. B., Jr. and Flinn, J. H. (1959). Reduction of serum cholesterol levels and beta-lipoprotein cholesterol levels by nicotinic acid. *Archives of Internal Medicine* **103**: 123-130.

Parsons, W. B. J. (1961b). Reduction in hepatic synthesis of cholesterol from C^{14}-acetate in hypercholesterolemic patients by nicotinic acid. *Circulation* **24**: 1099-1100.

Patrick, L. (2002). Nonalcoholic fatty liver disease: relationship to insulin sensitivity and oxidative stress. Treatment approaches using vitamin E, magnesium, and betaine. *Alternative Medicine Review* **7**: 276-291.

Pavia, M., Pileggi, C., Nobile, C. G. A. and Angelillo, I. F. (2006). Association between fruit and vegetable consumption and oral cancer: a meta-analysis of observational studies. *American Journal of Clinical Nutrition* **83**: 1126-1134.

Pellegrini, N., Serafini, M., Colombi, B., Del Rio, D., Salvatore, S., Bianchi, M. and Brighenti, F. (2003). Total antioxidant capacity of plant foods, beverages and oils consumed in Italy assessed by three different *in vitro* assays. *Journal of Nutrition* **133**: 2812-2819.

Peluso, M. R. (2006). Flavonoids attenuate cardiovascular disease, inhibit phosphodiesterase, and modulate lipid homeostasis in adipose tissue and liver. *Experimental Biology and Medicine* **231**: 1287-1299.

Perlman, I. and Chaikoff, I. L. (1939). Radioactive phosphorus as an indicator of phospholipid metabolism. *Journal of Biological Chemistry* **130**: 593-600.

Perlzweig, W. A., Bernheim, M. L. C. and Bernheim, F. (1943). The methylation of nicotinamide by rat liver *in vitro*. *Journal of Biological Chemistry* **150**: 401-406.

Perrault, M. and Dormard, Y. (1966). Lipotropic effect of betaine aspartate on experimental hepatic steatosis. Study using triolein-C^{14}. *Thérapie* **21**: 719-731.

Perry, W. F. (1960). Effect of nicotinic acid and nicotinamide on incorporation of acetate into cholesterol, fatty acids and CO_2 by rat liver slices. *Metabolism-Clinical and Experimental* **9**: 686-689.

Pettinelli, P., del Pozo, T., Araya, J., Rodrigo, R., Araya, A. V., Smok, G., Csendes, A., Gutierrez, L., Rojas, J., Korn, O., Maluenda, F., Diaz, J. C., Rencoret, G., Braghetto, I., Castillo, J., Poniachik, J. and Videla, L. A. (2009). Enhancement in liver SREBP-1c/PPAR-alpha ratio and steatosis in obese patients: correlations with insulin resistance and n-3 long-chain polyunsaturated fatty acid depletion. *Biochimica et Biophysica Acta-Molecular Basis of Disease* **1792**: 1080-1086.

Pfiffner, J. J. and Bird, O. D. (1956). Water-soluble vitamins, Part I. *Annual Review of Biochemistry* **25**: 397-434.

Pilvi, T. K., Seppanen-Laakso, T., Simolin, H., Finckenberg, P., Huotari, A., Herzig, K. H., Korpela, R., Oresic, M. and Mervaala, E. M. (2008). Metabolomic changes in fatty liver can be modified by dietary protein and calcium during energy restriction. *World Journal of Gastroenterology* **14**: 4462-4472.

Poirier, L. A. and Whitehead, V. M. (1973). Folate deficiency and formiminoglutamic acid excretion during chronic diethylnitrosamine administration to rats. *Cancer Research* **33**: 383-388.

Popper, H. and Schaffner, F. (1952). Laboratory diagnosis of liver disease: coordinated use of histological and biochemical observations. *Journal of the American Medical Association* **150**: 1367-1372.

Preuss, H. G., Bagchi, D., Bagchi, M., Rao, C. V. S., Dey, D. K. and Satyanarayana, S. (2004a). Effects of a natural extract of (-)-hydroxycitric acid (HCA-SX) and a combination of HCA-SX plus niacin-bound chromium and *Gymnema sylvestre* extract on weight loss. *Diabetes, Obesity and Metabolism* **6**: 171-180.

Preuss, H. G., Bagchi, D., Bagchi, M., Rao, C. V. S., Satyanarayana, S. and Dey, D. K. (2004b). Efficacy of a novel, natural extract of (-)-hydroxycitric acid (HCA-SX) and a combination of HCA-SX, niacin-bound chromium and *Gymnema sylvestre* extract in weight management in human volunteers: A pilot study. *Nutrition Research* **24**: 45-58.

Prior, R. L. (2003). Fruits and vegetables in the prevention of cellular oxidative damage. *American Journal of Clinical Nutrition* **78**: 570S-578S.

Quan, P. C. and Le Breton, E. (1973). Study of fatty acid composition of 3 main classes of phospholipid in the liver, in rats having eaten, after weaning, during 3 or 45 days, diets containing different oils. Effects of fasting and lipotropic agents. Comparison with cardiac phospholipids. *Comptes-Rendus Hebdomadaires des Séances de l'Académie des Sciences. Série D: Sciences Naturelles* **276**: 1585-1588.

Qureshi, A. A., Bradlow, B. A., Salser, W. A. and Brace, L. D. (1997). Novel tocotrienols of rice bran modulate cardiovascular disease risk parameters of hypercholesterolemic humans. *Journal of Nutritional Biochemistry* **8**: 290-298.

Qureshi, A. A., Burger, W. C., Peterson, D. M. and Elson, C. E. (1986). The structure of an inhibitor of cholesterol biosynthesis isolated from barley. *Journal of Biological Chemistry* **261**: 10544-10550.

Rader, J. I., Calvert, R. J. and Hathcock, J. N. (1992). Hepatic toxicity of unmodified and time-release preparations of niacin. *American Journal of Medicine* **92**: 77-81.

Rahman, I., Biswas, S. K. and Kirkham, P. A. (2006). Regulation of inflammation and redox signaling by dietary polyphenols. *Biochemical Pharmacology* **72**: 1439-1452.

Recknagel, R. O. (1967). Carbon tetrachloride hepatotoxicity. *Pharmacological Reviews* **19**: 145-208.

Reddy, N. R., Sathe, S. K. and Salunkhe, D. K. (1982). Phytates in legumes and cereals. *Advances in Food Research* **28**: 1-92.

Reeves, P. G., Nielsen, F. H. and Fahey, G. C., Jr. (1993). AIN-93 purified diets for laboratory rodents: final report of the American Institute of Nutrition *ad hoc* writing committee on the reformulation of the AIN-76A rodent diet. *Journal of Nutrition* **123**: 1939-1951.

Reid, A. E. (2001). Nonalcoholic steatohepatitis. *Gastroenterology* **121**: 710-723.

Reimund, E. and Ramos, A. (1994). Niacin-induced hepatitis and thrombocytopenia after 10 years of niacin use. *Journal of Clinical Gastroenterology* **18**: 270-271.

Rejman, J. and Kozubek, A. (2003).). Inhibitory effect of natural phenolic lipids upon nad-dependent dehydrogenases and on triglyceride accumulation in 3T3-L1 cells in culture. *Journal of Agricultural and Food Chemistry* **52**: 246-250.

Rhew, T. H. and Sachan, D. S. (1986). Dose-dependent lipotropic effect of carnitine in chronic-alcoholic rats. *Journal of Nutrition* **116**: 2263-2269.

Rikans, L. L., Arata, D. and Cederquist, D. C. (1964). Fatty livers produced in albino rats by excess niacin in high fat diets: I. Alterations in enzyme and coenzyme systems induced by supplementing 40% fat diets with 0.1% of niacin. *Journal of Nutrition* **82**: 83-87.

Rikans, L. L., Arata, D. and Cederquist, D. C. (1965). Fatty livers produced in albino rats by excess niacin in high fat diets. II. Effect of choline supplements. *Journal of Nutrition* **85**: 107-112.

Rissanen, T. H., Voutilainen, S., Virtanen, J. K., Venho, B., Vanharanta, M., Mursu, J. and Salonen, J. T. (2003). Low intake of fruits, berries and vegetables is associated with excess mortality in men: the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study. *Journal of Nutrition* **133**: 199-204.

Rogers, A. E. (1975). Variable effects of a lipotrope-deficient, high-fat diet on chemical carcinogenesis in rats. *Cancer Research* **35**: 2469-2474.

Rogers, A. E. and Newberne, P. M. (1969). Aflatoxin B1 carcinogenesis in lipotrope-deficient rats. *Cancer Research* **29**: 1965-1972.

Rong, N., Ausman, L. and Nicolosi, R. (1997). Oryzanol decreases cholesterol absorption and aortic fatty streaks in hamsters. *Lipids* **32**: 303-309.

Rosenfeld, B. (1973). Regulation by dietary choline of hepatic fatty acid synthetase in the rat. *Journal of Lipid Research* **14**: 557-562.

Rosolova, H., Mayer, O., Jr. and Reaven, G. (1997). Effect of variations in plasma magnesium concentration on resistance to insulin-mediated glucose disposal in nondiabetic subjects. *Journal of Clinical Endocrinology and Metabolism* **82**: 3783-3785.

Ross, A. B., Chen, Y., Frank, J., Swanson, J. E., Parker, R. S., Kozubek, A., Lundh, T., Vessby, B., Aman, P. and Kamal-Eldin, A. (2004a). Cereal alkylresorcinols elevate gamma-tocopherol levels in rats and inhibit gamma-tocopherol metabolism *in vitro*. *Journal of Nutrition* **134**: 506-510.

Ross, A. B., Kamal-Eldin, A. and Aman, P. (2004b). Dietary alkylresorcinols: absorption, bioactivities, and possible use as biomarkers of whole-grain wheat- and rye-rich foods. *Nutrition Reviews* **62**: 81-95.

Rubis, B., Paszel, A., Kaczmarek, M., Rudzinska, M., Jelen, H. and Rybczynska, M. (2008). Beneficial or harmful influence of phytosterols on human cells? *British Journal of Nutrition* **100**: 1183-1191.

Rumpler, W., Seale, J., Clevidence, B., Judd, J., Wiley, E., Yamamoto, S., Komatsu, T., Sawaki, T., Ishikura, Y. and Hosoda, K. (2001). Oolong tea increases metabolic rate and fat oxidation in men. *Journal of Nutrition* **131**: 2848-2852.

Rushmore, T. H., Morton, M. R. and Pickett, C. B. (1991). The antioxidant responsive element. Activation by oxidative stress and identification of the DNA consensus sequence required for functional activity. *Journal of Biological Chemistry* **266**: 11632-11639.

Russakoff, A. H. and Blumberg, H. (1944). Choline as an adjuvant to the dietary therapy of cirrhosis of the liver. *Annals of Internal Medicine* **21**: 848-862.

Ryu, M. H. and Cha, Y. S. (2003). The effects of a high-fat or high-sucrose diet on serum lipid profiles, hepatic acyl-CoA synthetase, carnitine palmitoyltransferase-I, and the acetyl-CoA carboxylase mRNA levels in rats. *Journal of Biochemistry and Molecular Biology* **36**: 312-318.

Sachan, D. S. and Hongu, N. (2000). Increases in VO2max and metabolic markers of fat oxidation by caffeine, carnitine, and choline supplementation in rats. *Journal of Nutritional Biochemistry* **11**: 521-526.

Saheb, J. L. and Demers, J. M. (1972). Effect of Lipotropic Factors on Cholesterol Metabolism in Duckling. *Annales De Biologie Animale Biochimie Biophysique* **12**: 149. 149-157

Sahyoun, N. R., Jacques, P. F., Zhang, X. L., Juan, W. and McKeown, N. M. (2006). Whole-grain intake is inversely associated with the metabolic syndrome and mortality in older adults. *American Journal of Clinical Nutrition* **83**: 124-131.

Sakakibara, K., Shibata, Y., Higashi, T., Sanada, S. and Shoji, J. (1975). Effect of ginseng saponins on cholesterol-metabolism .1. Level and synthesis of serum and liver cholesterol in rats treated with ginsenosides. *Chemical and Pharmaceutical Bulletin* **23**: 1009-1016.

Sakamoto, A., Nishimura, Y., Ono, H. and Sakura, N. (2002). Betaine and homocysteine concentrations in foods. *Pediatrics International* **44**: 409-413.

Sakamoto, K., Vucenik, I. and Shamsuddin, A. M. (1993). [^{3}H]Phytic acid (inositol hexaphosphate) is absorbed and distributed to various tissues in rats. *Journal of Nutrition* **123**: 713-720.

Salama, R. H. M., Nassar, A. Y. A., Nafady, A. A. M. and Mohamed, H. H. T. (2007). A novel therapeutic drug (copper nicotinic acid complex) for non-alcoholic fatty liver. *Liver International* **27**: 454-464.

Samman, S., Sivarajah, G., Man, J., Ahmad, Z., Petocz, P. and Caterson, I. (2002). Supplementation with a mixed fruit and vegetable concentrate increases plasma antioxidant vitamins and lowers plasma homocysteine in men. *FASEB Journal* **16**: A238-A238.

Sanchez-Lozada, L., Mu, W., Roncal, C., Sautin, Y., Abdelmalek, M., Reungjui, S., Le, M., Nakagawa, T., Lan, H., Yu, X. and Johnson, R. (2010). Comparison of free fructose and glucose to sucrose in the ability to cause fatty liver. *European Journal of Nutrition* **49**: 1-9.

Sandberg, A. S. and Andersson, H. (1988). Effect of dietary phytase on the digestion of phytate in the stomach and small intestine of humans. *Journal of Nutrition* **118**: 469-473.

Sandberg, A.-S., Andersson, H., Carlsson, N.-G. and Sandstrom, B. (1987). Degradation products of bran phytate formed during digestion in the human small intestine: effect of extrusion cooking on digestibility. *Journal of Nutrition* **117**: 2061-2065.

Sandberg, A. S. and Andlid, T. (2002). Phytogenic and microbial phytases in human nutrition. *International Journal of Food Science and Technology* **37**: 823-833.

Sanders, L. M. and Zeisel, S. H. (2007). Choline. *Nutrition Today* **42**: 181-186.

Sanz, M. L., Villamiel, M. and Martinez-Castro, I. (2004). Inositols and carbohydrates in different fresh fruit juices. *Food Chemistry* **87**: 325-328.

Schade, H. and Saltman, P. (1959). Influence of nicotinic acid on hepatic cholesterol synthesis in rabbits. *Proceedings of the Society for Experimental Biology and Medicine* **102**: 265-267.

Schaefer, A. E., McKibbin, J. M. and Elvehjem, C. A. (1942). Pantothenic acid deficiency studies in dogs. *Journal of Biological Chemistry* **143**: 321-330.

Scharrer, E. and Langhans, W. (1986). Control of food intake by fatty acid oxidation. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology* **250**: R1003-1006.

Schatzkin, A., Park, Y., Leitzmann, M. F., Hollenbeck, A. R. and Cross, A. J. (2008). Prospective study of dietary fiber, whole grain foods, and small intestinal cancer. *Gastroenterology* **135**: 1163-1167.

Schneeman, B. O. and Richter, D. (1993). Changes in plasma and hepatic lipids, small-intestinal histology and pancreatic-enzyme activity due to aging and dietary fiber in rats. *Journal of Nutrition* **123**: 1328-1337.

Schön, H. (1958). Effect of nicotinic acid on the cholesterol contents of rat-livers. *Nature* **182**: 534.

Schwarz, J. M., Chen, T. W. and Linfoot, P. (1999). Effect of hydroxycitrate on hepatic *de novo* lipogenesis, gluconeogenesis and glucose production in obese hyperinsulinemic subjects. *Circulation* **100 (Suppl. I)**: 196-197 (abstract n°1015).

Schweikart, J., Reimann, J. and Schön, C. (2009). Investigation of niacin on parameters of metabolism in a physiologic dose: randomized, double-blind clinical trial with three different dosages. *International Journal of Food Sciences and Nutrition* **60**: 192 - 202.

Schweizer, T. F., Horman, I. and Würsch, P. (1978). Low molecular weight carbohydrates from leguminous seeds; a new disaccharide: Galactopinitol. *Journal of the Science of Food and Agriculture* **29**: 148-154.

Schwenk, T. L. and Fisher, M. (1994). Hepatitis caused by low-dose sustained-release niacin. *Journal of the American Board* of *Family Practice* **7**: 242-244.

Scriban, R. (1970). Vitamins of barley, malt and beer. *Annales de la Nutrition et de l'Alimentation* **24**: B377-B399.

Sealls, W., Gonzalez, M., Brosnan, M. J., Black, P. N. and DiRusso, C. C. (2008). Dietary polyunsaturated fatty acids (C18:2 ω6 and C18:3 ω3) do not suppress hepatic lipogenesis. *Biochimica et Biophysica Acta-Molecular and Cell Biology of Lipids* **1781**: 406-414.

Seetharamaiah, G. S. and Chandrasekhara, N. (1988). Hypocholesterolemic activity of oryzanol in rats. *Nutrition Reports International* **38**: 927-935.

Seetharamaiah, G. S. and Chandrasekhara, N. (1993). Comparative hypocholesterolemic activities of oryzanol, curcumin and ferulic acid in rats. *Journal of Food Science and Technology-Mysore* **30**: 249-252.

Seifert, R. M. (1972). Analysis of myoinositol in dry beans by gas-chromatography of its hexaacetate. *Journal of the Association of Official Analytical Chemists* **55**: 1194-1198.

Sekiya, M., Yahagi, N., Matsuzaka, T., Najima, Y., Nakakuki, M., Nagai, R., Ishibashi, S., Osuga, J.-i., Yamada, N. and Shimano, H. (2003). Polyunsaturated fatty acids ameliorate hepatic steatosis in obese mice by SREBP-1 suppression. *Hepatology* **38**: 1529-1539.

Seline, K. G. and Johein, H. (2007). The determination of L-carnitine in several food samples. *Food Chemistry* **105**: 793-804.

Sener, G., Balkan, J., Cevikbas, U., Keyer-Uysal, M. and Uysal, M. (2004). Melatonin reduces cholesterol accumulation and prooxidant state induced by high cholesterol diet in the plasma, the liver and probably in the aorta of C57BL/6J mice. *Journal of Pineal Research* **36**: 212-216.

Seppala-Lindroos, A., Vehkavaara, S., Hakkinen, A.-M., Goto, T., Westerbacka, J., Sovijarvi, A., Halavaara, J. and Yki-Jarvinen, H. (2002). Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. *Journal of Clinical Endocrinology and Metabolism* **87**: 3023-3028.

Shamsuddin, A. M. (2002). Anti-cancer function of phytic acid. *International Journal of Food Science and Technology* **37**: 769-782.

Shara, M., Ohia, S., Schmidt, R., Yasmin, T., Zardetto-Smith, A., Kincaid, A., Bagchi, M., Chatterjee, A., Bagchi, D. and Stohs, S. (2004). Physico-chemical properties of a novel (-)-

hydroxycitric acid extract and its effect on body weight, selected organ weights, hepatic lipid peroxidation and DNA fragmentation, hematology and clinical chemistry, and histopathological changes over a period of 90 days. *Molecular and Cellular Biochemistry* **260**: 171-186.

Shara, M., Ohia, S. E., Yasmin, T., Zardetto-Smith, A., Kincaid, A., Bagchi, M., Chatterjee, A., Bagchi, D. and Stohs, S. J. (2003). Dose- and time-dependent effects of a novel (-)-hydroxycitric acid extract on body weight, hepatic and testicular lipid peroxidation, DNA fragmentation and histopathological data over a period of 90 days. *Molecular and Cellular Biochemistry* **254**: 339-346.

Sharabi, Y. and Eldad, A. (2000). Nonalcoholic fatty liver disease is associated with hyperlipidemia and obesity. *American Journal of Medicine* **109**: 171-171.

Shechter, M., Merz, C. N. B., Paul-Labrador, M., Meisel, S. R., Rude, R. K., Molloy, M. D., Dwyer, J. H., Shah, P. K. and Kaul, S. (1999). Oral magnesium supplementation inhibits platelet-dependent thrombosis in patients with coronary artery disease. *American Journal of Cardiology* **84**: 152-156.

Shepherd, J., Packard, C. J., Patsch, J. R. and Gotto, A. M. (1979). Effects of nicotinic-acid therapy on plasma high-density lipoprotein subfraction distribution and composition and on apolipoprotein a metabolism. *Journal of Clinical Investigation* **63**: 858-867.

Shi, Z., Hu, X., Yuan, B., Hu, G., Pan, X., Dai, Y., Byles, J. E. and Holmboe-Ottesen, G. (2008). Vegetable-rich food pattern is related to obesity in China. *International Journal of Obesity* **32**: 975-984.

Shieh, J., Wu, H., Cheng, K. and Cheng, J. (2009). Melatonin ameliorates high fat diet-induced diabetes and stimulates glycogen synthesis via a PKCζ-Akt-GSK3β pathway in hepatic cells. *Journal of Pineal Research* **47**: 339-344.

Shils, M. E. and Stewart, W. B. (1954). Development of portal fatty liver in rats on corn diets - response to lipotropic agents. *Proceedings of the Society for Experimental Biology and Medicine* **85**: 298-303.

Shimada, M., Hashimoto, E., Taniai, M., Hasegawa, K., Okuda, H., Hayashi, N., Takasaki, K. and Ludwig, J. (2002). Hepatocellular carcinoma in patients with non-alcoholic steatohepatitis. *Journal of Hepatology* **37**: 154-160.

Shimizu, H., Oh-I, S., Okada, S. and Mori, M. (2007). Leptin Resistance and Obesity. *Endocrine Journal* **54**: 17-26.

Shimotoyodome, A., Haramizu, S., Inaba, M., Murase, T. and Tokimitsu, I. (2005). Exercise and green tea extract stimulate fat oxidation and prevent obesity in mice. *Medicine and Science in Sports and Exercise* **37**: 1884-1892.

Silverman, J. F., Obrien, K. F., Long, S., Leggett, N., Khazanie, P. G., Pories, W. J., Norris, H. T. and Caro, J. F. (1990). Liver pathology in morbidly obese patients with and without diabetes. *American Journal of Gastroenterology* **85**: 1349-1355.

Silverman, J. F., Pories, W. J. and Caro, J. F. (1989). Liver pathology in diabetes-mellitus and morbid-obesity - clinical, pathological, and biochemical considerations. *Pathology Annual* **24**: 275-302.

Singal, S. A. and Eckstein, H. C. (1939). Supplementary proteins and amino acids and dietary production of fatty livers in mice. *Proceedings of the Society for Experimental Biology and Medicine* **41**: 512-513.

Singal, S. A., Hazan, S. J., Sydenstricker, V. P. and Littlejohn, J. M. (1953). The production of fatty livers in rats on threonine- and lysine-deficient diets. *Journal of Biological Chemistry* **200**: 867-874.

Singh, U., Yokota, K., Gupta, C. and Shinozuka, H. (1990). Choline deficiency activates phospholipases A2 and C in rat liver without affecting the activity of protein kinase C. *Journal of Nutritional Biochemistry* **1**: 434-439.

Siripurkpong, P. and Na-Bangehang, K. (2009). Effects of niacin and chromium on the expression of ATP-binding cassette transporter A1 and apolipoprotein A-1 genes in HepG2 cells. *Journal of Nutritional Biochemistry* **20**: 261-268.

Slavin, J. (2003). Why whole grains are protective: biological mechanisms. *Proceedings of the Nutrition Society* **62**: 129-134.

Slow, S., Donaggio, M., Cressey, P. J., Lever, M., George, P. M. and Chambers, S. T. (2005). The betaine content of New Zealand foods and estimated intake in the New Zealand diet. *Journal of Food Composition and Analysis* **18**: 473-485.

Smith, C. M. and Song, W. O. (1996). Comparative nutrition of pantothenic acid. *Journal of Nutritional Biochemistry* **7**: 312-321.

Song, B. J., Moon, K. H., Olsson, N. U. and Salem, N. (2008). Prevention of alcoholic fatty liver and mitochondrial dysfunction in the rat by long-chain poly unsaturated fatty acids. *Journal of Hepatology* **49**: 262-273.

Song, B.-L. and DeBose-Boyd, R. A. (2006). Insig-dependent ubiquitination and degradation of 3-hydroxy-3-methylglutaryl coenzyme A reductase stimulated by α- and γ-tocotrienols. *Journal of Biological Chemistry* **281**: 25054-25061.

Sorrell, M. F., Baker, H., Tuma, D. J., Frank, O. and Barak, A. J. (1976). Potentiation of ethanol fatty liver in rats by chronic administration of nicotinic-acid. *Biochimica et Biophysica Acta* **450**: 231-238.

Sosulski, F. W., Elkowicz, L. and Reichert, R. D. (1982). Oligosaccharides in eleven legumes and their air-classified protein and starch fractions. *Journal of Food Science* **47**: 498-502.

Souci, S. W., Fachmann, W. and Kraut, H. (2008). Food composition and nutritional tables, 7th revised and completed edition. Taylor and Francis, Medpharm Scientific Publishers, Stuttgart, Germany.

Spadaro, L., Magliocco, O., Spampinato, D., Piro, S., Oliveri, C., Alagona, C., Papa, G., Rabuazzo, A. M. and Purrello, F. (2008). Effects of n-3 polyunsaturated fatty acids in subjects with nonalcoholic fatty liver disease. *Digestive and Liver Disease* **40**: 194-199.

Spaniol, M., Kaufmann, P., Beier, K., Wuthrich, J., Torok, M., Scharnagl, H., Marz, W. and Krahenbuhl, S. (2003). Mechanisms of liver steatosis in rats with systemic carnitine deficiency due to treatment with trimethylhydraziniumpropionate. *Journal of Lipid Research* **44**: 144-153.

Sreekumar, R., Wiesner, R. H., Nagorney, D. M., Rosen, C. B. and Charlton, M. R. (2001). Unique hepatic gene expression in NASH - Candidates for a genetic basis of disease. *Gastroenterology* **120**: 580.

St. Greif, von and Wenning, F. (1954). Lipotropic effects of vitamin B12 and folic acid. *Wiener Medizinische Wochenschrift* **104**: 35-36.

Stanner, S., Hughes, J., Kelly, C. and Buttriss, J. (2004). A review of the epidemiological evidence for the 'antioxidant hypothesis'. *Public Health Nutrition* **7**: 407-422.

Steadman, K. J., Burgoon, M. S., Schuster, R. L., Lewis, B. A., Edwardson, S. E. and Obendorf, R. L. (2000). Fagopyritols, D-*chiro*-inositol, and other soluble carbohydrates in buckwheat seed milling fractions. *Journal of Agricultural and Food Chemistry* **48**: 2843-2847.

Steffen, L. M., Jacobs, D. R., Jr., Stevens, J., Shahar, E., Carithers, T. and Folsom, A. R. (2003). Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *American Journal of Clinical Nutrition* **78**: 383-390.

Stella, C., Beckwith-Hall, B., Cloarec, O., Holmes, E., Lindon, J. C., Powell, J., van der Ouderaa, F., Bingham, S., Cross, A. J. and Nicholson, J. K. (2006). Susceptibility of human metabolic phenotypes to dietary modulation. *Journal of Proteome Research* **5**: 2780-2788.

Stern, R. H. (2007). The role of nicotinic acid metabolites in flushing and hepatotoxicity. *Journal of Clinical Lipidology* **1**: 191-193.

Stewart, J. R., Fryer, E. B. and Fryer, H. C. (1987). Effects of dietary fiber, carbohydrate, lipid and protein-levels on serum and liver lipids in rats. *Journal of Nutrition* **117**: 650-659.

Story, J. A., Baldino, A., Czarnecki, S. K. and Kritchevsky, D. (1981). Modification of liver cholesterol accumulation by dietary fiber in rats. *Nutrition Reports International* **24**: 1213-1219.

Subramanian, P., Mirunalini, S., Pandi-Perumal, S. R., Trakht, I. and Cardinali, D. P. (2007). Melatonin treatment improves the antioxidant status and decreases lipid content in brain and liver of rats. *European Journal of Pharmacology* **571**: 116-119.

Subramanian, V., Byrne, J. J., Kaye, P., Daykin, C. A. and Aithal, G. P. (2008). Serum metabolomics reveals novel metabolic markers of non alcoholic fatty liver disease. *Hepatology* **48**: 811A (Abstract N°1130).

Sugano, M., Tanaka, K. and Ide, T. (1982). Secretion of cholesterol, triglyceride and apolipoprotein A-I by isolated perfused liver from rats fed soybean protein and casein or their amino acid mixtures. *Journal of Nutrition* **112**: 855-862.

Sugatani, J., Wada, T., Osabe, M., Yamakawa, K., Yoshinari, K. and Miwa, M. (2006). Dietary inulin alleviates hepatic steatosis and xenobiotics-induced liver injury in rats fed a high-fat and high-sucrose diet: association with the suppression of hepatic cytochrome P450 and hepatocyte nuclear factor 4 alpha expression. *Drug Metabolism and Disposition* **34**: 1677-1687.

Sugiyama, K., Kanamori, H., Akachi, T. and Yamakawa, A. (1996). Amino acid composition of dietary proteins affects plasma cholesterol concentration through alteration of hepatic phospholipid metabolism in rats fed a cholesterol-free diet. *Journal of Nutritional Biochemistry* **7**: 40-48.

Suh, M. H., Yoo, S. H., Chang, P. S. and Lee, H. G. (2005). Antioxidative activity of microencapsulated γ-oryzanol on high cholesterol-fed rats. *Journal of Agricultural and Food Chemistry* **53**: 9747-9750.

Sullivan, A., Triscari, J., Hamilton, J. and Miller, O. (1974a). Effect of (-)-hydroxycitrate upon the accumulation of lipid in the rat: II. Appetite. *Lipids* **9**: 129-134.

Sullivan, A., Triscari, J., Hamilton, J., Miller, O. and Wheatley, V. (1974b). Effect of (-)-hydroxycitrate upon the accumulation of lipid in the rat: I. Lipogenesis. *Lipids* **9**: 121-128.

Sullivan, A., Triscari, J. and Spiegel, J. (1977). Metabolic regulation as a control for lipid disorders. II. Influence of (-)-hydroxycitrate on genetically and experimentally induced hypertriglyceridemia in the rat. *American Journal of Clinical Nutrition* **30**: 777-784.

Sullivan, A. C., Hamilton, J. G., Miller, O. N. and Wheatley, V. R. (1972). Inhibition of lipogenesis in rat liver by (-)-hydroxycitrate. *Archives of Biochemistry and Biophysics* **150**: 183-190.

Sullivan, C. and Triscari, J. (1977). Metabolic regulation as a control for lipid disorders. I. Influence of (--)-hydroxycitrate on experimentally induced obesity in the rodent. *American Journal of Clinical Nutrition* **30**: 767-776.

Summers, P. S. and Weretilnyk, E. A. (1993). Choline synthesis in spinach in relation to salt stress. *Plant Physiology* **103**: 1269-1276.

Sundkvist, G., Dahlin, L. B., Nilsson, H., Eriksson, K. F., Lindgarde, F., Rosen, I., Lattimer, S. A., Sima, A. A. F., Sullivan, K. and Greene, D. A. (2000). Sorbitol and *myo*-inositol levels and morphology of sural nerve in relation to peripheral nerve function and clinical neuropathy in men with diabetic, impaired, and normal glucose tolerance. *Diabetic Medicine* **17**: 259-268.

Suzuki, K., Nakamura, T., Fujita, M., Iwami, T., Abe, M. and Okada, M. (1976). Factors affecting liver lipid-content in pyridoxine-deficient rats. 1. Dietary-protein levels. *Journal of Nutritional Science and Vitaminology* **22**: 291-298.

Takeuchi, H., Nakamoto, T., Mori, Y., Kawakami, M., Mabuchi, H., Ohishi, Y., Ichikawa, N., Koike, A. and Masuda, K. (2001). Comparative effects of dietary fat types on hepatic enzyme activities related to the synthesis and oxidation of fatty acid and to lipogenesis in rats. *Bioscience, Biotechnology, and Biochemistry* **65**: 1748-1754.

Tandy, S., Chung, R. W. S., Wat, E., Kamili, A., Berge, K., Griinari, M. and Cohn, J. S. (2009). Dietary krill oil supplementation reduces hepatic steatosis, glycemia, and hypercholesterolemia in high-fat-fed mice. *Journal of Agricultural and Food Chemistry* **57**: 9339-9345.

Tato, F., Vega, G. L. and Grundy, S. M. (1998). Effects of crystalline nicotinic acid-induced hepatic dysfunction on serum low-density lipoprotein cholesterol and lecithin cholesteryl acyl transferase. *American Journal of Cardiology* **81**: 805-807.

Taysi, S., Koc, M., Buyukokuroglu, M. E., Altinkaynak, K. and Sahin, Y. N. (2003). Melatonin reduces lipid peroxidation and nitric oxide during irradiation-induced oxidative injury in the rat liver. *Journal of Pineal Research* **34**: 173-177.

The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group (1994). The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *New England Journal of Medicine* **330**: 1029-1035.

Thomas, M., Leelamma, S. and Kurup, P. A. (1983). Effect of blackgram fiber (phaseolus-mungo) on hepatic hydroxymethylglutaryl-CoA reductase-activity, cholesterogenesis and cholesterol degradation in rats. *Journal of Nutrition* **113**: 1104-1108.

Thompson, H. J., Heimendinger, J., Diker, A., O'Neill, C., Haegele, A., Meinecke, B., Wolfe, P., Sedlacek, S., Zhu, Z. J. and Jiang, W. Q. (2006). Dietary botanical diversity affects the reduction of oxidative biomarkers in women due to high vegetable and fruit intake. *Journal of Nutrition* **136**: 2207-2212.

Thompson, H. J., Heimendinger, J., Gillette, C., Sedlacek, S. M., Haegele, A., O'Neill, C. and Wolfe, P. (2005). *In vivo* investigation of changes in biomarkers of oxidative stress induced by plant food rich diets. *Journal of Agricultural and Food Chemistry* **53**: 6126-6132.

Thor, H., Smith, M. T., Hartzell, P., Bellomo, G., Jewell, S. A. and Orrenius, S. (1982). The metabolism of menadione (2-methyl-1,4-naphtoquinone) by isolated hepatocytes. A study of the implication of oxidative stress in intact cells. *Journal of Biological Chemistry* **257**: 12419-12425.

Thuillier, J. (1956). Betaine, a lipotropic factor. *Le Concours Médical* **78**: 243-244.

Thurston, J. H. and Hauhart, R. E. (1992). Amelioration of adverse-effects of valproic acid on ketogenesis and liver coenzyme-a metabolism by cotreatment with pantothenate and carnitine in developing mice - possible clinical-significance. *Pediatric Research* **31**: 419-423.

Tokmakjian, S. and Haines, D. S. M. (1979). Influence of dietary choline intake upon liver ethanolamine metabolism. *Canadian Journal of Biochemistry* **57**: 566-572.

Tomita, K., Okuhara, Y., Shigematsu, N., Suh, H. and Lim, K. (2003). (-)-Hydroxycitrate ingestion increases fat oxidation during moderate intensity exercise in untrained men. *Bioscience, Biotechnology and Biochemistry* **67**: 1999-2001.

Toussant, M. J., Wilson, M. D. and Clarke, S. D. (1981). Coordinate suppression of liver acetyl-CoA carboxylase and fatty acid synthetase by polyunsaturated fat. *Journal of Nutrition* **111**: 146-153.

Tucker, H. F. and Eckstein, H. C. (1937). The effect of supplementary methionine and cystine on the production of fatty livers by diet. *Journal of Biological Chemistry* **121**: 479-484.

Tucker, H. F. and Eckstein, H. C. (1938). The effect of supplementary lysine, methionine, and cystine on the production of fatty livers by high fat diets containing gliadin. *Journal of Biological Chemistry* **126**: 117-123.

Turchetto, E., Infante, R. and Sechi, A. M. (1955). Effect of thyroxin on lipotropic activity of pantothenic acid. *Bollettino- Societa Italiana Biologia Sperimentale (Napoli)* **31**: 233-234.

Tyner, E. P., Lewis, H. B. and Eckstein, H. C. (1950). Niacin and the ability of cystine to augment deposition of liver fat. *Journal of Biological Chemistry* **187**: 651-654.

USDA (2004). USDA database for the proanthocyanidin content of selected foods. United States Department of Agriculture (USDA). <http://www.nal.usda.gov/fnic/foodcomp/Data/PA/PA.pdf>.

USDA (2005a). USDA national nutrient database for standard reference, release 18. United States Department of Agriculture (USDA). <http://www.nal.usda.gov/fnic/foodcomp/Data/SR18/reports/sr18page.htm>

USDA (2005b). USDA national nutrient database for standard reference, release 18: cereal grains and pasta. United States Department of Agriculture (USDA). < http://www.nal.usda.gov/fnic/foodcomp/Data/SR18/reports/sr18fg20.pdf>.

USDA (2005c). USDA national nutrient database for standard reference, release 18: legumes and legume products. United States Department of Agriculture (USDA). < http://www.nal.usda.gov/fnic/foodcomp/Data/SR18/reports/sr18fg16.pdf>.

USDA (2005d). USDA national nutrient database for standard reference, release 18: nuts and seed products. United States Department of Agriculture (USDA). < http://www.nal.usda.gov/fnic/foodcomp/Data/SR18/reports/sr18fg12.pdf>.

USDA (2005e). USDA national nutrient database for standard reference, release 18: fats and oils. United States Department of Agriculture (USDA). < http://www.nal.usda.gov/fnic/foodcomp/Data/SR18/reports/sr18fg04.pdf>.

USDA (2007). USDA database for the flavonoid content of selected foods, release 2.1. United States Department of Agriculture (USDA). <http://www.nal.usda.gov/fnic/foodcomp/Data/Flav/Flav02-1.pdf>.

USDA(2008). USDA database for the isoflavone content of selected foods, release 2.0. United States Department of Agriculture (USDA).< http://www.ars.usda.gov/SP2UserFiles/Place/12354500/Data/isoflav/Isoflav_R2.pdf>.

USDA (2008). USDA database for the choline content of common foods, release 2. United States Department of Agriculture (USDA). <http://www.nal.usda.gov/fnic/foodcomp/Data/Choline/Choln02.pdf>.

Ueshima, T., Shigata, Y., Wada, M., Oji, K. and Yoshida, T. (1956). Studies on the metabolism of pantothenic acid in liver damage. I. Urinary excretion of pantothenic acid in patients with various liver diseases and its correlation with liver function. *Journal of Vitaminology* **2**: 299-306.

Ueshima, T., Unno, H., Shigeta, Y., Wada, M., Oji, K. and Yoshida, T. (1958). Studies on the metabolism of pantothenic acid in liver damage. II. Pantothenic acid treatment in patients with liver disease. *Journal of Vitaminology* **4**: 149-155.

Vaishwanar, I., Jiddewar, G. G., Shukla, R. D. and Kowale, C. N. (1972). Effect of nicotinic-acid on serum and hepatic lipids in experimentally induced fatty liver. *Indian Journal of Experimental Biology* **10**: 428-430.

Valtuena, S., Pellegrini, N., Ardigo, D., Del Rio, D., Numeroso, F., Scazzina, F., Monti, L., Zavaroni, I. and Brighenti, F. (2006). Dietary glycemic index and liver steatosis. *American Journal of Clinical Nutrition* **84**: 136-142.

van de Vijver, L. P. L., van den Bosch, L. M. C., van den Brandt, P. A. and Goldbohm, R. A. (2009). Whole-grain consumption, dietary fibre intake and body mass index in the Netherlands cohort study. *European Journal of Clinical Nutrition* **63**: 31-38.

Van den Veyver, I. B. (2002). Genetic effects of methylation diets. *Annual Review of Nutrition* **22**: 255-282.

van der Hoorn, J. W. A., de Haan, W., Berbee, J. F. P., Havekes, L. M., Jukema, J. W., Rensen, P. C. N. and Princen, H. M. G. (2008). Niacin increases hdl by reducing hepatic expression and plasma levels of cholesteryl ester transfer protein in APOE*3Leiden.CETP mice. *Arteriosclerosis Thrombosis and Vascular Biology* **28**: 2016-2022.

van Duijnhoven, F. J., Bueno-De-Mesquita, H. B., Ferrari, P., Jenab, M., Boshuizen, H. C., Ros, M. M., Casagrande, C., Tjonneland, A., Olsen, A., Overvad, K., Thorlacius-Ussing, O., Clavel-Chapelon, F., Boutron-Ruault, M.-C., Morois, S., Kaaks, R., Linseisen, J., Boeing, H., Nothlings, U., Trichopoulou, A., Trichopoulos, D., Misirli, G., Palli, D., Sieri, S., Panico, S., Tumino, R., Vineis, P., Peeters, P. H., van Gils, C. H., Ocke, M. C., Lund, E., Engeset, D., Skeie, G., Suarez, L. R., Gonzalez, C. A., Sanchez, M.-J., Dorronsoro, M., Navarro, C., Barricarte, A., Berglund, G., Manjer, J., Hallmans, G., Palmqvist, R., Bingham, S. A., Khaw, K.-T., Key, T. J., Allen, N. E., Boffetta, P., Slimani, N., Rinaldi, S., Gallo, V., Norat, T. and Riboli, E. (2009). Fruit, vegetables, and colorectal cancer risk: the European Prospective Investigation into Cancer and Nutrition. *American Journal of Clinical Nutrition* **89**: 1441-1452.

van Hung, L. (1953). Acetylation of p-aminobenzoic acid in fatty degeneration of the liver in rat. *Journal of Physiology - Paris* **45**.

van Loon, L. J. C., van Rooijen, J. J. M., Niesen, B., Verhagen, H., Saris, W. H. M. and Wagenmakers, A. J. M. (2000). Effects of acute (-)-hydroxycitrate supplementation on substrate metabolism at rest and during exercise in humans. *American Journal of Clinical Nutrition* **72**: 1445-1450.

Varady, K. A., Wang, Y. and Jones, P. J. H. (2003). Role of policosanols in the prevention and treatment of cardiovascular disease. *Nutrition Reviews* **61**: 376-383.

Venables, M. C., Hulston, C. J., Cox, H. R. and Jeukendrup, A. E. (2008). Green tea extract ingestion, fat oxidation, and glucose tolerance in healthy humans. *American Journal of Clinical Nutrition* **87**: 778-784.

Venn, B. J. and Mann, J. I. (2004). Cereal grains, legumes and diabetes. *European Journal of Clinical Nutrition* **58**: 1443-1461.

Villegas, R., Shu, X. O., Gao, Y.-T., Yang, G., Elasy, T., Li, H. and Zheng, W. (2008). Vegetable but not fruit consumption reduces the risk of type 2 diabetes in chinese women. *Journal of Nutrition* **138**: 574-580.

Vucenik, I. and Shamsuddin, A. M. (1994). [^{3}H]inositol hexaphosphate (phytic acid) is rapidly absorbed and metabolized by murine and human malignant cells *in vitro*. *Journal of Nutrition* **124**: 861-868.

Vuppalanchi, R. and Chalasani, N. (2009). Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. *Hepatology* **49**: 306-317.

Walsh, M. C., Brennan, L., Pujos-Guillot, E., Sebedio, J. L., Scalbert, A., Fagan, A., Higgins, D. G. and Gibney, M. J. (2007). Influence of acute phytochemical intake on human urinary metabolomic profiles. *American Journal of Clinical Nutrition* **86**: 1687-1693.

Wang, W., Basinger, A., Neese, R. A., Shane, B., Myong, S. A., Christiansen, M. and Hellerstein, M. K. (2001). Effect of nicotinic acid administration on hepatic very low density lipoprotein-triglyceride production. *American Journal of Physiology-Endocrinology and Metabolism* **280**: E540-E547.

Wang, X., Song, K.-S., Guo, Q.-X. and Tian, W.-X. (2003). The galloyl moiety of green tea catechins is the critical structural feature to inhibit fatty-acid synthase. *Biochemical Pharmacology* **66**: 2039-2047.

Wang, X. and Tian, W. (2001). Green tea epigallocatechin gallate: a natural inhibitor of fatty-acid synthase. *Biochemical and Biophysical Research Communications* **288**: 1200-1206.

Warembourg, H. and Bertrand, M. (1964). Clinical study of a lipotropic formula: Ornitaine. *Lille Med* **37**: 285-289.

Watson, J. A., Fang, M. and Lowenstein, J. M. (1969). Tricarballylate and hydroxycitrate: substrate and inhibitor of ATP: Citrate oxaloacetate lyase. *Archives of Biochemistry and Biophysics* **135**: 209-217.

Wegkamp, A., van Oorschot, W., de Vos, W. M. and Smid, E. J. (2007). Characterization of the role of para-aminobenzoic acid biosynthesis in folate production by Lactococcus lactis. *Applied and Environmental Microbiology* **73**: 2673-2681.

Welsh, A. L. and Ede, M. (1961). Inositol hexanicotinate for improved nicotinic acid therapy. Preliminary report. *International Record of Medicine* **174**: 9-15.

Weltman, M. D., Farrell, G. C. and Liddle, C. (1996). Increased hepatocyte CYP2E1 expression in a rat nutritional model of hepatic steatosis with inflammation. *Gastroenterology* **111**: 1645-1653.

Wenru, T., Changle, Z., Li, S. J., Zhou, J. P., Yang, H. J., Wang, T., Hu, Q. D., Bai, Y. M., Ma, C. C. and Yang, D. J. (1994). Efficacy of oral nicotinic acid and choline in the treatment and prevention of fatty liver in dairy cow. *Journal of Northeast Agricultural University* **1**: 42-49.

Williams, M. A., Chu, L. C., McIntosh, D. J. and Hincenbe.I (1968). Effects of dietary fat level on pantothenate depletion and liver fatty acid composition in rat. *Journal of Nutrition* **94**: 377-382.

Williams, P. G., Grafenauer, S. J. and O'Shea, J. E. (2008). Cereal grains, legumes, and weight management: a comprehensive review of the scientific evidence. *Nutrition Reviews* **66**: 171-182.

Wirtschafter, Z. T. and Walsh, J. R. (1962). Hepatocellular lipoid changes in pantothenic acid deficiency. *American Journal of Clinical Nutrition* **10**: 525-530.

Wishart, D. S., Tzur, D., Knox, C., Eisner, R., Guo, A. C., Young, N., Cheng, D., Jewell, K., Arndt, D., Sawhney, S., Fung, C., Nikolai, L., Lewis, M., Coutouly, M. A., Forsythe, I., Tang, P., Shrivastava, S., Jeroncic, K., Stothard, P., Amegbey, G., Block, D., Hau, D. D., Wagner, J., Miniaci, J., Clements, M., Gebremedhin, M., Guo, N., Zhang, Y., Duggan, G. E., MacInnis, G. D., Weljie, A. M., Dowlatabadi, R., Bamforth, F., Clive, D., Greiner, R., Li, L., Marrie, T., Sykes, B. D., Vogel, H. J. and Querengesser, L. (2007). HMDB: the human metabolome database. *Nucleic Acids Research* **35**: D521-D526.

Wojcicki, J., Samochowiec, L., Kadlubowska, D. and Lutomski, J. (1977). Studies on saponin fraction from root of *Aralia Mandshurica* Rupr. et Maxim. Part IV. Influence of saponosides on content of lipids in blood serum and liver in experimental hyperlipemia. *Herba Polonica* **23**: 285-289.

Woodruff, C. W., Clark, S. L., Jr. and Bridgeforth, E. B. (1953). Folic acid deficiency in the Guinea pig. *Journal of Nutrition* **51**: 23-34.

Wright, R. S., Anderson, J. W. and Bridges, S. R. (1990). Propionate inhibits hepatocyte lipid-synthesis. *Proceedings of the Society for Experimental Biology and Medicine* **195**: 26-29.

Wu, D., Keller, W. L. and Park, C. S. (1998). Lipotrope deficiency inhibits cell growth and induces programmed cell death in human breast cancer cell line MCF-7. *Nutrition and Cancer-an International Journal* **32**: 13-19.

Wu, H., Dai, Q., Shrubsole, M. J., Ness, R. M., Schlundt, D., Smalley, W. E., Chen, H., Li, M., Shyr, Y. and Zheng, W. (2009). Fruit and vegetable intakes are associated with lower risk of colorectal adenomas. *Journal of Nutrition* **139**: 340-344.

Wu, L. L. and Wu, J. T. (2002). Hyperhomocysteinemia is a risk factor for cancer and a new potential tumor marker. *Clinica Chimica Acta* **322**: 21-28.

Wu, X., Beecher, G. R., Holden, J. M., Haytowitz, D. B., Gebhardt, S. E. and Prior, R. L. (2004a). Lipophilic and hydrophilic antioxidant capacities of common foods in the united states. *Journal of Agricultural and Food Chemistry* **52**: 4026-4037.

Wu, X. L., Gu, L. W., Holden, J., Haytowitz, D. B., Gebhardt, S. E., Beecher, G. and Prior, R. L. (2004b). Development of a database for total antioxidant capacity in foods: a preliminary study. *Journal of Food Composition and Analysis* **17**: 407-422.

Wutzke, K. D. and Lorenz, H. (2004). The effect of L-carnitine on fat oxidation, protein turnover, and body composition in slightly overweight subjects. *Metabolism-Clinical and Experimental* **53**: 1002-1006.

Xin, Y. N., Xuan, S. Y., Zhang, J. H., Zheng, M. H. and Guan, H. S. (2008). Omega-3 polyunsaturated fatty acids: a specific liver drug for non-alcoholic fatty liver disease (NAFLD). *Medical Hypotheses* **71**: 820-821.

Yagi, K. and Kotaki, A. (1969). The effect of massive doses of *myo*-inositol on hepatic phospholipid metabolism. *Annals of the New York Academy of Sciences* **165**: 710-725.

Yang, J., Xu, G. W., Zheng, Y. F., Kong, H. W., Pang, T., Lv, S. and Yang, Q. (2004). Diagnosis of liver cancer using HPLC-based metabonomics avoiding false-positive result from hepatitis and hepatocirrhosis diseases. *Journal of Chromatography B-Analytical Technologies in the Biomedical and Life Sciences* **813**: 59-65.

Yang, L. and Kadowaki, M. (2009). Effects of rice proteins from two cultivars, koshihikari and shunyo, on hepatic cholesterol secretion by isolated perfused livers of rats fed cholesterol-enriched diets. *Annals of Nutrition and Metabolism* **54**: 283-290.

Yang, L., Kumagai, T., Kawamura, H., Watanabe, T., Kubota, M., Fujimura, S., Watanabe, R. and Kadowaki, M. (2007). Effects of rice proteins from two cultivars, koshihikari and shunyo, on

cholesterol and triglyceride metabolism in growing and adult rats. *Bioscience, Biotechnology, and Biochemistry* **71**: 694-703.

Yang, M.-Y., Peng, C.-H., Chan, K.-C., Yang, Y.-S., Huang, C.-N. and Wang, C.-J. (2010). The hypolipidemic effect of *Hibiscus sabdariffa* polyphenols via inhibiting lipogenesis and promoting hepatic lipid clearance. *Journal of Agricultural and Food Chemistry* **58**: 850-859.

Yao, Z. and Vance, D. (1988). The active synthesis of phosphatidylcholine is required for very low density lipoprotein secretion from rat hepatocytes. *Journal of Biological Chemistry* **263**: 2998-3004.

Yao, Z. and Vance, D. (1989). Head group specificity in the requirement of phosphatidylcholine biosynthesis for very low density lipoprotein secretion from cultured hepatocytes. *Journal of Biological Chemistry* **264**: 11373-11380.

Yao, Z. and Vance, D. E. (1990). Reduction in VLDL, but not HDL, in plasma of rats deficient in choline. *Biochemistry and Cell Biology-Biochimie et Biologie Cellulaire* **68**: 552-558.

Yasuhara, M., Ohama, T., Matsuki, N., Saito, H., Shiga, J., Inoue, K., Kurokawa, K. and Teramoto, T. (1991). Induction of fatty liver by fasting in suncus. *Journal of Lipid Research* **32**: 887-891.

Yatsuji, S., Hashimoto, E., Toban, M., Takakura, M., Taniai, M., Tokushige, K., Shiratori, K., Shibata, N. and Kobayashi, M. (2006). Liver carcinogenesis in non-alcoholic steatohepatitis (NASH) - Relation to oxidative stress and apoptosis. *Gastroenterology* **130**: A819-A819.

Yeh, Y. Y. (1976). Nicotinic-acid reverses fasting ketosis by lowering level of cyclic-AMP. *Life Sciences* **18**: 33-38.

Yeh, Y.-Y. and Liu, L. (2001). Cholesterol-lowering effect of garlic extracts and organosulfur compounds: human and animal studies. *Journal of Nutrition* **131**: 989S-993.

Yeh, Y.-Y. and Yeh, S.-M. (1994). Garlic reduces plasma lipids by inhibiting hepatic cholesterol and triacylglycerol synthesis. *Lipids* **29**: 189-193.

Yokoishi, T. and Tanimoto, S. (1994). Seed-germination of the halophyte *Suaeda japonica* under salt stress. *Journal of Plant Research* **107**: 385-388.

Yokota, F., Esashi, T., Takahash.S and Suzue, R. (1974). Effects of excess methionine and glycine on incorporation of sodium acetate-1-^{14}C into lipid of rat liver. *Nutrition Reports International* **10**: 405-408.

York, L. W., Puthalapattu, S. and Wu, G. Y. (2009). Nonalcoholic fatty liver disease and low-carbohydrate diets. *Annual Review of Nutrition* **29**: 365-379.

Young, R. J., Lucas, C. C., Patterson, J. M. and Best, C. H. (1965). Lipotropic dose-response studies in rats: comparisons of choline, betaine, and methionine. *Canadian Journal of Biochemistry and Physiology* **34**: 713.

Youssef, J., Cunningham, M. L. and Badr, M. (1994). Down-regulation of hepatic peroxisomal beta-oxidation due to pantothenic acid-deficiency. *FASEB Journal* **8**: A736-A736.

Zeisel, S., Da Costa, K., Franklin, P., Alexander, E., Lamont, J., Sheard, N. and Beiser, A. (1991). Choline, an essential nutrient for humans. *FASEB Journal* **5**: 2093-2098.

Zeisel, S. H. (1981). Dietary choline: biochemistry, physiology, and pharmacology. *Annual Review of Nutrition* **1**: 95-121.

Zeisel, S. H. and Costa, K.-A. d. (2009). Choline: an essential nutrient for public health. *Nutrition Reviews* **67**: 615-623.

Zeisel, S. H., Mar, M. H., Howe, J. C. and Holden, J. M. (2003). Concentrations of choline-containing compounds and betaine in common foods. *Journal of Nutrition* **133**: 1302-1307.

Zhang, L.-H., Kamanna, V. S., Zhang, M. C. and Kashyap, M. L. (2008). Niacin inhibits surface expression of ATP synthase β chain in HepG2 cells: implications for raising HDL. *Journal of Lipid Research* **49**: 1195-1201.

Zilversmit, D. B. and Diluzio, N. R. (1958). The role of choline in the turnover of phospholipids. *American Journal of Clinical Nutrition* **6**: 235-241.

Zivkovic, A. M., German, J. B., Esfandiari, F. and Halsted, C. H. (2009). Quantitative lipid metabolomic changes in alcoholic micropigs with fatty liver disease. *Alcoholism-Clinical and Experimental Research* **33**: 751-758.

Figure captions

Figure 1 Molecular structure of main lipotropes and of phytochemicals for which at least one significant hepatic total lipids/fat or triglyceride content reduction has been reported in animal studies. Gamma (γ)-oryzanol is a mixture of ferulic acid esters of triterpene alcohols and sterols. *ABBREVIATIONS*: SCFA, Short-Chain Fatty Acid; PUFA: Poly-Unsaturated Fatty Acid.

Figures 2 A-D. The different potential mechanisms by which lipotropes may prevent excess fat deposits in the liver: A - The lipotropic action of choline, betaine, *myo*-inositol, methionine and folate (vitamin B9) as methyl donors in the transmethylation pathway for methionine synthesis, as phospholipids precursors for triglyceride-rich lipoprotein formation and as osmolytes possibly participating in cell volume regulation, cell shrinkage being a catabolic signal likely to decreased lipogenesis; B - The lipotropic action of pantothenic acid (vitamin B5), magnesium and carnitine in the β-oxidation pathway: pantothenic acid is precursor and constitutive of coenzyme A, magnesium is cofactor of the enzymatic reaction that allows transformation of free fatty acids into acyl-CoA while carnitine allows acyl-CoA to be transferred into mitochondria for β-oxidation; C - The multi-factorial lipotropic action of niacin that may exert by 1°) favouring carnitine synthesis from its two precursors lysine and methionine, 2°) inhibiting activity of enzymes involved in FA and TG syntheses (*i.e.* ACC and DGAT), 3°) up-regulating expression of genes that code for PPARα; and 4°) reducing the release of FFA in plasma through inhibition of catecholamine stimulation of TG lipolysis in adipose tissue; mechanisms by which niacin may inhibit cholesterol synthesis and favour and reduce efflux of respectively Apo A (HDL)- and Apo B (LDL and VLDL)-containing lipoproteins outside livers are also presented. D - The lipotropic effects of other phytochemicals which is mainly based on the up- and down-regulation of gene expression for enzymes and/or transcription factors involved respectively in FA oxidation and synthesis, but which is also based on the specific actions of fiber on incorporation of acetate into cholesterol and FA, of HCA on CCE activity inhibition, of melatonin on decreased oxidative stress and insulino-resistance and of

oligofructose on FA re-esterification inhibition. Figures 1 A-D have been mainly elaborated from results presented in Supplemental Tables 1-4. *ABBREVIATIONS*: ABCA, ATP-Binding Cassette Transporter; ACC, Acetyl-CoA Carboxylase; ACO, Acyl-CoA Oxidase; AMP, Adenosine MonoPhosphate; Apo A, Apolipoprotein A; Apo B, Apolipoprotein B; ATP, Adenosine TriPhosphate; ATPCL/CCE, ATP-Citrate Lyase/Citrate Cleavage Enzyme; BHMT, Betaine Homocysteine MethylTransferase; CE, Cholesteryl Ester; CETP, Cholesteryl Ester Transfer Protein; CoA, Coenzyme A; CPT, Carnitine Palmitoyl Transferase; DGAT, DiacylGlycerol O-AcylTransferase; FA, Fatty Acid; FAS, Fatty Acid Synthase; FC, Free Cholesterol; FFA, Free Fatty Acid; Glycerol 3-P, Glycerol 3-Phosphate; G6PDH, Glucose-6-Phosphate-DesHydrogenase; GSH, reduced glutathione; HCA, HydroxyCitric Acid; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; ME, Malic Enzyme; Mg, Magnesium; MS, Methionine Synthetase; MUFA, Mono-Unsaturated Fatty Acid; NF-κB, Nuclear Factor Kappa B; PEMT, PhosphatidylEthanolamine-*N*-MethylTransferase; PP, PyroPhosphate; PPARα, Peroxisome Proliferator Activated Receptor alpha; PUFA, PolyUnsaturated fatty Acid; SREBP, Sterol Regulatory Element Binding Protein; TC, Total Cholesterol; TG, triglyceride; THF, TetraHydroFolate; VLDL, Very Low Density Lipoprotein.

Figures 3 A-C. Percentage changes for: A - hepatic total lipids/fat content, B – triglyceride content and C - cholesterol content following lipotrope consumption by rats initially fed steatogen diet (control group). Ranges for duration of the feeding periods and percentages of lipotrope supplementation are presented in Tables 2 and 3. Red crosses and horizontal bars respectively indicate the means and the median. Concerning unsaturated FA, reductions of total/lipid and triglyceride levels have been obtained with arachidonic acid only (Supplemental Table 2). *ABBREVIATIONS*: HCA, Hydroxycitric Acid; PUFA, Poly-Unsaturated Fatty Acid

Figures 4 A-E. Percentage changes for lipogenic enzyme activities following lipotrope consumption by rats initially fed steatogen diet (control group): A – Fatty Acid Synthase (FAS); B – Malic Enzyme (ME); C – Glucose-6-Phosphate dehydrogenase (G6PDH); D – Acetyl-CoA Carboxylase (ACC), E – ATP-Citrate Lyase/Citrate Cleavage Enzyme (ATP-CL/CCE). Enzymes are those directly involved in FA synthesis, *i.e.* FAS (Fatty Acid Synthase), ACC (Acetyl-CoA Carboxylase) and ATP-CL/CCE (ATP-Citrate Lyase or Citrate Cleavage Enzyme) and those yielding $NADPH,H^+$ directly used for FA synthesis, *i.e.* ME (Malic Enzyme) and G6PDH (Glucose-6-Phosphaphate DeHydrogenase). Concerning unsaturated FA, reductions of FAS, ME and G6PDH activities have been obtained with methyl linolenate, methyl linoleate, methyl oleate and ethyl linoleate; and reduction of ACC activity with ethyl linoleate only (Supplemental Table 2). *ABBREVIATIONS*: PUFA, Poly-Unsaturated Fatty Acid

Table 1 Protective effect of PBF against chronic disease and all-cause mortality risks[1]

	All-cause mortality	Weight control/obesity	Cancers	CVD	Type 2 Diabetes
Cereals (whole-grain)	+	+	+	+	+
Legumes	+	±	±	±	±
Fruits (not juices)	±	+	±	+	±
Vegetables	±	+	±	+	+
Fruits & Vegetables	+	±	+	±	±

[1]+ indicates convincing protective effect; ± indicates that results are not sufficiently convincing or inconclusive, with studies showing both significant positive effect and no significant effect; results are only tendencies deduced from positive or no association and they do not include results of intervention studies

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Table 2 Lipotropic effects of main plant lipotropes, micronutrients and other compounds on main markers of lipid metabolism in rats

		Main lipotropes				Vitamins B			Other phytochemicals				
		Choline	Betaine	*Myo*-inositol	Methionine	Niacin	Pantothenic acid	Folates	HCA	Carnitine	Organosulfurs	MUFA/PUFA	Melatonin
TL/fat content	n[a]	9	2	6	6	3	1	1	3	7	1	1	-[b]
	Duration (days)	14-65	21	13-21	14-65	10-21	16-18	64	10-26	7-56	14	30	-
	% of diet	0.16-0.64	0.16-0.64	0.1-0.515	0.15-0.68	0.2-4	0.001-0.005	≈ 1-25 ppm[c,d]	-9/+67	0.1-1.6	0.5	≈ 0.1	-
	Change (range, %)[e]	-84/-39	-79/-64	-50/0	-87/-10	-46/-9	-62/-51	-48/+11	-	-55/-7	-11/-1	-63	-
TG content	n	2	2	8	-	-	1	-	-	8	-	1	1
	Duration (days)	2-3	14-21	3-16.5	-	-	4-21	-	-	7-56	-	30	84
	% of diet	0.4-0.5	0.5	0.1-0.515	-	-	0.01	-	-	0.1-1.6	-	≈ 0.1[c]	≈ 0.003-0.014[c]
	Change (range, %)	-84/-60	-62/-51	-81/-17	-	-	-79/-23	-	-	-64/-4	-	-83	-17/-9
Cholesterol content	n	1	-	9	1	-	-	1	-	5	2	-	1
	Duration (days)	21	-	7-56	42	-	-	45	-	7-56	14-45	-	30-84
	% of diet	0.2	-	0.1-0.515	0.2-0.5	-	-	0.5 ppm[d]	-	0.1-1.6	0.5	-	≈ 0.003-0.014[c]
	Change (range, %)	-56/-52	-	-37/0	-12	-	-	-51/-6	-	-60/+16	-21/-10	-	-28/-7
FAS[4] activity	n	1	-	3	-	-	-	-	-	-	-	2	-
	Duration (days)	2	-	3-14.5	-	-	-	-	-	-	-	1-7	-
	% of diet	0.4	-	0.1-0.5	-	-	-	-	-	-	-	3-5	-
	Change (range, %)	-21	-	-31/-29	-	-	-	-	-	-	-	-63/0	-
ME activity	n	-	-	5	-	-	-	-	-	-	1	1	-
	Duration (days)	-	-	13-16.5	-	-	-	-	-	-	45	7	-
	% of diet	-	-	0.1-0.515	-	-	-	-	-	-	0.5	3	-

	Change (range, %)	-	-	-42/-12	-	-	-	-	-	-	-10	-57/+3	-
G6PDH activity	n	-	-	5	-	-	-	-	-	-	-	1	-
	Duration (days)	-	-	13-16.5	-	-	-	-	-	-	-	7	-
	% of diet	-	-	0.1-0.515	-	-	-	-	-	-	-	3	-
	Change (range, %)	-	-	-43/-24	-	-	-	-	-	-	-	-69/0	-
ACC activity	n	-	-	1	-	-	-	-	-	-	-	1	-
	Duration (days)	-	-	3-13	-	-	-	-	-	-	-	1-4	-
	% of diet	-	-	0.1-0.5	-	-	-	-	-	-	-	5	-
	Change (range, %)	-	-	-31/-20	-	-	-	-	-	-	-	-57/-11	-
ATPCL activity	n	-	-	1	-	-	-	-	-	-	-	-	-
	Duration (days)	-	-	3-13	-	-	-	-	-	-	-	-	-
	% of diet	-	-	0.1-0.5	-	-	-	-	-	-	-	-	-
	Change (range, %)	-	-	-31/-20	-	-	-	-	-	-	-	-	-

[a]Number of references extracted from Supplemental Tables 1 and 2

[b]No data found

[c]The sign "≈" indicates that for some references, the compound percentage of the diet has been calculated from the dose given in mg/kg b.w. or from the dose given daily, assuming – when data was not given in article - that rats generally consume around 20 g chow diet daily

[d]ppm = 10^{-6}, *i.e.* 1 mg/kg

[e]Max- and min-values for reduced and/or increased percentages are given: they include both significant and unsignificant results since an absence of effect (notably 0 change) deserves to be mentioned (for significance of results, see corresponding Supplemental Tables)

ABBREVIATIONS: ACC, Acetyl-CoA Carboxylase; ATPCL, ATP-Citrate Lyase or Citrate Cleavage Enzyme; FAS, Fatty Acid Synthase; G6PDH, Glucose-6-Phosphate Dehydrogenase; HCA, HydroxyCitric Acid; ME, Malic Enzyme; MUFA, Mono-Unsaturated Fatty Acid; PUFA, Poly-Unsaturated Fatty Acid; TG, TriGlyceride; TL, Total Lipids

Tableau 3 Lipotropic effects of fiber compounds, polyphenols and derived compounds on main markers of lipid metabolism in rats*

		Fiber-type compounds			Polyphenol-type compounds							
		Fiber	Phytic acid	Oligo-fructose	Phenolic acids	Flavonoids	Lignans	Curcumin	Saponins	Phytosterols	γ-oryzanol	Mixture or plant extract
TL/fat content	n[a]	5	5	1	1	-[b]	2	1	3	-	-	-
	Duration (days)	19-63	12-30	42	28	-	28	28	14-84	-	-	-
	% of diet	6.5-16	0.1-2.5	10	0.4	-	0.002-0.2	0.2	0.001-0.07	-	-	-
	Change (range, %)[c]	-60/+12	-52/-29	-43	-9	-	-24/+7	-4	-45/+8	-	-	-
TG content	n	6	5	6	1	4	4	1	2	2	2	3
	Duration (days)	28-56	12-30	19-70	49	28-42	10-15	49	21-84	31-35	49	35-63
	% of diet	3-10	0.1-2.5	5-10	0.075	0.1-1	0.06-0.5	0.15	≈ 0.005-1[d]	0.1-2	0.2-1.2	≈ 0.15-2.5[d,e]
	Change (range, %)	-85/+47	-84/-42	-57/-1	-19	-23/+3	-68/+136	-22	-40/-35	-12/+16	-33/-7	-27/+35
Cholesterol content	n	14	4	3	2	4	5	2	3	4	3	3
	Duration (days)	9-63	13-30	19-56	28-49	28-42	10-28	28-49	19-84	13-35	28-49	35-63
	% of diet	0.6-30	0.5-1.02	5-10	0.075-0.4	0.1-1	0.06-0.5	0.15-0.2	≈ 0.005-1[d]	0.1-5	0.01-1.2	≈ 0.15-0.61[d]
	Change (range, %)	-75/+23	-13/0	-14/-3	-3/+1	-28/+14	-39/+21	-37/-16	-52/+14	-76/-18	-26/-14	-19/-7
FAS[5] activity	n	-	2	4	-	1	6	-	-	-	-	-
	Duration (days)	-	12-13	21-70	-	182	10-15	-	-	-	-	-
	% of diet	-	0.1-2.5	10	-	≈ 0.0018[d]	0.06-0.5	-	-	-	-	-
	Change (range, %)	-	-65/-26	-41/0	-	0	-63/-21	-	-	-	-	-
ME activity	n	-	5	2	-	-	2	-	-	-	-	-
	Duration (days)	-	12-13	42-70	-	-	15	-	-	-	-	-
	% of diet	-	0.1-2.5	10	-	-	0.1-0.5	-	-	-	-	-

	Change (range, %)	-	-44/-2	-16/0	-	-	-50/+125	-	-	-	-	-
G6PDH activity	n	-	5	-	-	-	5	-	-	-	-	-
	Duration (days)	-	12-13	-	-	-	10-15	-	-	-	-	-
	% of diet	-	0.1-2.5	-	-	-	0.06-0.4	-	-	-	-	-
	Change (range, %)	-	-47/+5	-	-	-	-77/-3	-	-	-	-	-
ACC activity	n	-	1	-	-	1	2	-	-	-	-	-
	Duration (days)	-	13	-	-	182	15-28	-	-	-	-	-
	% of diet	-	0.5	-	-	≈ 0.0018	0.1-0.4	-	-	-	-	-
	Change (range, %)	-	-16	-	-	0	-57/-36	-	-	-	-	-
ATPCL activity	n	-	1	2	-	-	5	-	-	-	-	-
	Duration (days)	-	13	42-70	-	-	10-15	-	-	-	-	-
	% of diet	-	0.5	10	-	-	0.06-0.4	-	-	-	-	-
	Change (range, %)	-	-37	-26/0	-	-	-70/-30	-	-	-	-	-
PPARα mRNA level	n	-	-	-	-	1	-	-	-	-	-	-
	Duration (days)	-	-	-	-	182	-	-	-	-	-	-
	% of diet	-	-	-	-	≈ 0.0018[d]	-	-	-	-	-	-
	Change (range, %)	-	-	-	-	+160	-	-	-	-	-	-
SREBP mRNA level	n	-	-	-	-	-	2	-	-	-	-	-
	Duration (days)	-	-	-	-	-	14-28	-	-	-	-	-
	% of diet	-	-	-	-	-	0.002-0.4	-	-	-	-	-
	Change (range, %)	-	-	-	-	-	-55/-9	-	-	-	-	-

[a]Number of references extracted from Supplemental Tables 3 and 4

[b]No data found

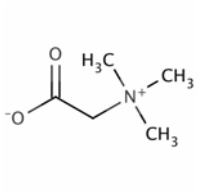
[c]Max- and min-values for reduced and/or increased percentages are given: they include both significant and unsignificant results since an absence of effect (notably 0 change) deserves to be mentioned (for significance of results, see corresponding Supplemental Tables)

[d]The sign "≈" indicates that for some references, the compound percentage of the diet has been calculated from the dose given in mg/kg b.w. or from the dose given daily, assuming – when data was not given in article - that rats generally consume around 20 g chow diet daily

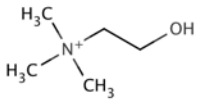
[e]Range of the compound percentage is that of 2 references among the three selected since one reference did not give the percentage; the upper limit was evaluated from percentage in drinking water assuming that an adult rat consumes around 20 mL water daily

ABBREVIATIONS: ACC, Acetyl-CoA Carboxylase; ATPCL, ATP-Citrate Lyase or Citrate Cleavage Enzyme; FAS, Fatty Acid Synthase; G6PDH, Glucose-6-Phosphate Dehydrogenase; ME, Malic Enzyme; mRNA, messenger RiboNucleic Acid; PPARα, Peroxisone Proliferator Activated Receptor *alpha*; SREBP, Sterol Regulatory Element-Binding Proteins; TG, TriGlyceride; TL, Total Lipids

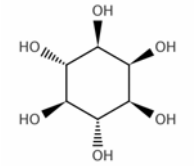
Figure 1



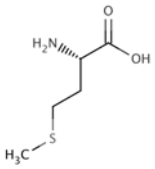
Betaine



Choline



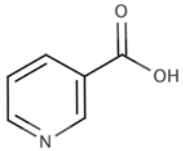
Myo-inositol



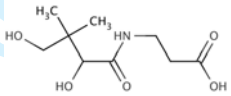
Methionine

Mg^{2+}

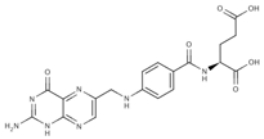
Magnesium



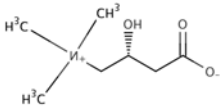
Niacin



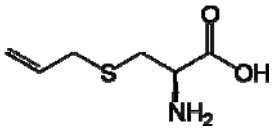
Pantothenic acid



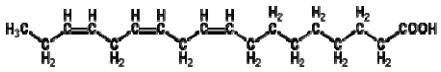
Folates



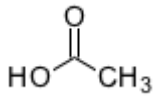
Carnitine



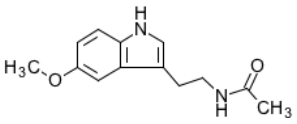
s-allyl cysteine (organosulfur compound)



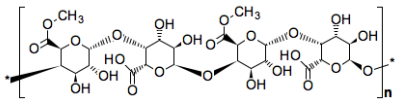
Acide α-linolenic (PUFA)



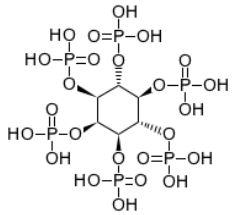
Acetic acid (SCFA)



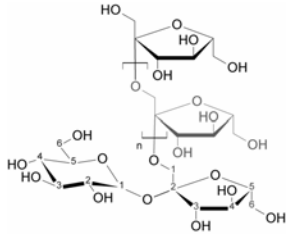
Melatonin



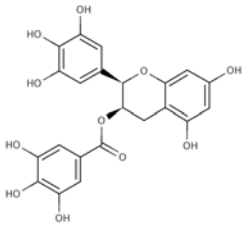
Pectin (soluble fiber)



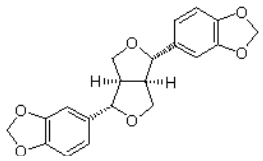
Phytic acid



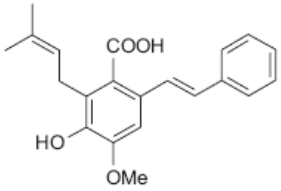
Fructans (oligofructose)



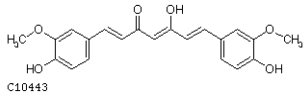
Epigallocatechin gallate (flavonoid)



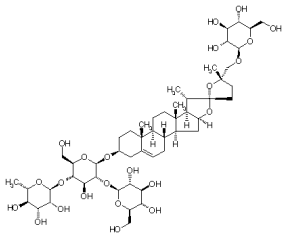
Sesamin (lignan)



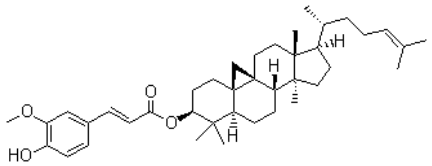
Cajanin (stilbene)



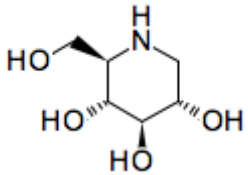
Curcumin



Avenacoside A (saponin)



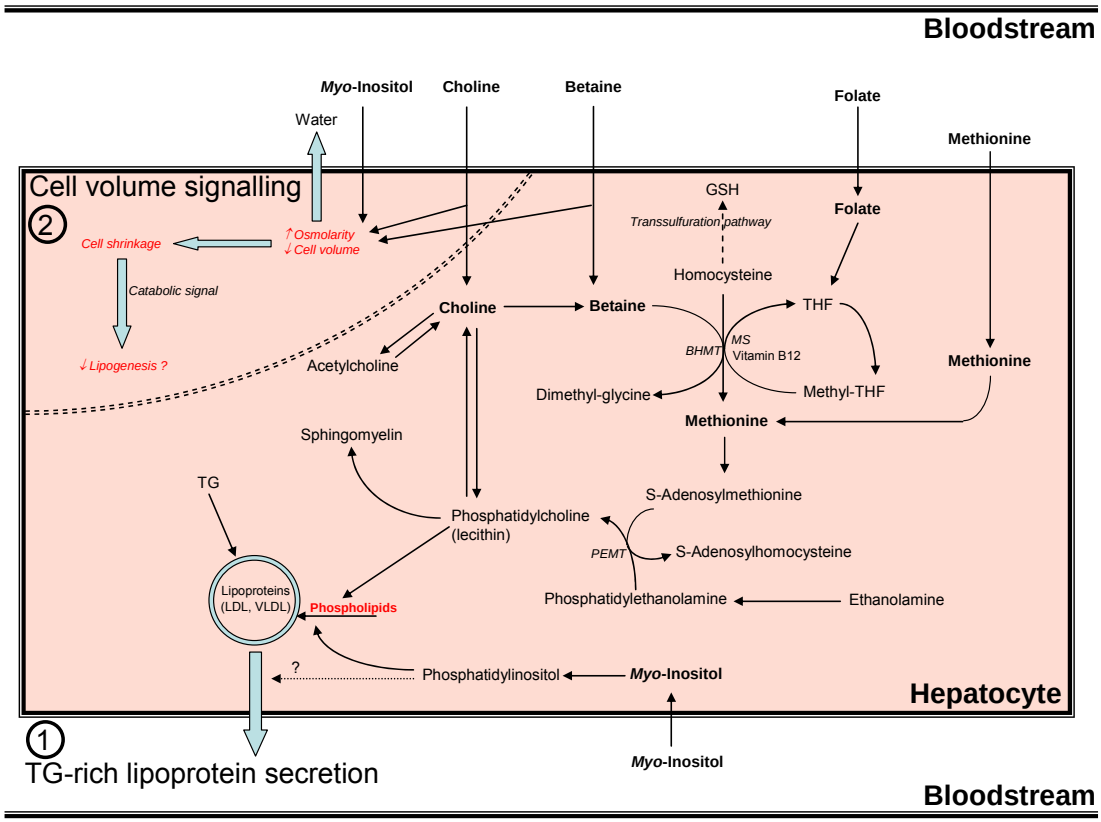
γ-oryzanol



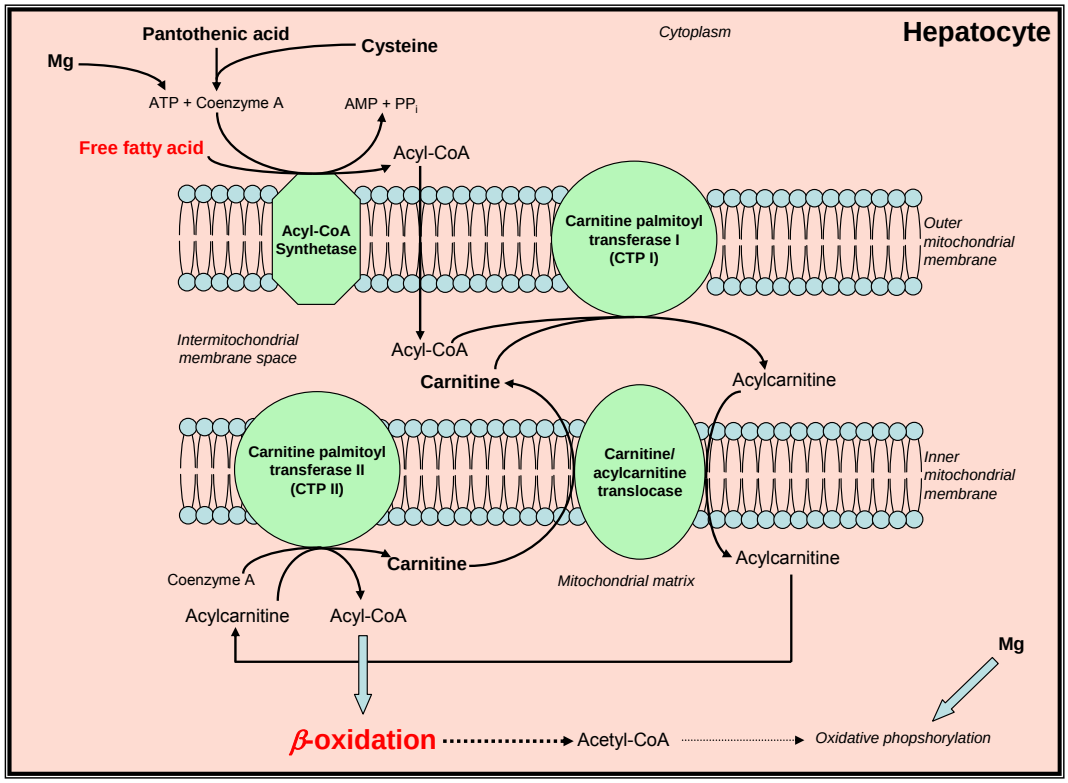
1-Deoxynojirimycin

Figure 2 A-D

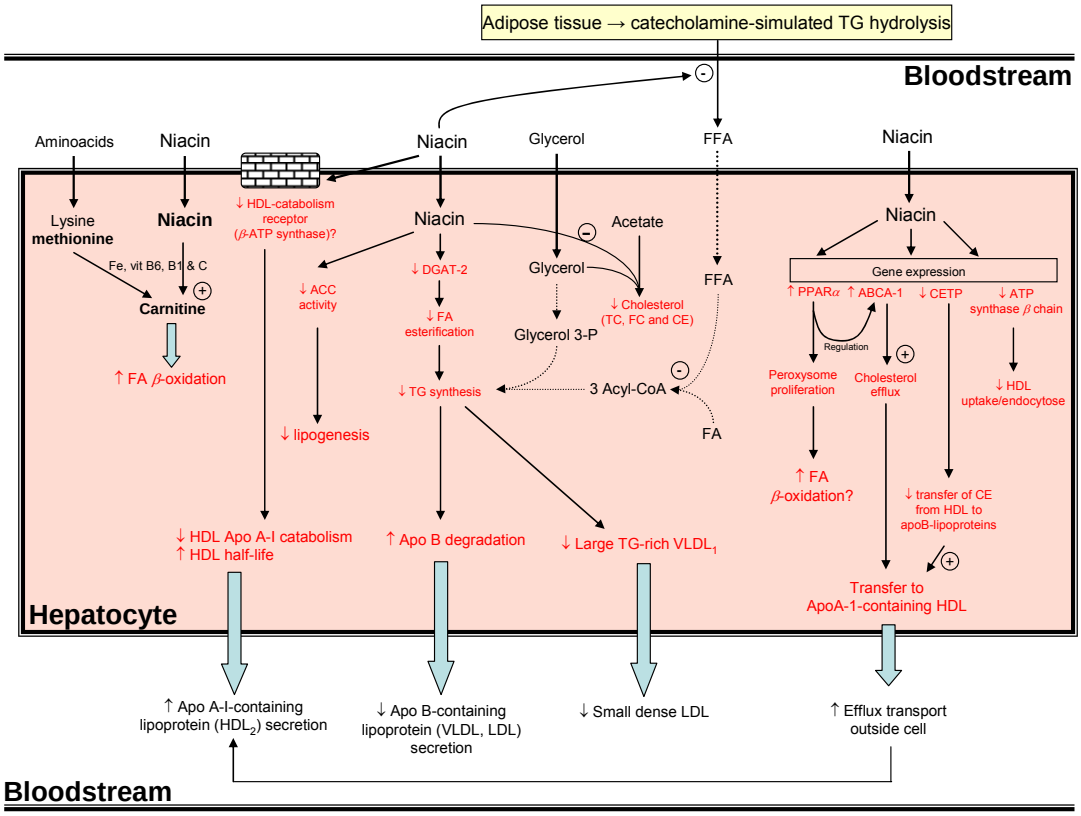
A)



B)



C)



D)

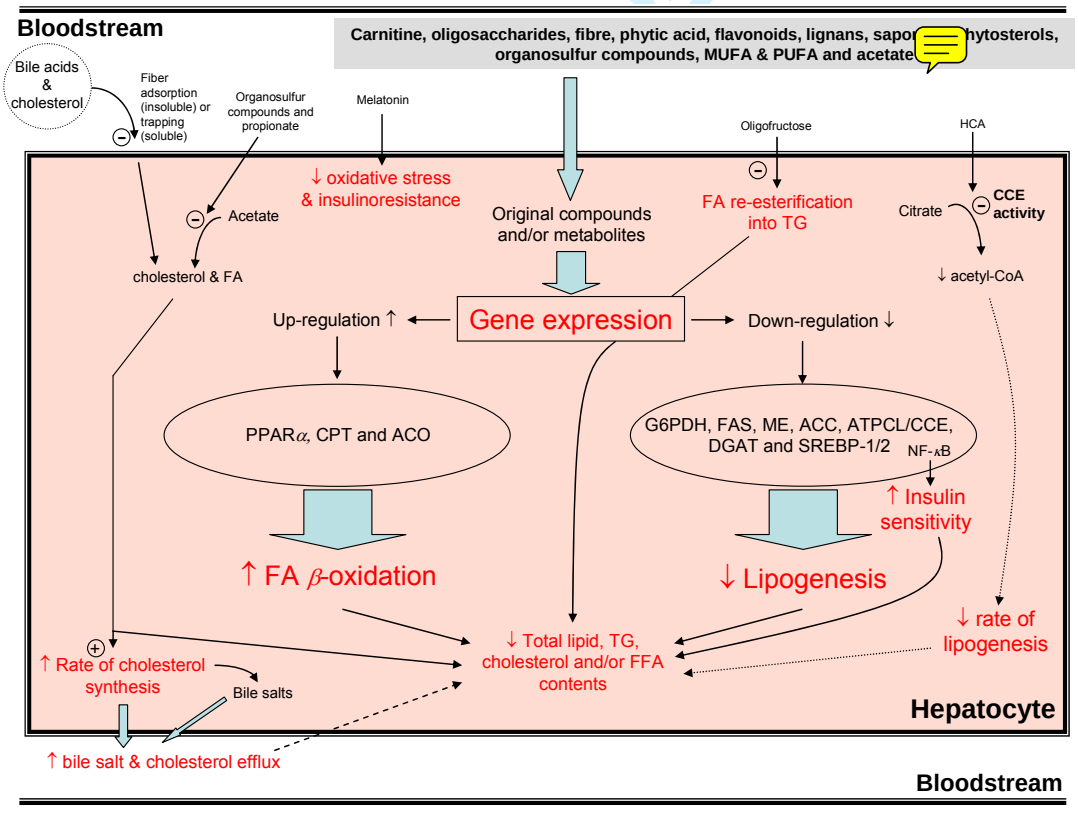
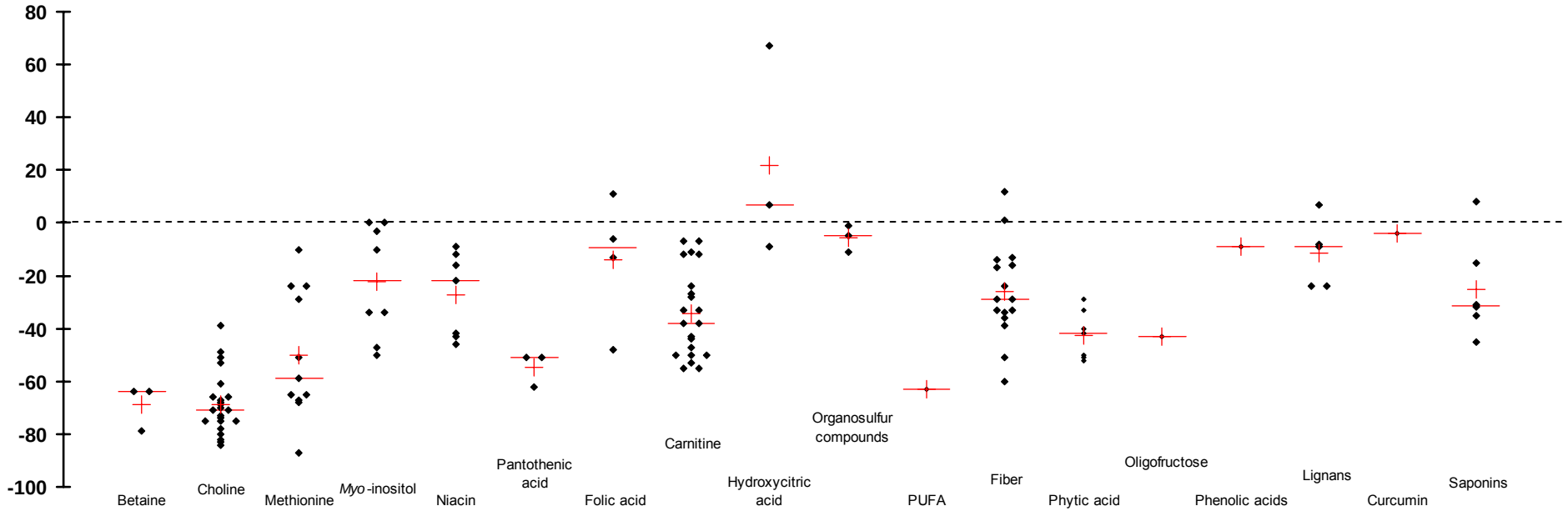


Figure 3 A-C

TL

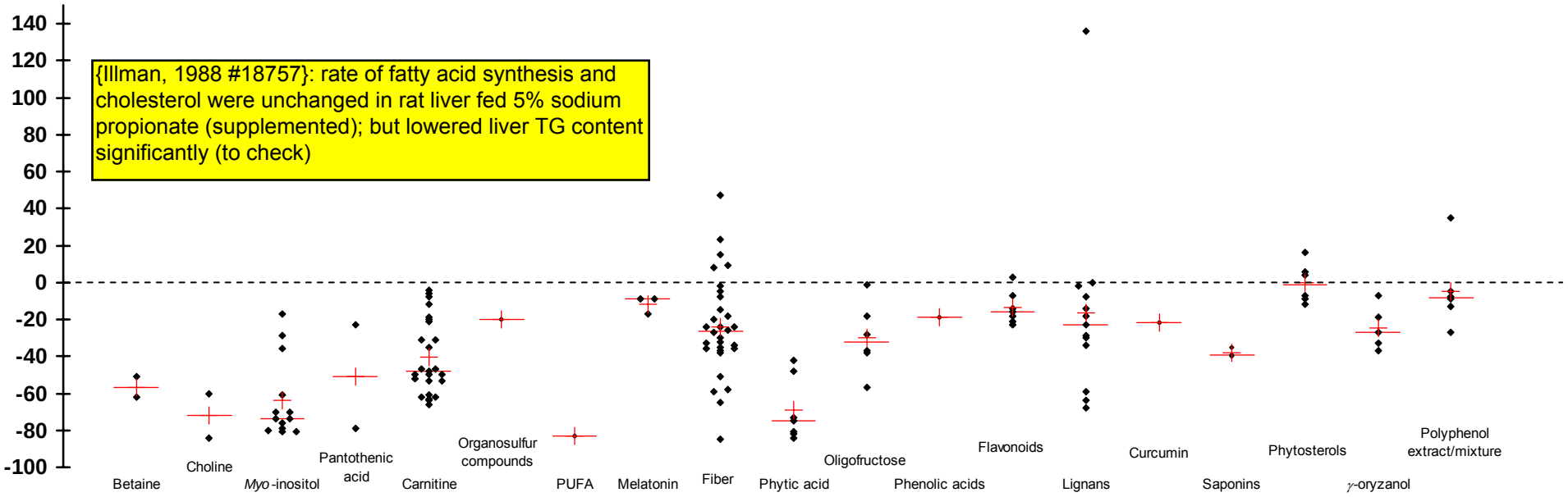
A)



Retirer valeurs de Schön (1958) et les mettre dans Total Cholesterol.

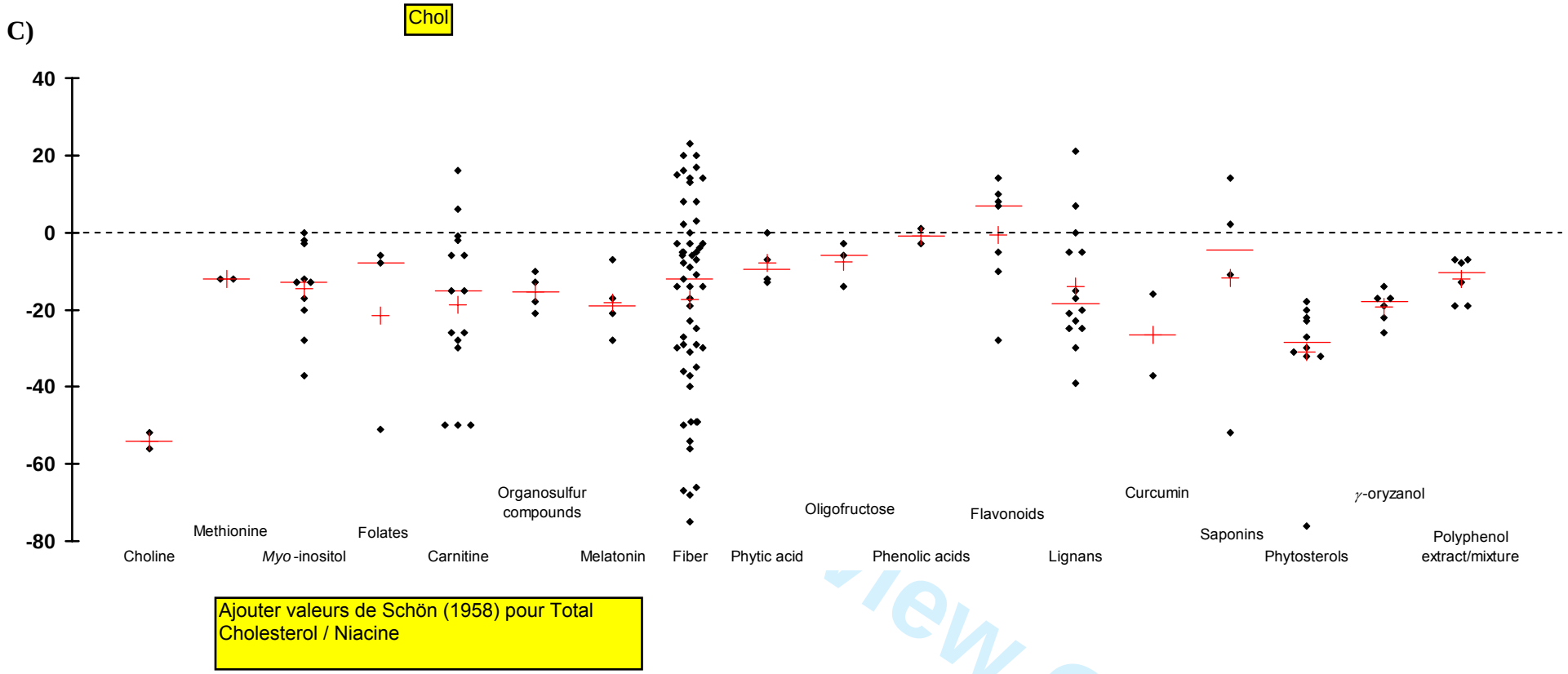
B)

TG: vérifier pour resistant starch si valeurs à ajouter



Coumarin: auraptene reduced hepatic TG in long evan fatty rats {Nagao, 2010 #22917}

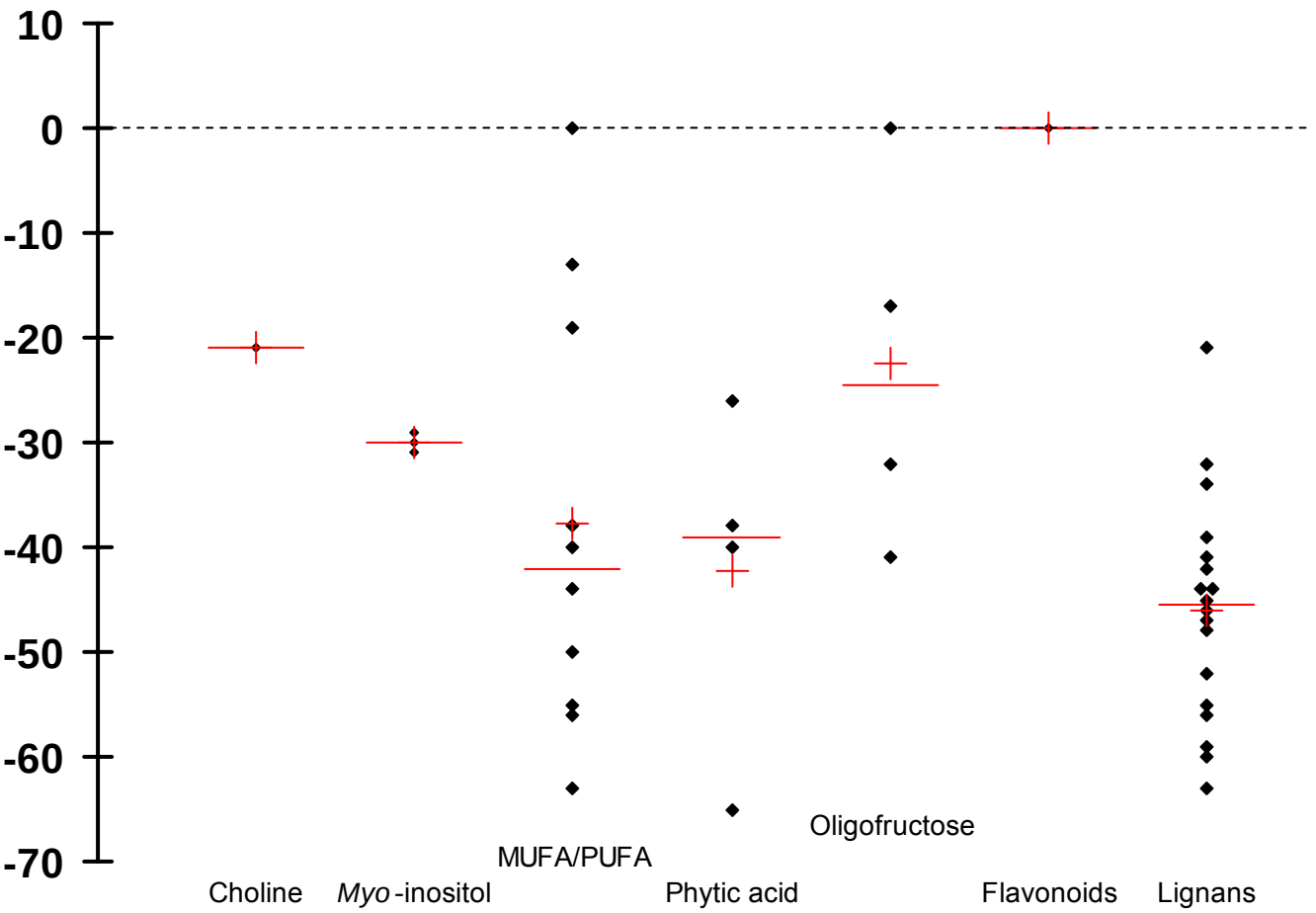
C)



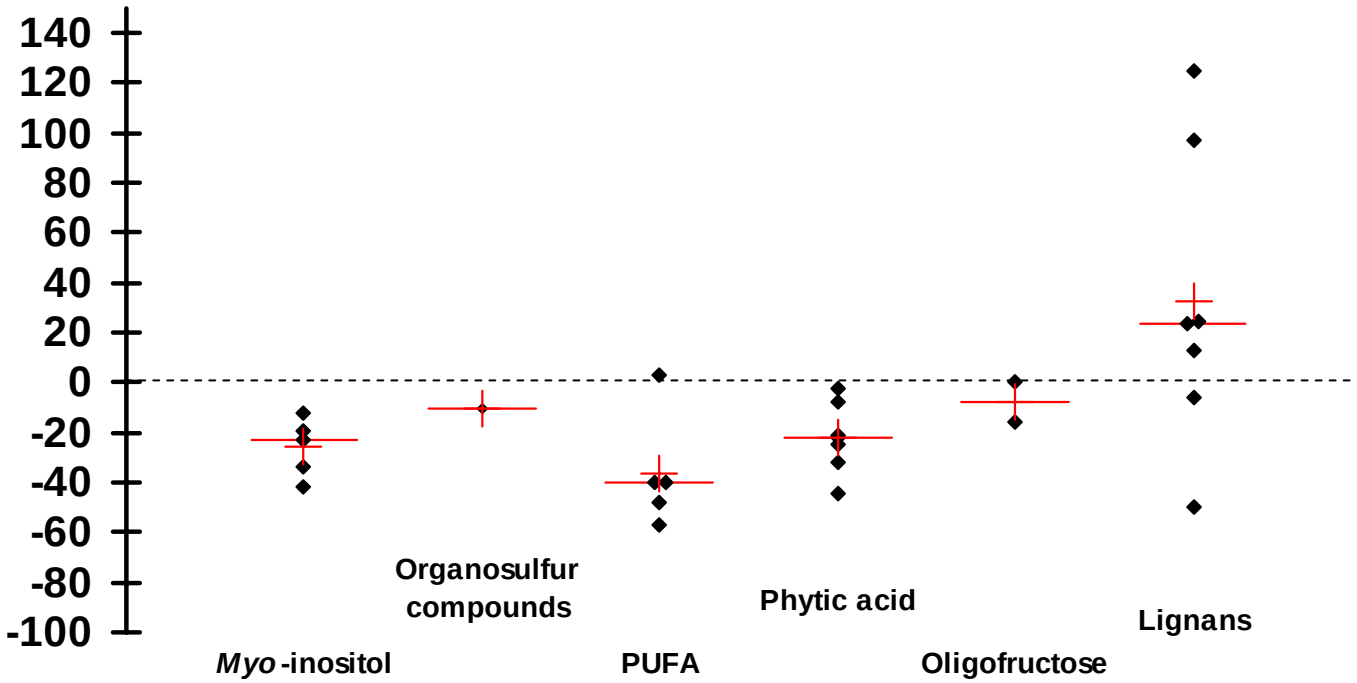
Ajouter valeurs de Schön (1958) pour Total Cholesterol / Niacine

Figure 4 A-E

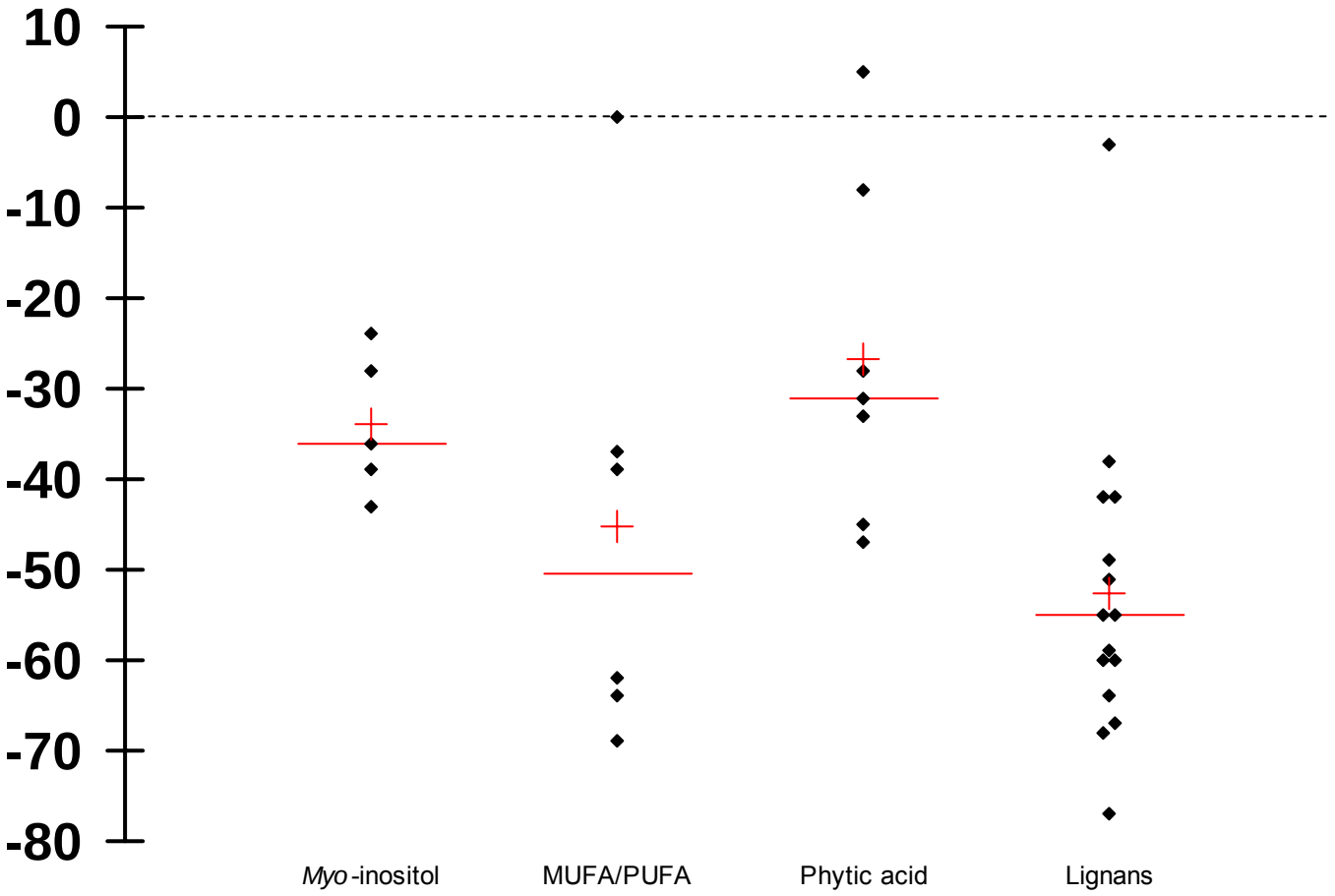
A)



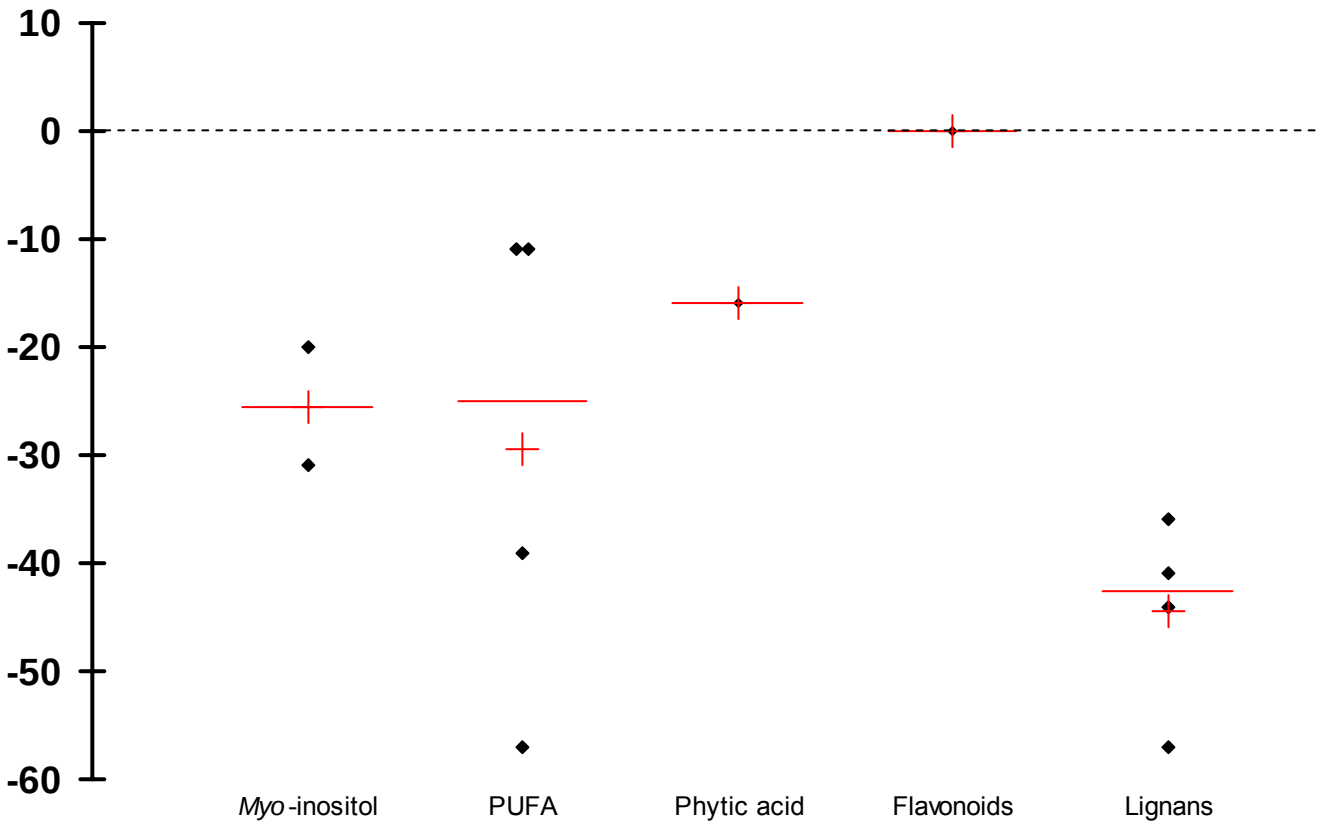
B)



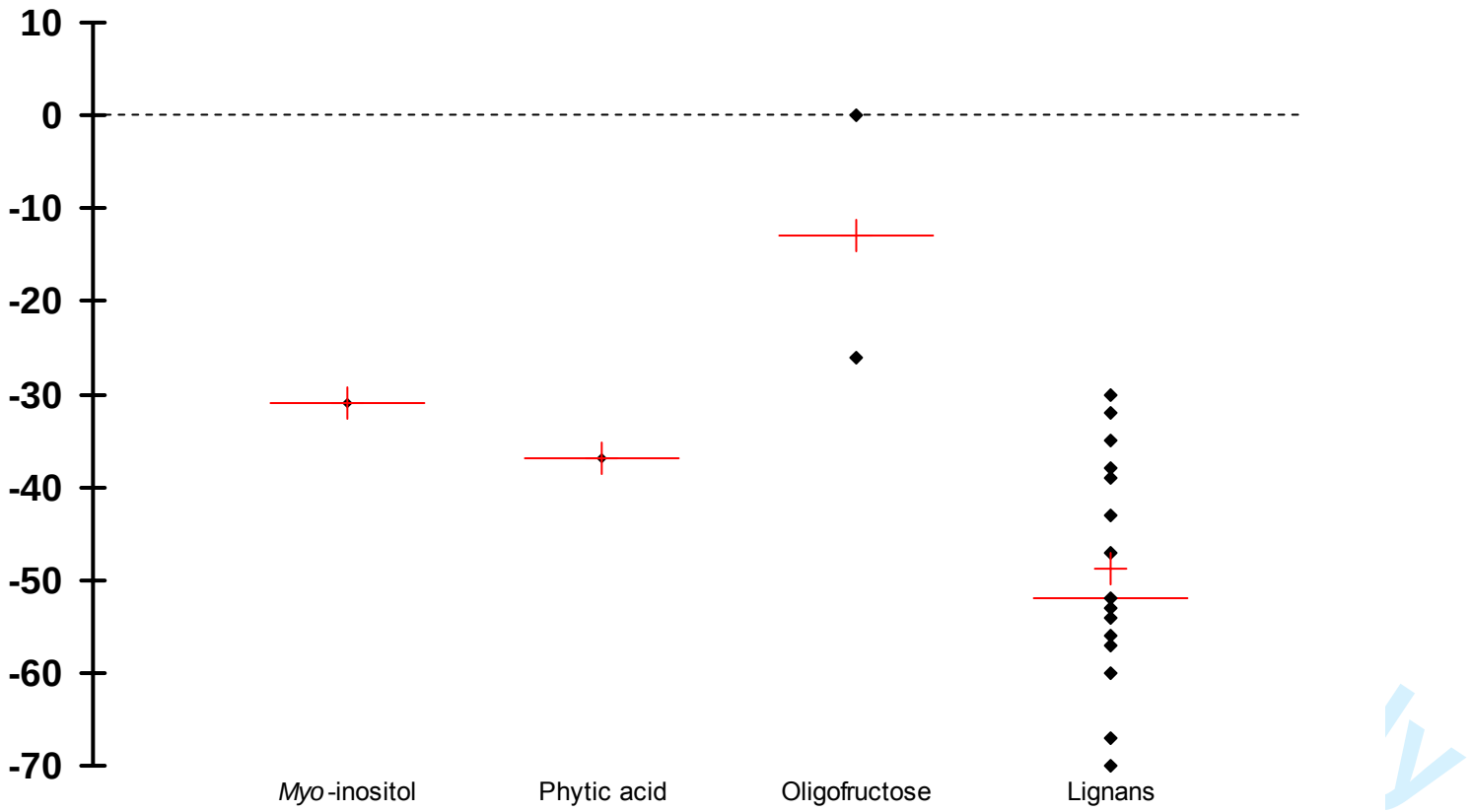
C)



D)



E)



Supplemental Tables

Supplemental Table 1 *In vivo*, *ex vivo* and *in vitro* studies reporting effects on hepatic lipid metabolism following deficiency or supplementation of betaine, choline, methionine, *myo*-inositol, magnesium, niacin, pantothenic acid and folates

Lipotropic compounds	*In vivo* or *in vitro* models	Supplemented daily dose	Duration of lipotrope exposition	Hepatic effect(s)	References
A - Main lipotropes					
A1 - Betaine					
Betaine	Rats fed high-fat (40%) diet	120 mg	21 days	↓ FA percentage (-59%)[b]	(Best and Huntsman, 1932)
Betaine	Rats fed high-fat (40%) diet	100 mg	21 days	↓ FA percentage (-82%)	(Best, 1934)
Betaine hydrochloride	Rats fed high-fat (20%) and high-sucrose (48.9%) diet	From 100 to 200 mg	8 days	↓ fat percentage (-51%)	(Griffith and Mulford, 1941)
	Rats fed high-fat (20%) and high-sucrose (48.9%) diet added with 0.3% cystine	From 50 to 200 mg	8 days	↓ fat percentage (-54%)	
Betaine hydrochloride	Rats fed fat-free and methionine-restricted diet	0.16% free betaine	21 days	↓ TL percentage (≈ -64%)	(Best et al., 1950)
	Rats fed high-fat (30%) and methionine-restricted diet	0.32% free betaine	21 days	↓ TL percentage (≈ -64%)	
Betaine hydrochloride	Rats fed high-sucrose (45.8%) and betaine-deficient diet supplemented with histidine, lysine and threonine	From 0.08 to 0.64%	21 days	↓ TL percentage (from 0 to -79%): sharp decrease begins at a level of 0.16% betaine HCl supplementation (-42%)	(Young et al., 1965)
Betaine aspartate	Rats fed high-fat (40%) diet	250 mg free betaine /kg bw	30 days	↑ C^{14}-trioleine catabolism (-44% trioleine retention rate)	(Perrault and Dormard, 1966)
Anhydrous betaine	Rats fed semiliquid ethanol diet	0.5% of diet	14 days	↓ TG content (-62%), ↑ SAM (+354%) and betaine (+305%) concentrations and ↑ BHMT activity (+46%)	(Barak et al., 1996)
Anhydrous betaine	Rats fed ethanol diet	0.5% of diet	21 days	↓ TG content (-51%), ↑ SAM concentrations (+722%) and ↑ BHMT activity (+92%)	(Barak et al., 1997)
Betaine anhydrous solution	Humans with NASH	20 g solution daily	1 year	Improvement in degree of steatosis, necroinflammatory grade and stage of fibrosis, ↓ ALT and AST concentrations (-69%)	(Abdelmalek et al., 2001)
Betaine (crystalline white granule)	Rats fed low-protein (14.7%)/low-fat (≈ 3%) diet (BIBRA diet) ±betaine for 28 days then the same diet without betaine for 28 days	1, 2 or 5%	28 days	Liver histology: ↑ lipid droplet and microvacuolisation upon betaine treatment (resp. +45, +90 and +125%), then ↓ microvacuolisation upon the last 28 datys without betaine (resp. -62, -59 and -71%)	(Hayes et al., 2003)
	Rats fed balanced diet (≈ 8% fat and 23.5% protein; Brandeis University diet)	0.5, 0.75, 1.0 or 5.0% of diet	28 days	↓ TG content (resp. -11%, NS, -20%, NS, -13%, NS, and -39%)	
Betaine	Intragastric alcohol-fed mice	0.5 or 1.5% of diet	28 days	↓ cholesterol (-18 and -47%) and TG (-29 and -67%) levels, ↓ SREBP-1 relative mRNA expression (≈ -50 and ≈ - 70%)	(Ji and Kaplowitz, 2003)
Betaine	Ethanol-treated guinea pigs for the last 10 days	2% of diet	30 days	↓ TG level (-43%)	(Balkan et al., 2004)
Betaine	Isolated hepatocytes from ethanol-fed rats for 4 weeks	1 mM	4 hrs	↓ TG content (≈ -20%)	(Kharbanda et al., 2005)
Betaine	Mice fed high-fat (20% energy) diet	1.5% of diet	8 months	↓ histologic liver injury (0.7 *vs* 3.5, $p < 0.01$)	(Borgschulte et al., 2008)
A2 - Choline					
Choline	Rats fed high-fat (40%) diet	70 mg	21 days	↓ FA percentage (-64%)	(Best and Huntsman, 1932)
		From 10 to 117 mg	21 days	↓ FA percentage (from -40 to -69%)	
Choline	Rats fed high-fat (40%) diet	75 mg	21 days	↓ FA percentage (-68%)	(Best, 1934)
Choline	Rats fed high-fat (40%) diet	70 mg	21 days	↓ FA percentage (-66%)	(Best and Huntsman, 1935)
Choline chloride	Rats fed high-fat (20%) and high-sucrose (48.9%) diet	From 20 to 40 mg	8 days	↓ fat percentage (-37%)	(Griffith and Mulford, 1941)
	Rats fed high-fat (20%) and high-sucrose (48.9%) diet added with 0.3% cystine	From 15 to 75 mg	8 days	↓ fat percentage (-60%)	
Choline chloride	Patients (n = 10) with decompensated portal	0.5 g thrice	18 months	Case 2: complete disappearance of ascites and smaller liver	(Russakoff and Blumberg, 1944)

Commentaire [A.F.:
caloric restriction to add?:
- in humans {Elias, 2010 #25149}
- see in animals

{Ji, 2007 #21172}: "Role of the blunt and betaine system in alcoholic and non-alcoholic hyperhomocysteinemia and liver steatosis" in BHMT transgenic mice

	cirrhosis of the liver (cirrhosis is frequently associated with extensive fatty infiltration of the liver) and treated with a high protein, high carbohydrate and low fat diet	0.5 g 4 times	3 weeks	Case 3: complete disappearance of ascites, improved liver function tests, feeling of well-being and good health
		4.5 g	≈ 9 months	Case 5: marked improvement (*e.g.* ↓ ascites)
		6 g then 4.5 g	≈ 6 months then 6 months	Case 7: improvements (*e.g.* less abdominal paracenteses required)
		4-6 g	45 days	Case 8: steadily improvement (*e.g.* ascites disappeared)
		1.5 g thrice	≥4 weeks	Case 9: continued improvement (*e.g.* ↓ ascites and ↓ icterus index)
		6 g	≥10 days	Case 10: considerable improvements (*e.g.* ↓ ascites)
				[Cases 1, 4 and 6: death or no improvement]
Choline chloride (dessicated)	Rats fed fat-free and methionine-restricted diet	0.16% free choline	21 days	↓ TL percentage (≈ -75%), ↓ CE (≈ -69%) (Best et al., 1950)
	Rats fed high-fat (30%) and methionine-restricted diet	0.32% free choline	21 days	↓ TL percentage (≈ -73%)
Choline chloride	Rats fed steatogen diet (76% bolted white corn meal and 3% casein)	0.25% of diet	65 days	↓ fat percentage (-78%) (Shils and Stewart, 1954)
Choline chloride	Rats fed 20% protein choline-deficient diet	0.26% of diet	3 weeks	↓ lipid percentage (-68%) (Fritz and Dupont, 1957)
Choline	Rats fed high-sucrose (69%) and soy protein (low methionine) diet	0.3% of diet	14 days	↓ lipid percentage (-80%) (Olson et al., 1958)
	Rats fed high-sucrose (69%) and casein (adequate methionine) diet → moderate fatty liver	0.3% of diet	14 days	↓ lipid percentage (-51%)
	Rats fed high-fat (lard: 39.9%) and soy protein (low methionine) diet	0.3% of diet	14 days	↓ lipid percentage (-83%)
	Rats fed high-fat (lard: 39.9%) and casein (adequate methionine) diet	0.3% of diet	14 days	↓ lipid percentage (-75%)
	Rats fed high-fat (butter fat: 39.9%) and soy protein (low methionine) diet	0.3% of diet	14 days	↓ lipid percentage (-71%)
	Rats fed high-fat (corn oil: 39.9%) and soy protein (low methionine) diet	0.3% of diet	14 days	↓ lipid percentage (-66%)
	Rats fed high-fat (butter fat: 39.9%) and casein (adequate methionine) diet → less drastic fatty liver	0.3% of diet	14 days	↓ lipid percentage (-70%)
	Rats fed high-fat (corn oil: 39.9%) and casein (adequate methionine) diet → less drastic fatty liver	0.3% of diet	14 days	↓ lipid percentage (-67%)
Choline chloride	Mice fed high-fat (28%), low-protein and hypolipotropic diet	0.002% of diet	4 weeks	↓ importantly quantity and size of fat droplets (histological observations) (Ball, 1964)
Choline Cl	Rats fed high-sucrose (45.8%) and choline-deficient diet supplemented with histidine, lysine and threonine	From 0.01 to 0.64% of diet	21 days	↓ TL percentage (from -10 to -84%; -82% at 0.16%): sharp decrease begins at a level of 0.06% choline Cl supplementation (-60%) (Young et al., 1965)
Choline chloride	Rats fed basal hypolipotropic and choline-deficient diet	0.6% of diet	-[c]	↓ total esterified FA content (-89%) (Haines and Mookerjea, 1965)
	Rats fed choline-deficient diet for 10 days then injected subcutaneously with choline chloride	8, 20 or 40 mg injected	1 day	↑ plasma PL FA level for 40 mg only (+30%)
Choline	Rats fed high-fat (40%) and 0.1% niacin diet	0.30 or 0.50% of diet	14 days	↓ fat percentage (resp. -39 and -49%) compared to 0.15% choline (Rikans et al., 1965)
		0.75 or 1.00% of diet	14 days	↓ fat percentage for 1% choline only (-36%) compared to 0.50% choline + 0.1% niacin
		1.00% of diet	14 days	↓ total fat (-19%), PL (-14%) and neutral fat (-22%) percentages, ↓ PL in fat of 2.2% compared to 0.25% choline + 0.1% niacin
Choline chloride	Rats fed hypolipotropic and high-sucrose (62%) diet at 21°C	0.2% free choline	21 days	↓ lipid percentage (-66 ±12%, n = 4 experiments) (Chahl and Kratzing, 1966a)
Choline	Rats fed high-sucrose (69%) and casein diet at 21°C	0.05, 0.1 or 0.2% of diet	21 days	↓ lipid percentage (respectively -70, -74 or -75%) (Chahl and Kratzing, 1966b)
	Rats fed high-peanut meal (30%) and casein diet at 21°C	0.025, 0.05, 0.1 or 0.2% of diet		↓ lipid percentage (respectively -36, -71, -73 or -73%)
Choline chloride	Rats fed choline-deficient diet	0.6% of diet	15-18 hours	↓ TG content (-60 ±5%, n = 4 experiments), ↑ PL (+21%, n = 1) (Lombardi et al., 1968)

				↑TG content in plasma VLDL (+85%)	
Choline chloride	Rats fed choline-deficient diet	0.5% of diet	2 days	↓TG (-60%) and PE (-28%) content, ↑PC content (+21%), lower incorporation of ethanolamine into CDP-E/choline-deficient rats	(Haines and Rose, 1970)
Choline	Rats fed hypolipotropic and high-sucrose (60%) diet	0.4% of diet	2 days	↓floating lipid fraction (-71%), ↓FAS specific activity (-21%)	(Rosenfeld, 1973)
Choline chloride	Rats fed choline-deficient diet	0.5% of diet	> 3 days	↓TG (-84%), PE (-15%), CDP-E (-64%) and ethanolamine (-76%) content, and ↑PC content (+27%)	(Tokmakjian and Haines, 1979)
Choline dihydrogen citrate	Rats fed high-glucose (60%) diet not supplemented with choline	0.01, 0.02 or 0.06% free choline	7 days	↓TG content (respectively -27, -29 or -73%)	(Andersen and Holub, 1980b)
Choline chloride	Rats fed low-choline, 38% sucrose and 20% beef tallow or safflower oil diet	0.2% of diet	21 days	↓lipid content (-69%/beef tallow or -61%/safflower oil)	(Carroll and Williams, 1982)
	Rats fed low-choline, 38% sucrose and 20% high beef tallow or high safflower blend diet	0.2% of diet	21 days	↓lipid content (-71%/beef tallow or -53%/safflower oil) ↓cholesterol content (-56%/beef tallow or -52%/safflower oil) ↓PL content (-21%/beef tallow or -16%/safflower oil) ↑ % cholesterol of total lipid (+47%/beef tallow or no change/safflower oil) ↑ % PL of total lipid (+143%/beef tallow or +72%/safflower oil)	
Choline	Healthy humans fed choline-deficient diet	500 mg	21 days	↓serum ALT activity (-34%) and plasma PC (-32%), ↑ serum TC (+18%); signs of incipient liver dysfunction in choline-deficient patients	(Zeisel et al., 1991)
Choline	Rats fed choline-deficient diet	0.69% of diet	1, 2 or 4 weeks	↓phospholipase A_2 (resp. ≈ -35, ≈ -43 and ≈ -69%) and phospholipase C (resp. ≈ -20, ≈ -31 and ≈ -48%) activities No significant effect on proteine kinase C activity	(Singh et al., 1990)
Choline	Rats fed choline-defient then refed with choline-supplemented diet	0.48% of diet	16 weeks	↓FFA (-87%), ↑DRG (+915%)	(Da Costa et al., 1995)
Choline chloride	Long-term total parenteral nutrition patients with low plasma free choline and hepatic steatosis	1 to 4 g in TPN solution	6 weeks	↓and completely resolved hepatic steatosis (significant ↑liver density by an average of ±16.5 HU)	(Buchman et al., 1995)
Choline chloride	Total parenteral nutrition patients with hepatic steatosis	2 g in TPN solution		Hepatic steatosis resolved completely (baseline liver-spleen HU higher: 1.5 ±10.8 in choline-supplemented group *vs* -11.6 ±7.9 in placebo) with more serious adverse events in choline-deficient patients, significant correlation between plasma free choline and liver and liver-spleen HU, ↓serum alkaline phosphatase; significant positive correlation between plasma PL-bound choline concentration and total serum cholesterol/total serum TG/HDL/LDL concentrations and between plasma free choline and serum TG concentrations, significant negative correlation between serum TG concentration and liver HU	(Buchman et al., 2001)
Choline	129S6 mice (susceptible to IR and NAFLD) fed high-fat (40%) diet	No	4 months	Mice strain that mimic choline-deficient diet: microbiota-related reduced choline bioavailability → impaired VLDL assembly and ↑ liver TG	(Dumas et al., 2006)
A3 - Methionine					
Methionine	Rats fed high-fat (40%) diet	0.5% of diet	18-19 days	↓TL (-87%)	(Tucker and Eckstein, 1937)
dl-Methionine	Rats fed high-fat (40%), high-glucose (46%) and 5% gliadin diet	0.58% of diet	17-18 days	↓TL percentage (-78%)	(Tucker and Eckstein, 1938)
dl-Methionine	Rats fed high-fat (40%) diet	0.06, 0.125, 0.15, 0.25, 0.5, 1.0 or 2.0% of diet	21 days	↓fat percentage (resp. -26% [n = 2 experiments], -24, -10, -24 [n = 2], -40 ±7 [n = 3], -28 [n = 2] and -20%)	(Best and Ridout, 1940)
d-Methionine	Rats fed high-fat (40%) diet	0.06, 0.15, 0.25 or 0.5% of diet	21 days	↓fat percentage (resp. -23% [n = 2 experiments], -16, -26, and -58%)	
l-Methionine	Rats fed high-fat (40%) diet	0.06, 0.15 or 0.25% of diet	21 days	↓fat percentage (resp. -30% [n = 2 experiments], -21 and -20%)	
Methionine	Mice fed high-fat (40%), high-glucose (40%) and low-methionine (5% arachin)	0.64% of diet	15-17 days	↓TL percentage (-49 ±10%, n = 6 experiments)	(Singal and Eckstein, 1941)
dl-Methionine	Rats fed high-fat (20%) and high-sucrose	From 75 to 300	8 days	↓fat percentage (-64%)	(Griffith and Mulford, 1941)

	(48.9%) diet	mg			
Methionine	Rats fed high-fat (40%) and 35% gelatin diet	0.774% of diet	21 days	↓ crude FA content (-69%)	(Beveridge et al., 1945)
DL-Methionine	Rats fed high-fat (35%) and low casein (5%) diet	1.02% of diet	21 days	↓ TL percentage (-63%)	(Eckstein, 1952)
DL-Methionine	Rats fed choline-deficient, high-sucrose and 20% casein diet	0.6 and 1.0% of diet	14 days	↓ fat percentage (resp. -29 and -33%)	(Harper et al., 1954)
DL-Methionine	Rats fed steatogen diet (76% bolted white corn meal and 3% casein)	0.5% of diet	27-37 days	↓ lipid percentage (mean decrease of -65%)	(Shils and Stewart, 1954)
			65 days	↓ fat percentage (mean decrease of -59%)	
		1.0% of diet	65 days	↓ fat percentage (mean decrease of -64%)	
Methionine	Rats fed high-sucrose (45.8%) and methionine-deficient diet	From 0.08 to 0.48% of diet	21 days	↓ TL percentage (from 0 to -65%): sharp decrease begins at a level of 0.24% methionine supplementation (-51%)	(Young et al., 1965)
	Rats fed high-sucrose (45.8%) and methionine-deficient diet supplemented with 0.2% cystine	From 0.08 to 0.48% of diet	21 days	↓ TL percentage (from 0 to -73%): sharp decrease begins at a level of 0.16% methionine supplementation (-39%)	
L-Methionine	Rats fed high-sucrose (69%), casein and choline-deficient diet at 21°C	0.34 % of diet 0.68 % of diet	21 days	↓ lipid percentage (-67%) ↓ lipid percentage (-68%)	(Chahl and Kratzing, 1966b)
L-Methionine	Rats fed low-protein (5% casein) diet	0.02, 0.2 and 0.5% of diet	6 weeks	↓ cholesterol content (respectively ≈ -17, ≈ -12 and ≈ -12%, NS), ↑ PL (+20% for 200 mg/kg and no change for other doses)	(Osumi et al., 1969)
	Rats fed low-protein diet (5% casein)	0.5% of diet	3 weeks	↑ total-coenzyme A (+17%) and acyl-coenzyme A (+6%) activities	
L-Methionine	Rats fed a 9% casein-based diet	2.5% of diet	3 or 7 days	After 3 days: ↓ incorporation of sodium acetate into lipids (-26%) After 7 days: ↑ incorporation of sodium acetate into lipids (+118%)	(Yokota et al., 1974)
Methionine	Mice fed methionine-deficient diet	No	1-15 days	↑ liver injury but lipid (mainly TG and FFA) accumulation was less than with choline- and choline+methionine-deficient diets	(Caballero et al., 2008)
A4 - *Myo*-Inositol (free)					
Inositol	Rats injected daily biotin subcutaneously in conjunction with thiamine, riboflavin, pyridoxine and pantothenic acid in the diet	-	-	Prevents acutely "biotin" type of fatty liver development and cholesterol accumulation	(Gavin and Mchenry, 1941)
Inositol	Rats fed high-sucrose (78%) diet	5, 10, 20 and 40 mg	21 days	↓ fat percentage (respectively -30, -28, -34 and -22%)	(Engel, 1942)
Inositol	Depancreatized dogs	-	-	Small lipotropic activity but no so marked than a preparation of lipocaic	(Owens, 1942)
Inositol	Rats fed high-fat and cholesterol diet	-	-	Moderate lipotropic action	(Mchenry and Patterson, 1944)
	Rats fed fat-free diet, thiamine, riboflavin, pyridoxine and pantothenic acid and/or cholesterol			Moderate lipotropic action	
Inositol	Rats fed fat-free and methionine-restricted diet	0.16% of diet	21 days	↓ TL (≈ -34%) and CE (≈ -45%) percentages	(Best et al., 1950)
	Rats fed 12%-fat and methionine-restricted diet	0.32% of diet	21 days	No effect on TL percentage	
	Rats fed high-fat (30%) and methionine-restricted diet	0.32% of diet	21 days	No effect on TL percentage	
Inositol	Humans with hepatic dysfunctions	1 g dissolved in 100 mL	-	↓ cholesterolemia	(Gargini, 1951)
Inositol	Rats fed high-fat (51%) diet	2.0 mg (3 x week)	64 days	↓ fat content (-17%)	(Drill, 1954)
		4.0 mg (3 x week)	64 days	↓ fat content (-24%)	
Myoinositol	Rats fed high-sucrose (84%) diet	30 mg	7 days	↓ TL (-67%) and total cholesterol (-35%) contents, ↓ and ↑ 1-^{14}C-acetate incorporation in respectively liver and adipose cholesterol	(Kotaki et al., 1968)
Myo-inositol	Young rats injected large dose of *myo*-inositol	40 mg/rat	1 hour	↑ PI/PC ratio in liver (+45%) and mitochondrial (+8%) microsomes after 1 hour injection	(Yagi and Kotaki, 1969)
Inositol	Rats fed high-cholesterol (1%) diet	0.5% of diet	8 or 12 weeks	↓ TC content (respectively -37 and -56%)	(Chakrabarti and Banerjee, 1969)
Inositol	Rats fed high-fat (51%) diet	3 x 2 mg per week	33 days	↓ fat percentage (-17%, NS)	(Laird and Drill, 1971)
		3 x 4 mg per week	33 days	↓ fat percentage (-24%)	
	Rats fed high-fat (51%) diet and administered 3	3 x 2 mg per	71 days	No significant change	

	x 2 mg choline, 1 μg cobalamin (B12) and 2.5 μg folic acid per week	week			
Myo-inositol	Rats fed a high-sucrose (65.5%), 10%-fat (hydrogenated cottonseed oil) and *myo*-inositol-deficient diet	0.5% of diet	1 week	↓ TG (-61%), cholesterol (-13%), non-esterified FA (-16%) and PL (no significant change) contents	(Hayashi et al., 1974a)
	Rats fed a high-sucrose (65.5%), 10%-fat (hydrogenated cottonseed oil) and *myo*-inositol-deficient diet	0.5% of diet	2 weeks	↓ TG (-81%), cholesterol (-28%) and non-esterified fatty acid (no significant change) contents, ↑ PL content (+14%)	
	Rats fed a high-sucrose (65.5%), 10%-fat (natural cottonseed oil) and *myo*-inositol-deficient diet	0.5% of diet	1 week	Natural *vs* hydrogenated cottonseed oil: no effect on TG and cholesterol contents	
	Rats fed a high-sucrose (65.5%), 10%-fat (hydrogenated soybean oil) and *myo*-inositol-deficient diet	0.5% of diet	1 week	↓ TG (-79%) and cholesterol (-17%) contents	
	Rats fed a high-sucrose (65.5%), 10%-fat (coconut oil) and *myo*-inositol-deficient diet	0.5% of diet	1 week	↓ TG (-36%) and cholesterol (-12%, NS) contents	
Myo-inositol	Rats fed a high-sucrose (65.5%) and *myo*-inositol-deficient diet	No	1 week + 24 hr after palmitate incubation of epididymal fat pads	↑ 2.7 times the rate of [1-^{14}C]palmitate incorporation into liver lipids from labelled epididymal fat pads → ↑ FA mobilization from adipose tissues to the liver	(Hayashi et al., 1974b)
	Rats fed a high-sucrose (65.5%) and *myo*-inositol-deficient diet	No	1 week + 24 hr after palmitate injection in tail vein	↑ 2.5 times the level of [1-^{14}C]palmitate incorporation into liver lipids → ↓ disappearance (by transport and degradation) rate of FA from the liver	
	Rats fed a high-sucrose (65.5%) and *myo*-inositol-deficient diet	No	2 weeks	↓ L-glycerol 3-phosphate (direct precursor of TG) content (-62%)	
Myo-inositol	Lactating rat dams fed *myo*-inositol-deficient and high-sucrose (62.1%) diet + 0.5% phthalylsulfathiozole	0.5% of diet	21 days lactation	↓ TG (≈ -96%) and CE (≈ -95%) contents, ↑ PL (≈ +93%) content, no change in free cholesterol content; numerous large intracellular droplets in *myo*-inositol defcient dams; ↓ plasma FFA (≈ -21%) concentration, ↑ plasma TG (≈ +203%), PL (≈ +38%), PI (≈ +210%), free cholesterol (≈ +31%) and lipoprotein lipid (≈ +46%) concentrations, no change in plasma CE concentration	(Burton and Wells, 1977)
	Lactating rat dams fed *myo*-inositol-deficient and high-sucrose (62.1%) diet + 0.5% phthalylsulfathiozole	0.01, 0.05 and 0.5% of diet	14 days lactation	↓ TL (respectively -75, -75 and -82%), TG (respectively -75, -83 and -96%) and CE (respectively -70, -91 and -96%) contents, ↑ cholesterol (respectively +13, +7 and +29%) and PL (respectively +28, +29 and +91%) contents; distribution of phospholipids: +4.0% PI, -4.3% PE and no significant change for LPC, Sph, PC and PS percentages; ↑ serum VLDL (+159%), IDL (+168%) and HDL (+107%) concentrations, no significant change for serum LDL concentration	
Myo-inositol	Young rats fed high-glucose (60%) and *myo*-inositol-deficient diet	0.5% of diet	7-14 days	↓ TG level (-70%, n = 2 experiments, NS)	(Andersen and Holub, 1980a)
	Old rats fed high-glucose (60%) and *myo*-inositol-deficient diet	0.5% of diet	14 days	↓ TG level (-6%, NS)	
Myo-inositol	Rats fed high-glucose (60%) diet not supplemented with *myo*-inositol	0.075 and 0.5% of diet	7 days	↓ TG level (respectively -48 and -76%)	(Andersen and Holub, 1980b)
	Rats fed high-glucose (60%) and *myo*-inositol- and choline-deficient diet	≈ 0.072 % of diet	7 days	↓ TG level (-71%)	
		≈ 0.072 % myo-inositol % + ≈ 0.015% choline	7 days	↓ TG level (-77%)	
		0.5 % of diet	7 days	↓ TG level (-74%)	
		0.5 % myo-inositol % +	7 days	↓ TG level (-92%)	

		0.056% choline			
Myo-inositol	Rats fed *myo*-inositol-deficient and balanced diet	0.5% of diet	14 days 3 days 12 hours	↓ TG level (≈-70%) ↓ FAS (≈-31%: maximum reached) and ACC/CBX (≈-31%) specific activity ↓ rate of FAS synthesis (≈-40%: maximum reached)	(Beach and Flick, 1982)
Myo-inositol	Rat dam fed *myo*-inositol-deficient and low-protein (8%) diet	0.48% of diet	14 days	↓ neutral lipid content (-67%), no change for PL content	(Leclerc and Miller, 1989)
	Rat dam fed *myo*-inositol-deficient, high-fructose (40%) and normal-protein (20%) diet	0.48% of diet	14 days	↓ neutral lipid content (-78%), no change for PL content	
Inositol	Mice (germ-free *vs* conventional) fed inositol-deficient and high-sucrose (60%) diet	No	23 days	Degree of fatty liver more evident in conventional mice ↓ ME activity/ g protein (≈-50% in germ-free *vs* ≈-27% in conventional mice) ↓ G6PDH activity/g protein (≈-45% in germ-free *vs* ≈-32% in conventional mice) ↓ ACC activity/g protein (≈-32% in germ-free *vs* no change in conventional mice) ↑ plasma TG (+29%, NS), FFA (+38%) and total cholesterol (+15%, NS) levels in germ-free mice ↑ plasma TG (+42%), FFA (+4%, NS) and total cholesterol (+6%, NS) levels in conventional mice	(Ikeda et al., 1992)
Myo-inositol	Rats fed AIN formula diet supplemented with 0.1% DDT	0.2% of diet	13-14 days	↓ TL (-38%), cholesterol (-34%) and TG (-66%) contents ↑ PL content (+8%)	(Katayama, 1993)
Myo-inositol	Rats fed high-starch/high-sucrose (65%) and *myo*-inositol-deficient diet	0.1% of diet	16-17 days	Starch: ↓ TL (-2%, NS), cholesterol (-2%, NS), and TG (-22%, NS) contents; ↑ PL content (+9%, NS); ↓ G6PDH (-26%, NS) and ME (-13%, NS) activities Sucrose: ↓ TL (-47%), cholesterol (-20%), and TG (-74%) contents; ↑ PL content (+6%, NS) ; ↓ G6PDH (-43%) and ME (-34%) activities	(Katayama, 1994)
Myo-inositol	Rats fed high-starch/high-sucrose (65%) and *myo*-inositol-deficient diet	0.1% of diet	12-13 days	Starch: ↓ TL (-3%, NS) and TG (-20%, NS) contents; no effect on cholesterol and PL contents; no effect on plasma TG, cholesterol, PL and FFA levels; ↓ G6PDH (-27%, NS), ME (-19%, NS), FAS (-38%, NS), CCE (-9%, NS) and CBX (-9%, NS) activity/mg protein Sucrose: ↓ TL (-50%) and TG (-81%) contents; no effect on cholesterol and PL contents; no effect on plasma TG, cholesterol, PL and FFA levels; ↓ G6PDH (-39%, NS), ME (-42%, NS), FAS (-29%, NS), CCE (-31%, NS) and CBX (-20%, NS) activity/mg protein	(Katayama, 1997b)
Myo-inositol	Rats fed high-sucrose (65%) diet	0.515% of diet	13 days	↓TL (-34%), TG (-80%), cholesterol (-13%) and PL (-8%, NS) concentrations; ↓G6PDH (-36%) and ME (-23%) activities	(Onomi and Katayama, 1997)
	Rats fed diet with orotic acid (1.5%)	1.03% of diet	8 days	↑TL (+5%, NS), TG (+14%, NS), cholesterol (+10%, NS) and PL (≈ 0) concentrations; ↑G6PD (+58%, NS) and ME (+10%, NS) activity	
Myo-inositol	Rats fed high-starch/high-sucrose (50.2%) and *myo*-inositol-deficient diet	0.2% of diet	14-15 days	Starch: ↓ TL (-19%, NS), TG (-41%, NS) and cholesterol (-5%, NS) levels, ↑ PL level (+9%, NS), no change in plasma TG, cholesterol and PL levels; ↓ and ↑ ME (7%, NS), G6PDH (+5%, NS) and FAS (-4%, NS) activities (/mg protein) Sucrose: ↓ TL (-10%, NS), TG (-29%, NS) and cholesterol (-2%, NS) levels, ↑ PL level (+19%), no change in plasma TG, cholesterol and PL levels; ↓ ME (-19%, NS), G6PDH (-24%, NS) and FAS (-30%, NS) activities (/mg protein)	(Okazaki and Katayama, 2003)
		0.2% +0.07% DDT	14-15 days	Starch: ↓ TL (-34%), TG (-44%), cholesterol (-23%, NS) and PL (-4%, NS) levels, no change in plasma TG, cholesterol and PL levels; ↓ ME (-23%, NS), G6PDH (-41%) and FAS (-30%, NS) activity/mg protein Sucrose: ↓ total lipid (-40%), TG (-40%S), cholesterol (-33%) and	

				PL (-5%, NS) levels; no change in plasma TG, cholesterol and PL levels; ↓ ME (-37%), G6PDH (-44%) and FAS (-21%, NS) activity/mg protein	
Myo-, D-*chiro*-and L-*chiro*-inositol	Rats fed high-sucrose (50.2%) and *myo*-inositol-deficient diet with 0.07% DDT	0.2% *myo*-inositol	14 days	↓ TL (-24%), TG (-62%) and cholesterol (-28%) levels, ↑ PL level (+5%, NS) levels; no change in plasma TG, cholesterol and PL levels; ↓ ME (-42%) and G6PDH (-47%) activity/mg protein; ↑ PI percentage/total PL (+0.9%) and PI/PC ratio (+10%), no change for PC, PE, PS, LPC and Sph percentages/total PL	(Okazaki et al., 2006)
		0.2% D-*chiro*-inositol	14 days	↓ cholesterol (-2%, NS) and PL (-6%, NS) levels, ↑ total lipid (+17%, NS) and TG (+29%, NS) levels; no change in plasma TG, cholesterol and PL levels; ↓ ME (-11%, NS) and ↑ G6PDH (≈ +1%, NS) activity/mg protein; ↓ PI percentage/total PL (-1.3%) and PI/PC ratio (-10%), no significant change for PC, PE, PS, LPC and Sph percentages/total PL	
		0.2% L-*chiro*-inositol	14 days	↑ TL (+23%), TG (+47%), cholesterol (+2%, NS) and PL (+8%, NS) levels; no change in plasma TG, cholesterol and PL levels; ↓ ME (-13%, NS) and ↑ G6PDH (+6%, NS) activity/mg protein; no significant change for PI, PC, PE, PS, LPC and Sph percentages/total PL and for PI/PC ratio	
Myo-inositol	Rats fed high-sucrose (50.3%) and *myo*-inositol-deficient diet	0.2% *myo*-inositol	14 days	↓ TL (-3%, NS), TG (-17%, NS) and cholesterol (-3%, NS) levels, no change in PL level; ↓ ME (-12%, NS) and G6PDH (-28%, NS) activities (/mg protein); no significant effect on serum TG, cholesterol and PL concentrations; no significant change for PI, PE, PS, LPC and Sph percentages/total PL and for PI/PC ratio, ↑ PC percentage (+1.5%)	(Okazaki and Katayama, 2008)
	Rats fed high-sucrose (50.3%) and *myo*-inositol-deficient diet +0.07% DDT	0.2% *myo*-inositol	14 days	↓ TL (-45%), TG (-50%) and cholesterol (-18%) levels, ↑ PL level (+10%); ↓ ME (-29%) and G6PDH (-43%) activity/mg protein; ↓ serum TG concentration (-30%), no significant effect on serum cholesterol and PL concentrations; no significant change for PC, PE, PS, LPC and Sph percentages/total PL, ↑ PI/PC ratio (+7%), ↑ PI percentage (+0.6%)	
B - Magnesium and vitamins B					
B1 - Magnesium					
Magnesium	Heart muscle mitochondria +0.5 mM carnitine or acetylcarnitine	From 0.01 to 5 mM	30 min	↑ palmitate oxidation by ≈ 800% with carnitine and by ≈ 950% with acetylcarnitine	(Fritz, 1959)
Magnesium	Pigeon liver extract containing pantothenic acid	1.13 mM ATP	1 hour	↑ CoA synthesis and ↓ pantothenic acid content	(Andrieux-Domont and Le Van, 1970)
		1.13 mM ATP + 0.67 mM Mg	1 hour	↑ CoA content (≈ +149%) and ↓ pantothenic acid content (≈ -69%) as compared with ATP alone	
B2 - Niacin (vitamin B3)					
Niacin	Rats fed low protein, high fat (40%) and choline-free diet ±0.5% L-cystine	0.375 or 0.15% of diet	3 weeks	No cystine: ↓ TL (-9% for high *vs* low niacin percentage) With cystine: ↓ TL (-16% for high *vs* low niacin percentage)	(Tyner et al., 1950)
Nicotinic acid	Rabbits fed high-cholesterol (2%) diet	0.4% of diet	8 weeks	↓ cholesterol content (-77%)	(Merrill and Lemley-Stone, 1957)
Nicotinic acid	Rats fed hypolipotropic and free-cholesterol diet	1, 2, 3 or 4% of diet	21 days	↓ TC percentage (resp. -12, -22, -42 and -46%)	(Schön, 1958)
Nicotinic acid	Liver slices (of rabbits fed 6 months standard diet) incubated in acetate-1-C^{14}	0.5% of diet	3 hours incubation	↓ TC content (-28%) and relative rate of cholesterol synthesis (-48%)	(Schade and Saltman, 1959)
	Liver slices (of rabbits fed 6 months high-cholesterol diet, 2%) incubated in acetate-1-C^{14}	0.5% of diet	3 hours incubation	↓ TC content (-10%) and relative rate of cholesterol synthesis (-36%)	
Nicotinic acid	Rat liver slices incubated in 2-C^{14} sodium acetate	1 mg/mL solution	2.5 hours	↓ incorporation level of acetate into cholesterol (-33%) and FA (-25%)	(Perry, 1960)

Nicotinic acid	Nondiabetic patients injected with C^{14}-acetate	3 to 6 g	2 weeks	↓ plasma cholesterol (-32%)	(Nunn et al., 1961)
Nicotinic acid	Hypercholesterolemic patients	1 to 2 g three times	-	↓ serum cholesterol suggesting marked reduction in hepatic synthesis	(Parsons, 1961)
Nicotinic acid	Rats fed standard laboratory diet and intramuscularly injected with 0.25 mL of 45% CCl_4 diluted solution	25 mg/100 g b.w. injected	4, 48 and 168 hours	↓ cholesterol (resp. -39, -8 and -11%), TG (resp. -40, -68 and -100%), total lipid (resp. -34, -47 and -28%) and lipid phosphorus (resp. -34, -42% and no change) contents	(Vaishwanar et al., 1972)
	Rats fed standard laboratory diet supplemented with 2% orotic acid	25 mg/100 g b.w. injected	10 days	↓ TL (-45%), lipid phosphorus (-31%) and cholesterol (-31%) contents; ↑ TG content (+7%)	
Nicotinic acid	Rats intragastrically fed with single dose ethanol (6 g/kg, 50% solution) 8 hours before killing	250 mg/kg (intragastrically with a catheter)	10 days	↓ total fat (-43%), neutral fat (-45%) and non-esterified FA (-46%) contents (in mg/100 mg N)	(Baker et al., 1973)
Nicotinamide	33 weeks-old laying hens fed diet without nicotinamide	0.002% of diet	-	↓ fat percentage (-12%)	(Hartfiel and Kirchner, 1973)
	41 weeks-old laying hens fed diet without nicotinamide	0.002 and 0.005 % of diet	-	↓ fat percentage (resp. -16 and -29%)	
	45 weeks-old laying hens fed diet without nicotinamide	0.005 and 0.01 % of diet	-	↓ fat percentage (resp. -8 and no change)	
Nicotinic acid	Hepatocytes isolated from rats fed cereal based stock diet	1 mM	30 min	↑ acetyl-CoA concentration (+39%, mmol per incubation), acetyl-CoA being produced *via* β-oxidation	(Yeh, 1979)
Nicotinic acid	Partially purified ACC from chicken liver incubated *in vitro*	10, 20, 50 and 100 mkmoles/0.9 mL	-	↓ ACC activity (resp. -19, -45, -70 and -100%)	(Fomenko et al., 1979)
Nicotinic acid	Hyperlipidemic male patients	1 g thrice	5 weeks	↑ biliary output of cholesterol (+26%) and lecithin (phospholipids, +17%, NS);	(Grundy et al., 1981)
			48 hours	↓ plasma VLDL-TG activity	
Niacin	HepG2 cells	Incubated from 0.25 to 3 mM	72 hours	↑ accumulation of apoA-I in the incubation medium (min. of +19 for 0.25mmol/L and max. of +47% for 1-2 mmol/L)	(Jin et al., 1997)
	HepG2 cells incubated 16 hours with ^{125}I-apoA-I HDL (100 μg protein/mL) or ^{125}I-apoA-I-containing HDL particles and niacin	Incubated from 0.25 to 3 mM	48 hours preincubation with niacin + 16 hours	↓ ^{125}I-ApoA-I HDL (up to 16%) and ^{125}I-apoA-I-containing HDL particle (up to 17%) uptake	
Niacin	HepG2 cells	Incubated from 0.25 to 3 mM	48 hours preincubation with niacin + 2 hours	↑ ApoB degradation (effect is dose-dependent: +3% at 0.25 mmol/L, +27% at 0.5 mmol/L and +36% at 3 mmol/L)	(Jin et al., 1999)
	HepG2 cells incubated with 0.4 mmol/L oleic acid (inihibits early apoB degradation)	Incubated from 0.25 to 3 mM	48 hours preincubation with niacin + 2 hours	↑ apoB degradation, but less than with niacin alone (+10% at 0.5 mmol/L and +13% at 3 mmol/L)	
	HepG2 cells incubated with ^{14}C-acetate (1 μCi/mL), ^{3}H-glycerol (5 μCi/mL) or ^{3}H-oleic acid (1 μCi/mL)	Incubated from 0.25 to 3 mM	48 hours preincubation with niacin + 4 hours	↓ incorporation of ^{14}C-acetate into TG (≈ -20 to -40%) and FFA (≈ -20 to -40%) ↓ incorporation of ^{3}H-glycerol into TG (≈ -20 to -40%) ↓ incorporation of ^{3}H-oleic acid into TG (≈ -10 to -15%)	
Nicotinic acid	Healthy patients	Increasing doses up to 2 g (500 mg 4 times)	1 month (chronic administration)	↓ VLDL-TG production into plasma (≈ -33% after an overnight fasting and just before acute administration of nicotinic acid)	(Wang et al., 2001)
	Healthy patients i.v. infused with [U-$^{13}C_6$]glucose, [2-$^{13}C_1$]glycerol and [1,2,3,4-$^{13}C_4$]palmitate	500 mg	6 hours (acute administration)	↓ incorporation of glycerol into plasmatic VLDL-TG (≈ -45% at 1 hour and ≈ -40% at 6 hour); ↓ plasmatic VLDL-TG palmitate enrichment (≈ -21% at 1 hour and ≈ -40% at 6 hour)	
Niacin	Human hepatoblastoma (Hep G2) cells incubated with with [1-^{14}C]oleoyl-CoA and	From 0.05 to 3.0 mM	30 min	↓ total DGAT activity (dose-dependent with a maximum at 3.0 mM niacin: -35 to 50% inhibition, n = 6 experiments) and	(Ganji et al., 2004)

	sn-1,2-dioleoylglycerol			selectively ↓ DGAT-2 activity (-100%), not DGAT-1 activity (no change)	
Copper nicotinic acid complex	Rats fed high-carbohydrate (40% starch and 40% sucrose) and fat-free semi-syntehtic diet	400 mg/kg Cu-nicotinate complex (stomach tubing)	1, 2, 3 and 4 weeks	↓ TL content (resp. -47, -59, -70 and -82%)	(Salama et al., 2007)
Niacin	*APOE*3Leiden.CETP* transgenic mice (develop atherosclerosis upon cholesterol feeding and respond in a human-like manner to drugs used for treatment of CVD) fed a Western-type diet	0.03, 0.1, 0.3 or 1% of diet	3 weeks	↓ TG (-38%), TC (-21%), FC (-15%) and CE (-22%) contents (μg/mg protein); ↓ CETP mRNA expression (-74% at 0.1% niacin and -88% at 1% niacin); ↓ dose-dependently uptake of ^{125}I-activity by liver (≈ -35% at 0.1% niacin and ≈ -42% at 1% niacin)	(Van Der Hoorn et al., 2008)
Niacin	Hyperlipidemic male patients fed therapeutic lifestyle changes diet	500 mg from 1 to 4 weeks, 1 g from 5 to 8 weeks and 2 g from 9 to 12 weeks	12 weeks	↓ plasma TC (-14%) and TG (-49%) concentrations ↑ plasma HDL-C concentration (+35%) Plasma ApoA-I: ↑ concentration (+16%) and production rate (+21%); no significant effect upon fractional catabolic rate Plasma ApoA-II: no effect upon concentration, production rate and fractional catabolic rate Plasma ApoB-100 in TG-rich lipoprotein: ↓ concentration (+-39%) and ↑ fractional catabolic rate (+48%); no significant effect upon production rate Plasma ApoB-48 in TG-rich lipoprotein: ↓ concentration (+-28%) and ↑ fractional catabolic rate (+46%); no significant effect upon production rate	(Lamon-Fava et al., 2008)
Niacin	HepG2 cells preincubated with or without niacin for 48 hours, then incubated 16 hours with ^{125}I-labeled HDL (5-10 μg/mL)	0.25, 0.5 and 1 mM	48 + 16 hours	↓ surface expression of ATP synthase β chain in HepG2 cell (resp. -8, -24 and -27%) and ↓ ^{125}I-labeled HDL uptake by HepG2 cell (resp. -17, -34 and -35%)	(Zhang et al., 2008)
Niacin	HepG2 cells	1 and 5 mM	48 hours	↑ ABCA1 (resp. ≈ 1.35 and 1.45-fold) and PPARα (resp. ≈ 1.35 and 1.95-fold) gene expression; no significant effect upon ApoA-1 transcription levels	(Siripurkpong and Na-Bangehang, 2009)
	HepG2 cells first loaded 24 h with cholesterol	1, 3 and 5 mM	48 hours	↓ intracellular cholesterol (resp. ≈ -20, -36 and -32%)	
B3 - Pantothenic acid (vitamin B5)					
Pantothenic acid	Dogs fed high-sucrose (66%) and pantothenic acid-deficient diet	No	≥ 4 weeks	↑ fat percentage (+202%); necropsy reveals fatty livers	(Schaefer et al., 1942)
Pantothenic acid	Rats fed high-glucose (73%) and pantothenic acid-deficient diet and injected i.p. with PAB (1 and 2.5 mg)	No	4 months	↓ acetylation percentage of PABA (-27% and -45% for respectively 1 and 2.5 mg injected PABA; pantothenic acid being constitutive of acetyl-CoA a coenzyme necessary for acetylation process and fatty acid β-oxidation)	(Riggs and Hegsted, 1948)
Pantothenic acid	Rats with liver steatosis provoked by phosphorus	0.0025 or 0.005% of diet	30 days	↓ TL percentage (respectively -48 and -55%)	(Catolla Cavalcanti and Levis, 1950)
Pantothenic acid	Rats fed high-sucrose (59%) and pantothenic acid-deficient diet	0.001, 0.002 or 0.005% of diet	16 days	↓ TL percentage (respectively -51, -51 and -62%)	(Turchetto et al., 1955)
Pantothenic acid	Patients with various liver damages intramuscularly injected with pantothenic acid	20 mg	6 hours	Pantothenic acid deficiency exists in patients with liver diseases leading to impairment of liver functions, notably hypuric acid synthesis that involves CoA, and the metabolism of α-keto acid and cholesterol	(Ueshima et al., 1956)
Pantothenic acid	Rats fed control diet	5 mg	5 days	↑ CoA content at 1 (+34%) and 2 (+18%) days; ↓ CoA content from 3-5 days (-8, -28 and -15%)	(Causi et al., 1958)
Ca-pantothenate	Rats fed pantothenate-deficient diet	0.002% of diet	10 weeks	↑ CoA content (+39%)	(Aiyar et al., 1959)
Ca-pantothenate	Rats fed pantothenic acid-deficient diet	No	2, 4 and 6 weeks	Marked increase of fat droplets in the centrolobular and periportal areas at 4 and 6 weeks, and in mid zonal areas at 4 weeks	(Wirtschafter and Walsh, 1962)
Pantothenic acid	Cats fed calcium pantothenate-deficient (0, 1 and 3 mg/kg) diet	No	2-9.5 months	Marked fatty metamorphosis and fine and coarse vacuolar formation with lipids evenly deposited (no zonal preference)	(Gershoff and Gottlieb, 1964)
Pantothenic acid	Guinea pigs fed pantothenic acid-deficient diet	No	25 days (means)	↓ CoA concentration (-51%); ↑ fat concentration (+1112%, also ascribed to ↓ food intake)	(Hurley et al., 1965)

	Offspring of a transitory pantothenic acid deficiency during gestation in guinea pigs	No	Deficiency during the 10^{th}, 9^{th}, 7^{th} and 6^{th} week	<u>Killed at birth</u>: ↑ fat percentage (resp. ≈ +35, +18 and +25%); ↓ fat percentage (-21%)/6^{th} week deficiency <u>Killed at 7 days</u>: ↑ fat percentage (resp. ≈ +33, +260 and +13%); ↓ fat percentage (-7%)/7^{th} week deficiency	
Pantothenate	Rats fed low- (6%) or high- (18%) fat and pantothenate-deficient diet	0.003%	6 weeks	↑ total (resp. +50 and +25%), acid-soluble (resp. +44 and +29%) and long-chain acyl CoA (resp. +64 and +18%) contents	
Calcium pantothenate	Rats fed low-protein (5% casein) diet	0.01% of diet	3 weeks	↓TG content (-23%); ↑ total-coA (+4%) and acyl-coA (+21%) activities	(Osumi et al., 1969)
	Rats fed low-protein (5% casein) diet for 3 weeks then commercial standard diet for 4 days	0.01% of commercial standard diet	4 days	↓TG content (≈ -79%) relative to low-protein diet and ↓TG content (≈ -40%) relative to commercial standard diet ↓oleic acid percentage (≈ -42%) relative to low-protein diet and ↓ oleic acid percentage (≈ -27%) relative to commercial standard diet ↑ stearic acid percentage (≈ +25%) relative to low-protein diet and ↑ stearic acid percentage (≈ +10%) relative to commercial standard diet ↑ arachidonic acid percentage (≈ +75%) relative to low-protein diet and ↑ arachidonic acid percentage (≈ +9%) relative to commercial standard diet	
Ca-pantothenate	Duckling fed pantothenate-deficient diet	No	21 days	↑ lipid percentage (+17%, NS); ↑ total cholesterol (+5%, NS) and CE (+10%, NS)	(Saheb and Demers, 1972)
Ca-pantothenate deficiency	Rats fed daily a vitamin tablet of 0.2 mg pantothenic acid	No	75-116 days	↓ microsomal PC content (-40%); no significant effect on microsomal PE, PI, PS, Sph and lysolecithin contents	(Mahboob, 1975)
Pantothenate	Weanling rats fed pantothenate-deficient diet	No	11, 22, 33 or 44 days	↓total CoA (resp. -10, -28, -36 and -27%), free CoA (resp. -24, -18, NS, -42 and -52%), short-chain acyl-CoA (resp. -8, NS, +12, NS, -13, NS and -38%) and long-chain acyl-CoA (resp. +2%, NS, -57, -38 and -41%) concentrations; ↓CoASH/total CoA ratio (resp. -6, -2, NS, -24 and -17%), ↓total solubilized CoA and the CoA biosynthetic precursor (resp. -24, -37, -43 and -60%) concentration	(Moiseenok et al., 1987)
Pantothenic acid and pantethine	Rats i.p. injected with a single dose of CCl_4 (0.5 mL/kg) after 5 days pantothenic acid/pantethine daily i.p. injection	i.p. dose of 500 mg/kg (pantethine) i.p. dose of 100 mg/kg (pantotehnic acid)	12 or 24 hours	<u>Pantethine</u>: At 12 hr: ↓TG content (-37%), ↑ total cholesterol (+13%, NS) and CE (+10%, NS) contents At 24 hr: ↓TG (-16%), total cholesterol (-6%, NS) and CE (-10%, NS) contents <u>Pantothenic acid</u>: At 12 hr: ↓TG content (-34%), ↑ total cholesterol (+12%, NS) and CE (+8%, NS) contents At 24 hr: ↓TG (-8%, NS), total cholesterol (-13%) and CE (-20%) contents	(Nagiel-Ostaszewski and Lau-Cam, 1990)
Pantothenic acid	Dogs fed commercial-type food mash initially containing 0.0025% pantothenic acid and supplemented with calcium hopantenate (pantothenic acid antagonist, 30 mg/kg/day for 4 weeks, then 50, 100 and 200 mg/kg/day each weeks)	Same quantities as calcium hopantenate	8 weeks	Antagonist produces hepatic steatosis by inducing pantothenic acid deficiency: 6/7 dogs had macroscopically fatty liver and all had microvesicular steatosis on light microscopy → such damages were not observed in dogs supplemented with pantothenic acid	(Noda et al., 1991)
D-Pantothenic acid, hemi-calcium salt	Valproate[d]-treated suckling mice (s.c. injection of 20 mL/kg)	2 mmol/kg co-injected	90 min	↑ CoA (+46%), acetyl CoA (+70%, NS) and medium-chain acyl CoA (+31%) levels	(Thurston and Hauhart, 1992)
Pantothenic acid	Rats fed pantothenic acid-deficient diet for 4 weeks, then supplemented with pantothenic acid during the fifth week	100 mg/kg	≈ 1 week	↓peroxisomal β-oxidation (-38%) and ↓long-chain acyl-CoA synthetase activity after pantothenic acid deficiency → complete restauration upon pantothenic acid supplementation	(Youssef et al., 1994)
Pantothenic acid derivatives (CoA precursors)	Mice with hypothalamic obesity induced by aurothioglucose injected i.p. (300 mg/kg) for 6 weeks → supplementation with pantothenic acid derivatives during the last 10 days	150 mg/kg	10 days	<u>Phosphopantothenate</u>: ↓ TG (-38%), total cholesterol (-7%, NS), CE (-48%, NS) and FFA (-5%, NS) contents; no significant change in total PL content; ↑ free cholesterol content (+11%) <u>Pantethine</u>: ↓ TG (-29%), total cholesterol (-24%), free cholesterol (-15%, NS) and CE (-46%, NS) contents; no significant change in total PL content; ↑ FFA content (+38%)	(Naruta and Buko, 2001)

				Panthenol: ↓ TG content (-42%), total cholesterol (-26%), CE (-16%) and CE (-54%) contents; no significant change in total PL content; ↑ FFA content (+43%)	
B4 - Folates (vitamin B9)					
Folic acid	Rats fed high-sucrose (58%) and 10% glycine diet	0.0005% of diet	60 days	↓total FA content (-36%)	(Kelley et al., 1950)
	Rats fed high-sucrose (56%), 10% glycine and 2% ribonucleic acid diet	0.0005% of diet	60 days	↓total FA content (-56%)	
	Rats fed high-sucrose (68%) diet	0.0005% of diet	45 days	↓cholesterol content (-8%, NS); ↓total FA content (-46%); ↓neutral fat percent (-84%); ↑ PL percent (+7%, NS)	
	Rats fed high-sucrose (58%) and 10% glycine diet	0.0005% of diet	45 days	↓cholesterol content (-6%, NS); ↓total FA content (-46%); ↓neutral fat fatty acid percent (-89%); ↑ phospholipide FA percent (+43%, NS)	
	Rats fed high-sucrose (66%), 2% ribonucleic acid and vitamin B12 (5 μg/100 g) diet	0.0005% of diet	45 days	↓cholesterol content (-51%) and ↓total FA content (-75%); ↓neutral fat fatty acid percent (-94%); ↑ phospholipide fatty acid percent (+124%, NS)	
Folic acid	Rats fed high-fat (51%) diet	2.5 μg (3 x week)	64 days	↓fat content (-13%)	(Drill, 1954)
		25.0 μg (3 x week)	64 days	↑fat content (+11%)	
Folic acid	Rats fed high-fat (51%) diet with + 2 mg/day choline and + 1 μg vitamin B12/day	25 μg	64 days	↓fat content (-6%)	
Folic acid	Rats fed high-fat (51%) diet and injected 3 times weekly with 1 μg vitamin B12 and 2 mg choline in solutions	25.0 μg (3 x week)	64 days	↓fat percentage (-48%)	(Laird et al., 1965)
Folate deficiency	Micropigs fed standard diet ±folates in excess requirement (14 μg/kg b.w.) ±ethanol (40% of energy)	No (complete deletion from vitamin mix)	14 weeks	Liver histology: abnormal histopathology demonstrating features of steatosis, necrosis and inflammation compared to other 3 groups (normal folates, folate deficient and normal folate +ethanol) Ethanol + folate *vs* normal + folates: ↓methionine level (-39%) Ethanol - folate *vs* normal + folates: ↓methionine level (-68%) Normal *vs* normal - folates: ↓methionine level (-25%) No significant effect of folate deficiency on MS activity Ethanol - folates *vs* ethanol + folates: ↑BHMT (+14%)	(Halsted et al., 2002)
Folic acid	Micropigs fed standard diet with excess choline (60.3 mg/kg b.w.) and methionine (675 mg/kg b.w.) ±folates and ±ethanol (40% of energy)	No	14 weeks	Significant effect on gene expression in relation with lipid metabolism *vs* control (standard diet + folates): • Standard diet - folates: ↓ long-chain acyl-coenzyme A dehydrogenase (2.10-fold) and farnesyl diphosphate synthase (3.60-fold) gene expression • Ethanol diet - folates: ↓ long-chain acyl-coenzyme A dehydrogenase (2.50-fold) and farnesyl diphosphate synthase (7.39-fold) gene expression Without ethanol: folate deficiency ↑ SREBP-1c mRNA (≈ +67%) and nuclear protein (≈ +125%) expressions; folate deficiency ↑ ACC (≈ +50%) and SCD (≈ +160%) mRNA expressions; folate deficiency had no effect on FAS mRNA expression With ethanol: folate deficiency ↑ SREBP-1c mRNA (≈ +11%) and nuclear protein (≈ +78%) expressions; folate deficiency ↑ ACC mRNA expression (≈ +20%) and ↓SCD mRNA expression (≈ -8%); folate deficiency had no effect on FAS mRNA expression	(Esfandiari et al., 2005)
Folic acid	Fetal liver from female rats fed folic acid-deficient (AIN)-76 formula diet	No	21 days of gestation	Affects fat metabolism: ↑ PEBP (+36%), 4-trimethylaminobutyraldehyde dehydrogenase (+44%) and dienoyl-CoA isomerase (+44%) relative abundance (*i.e.* up-regulation); ↑ L-CPT-1 (+174%) and ↓CD36 (-40%) gene expression	(Mcneil et al., 2009) {Christensen, 2010 #23801}: folate deficiency in mice

[a]All terms used in the Table are precisely those of the article considered: for exemple, the hepatic content in TG was named “content”, “concentration” or “level”, and in some case no term was used; studies reporting both lipotrope-like and non-lipotropic effects (*i.e.* an increase in hepatic lipid content and/or lipogenic enzyme activities) are also presented to allow compar
relevant interpretations

[b]Indicates the decreased or increased percentage induced by the lipotrope compared to the control, *i.e.* steatogen diet (NS - Not Significant - means absence of significativity for the change observed; in other cases, the effect was either significant or no information was given in the article)

[c]No data given in the reference

[d]Valproate is an antiepileptic drug and it may inhibit fatty acid oxidation in rat hepatocytes (Coudé et al., 1983) and produces important decreases in hepatic free CoA, acetyl-CoA and free carnitine levels (Thurston et al., 1985)

ABBREVIATIONS: ABCA1, ATP-Binding Cassette transporter A1 (also known as the Cholesterol Efflux Regulatory Protein or CERP, effluxes excess cellular cholesterol to ApoA-1 to form nascent HDL); ACC/CBX, Acetyl-CoA Carboxylase; Ain, American Institute of Nutrition; ALT, ALanine aminoTransferase; ApoA/B, Apolipoprotein A/B; ATP, Adenosite TriPh
Betaine Homocysteine MethyTransferase; b.w., body weight; CCE, Citrate Cleavage Enzyme (or ATP-Citrate Lyase, ATPCL); CCl_4, Carbone tetrachloride; CD36, fatty acid translocase (long chain fatty acid transporter); CDP-E, CytidineDiphospho-Ethanolamine; CE, Cholesteryl Esters; CETP, Cholesteryl Ester Transfer Protein (plasma protein that facilitates the transp
esters and triglycerides between the lipoproteins, *e.g.* mediates the transfer of cholesteryl esters from HDL to pro-atherogenic apoB-lipoproteins); CoA, Coenzyme A; L-CPT, Liver type Carnitine Palmitoyl Transferase; DDT, DichloroDiphenylTrichloroethane; DGAT, DiacylGlycerol AcylTransferase (plays a central role in esterification of fatty acids to form TG); DRG,
(mainly 1,2-*sn*- species); FAS, Fatty Acid Synthase/Synthetase; FA, Fatty Acid; FC, Free Cholesterol; FFA, Free Fatty Acid; G6PDH, Glucose-6-Phosphate DeHydrogenase; HCl, HydroChloric acid; HDL, High Density Lipoprotein; HU, Hounsfield Unit measured by computed tomography; i.p., intraperitoneally; IR, Insulin Resistance; LDL, Low Density L
LysoPhosphatidylCholine; ME, Malic Enzyme; mRNA, messenger RiboNucleic Acid; MS, Methionine Synthase (involved in methylation of homocysteine into methionine); NAFLD, Non-Alcohol Fatty Liver Disease; NASH, NonAlcoholic SteatoHepatitis; NS, Not Significant; PABA, Para-AminoBenzoic Acid; PC, PhosphatidylCholine; PE, PhosphatidylEthar
PhosphatidylEthanolamine-Binding Protein; PI, PhosphatidylInositol; PL, PhosphoLipids; PPARα, Peroxisome Proliferator-Activated Receptor alpha; PS, PhosphatidylSerine; resp., respectively; SAM, S-AdenosylMethionine; s.c., subcutaneously; SCD, Stearoyl-CoA Desaturase (catalyzes the rate-limiting step in the biosynthesis of monounsaturated FA and its deficienc
acid oxidation by activating hepatic AMP-activated protein kinase); Sph, Sphingomyelin; SREBP, Sterol Regulatory Element-Binding Proteins; TC, Total Cholesterol; TG, TriGlyceride; TL, Total Lipids; VLVL, Very Low Density Lipoprotein

Supplemental Table 2 ***In vivo, ex vivo*** **and** ***in vitro*** **studies reporting effects on hepatic lipid metabolism following deficiency or supplementation of carnitine, hydroxycitric acid, organosulfur compounds, mono- and poly-unsaturated f short-chain fatty acids, melatonin, tocotrienol, policosanol and** ***para*****-aminobenzoic acid**[a]

Lipotropic compounds	*In vivo* or *in vitro* models	Supplemented daily dose	Duration of lipotrope exposition	Hepatic effect(s)	References
Carnitine					
dl-carnitine hydrochloridre	Rat liver slices incubated with C^{14} long-chain FA (from 63 to 142 μM), *i.e.* octanoate, palmitate and stearate	0.3 mM	1 hour	↑ FA oxidation in carboxyl group of β-ketonic acids (from +3.3% for octanoate to +111% for stearate)[b] and in CO_2 for stearate only (+9.5%)[b]	(Fritz, 1959)
	Rat liver particulates incubated with C^{14} long-chain FA (from 63 to 142 μM) *i.e.* butyrate, octanoate, laurate, palmitate and stearate	0.3 mM	30 min	↑ FA oxidation in CO_2 (from +1.5 for octanoate to +106% for stearate) and in carboxyl group of β-ketonic acids (from +3% for octanoate to +470% for stearate)	
DL-Carnitine	Homogenates and slices from rat liver	0.5 mM	30 min	↑ palmitate oxidation (resp. ≈ +50 and ≈ +7°%)	(Fritz, 1964)
	Liver slices from rat	0.1 or 1 mM	30 min	↑ palmitate conversion into CO_2 (resp. ≈ +30 and ≈ +37%) and ketones (resp. ≈ +260 and ≈ +400%); no effect on plmitate conversion into lipids (free of FFA); ↓ palmitate conversion into FFA (≈ 0 and ≈ -50%)	
	Liver homogenates (from rats)	0.5 mM	30 min	↑ palmitate conversion into CO_2 (≈ +22%); ↓ palmitate conversion into neutral glycerides (≈ -47%) and PL (≈ -39%)	
DL-Carnitine	Rats fed choline-methionine-deficient, high-fat (30%) and 10% (α-protein) or 9% protein (casein) diet	0.00016% of diet	14 days	↓ TL[3] (-38 for α-protein-based diet and -25% for casein-based diet)	(Khairallah and Wolf, 1965)
	Rats fed low protein and methionine diet and supplemented with:				
	- 0.3% L-methionine	0.2% of diet	14 days	↓ TG content (-53%)	
	- 0.2% L-methionine	0.2% of diet	14 days	↓ TG content (-35 and -21%, NS, n = 2 experiments)	
	Rats fed threonine-imbalanced diet	0.2% of diet	14 days	↓ TG content (-47%)	
Carnitine	Rats fed control diet and then injected i.p. with ethanol (4 g/kg b.w.) 24 and 12 hours before killing	0.1 and 0.5 mg/kg b.w. injected with ethanol	24 hours	↓ TG content (-43% at 0.5 mg/kg b.w.); tended to ↑ at 0.1 mg/kg b.w. (+16%) ↓ TL content (resp. -19 and -18%)	(Hosein and Bexton, 1975)
DL-Carnitine	Protein-depleted rats fed a 8% protein diet from plant sources	-[c]	4, 8, 12, 16 and 32 days	↓ fat (TG, cholesterol and FFA) content; ↓ fat content to normal content found in rats fed adequate protein diet	(Hu, 1975)
Carnitine	Hepatocytes from rats fed high-sucrose and free-fat diet incubated with glucagons and RMI 14,514 (inhibits hepatic fatty acid synthesis and malonyl-CoA formation)	1 mM	15-60 min	↑ stimulation of FA oxidation (+29%) and ketogenesis (+56%)([1-^{14}C]oleate converted into respectively total acid-soluble products and CO_2 and ketones)	(Mcgarry and Foster, 1979)
DL-Carnitine	Rats infused with hypercaloric TPN diet	10, 50 and 100 mg/100 g b.w.	14 days	↓ fat percent (resp. -12, -27 and -32% on a d.w.b.)	(Tao et al., 1981)
DL-Carnitine	Rats fed ethanol-rich (36% of calories) diet	1% of diet	8 weeks	↓ TL (-44%) and TG (-62%) contents; ↓ cholesterol content but to a lesser extent	(Sachan and Rhew, 1982)
DL-Carnitine	Rats fed liquid ethanol diet	1% of diet	8 weeks	↓ TL (-43%), TG (-48%), TC (-26%), FC (-8%) and PL (-27%)	(Sachan and Rhew, 1983)
DL-Carnitine, L-lysine + L-methionine (carnitine precursors) or DL-carnitine + L-lysine + L-methionine	Rats fed liquid ethanol (36% of energy) diet	1%, 0.5 + 0.2% or 1.7% of diet	56 days	↓ TL (≈ -50%), TG (≈ -50%), cholesterol (≈ -50%) and PL (≈ -50%)	(Rhew and Sachan, 1983)
DL-Carnitine-HCl	Rats fed ethanol-rich (36% of calories) diet	1% of diet (±0.5% L-lysine-HCl and 0.2% L -methionine, 2	56 days	Ethanol *vs* ethanol+carnitine: ↓ TL (-28%), TG (-62%), CE (-28%), FC (-14%), TC (-26%), PL (-20%) and FFA (+9%, NS) Ethanol *vs* ethanol+lysine+methionine: ↓ TL (-24%), TG (-46%), CE (-24%), FC (-11%), TC (-22%), PL (-	(Sachan et al., 1984)

		carnitine precursors)		13%, NS) and FFA (+32%) Ethanol *vs* ethanol+carnitine+lysine+methionine: ↓ TL (-27%), TG (-47%), CE (-31%), FC (-14%), TC (-28%), PL (-2%, NS) and FFA (+24%, NS)	
DL-Carnitine	Rats fed liquid ethanol diet	0.1, 0.4, 0.8, 1.2 or 1.6%	45 days	↓ TL (resp. -12, -33, -55, -53 and -38%) and TG (resp. -6, -31, -66, -63 and -53%) concentrations	(Rhew and Sachan, 1984)
L-Carnitine Carnitine deficiency	Pregnant rats fed wheat gluten (unsupplemeted, *i.e.* 1% lysine, or supplemented with 7 or 12% lysine)-based diet at a low or high protein level (lysine is a carnitine precursor); controls are nonpregnant rats	7 or 12% of proteins	21 days of gestation	Low protein level: ↓ TG content for nonpregnant rats (resp. -48 and -34%, NS) and pregnant rats (resp. -45%, NS, and -32%, NS) No signicant effect on PL content in nonpregnant rats (resp. -4 and +5%); ↓ PL content in pregnant rats (resp. -9%, NS, and -14%, NS) No significant effect on cholesterol content for both un- and pregnant rats High protein level: No significant effect on TG, Pl and cholesterol contents for both un- and pregnant rats	(Ortega, 1989)
DL-Carnitine	Rats fed liquid ethanol-rich (36% of calories) diet	0.1, 0.4, 0.8, 1.2 or 1.6% of diet	46 days	TL: resp. -11 (NS) -33, -55, -47 and -38% TG: resp. -4 (NS), -31, -64, -61 and -52% FC: resp. -1 (NS), -10 (NS), -14 (NS), -7 (NS), and -2% (NS), CE: resp. -3 (NS), -4 (NS), -15 (NS), -5 (NS) and +9% (NS) TC: resp. -2 (NS), -6 (NS), -15, -6 (NS) and +6% (NS) PL: resp. +5 (NS), -8 (NS), -6 (NS), -4 (NS) and -16 (NS) ↑ nonesterified FA concentrations (NS): resp. +0.3, +16, +19, +19 and +25%	(Rhew and Sachan, 1986)
L-Carnitine	3 females on home parenteral nutrition (carnitine deficiency) with abnormalities in standard liver function tests (notably moderate or severe steatosis, *i.e.* grade ≥2)	1 g daily i.v.	1 month	Liver histology (light microscopy): no significant change in the grade of steatosis No significant effect on TG content (resp. +4, +34 and +25%)	(Bowyer et al., 1988)
Carnitine	Rats fed high-fat (30%) or high-cholesterol (1% + 0.25% cholic acid)	0.3% of diet	1, 2, 3 weeks or 10 days	High-fat *vs* high-fat+carnitine: 1 week: ↓ TL (-12%, NS), TG (-20%) and cholesterol (-30%) levels 2 weeks: ↓ TL (-24%), TG (-12%, NS) and cholesterol (-1%, NS) levels 3 weeks: ↓ TL (-7%, NS), TG (-19%) and cholesterol (-15%) levels Control *vs* Carnitine (3 weeks): ↓ TL (-3%, NS), TG (-10%, NS) and cholesterol (-22%) levels Cholesterol *vs* chol+carnitine (10 days): ↓ TL (-7%, NS) and TG (-8%, NS) levels; ↑ cholesterol level (+16%, NS)	(Shimura and Hasegawa, 1993)
L-Carnitine-HCl	*jvs*/*jvs* mice (homozygous mutant strain that develops a swollen fatty liver)	1 mg injected i.p. from 10-30 days, then 2 mg from 30-56 days	2, 4 and 8 weeks for killing	↓ relative CPT II mRNA abundance: - at week 4: from ≈ 2.7 to ≈ 1.5-fold compared to control (+/+) at 1 - at week 8: from ≈ 2.8 to ≈ 1.2-fold compared to control (+/+) at 1	(Hotta et al., 1996)
Carnitine	Normal and cirrhotic rats (treated 10 weeks with CCl_4) then submitted to TPN (40% energy as fat)	100 mg/kg b.w.	1 week	Normal rats: ↓ TG (-57%) and cholesterol (-32%) contents Cirrhotic rats: ↓ TG (-51%) and cholesterol (-22%) contents Histological observations: ↓ severity of steatosis	(Liang et al., 1999)
Carnitine-deficiency	Rats fed vegetarian food poor in carnitine and fed THP (20 mg/100 g/day)	-	6 weeks	↓ CPT I activity (-24%) and [1-^{14}C]palmitic acid β-oxidation (-48%); ↑ total CoA in total liver (+39%) and liver cytosol (+78%); ↓ total CoA in liver mitochondria (-32%); ↑ hepatic VLDL production; ↑ peroxisomal fatty acid acyl-CoA oxidase activity (≈ +36%)	(Spaniol et al., 2003)
L-Carnitine L-tartrate	Ovariectomized rats fed AIN-93M diet	0.015% of diet	8 weeks	↓ total TG content (-38%)	(Clark et al., 2007)
Carnitine-deficiency	Mildronate (that yields carnitine depletion)-treated rats (fed *vs* fasted state)	-	10 days	Fed state: ↑ TG content (+275%); ↓ PL (-22%), FFA -7%, NS), total acyl-CoA (-11%, NS) and malonyl-CoA (-17%, NS) contents Fasted (18 hours) state: ↑ TG (+815%) and FFA (+70%) contents; ↓ PL (-36%), total acyl-CoA (-4%, NS) and malonyl-CoA (-33%, NS) contents	(Degrace et al., 2007)
	Perfused livers from mildronate-treated rat (fed	-	90 min	Fasted state: ↓ palmitate oxidation/metabolisation level (≈ -50%); ↑	

	vs fasted state) with [1-^{14}C]palmitic acid			palmitate esterification level into TG (≈ +116%); ↓ palmitate esterification level into PL (≈ -35%); no change in CTPpct, ApoB, LPL and PPARγ2 mRNA levels; ↑ DGAT1 (≈ +90%), LDLR (≈ +120%), FAT/CD36 (≈ +40%), FABpm (≈ +40%), ACO (≈ +335%) and PPARα (≈ +20%, NS) mRNA levels Fed state: no change for levels of oxidation and esterification; ↓ FABPpm (≈ -50%); no change in CPT Iα and CPT Iβ isoforms, mRNA, mtGPAT, microsomal DGAT1, CTPpct, ApoB, LDLR, LPL and FAT/CD36 mRNA levels	
L-Carnitine	Rats fed high-fat (hydrogenated fat - HF - rich in saturated fatty acids *vs* peanut oil - PO - rich in monounsaturated fatty acids, 30% as energy) diet ±exercise (1 hour swimming 6 days a week): *i.e.* sedentary (S) *vs* exercised rats (E)	0.5% of diet (d.w.b.)	24 weeks	↓ and ↑ total fat content (-2% for HFS, NS, -12%, NS for POS, +3%, NS, for HFE and -2%, NS, for POE) ↓ TG content (-31 for HFS, -14%, NS, for POS, -12%, NS, for HFE and -23%, NS, for POE) ↑ cholesterol content (resp. +44% for HFS, +22%, NS, for POS, +33% for HFE and +11%, NS, for POE) ↑ FFA contents (+18% for HFS, NS and +20% for POS, NS) and ↓ (-48% for HFE and -42% for POE)	(Karanth and Jeevaratnam, 2009)
Hydroxycitric acid (HCA)					
(-)-Hydroxycitrate (from *Garcinia cambogia*)	Citrate + purified CCE from livers of rats fed a high-fructose diet (to reach high levels of enzyme)	3.5 mM and 35 μM	≥ 15 min incubation	At 3.5 mM: ↓CCE activity (-62% for 24 mM citrate) At 35 μM: ↓CCE activity (-65 and -31% for resp. 0.3 and 9 mM citrate)	(Watson et al., 1969)
(-)-*Allo*-hydroxycitrate (from *Hibiscus sabdariffa*)	Citrate + purified CCE from livers of rats fed a high-fructose diet	5 mM, 50 and 5000 μM	≥ 15 min incubation	At 5 mM: changes CCE activity (-19% for 0.9 mM and +7% for 24 mM citrate) At 50 μM: changes CCE activity (+3% for 0.3 mM and -4% for 9 mM citrate) At 5000 μM: ↓CCE activity (-81 and -22% for resp. 0.3 and 9 mM citrate)	
Sodium (-)-hydroxycitrate	Rats fed 10-15 days with high-glucose/high-fructose (58%) diet, then i.v. injected with ^3H_2O 45 min after i.p. HCA injection and killed 45-60 min after ^3H_2O injection	From 0.1 to 4.0 mmoles/kg b.w.	i.p. injection 45 min before ^3H_2O injection	↓ FA synthesis (-25-30% at 0.1 mmole/kg b.w.) High-fructose: ↓ FA synthesis (≈ -67, -73, -77 and -82% at resp. ≈ 0.6, 1.3, 2.3 and 4.0 mmoles/kg b.w.) High-glucose: ↓ FA synthesis (≈ -55, -74 and -85% at resp. ≈ 0.3, 0.8 and 1.5 mmoles/kg b.w.)	(Lowenstein, 1971)
(-)-Hydroxycitrate lactone (from *Garcinia cambogia*)	Liver high-speed supernatants collected 5-7 days after feeding rats with a high-glucose (70%) diet, and added with 5 or 10 μmol/mL of [1,5-^{14}C]citrate	From 0.01 to 2.0 mM	20 min incubation	↓ dose-dependently rate of lipogenesis (from 16 to 79% for 5 mM citrate and from 6 to 59% for 10 mM citrate)	(Sullivan et al., 1972)
	Liver slices from rats killed 5-7 days after being fed with a high-glucose (70%) diet, and added with [^{14}C]alanine (fatty acid precursor, 10 μCi/g tissue)	From 5 to 5000 mM	60 min incubation	↓ dose-dependently rate of lipogenesis (from 7 to 57%)	
	Rats fed 12 days with high-glucose (70%) diet, then i.v. injected with [^{14}C]alanine and killed 5 hours after beginning of feeding	0.017 mmol/kg b.w. injected i.v.	Injected 0, 30, 90 and 120 min before radioactive pulse	↓rate of lipogenesis (resp. -42, -52, -60 and -34%)	
	Rats fed 12 days with high-glucose (70%) diet, then i.v. injected with [^{14}C]alanine and killed 5 hours after beginning of feeding	5.23 mmoles/kg b.w. fed orally (by stomach tube)	From 2 hour before to 4.5 hours after beginning of feeding	↓rate of lipogenesis 2.0 (-54%), 1.5 (-64%), 1.0 (-77%) and 0.5 (-76%) hour before and 1.0 hour after (-4%) beginning of feeding; no change at 0, 2.5 and 4.5 hours after beginning of feeding	
	Rats fed 7 days with high-glucose (70%) diet, then i.v. injected with [^{14}C]alanine and killed 3 hours after beginning of feeding	5.26, 3.95, 2.63, 1.32 or 0.66 mmoles/kg	60 min before feeding	↓ dose-dependently FA synthesis (resp. -80, -71, -68, -33 and -23%) ↓ cholesterol synthesis (resp. -69, -40, -35, 0 and 0%)	

		b.w. fed orally (by stomach tube)	(stomach tube)		
(-)-Hydroxycitrate (+)-Hydroxycitrate	Liver high-speed supernatants collected 13 days after feeding rats with a high-glucose (70%) diet, and added with 5 or 10 μmol/mL of [1,5-^{14}C]citrate	1.0 and 0.1 mM	20 min	↓rate of lipogenesis (resp. -72 and -52% at 5 mM citrate; -54 and -35% at 10 mM citrate) ↑ rate of lipogenesis (resp. +55 and +4% of control at 5 mM citrate; +31% of control at 10 mM citrate); ↓rate of lipogenesis at 10 mM citrate (-10%)	
(-)-*Allo*-Hydroxycitrate (+)-*Allo*-Hydroxycitrate				↓rate of lipogenesis (resp. -10 and -6% at 5 mM citrate; -12 and -2% at 10 mM citrate) ↑ rate of lipogenesis (resp. +31 and +4% at 5 mM citrate; +8 and +3% at 10 mM citrate)	
(-)-Hydroxycitrate (+)-Hydroxycitrate (-)-*Allo*-Hydroxycitrate (+)-*Allo*-Hydroxycitrate	Rats fed 13 days with high-glucose (70%) diet, then i.v. injected with [^{14}C]alanine and killed 3 hours after beginning of feeding	2.63 mmoles/kg b.w. (by stomach tube)	60 min before feeding	↓rate of lipogenesis (-42%) ↑rate of lipogenesis (+16%) ↓rate of lipogenesis (-2%) ↑ rate of lipogenesis (+4%)	
(+)-Hydroxycitrate	Liver from rats fed 70% glucose diet for 7 days and killed 30 min after i.v. injection of [^{14}C]alanine or $^{3}H_20$	2.63 mmoles/kg b.w. (orally) the last day beore killing	2, 4, 6, 8, 10, 12, 15, 18, 21 or 24 hours	Rate of lipogenesis from [^{14}C]alanine: ≈ -76% at 2 hrs, ≈ -71% at 4 hrs, ≈ -64% at 6 hrs, ≈ -64% at 8 hrs, ≈ -49% at 10 hrs (NS), ≈ +18% at 12 hrs (NS), ≈ -52% at 15 hrs (NS), ≈ +33% at 18 hrs (NS), ≈ +520% at 21 hrs (NS) and ≈ +175% at 24 hrs Rate of lipogenesis from $^{3}H_20$: ≈ -52% at 2 hrs, ≈ -61% at 4 hrs, ≈ -54% at 6 hrs, ≈ -39% at 8 hrs, ≈ -30% at 10 hrs (NS), ≈ 0 at 12 hrs, ≈ +17% at 15 hrs (NS), ≈ +19% at 18 hrs (NS), ≈ +63% at 21 hrs (NS) and ≈ +60% at 24 hrs (NS)	(Sullivan et al., 1974b)
	Rats fed 70% glucose diet for 9 days and killed 30 min after i.v. injection of [^{14}C]alanine	2.63, 5.26 or 10.52 mmol/kg b.w. (orally) the last day	4 hours before killing	↓rate of lipogenesis (resp. -42, -78 and -89%)	
	Liver from rats fed 70% glucose diet for 30 days, then incubated *in vitro* with 10 mM [^{14}C]citrate	0.17, 0.33, 0.66, 1.32 or 2.63 mmol/kg b.w. (orally) ±1 mM added *in vitro* after killing	30 days	Without 10 mM hydroxycitric acid added: ↑rate of lipogenesis (resp. ≈ +13, NS, ≈ +25%, NS, ≈ +56, ≈ +104 and ≈ +108%) With 10 mM hydroxycitric acid added: ↑rate of lipogenesis (resp. ≈ 0, ≈ +18%, NS, ≈ +55, ≈ +105 and ≈ +118%) Rate of lipogenesis was lower when adding 1 mM hydroxycitric acid *in vitro* (from ≈ -54 to ≈ -53%)	
	Rats fed 70% glucose diet for 9 days and killed 30 min after i.v. injection of [^{14}C]alanine or $^{3}H_20$	0.33, 0.66, 1.32 or 2.63 mmol/kg b.w. (*via* stomach tube)	11 days	↓rate of lipogenesis from [^{14}C]alanine (resp. -27, NS, -21, NS, -76 and -43%) ↓rate of lipogenesis from $^{3}H_20$ (resp. -22, NS, -13, NS, -49 and -37%)	
	Rats fed 70% glucose diet for 30 days and killed 30 min after i.v. injection of [^{14}C]alanine or $^{3}H_20$	0.66, 1.32 or 2.63 mmol/kg b.w. (orally)	30 days	↓rate of lipogenesis from [^{14}C]alanine (resp. -6, NS, -29 and -49%) ↓rate of lipogenesis from $^{3}H_20$ (resp. 0, -20 and -32%)	
(-)-Hydroxycitrate $(Na)_3$	Rats fed 70% glucose diet	1.32 mmol/kg b.w.	11 days	↓lipid content (-9%, NS)	(Sullivan et al., 1974a)
(-)-Hydroxycitrate	3-hr meal-fed rats	-	24 hours	↓significantly the rate of FA synthesis over 8-hr period when control animals had elevated rates ↓cholesterol synthesis	(Sullivan et al., 1974c)
(-)-Hydroxycitrate	Obese Zucker rats fed high-glucose (70%) diet	1.32 mmoles/kg twice	7-13 days	No significant effect on TL content (7%) ↓FA synthesis rate from [^{14}C]alanine (-63%) and $^{3}H_2O$ (-47%)	(Sullivan et al., 1977)
	Fed and fasted rats fed a 10%-fructose solution for 28 hours	1.32 mmoles/kg three times	28 hours	↓FA synthesis rate from [^{14}C]alanine (fed: -40%; fasted: -62%) and $^{3}H_2O$ (fed: -36%; fasted: -39%)	
	Rats fed high-fructose (70%) diet for 6 days and i.v. injected with [^{14}C]alanine or $^{3}H_2O$	2.63 mmol/kg b.w. (oral intubation)	3, 6 and 21 hours	↓FA synthesis rate from [^{14}C]alanine (resp. -57, -62% and no effect) and $^{3}H_2O$ (resp. -59, -31% and no effect)	
	Rats fed high-glucose (70%) diet for 6 days and				

	i.v. injected with Triton WR 1339[4bis] (250 mg/kg)	2.63 mmol/kg b.w. (oral intubation)	6 hours	↓FA synthesis rate from $^{3}H_2O$ (-43%)	
(-)-Hydroxycitrate	Hep G2 cells incuted with [1,5-^{14}C]citrate	≥0.01 and ≤10 mM	2.5 hour preincubation	↓incorporation of [1,5-^{14}C]citrate into FA and cholesterol: IC_{50} (concentration given 50% inhibition) = 0.01-0.5 mM	(Berkhout et al., 1990)
	Hep G2 cells incuted with $^{3}H_2O$	1 mM	18 hours	↓cholesterol (-73%) and FA (-34%, NS) syntheses	
	Hep G2 cells incuted 3 hours with ^{125}I-LDL (10 μg/mL)	2.5 mM	18 hours preincubation	↑ LDL-receptor-mediated association (≈ +49%) and degradation (≈ +107%)	
	Hep G2 cells incuted 2.5 hours with ^{125}I-LDL (from ≈ 4 to ≈ 38 μg/mL)	2 mM	16 hours preincubation	↑ receptor-mediated binding of LDL to Hep G2 cells (≈ +64% at ≈ 4 μg/mL ^{125}I-LDL and ≈ +41% at ≈ 38 μg/mL ^{125}I-LDL)	
Hydroxycitrate	Hyperinsulinemic obese subjects fed controlled high carbohydrate diet (68% energy)	6 g	6 days	No decrease in hepatic *de novo* lipogenesis measured after fasting or fructose infusion	(Schwarz et al., 1999)
(-)-Hydroxycitrate	Overweight subjects	750 mg	8 weeks	↓blood TG (-7%), VLDL (-15%, NS) and LDL (-6%) levels	(Badmaev et al., 2002)
(-)-Hydroxycitrate (from a calcium-potassium salt of 60% HCA extract from *Garcinia cambogia*)	Obese subjects	2800 mg	Middle time (0 < time < 8 weeks) and 8 weeks	↓blood LDL (resp. -4%, NS, and -12%), TG (resp. -4%, NS, and -9%) and TC (resp. -3%, NS, and -6%) concentrations; ↑ HDL concentration (resp. +0.3%, NS, and +11%); ↓VLDL concentration (resp. -3%, NS, and -3%, NS)	(Preuss et al., 2004b)
(-)-Hydroxycitrate (from a calcium-potassium salt of 60% HCA extract from *Garcinia cambogia*)	Obese subjects	2800 mg	4 and 8 weeks	↓blood LDL (resp. -7 and -13%), TG (resp. -3%, NS, and -6%, NS) and TC (resp. -3%, NS, and -7%) concentrations; ↑ blood HDL (resp. +5 and +8%) and VLDL (resp. +7%, NS, and +4%, NS) concentrations	(Preuss et al., 2004a)
SuperCitriMax-600-SXG® (60% HCA)	Rats fed high-fructose (48%) diet	0.018% of diet	26 days	↑ post-prandial lipid content (≈ +67%)	(Brandt et al., 2006)
Hydroxycitric acid	Rats fed high-carbohydrate or high-fat diet	1.6 or 3.2% of diet	8 weeks	Tends to ↓ATPCL/CCE activity and ↑ CPT activities	(Hong et al., 2007)
Calcium-hydroxycitrate (water soluble) from *Garcinia atroviridis*	Obese women	1.15 g *Garcinia atrovitridis* 3 times	2 months	↓serum TG (-23%) and TC (-5%, NS) contents; ↑ serum HDL level (+3%, NS)	(Roongpisuthipong et al., 2007)
Organosulfur compounds					
Sulfur-containing amino acids	Rats fed high-cholesterol (1%) diet	0.5% of diet	2 weeks	s-methyl-L-cysteine sulfoxide: ↓ TL (-11%, NS), TC (-18%), FC (-24%) and cholesterol/PL (-18%); no effect on PL content s-allyl-L-cysteine sulfoxide: ↓ TL (-5%, NS), TC (-21%), FC (-24%) and cholesterol/PL (-18%); no effect on PL content s-methyl-cysteine: ↓ TL (-1%, NS), TC (-10%, NS), FC (-9%, NS) and cholesterol/PL (-11%, NS); no effect on PL content	(Itokawa et al., 1973)
S-allyl cysteine	Hepatocytes isolated from rat liver and incubated with 0.5 mM [1-^{14}C]acetate	0.05, 0.1, 0.5, 1.0, 2.0 and 4.0 mM	4 hours	↓ rate of [1-^{14}C]acetate incorporation into cholesterol at 2.0 (-21%) and 4.0 (-27%) mM; no significant changes at other concentrations No significant reduction in rate of FA synthesis from [1-^{14}C]acetate	(Yeh and Yeh, 1994)
Petroleum ether-, methanol- and water-extractable fractions of fresh garlic	Hepatocytes isolated from rat liver and incubated with 0.5 mM [1-^{14}C]acetate or 0.1 mM [2-^{3}H]glycerol (+oleic acid or +acetic acid)	1x or 5x (≅ 0.25 and 1.25 mg dry garlic powder added to 2 mL incubation medium)	4 hours	At 1x concentration: ↓ [1-^{14}C]acetate incorporation into cholesterol (resp. -10%, NS, -15%, NS, and -53%) and FA (resp. -9%, NS, -62 and -64%) At 5x concentration: - ↓ [1-^{14}C]acetate incorporation rate into cholesterol (resp. -36, -44 and -64%) and FA (resp. -29, -59 and -62%); - ↑ [2-^{3}H]glycerol incorporation rate into TG (resp. +8%, NS, +15%	

				and +9%, NS) and PL (resp. ≈ 0, +9 and +28%) in presence of oleic acid - ↓[2-^{3}H]glycerol incorporation rate into TG (resp. -14, -9 and -12%), diacylglycerols (resp. -21, -9 and -20%) and PL (resp. -26, -21 and -21%) in presence of acetic acid	
S-methyl cysteine sulphoxide (from *Allium cepa*)	Diabetic (alloxan-treated) rats	200 mg/kg b.w. (by stomach tube)	45 days	↓ TC (-10%), TG (-13%) and PL (-6%) contents	(Kumari et al., 1995)
Organosulfur compounds (from *Allium sativum*)	Hepatocytes (from rats fed a standardized diet) incubated with [^{14}C]acetate or [^{14}C]mevalonate	From 0.1 to 1000 μM	2 hours	↓ biosynthesis of nonsaponifiable neutral lipids from [^{14}C]acetate: - allicin: -11% (NS) at 50 mM and -32% at 500 mM - diallyl disulfide: -3% (NS) at 100 mM, -9% at 250 mM and -15% at 500 mM - allyl mercaptan: -4% (NS) at 100 mM, -8% at 250 mM and -13% at 500 mM ↓ incorporation of [^{14}C]mevalonate into nonsaponifiable neutral lipids (≈ -38%): 1,2-vinyl-dithiin at 1000 μM ↓ incorporation of [^{14}C]acetate into cholesterol: - diallyl disulfide: -22 (10 μM), -56 (100 μM), -93 (200 μM) and -99% (1000 μM) - allyl mercaptan: -10 (100 μM), -16 (200 μM) and -77% (1000 μM)	(Gebhardt and Beck, 1996)
Organosulfur compounds (from *Allium sativum*)	Hepatocytes isolated from rats fed a standard non purified diet and incubated with sodium salt of [2-^{14}C]acetate	0.05-4.0 mM	4 hours	Water-soluble compounds (*S*-allyl-cysteine, *S*-ethyl-cysteine, *S*-propyl-cysteine, γ-glutamyl-*S*-allyl cysteine, γ-glutamyl-*S*-methyl cysteine, γ-glutamyl-*S*-propyl cysteine and *S*-allyl mercaptocysteine): ↓ incorporation of [^{14}C]acetate into FA from 42 to 55% maximal inhibition (IC_{50} from 0.58 for *S*-methyl cysteine to 1.72 mM for γ-glutamyl-*S*-propyl cysteine) Lipid-soluble compounds (diallyl sulphide, diallyl disulfide, diallyl trisulfide, dipropyl sulphide and dipropyl disulfide): ↓ incorporation of [^{14}C]acetate into FA from 0 to ≈ 25% at 0.05 mM and from ≈ 42 to 100% at 4 mM	(Liu and Yeh, 2000)
Water- (WEF), methanol- (MEF) and petroleum ether-(PEF) extractable fractions of garlic, Kyolic[5], water- and lipid-soluble organosulfur comounds (from *Allium sativum*)	HepG2 cells incubated with [2-^{14}C]acetate or [2-^{3}H]glycerol and garlic extracts (MEF, PEF and WEF at 1.25 g/L) or organosulfur compounds	0.05-4.0 mM	-	↓ incorporation of [2-^{14}C]acetate into cholesterol (-44% for MEF, -36% for PEF, -64% for WEF, -77% for Kyolic - ≅ 0.4 mM *S*-allyl cysteine - and ≈ -22% for *S*-allyl cysteine at 2 mM) ↓ incorporation of [2-^{3}H]glycerol into TG (from -9 to -14% for WEF, MEF and PEF), but only in presence of acetate, not FA Water-soluble compounds (*S*-allyl, *S*-ethyl and *S*-propyl cysteine): ↓ dose-dependently incorporation of [2-^{14}C]acetate into cholesterol (maximal inhibition of 40-60% at 2.0-4.0 mM) Water-soluble glutamate derivatives (γ-glutamyl *S*-allyl/methyl/propyl cysteine): ↓ incorporation of [2-^{14}C]acetate into cholesterol (from -20 to -35%) Water-soluble alliin, *S*-allyl acetylcysteine and *S*-allyl sulfonylalanine: no effect on incorporation of [2-^{14}C]acetate into cholesterol Lipid soluble compounds (diallyl sulphide/trisulfide, dipropyl sulphide/disulfide and methyl allylsulfide): ↓ incorporation of [2-^{14}C]acetate into cholesterol (from -10 to -15% at 0.05-0.5 mm); cytotoxic at 1.0-4.0 mM IC_{50} of water-soluble compounds: from 0.34 (S-propyl cysteine) to 1.88 (γ-glutamyl *S*- propylcysteine) mM	
Kyolic[d] and water-soluble organosulfur comounds (from *Allium sativum*)	HepG2 cells incubated with [2-^{14}C]acetate	0.05-0.8 mM	-	Kyolic: ↓ incorporation of [2-^{14}C]acetate into cholesterol (-30% at 0.2 mM and -55% at 0.4 mM: equivalent to 0.2 and 0.4 mM of *S*-allyl-cysteine) *S*-allyl- and *S*-propyl cysteine: no effect at 0.05-0.2 mM Kyolic (≅ 0.3 mM *S*-allyl-cysteine) + *S*-allyl-cysteine (0.4 and 0.8 mM): further ↓ incorporation of [2-^{14}C]acetate into cholesterol Kyolic + *S*-propyl cysteine (0.4 mM): similar additive effect on ↓ incorporation of [2-^{14}C]acetate into cholesterol	(Lee and Yeh, 2003)

Organosulfur compounds	Mice fed high-fat (18%) diet	1 g/L of drinking water	4 weeks	*N*-acetyl cysteine: ↓ TG (-5%) and cholesterol (-23%) contents; ↓ ME (-19%) and FAS (-24%) activities *S*-allyl cysteine: ↓ TG (-11%) and cholesterol (-24%) contents; ↓ ME (-11%) and FAS (-29%) activities *S*-ethyl cysteine: ↓ TG (-7%) and cholesterol (-11%, NS) contents; ↓ ME (-12%) and FAS (-22%) activities *S*-methyl-cysteine: ↓ TG (-15%) and cholesterol (-24%) contents; ↓ ME (-18%) and FAS (-26%) activities *S*-propyl-cysteine: ↓ TG (-14%) and cholesterol (-15%, NS) contents; ↓ ME (-13%) and FAS (-33%) activities	(Lin et al., 2004)
Organosulfur compounds	Diabetic (streptozotocin-induced) mice	1 g/L of drinking water	4 weeks	*N*-acetyl cysteine: ↓ TG (-33%) and cholesterol (-25%) contents *S*-allyl cysteine: ↓ TG (-37%) and cholesterol (-23%) contents *S*-ethyl cysteine: ↓ TG (-30%) and cholesterol (-11%, NS) contents *S*-methyl-cysteine: ↓ TG (-25%) and cholesterol (-9%, NS) contents *S*-propyl-cysteine: ↓ TG (-43%) and cholesterol (-28%) contents	(Hsu et al., 2004)
S-methyl cysteine sulfoxide (from *Allium cepa* Linn)	Rats fed high-cholesterol (1% and 0.2% cholic acid) diet	200 mg.kg b.w.	45 days	↓ PL (≈ -7%), cholesterol (≈ -13%) and TG (≈ -20%) levels; ↓ ME activity (-10%)	(Kumari and Augusti, 2007)
	Rats fed high-cholesterol (1% and 0.2% cholic acid) diet, then killed 3 hours after being injected with 1,2-^{14}[C] sodium acetate (50 mM)	200 mg.kg b.w.	45 days	↓ incorporation of [^{14}C] acetate into cholesterol (-3%); ↓ FFA (-14%) level	
Cysteine-containing compounds	Mice fed high-fat (70% energy) diet	1 g/L of drinking water	4 weeks	*n*-acetyl cysteine: ↓ TG (≈ -15%) and TC (≈ -32%) concentrations; ↓ malic enzyme (-22%), FAS (-35%) and HMG-CoA reductase (-25%) activities; ↓ mRNA expression of malic enzyme (≈ -27%), FAS (≈ -20%), HMG-CoA reductase (≈ -30%), SREBP-1c (≈ -23%) and SREBP-2 (≈ -31%) *s*-ethyl-cysteine: ↓ TG (≈ -24%) and TC (≈ -26%) concentrations; ↓ malic enzyme (-28%), FAS (-37%) and HMG-CoA reductase (-22%) activities; ↓ mRNA expression of malic enzyme (≈ -29%), FAS (≈ -13%), HMG-CoA reductase (≈ -34%), SREBP-1c (≈ -25%) and SREBP-2 (≈ -20%) *s*-propyl-cysteine: ↓ TG (≈ -19%) and TC (≈ -33%) concentrations; ↓ malic enzyme (-26%), FAS (-30%) and HMG-CoA reductase (-20%) activities; ↓ mRNA expression of ME (≈ -25%), FAS (≈ -26%), HMG-CoA reductase (≈ -18%), SREBP-1c (≈ -27%) and SREBP-2 (≈ -17%)	(Lin and Yin, 2008)
Cysteine-containing compounds	Mice fed choline and methionine-deficient diet	1 g/L of drinking water	7 weeks	*s*-allyl-cysteine: ↓ TG content (≈ -47%); ↓ FAS activity (-30%); no significant effect upon TC content and malic enzyme and HMG-CoA reductase activities *s*-ethyl cysteine: ↓ TG content (≈ -53%); ↓ FAS activity (-35%); no significant effect upon TC content and malic enzyme and HMG-CoA reductase activities	(Lin et al., 2008)
Mono- and poly-unsaturated fatty acids					
Methyl linoleate	Mice fed 18 days with linoleic acid-deficient diet (2% hydrogenated coconut oil + 1% cholesterol), then with methyl linoleate-rich diet	2% of diet (in place of coconut oil)	10 days	↓FAS activity (≈ -78%) and level of malonyl-2-^{14}C CoA incorporation into fatty acids (≈ -85%)	(Allmann and Gibson, 1965)
Methyl linolenate (C18:3) *vs* methyl stearate (C18:0)	Rats fed fat-free and high-glucose (72%) diet	3% of diet	7 days	Linolenate: ↓FAS (-55%), G6PDH (-62%) and ME (-40%, NS) activities, and rate of FA synthesis from [U-^{14}C]glucose (-50%) Stearate: ↑ FAS (+36%), G6PDH (+25%) and ME (+20%, NS) activities, and rate of FA synthesis from [U-^{14}C]glucose (+27%, NS)	(Clarke et al., 1977)
Methyl linoleate (C18:2) *vs* methyl palmitate (C16:0)	Rats fed fat-free and high-sucrose (72%) diet	3% of diet	7 days	Linoleate: ↓FAS (-40%, NS), G6PDH (-37%) and ME (-40%) activities, and rate of FA synthesis from [U-^{14}C]glucose (-24%, NS)	

				Palmitate: ↑ G6PDH (+15%, NS) and ME (+8%, NS) activities, and ↓ FAS activity (-20%, NS) and rate of FA synthesis from [U-^{14}C]glucose (-18%, NS)	
Methyl linoleate (C18:2) *vs* methyl oleate (C18:1)	Rats fed fat-free and high-glucose (72%) diet	3% of diet	7 days	Linoleate: ↓FAS activity (-13%, NS) and rate of FA synthesis from [U-^{14}C]glucose (-24%, NS) and $^{3}H_2O$ (-6%, NS); no effect on G6PDH (0%) and ME (+3%, NS) activities Oleate: ↓FAS (-38%), G6PDH (-39%) and ME (-31%) activities, and rate of FA synthesis from [U-^{14}C]glucose (-26%) and $^{3}H_2O$ (-16%)	
Methyl linoleate (C18:2) *vs* methyl linolenate (C18:3) *vs* methyl palmitate (C16:0)	Rats fed fat-free and high-glucose (72%) diet	Resp. 3% *vs* 3% *vs* 7%	7 days	Linoleate: ↓FAS (-50%), GPDH (-64%) and ME (-48%) activities, and ↓rate of FA synthesis from $^{3}H_2O$ (-54%) Linolenate: ↓FAS (-63%), GPDH (-69%) and ME (-57%) activities, and ↓rate of FA synthesis from $^{3}H_2O$ (-60%) Palmitate: ↑ FAS (+6%, NS), GPDH (+30%) and ME (+17%, NS) activities, and ↑ rate of FA synthesis from $^{3}H_2O$ (+8%, NS)	
Ethyl linoleate (C18:2)	Rats fed fat-free and high-glucose (72%) diet for 7 days then supplemented with PUFA, injected with $^{3}H_2O$ and killed 20 min after injection	5% of diet	1, 2, 3 or 4 days	↓FA synthesis (resp. 0, -25, 41 and -59%) ↓FAS (resp. 0, -19%, NS, -44 and -56%) and ACC (resp. -11%, NS, -11%, NS, -39 and -57%) activities	(Toussant et al., 1981)
Arachidonic acid	Rats fed liquid ethanol (50 g/L) and fat-free diet	1 g/L	30 days	↓fat (-63%), TG (-83%), PL (-5%, NS) and CE (-95%) levels	(Goheen et al., 1983)
Methyl 3-thia-TODT	Rats fed a conventional pelleted chow diet and injected palmitic acid (control)	150 mg/kg b.w. (gastric intubation)	10 days	↓TG (-42%), cholesterol (-10%, NS) and PL (-3%, NS) contents ↑ mitochondrial (+37% with palmitoyl-CoA as substrate and +35% with palmitoyl-L-carnitine as substrate) and peroxisomal β-oxidation ↑ CPT (+66%), 2,4-dienoyl-CoA reductase (+18%), ACO (+200%), glycerophosphate acyl-transferase (+137% in microsomal fraction and +78% in mitochondrial fraction), Acyl-CoA:DGAT (+190%) and CTPpct (+29%) activities; ↓HMG-CoA reductase (-80%) and Acyl-CoA:CAT (-33%) activities ↑ relative mRNA levels of CPT-II (+69%), 2,4-dienoyl-CoA reductase (+191%) and ACO (+72%)	(Willumsen et al., 1997)
	Rat hepatocytes incubated with [1-^{14}C]oleic acid	Ratio methyl 3-thia-TODT:BSA = 2.5:1	4 hours	↑ FA oxidation (≈ +142%)	
Triolein	Transgenic mice fed low carbohydrate (4.25%) and high-protein (71%) diet	10% of diet	17 days	SREBP-mediated suppression of FAS promoter	(Moon et al., 2002)
EPA ethyl ester	Leptin-deficient *ob/ob* mice (obesity model) fed high-carbohydrate and fat-free diet	15% triolein+5% EPA or 20% tuna fish oil	7 days	↓SREBP-1 nuclear form expression (≈3-fold lower) Suppress expression of SREBP-1-target lipogenic genes (FAS and SCD1) and of S_{14} gene Induced expression of PPARα and ACO ↓TG (resp. ≈ -26 and ≈ -44%) and TC (resp. ≈ -11%, NS and ≈ -15%, NS) contents	(Sekiya et al., 2003)
Omega-3 fatty acids (from fish oil)	Mice fed high-carbohydrate and fat-free diet for 19 days, then ±PUFA for 10 days	2.4 g/kg b.w.	10 days	↓fat percentage (-41%, magnetic resonance spectroscopy) and only slight macrovesicular steatosis (histological observations)	(Alwayn et al., 2005a)
	Leptin-deficient B6.V-*Lep^{ob}* mice fed standard chow	2.4 g/kg b.w.	30 days	No difference in fat percentage ↓macrovesicular steatosis (-10%, digital image analysis	
Omega-3 fatty acids (from fish oil)	Mice fed fat-free and high-carbohydrate diet	600μL (oral or i.v.)	19 days	↓fat content (resp. -70 and -62%) Had only minor micro-vesicular steatosis	(Alwayn et al., 2005b)
n-3 long-chain PUFA ethyl esters (EPA/DHA, 0.9/1.5)	Patients with NAFLD	1 g	12 months	↑ Dopler perfusion index (inversely associated with histological grade of fatty liver, +62%): ↓degree of steatosis from 0/19/45.3/35.7 to 23.8/33.3/28.6.4/14.3 (percentage of subjects with no or steatosis of various degrees: absence/mild/moderate/severe)	(Capanni et al., 2006)
Linseed oil (ALA-rich)	Male and female hamsters fed high-fat diet (12.5% butter + 2.5% sunflower oil: control)	15.4 % of diet (complemented with 1.6% water+0.027% cholesterol)	7 weeks	Females: ↑ PL content (+3%) ; no effect on TC, FC, CE and TG contents Males: ↓TC (-25%), FC (-13%), CE (-26%) and TG (-20%) contents ; no effect on PL content	(Morise et al., 2006)

PUFA	Rats fed ethanol diet containing 0.3% 18:2n-6 and 0.3% 18:3n-3	0.5% 20:4n-6 (AA) and 0.5% 22:6n-3 (DHA)	9 weeks	↓liver histology score (≈ -54%), *i.e.* ↓hepatocellular vacuolation and fat content from ≈51-75% to ≈>25% ↓TG (≈ -29%) and cholesterol (≈ -25%) levels	(Song et al., 2008)
PUFA	Subjects with non-invasive diagnosis of NAFLD	1 g twice	6 months	↓degree of steatosis from 0/0/39/61 to 33.4/22.2/44.4/0 (percentage of subjects with no or steatosis of various degrees: absence/mild/moderate/severe) ↓TG content (resp. -14%, NS, -42% and -61%)	(Spadaro et al., 2008)
EPA, DPA and DHA	*db*/*db* mice (with hyperlipidemic, diabetic and obese symptoms) fed high-sucrose (46%) diet	1% of diet	4 weeks	↑ TC (resp. +21%, NS, +9%, NS and +22%, NS) and PL (resp. +6%, NS, +10%, NS and +12%, NS) contents EPA and DPA: no significant effect on FAS, ME, CPT and peroxisomal β-oxidation (in mitochondria and liver homogenate), and PAP activities, and had no significant effect on relative mRNA levels of FAS, ACC2 and SREBP-1 DHA: ↓ FAS (-40%) and ME (-32%) activities and no significant effects on other enzymes; ↓ ACC2 relative mRNA level (-57%)	(Gotoh et al., 2009)
Linseed oil (ALA-rich)	Wild-type (WT) and PPARα-null (KO) male and female mice fed high-fat diet (13% butter + 4% sunflower oil: control)	15.4 % of diet (complemented with 1.6% water + 0.027% cholesterol)	5 weeks	Male WT: no significant effect on TG and cholesterol concentrations, mRNA levels of L-FABP, ACC, FAS, CPT1 and ACO, and CPT and ACO activities; ↑ PPARα expression (≈ +98%) and no effect on PPARγ, SREBP1c and SREBP2 expressions Female WT: no significant effect on TG and cholesterol concentrations, mRNA levels of ACC, FAS and CPT1, and CPT and ACO activities; ↑ mRNA levels of L-FABP (+41%) and ACO (+32%); ↑ PPARα expression (+61%) and no effect on PPARγ, SREBP1c and SREBP2 expressions Male KO: no effect on TG concentration, ↓ cholesterol concentration (≈ -20%); no significant effect on mRNA levels of L-FABP, ACC, FAS and ACO; ↓ mRNA level of CPT1 (-36%); no effect on CPT and ACO activities; no effect on PPARα and SREBP2 expressions; ↓ PPARγ expression (-99%) and ↑ SREBP1c expression (+80%) Female KO: ↓ TG (≈ -49%) and cholesterol (≈ -10%) concentrations; ↓ mRNA level of L-FABP (-58%) and CPT1 (-66%), no effect on mRNA levels of ACC, FAS and ACO; ↓ CPT activity (-12%) and no effect on ACO activity; ↑ SREBP1c expression (+133%) and no effect on PPARα, PPARγ and SREBP2 expressions	(Morise et al., 2009)
LA (18:2 n-6), DPA 22:5 n-6), OA 18:1 n-9), AA 20:4 n-6), ALA (18:3 n-3), EPA (20:5 n-3) and DHA (22:6 n-3)	HepG2 cells	6, 60 or 120 μM	21 hours	LA: ↓ SRE-luciferase activity (resp. ≈ -55, ≈ -80 and ≈ -70%) DPA: ↓ SRE-luciferase activity (resp. ≈ -12%, NS, ≈ -55 and ≈ -64%) OA: ↓ SRE-luciferase activity (resp. ≈ -4%, NS, ≈ -30 and ≈ -20%, NS) AA: ↓ SRE-luciferase activity (resp. ≈ -55, ≈ -84 and ≈ -80%) ALA: ↓ SRE-luciferase activity (resp. ≈ -19%, NS, ≈ -67 and ≈ -59%) EPA: ↓ SRE-luciferase activity (resp. ≈ -55, ≈ -86 and ≈ -84%) DHA: ↑and↓ SRE-luciferase activity (resp. ≈ +7%, NS, ≈ -67 and ≈ -68%)	(Di Nunzio et al., 2010)
Short-chain fatty acids					
Propionate	Liver cells from male rats fed standard chow incubated with [1-^{14}C]acetate (5 mM) and [2-^{14}C]mevalonate (1 mM) and $^{3}H_2O$ (2 mCi)	0.1-25 mM	60 min	↓dose-dependently cholesterol (from -3%, NS, to -58%) and FA (from -3%, NS, to -93%) synthesis from [1-^{14}C]acetate ↓dose-dependently cholesterol (from -16%, NS, to -61%) synthesis from $^{3}H_2O$; no change for FA synthesis ↓dose-dependently cholesterol (from -1%, NS, to -40%) synthesis from [2-^{14}C]mevalonate; no change for FA synthesis	(Wright et al., 1990)
SCFA	Isolated liver cells from rats fed standard chow diet and incubated with $^{3}H_2O$ and ^{14}C-labelled	1.2 mM (propionate	30 min	Propionate: ↓intracellular citrate (-20%) and ketone body (-25%, NS, for β-HB and -7%, NS, for acetoacetate) concentrations; ↓FA	(Demigné et al., 1995)

	substrates in near-physiological concentration of glucose, glutamine and acetate	and butyrate) and 2 mM (acetate)		(≈ -55%) and cholesterol (≈-30%) synthesis from ^3H_2O; ↓FA (≈ -51-70% for 0.3-2.5 mM acetate/0.6 mM propionate and ≈ -62-70% for 0.3-2.5 mM acetate/1.2 mM propionate) and cholesterol (≈ -27-64% for 0.3-2.5 mM acetate/0.6 mM propionate and ≈ -33-55% for 0.3-2.5 mM acetate/1.2 mM propionate) synthesis from 1-[^{14}C]acetate; no inhibition of FA and cholesterol synthesis from 1-[^{14}C]butyrate Acetate: ↑ intracellular citrate (+19%, NS) and ketone body (+25%, NS, for β-HB and +14%, NS, for acetoacetate) concentrations Butyrate: ↑ intracellular citrate (+89%) and ketone body (+275% for β-HB and +121% for acetoacetate) concentrations Propionate + acetate: ↓intracellular citrate (-2%, NS) and ketone body (0% for β-HB and -14%, NS, for acetoacetate) concentrations; ↓FA (≈ -50%) and cholesterol (≈-30%) synthesis from ^3H_2O Propionate + butyrate: ↑intracellular citrate (-80%) and ketone body (+200% for β-HB and +93% for acetoacetate) concentrations; ↑ FA synthesis (≈ +18%, NS) and ↓cholesterol synthesis (≈-12%, NS) synthesis from ^3H_2O	
SCFA mixture sodium salts of acetic, propionic and butyric acids simulating fermentation products of SBF produced by cecal bacteria)	Liver slices from rats fed 14 days sucrose-based diet (≈65%) or sugar beet fiber-base diet (10%) and incubated with ^3H_2O	3.5% acetate, 2.2% propionate and 9% butyrate in rat diet (14 days)	1.5 hours	↑cholesterol synthesis rate *vs* fibre-free diet (≈ +60%, NS) ↓cholesterol synthesis rate *vs* sugar beet fibre diet (≈ -14%, NS)	(Hara et al., 1999)
	Rats fed fibre-free and sucrose-based or sugar beet fibre (10%) diets and i.v. injected ^3H_2O the last day		14 days	↓cholesterol synthesis rate *vs* fibre-free diet or sugar beet fibre diet (≈ -36%)	
Propionate	Hepatocytes isolated from Zucker *fa/fa* rats fed control diet, and incubated with [1-^{14}C]-acetate (2 mM) or [1-^{14}C]-palmitate (0.2 mM) and with propionate at higher and mean concentrations found in portal vein of fructan-treated (10% of diet) Zucker rats (resp. 0.3 and 0.6 mM)	0.3 and 0.6 mM	180 min	↓TL (intracellular + extracellular) synthesis (resp. -30%, NS, and -35%); no effect on TG synthesis	(Daubioul et al., 2002)
Acetic acid	Mice fed high-fat (27.1%) diet	0.3 or 1.5% solution at 10 mL/kg b.w. administered *via* a stomach tube	42 days	↓TG (resp. -15 and -17%) and TC contents (resp. -13 and -14%) ↑ PPARα (resp. 1.15- and 1.16-fold), ACO (resp. 1.78- and 1.60-fold), CPT-1 (resp. 1.42- and 1.28-fold) and ACC (resp. 1.03- and 1.03-fold, NS) mRNA levels/expression; no effect on SREBP-1 mRNA level/expression; ↓ mRNA level/expression of FAS (resp. 0.73- and 0.79-fold, NS)	(Kondo et al., 2009)
	HepG2 cells transfected with a negative-control number 1 siRNA or validated siRNAs targeting human α2 (catalytic subunit) AMPK	100, 200 or 500 μM	3 hours	↑ PPARα (resp. ≈1.45-, ≈1.7- and ≈1.65-fold), ACO (resp. ≈1.2-, NS, ≈1.65- and ≈1.9-fold) and CPT-1 (resp. ≈1.4-, ≈1.6- and ≈1.85-fold) mRNA levels in HepG2 cells transfected with a negative-control No change in HepG2 cells transfected with a validated siRNAs targeting human α2 AMPK	
Melatonin					
Melatonin	Rats fed high-cholesterol (1% +0.5% bile salts) diet	12.5 mg/kg b.w. i.p.	30 days	↓ cholesterol level (-21%)	(Chan and Tang, 1995)
Melatonin	Mink (*Mustela vison*) fed diet with 33% energy coming from fat, 46% from proteins and 21% from carbohydrates	Subcutaneous 2.7-mg implant, *i.e.* ≈ 10 μg daily	≈2-3 months 4 months	Males: ↓ polar lipid (-3%, NS), cholesterol (-5%, NS), TG levels (-65%) and FFA (-10%, NS) contents; ↓ lipase esterase activity (-30%) Females: ↓ cholesterol (-29%), TG levels (-87%) and FFA (-25%, NS) contents; no change in polar lipid content (+0.3%, NS); ↓ lipase esterase activity (-1%, NS)	(Nieminen et al., 2001)

Melatonin	Mice fed high-cholesterol (1.5% + 0.5% cholic acid) diet	10 mg/L of drinking water	12 weeks	↓cholesterol (≈ -63%) and TG levels (≈ -35%) (Sener et al., 2004)
Melatonin	Rats fed high-cholesterol (2%) diet	2.5, 5 and 10 mg/kg i.p. injected	45 days	↓mean histological grade for steatosis from the highest level (with 6 rats at grade IV for high-fat diet) to the lowest (with 8 rats at grade I for 10 mg melatonin injected/kg) (Pan et al., 2006) ↓TC (resp. -7%, NS, -17 and -28%) and TG (resp. -9%, NS, -9%, NS, and -17%) contents
Melatonin	Rats fed standard pellets	0.5 and 1.0 mg/kg b.w. i.p. injected	8 weeks	↓cholesterol (resp. ≈ -71 and -71%), PL (resp. ≈ -36 and -37%), TG (resp. ≈ -57 and -58%) and FFA (resp. ≈ -34 and -36%) levels (Subramanian et al., 2007)
Melatonin	Rats fed high-fat diet	10 and 50 mg/kg b.w.injected i.p.	12 weeks	↓steatohepatitis and markers of oxidative stress (Kuzu et al., 2007)
Melatonin	Mice fed high-fat (34.9%) diet	10 mg/kg i.p. injected		Histological analyses: ameliorates liver steatosis (Shieh et al., 2009)
Tocotrienols				
d-α-tocotrienol	Broiler cockerels fed commercial diet for 21 days, then fasted 2 days and refed for 3 days	From 0.00025 to 0.002% of diet	21 + 3 days	↓HMG-CoA reductase (from -13%, NS, to -34%) and cholesterol 7α-hydroxylase (from -7%, NS, to -22%) activities; ↑FAS activity (from +18%, NS, to +40%) (Qureshi et al., 1986)
	White Leghorn cockerels fed commercial diet for 4 weeks, then fasted 2 days and injected i.p. for 3 days (refeeding period) before killing	From 5 to 25 mg	3 days	↓HMG-CoA reductase (from -7%, NS, to -319%) and cholesterol 7α-hydroxylase (from -11%, NS, to -37%) activities; ↑FAS activity (from +4%, NS, to +26%)
γ-tocotrienols	HepG2 cells incubated with [2-^{14}C]acetate	From 0.3 to 30 μM	2 or 4 hours	↓dose-dependently cholesterol synthesis (resp. ≈ -71 and ≈ -81% inhibition at 30 μM) (Parker et al., 1993)
	HepG2 cells incubated with [2-^{14}C]acetate, then isolation of microsomal membranes	From 0.5 to ≈ 10-11 μM	4 hours	↓dose-dependently HMG-CoA reductase activity (≈ -74% at ≈ 10-11 μM)
	HepG2 cells	10 μM	16 hours	↓HMG-CoA reductase protein level (≈ -75%) and LDL receptor protein level (≈ +75%)
α-tocotrienols	HepG2 cells incubated with [2-^{14}C]acetate	From 3 to 300 μM	2 or 4 hours	↓dose-dependently cholesterol synthesis (resp. ≈ -41 and ≈ -58% inhibition at 300 μM)
Tocotrienols	Male guinea pigs efd with standard pellets	5, 8 or 10 mg injected i.p.	6 days	↓HMG-CoA reductase activity (resp. -50, -30 and -8%) (Khor et al., 1995)
Tocotrienols (isolated from palm oil FA distillate)[e]	Hamsters fed high-fat (20% corn oil) diet for 45 days	10 mg i.p. ± 5 mg α-tocopherol	6 last days	↓HMG-CoA reductase activity (-48 and -13%, NS, with α-tocopherol) (Khor and Ng, 2000)
Policosanol[f]				
Policosanol	Rats fed standard diet	500 mg/kg b.w.	4 weeks	↓cholesterol biosynthesis from ^3H_2O (-26%) (Menendez et al., 1996)
	Liver microsomes	5 or 50 μg/mL	60 min	No significant effect on HMG-CoA reductase activity
Policosanol	Rabbits fed 27%-casein diet (hypercholesterolaemic diet)	50 mg/kg b.w.	30 days	↓cholesterol biosynthesis from ^3H_2O (≈ -48%) (Menendez et al., 1997)
Policosanol or geraniol[g]	Mice fed for 7 days control diet and i.v. injected with Triton WR1339[h] 3 hours before killing	10 or 67 mg/kg b.w.	7 days	↓newly synthesized cholesterol (resp. -24 and -28%) (Wu et al., 2005)
Para-aminobenzoic acid				
Para-aminobenzoic acid	Man	2 g 4 times	≈ 5 days	↓serum cholesterol level (-12%) (Failey and Childress, 1962)

[a] All terms used in the Table are precisely those of the article considered: for exemple, the hepatic content in TG was named "content", "concentration" or "level", and in some case no term was used; studies reporting both lipotrope-like and non-lipotropic effects (*i.e.* an increase in hepatic lipid content and/or lipogenic enzyme activities) are also presented to allow compar relevant interpretations

[b] Indicates the decreased or increased percentage induced by the lipotrope compared to the control, *i.e.* steatogen diet (NS - Not Significant - means absence of significativity for the change observed; in other cases, the effect was either significant or no information was given in the article)

[c] No data given in the reference

[d] Kyolic is an aged garlic extract containing s-allyl cysteine, s-ethyl cysteine and s-propyl cysteine

[e] Contains 23.3% of α-tocotrienol, 50.8 of γ-tocotrienol, 24.6% of δ-tocotrienol, 0.2% α-tocopherol and 1.1% of γ-tocopherol

[f] Mixture of high-molecular-mass aliphated alcohols isolated and purified from sugar cane wax (main component is octacosanol followed by triacontanol and hexacosanol; other alcohols – tetracosanol, heptacosanol, nonacosanol, dodriacontanol and tetratriacontanol - are minor components)

[g]Geraniol is a monoterpenoid alcohol
[h]Triton WR1339 induces hyperlipidemia by inhibiting lipoprotein lipase and thus preventing catabolism of TG-rich lipoproteins
ABBREVIATIONS: AA, Arachidonic Acid; ACC, Acetyl CoA Carboxylase; ACO, Acyl-CoA Oxidase (involved in long chain FA oxidation in peroxisomes); AIN, American Institute of Nutrition; ALA, Alpha-Linolenic Acid; AMPK, AMP-activated protein Kinase (key enzyme relative to energy adjustment in the cells and sensor of fuel level); ApoB, Apolipoprotein B; BSA Albumine; b.w., body weight; CCE/ATPCL, Citrate Cleavage Enzyme (or ATP-Citrate Lyase, an important step in fatty acid biosynthesis; CCl_4, Carbon tetraChloride; CE, Cholesteryl Esters; CoA, Coenzyme A; CPT, Carnitine Palmitoyl Transferase; CTPpct, CTP:phosphocholine cytidylyltransferase (involved in PL synthesis); DGAT, DiAcylGlycerol Transferase synthesis); DHA, DocosaHexaenoic Acid; DPA, DocosaPentaenoic Acid; d.w.b., dry weight basis; EPA, EicosaPentaenoic Acid; FABPpm/L-FABP, Fatty Acid Binding Protein plasma membrane (small protein involved in the intracellular transport of long-chain fatty acids in the liver and regarded as a sensitive marker for liver cell damage); FAS, Fatty Acid Synthase; FA of Differentiation 36 also known as FAT (membrane protein involved in transfer of lipids into hepatocytes); FC, Free Cholesterol; FA, Fatty Acids; FFA, Free Fatty Acids; β-HB, β-hydroxybutyrate; HCA, HydroxyCitric Acid; HCl, HydroChloric acid; HDL, High-Density Lipoprotein; HF, Hydrogenated Fat; HFE/S, High-Fat Exercise/Sedentary; HMG-CoA reductas MethylGlutaryl Coenzyme A reductase; IC_{50}, concentration required for 50% maximal inhibition; i.p., intraperitoneally; i.v., intravaneously; LA, Linoleic Acid; LDL, Low-Density Lipoprotein; LDLR, Low-Density Lipoprotein Receptor (involved in transfer of lipids into hepatocytes); LPL, LipoProtein Lipase (involved in transfer of lipids into hepatocytes); ME, Malic E messenger RiboNucleic Acid; mtGPAT, mitochondrial Glycerol-3-Phosphate AcylTransferase (involved in glycerolipid esterification); NAFLD, Non-Alcohol Fatty Liver Disease; NS, Not Significant; OA, Oleic Acid; PL, PhosphoLipid; resp., respectively; POE/S, Peanut Oil Exercise/Sedentary; PPAR, Peroxisone Proliferator-Activated Receptor (transcription factor of g lipogenesis); PUFA, Poly-Unsaturated Fatty Acid; RMI 14,514, (5-(tetradecyloxy)-2-furoic acid); SCD, Stearoly-CoA Desaturase (catalyzes the rate-limiting step in the biosynthesis of monounsaturated FA and its deficiency increases fatty acid oxidation by activating hepatic AMP-activated protein kinase); SCFA, Short-Chain Fatty Acid; SRE, Sterol Regulatory Elemen Regulatory Element-Binding Proteins; TC, Total Cholesterol; TG, TriGlyceride; THP, TrimethylHydraziniumPropionate (induces carnitine deficiency); TL, Total Lipids; TODT, ThiaOctaDeca-6,9,12,15-Tetraenoate; TPN, Total Parenteral Nutrition; VLDL, Very Low-Density Lipoprotein

Supplemental Table 3 ***In vivo*** **and** ***ex vivo*** **studies reporting effects on hepatic lipid metabolism following supplementation of soluble and insoluble fiber, phytic acid and oligosaccharides**[a]

Lipotropic compounds	*In vivo* or *in vitro* models	Supplemented daily dose	Duration of lipotrope exposition	Hepatic effect(s)	References
Fibre					
Pectin (from citrus), gum arabic (from acacia powder) and agar	Exp. 1: Rats fed once a day a 10%-fat and 0.2%-cholesterol diet with 0% cellulose	5.0% of diet	14 days	↓cholesterol (resp. -14, -5%, NS, and -3%, NS)[b] and long-chain FA (resp. -20, -11%, NS, and -20%) levels	(Kelley and Tsai, 1978)
	Exp. 2: Rats fed *ad libitum* a 10%-fat and 0.2%-cholesterol diet with 0% cellulose for 14 days then fed once a day the diet for 9 days with [^{14}C]glucose in the last meal before killing	5.0% of diet	23 days	↓cholesterol (resp. -49, -6%, NS, and +8%, NS) and long-chain FA (resp. -34, -36 and -23%, NS) levels; ↓[^{14}C]long-chain FA, *i.e.* lipogenesis (resp. -59, -29, NS, and -18%, NS)	
Cellulose	Rats fed 10% fat diet containing adequate amount of dietary copper with either marginal or abundant (0.12% of diet) dietary zinc	8 or 16% of diet	9 weeks	Marginal zinc content: no signficant effect on cholesterol (resp. -7 and -5%) and lipid (resp. -13 and -17%) concentration Abundant zinc content: no signficant effect on cholesterol (resp. +8 and +13%) and lipid (resp. -16 and +1%) concentration	(Looney and Lei, 1978)
Alfalfa, cellulose or lignin	Rats fed 10% fat and 1% cholesterol diet	5% of diet	28 days	Alfalfa: no significant effect on TC (-3%), FC (+2%) and TG (-15%) contents Cellulose: no significant effect on TC (+15%), FC (+8%) and TG (+15%) contents Lignin: no significant effect on TC (-19%) and FC (-1%) contents; ↓TG content (-85%)	(Story et al., 1981)
Cellulose, lignin or pectin	Rats fed 10% fat and 0.5% cholesterol diet	5% of diet	28 days	Cellulose: ↓TC (-30%, NS), FC (-22%, NS) and TG (-36%, NS) contents Lignin: ↓TC (-66%), FC (-18%, NS) and TG (-18%, NS) contents Pectin: ↓TC (-75%), FC (-27%, NS) and TG (-58%) contents	
Neutral detergent fiber (from blackgram)	Rats fed a 11%-fat and fibre-free diet: - liver slices incubated with [U-^{14}C]glucose 10 mM (5 μCi) - liver slices from rats injected i.p. 3 hours before killing with 1 mL of [1,2-^{14}C]Na-acetate 50 mM (5 μCi)	30% of diet	1 month	↓cholesterol concentration (-9%); ↑ HMG-CoA reductase (*i.e.* ↓ HMG-CoA/mevalonate ratio by 36%) ↑ incorporation of [U-^{14}C]glucose into cholesterol (+80%) ↑ incorporation of [1,2-^{14}C]Na-acetate into cholesterol (+258%)	(Thomas et al., 1983)
Citrus pectin (purified)	Rats fed standard diet containing 14% cellulose	10% of diet	5 weeks	↓TL (-68%) and TC (-63%) contents	(Rotenberg and Eggum, 1986)
Neutral detergent fiber (from wheat bran)	Rats fed diets with various contents in carbohydrate (C: 40-60%), lipid (L: 9-19%) and protein (P: 9-37%), *i.e.* n = 32 diets	0-14% of diet	28 days	From 2.83 to 11.17% fiber, *i.e.* +8.34% of fiber - 44%C, 11%L and from 37.01 to 27.31%P: ↓cholesterol (-14%) and TG (-24%) contents - from 44 to 56%C, from 17 to 11%L and from 15.31 to 31.01%P: ↑ cholesterol (+14%) and TG (+9%) contents - 56%C, 17%L and from 19.01 to 9.31%P: ↓cholesterol content (-6%) and ↑ TG content (+47%)	(Stewart et al., 1987)
Methylcellulose (low, medium and high viscosity: LV, MV and HV)	Rats fed sucrose-based diet	8% of diet	10 days	MV and HV: ↓rate of FA synthesis compared to LV (resp. -22%, NS, and -55%, NS); ↓TG concentration (resp. -14%, NS, and -11%, NS) compared to LV; no effect on rate of cholesterol synthesis and on cholesterol concentration	(Topping et al., 1988)
Particulate (alfalfa, cellulose or wheat bran), soluble/ionic (pectin) and soluble/noionic fiber (guar gum or Metamucil®)	Rats fed a 14%-fat diet	5 (pectin and guar gum) or 10% (particulate fiber and Metamucil) of diet	28 days	↑ cholesterol content (resp. +20, +16, 0, +20, +14 and +23%) ↑ and ↓ TG content (resp. +23, -5, +8, -2, -32 and -26%) ↓ PL content (resp. 0, -27, -5, 0, 0 and -11%) ↑ PC content (resp. +25, +8, +10, +24, +13 and +11%) ↓ PE (resp. -11, 0, -10, -14, -11 and -6%) and Sph (resp. -53, -23, -20, -39, -25 and -26%) contents ↑ and ↓ LPC (resp. -8, +3, +7, -15, +8 and +15%) and PI+PS (resp. -5, 0, +17, -3, +8 and +4%) contents	(Kritchevsky et al., 1988)
Citrus pectin	Rats fed fiber-free diet	1, 3, 6 or 10% of diet	26 days	↓ cholesterol (resp. ≈ -7%, NS, ≈ -9%, NS, ≈ -11%, NS, and ≈ -13%, NS) and TG (resp. ≈ -23%, NS, ≈ -41, ≈ -59 and ≈ -73%) concentrations	(Ide and Horii, 1989)
Wheat bran (GMD:	Rats fed high-sucrose (49%) diet containing 5%	5, 7.5 or 10% of	6 weeks	Fine beet fiber: ↓TG (resp. -20, -34 and -37%) and cholesterol	(Klopfenstein, 1990)

492 μm), or coarse (436 μm) and fine (185 μm) sugar beet fiber	cellulose (GMD: 179 μm)	diet		(resp. +2%, NS, -14 and -27%) levels Coarse beet fiber: ↓TG (resp. -24, -35 and -51%) and cholesterol (resp. -3%, NS, -12% and -37%) levels Wheat bran (5% only): ↓TG content (-8%, NS); no effect on cholesterol level (+3%, NS)	
Oat bran, pectin or psyllium	Rats fed 10%-fat and 0.3%-cholesterol diet containing 7.5% cellulose	7.5% of diet	3 weeks	↓TL (resp. -33, -24 and -14%) and TC (resp. -68, -56 and -35%) levels	(Arjmandi et al., 1992a)
Pectin, psyllium or oat bran	Rats fed 10%-fat and 0.3%-cholesterol diet containing 10% cellulose	10% of diet	3 weeks	Pectin and psyllium: ↓TL (resp. -29 and -29%) and TC (resp. -54 and -40%) levels Oat bran: ↑ TL (+12%, NS) and TC (+17%) levels	(Arjmandi et al., 1992b)
Guar gum	Quails fed 5% cellulose diet ±50 ppm of tocotrienol-rich fraction (from palm oil)	5% of diet	4 or 44 weeks	No tocotrienol-rich fraction: ↓lipid percentage (resp. -14%, NS, and -13%, NS); no effect on cholesterol content (resp. +1% and -21%); ↓cholesterol synthesis at 44 weeks (-18%, NS) With tocotrienol-rich fraction: ↓lipid percentage (resp. -28%, NS, and -17%, NS) and cholesterol content (resp. -6%, NS, and -16%, NS); ↑cholesterol synthesis at 44 weeks (+7%, NS)	(Hood and Sidhu, 1992)
Fiber from defatted oat, barley or wheat	Rats fed hypercholesterolemic (1% cholesterol and 0.25% sodium cholate) diet containing 5% cellulose	Resp. 1.9, 2.8 and 0.6 soluble fiber or 3.1, 2.2 and 4.4% insoluble fiber	9 days	Soluble fiber: ↓cholesterol (-31% for oat, -49% for barley, and -11% for wheat, NS) concentration Insoluble fiber: ↓cholesterol (-4% for oat, NS, -5% for barley, NS, and -8% for wheat, NS) concentration	(Oda et al., 1993)
Wheat bran, psyllium husk or oat bran	Rats fed basal diet containing 9.09% wheat bran, 4.00% psyllium husk or 15.38% oat bran	7.2-7.6% of fiber	3.5, 10, 15 and 18.5 months	Cholesterol: no significant changes (except a tendency to ↓at 15 and 18.5 months for wheat bran and psyllium) CE: no significant changes (except a slight tendency to ↓at 18.5 months) TG: no significant changes (except a slight tendency to ↓at 18.5 months)	(Schneeman and Richter, 1993)
Oat bran, guar gum, cellulose or xylan	Hamsters fed hypercholesterolemic (0.1% cholesterol and 10% fat) diet	≈ 10% of diet	4 weeks	↓cholesterol (-18% for oat bran, NS, -24% for guar gum, NS, and -29% for xylan, NS) concentration; ↑cholesterol (+44% for cellulose) concentration	(Jonnalagadda et al., 1993)
Prune fiber or pectin	Rats fed high cholesterol (1% + 0.1% cholic acid) AIN-76 diet	3 or 6% of diet	28 days	3% prune fiber: ↓cholesterol (-25%) and TG (-27%) contents; no effect on CE:TC 6% prune fiber: ↓cholesterol (-29%), CE:TC (-11%, NS) and TG (-24%) contents 3% pectin: ↓cholesterol (-36%), CE:TC (-5%, NS) and TG (-33%) contents	(Tinker et al., 1994)
Oat bran	Rats fed high cholesterol (1% + 0.1% cholic acid) AIN 76 diet	7.5% of NSP + lignin	14 days	↓cholesterol pool (-23%)	(Jackson et al., 1994)
Rice bran, oat bran, or psyllium	Rats fed 0.25%-cholesterol diet containing 5% cellulose	5% of diet	4 weeks	↓TC content (resp. -21, -41 and -47%) ↑bile acid synthesis (resp. +65, +118, +60% and no effect)	(Chezem et al., 1996)
Guar gum	Rats and gerbils fed high-fat (40%) and 6.5% cellulose diet	6.5% of diet	21 (gerbils) and 19 (rats) days	Gerbils: ↓ TC (-47%) and FC (-10%) contents, and ↑TL content (+5%, NS) Rats: ↓ TL (-39%), and ↑ TC (-50%) and FC (0%) contents	(Onning and Asp, 1995) (Tsai and Tsai, 1999)
Cellulose, guar gum, pectin, konjac mannan or gum arabic	Rats fed high-fat (15% fish oil) diet	10% of diet	8 weeks	↓TL (resp. -36, -60, -51, -34 and -33%), TG (resp. ≈ -30, ≈ -65, ≈ -59, ≈ -38 and ≈ -36%) and cholesterol (resp. ≈ -30, ≈ -67, ≈ -49, ≈ -29% and ≈ -17%, NS) contents Histological observations: ↓size of lipid vacuoles with pectin and guar gum	
Psyllium and pectin	Male, female and ovariectomized guinea pigs fed control diet	5% + 5% of diet	-[c]	↑ CYP7A1 activity (+45%) and mRNA level	(Roy et al., 2000)
Dietary fiber complex[d]	Rats fed AIN-76A diet containing 10% cellulose	10% of diet	21 days	↓cholesterol content (-17%); ↑ TG content (+36%, NS)	(Kritchevsky and Tepper, 2005)
β-glucan concentrate	Rats fed modified AIN-93G diet containing 0.25% cholesterol	5% of diet	28 days	↓TC content (≈ -30%)	(Gallaher and Plate, 2005)
Psyllium husks	Mice fed standard AIN-93M diet	10% of diet	3 and 10 weeks	At week 3: Up-regulation of genes involved in fatty acid β-oxidation (*e.g.* 1.6-fold for CPT1a) and down-regulation of genes involved in lipid biosynthesis (*e.g.* 3.7-fold for SREBF1	(Chan and Heng, 2008)

				and 4-fold for FAS); up-regulation of genes involved in cholesterol synthesis pathway (between 1.5- and 1.9-fold) At week 10: Down-regulation of genes involved in fatty acid β-oxidation (*e.g.* CPT1a, CPT2 and DCI, and 2.3-fold for PPARα) and up-regulation of genes involved in lipid biosynthesis (*e.g.* 1.7-fold for FAS); up-regulation of genes involved in cholesterol synthesis pathway	
Sugar beet fiber-based white wheat bread	Rats fed AIN-93G diet containing 30% white wheat bread powder and 5% cellulose	10% of diet	4 weeks	↓cholesterol content (-36%, NS) No effect on LDL-receptor, HMG-CoA, SREBP-2, CYP7A1, SREBP-1c and FAS mRNA expressions	(Nakamura et al., 2009)
Tartary buckwheat bran extract (oil removed and 9.83% extraction rate)	Rats fed high-fat (10%) diet	0.2 (low), 0.5 (medium) and 1.0 (high) g/kg b.w. (stomach gavage)	6 weeks	↓TG (resp. -60, -44 and -37%) and TC (-60, -49 and 42%) levels, in a range similar to that obtained by supplementing high-fat diet with *Gynostemma pantaphyllum* total glucoside tablet at 0.032 g/kg b.w. ↓LI (resp. -10, NS, -4, NS, and -1%, NS)	(Wang et al., 2009b)
Phytic acid					
Sodium phytate	Rats fed high-sucrose (65%) diet	0.5% of diet	29-30 days	↓TL (-52%), TG (-75%) and cholesterol (-13%) levels; ↑PL level (+9%, NS) ↓$NADPH,H^+$-generating enzyme activities: G6PDH (-31%), ME (-25%) and 6PGD (-17%)	(Katayama, 1995)
Sodium phytate	Rats fed high-sucrose (65%) diet	0.515% of diet	13 days	↓TL (-33%), TG (-82%), cholesterol (-12%) and PL (-5%, NS) concentrations; ↓G6PD (-33%) and ME (-22%) activities	(Onomi and Katayama, 1997)
	Rats fed diet with orotic acid (1.5%)	1.03% of diet	8 days	↑TL (+16%, NS), TG (+21%, NS), cholesterol (+19%, NS) and PL (+4%, NS) concentrations; ↑G6PDH activity (+51%, NS); ↓ME activity (-6%, NS)	
Sodium phytate	Rats fed high-sucrose/starch (65%) diet	0.5% of diet	12-13 days	Starch: no change for lipid status; ↓G6PDH (-33%, NS), ME (-24%, NS), FAS (-34%, NS), CCE (-23%, NS) and ACC/CBX (-32%, NS) activity/mg protein Sucrose: ↓TL (-51%) and TG (-84%) contents, no effect on cholesterol and PL contents, no effect on plasma TG, cholesterol, PL and FFA levels; ↓G6PDH (-45%, NS), ME (-32%, NS), FAS (-38%, NS), CCE (-37%, NS) and ACC/CBX (-16%, NS) activity/mg protein	(Katayama, 1997b)
Sodium phytate	Rats fed high-sucrose diet	0.1, 0.5 or 2.5% of diet	12 days	↓TL (resp. -29, -42 and -50%) and TG (resp. -42, -73 and -81%) levels; ↓G6PD (resp. -8%, NS, -28 and -47%), ME (resp. -8%, NS, -21 and -44%) and FAS (resp. -26%, NS, -40%, NS, and -65%)	(Katayama, 1997a)
Sodium phytate	Rats fed standard chow diet +0.07% DDT	1.02% of diet	14-15 days	↓TL (-36%), TG (-56%) and cholesterol (-30%) levels; no change in PL level ↓lipogenic enzyme activities: ME (-40%), FAS (-58%) and G6PDH (-43%)	(Okazaki et al., 2003)
Sodium phytate	Diabetic KK mice fed purified diet with 15% lipids	0.5, 1.0 or 1.5% of diet	8 weeks	↓TL (resp. -27, -29 and -31%), TG (resp. -14, NS, -7, NS, and -12%) and cholesterol (resp. -30, -23 and -22%) contents	(Lee et al., 2005)
Sodium phytate	Aged ICR male mice fed purified diet with 15% lipids	0.5, 1.0 or 1.5% of diet	12 weeks	↓TL (resp. -10, NS, -31 and -34%), TG (resp. -11, NS, -44, NS, and -53%) and TC (resp. -28, NS, -33 and -34%) concentrations Histology (light microscopy): ↓severity of fatty liver	(Lee et al., 2007)
Inositol hexakisphosphate (IP6)	Rats fed high-sucrose (50.3%) and *myo*-inositol-deficient diet	1.02% of diet	14 days	↓TL (-13%, NS), TG (-26%, NS) and cholesterol (-7%, NS) levels, ↑PL level (+8%); ↓ME (-2%, NS) and ↑G6PDH (+5%, NS) activity/mg protein; no significant effect on serum TG, cholesterol and PL concentrations; no significant change for PI, PE, PS, LPC and Sph percentages/total PL and for PI/PC ratio, ↑PC percentage (+1.4%)	(Okazaki and Katayama, 2008)
	Rats fed high-sucrose (50.3%) and *myo*-inositol-deficient diet +0.07% DDT	1.02% of diet	14 days	↓TL (-40%), TG (-48%) and cholesterol (-19%) levels, ↑PL level (+2%, NS); ↓ME (-8%, NS) and G6PDH (-12%, NS) activity/mg protein; ↓serum TG (-37%), cholesterol (-19%) and	

Article Isken et al. (2010) montre que fibre insoluble (cereal) plus efficace que soluble (guar gum) pour réduite hepatic TG
{Bartley, 2010 #18762}: "Hypocholesterolemic Effects of Hydroxypropyl Methylcellulose Are Mediated by Altered Gene Expression in Hepatic Bile and Cholesterol Pathways of Male Hamsters"

				PL (-23%) concentrations; no significant change for PC, PE, PS, LPC and Sph percentages/total PL, ↑ PI/PC ratio (+8%), ↑ PI percentage (+0.7%)	
Oligosaccharides					
Oligofructose[e]	Rats fed standard diet	10% of diet	30 days	↓TG (-23%), PL (-10%) and TC (-6%, NS) levels; ↑glycerol-3-phosphate level (+58%) ↓FAS (-41%), PAP (-11%, NS), CPT I (-8%, NS) and GPAT (-11%) activities	(Kok et al., 1996b)
	Hepatocytes from rats fed standard or oligofructose-supplemented diet and incubated with 2 mM [1-^{14}C]acetate	10% of diet	180 min	↓TG synthesis from ^{14}C-acetate (-53%)	
Oligofructose[e]	Rats fed standard diet for 30 days then received either 10% fructose drinking solution or tap water for 48 hours	10% of diet	32 days	Water: ↓TG (-24%), PL (-12%) and TC (-9%, NS); ↑ FFA (+36%, NS) and glycerol-3-phosphate (+49%) levels; ↓FAS (-41%), PAP (-7%, NS) and CPT I (-8%, NS) activities Fructose: ↓TG (-18%) and TC (-6%, NS); ↑ PL (+4%, NS), FFA (+17%, NS) and glycerol-3-phosphate (+23%) levels; ↓FAS (-41%), PAP (-7%, NS) and CPT I (-8%, NS) activities	(Kok et al., 1996a)
Short-chain FOS	Sucrose-fed insulin-resistant rats (diet contains 57.5% of sucrose and 14% fat)	10% of diet	3 weeks	↓liver weight (-11%) ↓FAS activity (-32% in mU/mg protein and -36% in mU/g tissue)	(Aghelli et al., 1998)
Oligofructose	Rats fed high-fat (14% +0.15% cholesterol) diet	10% of diet	19 days	Histological examination: only microvacuolar accumulation of fat was present, not macrovacuolar as in the high-fat diet only No effect on TG (-1%, NS), PL (-5%, NS) and TC (-3%, NS) contents	(Kok et al., 1998)
Oligofructose[e]	Rats fed standard diet	10% of diet	3-5 weeks	↓TG (-26%), PL (-12%), TC (-8%, NS) and glycerol-3-phosphate (+58%) levels ↓ME (-51%), ATPCL (-45%), G6PDH (-46%) and ACC (-40%) activities; ↓FAS mRNA/18S rRNA ratio (-42%)	(Delzenne and Kok, 1999)
	Hepatocytes from rats fed standard or oligofructose-supplemented diet and incubated with 2 mM [1-^{14}C]acetate	10% of fiet	180 min	↓TG synthesis from ^{14}C-acetate (-57%)	
Inulin (from *Platycodi radix*)	Female ICR mice fed high-fat (40%) diet	0.5 or 1% of diet	8 weeks	↓LI (resp. -12 and -14%); no effect on TG and TC concentrations	(Han et al., 2000)
Oligofructose[5]	Obese Zucker *fa/fa* rats fed control diet	10% of diet	10 weeks	↓TG (-57%) and PL (-30%) levels ↓fatty degeneration of hepatocytes (histological observations) ↓FAS (-17%, NS) , ME (-16%), ATPCL (-26%, NS) and PAP (-8%) activities; ↓FAS mRNA (-9%, NS)	(Daubioul et al., 2000)
Fructans or cellulose[f]	Obese Zucker *fa/fa* rats fed control diet	10% of diet	6 (for NMR analyses) or 8 weeks	Fructans: ↓fat (≈ -43%, as measured from fat signal with NMR spectroscopy at 6 weeks) and TG (-37%, NS) contents; scarcity of enlarged hepatocytes with micro- and macrovacuoles (*via* histology); no effect on FAS, ME, ATPCL/CCE and phosphatidate phosphohydrolase activities (key enzymes in fatty acid synthesis) Cellulose: ↓fat content (≈ -2%, NS); ↑TG content (+21%, NS)	(Daubioul et al., 2002)
Oligofructose[e]	Rats fed high-fructose (65%) diet	10% of diet	4 weeks	↓TG concentration (-28%)	(Busserolles et al., 2003)
Inulin[g]	Rats fed high-sucrose and high-fat diet for 8 weeks, then injected i.p. with phenobarbital (80 mg/kg)[7] or vehicle only (0.9% sodium chloride)	5% of diet	56 days	↓lipid droplet accumulation (histological observations) Vehicle: ↓TG (-38%), TC (-14%, NS) and FFA (-12%) levels Phenobarbital: ↓TG level (-9%, NS); ↑TC (+20%, NS) and FFA (+13%, NS) levels	(Sugatani et al., 2006)
Oligosaccharides (from soybean)	Rats fed high-fat (16%) diet	150, 300 and 450 mg/kg b.w.	45 days	↓LI (-1%, NS, -6 and -10%)	(Chen et al., 2010a)
Other compounds					
1-Deoxynojirimycin[h] (from mulberry	Rats fed standard diet	1 mg/kg b.w. (direct	4 weeks	↓TG level (-21%) No effect on TC and PL levels	(Tsuduki et al., 2009)

Resistant starch:

- Shimotoyodome (2010): high-fat mice
- Han (2005): high-cholesterol fed rats (no effect on cholesterol content)
- Han (2003): cholesterol-free diet fed rats
- Shao (2002): cholesterol (0.2 g/day : environ 1% diet?) fed rats
- Lopez (2001): normal rats (TG decrease)
- Cheng and Lai (2000): high-cholesterol rats (effect on TG)
- Fernandez (2000): hypercholesterolemic guinea pigs
- Levrat (1996): 0.4%-cholesterol fed rats
- Ranhotra (1996): 10%-fat hamsters (no decrease in liver lipid)
- Morand (1994): normal rats (thèse Levrat)
- Zhang et al (2006): RS increased activity of cholesterol 7alpha-hydroxylase in normal rats

leaves, *Morus alba*)	stomach intubation)	↑ FAS (≈+13%, NS), CPT (≈+56%) and ACO (≈+45%) activities; ↓ ME (≈-12%, NS) ↑ CPTI (≈+50%), ACO (≈+110%) and AMPK (≈+145%) mRNA expressions; ↓PPARα mRNA expression (≈-25%, NS)

[a]All terms used in the Table are precisely those of the article considered: for exemple, the hepatic content in TG was named "content", "concentration" or "level", and in some case no term was used; studies reporting both lipotrope-like and non-lipotropic effects (*i.e.* an increase in hepatic lipid content and/or lipogenic enzyme activities) are also presented to allow compar
relevant interpretations

[b]Indicates the decreased or increased percentage induced by the lipotrope compared to the control, *i.e.* steatogen diet (NS - Not Significant - means absence of significativity for the change observed; in other cases, the effect was either significant or no information was given in the article)

[c]No data given in the reference

[d]Contained oat bran, citrus pectin, guar gum, cellulose, apple pulp fiber, rice fiber, locust bean gum, date fiber, prune fiber, and fructo oligosaccharides

[e]Oligofructose is from Raftilose P95 (Raffinerie Tirlemontoise, Tienen, Belgium), a mixture of glucosyl-(fructosyl)n-fructose and (fructosyl)m-fructose with an average degree of polymerization of 4–8

[f]Fructans are from highly fermented Synergy 1 (Raffinerie Tirlemontoise, Tienen, Belgium) that consists of a 50/50 mixture of Raftilose P95 and raftiline (both are mixture of glucosyl-(fructosyl)-fructose and (fructosyl)-fructose with an average degree of polymerization of 5 for Raftilose P95 and 10-20 for raftiline); cellulose is from poorly fermented Vivapur Microcrystall
is a polymer of glucose included in the insoluble fiber family

[g]Is synthesized enzymatically from sucrose by inulin-producing enzyme and consists of a linear polymer (average ratio of glucose/fructose, 1:17) having β(2-1) linkages of D-fructose with one terminal glucose and

[h]D-glucose analogue in which the oxygen atom of the pyranose ring is substituted by an NH group

ABBREVIATIONS: ACC/CBX, Acetyl-CoA Carboxylase (involved in FA synthesis; is ihibited when phosphorylated); ACO, Acyl-CoA Oxidase; AIN, American Institute of Nutrition; AMPK, AMP-activated protein Kinase (AMPK regulates several intracellular systems including β-oxidation of fatty acids *via* phosphorylation of its substrates and control of gene transcripti
to react to fluctuations in the AMP:ATP ratio); ATPCL/CCE, ATP Citrate Lyase/Citrate Cleavage Enzyme (an important step in fatty acid biosynthesis); b.w., body weight; CE, Cholesteryl Esters; CoA, Coenzyme A; CPT/CAPT, Carnitine PalmitoylTransferase; CYP7A1, Cholesterol 7α Hydroxylase (enzyme for the initial rate-limiting step of bile acid synthesis from c
Dodecenoyl-Coenzyme A delta Isomerase; DDT, DichloroDiphénylTrichloroéthane; FAS, Fatty Acid Synthase/Synthetase; FC, Free Cholesterol; FA, Fatty Acid; FFA, Free Fatty Acids; FOS, Fructo-OligoSaccharides (mixture of 2-, 3- and 4-linked fructose moieties bound to a glucose molecule); GMD, Geometric Mean Diameter; GPAT, Glycerol-3-Phosphate Acyl Tran
Glucose-6-Phosphate Dehydrogenase (NADPH,H$^+$-generating enzyme); HMG-CoA, 3-Hydroxy-3-MethylGlutaryl Coenzyme A; i.p., intraperitoneally; ICR, Imprinting Control Region; LDL, Low-Density Lipoprotein; LDL Receptor, Low-Density Lipoprotein Receptor (involved in transfer of lipids into hepatocytes); LI, Liver Index (liver weight/body
LysoPhosphatidylCholine; ME, Malic Enzyme; mRNA, messenger RiboNucleic Acid; NMR, Nuclear Magnetic Resonance; PAP, Phosphatidate Phosphohydrolase (involved in TG synthesis; catalyses the release of orthophosphates from phosphatidylglycerophosphate); NS, Not Signficant; PC, PhosphatidylCholine; PE, PhosphatidylEthanolamine; PI, Phosphat
PhospholipId; resp., respectively; PPAR, Peroxisone Proliferator-Activated Receptor; rRNA, ribosomal RiboNucleic Acid; PS, PhosphatidylSerine; Sph, Sphingomyelin; SREBF1, Sterol Regulatory Element Binding Factor 1 (membrane-bound transcription factor that enhances transcription of genes required for fatty acid synthesis); SREBP, Sterol Regulatory Element-I
TC, Total Cholesterol; TG, TriGlyceride; TL, Total Lipids

Supplemental Table 4 *In vivo*, *ex vivo* and *in vitro* studies reporting effects on hepatic lipid metabolism following supplementation of carotenoids, pholyphenols and polyphenol-derived compounds[a]

Lipotropic compounds	*In vivo* or *in vitro* models	Supplemented daily dose	Duration of lipotrope exposition	Hepatic effect(s)	References
A - Carotenoids					
Astaxanthin and canthaxanthin	Rainbow trouts fed commercial extruded basal diet	0.01% of diet	21 days	↓ TL (resp. -41 and -39%)[b] and unsaturated lipid (resp. -5%, NS, and -34%, NS) level (as evaluated by image analysis, *i.e.* mean grey-scale values for differential hepatic histochemical staining)	(Page et al., 2005)
Lycopene	Rats fed standard AIN-93M-based diet	0.65% of diet	5 weeks	↓ cholesterol level (≈ -34%) and ↑ TG level (≈ +6%, NS)	(Alshatwi et al., 2010)
B - Polyphenols					
B1 - Undefined, mixture or extracts					
Oryzanol[c] from rice bran oil	Rats fed high-cholesterol (1% +0.15% bile salts) diet	0.2, 0.5, 1.0 or 1.2% of diet	7 weeks	↓ TC (resp. -14, -17, -17 and -22%), CE (resp. -16, -21, -19 and -22%), TG (resp. -7%, NS, -37%, -27%, NS, and -33%) and PL (resp. -14, -38, -33 and -29%) contents; no significant effect on FC content (resp. -2, +3, -1 and -17%)	(Seetharamaiah and Chandrasekhara, 1988)
Oryzanol[c]	Rats fed high-cholesterol (1% +0.15% bile salts) diet	0.5% of diet	7 weeks	↓ TC (-26%), FC (-5%), CE (-31%), TG (-19%, NS) and PL (-26%) contents	(Seetharamaiah and Chandrasekhara, 1993)
Oryzanol[c]	Hamsters fed hypercholesterolemic (0.1% +5% coconut oil) diet	1% of diet	8.5 weeks	↓ HMG-CoA reductase activity (-15%, NS)	(Rong et al., 1997)
Grape skin and seed polyphenols (≈ 12%)	Rats fed liquid ethanol-rich (36% as energy) diet (Lieber-DeCarli diet)	50 mg/L	2 months	Histological assessment: signficantly less hepatic damages, *i.e.* no evidence of steatosis, a highly organized structure comparable to that observed in liver of rats fed basal diet, and absence of a alrge number of lipid vacuoles with a large extent of distribution No effect on TG and PL levels	(Sun et al., 1999)
Polyphenon-100®[d] (green tea polyphenols)	Male rats fed standard diet	0.01, 0.05, 0.1, 0.2 and 0.5 g/kg b.w.	23 days	TC: no effect (+17% at 1 g/kg b.w., NS) TG: resp. ≈ 0, +20%, NS, ≈ 0, +36%, NS, +45 and +47% PL: no effect (+29% at 1 g/kg b.w., NS)	(Nakamura et al., 2001)
Polyphenols from virgin olive oil	Rats fed 1%-cholesterol diet	≅ quantity extracted from 30% virgin olive	5 weeks	No effect on liver TC (-8%), TG (+35%), total PL (+6%), LPC (+4%), PC (≈ 0), PE (+1%) and microsomal TC (-15%) ↓ HMG-CoA reductase activity (-41%) in microsomes (without olive oil); no effect with olive oil ↑ CYP7A1 activity in microsomes (+22%, NS, without olive oil and +88% with olive oil)	(Benkhalti et al., 2002)
Polyphenol-rich ethylacetate extract (from defatted safflower seed powder	Ovariectomized rats fed standard diet (11.5% fat)	1% of diet	4 weeks	↓ cholesterol (-15%) and TG (-8%, NS) levels	(Cho et al., 2004)
γ-oryzanol[c] (normal *vs* microencapsulated)	Rats fed high-cholesterol diet (10% heat-treated lard, 1% cholesterol and 0.5% cholic acid)	0.01% of diet	4 weeks	↓ LI (resp. -19%, NS, and -23%) and cholesterol level (resp. -19 and -15%)	(Suh et al., 2005)
Oligonol® (oligomerized polyphenols from lychee fruit and green tea)	Mice fed choline deficient and L-amino acid defined diet	0.02% of diet	4 weeks	↓ fat deposit; up-regulation of PPARγ coactivator-1α (promotes β-oxidation) and ↑ β-oxidation enzyme expression	(Tojo et al., 2008)
Green tea extract (30% catechin)[e]	Male leptin-deficient (*ob*/*ob*) mice fed standard AIN-93G diet	1 or 2% of diet	6 weeks	Hepatic histologic evaluation: marked reduction in the degree of steatosis; 4/16 obese mice responded maximally to green tea	(Bruno et al., 2008)

				extract, resulting in grade 1 histologic score; for most, effect was dramatic Hepatic steatosis grading: 2.0 at 1% green tea extract and 2.1 at 2% (grades 1, 2 and 3 correspond respectively to fatty hepatocytes occupying <33%, 33-66% and >66% of the hepatic parenchyma; *ob*/*ob* mice are graded 3) ↓ dose-dependently TL (resp. ≈ -21 and ≈ -39%) and TG (resp. ≈ -20 and ≈ -41%) concentrations; no significant effect on cholesterol concentration (resp. ≈ -7 and ≈ +13%)	
Provinol®[f] (powdered wine polyphenol extract, 95%)	Rats fed high-fat (19%) high-sucrose (30%) diet for 6 weeks, then ±Provinol for 6 weeks	0.2% of diet	6 weeks	Histological examination: no preponderance of large droplets in which bulky fat vacuole distends the hepatocyte, and similar appearance to that of control (4% fat)	(Feillet-Coudray et al., 2009)
Polyphenol-rich extract (45%) from walnut (*Juglans regia* L.)	Mice fed high-fat (32%) diet	50, 100 or 200 mg/kg suspended in water and given orally once a day	13 days	↓ TG content (resp. ≈ 0, -19 and -19%) No significant effect on cholesterol content Tended to ↓ mitochondrial β-oxidation (resp. -15%, NS, -29%, NS, and -18%, NS) and ↑ cytosolic β-oxidation (resp. +28%, NS, +20%, NS, and +43%, NS) ↑ PPARα (resp. ≈ 1.45-fold, NS, 1.7-fold and 1.4-fold, NS) and ACOX1 (resp. ≈ 1.6-fold, 1.4-fold and 3.3-fold) mRNA expression ratio *vs* control; no significant effect on CPT1A mRNA expression	(Shimoda et al., 2009)
	HepG2 cells	10, 30 or 100 μg/mL 1, 10 or 100 μg/mL	48 hours	↑ TG accumulation within cells (resp. +47, +42 and +43%) ↑ PPARα (≈ 1.65-fold at 1 μg/mL and 1.7-fold at 100 μg/mL), CPTA1 (resp. ≈ 1.2-fold, NS, 1.15-fold, NS, and 4-fold, NS) and ACOX1 (resp. ≈ 1.3-fold, 1.3-fold and 1.3-fold) mRNA expression ratio *vs* control	
Polyphenol extract from *Nelumbo nucifera* leaf (14.8% phenolic acids and 56% flavonoids)	Hamsters fed high-fat (10%) diet containing 0.2% cholesterol	1 or 2% of diet	10 weeks	↓ cholesterol (resp. -27 and -40%) and TG (resp. -10 and -39%) levels Histological examinations: significantly and dose-dependently ↓ number of lipid vesicles increased by the high-fat diet	(Lin et al., 2009)
Silymarin (extract from milk thistle seeds, *Silybum marianum*)		0.01% of diet	10 weeks	↓ cholesterol (-22%) and TG (-25%) levels Histological examinations: significantly ↓ number of lipid vesicles increased by the high-fat diet	
Polyphenol-rich extract from *Hibiscus sabdariffa* (≈ 74% polyphenols)[g]	Male hamsters fed calorie-rich-fat (0.2% cholesterol and 10% coconut oil) diet	0.1 or 0.2% of diet	10 weeks	↓ cholesterol (resp. ≈ -53 and ≈ -58%) and TG (resp. ≈ -39 and ≈ -49%) levels	(Yang et al., 2010b)
	HepG2 cells	0.1, 0.5 or 1.0 mg/mL	6 hours	↓ cholesterol (resp. ≈ -28%, NS, ≈ -48 and ≈ -79%) and TG (resp. ≈ -43, ≈ -54 and ≈ -62%) contents ↓ dose-dependently FAS (resp. -14, -53 and -75%) and HMG-CoA reductase (resp. -7, -46 and -69%) protein expression; ↓ HMG-CoA reductase (resp. 0, -75 and 79%) and SREBP-1c (resp. -66, -64 and -69%) protein expression ↑ AMPKphosphorylated (resp. +49, +46 and +45%), PPARα (resp. +14, +22 and +37%; dose-dependent) and LDLR (resp. +42, +44 and +144%) protein expression No effect on AMPK and β actin protein expression	
	HepG2 cells	0.05 or 0.5 mg/mL	18 hours	↑ LDL uptake (resp. ≈ +10 and 65%)	
Polyphenol-rich longan (*Dimocarpus longans* Lour.) flower water extract[h]	Rats fed hypercaloric diet	1.25 or 2.5% (w/v) as drinking water	9 weeks	↓ TG (resp. -5%, NS, and -27%) and cholesterol (resp. -19 and -19%) contents ↑ LDLR (resp. ≈ +50 and ≈ +88%), PPARα (resp. ≈ +43 and ≈ +50%) and UCP2 (resp. ≈ +14%, NS, and ≈ +16%, NS) mRNA expression; ↓ SREBP-1c (resp. 0 and ≈ -14%) and FAS (resp. ≈ -10%, NS, and ≈ -16%) mRNA expression	(Yang et al., 2010a)
Anthocyanin-rich	Ethanol-fed (3.7 g/kg b.w. *via* intragastric tube)	125, 250 or 500	45 days	↓ TC (resp. -7%, NS, -7%, NS, and -13%) and TG (resp. -8%, NS, -	(Hou et al., 2010)

extract (from black rice)	rats	mg/kg b.w. i.g. injected		9 and -13%) levels Histopathological examinations: ↓ alterations (apparently in relation with lipid accumulation)	
B2 - Phenolic acids					
Ferulic acid	Rats fed high-cholesterol (1% +0.15% bile salts) diet	0.075% of diet	7 weeks	↓ TG (-19%, NS) and PL (-23%) contents; ↑ TC (+1%, NS), FC (+5%, NS) and CE (+1%, NS) contents	(Seetharamaiah and Chandrasekhara, 1993)
Ferulic acid	Rats fed 10%-fat diet	0.4% of diet	4 weeks	↓ TC (-3%, NS) and lipid (-9%, NS) contents	(Kamal-Eldin et al., 2000)
Ferulic acid, *m*-hydroxycinnamic acid or 3,4-dihydroxyphenyl-propionic acid[i]	Rats fed high-cholesterol (1%) diet	0.013, 0.011 or 0.012% of diet	5 weeks	No effect on TG and cholesterol contents ↓ HMG-CoA reductase (resp. ≈ -54, ≈ -40 and ≈ -51%) and ACAT (resp; ≈ -36, ≈ -34 and ≈ -41%) activities	(Kim et al., 2003)
Gallic acid	FAS from chicken liver	0.5 mM	3 hours	FAS residual activity ≈ 97%	(Wang et al., 2003)
Ferulic acid	Male ICR mice fed 10%-fat (palm oil) diet	1% of diet	15 days	↓ FAS (≈ -21%, NS), ATPCL (≈ -23%, NS), ME (≈ 0%) and G6PDH (≈ -26%, NS) activities ↓ ACC (≈ 0%), FAS (≈ -10%, NS) and ATPCL (≈ -8%, NS) mRNA levels ↑ SREBP-1c (≈ +8%, NS) ↓ mRNA levels of proteins involved in regulation of lipogenesis: spot 14 (≈ -20%, NS) and adiponutrin (≈ -3%, NS) ↑ SREBP-1c (≈ +2%, NS) mRNA level	(Odbayar et al., 2006)
Ellagic acid	HepG2 cells	1, 3 or 10 μg/mL	24 hours	↓ PPARα (resp. 0.59-fold, 0.94-fold, NS, and 0.64-fold), CPT1A (resp. 0.63-fold, 0.88-fold, NS, and 0.69-fold) and ACOX1 (resp. 0.94-fold, NS, 0.63-fold and 0.60-fold) mRNA expression (*vs* control)	(Shimoda et al., 2009)
B3 - Flavonoids					
Jasmine green tea epicatechins (mainly EC, EGC, ECG and EGCG)	Hamsters fed hyperlipidemic (20% fat and 1% cholesterol) diet	0.57% of diet	5 weeks	↓ TG (-44%), FFA (-36%) and cholesterol (-56%) concentrations	(Chan et al., 1999)
Naringin + hesperidin	Rats fed high-cholesterol (1%) diet	0.05 + 0.05% of diet	6 weeks	↓ cholesterol (-28%) and TG (-21%) contents ↓ HMG-CoA reductase (-31%) and ACAT (-31%) activities	(Bok et al., 1999)
Soy isoflavone powder (83.3% isoflavones)	Rats fed atherogenic diet (9% fat, 1.2% cholesterol and 0.2% cholic acid)	20% of diet	63 days	↓ TG (-33%) and ↑ TC (+10%, NS), CE (+9%, NS) and unesterified cholesterol (+17%) concentrations	(Peluso et al., 2000)
Epigallocatechin gallate (EGCG)	FAS from chicken liver	≈ 27-110 μM	60 min	↓ FAS activity (reversible fast-binding inhibition): IC_{50} = 52 μM	(Wang and Tian, 2001)
Tannic acid	Male rats fed standard diet	0.1, 0.2, 0.5 and 1.0 g/kg b.w.	23 days	TC: no effect TG: resp. +34, +38, ≈ 0 and +47% PL: resp. +17%, NS, +18%, NS, +33%, +29%, NS	(Nakamura et al., 2001)
Hesperetin (from citrus)	Rats fed 1%-orotic acid diet containing 10% fat	1% of diet	10 days	↓ microsomal PAP (≈ -30%), G6PDH (≈ -44%), ME (≈ -41%) and DGAT (≈ -48%) activities	(Cha et al., 2001)
Naringenin or hesperetin	HepG2 cells	10-200 or 50-200 μM	24 hours	↓ dose-dependently ApoB accumulation into the media: Naringenin: from ≈ -7% (10 μM), NS, to ≈ -83% (200 μM) Hesperetin: from ≈ -39% (50 μM), NS, to ≈ -75% (200 μM)	(Wilcox et al., 2001)
Naringenin	HepG2 cells pre-incubated 24 h with flavonoid and incubated 20 min ±0.1 mM oleate	50 or 200 μM	24 hours (+ 20 min)	↓ cellular (resp. ≈ -36 and ≈ -72%) and secreted (resp. ≈ -27 and ≈ -68%), new synthesized ApoB	
Naringenin or hesperetin	HepG2 cells	50 or 200 μM	24 hours	↓ cellular CE mass: Naringenin: resp. ≈ -8%, NS, and ≈ -26% Hesperetin: resp. ≈ -17%, NS, and ≈ -21% ↑ cellular FC mass: Naringenin: resp. ≈ +4%%, NS, and ≈ +7%, NS Hesperetin: resp. ≈ +3%%, NS, and ≈ +3%, NS ↑ cellular TG mass:	

				Naringenin: resp. ≈ +14%%, NS, and ≈ +34%, NS Hesperetin: resp. ≈ +3%%, NS, and ≈ +50%, NS	
Naringenin or hesperetin	HepG2 cells ±19 hours-preincubation with flavonoids) and incubated 5 hours with [1-^{14}C]oleic acid or [1-^{14}C]acetic acid	50 or 200 μM	5 hours	Without 19 hours-preincubation with flavonoids: Naringenin: ↓ rate of incorporation of oleate into CE (resp. -37 and -70%); ↑ rate of incorporation of oleate into TG (resp. +13%, NS, and +29%) and PL (resp. +4%, NS, and +2%, NS) Hesperetin: ↓ rate of incorporation of oleate into CE (resp. -22%, NS, and -57%); ↑ rate of incorporation of oleate into TG (resp. +21%, NS, and +35%, NS) and PL (resp. +20%, NS, and +16%, NS) With 19 hours-preincubation with flavonoids: Naringenin: ↓ rate of incorporation of oleate into CE (resp. -60 and -84%); ↑ rate of incorporation of oleate into TG (resp. +4%, NS, and +27%); no effect on rate of incorporation of oleate into PL Hesperetin: ↓ rate of incorporation of oleate into CE (resp. -31%, NS, and -70%) and PL (resp. -7%, NS, and -12%, NS); ↑ rate of incorporation of oleate into TG (resp. ≈ 0 and +9%, NS)	
Naringenin or hesperetin	HepG2 cells incubated with [1-^{14}C]oleic acid in presence of 10 μM ACAT inhibitor	200 μM	24 hours	↓ rate of CE hydrolysis (resp. -34 and -36%)	
Naringenin	HepG2 cells	200 μM	24 hours or 5 days	24 hours: no significant effect on MTP large subunit expression 5 days: nearly complete depletion of MTP large subunit expression	
Naringenin or hesperetin	HepG2 cells	50, 100 or 200 μM	24 hours	↓ MTP activity: - Naringenin: resp. -19, -32 and -40% - Hesperetin: resp. -8%, NS, -33 and -22%	
Naringenin or hesperetin	HepG2 cells	200 μM	24 hours	↑ LDL receptor activity: ↑ ^{125}I-LDL cell binding (resp. ≈ 0 and ≈ +200%), uptake (resp. ≈ +67 and ≈ +150%) and degradation (resp. ≈ +18%, NS, and ≈ +164%)	
Naringenin or hesperetin	HepG2 cells	50 or 200 μM	24 hours	Naringenin: ↑ and ↓ ApoB (resp. -13%, NS, and -4%, NS), ACAT1 (resp. -4%, NS, and -9%), ACAT2 (resp. +9%, NS, and -49%), MTP (resp. +8%, NS, and -31%), LDLR (resp. +41%, NS, and +387%), HMG-CoA reductase (resp. -14%, NS, and ≈ 0) and GAPDH (resp. +30%, NS, and -15%, NS) mRNA levels Hesperetin: ↑ and ↓ ApoB (resp -1%, NS, and -14%, NS), ACAT1 (resp. +4%, NS, and -13%, NS), ACAT2 (resp. -13%, NS, and -53%), MTP (resp. +16%, NS, and -47%), LDLR (resp. +16%, NS, and +556%), HMG-CoA reductase (resp. -10%, NS, and +19%, NS) and GAPDH (+21%, NS, and +6%, NS) mRNA levels	
Proanthocyanidins (from grape seeds)	Rats fed normal diet or lithogenic diet (1% cholesterol + 0.5% cholic acid)	0.01, 0.05, 0.1, 0.2, 0.5 or 1 g/kg b.w. 0.1, 0.2, 0.5 or 1 g/kg b.w.	28 days	Normal diet: - ↓ LI (-12% at 0.5 g/kg) - ↓ cholesterol (-25% at 1 g/kg, NS), TG (-25% at 1 g/kg, NS) and PL (-32% at 1 g/kg) contents (mg/liver) Lithogenic diet: - ↓ LI (-15% at 0.5 g/kg) - no effect on cholesterol (resp. +8%, NS, +10%, NS, -5%, NS, and +14%, NS), TG (resp. +3%, NS, -18%, NS, -14%, NS, and -16%, NS) and PL (resp. +8%, NS, 0, -4%, NS, and +17%, NS) concentrations	(Nakamura and Tonogai, 2002)
Taxifolin	HepG2 cells	⌟	24 hours	↓ dose-dependently TG synthesis and secretion (resp. -59 and -68% at optimum concentration of 200 μM); ↓ PL synthesis and secretion (resp. -15 and -57%) ↓ dose-dependently DGAT activity (-60%), but no effect of quercetin and genistein; ↓ MTP activity (-27%) Shifted metabolic pathway from Tg to PL synthesis	(Theriault et al., 2002)
Flavonoid glycoside fraction from *Salix matsudana* leaves	Female ICR mice fed high-fat (40%) diet	2% or 5%	9 weeks	↓ TG (resp. -13%, NS, and -16%) and TC (resp. -27 and -30%) contents; no effect on LI	(Han et al., 2003)

Hesperetin	Rats fed high-cholesterol (1%) diet	0.02% of diet	5 weeks	No effect on TG and cholesterol contents ↓ HMG-CoA reductase (≈ -41%) and ACAT (≈ -45%) activities	(Kim et al., 2003)
Epicatechin gallate (ECG)	FAS from chicken liver	-	-	IC_{50} = 42 μM	(Wang et al., 2003)
		0.5 mM	3 hours	FAS residual activity ≈ 21%	
(+)-catechin	FAS from chicken liver	-	-	IC_{50} = 1.6 mM	
		0.5 mM	3 hours	FAS residual activity ≈ 100%	
(-)-epicatechin	FAS from chicken liver	-	-	IC_{50} = 3.8 mM	
		0.5 mM	3 hours	FAS residual activity ≈ 93%	
Epigallocatechin gallate (EGCG)	FAS from chicken liver	0.5 mM	3 hours	FAS residual activity ≈ 21%	
Epigallocatechin (EGC)	FAS from chicken liver	0.5 mM	3 hours	FAS residual activity ≈ 91%	
Hesperidin or α-glucosylhesperidin	Ovariectomized ddY mice fed AIN-93G-based diet	Resp. 0.5% and 0.7% of diet	4 weeks	↓ TC (resp. -20 and -15%) and TG (resp. -16 and -16%) concentrations	(Chiba et al., 2003)
Taxifolin	HepG2 cells	75-200 μM	24 hours	↓ dose-dependently ApoB secretion (≈ -62% at 200 μM)	(Casaschi et al., 2004)
	HepG2 cells preicubated 22 with taxifolin then incubated 2 hours with [^{3}H]glycerol and taxifolin	200 μM	24 hours	↓ newly synthesized TG in cytosol (-39%), and microsomal membrane (-26%) and lumen (-38%)	
	HepG2 cells	200 μM	24 hours	↓ non-competitively DGAT activity (-35%), and MTP activity (≈ -41%); post-transcriptional regulation of DGAT activity	
	HepG2 cells	100 or 200 μM	24 hours	↓ and ↑ DGAT-1 (resp. +3%, NS, and +8%, NS) and DGAT-2 (resp. +4%, NS, and -6%, NS) mRNA levels	
Acacetin (flavone)	Ovariectomized rats fed standard diet (11.5% fat)	0.02% of diet	4 weeks	↓ cholesterol (-12%, NS) and TG (-17%, NS) levels	(Cho et al., 2004)
	HepG2 cells	0.01, 0.1 and 1 μM	3 days	↓ cholesterol (resp. -39, -35 and -7%, NS) and TG (resp. -28, -32 and -2%, NS) contents	
Flavonoids	FAS (5 mM) from duck	-	-	IC_{50} (μM): morin (2.33), luteolin (2.52), quercetin (4.29), kaempferol (10.38), fisetin (18.78), myricetin (27.18), baicalein (111.69), galangin (> 100), flavone (n.i.), flavonol (n.i.), rutin (n.i.), (±)-taxifolin (41.16), hesperetin (68.86), (±)-EC (n.i.), (-)-EGC (n.i.)	(Li and Tian, 2004)
Daidzein + glycitein[k]	Enzyme assay: 5.3 μg of MHG-CoA reductase/150 μL	4.5 μg/150 μL	-	↓ HMG-CoA reductase (-64%)	(Sung et al., 2004)
Genistein[k]		3.8 μg/150 μL	-	↓ HMG-CoA reductase (-50%)	
Soy extract[l]	HepG2 cells	10 mg/L	24 hours	↑ mature SREBP-2 form and HMG-CoA reductase levels, and HMG-CoA syntahse mRNA level; no effect on SREBP-1 ↑ SRE-regulated expression of HMG-CoA synthase (≈ +315%) and LDL receptor (≈ +55%, NS)	(Mullen et al., 2004)
Genistein, glycitein or daidzein	HepG2 cells	20 μM	24 hours	Genistein or daidzein: ↑ mature SREBP-2 form and HMG-CoA reductase levels, and HMG-CoA syntahse mRNA level; no effect on SREBP-1 ↑ SRE-regulated expression of HMG-CoA synthase (resp. ≈ +370, ≈ +25%, NS, and ≈ +280%) and LDL receptor (resp. ≈ +25%, NS, ≈ -30%, NS, and ≈ +80%, NS)	
Genistein	HepG2 cells	10 μM	0-48 hours	↑ mRNA levels of genes involved in mitochondrial β-oxidation and ketone body metabolism, *e.g.* at 24 hours : CPT1 (≈ 6-fold), ACS (≈ 2-fold), MCAD (≈ 5-fold) and HMGCS2 (≈ 4-fold) ↑ mRNA levels of genes involved in peroxisomal β-oxidation, *e.g.* at 24 hours : ACO1 (≈ 7-fold), ACO2 (≈ 5.5-fold), ECH1 (≈ 3-fold) and MCAD (≈ 5-fold)	(Kim et al., 2004)
	HepG2 cells incubated or not with ER antagonist (0.1 μM)	10 μM	24 hours	↑ CPT1 gene expression: ≈ +330% without ER antagonist and ≈ +460% with ER antagonist	
	HepG2 cells	1, 10 or 100 μM	24 hours	↑ PPARα mRNA level (resp. ≈ +80, ≈ +280 and ≈ +240%)	
		10 μM	6, 24 or 48 hours	↑ PPARα mRNA level: maximum at 24 hours (3.9-fold) ↑ PPARα protein level: maximum at 24 hours	
	HepG2 cells	0.1, 1 or 5 μM	24 hours	↑ PPARα transcriptional activity (resp. ≈ +150, ≈ +169 and ≈ +200%)	

Isoflavone aglycone- or glucoside-rich powder (resp. 26.3 or 32.0% aglycone moieties)	Rats fed 10%-fat diet	0.365 or 0.3% of diet	40 days	↓ and ↑ TC (resp. -10 and +7%, NS), TG (resp. -23 and -7%, NS) and PL (resp. +4%, NS, and +4%, NS) levels ↓ and ↑ CYP7A1 (resp. ≈ +20%, NS, and ≈ +30%, NS) and Δ6 desaturase[m] (resp. ≈ -40 and ≈ -38%) activities ↓ linoleic acid saturation index of liver PL, *i.e.* (20:3n-6 + 20:4n-6)/(18:2n-6): resp. ≈ -15 and ≈ -15% for PC, and ≈ -24 and ≈ -24% for PE	(Kawakami et al., 2005)
C-iso[a], U-iso[a], daidzein, glycitein and genistein (from soy)	HepG2 cells	10 ng/L	24 hours	↑ PPARα (resp. ≈ +40, ≈ +150, ≈ +45, ≈ -20 and ≈ +45%) and PPARγ (resp. ≈ +105, ≈ +325, ≈ +375, ≈ +235 and ≈ +130%)	(Ricketts et al., 2005)
Genistein	Mice fed high-fat (18%) diet	0.2% of diet	12 weeks	↓ LI (-7%), and TL (-42%), TG (-20%) and TC (-13%, NS) contents <u>Gene expression of cholesterol biosynthetic pathway enzymes</u>: - farnesyl diphosphate farnesyl transferase 1: from 0.35- to 1.10-fold - squalene expoxidase: from 0.19- to 1.12-fold - ACAT 1: from 3.90- to 4.20-fold - 7-dehydrocholesterol reductase: from 1.05- to 0.25-fold <u>Gene expression of FA metabolism</u>: - FAS: from 0.32- to 1.17-fold - ACO: from 1.70- to 3.05-fold - carnitine *o*-octanoyltransferase: from 1.15- to 4.40-fold - CPT1: from 2.3- to 2.5-fold - CPT2: from 2.6- to 3.5-fold - PPARα: from 2.2- to 5.3-fold - PPARγ: from 3.4- to 4.9-fold	(Kim et al., 2005)
Quercetin dehydrate and rutin	Male ICR mice fed 10%-fat (palm oil) diet	1% of diet	15 days	↓ FAS (resp. ≈ -40 and -17%, NS), ATPCL (resp. ≈ -54 and -27%), ME (resp. ≈ -37 and -26%) and G6PDH (resp. ≈ -54 and -11%, NS) activities ↓ ACC (resp. ≈ -44 and -21%, NS), FAS (resp. ≈ -50 and -24%, NS), ATPCL (resp. ≈ -245 and -28%, NS) and ME (resp. ≈ -43 and -33%) mRNA levels ↓ mRNA levels of proteins involved in regulation of lipogenesis: spot 14 (resp. ≈ -45 and -20%, NS), adiponutrin (resp. ≈ - 87 and -45%) and SREBP-1c (resp. ≈ -13, NS, and -3%, NS)	(Odbayar et al., 2006)
Green tea extract	FAS from duck liver	≈ 3.5-60 μg/mL	-	$IC_{50} \cong$ 12.2 μg/mL (< IC_{50} of EGCG and ECG)	(Zhang et al., 2006)
Catechin gallate ((-)-CG)		≈ 1-42 μM	-	IC_{50} = 1.5 μg/mL (16-fold and 12-fold higher than EGCG and ECG)	
Naringenin and hesperetin (citrus flavonoids)	Male ICR mice fed 10%-fat standard diet	1% of diet	21 days	↑ β-oxidation enzyme activities: peroxisomal palmytoyl-CoA oxidation (resp. ≈ +58 and ≈ +25%, NS%), ACO (resp. ≈ +60 and ≈ +26%, NS), CPT (resp. ≈ +17 and ≈ +10%, NS), enoyl-CoA hydratase (resp. ≈ +27 and ≈ +9%, NS) , 3-hydroxyacyl-CoA dehydrogenase (resp. ≈ +10 and ≈ +5%, NS) and 3-ketoacyl-CoA thiolase (resp. ≈ +24 and ≈ +10%, NS) Naringenin: significantly ↑ mRNA levels of enzymes involved in fatty acid oxidation (carnitine octanoyltransferase, ACO, peroxisomal bifunctional enzyme and 3-ketoacyl-CoA thiolase, mitochondrial trifunctional enzyme subunit β and cytochrome P-450 IV A1); no effect of hesperetin No effect on TG, cholesterol and PL levels	(Doan Thi Thanh et al., 2006)
Catechins (from green tea) and green tea extract (≥ 58% catechins)	HepG2 cells	0-200 μM	24 hours	↑ LDL receptor binding activity (resp. ≈ +50%, NS, ≈ +20%, NS, ≈ +28%, NS, ≈ +118 and +86%) at 100 μM <u>EGCG</u>: Significantly ↑ LDL receptor binding activity (≈ +220%), LDL receptor protein (≈ +146%), medium cholesterol (≈ +27%) and cell lathosterol (≈ +46%) concentrations (max. at 200 μM); No effect on FC and chenodeoxycholic acid concentrations	(Bursill and Roach, 2006)

				↓ TC concentration (≈ -28%) ↑ active transcription factor form of SREBP-1 (≈ +42-56%, from nuclear cell fraction) and ↓inactive precursor form of SREBP-1 (from membrane fraction) to undetectable levels	
Chamiloflan[o] (flavonoids from *Chamomilla recutita*)	Three-, 24 or 27-28-months old rats fed standard diet with 700 μL ethanol/kg b.w.	160 mg/kg b.w.	3, 24 or 27-28 months	↑ PC (resp. no effect, ≈ +92 and ≈ +92%) and SM (resp. no effect, ≈ +26 and ≈ +75%) contents ↓ ceramide (precursor of SM) content (resp. no effect, ≈ -46 and ≈ -70%)	(Babenko and Shakhova, 2006)
		160 mg/kg b.w.	1 week	↓ ceramide production from [^{14}C]palmitic acid pre-labeled Sph (-28%); no effect on sphingoside production	
Chamiloflan, AP7Glu or ALU7Glu[o]	Hepatocytes isolated from 90- and 720-day-old male rats and incubated with 30 mM ethanol	500 μg/mL, 30 μM or 30 μM	4 or 24 hours	No effect on ceramide content and on ceramide/Sph ratio	
(-)-epigallocatechin-3-gallate	Mice fed high-fat (34.9%) diet	0.32% of diet	16 weeks	↓ LI (-22%), fatty liver incidence (from 21/22 mice in high-fat group to 4/22 mice in high-fat +EGCG-supplemented group and TG content (-69%) Gross examination: around 3-fold less in size/volume and similar to control group (4.3% fat) Histological/microscopic examinations: marked ↓ in liver lipid accumulation similar to control group (4.3% fat)	(Bose et al., 2008)
Daidzein derivative (LRXH609)	Male ICR mice fed high-fat (45%) diet	25, 50 and 100 mg/kg b.w.	30 days	↓ dose-dependently TC (resp. -14%, NS, -20 and -31%) and FFA (resp. -15%, NS, -32 and -37%) concentrations, and ↓ TG concentration (-11%, NS) at the dose of 100 mg/kg; ↑ TG concentration at the dose of 25 (+20%, NS) and 50 (+12%, NS) mg/kg ↓ LPL activity (resp. ≈ 0, -17 and -46%)	(Guo et al., 2009)
Total flavonoids[p] from the dried leaves of *Litsea coreana* leve (59.5% total flavonoids)	Rats fed high-fat (10 mL/kg b.w. high-fat emulsion) diet for 4 weeks	0.01, 0.02 or 0.04% of diet (*via* gavage)	5 weeks	Morphological evaluation: fom 7/10 rats with severe steatosis (>76% of hepatocytes affected) to 0/10; ↓ dose-dependently the percentage of hepatocytes affected (resp. 0/10, 1/10 and 4/10 rats with no steatosis) ↓ TG (resp. ≈ -14, -20 and -27%) , TC (resp. ≈ -22, -33 and -44%) and FFA (resp. ≈ -20, -41 and -62%) contents ↑ PPARα protein expression (≈ +89%)	(Wang et al., 2009a)
Epigallocatechin-3-gallate (EGCG)	Rats fed high-fat (≈ 15%) diet	1 mg/kg b.w. administered in drinking water (as 100% of fluid intake)	26 weeks	↑ PPARα gene expression (≈ +160%); no effect on CPT-1, ACO, SREBP-1, MCD, FAS and ACC gene expressions No effect on TG content	(Chen et al., 2009)
Pedunculagin (tannin)	HepG2 cells	1, 3 or 10 μg/mL	24 hours	↓ PPARα (resp. 0.60-fold, 0.58-fold, and 0.82-fold), CPT1A (0.63-fold at 1 μg/mL and 0.74-fold at 3 μg/mL) and ACOX1 (0.63-fold at 1 μg/mL and 0.82-fold at 3 μg/mL) mRNA expression (*vs* control), and ↑ PPARα (1.31-fold) and ACOX1 (1.20-fold) mRNA expression at 10 μg/mL	(Shimoda et al., 2009)
Tellimagrandin I (tannin)	HepG2 cells	1, 3 or 10 μg/mL	24 hours	↑ PPARα (1.08-fold at 3 μg/mL, NS, and 1.14-fold at 10 μg/mL, NS), CPT1A (resp. 1.02-fold, NS, 1.09-fold, NS, and 1.23-fold) and ACOX1 (resp. 1.12-fold, NS, 1.33-fold and 1.69-fold) mRNA expression (*vs* control); ↓ PPARα mRNA expression at 1 μg/mL (0.84-fold)	
Tellimagrandin II (tannin)	HepG2 cells	1, 3 or 10 μg/mL	24 hours	No effect on PPARα mRNA expression; ↑ CPT1A (resp. 1.42-fold, 1.56-fold and 1.42-fold) and ACOX1 (1.13-fold, NS, at 3 and 10 μg/mL) mRNA expression (*vs* control); ↓ ACOX1 mRNA expression at 1 μg/mL (0.79-fold)	
Green tea extract (29.2% total catechins)[q]	Rad fed high-fructose (60%) diet	0.5 or 1.0% of diet	6 weeks	↓ TG (resp. -72 and -72%), TC (resp. -12%, NS, and -8%, NS), FC (resp. -6%, NS, and -19%, NS) and CE (resp. -16%, NS and 0%) contents ↓ SREBP1c (resp. ≈ -50 and ≈ -75%), FAS (resp. ≈ -50 and ≈ -68%), SCD1 (resp. ≈ -48 and ≈ -62%), HMG-CoA reductase (resp. ≈ -	(Shrestha et al., 2009)

				69 and ≈ -56%), ABCA1 (resp. ≈ -52 and ≈ -33%) and SR-B1 (resp. ≈ -29%, NS, and ≈ -43%, NS) relative mRNA abundance; no effect on ACAT1, ACAT2 and MTP relative mRNA abundance	
B4 - Lignans					
Silybin-dihemisuccinate (derived compound from the flavonolignan silybin)	Postmitochondrial supernatant of rat liver homogenates and rat liver slice incubated with [1-^{14}C]acetate or $^{3}H_2O$	150.6 mg/kg b.w.	i.v. injection 30 and 60 min before killing	↓ incorporation of [1-^{14}C]acetate or $^{3}H_2O$ in FA (≈ -25%)	(Schriewer et al., 1979)
	In vitro incubation mixture of liver homogenates	0.45-0.6 mM		↓ linearly and dose-dependently incorporation of [1-^{14}C]acetate or $^{3}H_2O$ in FA (≈ -25%)	
		0.1 mM		↓ ACC, ATPCL and FAS activities (≈ -50%)	
		1 mM		↓ NADP-malate-dehydrogenase[4] (-20%)	
Sesamin	Liver from rats fed standard chow ±sesamin, and perfused 4 h with exogenous oleic acid (100 μM)	0.2% of diet	14-16 days + 4 hour liver perfusion	No significant effect on TG and cholesterol content of postperfused liver ↑ PL content of postperfused liver (+49%) ↑ cumulative production of ketone bodies (+21%) ↓ β-hydroxybutyrate/acetoacetate ratio (-24%, NS) ↓ cumulative secretion of TG (-40%) and cholesterol (-2%, NS) ↓ TC (-39%) and lipid (-9%, NS) contents	(Fukuda et al., 1998)
Sesamin	Liver from rats fed standard chow ±sesamin, and perfused 4 h with an exogenous di-*trans* isomer (to differentiate from relative contribution of endogenous linoleic acid) of linoleic acid (linolelaidic acid, *trans*,trans-9,12-octadecadienoic acid)(100 μM)	0.2% of diet	14 days	No significant effect on TG and cholesterol content of postperfused liver ↑ PL content of postperfused liver (+20%) ↑ cumulative production of ketone bodies (+46%) ↓ β-hydroxybutyrate/acetoacetate ration (-34%) ↓ cumulative secretion of TG (-56%), cholesterol (-16%, NS) and PL (-37%)	(Fukuda et al., 1999)
Sesamin (1:1 mixture of sesamin and episesamin)	Whole-liver homogenates from rats fed a sesamin-free and 15%-fat diet, and incubated with a [1-^{14}C]palmitoyl-CoA substrate	0.1, 0.2 and 0.5% of diet	15 days	↑ dose-dependently mitochondrial (≈ +87% at 0.5% sesamin) and peroxisomal (≈ +1300% at 0.5% sesamin) palmitoyl-CoA oxidation rate ↑ dose-dependently hepatic FA oxidation enzyme activity: CPT I (≈ +143% in mitochondria and ≈ +280% in whole homogenate at 0.5% sesamin), acyl-CoA dehydrogenase (≈ +130%), acyl-CoA oxidase (≈ +1050%), enoyl-CoA hydratase (≈ +106%), 3-hydroxyacyl-CoA dehydrogenase (≈ 380%), 3-ketoacyl-CoA thiolase (≈ +360-650%), 2,4-dienoyl-CoA reductase (≈ +534%) and Δ^3,Δ^2-enoyl-CoA isomerase (≈ +550%) ↑ dose-dependently gene expression of mitochondrial FA oxidation enzymes: CPT I (≈ +95% at 0.5% sesamin), CPT II (≈ +275%), long-chain acyl-CoA dehydrogenase (≈ +160%), mitochondrial trifunctional enzyme subunits α (≈ +300%) and β (≈ +240%), mitochondrial 3-ketoacyl-CoA thiolase (≈ +360%), 2,4-dienoyl-CoA reductase (≈ +450%) and Δ^3,Δ^2-enoyl-CoA isomerase (≈ +835%) ↑ dose-dependently gene expression of peroxisomal FA oxidation enzymes: acyl-CoA oxidase (≈ +1400% at 0.5% sesamin), peroxisomal bifunctional enzyme (≈ +4800%) and peroxisomal 3-ketoacyl-CoA thiolase (≈ +480%) ↓ FAS and L-pyruvate kinase activities (resp. -44 and -62% at 0.5% sesamin) and gene expression (resp. ≈ -42 and ≈ -67% at 0.5% sesamin); ↑ ME activity (≈ +125% at 0.5% sesamin) and gene expression (≈ +100% at 0.5% sesamin) ↓ TG (resp. 0, -8%, NS, and -14%, NS) and cholesterol (resp. -5%, NS, -5%, NS, and -15%) concentrations; ↑ PL (resp. +9%, NS, +18 and +30%) concentration	(Ashakumary et al., 1999)
Sesamin (1:1 mixture	Rats fed 10%-fat diet	0.2% of diet	4 weeks	↓ TC (-39%) and lipid (-9%, NS) contents	(Kamal-Eldin et al., 2000)

of sesamin and episesamin)					
Sesamin (1:1 mixture of sesamin and episesamin)	Rats fed sesamin-free and 10%-fat diet	0.1 and 0.2% of diet	15 days	↑ dose-dependently hepatic FA oxidation enzyme activity: peroxisomal oxidation (resp. +22 and +130%), acyl-CoA oxidase (resp. +38 and +112%), CPT (resp. +61 and +135%), 3-hydroxyacyl-CoA dehydrogenase (resp. +56 and +90%) and 3-ketoacyl-CoA thiolase (resp. +72 and +116%) ↓ dose-dependently ACC, FAS, ATPCL, G6PDH and pyruvate kinase activities (resp. -36, -32, -30, -42 and -19% at 0.1%, and resp. -57, -46, -47, -59 and -44% at 0.2% sesamin) and gene expression (resp. -35, -36, -28, -36 and -25% at 0.1%, and resp. -52, -50, -48, -64 and -55% at 0.2% sesamin); no effect on ME activity (resp. -6 and +13%) and gene expression (resp. +2 and -7%) ↓ dose-dependently activity of hepatic enzymes involved in cholesterol synthesis: farnesyl pyrophosphate synthase (resp. -20 and -29%) and squalene synthetase (resp. -32 and -39%); no effect on HMG-CoA synthase ↓ dose-dependently gene expression (mRNA levels) of hepatic enzymes involved in cholesterol synthesis: HMG-CoA reductase (resp. -23 and -30%), farnesyl pyrophosphate synthase (resp. -21 and -35%), squalene synthetase (resp. -30 and -44%) and of LDL receptor (resp. -22 and -28%); ↑ mRNA level of HMG-CoA synthase (resp. +9%, NS, and +31%) ↓ mRNA level of SREBP-1 (resp. ≈ -30 and -35%) ↓ dose-dependently protein level of precursor and mature forms of SREBP-1 (resp. ≈ -13%, NS, and -37%)	(Ide et al., 2001)
		0.2 and 0.4% of diet	15 days	↑ dose-dependently hepatic FA oxidation enzyme activity: peroxisomal oxidation (resp. +207 and +600%), acyl-CoA oxidase (resp. +260 and +768%), CPT (resp. +127 and +232%), 3-hydroxyacyl-CoA dehydrogenase (resp. +148 and +329%) and 3-ketoacyl-CoA thiolase (resp. +139 and +275%) ↓ ACC, FAS, ATPCL, G6PDH and pyruvate kinase activities (resp. -44, -47, -43, -60 and -50% at 0.2% sesamin, and resp. -41, -39, -46, -55 and -56% at 0.4% sesamin) and gene expression (resp. -49, -59, -44, -48 and -66% at 0.2%, and resp. -47, -57, -40, -49 and -65% at 0.4% sesamin) with plateau reached at 0.2% sesamin; ↑ dose-dependently ME activity (resp. +24%, NS, and +97%) and gene expression (resp. +16%, NS, and +92%) ↓ activity of hepatic enzymes involved in cholesterol synthesis: farnesyl pyrophosphate synthase (-27% at 0.2% sesamin and no significant effect at 0.4% sesamin) and squalene synthetase (-37% at 0.2% sesamin and no significant effect at 0.4% sesamin); ↑ dose-dependently HMG-CoA synthase activity (resp. +66 and +189%) ↓ dose-dependently gene expression (mRNA levels) of HMG-CoA reductase (resp. -26 and -42%), farnesyl pyrophosphate synthase (-37% at 0.2% sesamin), squalene synthase (-34% at 0.1% sesamin) and of LDL receptor (resp. -30 and -47%); ↑ dose-dependently mRNA level of HMG-CoA synthase (+172% at 0.4% sesamin); no effect on mRNA level of farnesyl pyrophosphate synthase at 0.4% sesamin ↓ dose-dependently mRNA level of SREBP-1 (resp. ≈ -37 and -55%) ↓ protein level of precursor and mature forms of SREBP-1 (resp. ≈ -84 and -88%	
Sesamin or episesamin	Rats fed sesamin-free and 10%-fat diet	0.2% of diet	15 days	↑ FA oxidation enzyme activity: mitochondrial (resp. +73 and +129%) and peroxisomal (resp. +63 and +407%) palmitoyl-	(Kushiro et al., 2002)

				CoA oxidation, CPT (resp. +61 and +200%), acyl-CoA oxidase (resp. +47 and +495%), 3-hydroxyacyl-CoA dehydrogenase (resp. +31 and +167%), 3-ketoacyl-CoA thiolase (resp. +44 and +122%), Δ^3,Δ^2-enoyl-CoA isomerase (resp. +88 and +190%) and 2,4-dienoyl-CoA reductase (resp. +114 and +343%) ↑ mitochondrial gene expression (mRNA levels) of FA oxidation enzymes: CPT II (resp. +46 and +110%), long-chain acyl-CoA dehydrogenase (resp. +28 and +50%), trifunctional enzyme subunit α (resp. +80 and +182%) and β (resp. +70 and +178%), mitochondrial 3-ketoacyl-CoA thiolase (resp. +84 and +178%), short-chain Δ^3,Δ^2-enoyl-CoA isomerase (resp. +122 and +561%) and 2,4-dienoyl-CoA reducatse (resp. +180 and + 213%) ↑ peroxisomal gene expression (mRNA levels) of FA oxidation enzymes: carnitine octanoyltransferase (resp. +31%, NS, and +73%), ACO (resp. +67%, NS, and +312%), peroxisomal bifunctional enzyme (resp. +156 and +1347%) and 3-ketoacyl-CoA thiolase (resp. 117 and + 391%) ↓ lipogenic enzyme activities: FAS (resp. -59 and -52%), ATPCL (resp. -52 and -54%), G6PDH (resp. -44 and -52%) and pyruvate kinase (resp. -37 and -61%) ↓ lipogenic enzyme mRNA levels: ACC (resp. -35 and -43%), FAS (resp. -64 and -69%), ATPCL (resp. -47 and -41%), G6PDH (resp. -42 and -55%) and L-pyruvate kinase (resp. -49 and -65%) ↓ TG content (resp. -29%, NS, and -2%, NS); no effect on cholesterol content (resp. 0 and +7%, NS); ↑ PL content (resp. +5%, NS, and +50%)	
Sesamin and episesamin (1:1)	Male ICR mice fed 10%-fat diet	0.2% sesamin-episesamin of diet	15 days	↓ CPT (-10%, NS), 3-hydroxyacyl-CoA dehydrogenas (-14%, NS), 3-ketoacyl-CoA thiolase (-13%, NS), FAS (-2%, NS), ATPCL (-26%, NS), G6PDH (-37%, NS) and pyruvate kinase (-4%, NS) activities ↑ peroxisomal fatty acid oxidation (+18%, NS) and ACO activity (+15%, NS) ↓ mRNA levels of mitochondrial trifunctional enzyme subunits α (-6%, NS) and β (-27%, NS) and 3-ketoacyl-CoA thiolase (-8%, NS) ↑ mRNA levels of mitochondrial CPT (+8%, NS), of peroxisomal ACO (+20%, NS), bifunctional enzyme (+25%, NS) and 3-ketoacyl-CoA thiolase (+38%), of FAS (+3%, NS), ATPCL (+8%, NS) and L-pyruvate kinase (+13%, NS)	(Kushiro et al., 2004)
	Male rats fed 10%-fat diet	0.2% sesamin-episesamin of diet	15 days	↓ CPT (-3%, NS), ACO (-2%, NS), FAS (-21%, NS), ATPCL (-32%), G6PDH (-3%, NS) and pyruvate kinase (-13%) activities ↑ peroxisomal FA oxidation (+11%, NS), and 3-hydroxyacyl-CoA dehydrogenas (+16%, NS) and 3-ketoacyl-CoA thiolase (+14%, NS) activity ↑ mRNA levels of mitochondrial CPT (+70%), trifunctional enzyme subunits α (+145%) and β (+126%) and 3-ketoacyl-CoA thiolase (+142%), of peroxisomal ACO (+235%), bifunctional enzyme (+926%) and 3-ketoacyl-CoA thiolase (+399%) ↓ mRNA levels of FAS (-63%), ATPCL (-45%) and L-pyruvate kinase (-64%)	
	Male hamsters fed 10%-fat diet	0.2% sesamin-episesamin of diet	15 days	↑ CPT (+119%), peroxisomal FA oxidation (+243%), ACO (+259%), 3-hydroxyacyl-CoA dehydrogenas (+89%) and 3-ketoacyl-CoA thiolase (+80%) activity ↓ FAS (-57%), ATPCL (-55%), G6PDH (-66%) and pyruvate kinase (-64%) activities	
Sesamin (1:1 mixture	Rats fed 8%-fat (palm, safflower or fish oil) diet	0.2% of diet	15 days	↑ activity of the hepatic FA oxidation enzymes: mitochondrial	(Ide et al., 2004)

	of sesamin and episesamin)			(resp. ≈ +150, +87 and +58%; ≈ -33% for safflower oil and -52% for fish oil *vs* palm oil+sesamin) and peroxisomal (resp. ≈ +325, +320 and +300%; ≈ +10% for safflower oil, NS, and +110% for fish oil *vs* palm oil+sesamin) palmytoyl CoA oxidation, ACO (resp. ≈ +200, +325 and +400%; ≈ +50% for safflower oil, NS, and +290% for fish oil *vs* palm oil+sesamin), CPT (resp. ≈ +233, +140 and +78%; ≈ +10% for safflower oil, NS, and +40% for fish oil *vs* palm oil+sesamin), 3-ketoacyl-CoA thiolase (resp. ≈ +163, +200 and +196%; ≈ +15% for safflower oil, NS, and +60% for fish oil *vs* palm oil+sesamin), and 2,4-dienoyl-CoA reductase (resp. ≈ +247, +177 and +71%; ≈ +1% for safflower oil, NS, and -22% for fish oil *vs* palm oil+sesamin) ↑ mRNA levels of hepatic peroxisomal proteins (carnitine octanoyltransferase, ACO, bifunctional enzyme, 3-ketoacyl-CoA thiolase, and PEX11α) and of mitochondrial enzymes involved in hepatic fatty acid oxidation (CPT II, medium-chain acyl-CoA dehydrogenase, trifunctional enzyme subunits α and β, 3-ketoacyl-CoA thiolase, 2,4-dienoyl-CoA reductase and short-chain Δ^3,Δ^2-enoyl-CoA isomerase) ↓ FAS (resp. -45, -63 and -48, NS, %), ATPCL (resp. -53, -60 and -70%) and G6PDH (resp. -60, -77 and -38, NS, %) activities ↓ mRNA levels of enzymes involved in hepatic fatty acid synthesis (ACO, FAS, ATPCL and spot 14) TG level: resp. -68, -23 and +136% Cholesterol level: resp. -20, -21 and +21% PL level: resp. +19, +30 and +19%	
Matairesinol	Ovariectomized rats fed standard diet (11.5% fat)	0.02% of diet	4 weeks	↓ cholesterol (-6%, NS) and TG (-12%, NS) levels	(Cho et al., 2004)
	HepG2 cells	0.01, 0.1 and 1 μM	3 days	↓ cholesterol (resp. -30, -27 and -19%, NS) and TG (resp. ≈ 0, -15 and -12%, NS) contents	
Sesamin	Male rats fed standard diet	250 mg/5 mL olive oil/kg b.w.	3 days	Significantly up-regulated expression of genes encoding for proteins with a lipid-metabolizing function: acyl-CoA hydrolase (114.6-fold), very-long-chain acyl-CoA thioesterase (14.2- and 4.7-fold: different probe position in rat genome), acyl-CoA hydrolase-like protein (3.4-fold), acyl-CoA hydrolase (2.1-fold), peroxisomal 3-ketoacyl-CoA thiolase (8.3- and 3.4-fold), peroxisomal bifunctional enzyme (4.5-fold), 3,2-*trans*-enoyl-CoA isomerase (3.4-fold), enoyl CoA hydratase (3.0-fold), Δ^3,Δ^2-enoyl-CoA isomerase (3.0-fold), 2,4-dienoyl-CoA reductase 1 (2.6- and 2.2-fold), ACO (2.1-fold) and ME (2.8- and 2.2-fold) Significantly up-regulated gene expression of early-stage mitochondrial (CPT I like protein and CPT II) and peroxisomal (carnitine octanoyltransferase) β-oxidation enzymes Significantly up-regulated gene expression of late-stage mitochondrial (very-long-chain acyl-CoA dehydrogenase, trifunctional enzyme β, 2,4-dienoyl-CoA reductase 1, Δ^3,Δ^2-enoyl-CoA isomerase and 3,2-*trans*-enoyl-CoA isomerase) and peroxisomal (ACO, enoyl CoA hydratase, bifunctional enzyme, 3-ketoacyl-CoA thiolase and 2,4-dienoyl-CoA reductase) β-oxidation enzymes Significantly down-regulated gene expression of early-stage mitochondrial (acyl-CoA syntahse 5) β-oxidation enzymes Significantly down-regulated gene expression of L-type pyruvate kinase (0.37-fold) and Apo A-IV (0.48-fold)	(Tsuruoka et al., 2005)
Sesamin (1:1 mixture of sesamin and episesamin)	Rats fed 10%-fat (palm oil) diet	0.2 or 0.4% of diet	15 days	↑ activity of the hepatic fatty acid oxidation enzymes: peroxisomal palmytoyl-CoA- oxidation (resp. ≈ +550 and +1150%), ACO (resp. ≈ +267 and +667%), CPT (resp. ≈ +214 and +343%), 3-	(Arachchige et al., 2006)

				hydroxyacyl-CoA dehydrogenase (resp. ≈ +175 and 263%) and 3-ketoacyl-CoA thiolase (resp. ≈ +146 and +242%)
	Rats fed 10%-fat (8% palm oil + 2% DHA ethyl ester) diet	0.2% of diet	15 days	↑ activity of the hepatic FA oxidation enzymes: peroxisomal palmytoyl-CoA oxidation (≈ +500%), ACO (≈ +575%), CPT (≈ +211%), 3-hydroxyacyl-CoA dehydrogenase (≈ +183%) and 3-ketoacyl-CoA thiolase (≈ +151%)
	Rats fed 10%-fat (palm oil) diet	0.2% of diet	15 days	↑ activity of the hepatic FA oxidation enzymes: peroxisomal palmytoyl-CoA- oxidation (≈ +300%), ACO (≈ +300%), CPT (≈ +250%), enoyl-CoA hydratase (≈ +48%), 3-hydroxyacyl-CoA dehydrogenase (≈ +141%) and 3-ketoacyl-CoA thiolase (≈ +312%)
	Rats fed 10%-fat (8% palm oil + 2% EPA ethyl ester) diet	0.2% of diet	15 days	↑ activity of the hepatic FA oxidation enzymes: peroxisomal palmytoyl-CoA oxidation (≈ +420%), ACO (≈ +540%), CPT (≈ +140%), enoyl-CoA hydratase (≈ +73%), 3-hydroxyacyl-CoA dehydrogenase (≈ +188%) and 3-ketoacyl-CoA thiolase (≈ +333%) 4 experiments: ↑ mRNA levels of hepatic peroxisomal proteins (carnitine octanoyltransferase, ACO, bifunctional enzyme, 3-ketoacyl-CoA thiolase, and PEX11α) and of mitochondrial enzymes involved in hepatic fatty acid oxidation (CPT II, medium-chain acyl-CoA dehydrogenase, trifunctional enzyme subunits α and β, 3-ketoacyl-CoA thiolase, 3-hydroxy-3-methylglutaryl-CoA synthase)
Sesamin	Rats fed 10%-fat (palm oil) diet	0.06 or 0.2% of diet	10 days	↑ peroxisomal palmytoyl-CoA oxidation (resp. +8, NS, and +46%), and ACO (resp. +8, NS, and +31%), CPT (resp. +31 and +88%), enoyl-CoA hydratase (-3%, NS at 0.06% sesamin; +32% at 0.2% sesamin), 3-hydroxyacyl-CoA dehydrogenase (resp. +28 and +89%), 3-ketoacyl-CoA thiolase (resp. +12, NS, and +61%) and 2,4-dienoyl-CoA reductase (resp. +37 and +65%) activities ↓ FAS (resp. -41 and -60%), ATPCL (resp. -38 and -57%), G6PDH (resp. -49 and -64%) and pyruvate kinase (resp. -15%, NS, and -39%) activities ↓ TG (resp. -59 and -64%) and cholesterol (resp. -25 and -25%) levels; ↑ PL level (resp. 0 and +6%, NS)
Sesamolin	Rats fed 10%-fat (palm oil) diet	0.06 or 0.2% of diet	10 days	↑ peroxisomal palmytoyl-CoA oxidation (resp. +51 and +321%), and ACO (resp. +59 and +220%), CPT (resp. +64 and +279%), enoyl-CoA hydratase (resp. +24 and +100%), 3-hydroxyacyl-CoA dehydrogenase (resp. +68 and +228%), 3-ketoacyl-CoA thiolase (resp. +64 and +249%) and 2,4-dienoyl-CoA reductase (resp. +57 and +157%) activities ↓ FAS (resp. -34 and -55%), ATPCL (resp. -35 and -67%), G6PDH (resp. -51 and -68%) and pyruvate kinase (resp. -20 and -51%) activities ↓ TG (resp. -18 and -30%) and cholesterol (resp. -17 and -30%) levels; ↑ PL level (resp. +6%, NS, and +37%)
Sesamin + sesamolin	Rats fed 10%-fat (palm oil) diet	0.14+0.06% of diet	10 days	↑ peroxisomal palmytoyl-CoA oxidation (+148%), and ACO (+99%), CPT (+130%), enoyl-CoA hydratase (+76%), 3-hydroxyacyl-CoA dehydrogenase (+156%), 3-ketoacyl-CoA thiolase (+139%) and 2,4-dienoyl-CoA reductase (+101%) activities ↓ FAS (-56%), ATPCL (-56%), G6PDH (-67%) and pyruvate kinase (-45%) activities ↓ TG (-34%) and cholesterol (-23%) levels; ↑ PL level (+42%) All experiments: ↑ mRNA abundance of enzymes involved in FA oxidation (from +10% at 0.06% sesamin for trifunctional enzyme subunit β to

				+544% at 0.2% sesamolin for peroxisomal carnitine octanoyltransferase): - peroxisomal carnitine octanoyltransferase, ACO, bifunctional enzyme, 3-ketoacyl-CoA thiolase and P11α - mitochondrial CPT II, rifunctional enzyme subunits α and β, 3-ketoacyl-CoA thiolase, Δ^3,Δ^2-enoyl-CoA isomerase and 2,4-dienoyl-CoA reductase ↓ mRNA abundance of proteins involved in lipogenesis in almost all cases (from 0% for mixture of sesamin+sesamolin to -69% at 0.2% sesamolin for pyruvate kinase): ACC, FAS, ATPCL, G6PDH, pyruvate kinase, mitochondrial glycerol 3-phosphate dehydrogenase, DGAT 1 and 2, spot 14, adiponutrin, SREBP-1a and -1c	
Secoisolariciresinol (SECO) or secoisolariciresinol diglucoside (SDG)	Rats fed high-cholesterol (1%) diet	3 or 6 mg SDG/kg b.w.	4 weeks	SDG: -↓ LI (resp. -10%, NS, and -12%, NS) - ↓ median percentage fat accumulation (resp. -8%, NS, and -24%, NS) - histological observations: ↓ amount of lipids - ↑ ACAT2 (resp. +54 and +66%), CYP7A1 (+10%, NS, at 6 mg/kg), HMG-CoA reductase (resp. +28, NS, and +35%, NS), LDL receptor (+6%, NS, at 6 mg/kg) and PPARγ (+2%, NS, at 6 mg/kg) mRNA expression levels; ↓ ApoE (resp. -35%, NS, and -21%, NS), CYP7A1 (-7%, NS at 3 mg/kg), LDL receptor (-32%, NS, at 3 mg/kg), PPARγ (-14%, NS, at 3 mg/kg) and SREBP-2 (-27%, NS, and -19%, NS) mRNA expression levels	(Felmlee et al., 2009)
	Rats fed high-cholesterol (1%) diet	1.6 or 3.2 mg SECO/kg b.w.	4 weeks	SECO: -↓ LI (resp. -103%, NS, and -15%, NS) -↑ median percentage fat accumulation at 1.6 mg/kg (+7%, NS) and ↓ median percentage fat accumulation at 3.2 mg/kg (-24%, NS) - histological observations: ↓ amount of lipids - ↑ ApoE (+35%, NS, at 1.6 mg/kg), HMG-CoA reductase (resp. +28, NS, and +35%, NS), HMG-CoA reductase (+8%, NS, at 1.6 mg/kg) and PPAγ (resp. +17%, NS, and +17%, NS) mRNA expression levels; ↓ ACAT2 (resp. 0 and -7%, NS), ApoE (-0.6%, NS at 3.2 mg/kg), CYP7A1 (resp. -36%, NS, and -71%), HMG-CoA reductase (-6%, NS, at 3.2 mg/kg), LDL receptor (resp. -6%, NS, and -24%, NS) and SREBP-2 (resp. -15%, NS, and -22%, NS) mRNA expression levels	
Secoisolariciresinol diglucoside (SDG)	Hypertriacylglycerolaemic rats (10% fructose in drinking water)	3 and 6 mg/kg b.w.	2 weeks	↑ PPARα mRNA expression level (resp. +36 and +31%) ↓ SREBP-1c mRNA expression level (resp. -9 and -38%)	
B5 - Stilbenes					
Stilbenes containing extract-fraction (from *Cajanus cajan* L.), *i.e.* cajanin, and longistylin C and A	Mice fed hypercholesterolemic (2% cholesterol and 0.5% cholic acid) diet	100 and 200 mg/kg b.w.	4 weeks	↓ TC (resp. -10%, NS, and -23%) and TG (resp. -9%, NS, and -14%) contents ↑ HMG-CoA reductase (resp. ≈ +14%, NS, and ≈ +61%), CYP7A1 (resp. ≈ +20%, NS, and ≈ +48%) and LDL-receptor (resp. ≈ +28 and ≈ +84%) mRNA expressions	(Luo et al., 2008)
C - Phenolic-derived compounds					
C1 - Curcumin					
Curcumin	Rats fed high-cholesterol (1% +0.15% bile salts) diet	0.15% of diet	7 weeks	↓ TC (-16%), CE (-22%), TG (-22%) and PL (-18%, NS); ↑ FC content (+6%, NS)	(Seetharamaiah and Chandrasekhara, 1993)

Curcumin	Rats fed 10%-fat diet	0.2% of diet	4 weeks	↓ TC (-37%) and lipid (-4%, NS) contents	(Kamal-Eldin et al., 2000)
C2 - Saponins					
Ginsenosides (Rb_1, Rc, Rg_1, Rd and Re) prufied from ginseng (*Panax ginseng*)	Rats injected with ^{14}C-acetate from 30 to 120 min before killing	5 mg injected i.p. before killing	4 hours	↓ and ↑ TC (resp. -10, -19, -14, -5%, NS, and +8%) and FC (resp. 0, -21, -4%, NS, +23 and -53%) amounts, and FC/TC ratio At 90 min. before killing: ↑ rate of cholesterol synthesis from ^{14}C-acetate (resp. +209, +55, +32, +11%, NS, and +76%) Rb_1: ↑ rate of cholesterol synthesis from ^{14}C-acetate from 30 to 120 min before killing (max. at 90 min: +73%) Taking 100% as rate of cholesterol synthesis at 5 mg Rb_1 injected: ≈ +12% at ≈ 10 mg, ≈ -24% at ≈ 3 mg, ≈ -65% at ≈ 1.5 mg, ≈ -68% at ≈ 0.5 mg and ≈ -68% at 0 mg injected	(Sakakibara et al., 1975)
Purified saponosides from *Aralia mandshurica* (mixture of 9 oleanosides)	Rats fed fatty (40% margarine and 2% cholesterol) diet (with 0.01% methylthiouracil)	0.005 or 0.01 g/kg b.w.	12 weeks	0.005 g/kg: ↑ and ↓ TL (+8%), TG (-40%) and TC (+14%) contents 0.01 g/kg: ↓ TL (-35%), TG (-35%) and TC (-11%) contents	(Wojcicki et al., 1977)
Commercial white saponins (probably from European Soapwort, *Saponaria officinalis*)	Rats fed normal or high-cholesterol (1%) diet	1% of diet	3 weeks	↓ cholesterol (resp. -7%, NS, and -52%) and TG (resp. -20 and -39%) concentrations	(Oakenfull et al., 1979)
Commercial white saponins (probably from European Soapwort, *Saponaria officinalis*)	Rats fed standard diet containing methionine-supplemented sodium isolates of soybean or casein (25% energy)	1% of diet	56 days	Soybean-based diet: ↑ cholesterol content (+41%) Casein-based diet: ↓ cholesterol content (-4%)	(Pathirana et al., 1980)
Saponins (purified)	Laying hens (brown and white Leghorn) fed standard diet	0.1 or 0.5% of diet 0.1, 0.2 or 0.4% of diet 0.1, 0.2 or 0.4% of diet	5 or 8 weeks 8, 7 or 6 weeks 18 weeks	↓ lipid content (resp. -16%, NS, and -26%) No effect on cholesterol content (resp. -3%, NS, and +8%, NS) ↓ lipid content (resp. 0, -11%, NS, and -19%, NS) ↓ lipid content (resp. -15%, NS, -21 and -29%)	(Whitehead et al., 1981)
Steroid saponins (from *Gypsophila* plant roots) + citrus pectin washed with acidified ethanol	Rats fed standard diet ± citrus pectin washed with acidified ethanol	0.2% + 10% of diet	5 weeks	Compared to standard diet without citrus pectin: ↓ TL (-68%) and TC (-65%) contents Compared to standard diet with 10% citrus pectin: ↑ TL (+6%, NS) and TC (+13%, NS) contents	(Rotenberg and Eggum, 1986)
Mixture of avecanosides A and B (from oat meal)	Rats and gerbils fed high-fat (40%) and 6.5% ethanol-extracted oatmeal diet	0.07% of diet	21 (gerbils) and 19 (rats) days	Gerbils: ↓ TL (-4%, NS), TC (-6%, NS) and FC (-6%, NS) contents Rats: ↓ TL (-31%), and ↑ TC (+2%, NS) and FC (+6%, NS) contents	(Onning and Asp, 1995)
Soy saponins	HepG2 cells	10 ng/L	24 hours	↑ PPARα (≈ +60%) and PPARγ (≈ +80%)	(Ricketts et al., 2005)
Changkil saponins (from root of *Platycodon grandiflorum*)	Mice fed saponins for 7 days before ethanol administration (5 g/kg b.w.) for around 36 hours	0.5, 1 or 2 mg/kg b.w.	7 days	↓ dose-dependently TG content (-7%, NS, -22 and -36%) Histopathological observations: ↓ steatosis score (-49%)	(Khanal et al., 2009b)
Changkil saponins (from root of *Platycodon grandiflorum*)	Rats chronically fed with ethanol (enteral feeding) for 4 weeks	0.5, 1 or 2 mg/kg b.w.	Last 2 weeks	Histologic observations: ↓ fat deposition and faint micro- and macrovesicular fat droplets ↓ TL content (resp. ≈ -15%, NS, -32 and -45%) ↑ phosphorylated-AMPK level (resp. +16%, NS, +59 and +93%)	(Khanal et al., 2009a)

Saponins (from *Platycodi radix*)	90% pancreatectomized diabetic rats fed high-fat (40% as energy) diet	0.2 g/kg b.w.	8 weeks	↑ phosphorylated-ACC level (resp. +10%, NS, +40 and +70%) ↓ TG content (≈ -17%, NS)	(Kwon et al., 2009)
C3 - Phyto-sterols/stanols					
β-sitosterol	Mice fed high-cholesterol (1%) diet with 0.25, 0.5 or 1.0% of cholic acid	2.5% of diet	3 weeks	↓TC (resp. -27, -47 and -7% with $p \cong 0.05$ at 1.0% cholic acid)	(Beher and Anthony, 1955)
β-sitosterol	Normal and hypothyroid rats fed high-cholesterol (1%) diet	5% of diet	13 days	↓TC content (-76% for normal rats and -83% for hypothyroid rats) Prevented the increase in stainable lipids (microscopic observations)	(Best and Duncan, 1956)
Sterols (from soy)	Male (M) and female (F) mice fed cholesterol (0.5%) diet	1% of diet	12 days	↓neutral lipid (M: -7%, NS; F: -53%) and cholesterol (M: -48%; F: -68%) contents	(Katz et al., 1970)
		1% of diet	1, 3 and 5 days	↓cholesterol content (resp. -23%, NS, -50 and -65%)	
		1% of diet	5 days	β-sitosterol: ↓cholesterol content (-67%, n = 2 experiments) Stigmasterol: ↓cholesterol content (-57%, n = 2 experiments) Ergosterol: ↓cholesterol content (-53%, n = 2 experiments) Campesterol: ↓cholesterol content (-53%, n = 2 experiments) Steryl glucoside: ↓cholesterol content (-18%, NS)	
β-sitosterol	Rats fed diet containing combination of safflower oil (0 or 0.5%) and butter fat (9.5 or 10% containing ≈ 0.004% campesterol, ≈ 0.005% β-sitosterol and ≈ 0.28% cholesterol)	0.1, 0.5 or 2.0% of diet	31 days	9.5% butter fat, 0.5% safflower oil and 0.5% β-sitosterol: ↓ cholesterol content (-27%), and ↑TG (+6%, NS) and PL (+2%, NS) contents	(Sugano et al., 1982)
			35 days	10% butter fat, 0% safflower oil and 0.5% β-sitosterol: ↓cholesterol (-31%), TG (-9%, NS) and PL (-2%, NS) contents; ↑ApoA-I serum concentration (+40%)	
			33 days	10% butter fat and 0% safflower oil: 0.1% β-sitosterol: ↓cholesterol (-18%, NS) and TG (-7%, NS) contents; no effect on PL content; ↑ApoA-I (+22%) and ApoB (+7%, NS) serum concentrations 0.5% β-sitosterol: ↓cholesterol content (-23%), and ↑TG (+16%, NS) and PL (+6%, NS) contents; ↑ApoA-I (+19%, NS) and ↓ApoB (-9%, NS) serum concentrations 2.0% β-sitosterol: ↓cholesterol content (-32%), and ↑TG (+4%, NS) and PL (+4%, NS) contents; ↑ApoA-I (+7%, NS) and ApoB (+38%) serum concentrations	
	Mice fed diet containing safflower oil (0.5%) and butter fat (9.5 containing ≈ 0.004% campesterol, ≈ 0.005% β-sitosterol and ≈ 0.28% cholesterol)	0.5% of diet	40 days	↓cholesterol (-54%) and TG (-44%) contents	
Sitosterol and spinasterol	Mice fed ordinary powder diet	1% of diet	15 days	↓cholesterol (resp. -26 and -22%) and PL (resp. -4%, NS, and -3%, NS) levels	(Uchida et al., 1983)
Sitosterol	Hamsters fed standard chow	2% of diet	7 weeks	↓cholesterol concentration (-32%) and steroid 12α-hydroxylase activity (-30%)	(Kuroki et al., 1983)
Phytosterol mixture (57% β-sitosterol and 35% campesterol)	Rats fed high-cholesterol (1%) diet	3% of diet	7 days	↓ cholesterol level (-52%)	(Katagiri and Shimizu, 1992)
Phytosterols from maize (72.5% β-sitosterol, 20.5% campesterol and 7% stigmasterol)	Rats fed cholesterol diets (12 or 24 mg daily) for 4 weeks	12, 24 or 48 mg	3 last weeks	12 mg cholesterol daily: No significant effect on ACC (0 and -3%), ME (≈ 0) and G6PDH (resp. 0, -5 and +11%) activities except for ACC at 48 mg phytosterol daily (+23%) No significant effect on FA content (resp. +13, +16 and -3%); ↓ cholesterol content (resp. +1%, NS, and -3 and -8%)	(Laraki et al., 1993)
		24, 48 or 96 mg	3 last weeks	24 mg cholesterol daily: ↓ACC (resp. -68, -70 and -69%), ME (resp. -63, -63 and -63%) and G6PDH (resp. -81, -76 and -74%) activities	

				↓FA (resp. -64, -65 and -62%) and cholesterol (resp. -20, -30 and -32%) contents	
Plant sterol mixture (82% sitosterol, 12% sitostanol and 6% campesterol)	Rats fed standard diet Rats i.v. injected with liposomes	2% of diet 1% of liposomes (to mimick sisterolemia as found in humans)	7 days 42 hours	↑HMG-CoA reductase activity (+148%) and mRNA level (≈ +150%) No significant effect on HMG-CoA reductase activity (-3%), and ↑ HMG-CoA mRNA level (≈+160%) ↓CYP7A1 activity (-26%)	(Shefer et al., 1994)
Phytosterol mixtures naturally containing sitostanol[r] (from tall-oil) and sitostanol-free soybean phytosterol material	Rats fed high-cholesterol (1%) diet	1% of diet	10 days	↑serum HDL cholesterol (+49%) for phytosterol mixtures naturally containing sitostanol (≈16 or 20% content); no effect with sitostanol-free soybean phytosterol material (only unsaturated phytosterols)	(Ling and Jones, 1995)
Sitostanol	Hamsters fed 0.25% cholesterol standard diet	0.001, 0.2 or 1% of diet	45 days	↑hepatic cholesterol fractional synthetic rate (2-fold at 1%; no significant with both 0.001 and 0.2% levels)	(Ntanios and Jones, 1998a)
Plant sterol mixtures from soybean (0.01% sitostanol) and tall oil (0.2 and 0.8% sitostanol)	Rabbits fed atherogenic diet (0.5% cholesterol)	1% of diet	50 days	Soybean sterols (0.01% sitostanol): ↓median cholesterol level (-10%, NS) Tall oil sterols (0.2% sitostanol): ↑median cholesterol level (+24%, NS) Tall oil sterols (0.8% sitostanol): ↓median cholesterol level (-31%, NS)	(Ntanios et al., 1998a)
Plant sterol mixtures from soybean (0.01% sitostanol) and tall oil (0.2% sitostanol), and pure sitostanol	Rabbits fed cholesterol-enriched (0.25%) diet	1% of diet	45 days	↓cholesterol (≈ -74%, NS, for soybean sterols, and ≈ -92% for tall oil sterols and pure sitostanol) content	(Ntanios and Jones, 1998b)
Phytosterols (from tall oil or soybean)	Hamsters fed cholesterol-enriched (0.25%) diet	0.5 or 1%	90 days	Tall oil phytosterols: ↑hepatic cholesterol fractional synthetic rate (in % per day) (resp. +41%, NS, and +35%, NS) Soybean phytosterols: ↓hepatic cholesterol fractional synthetic rate in % per day (resp. -39%, NS, and -16%, NS)	(Ntanios et al., 1998b)
Phytosterol mixture (69% β-sitosterol, 16%, sitostanol and 15% campesterol)	ApoE-KO mice (model of atherogenesis) fed mouse diet	2% of diet	20 weeks	↓cholesterol level (-54%) ↑HMG-CoA reductase (+184%), cholesterol 7α-hydroxylase[11] (+18%, NS) and sterol 27-hydroxylase[11] (+3%, NS) activities	(Moghadasian et al., 2001)
Free phytosterol, esterified sterols or stanols	Gerbils fed 0.15%-cholesterol diet	0.75% of diet	-	↓TC (resp. -80, -76 and -76%) and CE (resp. -91, -88 and -88%) contents	(Wijendran et al., 2002)
Nonesterified (free) phytosterols (80%)/stanols (20%) from tall oil	Gerbils fed high-fat (13.7%) diet containing 0.05, 0.10 or 0.5% cholesterol	0.5% of diet	4-5 weeks	↓TC (resp. -57, -71 and -39%), FC (resp. 0, -38 and -11%, NS) and CE (resp. -72, -82 and -40%, NS) concentrations	(Hayes et al., 2002)
Nonesterified (free) phytosterols (80%)/stanols (20%) from tall oil	Gerbils fed high-fat (13.7%) diet containing 0.15% cholesterol	0.75% of diet	4 weeks	Phytosterols consumed with each dietary serving of cholesterol: ↓ TC (-78%), FC (-19%, NS) and CE (-89%) concentrations Phytosterol consumed in a way alternated between diet without phytosterols and diet with 0.15% of free phytosterol every other days: ↓TC (-66%), FC (-19%, NS) and CE (-74%) concentrations	
Free phytosterol from tall oil and esterified phytosterols (sterols and stanols) from	Gerbils fed high-fat (13.7%) diet containing 0.15% cholesterol	0.75% of diet	5 weeks	Free phytosterols: ↓TC (-80%), FC (-11%, NS) and CE (-91%) concentrations Sterol esters: ↓TC (-77%), FC (-11%, NS) and CE (-88%) concentrations Stanol esters: ↓TC (-76%), FC (0) and CE (-88%) concentrations	

commercial margarines				
Phytosterol mixture ±soy lecithin	Rats fed high-cholesterol (1%) diet	0.25 ±0.15% of diet	5 weeks	↓cholesterol (-22% and -8%, NS, plus lecithin) and TG (-12%, NS, and -43% plus lecithin) concentrations ↓HMG-CoA reductase (-1%, NS, and -4%, NS, plus lecithin) and ACAT (-12% and -12% plus lecithin) activities	(Shin et al., 2004)
Conjugated linoleyl β-sitosterol	Mice fed 2 weeks with hyperlipidemic diet then 2 weeks with basal diet	0.04% of diet	2 last weeks with hyperlipidemic diet	↓LI (-14%), and TC (-44%) and TG (-40%) levels	(Li et al., 2010)
Phytosterols and phytostanols[s]	*Inbread* rats with a mutation in the *Abcg5* gene (*i.e.* over absorb phytosterols and phytostanols)	0.2% of diet	5 weeks	↓cholesterol levels (resp. -40 and -16%)	(Chen et al., 2010b)
C4 - Alkylresorcinols					
5-*n*-alk(en)ylresorcinol (resorcinolic lipid homologues from wheat and rye brans)	Enzyme assays: methanolic solutions of resorcinolic lipids with enzyme (2 U/mL)	From 4 to 50 μM	Changes in absorbance for 15 min	5-*n*-pentadecylresorcinol: - from 50 (4 μM) to 100% (11 μM) inhibition fro GPDH activity - from 0 (4 μM) to 30% (50 μM) inhibition for ADH and LDH activities - from 0 (4 μM) to 20% (50 μM) inhibition for G6PDH activity - 0% inhibition from 4 μM to 50 μM for IDH	(Rejman and Kozubek, 2003)
	3T3-L1 cells (model to study adipocyte differentiation)	From 2.5 to 12.5 μM	7 days	↓TG content/accumulation: - from ≈ -15 to ≈ -59% for pentadecylresorcinol (C 15:0, IC_{50} = 10.7 μM) - from ≈ -35 to ≈ -93% for heneicosylresorcinol (C 21:0, IC_{50} = 5.0 μM) - intermediate between C 15:0 and C 21:0 ↓ for nona- (C 19:0, IC_{50} = 6.3 μM) and hepta-decylresorcinols (C 17:0, IC_{50} = 8.2 μM)	
Cardol, Cardanol and Anacardic acid[t]	3T3-L1 cells (model to study adipocyte differentiation)	From 2.5 to 12.5 μM		- from ≈ -32 to ≈ -80% for Cardanol - from ≈ -25 to ≈ -70% for Cardol - from ≈ -5 to ≈ -50% for anacardic acid	
Alkylresorcinols (from rye bran)	Rats fed standard diet (0.2% cholesterol)	0.1, 0.2 or 0.4% of diet	4 weeks	0.1 and 0.2%: no effect on TL, TC and cholesterol in liver lipids concentrations 0.4%: ↓ TL (-18%, NS), TC (-47%) and cholesterol in liver lipids (-35%) concentrations	(Ross et al., 2004)

C5 - Coumarin
Auraptene {Nagao, 2010 #22917}

[a]All terms used in the Table are precisely those of the article considered: for exemple, the hepatic content in TG was named "content", "concentration" or "level", and in some case no term was used; studies reporting both lipotrope-like and non-lipotropic effects (*i.e.* an increase in hepatic lipid content and/or lipogenic enzyme activities) are also presented to allow comparsions and further relevant interpretations
[b]Indicates the decreased or increased percentage induced by the lipotrope compared to the control, *i.e.* steatogen diet (NS - Not Significant - means absence of significativity for the change observed; in other cases, the effect was either significant or no information was given in the article)
[c]Mixture of ferulic acid esters of triterpene alcohols and sterols (isolated from rice bran oil)
[d]Polyphenon-100® contains more than 80% catechin, *i.e.* 9.4% EC, 13.4% EGC, 53.9% EGCG, 1.7% ECG, 2.9% GCG and 0% CG
[e]Catechins from green tea extract are composed of 48% EGCG, 31% EGC, 13% ECG and 8% EC
[f]Provinol® contains min. 95% of total polyphenols (proanthocyanidols 46%, prodelphinidol 21%, total anthocyanes 6.1%, catechin 3.8%, epicatechin gallate 3%, OH cinnamic acid 1.8%, flavanol 1.4%, resveratrol 0.15% and free anthocyane 0.095%)
[g]Contains protocatechuic acid (24.24%), catechin (2.67%), gallocatechins (2.44%), caffeic acid (19.85%) and gallocatechin gallates (27.98%)
[h]1.25% water extract contains 51.3 and 29.9 mg/100 mL of respectively phenolic acids and flavonoids; 2.5% water extract contains 97.1 and 58.9 mg/100 mL of respectively phenolic acids and flavonoids
[i]Metabolites of hesperetin
[j]No data given in the reference
[k]Isolated from fermented Korean soybean paste
[l]Contains 40, 1 and 18% of respectively genistein, glycitein and daidzein
[m]Δ6 desaturase, required for synthesis of highly unsaturated FA such as EPA, DHA and AA, e.g. rate-limiting enzyme for conversion of linoleic acid into arachidonic acid
[n]C-iso and U-iso are mixtures of respectively conjugated or unconjugated isoflavones
[o]Contains flavones (apigenin, luteolin, apigenin-7-glucoside - AP7Glu, luteolin-7-glucoside - LU7Glu) and flavonols (isorhamnetin and quercetin)
[p]Mainly contains quercetin-3-β-D-galactoside (2.9%), quercetin-3-β-D-glucoside (3.4%), kaempferol-3-β-D-glucoside (13.4%), kaempferol-3-β-D-galactoside (4.5%), (2R,3S)-catechin (29.8%) and (2R,3R)-epicatechin (2.6%)
[q]Contains 48% EGCG, 31% EGC, 13% ECG and 8% EC
[r]5-α-saturated derivative of sitosterol
[s]Phytosterols are composed of 22% of brassicasterol, 31.9% campesterol, 43.2% β-sitosterol and 2.9% others; phytostanols are composed of 54.7% campestanol and 44.8% sitostanol
[t]Cardol: natural mixture of unsaturated C15 alkylresorcinol congeners, Cardanol: natural mixture of unsaturated C15 alkylphenol congeners, Anacardic acid: natural mixture of unsaturated C15 alkylphenolic acid congeners

ABBREVIATIONS: ABCA, ATP-Binding CAssette transporter (also known as the cholesterol efflux regulatory protein that is encodes by ABCA1 gene); ACAT, Acetyl/Acyl-CoA:Cholesterol Acetyl/AcylTransferase (forms CE from cholesterol); ACC/CBX, Acetyl-CoA Carboxylase (involved in FA synthesis; is ihibited when phosphorylated); ACO/ACOX, Acyl-CoA Oxidase (ACO1, rate-limiting enzyme in peroxisomal β-oxidation of long-chain and saturated FA; ACO2, oxidizes branched-chain FA); ADH, Alcohol DeHydrogenase ($NADH^+$-generating enzyme involved in alcohol breakdown); AIN, American Institute of Nutrition; AMPKα, AMP-activated protein Kinase α (AMPK regulates several intracellular systems including β-oxidation of fatty acids *via* phosphorylation of its substrates and control of gene transcription; has an ability to react to fluctuations in the AMP:ATP ratio); ApoA/B/E, Apolipoprotein A/B/E; ATPCL/CCE, ATP Citrate Lyase/Citrate Cleavage Enzyme (an important step in fatty acid biosynthesis); b.w., body weight; CE, Cholesteryl Esters; CG, Catechin Gallate; CoA, Coenzyme A; CPT, Carnitine PalmytoylTransferase (allows transfer of long-chain FA across mitonchondrial membrane *via* carnitine binding); CYP7A1, CYtochrome P450 or Cholesterol 7α Hydroxylase (enzyme for the initial rate-limiting step of bile acid synthesis from cholesterol); DGAT, DiacylGlycerol AcetylTransferase (catalyzes the formation of TG from diacylglycerol and Acyl-CoA); EC, EpiCatechin; ECG, EpiCatechin Gallate; ECH1, Enoyl-CoA Hydratase/3-hydroxyacyl-CoA dehydrogenase (catalyses the second and third reactions of the fatty acid β-oxidation cycle); EGC, EpiGalloCatechin; EGCG, EpiGalloCatechin Gallate; ER, (o)Estrogen Receptor; FA, Fatty Acid; FAS, Fatty Acid Synthase/Synthetase; FC, Free Cholesterol; FFA, Free Fatty Acids; GAPDH, GlycerAldheyde-3-Phosphate DeHydrogenase (involved in glycolysis); G6PDH, Glucose-6-Phosphate Dehydrogenase ($NADPH,H^+$-generating enzyme); GPDH, Glycerol-3-Phosphate DeHydrogenase (key enzyme in TG synthesis); HMG-CoA, 3-Hydroxy-3-MethylGlutaryl Coenzyme A; HMGCS2, HMG-CoA/3-Hydroxy-3-MethylGlutaryl-Coenzyme A Synthase 2; i.p., intraperitoneally; IC_{50}, concentration required for 50% inhibition; ICR, Imprinting Control Region; IDH, Isocitrate DeHydrogenase; i.v., intravaneously; LDH, L-Lactate DeHydrogenase; LDL, Low-Density Lipoprotein; LDLR, Low-Density Lipoprotein Receptor (involved in transfer of lipids into hepatocytes); LI, Liver Index

(liver weight/body weight); LPC, LysoPhosphatidylCholine; LPL, LipoProtein Lipase; MCAD, Medium-Chain Acyl-CoA Dehydrogenase (involved in FA β-oxidation); MCD, Malonyl CoA Decarboxylase; ME, Malic Enzyme; mRNA, messenger RiboNucleic Acid; MTP, Microsomal Triglyceride Transfer protein (role in lipoprotein assembly); n.i., no inhibition (IC_{50} > 1 mM); NS, Not Signficant; PC, PhosphatidylCholine; PE, PhosphatidylEthanolamine; PEX11α, peroxisomal membrane protein; PL, PhosphoLipid; resp., respectively; PPAR, Peroxisone Proliferator-Activated Receptor (transcription factor of genes involved in lipogenesis); PPARα-null KO (Knock Out) mice, homozygous mice for deletion of PPARα gene; resp., respectively; SCD, Stearoyl-CoA Desaturase (catalyzes the rate-limiting step in the biosynthesis of monounsaturated FA and its deficiency increases fatty acid oxidation by activating hepatic AMP-activated protein kinase); SDG, Secoisolariciresinol DiGlucoside; SECO, SECOisolariciresinol; Sph, Sphingomyelin; SR-B1, Scavenger Receptor class B type 1 (oxidized LDL receptors); SRE, Sterol Regulatory Element; SREBP, Sterol Regulatory Element-Binding Proteins; TC, Total Cholesterol; TG, TriGlyceride; TL, Total Lipids; UCP2, mitochondrial UnCoupling Protein 2 (participates in excess calorie burning; increased UCP2 level lead to increased β-oxidation and energy expenditure, and decreased lipid levels)

Supplemental Table 5 ***In vivo*** **and** ***in vitro*** **studies reporting effects on hepatic lipid metabolism following supplementation of plant extracts or plant-based foods**[a]

Plant extract or plant-based foods	*In vivo* or *in vitro* models	Supplemented daily dose	Duration of lipotrope exposition	Hepatic effect(s)	References
Corn oil *vs* hydrogenated coconut oil (control)	Healthy male subjects fed *ad libitum* institutional American type diet	One ounce (24-33 g)	1 month	Corn oil: ↓liver cholesterol (-25%)[b] upon 1 month Hydrogenated coconut oil: ↓liver cholesterol (+9%, NS) upon 1 month	(Frantz and Carey, 1961)
Cottonseed *vs* coconut oils	Rats fed 10%-fat diet ±1% cholesterol	10% of diet	7 weeks	Males: adding cholesterol ↑ TL (+475 *vs* +110%)[2], TC (+1916 *vs* +600%), FC (+95 *vs* +27%) and PL (+227 *vs* -3%) contents Females: adding cholesterol ↑ TL (+218 *vs* +75%), TC (+2436 *vs* +493%), FC (+93 *vs* +80%) and PL (+26 *vs* +14%) contents	(Okey et al., 1961)
Arachis oil, 3 margarines[c] and butter	Rabbits fed 20%-fat diet (no control group)	20% of diet	42 weeks	Compared to 20%-butter group: arachis oil and margarines (M1, M2 and M3) lead to reduced total FA (resp. -84, -81, -60 and -72%), cholesterol (resp. -66, -51, -71 and 51%) and tetraenoic acid (resp. -59, -72, -72 and 51%) contents, and to enhanced dienoic acid content (resp. +85, +50, +14 and +152%)	(Krogh et al., 1961)
Whole wheat breads or rye breads	Rats fed white breads	-[d]	16 weeks	Whole wheat breads: ↓TG (NS) and cholesterol levels Rye breads: ↓TG level (NS)	(Yacowitz et al., 1976)
Safflower oil	Rats fed fat-free and high-fructose/glucose (72%) diet for 7 days then supplemented with PUFA, injected with ^3H_2O and killed 20 min after injection	5% or 10% of diet	3 or 4 days	Fructose: ↓FAS (-50-64% at 5% fat level), ACC (-57% at 10% fat level), glucokinase (-19%, NS at 10% fat level) and phosphofructokinase (-10%, NS at 5% fat level) activities; ↓FA synthesis (-32% at 5% fat level and -76% at 10% level) Glucose: ↓FAS (-71% at 5% fat level) and phosphofructokinase (-7%, NS at 5% fat level) activities; ↓FA synthesis (-53% at 5% fat level)	(Toussant et al., 1981)
Rice bran oil	Rats fed high-cholesterol (1% +0.5% cholic acid) diet	10% of diet	8 weeks	↓TC (-22%, NS) and TG (-32%, NS) contents	(Sharma and Rukmini, 1986)
Safflower or menhaden fish oil	Rats trained 10 days with high-glucose (58.43%) and fat-free diet, then supplemented 7 days with PUFA-rich oils or tripalmitin (control)	20% digestible energy of diet	-	↓FAS mRNA abundance (≈ -69% for n-6-rich safflower oil and ≈ -87% for n-3-rich menhaden fish oil)	(Clarke et al., 1990)
Menhaden fish oil	Rats trained 10 days with high-glucose (58.43%) and fat-free diet, then supplemented 7 days with PUFA-rich oil or tripalmitin (control)	20% digestible energy of diet	7 days	↓transcription rate of FAS (-94%) and S_{14} protein (putative lipogenic protein, -79%)	(Blake and Clarke, 1990)
Rice bran oil (RBO), defatted rice bran oil (DRB), RBO + DRB, and 4 levels of rice brans	Male hamsters fed 0.3%-cholesterol diets (all contains 10% fiber and 9% fat)	Resp. 9, 35, 35 + 8.9, and 43.7, 32.8, 21.8 and 10.9%	21 days	↓LI (resp. -11, -4%, NS, -9, -11, -9, -9 and -7%) ↓cholesterol content (resp. -5%, NS, -18, -15, -24, -8%, NS, -12%, NS, and -3%) ↑TG content (resp. ≈ 0, +17%, NS, +13%, NS, +11%, NS, +13%, NS, +14%, NS, and ≈ 0)	(Kahlon et al., 1992a)
Rice bran, defatted rice bran[e], rice bran oils (n = 2), and rice bran oil gum and wax	Hypercholesterolemic hamsters (control diet contains 0.3% cholesterol, 10% cellulose and 9% corn oil): all diets contain 10% fiber, 9% fat and 3% nitrogen	Resp. 50.2, 41.3-41.5, 7.9-9.0, 0.9 and 0.2% of diet	21 days	↓cholesterol and TG contents: - bran: resp. -37 and -33% - defatted bran: -12%, NS, and -26%, NS - defatted bran +rice bran oil gum: resp. -1%, NS, and -24% - defatted bran +rice bran oil wax: resp. -8%, NS, and -30% - defatted bran +rice bran oil-gum/wax: resp. -29 and -27%, NS - defatted bran +rice bran oil: resp. -2%, NS, and -14%, NS	(Kahlon et al., 1992b)
Wheat and oat brans, barley and malted barley	Rats fed AIN 76-based and high-cholesterol (1% + 0.1% cholic acid) diet	7.5% (NSP and lignin) of diet	14 days	↓cholesterol pool (-23%[3] for oat bran *vs* wheat bran; -13%, NS, for barley *vs* malted barley) esterol pool (+15%, NS, for barley *vs* wheat bran; +31% for malted barley *vs* wheat bran)	(Jackson et al., 1994)
Liquid aged garlic extract (Kyolic®)	Hepatocytes isolated from rat liver and incubated with 0.5 mM [1-^{14}C]acetate	0.01, 0.05, 0.1, 0.2 and 0.4 mM	4 hours	↓rate of [1-^{14}C]acetate incorporation into cholesterol at 0.1 (-72%), 0.2 (-76%) and 0.4 (-87%) mM; no significant changes at other concentrations	(Yeh and Yeh, 1994)
Oatmeal or its ethanol extract	Rats and gerbils fed high-fat (40%) and 6.5% cellulose diet	6.5% of diet	21 (gerbils) and 19 (rats) days	Gerbils: ↓ TL (resp. -2%, NS, and -1%, NS), TC (-38 and -34%) and FC (resp. -10 and -15%) Rats: ↓ TL (resp. -8%, NS, and -10%, NS), TC (-52 and -55%) and FC (resp. -10 and -24%)	(Onning and Asp, 1995)

Tangerine-peel extract[f]	Rats fed high-cholesterol (1%) diet	16.7% of diet	6 weeks	↓ HMG-CoA reductase (-36%) and ACAT (-38%) activities	(Bok et al., 1999)
Soy protein enriched with isoflavones[g] (low or high levels)	Lean and obese (*fa*/*fa*) Zucker rats fed standard AIN-76-based diet	20% of diet	70 days	Lean Zucker: no effect on LI; ↓ TG (resp. ≈ -54%, NS, and ≈ -54%, NS), TC (resp. ≈ -18%, NS, and ≈ -35%) and CE (resp. ≈ -51 and ≈ -88%) concentrations Obese Zucker: ↓ LI (resp. ≈ -26 and ≈ -43%), and TG (resp. ≈ -33 and ≈ -49%, NS), TC (resp. ≈ -34 and ≈ -48%) and CE (resp. ≈ -46 and ≈ -77%) concentrations	(Peluso et al., 2000)
	Rats fed standard AIN-76-based diet	20% of diet	42 days	↓ LI (resp. -7%, NS, and -6%, NS), and TG (resp. -17%, NS, and -27%, NS), TC (resp. -1%, NS, and -2%, NS) and CE (resp. -8%, NS, and -24%) concentrations; ↑ unesterified cholesterol (resp. +3%, NS, and +11%)	
	Rats fed atherogenic diet (9% fat, 1.2% cholesterol and 0.2% cholic acid)	20% of diet	63 days	↓ TG (-32%) and ↑ TC (+12%, NS), CE (+12%, NS) and unesterified cholesterol (+14%) concentrations	
Platycodi radix aqueous extract	Female ICR mice fed high-fat (40%) diet	2 or 5% of diet	8 weeks	↓ LI (resp. -12 and -14%) and TG concentration (-17%, NS, and -23%); no effect on TC concentration	(Han et al., 2000)
Rice starch	Rats fed high-cholesterol (1%) diet with increasing contents in rice starch (0, 15, 30, 45 and 63%, completed with corn starch to 63%) and resistant starch (1.26, 1.39, 1.52, 1.65 and 1.80%) contents	-	4 weeks	↑ serum propionate (resp. nondetectable, +40, +47 and +60 μM compared to 0%-rice starch content) ↓ TG concentrations (resp. -17, NS, -21, NS, -24, NS, and -28% compared to 0%-rice starch content) ↓ TC concentrations (resp. -1, NS, -10, -7 and -7% compared to 0%-rice starch content)	(Cheng and Lai, 2000)
10% (w/v) brewed green tea	HepG2 cells	0-200 μL	24 hours	↑ LDLR binding activity (≈ +80% at 200 μL) ↓ cholesterol (≈ -30% at at 200 μL) and FC (≈ -25% at at 200 μL) concentrations ↑ transcription factor form of SREBP-1 (+62-65% at 200 μL) ↓ (≈ -29% at 50 μL) and ↑ (≈ +107% at 200 μL) cholesterol synthesis ↑ extracellular media cholesterol concentration at 200 μL (≈ +25%) and tended to ↓ media chenodeoxycholic acid concentration (NS)	(Bursill et al., 2001)
Green tea dry solvent extracts	HepG2 cells	50 or 100 μM equivalence of EGC	24 hours	↑ LDLR binding activity (≈ +145% for methanol, ≈ 0 for hexane, ≈ +20%, NS, for chloroform, ≈ +167% for ethyl acetate and ≈ +50%, NS, for water extract) at 100 μM equivalence of EGC Ethyl acetate extract: ↑ dose-dependently LDLR activity (+312% at 100 μM equivalence of EGC), protein (+2100%) and mRNA (+2166%), and HMG-CoA reductase mRNA (+1335%) ↓ cholesterol concentration (resp. -54, -61 and -66%)	
Whole flours of different viscosity: wheat 1 (1.44 mL/g), wheat 2 (5.15 mL/g) and triticale (8.07 mL/g)	Rats fed semi-purified diet (75.3% starch)	70% of diet	21 days	No effect on TG concentration	(Adam et al., 2001)
Sesame seed powders (Masekin cultivar, and lines rich in sesamin and sesamolin - 0730 and 0732)	Rats fed high-sucrose (61.7%) diet	20% of diet	16 days	↑ FA oxidation enzyme activities: ACO (resp. +59%, NS, +366 and +442%), CPT (resp. +124, +333 and +262%), 3-hydroxyacyl-CoA dehydrogenase (resp. +235, +504 and +490%) and 3-ketoacyl-CoA thiolase (resp. +69, +226 and +176%) ↓ FA synthesis enzyme activities: FAS (resp. -71, -66 and -71%), G6PDH, ME (-32%, NS, for Masekin cultivar), ATPCL and pyruvate kinase (resp. -56, -60 and -63%) ↑ mitochondrial (resp. ≈ +44, +83 and +61%) and peroxisomal (resp. +33%, NS, +261 and +356%) FA oxidation rate ↓ TG (resp. -15%, NS, -26%, NS, and -14%, NS) and cholesterol (resp. -10%, NS, -3%, NS, and 0%) levels; ↑ PL levels (resp. +9%, NS, +56 and +52%)	(Sirato-Yasumoto et al., 2001)
Olive (oleic acid-rich), sunflower	Rats fed 10% fat (mixture of 64% tripalmitin, 16% tristearin and 20% corn oil; *i.e.* ≈ 80%	2% of diet (in place of corn	2 weeks	↓ and ↑ TC (resp. +15, -10%, NS, -23%, NS, and -3%, NS), TG (resp. +9%, NS, -25, -34 and -53%) and PL (resp. ≈ 0, -3%, NS, -	(Takeuchi et al., 2001)

(n-6 PUFA-rich), linseed (enriched with α-linolenic acid) or sardine oil (n-3 PUFA-rich)	saturated FA) diet	oil)		8%, NS, and +1%, NS) concentrations ↓ ACC (resp. ≈ 0, ≈ -50, ≈ -64 and ≈ -70%) and DGAT (resp. ≈ -14%, NS, ≈ -14%, NS, ≈ -16%, NS, and ≈ -23%) activities ↓ and ↑ G6PDH (resp. ≈ +11%, NS, ≈ -31, ≈ -23 and ≈ -65%), PAP (resp. ≈ +12%, NS, ≈ +16%, NS, ≈ -2%, NS, and ≈ -16%) and PCDGT (resp. ≈ -4%, NS, ≈ +46%, NS, ≈ +35%, NS, and ≈ 0) activities ↑ AST (resp. ≈ +46, ≈ +64, ≈ +90 and ≈ +95%) and CPT (resp. ≈ +156, ≈ +167, ≈ +222 and ≈ +222%) activities, and peroxisomal β-oxidation (resp. ≈ +100, ≈ +367, ≈ +633 and ≈ +567%)	
Wheat bran Whole wheat flour White wheat flour	Rats fed semi-purified diet (76% starch)	21.4% of diet 70.0% of diet 48.6% of diet	21 days	↓ TG (-40%) and cholesterol (-23%) concentrations ↓ TG (-45%) and cholesterol (-30%) concentrations ↓ TG (-32%) and cholesterol (-54%) concentrations	(Adam et al., 2002)
Whole wheat flour and whole wheat bread	Rats fed semi-purified diet (71.75% starch)	70% of diet	21 days	↓ TG (resp. -39 and -32%) and cholesterol (resp. -48 and -54%) concentrations	(Adam et al., 2003)
Soy protein enriched with isoflavones[h] (low or high levels)	Obese Zucker rats fed AIN-93-based diet	20% of diet	8 weeks (males) 11 weeks (females)	↓ liver weight (resp. -12%, NS, and -26%), and cholesterol (resp. -2%, NS, and -39%) and TG (-5%, NS, and -47%) concentrations ↓ liver weight (resp. -1%, NS, and -28%), and cholesterol (resp. -27 and -350%) and TG (≈ 0 and -38%) concentrations	(Mezei et al., 2003)
Sea buckhorn ±geraniol[i]	Mice fed for 7 days control diet and i.v. injected with Triton WR1339[j] 3 hours before killing	2.79 ± 0.067 g/kg b.w.	7 days	↓ newly synthesized cholesterol (resp. -44 and -45% with geraniol)	(Wu et al., 2005)
Olive or sunflower oil	Rats fed 1 month with high-fat (14% olive or sunflower oil) then 1 month with normal-fat (5%) diet	14% then 5% of diet	1 month + 1 month	Light micrography: ↓ degree of liver steatosis (accumulation of fat droplets): apparent complete steatosis disappearance with olive oil and less important effect with sunflower oil	(Hernandez et al., 2005)
Olive oil, fish oil or butter fat	Rats fed methionine-choline deficient diet	0.45 mg/g rat	2 months	Histology: ≈ 3, ≈ 3, 33 and 88% of rats had severe fatty infiltration (>60% hepatocytes affected) with methionine-choline deficient, olive oil, fish oil and butter fat diet, resp.; resp. 93, 90, 67 and 17% had mild-moderate fatty infiltration (<60% hepatocytes affected) ↓ and ↑ TG content (resp. ≈ -29%, ≈ +12%, NS, and ≈ +6%) Hepatic cholesterol (r = -0.8) and TG (r = -0.4) contents correlated with MDA	(Hussein et al., 2007)
Dried apricot	CCl_4-treated (1 mL/kg b.w. injected subcutaneously for 3 days at the end of the 5 months) rats	10 or 20% of diet	5 months	Ultrastructural observations (transmission electrom microscopy): ↓ volume and number of lipid globules	(Ozturk et al., 2009)
Green and black tea	Rats fed high-fat (≈ 15%) diet	100% of fluid intake	26 weeks	↑ PPARα (≈ +400 and ≈ +400%), CPT-1 (resp. ≈ +150 and ≈ +650%), ACO (resp. ≈ +1950 and ≈ +1300%), SREBP-1 (resp. ≈ +770 and ≈ +400%), MCD (resp. ≈ +1100 and ≈ +1230%), FAS (resp. ≈ +480 and ≈ +260%) and ACC (resp. ≈ +400 and ≈ +570%) gene expressions No effect on TG content	(Chen et al., 2009)
Diluted beverages from tomato and paprika	Specific-pathogen-free female mice fed standard commercial diet	100% of fluid intake	6 weeks	Tomato: - up-regulation of genes involved in fatty acid degradation (cytochrome P450, CPT-1a, acyl-CoA synthetase long-chain family member) and cholesterol synthesis (HMG-CoA reductase) - down-regulation of genes involved in FA synthesis (elongation of long-chain fatty acid, FAS, steroyl-CoA desaturase 1, ME, SREBP-1, ATPCL and ACCα) and degradation (acyl-CoA dehydrogenase, enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogense and acyl-CoA oxidase 2 branched chain), and in cholesterol synthesis and catabolism Paprika: - up-regulation of genes involved in FA synthesis (ME, FAS, ATPCL and ACCα) and degradation (acyl-CoA synthetase long-chain family member and CPT-1a), and in cholesterol synthesis (acetoacetyl-CoA synthetase) and lipid circulation	(Aizawa et al., 2009)

				(LDL receptor) - down-regulation of genes involved in cholesterol synthesis and catabolism (bile acid biosynthesis)	
Mulberry extract (0.53% of 1-deoxynojirimycin)	Rats fed standard diet	100 or 200 mg/kg b.w. (direct stomach intubation)	4 weeks	↓TG level (resp. -10%, NS, and -23%); no effect on TC and PL levels ↑ FAS (resp. ≈+31%, NS, and ≈+19%, NS), CPT (resp. ≈+45% and ≈+45%) and ACO (≈+36% at 200 mg/kg b.w. at 100 mg/kg b.w.) activities; ↓ME (resp. ≈-25%, NS, and ≈-2%, NS) and ACO (≈-8%, NS, at 100 mg/kg b.w.) activities ↑ CPTI (resp. ≈+50 and ≈+60%), ACO (resp. ≈+5%, NS, and ≈+85%), PPARα (≈+15%, NS, at 100 mg/kg b.w.) and AMPK (resp. ≈+60%, NS, and ≈+145%) mRNA expressions; ↓PPARα mRNA expression (≈-15%, NS, at 200 mg/kg b.w.)	(Tsuduki et al., 2009)
Monascus-fermented soybean or unfermented soybean[k] ethanol extracts	Rats fed hypelipidemic (10% pig oil, 10% powdered egg yolk and 1% cholesterol) diet	200 or 400 mg/kg b.w.	40 days	Unfermented: ↓ HMG-CoA reductase/mevalonate ratio (-16%) Fermented: ↑ HMG-CoA reductase/mevalonate ratio (+8%, NS, at 200 mg/kg b.w. and +39%) ↓ TC (resp; -16%, NS, -23 and -35%) and TG (resp. -16, -29 and –32%) levels	(Pyo and Seong, 2009)
Freezed dried melon juice extract	Male hamsters fed high-fat (24%) diet	0.7, 2.8 or 5.6 mg (aqueous solution by gavage)	12 weeks	Histological analysis: improved (at 2.8 mg) and disappearance (at 5.6 mg) hepatocellular ballooning degeneration ↓ lipid content (resp. -42, -71 and -73%)	(Décordé et al., 2009)
Freezed-dried coffee (3% caffeine) or decaffeinated coffee	Mice fed high-fat (30%) diet	1.1% of diet	8 weeks	↓TG content (resp. -38%, NS, and -10%, NS); no effect on TC content	(Fukushima et al., 2009)
Coconut oil, butter and flaxseed oil	Hamsters fed standard diet	7% of diet	6 weeks	↑ LI (resp. +21, +15 and +15%) ↑ cholesterol (resp. +193, +373 and +123%) and TG (resp. +37, +56 and +26%) contents: lower increases (*vs* control) with flaxseed oil	(Yang et al., 2009)
Sophora japonica L. powder (from dried mature fruits including pericarp and seed)	Mice fed high-fat (30%) diet	1 or 5% of diet	1 month	↓ TG content (resp. -37 and -61%); no effect on cholesterol content	(Park et al., 2009b)
Ginkgo biloba leaf extract	Rats fed high-fat (8% lard, 7% egg yolk powder and 0.5% sodium chocolate)	0.2% of diet	19 weeks	↓ TC content (-20%, NS) Histopathological detection: ↓ lipid accumulation (lipid droplets occupied a smaller area) Down- and up-regulation of gene involved in lipid metabolism: ↓ FA and cholesterol biosynthesis, ↓ conversion of cholesterol into bile acids, and ↑ FA metabolism	(Gu et al., 2009)
Cauliflower mushroom water extract	Genetically obese (*ob*/*ob*) mice fed standard diet	100 or 300 mg/kg b.w.	10 weeks	↓ liver weight (resp. -28 and -28%) , TG (resp. -43 and -42%) and TC (resp. -35 and -38%) contents	(Park et al., 2009a)
Cinnamon bark alcoholic extract	Mice fed standard diet for 4 days, and killed on day 5 12 hours after i.g. ethanol injection (6 g/kg b.w.)	0.5 mL/kg b.w. (in drinking water)	4 days before ethanol injection	Microscopic and image analyses: - blunted ethanol-induced hepatic steatosis by ≈ 45% - ↓ fat (≈ -36%, measured as % of microscopic field) and TG (≈ -58%, NS) accumulation	(Kanuri et al., 2009)
Garlic aqueous extract (20%, w/v)	Rabbits fed high-cholesterol (0.5 g/kg b.w. i.g.) diet for 4 months (GI), then standard diet for 3 months (GII)	1.5 mL/kg b.w.	3 last months	Histological examinations: ↓ mean steatosis grade (only 1/8 rat with steatosis of grade 1: <33% of hepatocytres were involved) compared to GI and GII ↓ cholesterol (-86% *vs* GI and -78% *vs* GII) and TG (-46% *vs* GI and -27% *vs* GII) levels	(Arhan et al., 2009)
Ziziphus Mauritania aqueous leaf extract *vs* sylimarin	Chronic alcohol (40% ethanol *via* gastric intubation, 1 mL/100 g b.w.) administered rats for 6 weeks	400 mg/kg b.w.	6 or 2 weeks	Pre-administration *via* gastric intubation (30 min before alcohol): ↓ cholesterol (resp. -47 and -43%) and TG (resp. -42 and -38%) contents Co-administration with alcohol: ↓ cholesterol (resp. -9%, NS, and -21%) and TG (resp. -16%, NS, and -44%) contents	(Dahiru and Obidoa, 2009)

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				Post-administration (2 weeks without alcohol) after 6 weeks alcohol: ↓ cholesterol (resp. -15 and -35%) and TG (resp. -30 and -38%) contents	
Platycodi radix extract	90% pancreatectomized diabetic rats fed high-fat (40% as energy) diet	2 g/kg b.w.	8 weeks	↓ TG content (≈ -44%)	(Kwon et al., 2009)
Codonopsis lanceolata root water extract	Rats fed liquid ethanol (36% of energy) diet	0.5% of liquid diet	8 weeks	↓ TG (≈ -33%) and cholesterol (≈ -36%) levels Liver histology: enlargement of the hepatocytes and increase in the number of lipid droplets were normalized ↓ TNFα (≈ -37%), LXRα (≈ -17%), SREBP-1c (≈ -21%), HMG-CoA reductase (≈ -41%) and LDLR (≈ -31%) mRNA levels ↑ AMPKα (≈ +6%, NS), ACC (≈ +48%), FAS (+29%) and SCD1 (≈ +10%, NS) mRNA levels ↑ phosphorylated/total ratio of AMPK (≈ +133%) and ACC (↑ +26%)	(Cho et al., 2009a)
Commercial low-*trans* fat or n-3-rich/low-*trans* structured fat (synthesizeed from flaxseed oil, anhydrous butterfat and palm stearin)	Apo E$^{-/-}$ mice fed a 10%-fat (commercial shortening, 53.4% *trans* FA) diet	10% of diet	12 weeks	↓ LI (resp. -34 and -44%), and cholesterol (resp. -31 and -41%) and TG (resp. -22 and -16%) levels ↓ HMG-CoA reductase (resp. -12%, NS, and -51%), ACAT (resp. -6%, NS, and -18%), G6PDH (resp. -52 and -66%), ME (resp. -25 and -47%) and PAP (resp. 0 and -12%) activities ↑ β-oxidation (resp. -4%, NS, and +96%) and CPT (resp. +17%, NS, and +88%) activity Hepatic tissue morphology: low-*trans* structured fat importantly ↓ accumulation of hepatic lipid droplets	(Cho et al., 2009b)
Fermented ginseng radix ethanol extract	HepG2 cells	500 μg/mL	From 1 to 24 hours	↑ phosphorylation of AMPK (max.: ≈ 2.7-fold at 12 hours) and ACC (max.: ≈ 2.7-fold at 24 hours) ↓ time-dependently SREBP1c, SCD1 and FAS gene expression; ↑ time-dependently PPARα gene expression	(Kim et al., 2009)
		100, 250 or 500 μg/mL	24 hours	↓ TG accumulation (resp. ≈ -80, ≈ -80 and ≈ -95%)	
	db/*db* mice fed standard chow diet	100 or 200 mg/kg b.w.	10 weeks	↑ gene expression of pAMPK and pACC (↑ phosphorylation of AMPK and ACC), and of CD36 and PPARα; ↓ gene expression of SREBP1a, SCD1 and FAS	
Garlic + medicinal plant extracts	Rats fed ethanol (10 mL of 20% ethanol/kg b.w./day) diet	(0.5 + 1.%) or (1.0 + 1.0)% of diet	4 weeks	↓ TL (resp. -14 and -28%), TC (resp. -17 and -23%) and TG (resp. -9%, NS, and -30%) levels	(Soo-Jung et al., 2009)
Refined rice bran oil, alone or blended with refined linseed oil (3:2, w/w) or cod liver oil (1:1)	Rats fed 10%-fat (refined groundnut oil) diet	10% of diet	60 days	↓ TC (resp. -14, -27 and -37%), PL (resp. -13, -35 and -40%) and TG (resp. -9, -19 and -26%) contents	(Chopra and Sambaiah, 2009)
Safflower oil or cocoa butter[l]	Rats fed standard chow (4% fat)	29.5 or 29% of diet[l]	3 days	↑ TG (resp. ≈ +59 and ≈ +60%) and cholesterol (resp. ≈ +21%, NS, and ≈ +71%) levels ↓ SCD-1 mRNA expression (resp. ≈ -62 and ≈ -81%) Cocoa butter: ↑ ATPCL (4.00-fold), ME 1 (1.81-fold), pyruvate kinase (1.59-fold), farnesyl diphosphate farnesyl transferase 1 (2.69-fold), mevalonate (diphospho) decarboxylase (2.12-fold), cholate-CoA ligase (2.01-fold), HMG-CoA synthase (1.89-fold), squalene epoxidase (1.87-fold), 7-dehydrocholesterol reductase (1.72-fold), lanosterol synthase (1.72-fold), farnesyl diphosphate synthase (1.66-fold), bile acid-CoA ligase (1.63-fold), ACAT 2 (2.00-fold), ACAT 1 (1.63-fold), FAD 1 (1.71-fold), FAD 2 (1.57-fold) and FAD 3 (1.69-fold) mRNA expression; ↓ GPDH 1 (0.63-fold), ABC subfamily A (0.46-fold), mitochondrial acyl-CoA thioesterase 1 (0.63-fold), peroxisomal acyl-CoA thioesterase 2B (0.63-fold), CPTpc (0.48-fold), SCD 2 (0.27-fold) and SCD 1 (0.22-fold) mRNA expression	(Gustavsson et al., 2009)

			↑ FA oxidation rate (≈ +75%, NS) ↑ AMPK phosphorylation (≈ +11%, NS) ↑ relative SREBP-1 protein level (≈ +62%) Safflower oil: ↑ ATPCL (2.44-fold), ABC subfamily G (2.34-fold) and CYP7A1 (3.64-fold) mRNA expression; ↓ mitochondrial acyl-CoA thioesterase 1 (0.42-fold), SCD 2 (0.08-fold) and SCD 1 (0.10-fold) mRNA expression ↑ FA oxidation rate (≈ +175%) ↓ AMPK phosphorylation (≈ -21%, NS) ↑ relative SREBP-1 protein level (≈ +23%)	
High-protein diet provided by eggs, ham, salami and tuna	Healthy male fed high-fat (+30% of total energy as fat compared to control normal diet: 1349 *vs* 674 Kcal) diet	Extra protein (+77% energy compared to high-fat diet: 784 *vs* 337 Kcal)	4 days	↓ intrahepatocellular lipids (≈ -22%) as calculated from ^{1}H-MR spectra	(Bortolotti et al., 2009)
Hibiscus sabdariffa extract (≈ 2% polyphenols)	Male hamsters fed calorie-rich-fat (0.2% cholesterol and 10% coconut oil) diet	1 or 2% of diet	10 weeks	↓ cholesterol (resp. ≈ -25 and ≈ -30%) and TG (resp. ≈ -27 and ≈ -34%) levels	(Yang et al., 2010b)
	HepG2 cells	0.1, 0.5 or 1.0 mg/mL	6 hours	↓ cellular cholesterol (resp. ≈ -15%, NS, ≈ -34 and ≈ -48%) and TG (resp. ≈ -30, ≈ -43 and ≈ -60%) contents ↓ dose-dependently FAS (resp. -10, -49 and -57%) and HMG-CoA reductase (resp. -6, -7 and 47%) protein expression; ↓ HMG-CoA reductase (resp. -24, -26 and -34%) and SREBP-1c (resp. 0, -25 and -38%) protein expression ↑ AMPKphosphorylated (resp. 31, +27 and +24%), PPARα (resp. +34, +30 and +37%) and LDLR (resp. +44, +47 and +51%) protein expression No effect on AMPK and β actin protein expression	
	HepG2 cells	0.1 or 1.0 mg/mL	18 hours	↑ LDL uptake (resp. ≈ +25 and 75%)	
Whole blueberry peels (pomace, 67.4% fiber), blueberry peel ethanol extract or residue from blueberry peel extraction	Hamsters fed high-fat (37% energy) diet	8, 6 or 2% of diet	3 weeks	↓ FC (resp. ≈ -30%, NS, ≈ -25%, NS, and ≈ -25%, NS), TC (resp. ≈ -40, ≈ -40 and ≈ -16%, NS) and TG (resp. ≈ -18%, NS, ≈ -26%, NS, and ≈ -19%, NS) contents; no effect on TL content ↓ and ↑ mRNA levels of CYP51 (resp. ≈ 0.6-, ≈ 2.3- and ≈ 1.9-fold), ABCG5 (resp. ≈ 0.1-, ≈ 0.15- and ≈ 0.4-fold), CYP7A1 (resp. ≈ 2.4-, ≈ 2.2- and ≈ 2.5-fold), ABCB11 (resp. ≈ 0.2-, ≈ 1.3- and ≈ 1.7-fold), PPARα (resp. ≈ 0.4-, ≈ 1.8- and ≈ 1.4-fold), ACO (resp. ≈ 0.4-, ≈ 0.7- and ≈ 0.6-fold) and SCD1 (resp. ≈ 0.6-, ≈ 0.8- and ≈ 1.0-fold)	(Kim et al., 2010)
Tomato powder	Rats fed standard AIN93M-based diet	10% of diet	5 weeks	↓ cholesterol (≈ -36%) and TG (≈ -22%) levels	(Alshatwi et al., 2010)
Dried chestnut inner shell (metahnol extract that contains 2 coumarins, *i.e.* scopoletin and scoparone)	Male mice fed high-fat (21% lard + 0.15% cholesterol)	150 mg/kg (i.g.)	77 days	Liver histology: clear improvement of the microvesiular hepatic steatosis ↓ TG (≈ -69%) and TC (≈ -47%) contents ↓ SREBP1c (≈ -40%), FAS (≈ -50%), ACC1 (≈ -83%), ACC2 (≈ -83%), HMG-CoA reductase (≈ -95%) and ACAT (≈ -89%) mRNA expressions	(Noh et al., 2010)

[a]All terms used in the Table are precisely those of the article considered: for exemple, the hepatic content in TG was named "content", "concentration" or "level", and in some case no term was used; studies reporting both lipotrope-like and non-lipotropic effects (*i.e.* an increase in hepatic lipid content and/or lipogenic enzyme activities) are also presented to allow comparsions and further relevant interpretations

[b]Indicates the decreased or increased percentage induced by the lipotrope compared to the control, *i.e.* steatogen diet (NS - Not Significant - means absence of significativity for the change observed; in other cases, the effect was either significant or no information was given in the article)

[c]Margarines are made of different mixtures from whale/coconut/rapeseed/cottonseed oils: M1 (30/45/25/0), M2 (75/0/25/0) and M3 (30/0/25/45)

[d]No data given in the reference

[e]Oil extracted at 54°C

[f]Contains 0.6% hesperidin and 0.03% naringin

[g]Low and high isoflavone soy protein-based diet respectively contains 0.0038 and 0.0578% of soy isoflavones, and respectively 0.0024/0.0012/0.0002% and 0.0370/0.0178/0.0030% of genistein/daidzein/glycitein

[h]Low- and high-isoflavone soy protein diets contains respectively <0.0009%, <0.0004%, <0.0005% and 0.116%, 0.0696%, 0.0754% of total isoflavones, genistein equivalents and aglycone isoflavones

[i]Geraniol is a monoterpenoid alcohol

[j]Triton WR1339 induces hyperlipidemia by inhibiting lipoprotein lipase and thus preventing catabolism of TG-rich lipoproteins

[k]Enriched with bioactive mevinolins (natural statins) and aglycone isoflavones (daidzein, glycitein and genistein)

[l]Safflower oil- and cocoa butter-enriched diet respectively contain 77 and 3% linoleic acid, 15 and 33% oleic acid, 6 and 25% palmitic acid, and 2 and 36% stearic acid

ABBREVIATIONS: ABCA, ATP-Binding CAssette transporter (also known as the cholesterol efflux regulatory protein); ABCB11, ATP-Binding CAssette transporter also known as BSEP (Bile Salt Export Pump); ACAT, Acetyl/Acyl-CoA:Cholesterol Acetyl/AcylTransferase (forms CE from cholesterol); ACC, Acetyl CoA Carboxylase (involved in FA synthesis; is ihibited when phosphorylated); ACO/ACOX, Acyl-CoA Oxidase; AIN, American Institute of Nutrition; AMPK, AMP-activated protein Kinase (AMPK regulates several intracellular systems including β-oxidation of fatty acids *via* phosphorylation of its substrates and control of gene transcription; has an ability to react to fluctuations in the AMP:ATP ratio); AST, Acyl-CoA SynThetase; ATPCL/CCE, ATP Citrate Lyase/Citrate Cleavage Enzyme (an important step in fatty acid biosynthesis); b.w., body weight; CPT, Carnitine Palmitoyl Transferase (involved in long chain FA oxidation in mitochondria); CCl_4, Carbon tetraChloride; CD36, , fatty acid translocase (long chain fatty acid transporter); CE, Cholesteryl Esters; CoA, Coenzyme A; CPT, Carnitine Palmitoyl Transferase; CPTpc, CTP:phosphocholine cytidylyltransferase; CYP51, Sterol 14 α-demethylase (involved in first step of cholesterol synthesis); CYP7A1, Cholesterol 7α Hydroxylase (enzyme for the initial rate-limiting step of bile acid synthesis from cholesterol); DGAT, DiacylGlycerol AcetylTransferase; EGC, EpiGalloCatechin; FA, Fatty Acid; FAD, Fatty Acid Desaturase; FAS, Fatty Acid Synthase; FC, Free Cholesterol; G6PDH, Glucose-6-Phosphate Dehydrogenase ($NADPH,H^+$-generating enzyme); GPDH, Glycerol-3-Phosphate DeHydrogenase (key enzyme in TG synthesis); HMG-CoA, 3-Hydroxy-3-MethylGlutaryl Coenzyme A; ICR, Imprinting Control Region; i.g., intragastrically; LDL, Low-Density Lipoprotein; LDLR, Low-Density Lipoprotein Receptor (involved in transfer of lipids into hepatocytes); LI, Liver Index (liver weight/body weight); LXRα, Liver X Receptor alpha (role in regulating expression of genes involved in hepatic FA synthesis); MCD, Malonyl CoA Decarboxylase; MDA, Malonyl DiAldehyde; ME, Malic Enzyme; mRNA, messenger RiboNucleotic Acid; NS, Not Significant; PCDGT, PhosphoCholine DiacylGlycerol Transferase; PL, PhosphoLipid; resp., respectively; PPAR, Peroxisone Proliferator-Activated Receptor; PUFA, Poly-Unsaturated Fatty Acid; SCD, Stearoyl-CoA Desaturase (catalyzes the rate-limiting step in the biosynthesis of monounsaturated FA); REBP, Sterol Regulatory Element-Binding Proteins; TC, Total Cholesterol; TG, TriGlyceride; TL, Total Lipids; TNFα, Tumor Necrosis Factor alpha (involved in the development of fatty liver)

REFERENCES

Abdelmalek, M. F., Angulo, P., Jorgensen, R. A., Sylvestre, P. B. and Lindor, K. D. (2001). Betaine, a promising new agent for patients with nonalcoholic steatohepatitis: results of a pilot study. *American Journal of Gastroenterology* **96**: 2711-2717.

Adam, A., Levrat-Verny, M. A., Lopez, H. W., Leuillet, M., Demigne, C. and Remesy, C. (2001). Whole wheat and triticale flours with differing viscosities stimulate cecal fermentations and lower plasma and hepatic lipids in rats. *Journal of Nutrition* **131**: 1770-1776.

Adam, A., Lopez, H. W., Leuillet, M., Demigne, C. and Remesy, C. (2003). Whole wheat flour exerts cholesterol-lowering in rats in its native form and after use in bread-making. *Food Chemistry* **80**: 337-344.

Adam, A., Lopez, H. W., Tressol, J. C., Leuillet, M., Demigne, C. and Remesy, C. (2002). Impact of whole wheat flour and its milling fractions on the cecal fermentations and the plasma and liver lipids in rats. *Journal of Agricultural and Food Chemistry* **50**: 6557-6562.

Aghelli, N., Kabir, M., Berni-Canani, S., Petitjean, E., Boussairi, A., Luo, J., Bornet, F., Slama, G. and Rizkalla, S. W. (1998). Plasma lipids and fatty acid synthase activity are regulated by short-chain fructo-oligosaccharides in sucrose-fed insulin-resistant rats. *Journal of Nutrition* **128**: 1283-1288.

Aiyar, A. S., Sulebele, G. A., Rege, D. V. and Sreenivasan, A. (1959). Pantothenic acid deficiency and ubiquinone levels in rat liver mitochondria. *Nature* **184**: 1867-1868.

Aizawa, K., Matsumoto, T., Inakuma, T., Ishijima, T., Nakai, Y., Abe, K. and Amano, F. (2009). Administration of tomato and paprika beverages modifies hepatic glucose and lipid metabolism in mice: a DNA microarray analysis. *Journal of Agricultural and Food Chemistry* **57**: 10964-10971.

Allmann, D. W. and Gibson, D. M. (1965). Fatty acid synthesis during early linoleic acid deficiency in the mouse. *Journal of Lipid Research* **6**: 51-62.

Alshatwi, A. A., Al Obaaid, M. A., Al Sedairy, S. A., Al-Assaf, A. H., Zhang, J. J. and Lei, K. Y. (2010). Tomato powder is more protective than lycopene supplement against lipid peroxidation in rats. *Nutrition Research* **30**: 66-73.

Alwayn, I. P. J., Andersson, C., Zauscher, B., Gura, K., Nosé, V. n. and Puder, M. (2005a). Omega-3 fatty acids improve hepatic steatosis in a murine model: potential implications for the marginal steatotic liver donor. *Transplantation Proceedings* **79**: 606-608.

Alwayn, I. P. J., Gura, K., Nosé, V., Zaosche, B., Javid, P., Garza, J., Verbesey, J., Voss, S., Ollero, M., Andersson, C., Bistrian, B., Folkman, J. and Puder, M. (2005b). Omega-3 Fatty Acid Supplementation Prevents Hepatic Steatosis in a Murine Model of Nonalcoholic Fatty Liver Disease. *Pediatric Research* **57**: 445-452.

Andersen, D. B. and Holub, B. J. (1980a). *Myo*-inositol-responsive liver lipid accumulation in the rat. *Journal of Nutrition* **110**: 488-495.

Andersen, D. B. and Holub, B. J. (1980b). The relative response of hepatic lipids in the rat to graded levels of dietary *myo*-inositol and other lipotropes. *Journal of Nutrition* **110**: 496-504.

Andrieux-Domont, C. and Le van, H. (1970). Influence of magnesium on enzymatic synthesis of coenzyme A. *Comptes Rendus des Séances de la Société de Biologie et de ses Filiales* **164**: 292-296.

Arachchige, P. G., Takahashi, Y. and Ide, T. (2006). Dietary sesamin and docosahexaenoic and eicosapentaenoic acids synergistically increase the gene expression of enzymes involved in hepatic peroxisomal fatty acid oxidation in rats. *Metabolism-Clinical and Experimental* **55**: 381-390.

Arhan, M., Ozturk, H. S., Turhan, N., Aytac, B., Guven, M. C., Olcay, E. and Durak, I. (2009). Hepatic oxidant/antioxidant status in cholesterol-fed rabbits: effects of garlic extract. *Hepatology Research* **39**: 70-77.

Arjmandi, B. H., Ahn, J., Nathani, S. and Reeves, R. D. (1992a). Dietary soluble fiber and cholesterol affect serum-cholesterol concentration, hepatic portal venous short-chain fatty-acid concentrations and fecal sterol excretion in rats. *Journal of Nutrition* **122**: 246-253.

Arjmandi, B. H., Craig, J., Nathani, S. and Reeves, R. D. (1992b). Soluble dietary fiber and cholesterol influence invivo hepatic and intestinal cholesterol-biosynthesis in rats. *Journal of Nutrition* **122**: 1559-1565.

Ashakumary, L., Rouyer, I., Takahashi, Y., Ide, T., Fukuda, N., Aoyama, T., Hashimoto, T., Mizugaki, M. and Sugano, M. (1999). Sesamin, a sesame lignan, is a potent inducer of hepatic fatty acid oxidation in the rat. *Metabolism* **48**: 1303-1313.

Babenko, N. A. and Shakhova, E. G. (2006). Effects of *Chamomilla recutita* flavonoids on age-related liver sphingolipid turnover in rats. *Experimental Gerontology* **41**: 32-39.

Badmaev, V., Majeed, M. and Conte, A. A. (2002). Open field, physician controlled clinical evaluation of a botanical weight loss formula based on Garcinia cambogia derived (-)hydroxycitric acid. *NutraCos* **1**: 10-14.

Baker, H., Luisada-Opper, A., Sorrell, M. F., Thomson, A. D. and Frank, O. (1973). Inhibition by nicotinic acid of hepatic steatosis and alcohol dehydrogenase in ethanol-treated rats. *Experimental and Molecular Pathology* **19**: 106-112.

Balkan, J., Oztezcan, S., Kucuk, M., Cevikbas, U., Kocak-Toker, N. and Uysal, M. (2004). The effect of betaine treatment on triglyceride levels and oxidative stress in the liver of ethanol-treated guinea pigs. *Experimental and Toxicologic Pathology* **55**: 505-509.

Ball, C. R. (1964). Actions of betaine, carnitine and choline on pattern of hepatic liposis in mice fed high-fat low-protein diet. *Anatomical Record* **149**: 677-689.

Barak, A. J., Beckenhauer, H. C., Badakhsh, S. and Tuma, D. J. (1997). The effect of betaine in reversing alcoholic steatosis. *Alcoholism: Clinical and Experimental Research* **21**: 1100-1102.

Barak, A. J., Beckenhauer, H. C. and Tuma, D. J. (1996). Betaine effects on hepatic methionine metabolism elicited by short-term ethanol feeding. *Alcohol* **13**: 483-486.

Beach, D. C. and Flick, P. K. (1982). Early effect of myoinositol deficiency on fatty-acid synthetic enzymes of rat-liver. *Biochimica et Biophysica Acta* **711**: 452-459.

Beher, W. T. and Anthony, W. L. (1955). Effects of *β*-sitosterol and ferric chloride on accumulation of cholesterol in mouse liver. *Proceedings of the Society for Experimental Biology and Medicine* **90**: 223-225.

Benkhalti, D., Prost, J., Paz, E., Perez-Jimenez, F., El Modafar, C. and El Boustani, E. (2002). Effects of feeding virgin olive oil or their polyphenols on lipid of rat liver. *Nutrition Research* **22**: 1067-1075.

Berkhout, T. A., Havekes, L. M., Pearce, N. J. and Groot, P. H. E. (1990). The effect of (-)-hydroxycitrate on the activity of the low-density-lipoprotein receptor and 3-hydroxy-3-methylglutaryl-CoA reductase levels in the human hepatoma-cell line Hep G2. *Biochemical Journal* **272**: 181-186.

Best, C. H. (1934). The role of the liver in the metabolism of carbohydrate and fat. III - The deposition of liver fat. *The Lancet* **223**: 1274-1277.

Best, C. H. and Huntsman, M. E. (1932). The effects of the components of lecithine upon deposition of fat in the liver. *Journal of Physiology* **75**: 405-412.

Best, C. H. and Huntsman, M. E. (1935). The effect of choline on the liver fat of rats in various states of nutrition. *Journal of Physiology* **83**: 255-274.

Best, C. H., Lucas, C. C., Ridout, J. H. and Patterson, J. M. (1950). Dose-response curves in the estimation of potency of lipotropic agents. *Journal of Biological Chemistry* **186**: 317-329.

Best, C. H. and Ridout, J. H. (1940). The lipotropic action of methionine. *Journal of Physiology* **97**: 489-494.

Best, M. M. and Duncan, C. H. (1956). Effects of sitosterol on the cholesterol concentration in serum and liver in hypothyroidism. *Circulation* **14**: 344-348.

Beveridge, J. M. R., Lucas, C. C. and O'Grady, M. K. (1945). The effect of dietary proteins and amino acids on liver fat. *Journal of Biological Chemistry* **160**: 505-518.

Blake, W. L. and Clarke, S. D. (1990). Suppression of rat hepatic fatty acid synthase and s14 gene transcription by dietary polyunsaturated fat. *Journal of Nutrition* **120**: 1727-1729.

Bok, S.-H., Lee, S.-H., Park, Y.-B., Bae, K.-H., Son, K.-H., Jeong, T.-S. and Choi, M.-S. (1999). Plasma and hepatic cholesterol and hepatic activities of 3-hydroxy-3-methyl-glutaryl-CoA reductase and acyl CoA: cholesterol transferase are lower in rats fed citrus peel extract or a mixture of citrus bioflavonoids. *Journal of Nutrition* **129**: 1182-1185.

Borgschulte, G., Kathirvel, E., Herrera, M., French, S. W., Morgan, T. R., Morgan, K. and Bottiglieri, T. (2008). Betaine treatment reverses insulin resistance and fatty liver disease without reducing oxidative stress or endoplasmic reticulum stress in an animal model of NAFLD. *Gastroenterology* **134**: A414-A415.

Bortolotti, M., Kreis, R., Debard, C., Cariou, B., Faeh, D., Chetiveaux, M., Ith, M., Vermathen, P., Stefanoni, N., Le, K.-A., Schneiter, P., Krempf, M., Vidal, H., Boesch, C. and Tappy, L. (2009). High protein intake reduces intrahepatocellular lipid deposition in humans. *American Journal of Clinical Nutrition* **90**: 1002-1010.

Bose, M., Lambert, J. D., Ju, J., Reuhl, K. R., Shapses, S. A. and Yang, C. S. (2008). The major green tea polyphenol, (-)-epigallocatechin-3-gallate, inhibits obesity, metabolic syndrome, and fatty liver disease in high-fat-fed mice. *Journal of Nutrition* **138**: 1677-1683.

Bowyer, B. A., Miles, J. M., Haymond, M. W. and Fleming, C. R. (1988). L-carnitine therapy in home parenteral-nutrition patients with abnormal liver tests and low plasma carnitine concentrations. *Gastroenterology* **94**: 434-438.

Brandt, K., Langhans, W., Geary, N. and Leonhardt, M. (2006). Beneficial and deleterious effects of hydroxycitrate in rats fed a high-fructose diet. *Nutrition* **22**: 905-912.

Bruno, R. S., Dugan, C. E., Smyth, J. A., DiNatale, D. A. and Koo, S. I. (2008). Green tea extract protects leptin-deficient, spontaneously obese mice from hepatic steatosis and injury. *Journal of Nutrition* **138**: 323-331.

Buchman, A. L., Ament, M. E., Sohel, M., Dubin, M., Jenden, D. J., Roch, M., Pownall, H., Farley, W., Awal, M. and Ahn, C. (2001). Choline deficiency causes reversible hepatic abnormalities in patients receiving parenteral nutrition: proof of a human choline requirement: A placebo-controlled trial. *Journal of Parenteral and Enteral Nutrition* **25**: 260-268.

Buchman, A. L., Dubin, M. D., Moukarzel, A. A., Jenden, D. J., Roch, M., Rice, K. M., Gornbein, J. and Ament, M. E. (1995). Choline deficiency: a cause of hepatic steatosis during parenteral nutrition that can be reversed with intravenous choline supplementation. *Hepatology* **22**: 1399-1403.

Bursill, C., Roach, P. D., Bottema, C. D. and Pal, S. (2001). Green tea upregulates the low-density lipoprotein receptor through the sterol-regulated element binding protein in HepG2 liver cells. *Journal of Agricultural and Food Chemistry* **49**: 5639-5645.

Bursill, C. A. and Roach, P. D. (2006). Modulation of cholesterol metabolism by the green tea polyphenol (-)-epigallocatechin gallate in cultured human liver (HepG2) cells. *Journal of Agricultural and Food Chemistry* **54**: 1621-1626.

Burton, L. E. and Wells, W. W. (1977). Characterization of the lactation-dependent fatty liver in *myo*-inositol deficient rats. *Journal of Nutrition* **107**: 1871-1883.

Busserolles, J., Gueux, E., Rock, E., Demigne, C., Mazur, A. and Rayssiguier, Y. (2003). Oligofructose protects against the hypertriglyceridemic and pro-oxidative effects of a high fructose diet in rats. *Journal of Nutrition* **133**: 1903-1908.

Caballero, F., Fernandez, A., Fernandez-Checa, J. C. and Garcia-Ruiz, C. (2008). Methionine deficiency accounts for the liver damage observed in a nutritional model of nonalcoholic steatohepatitis. *Journal of Hepatology* **48**: 917.

Capanni, M., Calella, F., Biagini, M. R., Genise, S., Raimondi, L., Bedogni, G., Svegliati-Baroni, G., Sofi, F., Milani, S., Abbate, R., Surrenti, C. and Casini, A. (2006). Prolonged n-3 polyunsaturated fatty acid supplementation ameliorates hepatic steatosis in patients with non-

alcoholic fatty liver disease: a pilot study. *Alimentary Pharmacology and Therapeutics* **23**: 1143-1151.

Carroll, C. and Williams, L. (1982). Choline deficiency in rats as influenced by dietary energy-sources. *Nutrition Reports International* **25**: 773-782.

Casaschi, A., Rubio, B. K., Maiyoh, G. K. and Theriault, A. G. (2004). Inhibitory activity of diacylglycerol acyltransferase (DGAT) and microsomal triglyceride transfer protein (MTP) by the flavonoid, taxifolin, in HepG2 cells: potential role in the regulation of apolipoprotein B secretion. *Atherosclerosis* **176**: 247-253.

Catolla Cavalcanti, A. and Levis, F. (1950). Steatosis of the liver due to phosphorus. I. Lipotropic action of pantothenic acid and of its combination with meso-inositol. *Archivio per le Scienze Mediche (Torino)* **90**: 529-541.

Causi, N., Romano, A. and Galfano, G. (1958). Coenzyme A in rat liver during administration of pantothenic acid and nicotinamide. *Bollettino-Societa Italiana Biologia Sperimentale (Napoli)* **34**: 163-164.

Cha, J. Y., Cho, Y. S., Kim, I., Anno, T., Rahman, S. M. and Yanagita, T. (2001). Effect of hesperetin, a citrus flavonoid, on the liver triacylglycerol content and phosphatidate phosphohydrolase activity in orotic acid-fed rats. *Plant Foods for Human Nutrition* **56**: 349-358.

Chahl, J. S. and Kratzing, C. C. (1966a). Environmental temperature and choline requirement in rats . 1. Choline deficiency in rats at various temperatures. *Journal of Lipid Research* **7**: 17-21.

Chahl, J. S. and Kratzing, C. C. (1966b). Environmental Temperature and Choline Requirements in Rats . 2. Choline and Methionine Requirements for Lipotropic Activity. *Journal of Lipid Research* **7**: 22-26.

Chakrabarti, C. and Banerjee, B. (1969). Influence of riboflavin, choline, inositol and niacin on hepatic biosynthesis of cholesterol of albino rats kept on a high cholesterol diet. *Journal of Vitaminology* **15**: 204-207.

Chan, M. Y. and Heng, C. K. (2008). Sequential effects of a high-fiber diet with psyllium husks on the expression levels of hepatic genes and plasma lipids. *Nutrition* **24**: 57-66.

Chan, P. T., Fong, W. P., Cheung, Y. L., Huang, Y., Ho, W. K. K. and Chen, Z.-Y. (1999). Jasmine green tea epicatechins are hypolipidemic in hamsters (*Mesocricetus auratus*) fed a high fat diet. *Journal of Nutrition* **129**: 1094-1101.

Chan, T. Y. and Tang, P. L. (1995). Effect of melatonin on the maintenance of cholesterol homeostasis in the rat. *Endocrine Research* **21**: 681-696.

Chen, N., Bezzina, R., Hinch, E., Lewandowski, P. A., Cameron-Smith, D., Mathai, M. L., Jois, M., Sinclair, A. J., Begg, D. P., Wark, J. D., Weisinger, H. S. and Weisinger, R. S. (2009). Green tea, black tea, and epigallocatechin modify body composition, improve glucose tolerance, and differentially alter metabolic gene expression in rats fed a high-fat diet. *Nutrition Research* **29**: 784-793.

Chen, H., Liu, L.-j., Zhu, J.-j., Xu, B. and Li, R. (2010a). Effect of soybean oligosaccharides on blood lipid, glucose levels and antioxidant enzymes activity in high fat rats. *Food Chemistry* **119**: 1633-1636.

Chen, Q., Gruber, H., Swist, E., Coville, K., Pakenham, C., Ratnayake, W. and Scoggan, K. (2010b). Dietary phytosterols and phytostanols decrease cholesterol levels but increase blood pressure in WKY inbred rats in the absence of salt-loading. *Nutrition and Metabolism* **7**: 11.

Cheng, H. H. and Lai, M. H. (2000). Fermentation of resistant rice starch produces propionate reducing serum and hepatic cholesterol in rats. *Journal of Nutrition* **130**: 1991-1995.

Chezem, J., Colon, I. and Matheson, H. (1996). Dietary fiber source alters liver cholesterol, bile acid synthesis and excretion in rats. *FASEB Journal* **10**: 2940-2940.

Chiba, H., Uehara, M., Wu, J., Wang, X. X., Masuyama, R., Suzuki, K., Kanazawa, K. and Ishimi, Y. (2003). Hesperidin, a citrus flavonoid, inhibits bone loss and decreases serum and hepatic lipids in ovariectomized mice. *Journal of Nutrition* **133**: 1892-1897.

Cho, K., Kim, S. J., Park, S. H., Kim, S. and Park, T. (2009a). Protective effect of *Codonopsis lanceolata* root extract against alcoholic fatty liver in the rat. *Journal of Medicinal Food* **12**: 1293-1301.

Cho, S. H., Lee, H. R., Kim, T. H., Choi, S. W., Lee, W. J. and Choi, Y. (2004). Effects of defatted safflower seed extract and phenolic compounds in diet on plasma and liver lipid in ovariectomized rats fed high-cholesterol diets. *Journal of Nutritional Science and Vitaminology* **50**: 32-37.

Cho, Y. Y., Kwon, E. Y., Kim, H. J., Park, Y. B., Lee, K. T., Park, T. and Choi, M. S. (2009b). Low trans structured fat from flaxseed oil improves plasma and hepatic lipid metabolism in apo E-/- mice. *Food and Chemical Toxicology* **47**: 1550-1555.

Chopra, R. and Sambaiah, K. (2009). Effects of rice bran oil enriched with n-3 PUFA on liver and serum lipids in rats. *Lipids* **44**: 37-46.

Clark, R. M., Balakrishnan, A., Waters, D., Aggarwal, D., Owen, K. Q. and Koo, S. I. (2007). L-carnitine increases liver alpha-tocopherol and lowers liver and plasma triglycerides in aging ovariectomized rats. *Journal of Nutritional Biochemistry* **18**: 623-628.

Clarke, S. D., Armstrong, M. K. and Jump, D. B. (1990). Dietary polyunsaturated fats uniquely suppress rat liver fatty acid synthase and S14 mRNA content. *Journal of Nutrition* **120**: 225-231.

Clarke, S. D., Romsos, D. R. and Leveille, G. A. (1977). Differential effects of dietary methyl esters of long-chain saturated and polyunsaturated fatty acids on rat liver and adipose tissue lipogenesis. *Journal of Nutrition* **107**: 1170-1181.

Coudé, F. X., Grimber, G., Pelet, A. and Benoit, Y. (1983). Action of the antiepileptic drug, valproic acid, on fatty acid oxidation in isolated rat hepatocytes. *Biochemical and Biophysical Research Communications* **115**: 730-736.

da Costa, K.-A., Garner, S. C., Chang, J. and Zeisel, S. H. (1995). Effects of prolonged (1 year) choline deficiency and subsequent re-feeding of choline on 1,2-*sn*-diradylglycerol, fatty acids and protein kinase C in rat liver. *Carcinogenesis* **16**: 327-334.

Dahiru, D. and Obidoa, O. (2009). Effect of aqueous extract of *Ziziphus mauritiana* leaf on cholesterol and triglyceride levels in serum and liver of rats administered alcohol. *Pakistan Journal of Nutrition* **8**: 1884-1888.

Daubioul, C., Rousseau, N., Demeure, R., Gallez, B., Taper, H., Declerck, B. and Delzenne, N. (2002). Dietary fructans, but not cellulose, decrease triglyceride accumulation in the liver of obese Zucker fa/fa rats. *Journal of Nutrition* **132**: 967-973.

Daubioul, C. A., Taper, H. S., De Wispelaere, L. D. and Delzenne, N. M. (2000). Dietary oligofructose lessens hepatic steatosis, but does not prevent hypertriglyceridemia in obese Zucker rats. *Journal of Nutrition* **130**: 1314-1319.

Décordé, K., Agne, A., Lacan, D., Ramos, J., Fouret, G., Ventura, E., Feillet-Coudray, C., Cristol, J.-P. and Rouanet, J.-M. (2009). Preventive effect of a melon extract rich in superoxide scavenging activity on abdominal and liver fat and adipokine imbalance in high-fat-fed hamsters. *Journal of Agricultural and Food Chemistry* **57**: 6461-6467.

Degrace, P., Demizieux, L., Du, Z. Y., Gresti, J., Caverot, L., Djaouti, L., Jourdan, T., Moindrot, B., Guilland, J. C., Hocquette, J. F. and Clouet, P. (2007). Regulation of lipid flux between liver and adipose tissue during transient hepatic steatosis in carnitine-depleted rats. *Journal of Biological Chemistry* **282**: 20816-20826.

Delzenne, N. M. and Kok, N. N. (1999). Biochemical basis of oligofructose-induced hypolipidemia in animal models. *Journal of Nutrition* **129**: 1467S-1470S.

Demigné, C., Morand, C., Levrat, M.-A., Besson, C., Moundras, C. and Rémésy, C. (1995). Effect of propionate on fatty acid and cholesterol synthesis and on acetate metabolism in isolated rat hepatocytes. *British Journal of Nutrition* **74**: 209-219.

Di Nunzio, M., van Deursen, D., Verhoeven, A. J. M. and Bordoni, A. (2010). n-3 and n-6 Polyunsaturated fatty acids suppress sterol regulatory element binding protein activity and increase flow of non-esterified cholesterol in HepG2 cells. *British Journal of Nutrition* **103**: 161-167.

Doan Thi Thanh, H., Takahashi, Y. and Ide, T. (2006). Activity and mRNA levels of enzymes involved in hepatic fatty acid oxidation in mice fed citrus flavonoids. *Nutrition* **22**: 546-552.

Drill, V. A. (1954). Lipotropic effects of vitamin-B12 and other factors. *Annals of the New York Academy of Sciences* **57**: 654-663.

Dumas, M. E., Barton, R. H., Toye, A., Cloarec, O., Blancher, C., Rothwell, A., Fearnside, J., Tatoud, R., Blanc, V., Lindon, J. C., Mitchell, S. C., Holmes, E., McCarthy, M. I., Scott, J., Gauguier, D. and Nicholson, J. K. (2006). Metabolic profiling reveals a contribution of gut microbiota to fatty liver phenotype in insulin-resistant mice. *Proceedings of the National Academy of Sciences of the United States of America* **103**: 12511-12516.

Eckstein, H. C. (1952). Dietary essential amino acids and the liver lipide content of young white rats. *Journal of Biological Chemistry* **195**: 167-174.

Engel, R. W. (1942). The relation of B-vitamins and dietary fat to the lipotropic action of choline. *Journal of Nutrition* **24**: 175-185.

Esfandiari, F., Villanueva, J. A., Wong, D. H., French, S. W. and Halsted, C. H. (2005). Chronic ethanol feeding and folate deficiency activate hepatic endoplasmic reticulum stress pathway in micropigs. *American Journal of Physiology-Gastrointestinal and Liver Physiology* **289**: G54-63.

Failey, R. B. and Childress, R. H. (1962). The effect of para-aminobenzoic acid on the serum cholesterol level in man. *American Journal of Clinical Nutrition* **10**: 158-162.

Feillet-Coudray, C., Sutra, T., Fouret, G., Ramos, J., Wrutnialc-Cabello, C., Cabello, G., Cristol, J. P. and Coudray, C. (2009). Oxidative stress in rats fed a high-fat high-sucrose diet and preventive effect of polyphenols: Involvement of mitochondrial and NAD(P)H oxidase systems. *Free Radical Biology and Medicine* **46**: 624-632.

Felmlee, M. A., Woo, G., Simko, E., Krol, E. S., Muir, A. D. and Alcorn, J. (2009). Effects of the flaxseed lignans secoisolariciresinol diglucoside and its aglycone on serum and hepatic lipids in hyperlipidaemic rats. *British Journal of Nutrition* **102**: 361-369.

Fomenko, A. I., Shushevich, S. I. and Khalmuradov, A. G. (1979). Inhibition of activity of acetyl coenzyme A carboxylase from chicken liver by nicotinic-acid and its derivatives. *Biokhimiya* **44**: 1005-1009.

Frantz, I. D. and Carey, J. B. (1961). Cholesterol content of human liver after feeding of corn oil and hydrogenated coconut oil. *Proceedings of the Society for Experimental Biology and Medicine* **106**: 800-801.

Fritz, I. B. (1959). Action of carnitine on long chain fatty acid oxidation by liver. *American Journal of Physiology* **197**: 297-304.

Fritz, I. B. (1964). Carnitine effects on palmitate-1-^{14}C conversion to CO_2 and glycerides by various tissues. *American Journal of Physiology* **206**: 1217-1222.

Fritz, I. B. and Dupont, P. (1957). Ineffectiveness of carnitine as a choline substitute in the prevention of fatty livers of rats maintained on a choline-deficient diet. *American Journal of Physiology* **190**: 453-454.

Fukuda, N., Miyagi, C., Zhang, L., Jayasooriya, A. P., Sakono, M., Yamamoto, K., Ide, T. and Sugano, M. (1998). Reciprocal effects of dietary sesamin on ketogenesis and triacylglycerol secretion by the rat liver. *Journal of Nutritional Science and Vitaminology* **44**: 715-722.

Fukuda, N., Zhang, L., Kodama, M., Sakono, M., Ide, T., Yamamoto, K. and Sugano, M. (1999). Effect of dietary sesamin on metabolic fate of an exogenous linolelaidic acid in perfused rat liver. *Journal of Nutritional Science and Vitaminology* **45**: 437-448.

Fukushima, Y., Kasuga, M., Nakao, K., Shimomura, I. and Matsuzawa, Y. (2009). Effects of coffee on inflammatory cytokine gene expression in mice fed high-fat diets. *Journal of Agricultural and Food Chemistry* **57**: 11100-11105.

Gallaher, D. D. and Plate, A. Y. A. (2005). Reduction in liver cholesterol by a beta-glucan concentrate in rats: correlation with intestinal contents viscosity. *FASEB Journal* **19**: A90-A90.

Ganji, S. H., Tavintharan, S., Zhu, D., Xing, Y., Kamanna, V. S. and Kashyap, M. L. (2004). Niacin noncompetitively inhibits DGAT2 but not DGAT1 activity in HepG2 cells. *Journal of Lipid Research* **45**: 1835-1845.

Gargini, G. (1951). Comparative experimental research on the lipotropic and hepatoprotective action of inositol, amino acids and lipocaic. *Rivista Critica di Clinica Medica* **51**: 195-214.

Gavin, G. and McHenry, E. W. (1941). The effect of biotin upon fat synthesis and metabolism. *Journal of Biological Chemistry* **141**: 619-625.

Gebhardt, R. and Beck, H. (1996). Differential inhibitory effects of garlic-derived organosulfur compounds on cholesterol biosynthesis in primary rat hepatocyte cultures. *Lipids* **31**: 1269-1276.

Gershoff, S. N. and Gottlieb, L. S. (1964). Pantothenic acid deficiency in cats. *Journal of Nutrition* **82**: 135-138.

Goheen, S., Larkin, E. and Rao, G. (1983). Severe fatty liver in rats fed a fat-free ethanol diet, and its prevention by small amounts of dietary arachidonate. *Lipids* **18**: 285-290.

Gotoh, N., Nagao, K., Onoda, S., Shirouchi, B., Furuya, K., Nagai, T., Mizobe, H., Ichioka, K., Watanabe, H., Yanagita, T. and Wada, S. (2009). Effects of three different highly purified n-3 series highly unsaturated fatty acids on lipid metabolism in C57BL/KsJ-db/db mice. *Journal of Agricultural and Food Chemistry* **57**: 11047-11054.

Griffith, W. H. and Mulford, D. J. (1941). Choline metabolism. VI. Hemorrhagic degeneration and the labile methyl supply. *Journal of the American Chemical Society* **63**: 929-932.

Grundy, S., Mok, H., Zech, L. and Berman, M. (1981). Influence of nicotinic acid on metabolism of cholesterol and triglycerides in man. *Journal of Lipid Research* **22**: 24-36.

Gu, X., Xie, Z., Wang, Q., Liu, G., Qu, Y., Zhang, L., Pan, J., Zhao, G. and Zhang, Q. (2009). Transcriptome profiling analysis reveals multiple modulatory effects of Ginkgo biloba extract in the liver of rats on a high-fat diet. *FEBS Journal* **276**: 1450-1458.

Guo, Y., Wu, G., Su, X., Yang, H. and Zhang, J. (2009). Antiobesity action of a daidzein derivative on male obese mice induced by a high-fat diet. *Nutrition Research* **29**: 656-663.

Gustavsson, C., Parini, P., Ostojic, J., Cheung, L., Hu, J., Zadjali, F., Tahir, F., Brismar, K., Norstedt, G. and Tollet-Egnell, P. (2009). Cocoa Butter and Safflower Oil Elicit Different Effects on Hepatic Gene Expression and Lipid Metabolism in Rats. *Lipids* **44**: 1011-1027.

Haines, D. S. M. and Mookerjea, S. (1965). Impairment of triglyceride transport from liver in choline deficiency. *Canadian Journal of Biochemistry* **43**: 507-520.

Haines, D. S. M. and Rose, C. I. (1970). Impaired labelling of liver phosphatidylethanolamine from ethanolamine-C^{14} in choline deficiency. *Canadian Journal of Biochemistry* **48**: 885-892.

Halsted, C. H., Villanueva, J. A., Devlin, A. M., Niemelä, O., Parkkila, S., Garrow, T. A., Wallock, L. M., Shigenaga, M. K., Melnyk, S. and James, S. J. (2002). Folate deficiency disturbs hepatic methionine metabolism and promotes liver injury in the ethanol-fed micropig. *Proceedings of the National Academy of Sciences of the United States of America* **99**: 10072-10077.

Han, L. K., Sumiyoshi, M., Zhang, J., Liu, M. X., Zhang, X. F., Zheng, Y. N., Okuda, H. and Kimura, Y. (2003). Anti-obesity action of Salix matsudana leaves (Part 1). Anti-obesity action by polyphenols of Salix matsudana in high fat-diet treated rodent animals. *Phytotherapy Research* **17**: 1188-1194.

Han, L.-K., Xu, B.-J., Kimura, Y., Zheng, Y.-n. and Okuda, H. (2000). *Platycodi radix* affects Lipid metabolism in mice with high fat diet-induced obesity. *Journal of Nutrition* **130**: 2760-2764.

Hara, H., Haga, S., Aoyama, Y. and Kiriyama, S. (1999). Short-chain fatty acids suppress cholesterol synthesis in rat liver and intestine. *Journal of Nutrition* **129**: 942-948.

Harper, A. E., Benton, D. A., Winje, M. E. and Elvehjem, C. A. (1954). On the lipotropic action of protein. *Journal of Biological Chemistry* **209**: 171-177.

Hartfiel, W. and Kirchner, I. (1973). The importance of nicotinic acid and its effect on the liver fat content of laying hens. *Archiv fur Geflugelkunde* **37**: 114-117.

Hayashi, E., Maeda, T. and Tomita, T. (1974a). Effect of myoinositol deficiency on lipid-metabolism in rats. 1. Alteration of lipid-metabolism in myoinositol deficient rats. *Biochimica et Biophysica Acta* **360**: 134-145.

Hayashi, E., Maeda, T. and Tomita, T. (1974b). Effect of myoinositol deficiency on lipid-metabolism in rats. 2. Mechanism of triacylglycerol accumulation in liver of myoinositol-deficient rats. *Biochimica et Biophysica Acta* **360**: 146-155.

Hayes, K. C., Pronczuk, A., Cook, M. W. and Robbins, M. C. (2003). Betaine in sub-acute and sub-chronic rat studies. *Food and Chemical Toxicology* **41**: 1685-1700.

Hayes, K. C., Pronczuk, A., Wijendran, V. and Beer, M. (2002). Free phytosterols effectively reduce plasma and liver cholesterol in gerbils fed cholesterol. *Journal of Nutrition* **132**: 1983-1988.

Hernandez, R., Martinez-Lara, E., Canuelo, A., del Moral, M. L., Blanco, S., Siles, E., Jimenez, A., Pedrosa, J. A. and Peinado, M. A. (2005). Steatosis recovery after treatment with a balanced sunflower or olive oil-based diet: involvement of perisinusoidal stellate cells. *World Journal of Gastroenterology* **11**: 7480-7485.

Hong, S. Y., Kim, Y. J. and Kim, M. K. (2007). Effect of hydroxycitric acid feeding on body weight and lipid profile in rats fed a high-carbohydrate or high-fat diet. *Faseb Journal* **21**: A1055-A1055.

Hood, R. L. and Sidhu, G. S. (1992). Effect of guar gum and tocotrienols on cholesterol metabolism on the Japanese quail. *Nutrition Research* **12**: S117-S127.

Hosein, E. A. and Bexton, B. (1975). Protective action of carnitine on liver lipid-metabolism after ethanol administration to rats. *Biochemical Pharmacology* **24**: 1859-1863.

Hotta, K., Kuwajima, M., Ono, A., Uenaka, R., Nakajima, H., Miyagawa, J., Namba, M., Hanafusa, T., Horiuchi, M., Nikaido, H., Hayakawa, J., Kono, N., Saheki, T. and Matsuzawa, Y. (1996). Altered expression of carnitine palmitoyltransferase II in liver, muscle, and heart of mouse strain with juvenile visceral steatosis. *Biochimica et Biophysica Acta-General Subjects* **1289**: 131-135.

Hou, Z., Qin, P. and Ren, G. (2010). Effect of anthocyanin-rich extract from black rice (*Oryza sativa* L. Japonica) on chronically alcohol-induced liver damage in rats. *Journal of Agricultural and Food Chemistry*.

Hsu, C.-c., Yen, H.-f., Yin, M.-c., Tsai, C.-m. and Hsieh, C.-h. (2004). Five cysteine-containing compounds delay diabetic deterioration in Balb/cA mice. *Journal of Nutrition* **134**: 3245-3249.

Hu, M. C. C. (1975). Lipotropic action of carnitine in a low protein diet from plant sources. *Dissertation Abstracts International, B* **36**: 655.

Hurley, L. S., Volkert, N. E. and Eichner, J. T. (1965). Pantothenic acid deficiency in pregnant and non-pregnant guinea pigs, with special reference to effects on the fetus. *Journal of Nutrition* **86**: 201-208.

Hussein, O., Grosovski, M., Lasri, E., Svalb, S., Ravid, U. and Assy, N. (2007). Monounsaturated fat decreases hepatic lipid content in non-alcoholic fatty liver disease in rats. *World Journal of Gastroenterology* **13**: 361-368.

Ide, T., Ashakumary, L., Takahashi, Y., Kushiro, M., Fukuda, N. and Sugano, M. (2001). Sesamin, a sesame lignan, decreases fatty acid synthesis in rat liver accompanying the down-regulation of sterol regulatory element binding protein-1. *Biochimica et Biophysica Acta-Molecular and Cell Biology of Lipids* **1534**: 1-13.

Ide, T., Hong, D. D., Ranasinghe, P., Takahashi, Y., Kushiro, M. and Sugano, M. (2004). Interaction of dietary fat types and sesamin on hepatic fatty acid oxidation in rats. *Biochimica et Biophysica Acta-Molecular and Cell Biology of Lipids* **1682**: 80-91.

Ide, T. and Horii, M. (1989). Hepatic carnitine and triglyceride lowering effect of dietary pectin in the rat. *Nutrition Reports International* **39**: 861-865.

Ikeda, M., Uno, Y., Iwai, M., Sato, H., Kawabe, H. and Sakakibara, B. (1992). Effects of the inositol-deficient diet on the development of fatty liver lipogenic enzyme activities and plasma lipid levels in germ-free and conventional mice. *Vitamins (Kyoto)* **66**: 43-49.

Itokawa, Y., Inoue, K., Sasagawa, S. and Fujiwara, M. (1973). Effect of s-methylcysteine sulfoxide, s-allylcysteine sulfoxide and related sulfur-containing amino acids on lipid metabolism of experimental hypercholesterolemic rats. *Journal of Nutrition* **103**: 88-92.

Jackson, K. A., Suter, D. A. I. and Topping, D. L. (1994). Oat bran, barley and malted barley lower plasma-cholesterol relative to wheat bran but differ in their effects on liver cholesterol in rats fed diets with and without cholesterol. *Journal of Nutrition* **124**: 1678-1684.

Ji, C. and Kaplowitz, N. (2003). Betaine decreases hyperhomocysteinemia, endoplasmic reticulum stress, and liver injury in alcohol-fed mice. *Gastroenterology* **124**: 1488-1499.

Jin, F. Y., Kamanna, V. S. and Kashyap, M. L. (1999). Niacin accelerates intracellular apoB degradation by inhibiting triacylglycerol synthesis in human hepatoblastoma (HepG2) cells. *Arteriosclerosis Thrombosis and Vascular Biology* **19**: 1051-1059.

Jin, F.-Y., Kamanna, V. S. and Kashyap, M. L. (1997). Niacin decreases removal of high-density lipoprotein apolipoprotein A-I but not cholesterol ester by Hep G2 cells : Implication for Reverse Cholesterol Transport. *Arteriosclerosis, Thrombosis and Vascular Biology* **17**: 2020-2028.

Jonnalagadda, S. S., Thye, F. W. and Robertson, J. L. (1993). Plasma total and lipoprotein cholesterol, liver cholesterol and fecal cholesterol excretion in hamsters fed fiber diets. *Journal of Nutrition* **123**: 1377-1382.

Kahlon, T. S., Chow, F. I., Sayre, R. N. and Betschart, A. A. (1992a). Cholesterol-lowering in hamsters fed rice bran at various levels, defatted rice bran and rice bran oil. *Journal of Nutrition* **122**: 513-519.

Kahlon, T. S., Saunders, R. M., Sayre, R. N., Chow, F. I., Chiu, M. M. and Betschart, A. A. (1992b). Cholesterol-lowering effects of rice bran and rice bran oil fractions in hypercholesterolemic hamsters. *Cereal Chemistry* **69**: 485-489.

Kamal-Eldin, A., Frank, J., Razdan, A., Tengblad, S., Basu, S. and Vessby, B. (2000). Effects of dietary phenolic compounds on tocopherol, cholesterol, and fatty acids in rats. *Lipids* **35**: 427-435.

Kanuri, G., Weber, S., Volynets, V., Spruss, A., Bischoff, S. C. and Bergheim, I. (2009). Cinnamon extract protects against acute alcohol-induced liver steatosis in mice. *Journal of Nutrition* **139**: 482-487.

Karanth, J. and Jeevaratnam, K. (2009). Effect of dietary lipid, carnitine and exercise on lipid profile in rat blood, liver and muscle. *Indian Journal of Experimental Biology* **47**: 748-753.

Katagiri, M. and Shimizu, S. (1992). Effects of dietary phytosterols on cholesterol levels in liver, serum and faeces of rats (a preliminary report). *Bulletin of IIDA Women's Junior College*: 60-67.

Katayama, T. (1993). Effect of dietary addition of *myo*-inositol on the metabolic changes in rats exposed to 1,1,1-trichloro-2, 2-bis (P-chlorophenyl) ethane. *Nutrition Research* **13**: 445-454.

Katayama, T. (1994). Effect of dietary addition of *myo*-inositol on lipid metabolism in rats fed sucrose or corn starch. *Nutrition Research* **14**: 699-706.

Katayama, T. (1995). Effect of dietary-sodium phytate on the hepatic and serum levels of lipids and on the hepatic activities of NADPH-generating enzymes in rats fed on sucrose. *Bioscience, Biotechnology and Biochemistry* **59**: 1159-1160.

Katayama, T. (1997a). Dietary phytic acid acts on hepatic lipid metabolism in a similar manner as dietary *myo*-inositol: is phytic acid a vitamin-like substance? *Recent Research Developments in Agricultural and Biological Chemistry* **1**: 321-330.

Katayama, T. (1997b). Effects of dietary *myo*-inositol or phytic acid on hepatic concentrations of lipids and hepatic activities of lipogenic enzymes in rats fed on corn starch or sucrose. *Nutrition Research* **17**: 721-728.

Katz, M., Budowski, P. and Bondi, A. (1970). Inhibition of cholesterol deposition in livers of mice fed phytosterols in short-term experiments. *Journal of Nutrition* **100**: 1141-1147.

Kawakami, Y., Tsurugasaki, W., Nakamura, S. and Osada, K. (2005). Comparison of regulative functions between dietary soy isoflavones aglycone and glucoside on lipid metabolism in rats fed cholesterol. *Journal of Nutritional Biochemistry* **16**: 205-212.

Kelley, B., Totter, J. R. and Day, P. L. (1950). The lipotropic effect of folic acid on rats receiving various purified diets. *Journal of Biological Chemistry* **187**: 529-535.

Kelley, J. J. and Tsai, A. C. (1978). Effect of pectin, gum arabic and agar on cholesterol absorption, synthesis, and turnover in rats. *Journal of Nutrition* **108**: 630-639.

Khairallah, E. A. and Wolf, G. (1965). Growth-promoting and lipotropic effect of carnitine in rats fed diets limited in protein and methionine. *Journal of Nutrition* **87**: 469-476.

Khanal, T., Choi, J. H., Hwang, Y. P., Chung, Y. C. and Jeong, H. G. (2009a). Protective effects of saponins from the root of Platycodon grandiflorum against fatty liver in chronic ethanol feeding via the activation of AMP-dependent protein kinase. *Food and Chemical Toxicology* **47**: 2749-2754.

Khanal, T., Choi, J. H., Hwang, Y. P., Chung, Y. C. and Jeong, H. G. (2009b). Saponins isolated from the root of Platycodon grandiflorum protect against acute ethanol-induced hepatotoxicity in mice. *Food and Chemical Toxicology* **47**: 530-535.

Kharbanda, K. K., Rogers, D. D., Mailliard, M. E., Siford, G. L., Barak, A. J., Beckenhauer, H. C., Sorrell, M. F. and Tuma, D. J. (2005). A comparison of the effects of betaine and S-adenosylmethionine on ethanol-induced changes in methionine metabolism and steatosis in rat hepatocytes. *Journal of Nutrition* **135**: 519-524.

Khor, H. T., Chieng, D. Y. and Ong, K. K. (1995). Tocotrienols inhibit liver HMG CoA reductase activity in the guinea pig. *Nutrition Research* **15**: 537-544.

Khor, H. T. and Ng, T. T. (2000). Effects of administration of alpha-tocopherol and tocotrienols on serum lipids and liver HMG CoA reductase activity. *International Journal of Food Sciences and Nutrition* **51**: S3-S11.

Kim, D. Y., Park, J. S., Yuan, H. D. and Chung, S. H. (2009). Fermented ginseng attenuates hepatic lipid accumulation and hyperglycemia through AMPK activation. *Food Science and Biotechnology* **18**: 172-178.

Kim, H., Bartley, G. E., Rimando, A. M. and Yokoyama, W. (2010). ~~H~~Hepatic gene expression related to lower plasma cholesterol in hamsters fed high-fat diets supplemented with blueberry peels and peel extract. *Journal of Agricultural and Food Chemistry*.

Kim, H. K., Jeong, T. S., Lee, M. K., Park, Y. B. and Choi, M. S. (2003). Lipid-lowering efficacy of hesperetin metabolites in high-cholesterol fed rats. *Clinica Chimica Acta* **327**: 129-137.

Kim, S., Shin, H. J., Kim, S. Y., Kim, J. H., Lee, Y. S., Kim, D. H. and Lee, M. O. (2004). Genistein enhances expression of genes involved in fatty acid catabolism through activation of PPARalpha. *Molecular and Cellular Endocrinology* **220**: 51-58.

Kim, S., Sohn, I. and Lee, Y. S. (2005). Hepatic gene expression profiles are altered by genistein supplementation in mice with diet-induced obesity. *Journal of Nutrition* **135**: 33-41.

Klopfenstein, C. F. (1990). Nutritional properties of coarse and fine sugar-beet fiber and hard red wheat bran. 1. Effects on rat serum and liver cholesterol and triglycerides and on fecal characteristics. *Cereal Chemistry* **67**: 538-541.

Kok, N., Roberfroid, M. and Delzenne, N. (1996a). Dietary oligofructose modifies the impact of fructose on hepatic triacylglycerol metabolism. *Metabolism* **45**: 1547-1550.

Kok, N., Roberfroid, M., Robert, A. and Delzenne, N. (1996b). Involvement of lipogenesis in the lower VLDL secretion induced by oligofructose in rats. *British Journal of Nutrition* **76**: 881-890.

Kok, N. N., Taper, H. S. and Delzenne, N. M. (1998). Oligofructose modulates lipid metabolism alterations induced by a fat-rich diet in rats. *Journal of Applied Toxicology* **18**: 47-53.

Kondo, T., Kishi, M., Fushimi, T. and Kaga, T. (2009). Acetic acid upregulates the expression of genes for fatty acid oxidation enzymes in liver to suppress body fat accumulation. *Journal of Agricultural and Food Chemistry* **57**: 5982-5986.

Kotaki, A., Sakurai, T., Kobayashi, M. and Yagi, K. (1968). Studies on myoinositol. IV. Effect of myoinositol on the cholesterol metabolism of rats suffering from experimental fatty liver. *Journal of Vitaminology (Kyoto)* **14**.

Kritchevsky, D. and Tepper, S. A. (2005). Influence of a fiber mixture on serum and liver lipids and on fecal fat excretion in rats. *Nutrition Research* **25**: 485-489.

Kritchevsky, D., Tepper, S. A., Satchithanandam, S., Cassidy, M. M. and Vahouny, G. V. (1988). Influence of a fiber mixture on serum and liver lipids and on fecal fat excretion in rats. *Lipids* **23**: 318-321.

Krogh, B., Funch, J. P. and Dam, H. (1961). Cholesterol and polyenoic fatty acids in liver, serum and aorta of rabbits given purified diets with butter, some margarines and arachis oil. *British Journal of Nutrition* **15**: 481-488.

Kumari, K. and Augusti, K. T. (2007). Lipid lowering effect of S-methyl cysteine sulfoxide from *Allium cepa* Linn in high cholesterol diet fed rats. *Journal of Ethnopharmacology* **109**: 367-371.

Kumari, K., Mathew, B. C. and Augusti, K. T. (1995). Antidiabetic and hypolipidemic effects of S-methyl cysteine sulfoxide isolated from *Allium cepa* linn. *Indian Journal of Biochemistry and Biophysics* **32**: 49-54.

Kuroki, S., Muramoto, S., Kuramoto, T. and Hoshita, T. (1983). Effect of feeding cholesterol and sitosterol on hepatic-steroid 12-alpha-hydroxylase activity in female hamsters. *Journal of Pharmacobio-Dynamics* **6**: 551-557.

Kushiro, M., Masaoka, T., Hageshita, S., Takahashi, Y., Ide, T. and Sugano, M. (2002). Comparative effect of sesamin and episesamin on the activity and gene expression of enzymes in fatty acid oxidation and synthesis in rat liver. *Journal of Nutritional Biochemistry* **13**: 289-295.

Kushiro, M., Takahashi, Y. and Ide, T. (2004). Species differences in the physiological activity of dietary lignan (sesamin and episesamin) in affecting hepatic fatty acid metabolism. *British Journal of Nutrition* **91**: 377-386.

Kuzu, N., Bahcecioglu, I. H., Metin, K., Ozercan, I. H., Tuzcu, M., Yalniz, M., Ustundag, B. and Sahin, K. (2007). Role of melatonin in treatment of nonalcoholic steatohepatitis in rats induced bu high fat diet. *Journal of Hepatology* **46**: S263.

Kwon, D. Y., Kim, Y. S., Hong, S. M. and Park, S. (2009). Long-term consumption of saponins derived from Platycodi radix (22 years old) enhances hepatic insulin sensitivity and glucose-stimulated insulin secretion in 90 % pancreatectomized diabetic rats fed a high-fat diet. *British Journal of Nutrition* **101**: 358-366.

Laird, R. D. and Drill, V. A. (1971). Lipotropic activity of inositol and chlortetracycline alone and in various combinations of choline, vitamin B_{12} and folic acid - activity of 3 liver extracts with

assays for these substances. *Archives Internationales de Pharmacodynamie et de Thérapie* **194**: 103-116.

Laird, R. D., McCormick, H. M. and Drill, V. A. (1965). Lipotropic activity of combinations of choline, vitamins B_{12} and B_{12b}, folic acid, and citrovorum factor. *Toxicology and Applied Pharmacology* **7**: 247-256.

Lamon-Fava, S., Diffenderfer, M. R., Barrett, P. H. R., Buchsbaum, A., Nyaku, M., Horvath, K. V., Asztalos, B. F., Otokozawa, S., Ai, M., Matthan, N. R., Lichtenstein, A. H., Dolnikowski, G. G. and Schaefer, E. J. (2008). Extended-release niacin alters the metabolism of plasma apolipoprotein (Apo) A-I and apoB-containing lipoproteins. *Arteriosclerosis Thrombosis and Vascular Biology* **28**: 1672-1678.

Laraki, L., Pelletier, X., Mourot, J. and Debry, G. (1993). Effects of dietary phytosterols on liver lipids and lipid metabolism enzymes. *Annals of Nutrition and Metabolism* **37**: 129-133.

Leclerc, J. and Miller, M. L. (1989). Inositol and choline levels in the diet and neutral lipid hepatic content of lactating rat. *International Journal for Vitamin and Nutrition Research* **59**: 180-183.

Lee, S. H., Park, H. J., Cho, S. Y., Jung, H. J., Cho, S. M., Cho, Y. S. and Lillehoj, H. S. (2005). Effects of dietary phytic acid on serum and hepatic lipid levels in diabetic KK mice. *Nutrition Research* **25**: 869-876.

Lee, S.-H., Park, H.-J., Chun, H.-K., Cho, S.-Y., Jung, H.-J., Cho, S.-M., Kim, D.-Y., Kang, M.-S. and Lillehoj, H. S. (2007). Dietary phytic acid improves serum and hepatic lipid levels in aged ICR mice fed a high-cholesterol diet. *Nutrition Research* **27**: 505-510.

Lee, Y. H. and Yeh, Y. Y. (2003). Inhibitory effects of garlic extract and water-soluble organosulfur compounds of garlic on cholestergenesis in HepG-2 cells. *FASEB Journal* **17**: A752-A752.

Li, B. H. and Tian, W. X. (2004). Inhibitory effects of flavonoids on animal fatty acid synthase. *Journal of Biochemistry* **135**: 85-91.

Li, R., Jia, C.-S., Yue, L., Zhang, X.-M., Xia, Q.-Y., Zhao, S.-L., Feng, B., Zhong, F. and Chen, W.-J. (2010). Lipase-catalyzed synthesis of conjugated linoleyl β-Sitosterol and its cholesterol-lowering properties in mice. *Journal of Agricultural and Food Chemistry* **58**: 1898-1902.

Liang, L. J., Yin, X. Y., Luo, S. M., Zheng, J. F., Lu, M. D. and Huang, J. F. (1999). A study of the ameliorating effects of carnitine on hepatic steatosis induced by total parenteral nutrition in rats. *World Journal of Gastroenterology* **5**: 312-315.

Lim, J. S., Adachi, Y., Takahashi, Y. and Ide, T. (2007). Comparative analysis of sesame lignans (sesamin and sesamolin) in affecting hepatic fatty acid metabolism in rats. *British Journal of Nutrition* **97**: 85-95.

Lin, C. C. and Yin, M. C. (2008). Effects of cysteine-containing compounds on biosynthesis of triacylglycerol and cholesterol and anti-oxidative protection in liver from mice consuming a high-fat diet. *British Journal of Nutrition* **99**: 37-43.

Lin, C. C., Yin, M. C., Hsu, C. C. and Lin, M. P. (2004). Effect of five cysteine-containing compounds on three lipogenic enzymes in Balb/cA mice consuming a high saturated fat diet. *Lipids* **39**: 843-848.

Lin, C. C., Yin, M. C. and Liu, W. H. (2008). Alleviative effects of s-allyl cysteine and s-ethyl cysteine on MCD diet-induced hepatotoxicity in mice. *Food and Chemical Toxicology* **46**: 3401-3406.

Lin, M., Kao, S., Chung, P., Chan, K., Yang, M. and Wang, C. (2009). Improvement for high fat diet-induced hepatic injuries and oxidative stress by flavonoid-enriched extract from *Nelumbo nucifera* leaf. *Journal of Agricultural and Food Chemistry* **57**: 5925-5932.

Ling, W. H. and Jones, P. J. H. (1995). Enhanced efficacy of sitostanol-containing versus sitostanol-free phytosterol mixtures in altering lipoprotein cholesterol levels and synthesis in rats. *Atherosclerosis* **118**: 319-331.

Liu, L. and Yeh, Y.-Y. (2000). Inhibition of cholesterol biosynthesis by organosulfur compounds derived from garlic. *Lipids* **35**: 197-203.

Lombardi, B., Pani, P. and Schlunk, F. F. (1968). Choline-deficiency fatty liver: impaired release of hepatic triglycerides. *Journal of Lipid Research* **9**: 437-446.

Looney, M. A. and Lei, K. Y. (1978). Dietary fiber, zinc and copper - effects on serum and liver cholesterol levels in rat. *Nutrition Reports International* **17**: 329-337.

Lowenstein, J. M. (1971). Effect of (-)-hydroxycitrate on fatty acid synthesis by rat liver *in vivo*. *Journal of Biological Chemistry* **246**: 629-632.

Luo, Q.-F., Sun, L., Si, J.-Y. and Chen, D.-H. (2008). Hypocholesterolemic effect of stilbenes containing extract-fraction from *Cajanus cajan* L. on diet-induced hypercholesterolemia in mice. *Phytomedicine* **15**: 932-939.

Mahboob, S. (1975). Effect of pantothenic-acid deficiency on microsomal lipids of rat-liver. *Annals of Nutrition and Metabolism* **19**: 91-95.

McGarry, J. D. and Foster, D. W. (1979). In support of the roles of malonyl-CoA and carnitine acyltransferase I in the regulation of hepatic fatty acid oxidation and ketogenesis. *Journal of Biological Chemistry* **254**: 8163-8168.

McHenry, E. W. and Patterson, J. M. (1944). Lipotropic factors. *Physiological Reviews* **24**: 128-167.

McNeil, C. J., Hay, S. M., Rucklidge, G. J., Reid, M. D., Duncan, G. J. and Rees, W. D. (2009). Maternal diets deficient in folic acid and related methyl donors modify mechanisms associated with lipid metabolism in the fetal liver of the rat. *British Journal of Nutrition* **102**: 1445-1452.

Menendez, R., Amor, A. M., Gonzalez, R. M., Fraga, V. and Mas, R. (1996). Effect of policosanol on the hepatic cholesterol biosynthesis of normocholesterolemic rats. *Biological Research* **29**: 253-257.

Menendez, R., Arruzazabala, L., Mas, R., DelRio, A., Amor, A. M., Gonzalez, R. M., Carbajal, D., Fraga, V., Molina, V. and Illnait, J. (1997). Cholesterol-lowering effect of policosanol on rabbits with hypercholesterolaemia induced by a wheat starch-casein diet. *British Journal of Nutrition* **77**: 923-932.

Merrill, J. M. and Lemley-Stone, J. (1957). Effects of nicotinic acid on serum and tissue cholesterol in rabbits. *Circulation Research* **5**: 617-619.

Mezei, O., Banz, W. J., Steger, R. W., Peluso, M. R., Winters, T. A. and Shay, N. (2003). Soy isoflavones exert antidiabetic and hypolipidemic effects through the PPAR pathways in obese Zucker rats and murine RAW 264.7 cells. *Journal of Nutrition* **133**: 1238-1243.

Moghadasian, M. H., Nguyen, L. B., Shefer, S., Salen, G., Batta, A. K. and Frohlich, J. J. (2001). Hepatic cholesterol and bile acid synthesis, low-density lipoprotein receptor function, and plasma and fecal sterol levels in mice: Effects of apolipoprotein E deficiency and probucol or phytosterol treatment. *Metabolism-Clinical and Experimental* **50**: 708-714.

Moiseenok, A. G., Sheibak, V. M. and Gurinovich, V. A. (1987). Hepatic CoA, s-acyl-CoA, biosynthetic precursors of the coenzyme and pantothenate-protein complexes in dietary pantothenic-acid deficiency. *International Journal for Vitamin and Nutrition Research* **57**: 71-77.

Moon, Y. S., Latasa, M. J., Griffin, M. J. and Sul, H. S. (2002). Suppression of fatty acid synthase promoter by polyunsaturated fatty acids. *Journal of Lipid Research* **43**: 691-698.

Morise, A., Mourot, J., Boué, C., Combe, N., Amsler, G., Gripois, D., Quignard-Boulangé, A., Yvan-Charvet, L., Fénart, E., Weill, P. and Hermier, D. (2006). Gender-related response of lipid metabolism to dietary fatty acids in the hamster. *British Journal of Nutrition* **95**: 709-720.

Morise, A., Thomas, C., Landrier, J.-F., Besnard, P. and Hermier, D. (2009). Hepatic lipid metabolism response to dietary fatty acids is differently modulated by PPARα in male and female mice. *European Journal of Nutrition* **48**: 465-473.

Mullen, E., Brown, R. M., Osborne, T. F. and Shay, N. F. (2004). Soy isoflavones affect sterol regulatory element binding proteins (SREBPs) and SREBP-regulated genes in HepG2 cells. *Journal of Nutrition* **134**: 2942-2947.

Nagiel-Ostaszewski, I. and Lau-Cam, C. A. (1990). Protection by pantethine, pantothenic-acid and cystamine against carbon tetrachloride-induced hepatotoxicity in the rat. *Research Communications in Chemical Pathology and Pharmacology* **67**: 289-292.

Nakamura, Y., Kaihara, A., Yoshii, K., Tsumura, Y., Ishimitsu, S. and Tonogai, Y. (2001). Effects of the oral administration of green tea polyphenol and tannic acid on serum and hepatic lipid contents and fecal steroid excretion in rats. *Journal of Health Science* **47**: 107-117.

Nakamura, Y., Kanazawa, M., Liyanage, R., Iijima, S., Han, K. H., Shimada, K., Sekikawa, M., Yamauchi, A., Hashimoto, N., Ohba, K. and Fukushima, M. (2009). Effect of white wheat bread containing sugar beet fiber on serum lipids and hepatic mRNA in rats fed on a cholesterol-free diet. *Bioscience, Biotechnology and Biochemistry* **73**: 1280-1285.

Nakamura, Y. and Tonogai, Y. (2002). Effects of grape seed polyphenols on serum and hepatic lipid contents and fecal steroid excretion in normal and hypercholesterolemic rats. *Journal of Health Science* **48**: 570-578.

Naruta, E. and Buko, V. (2001). Hypolipidemic effect of pantothenic acid derivatives in mice with hypothalamic obesity induced by aurothioglucose. *Experimental and Toxicologic Pathology* **53**: 393-398.

Nieminen, P., Kakela, R., Mustonen, A. M., Hyvarinen, H. and Asikainen, J. (2001). Exogenous melatonin affects lipids and enzyme activities in mink (*Mustela vison*) liver. *Comparative Biochemistry and Physiology C-Toxicology and Pharmacology* **128**: 203-211.

Noda, S., Haratake, J., Sasaki, A., Ishii, N., Umezaki, H. and Horie, A. (1991). Acute encephalopathy with hepatic steatosis induced by pantothenic-acid antagonist, calcium hopantenate, in dogs. *Liver* **11**: 134-142.

Noh, J.-R., Kim, Y.-H., Gang, G.-T., Yang, K.-J., Lee, H.-S., Nguyen, P. H., Oh, W.-K., Song, K.-S. and Lee, C.-H. (2010). Chestnut (*Castanea crenata*) inner shell extract inhibits development of hepatic steatosis in C57BL/6 mice fed a high-fat diet. *Food Chemistry* **121**: 437-442.

Ntanios, F. Y. and Jones, P. J. H. (1998a). Dietary sitostanol reduces cholesterol absorption and increases cholesterol synthesis in male hamsters. *FASEB Journal* **12**: 4739.

Ntanios, F. Y. and Jones, P. J. H. (1998b). Effects of variable dietary sitostanol concentrations on plasma lipid profile and phytosterol metabolism in hamsters. *Biochimica et Biophysica Acta-Lipids and Lipid Metabolism* **1390**: 237-244.

Ntanios, F. Y., Jones, P. J. H. and Frohlich, J. J. (1998a). Dietary sitostanol reduces plaque formation but not lecithin cholesterol acyl transferase activity in rabbits. *Atherosclerosis* **138**: 101-110.

Ntanios, F. Y., MacDougall, D. E. and Jones, P. J. H. (1998b). Gender effects of tall oil versus soybean phytosterols as cholesterol-lowering agents in hamsters. *Canadian Journal of Physiology and Pharmacology* **76**: 780-787.

Nunn, S. L., Tauxe, W. N. and Juergens, J. L. (1961). Effect of nicotinic acid on human cholesterol biosynthesis. *Circulation* **24**: 1099.

Oakenfull, D. G., Fenwick, D. E., Hood, R. L., Topping, D. L., Illman, R. L. and Storer, G. B. (1979). Effects of saponins on bile-acids and plasma-lipids in the rat. *British Journal of Nutrition* **42**: 209-216.

Oda, T., Aoe, S., Sanada, H. and Ayano, Y. (1993). Effects of soluble and insoluble fiber preparations isolated from oat, barley, and wheat on liver cholesterol accumulation in cholesterol-fed rats. *Journal of Nutritional Science and Vitaminology* **39**: 73-79.

Odbayar, T. O., Badamhand, D., Kimura, T., Takahashi, Y., Tsushida, T. and Ide, T. (2006). Comparative studies of some phenolic compounds (quercetin, rutin, and ferulic acid) affecting hepatic fatty acid synthesis in mice. *Journal of Agricultural and Food Chemistry* **54**: 8261-8265.

Okazaki, Y. and Katayama, T. (2003). Effects of dietary carbohydrate and *myo*-inositol on metabolic changes in rats fed 1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethane (DDT). *The Journal of Nutritional Biochemistry* **14**: 81-89.

Okazaki, Y. and Katayama, T. (2008). Dietary myositol hexakisphosphate, but not *myo*-inositol, clearly improves hypercholesterolemia in rats fed casein-type amino acid mixtures and 1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethane. *Nutrition Research* **28**: 714-721.

Okazaki, Y., Kayashima, T. and Katayama, T. (2003). Effect of dietary phytic acid on hepatic activities of lipogenic and drug-metabolizing enzymes in rats fed 1,1,1-trichloro-2,2-bis (P-chlorophenyl) ethane (DDT). *Nutrition Research* **23**: 1089-1096.

Okazaki, Y., Setoguchi, T. and Katayama, T. (2006). Effects of dietary *myo*-inositol, D-chiro-inositol and L-chiro-inositol on hepatic lipids with reference to the hepatic *myo*-inositol status in rats fed on 1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethane. *Bioscience, Biotechnology, and Biochemistry* **70**: 2766-2770.

Okey, R., Miljanich, P., Shannon, A., Tinoco, J. and Ostwald, R. (1961). Fatty acid components of rat liver lipids: effect of composition of diet and of restricted access to food. *Journal of Nutrition* **75**: 51-60.

Olson, R. E., Jablonski, J. R. and Taylor, E. (1958). The effect of dietary protein, fat, and choline upon the serum lipids and lipoproteins of the rat. *American Journal of Clinical Nutrition* **6**: 111-118.

Onning, G. and Asp, N. G. (1995). The effect of dietary protein, fat, and choline upon the serum lipids and lipoproteins of the rat. *British Journal of Nutrition* **73**: 275-286.

Onomi, S. and Katayama, T. (1997). Effects of dietary *myo*-inositol and phytic acid on hepatic lipids accumulation in rats fed on sucrose or orotic acid. *Nippon Eiyo Shokuryo Gakkaishi (Journal of the Japanese Society of Nutrition and Food Science)* **50**: 267-272.

Ortega, M. F. (1989). Effect of dietary lysine level and protein restriction on the lipids and carnitine levels in the liver of pregnant rats. *Annals of Nutrition and Metabolism* **33**: 162-169.

Osumi, Y., Nagasaka, Y. and Shimamot.K (1969). Lipid metabolism in rats with fatty liver caused by low protein diet and effects of oral administration of L-methionine L-cysteine pantethine and calcium pantothenate upon it. *Japanese Journal of Pharmacology* **19**: 74-88.

Owens (1942). The comparative effects of inositol and lipocaic in depancreatized dogs. *Federation Proceedings* **1**: 65.

Ozturk, F., Gul, M., Ates, B., Ozturk, I. C., Cetin, A., Vardi, N., Otlu, A. and Yilmaz, I. (2009). Protective effect of apricot (*Prunus armeniaca* L.) on hepatic steatosis and damage induced by carbon tetrachloride in Wistar rats. *British Journal of Nutrition* **102**: 1767-1775.

Page, G. I., Russell, P. M. and Davies, S. J. (2005). Dietary carotenoid pigment supplementation influences hepatic lipid and mucopolysaccharide levels in rainbow trout (*Oncorhynchus mykiss*). *Comparative Biochemistry and Physiology B-Biochemistry and Molecular Biology* **142**: 398-402.

Pan, M., Song, Y.-L., Xu, J.-M. and Gan, H.-Z. (2006). Melatonin ameliorates nonalcoholic fatty liver induced by high-fat diet in rats. *Journal of Pineal Research* **41**: 79-84.

Park, J. K., Lee, M. A., Chon, J. W., Wang, S. G. and Park, Y. K. (2009a). Effect of water extract of cauliflower mushroom on serum and hepatic lipids in C57BL/6J(OB/OB) mice. *Annals of Nutrition and Metabolism* **55**: 397-398.

Park, K. W., Lee, J.-E. and Park, K.-m. (2009b). Diets containing *Sophora japonica* L. prevent weight gain in high-fat diet-induced obese mice. *Nutrition Research* **29**: 819-824.

Parker, R. A., Pearce, B. C., Clark, R. W., Gordon, D. A. and Wright, J. J. (1993). Tocotrienols regulate cholesterol production in mammalian cells by post-transcriptional suppression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. *Journal of Biological Chemistry* **268**: 11230-11238.

Parsons, W. B. J. (1961). Reduction in hepatic synthesis of cholesterol from C^{14}-acetate in hypercholesterolemic patients by nicotinic acid. *Circulation* **24**: 1099-1100.

Pathirana, C., Gibney, M. J. and Taylor, T. G. (1980). Effects of soy protein and saponins on serum and liver cholesterol in rats. *Atherosclerosis* **36**: 595-596.

Peluso, M. R., Winters, T. A., Shanahan, M. F. and Banz, W. J. (2000). A cooperative interaction between soy protein and its isoflavone-enriched fraction lowers hepatic lipids in male obese Zucker rats and reduces blood platelet sensitivity in male Sprague-Dawley rats. *Journal of Nutrition* **130**: 2333-2342.

Perrault, M. and Dormard, Y. (1966). Lipotropic effect of betaine aspartate on experimental hepatic steatosis. Study using triolein-C^{14}. *Thérapie* **21**: 719-731.

Perry, W. F. (1960). Effect of nicotinic acid and nicotinamide on incorporation of acetate into cholesterol, fatty acids and CO_2 by rat liver slices. *Metabolism-Clinical and Experimental* **9**: 686-689.

Preuss, H. G., Bagchi, D., Bagchi, M., Rao, C. V. S., Dey, D. K. and Satyanarayana, S. (2004a). Effects of a natural extract of (-)-hydroxycitric acid (HCA-SX) and a combination of HCA-SX plus niacin-bound chromium and *Gymnema sylvestre* extract on weight loss. *Diabetes, Obesity and Metabolism* **6**: 171-180.

Preuss, H. G., Bagchi, D., Bagchi, M., Rao, C. V. S., Satyanarayana, S. and Dey, D. K. (2004b). Efficacy of a novel, natural extract of (-)-hydroxycitric acid (HCA-SX) and a combination of HCA-SX, niacin-bound chromium and *Gymnema sylvestre* extract in weight management in human volunteers: A pilot study. *Nutrition Research* **24**: 45-58.

Pyo, Y.-H. and Seong, K.-S. (2009). Hypolipidemic effects of monascus-fermented soybean extracts in rats fed a high-fat and -cholesterol diet. *Journal of Agricultural and Food Chemistry* **57**: 8617-8622.

Qureshi, A. A., Burger, W. C., Peterson, D. M. and Elson, C. E. (1986). The structure of an inhibitor of cholesterol biosynthesis isolated from barley. *Journal of Biological Chemistry* **261**: 10544-10550.

Rejman, J. and Kozubek, A. (2003). Inhibitory effect of natural phenolic lipids upon NAD-dependent dehydrogenases and on triglyceride accumulation in 3T3-L1 cells in culture. *Journal of Agricultural and Food Chemistry* **52**: 246-250.

Rhew, T. H. and Sachan, D. S. (1983). Effects of carnitine and its precursors on alcohol-induced fatty liver. *Federation Proceedings* **42**: 1308-1308 (Abstract 5960).

Rhew, T. H. and Sachan, D. S. (1984). Dose dependent effect of carnitine on ethanol-induced hepatic steatosis. *Federation Proceedings* **43**: 395-395 (abstract 645).

Rhew, T. H. and Sachan, D. S. (1986). Dose-dependent lipotropic effect of carnitine in chronic-alcoholic rats. *Journal of Nutrition* **116**: 2263-2269.

Ricketts, M.-L., Moore, D. D., Banz, W. J., Mezei, O. and Shay, N. F. (2005). Molecular mechanisms of action of the soy isoflavones includes activation of promiscuous nuclear receptors. A review. *Journal of Nutritional Biochemistry* **16**: 321-330.

Riggs, T. R. and Hegsted, D. M. (1948). The effect of pantothenic acid deficiency on acetylation in rats. *Journal of Biological Chemistry* **172**: 539-545.

Rikans, L. L., Arata, D. and Cederquist, D. C. (1965). Fatty livers produced in albino rats by excess niacin in high fat diets. II. Effect of choline supplements. *Journal of Nutrition* **85**: 107-112.

Rong, N., Ausman, L. and Nicolosi, R. (1997). Oryzanol decreases cholesterol absorption and aortic fatty streaks in hamsters. *Lipids* **32**: 303-309.

Roongpisuthipong, C., Kantawan, R. and Roongpisuthipong, W. (2007). Reduction of adipose tissue and body weight: effect of water soluble calcium hydroxycitrate in Garcinia atroviridis on the short term treatment of obese women in Thailand. *Asia Pacific Journal of Clinical Nutrition* **16**: 25-29.

Rosenfeld, B. (1973). Regulation by dietary choline of hepatic fatty acid synthetase in the rat. *Journal of Lipid Research* **14**: 557-562.

Ross, A. B., Chen, Y., Frank, J., Swanson, J. E., Parker, R. S., Kozubek, A., Lundh, T., Vessby, B., Aman, P. and Kamal-Eldin, A. (2004). Cereal alkylresorcinols elevate gamma-tocopherol levels in rats and inhibit γ-tocopherol metabolism *in vitro*. *Journal of Nutrition* **134**: 506-510.

Rotenberg, S. and Eggum, B. O. (1986). The effect of purified pectins with and without saponins in the diet on selected lipid parameters in liver and blood-plasma of rats. *Acta Agriculturae Scandinavica* **36**: 211-216.

Roy, S., Freake, H. C. and Fernandez, M. L. (2000). Dietary soluble fiber lowers plasma LDL cholesterol (LDL-C) by modulating hepatic cholesterol 7-alpha hydroxylase. *FASEB Journal* **14**: A298.

Russakoff, A. H. and Blumberg, H. (1944). Choline as an adjuvant to the dietary therapy of cirrhosis of the liver. *Annals of Internal Medicine* **21**: 848-862.

Sachan, D. S. and Rhew, T. H. (1982). Lipotropic effect of carnitine on alcohol-induced hepatic steatosis. *American Journal of Clinical Nutrition* **35**: R32, page xx.

Sachan, D. S. and Rhew, T. H. (1983). Lipotropic effect of carnitine on alcohol-induced hepatic steatosis. *Nutrition Reports International* **27**: 1221-1226.

Sachan, D. S., Rhew, T. H. and Ruark, R. A. (1984). Ameliorating effects of carnitine and its precursors on alcohol-induced fatty liver. *American Journal of Clinical Nutrition* **39**: 738-744.

Saheb, J. L. and Demers, J. M. (1972). Effect of lipotropic factors on cholesterol metabolism in duckling. *Annales de Biologie Animale Biochimie Biophysique* **12**: 149.

Sakakibara, K., Shibata, Y., Higashi, T., Sanada, S. and Shoji, J. (1975). Effect of ginseng saponins on cholesterol-metabolism. 1. Level and synthesis of serum and liver cholesterol in rats treated with ginsenosides. *Chemical and Pharmaceutical Bulletin* **23**: 1009-1016.

Salama, R. H. M., Nassar, A. Y. A., Nafady, A. A. M. and Mohamed, H. H. T. (2007). A novel therapeutic drug (copper nicotinic acid complex) for non-alcoholic fatty liver. *Liver International* **27**: 454-464.

Schade, H. and Saltman, P. (1959). Influence of nicotinic acid on hepatic cholesterol synthesis in rabbits. *Proceedings of the Society for Experimental Biology and Medicine* **102**: 265-267.

Schaefer, A. E., McKibbin, J. M. and Elvehjem, C. A. (1942). Pantothenic acid deficiency studies in dogs. *Journal of Biological Chemistry* **143**: 321-330.

Schneeman, B. O. and Richter, D. (1993). Changes in plasma and hepatic lipids, small-intestinal histology and pancreatic-enzyme activity due to aging and dietary fiber in rats. *Journal of Nutrition* **123**: 1328-1337.

Schön, H. (1958). Effect of nicotinic acid on the cholesterol contents of rat-livers. *Nature* **182**: 534.

Schriewer, H., Krämer, U., Rutkowski, G. and Borgis, K.-J. (1979). Influence of silibin dihemisuccinate on fatty acid synthesis in rat liver. *Arzneimittelforschung* **29**: 524-526.

Schwarz, J. M., Chen, T. W. and Linfoot, P. (1999). Effect of hydroxycitrate on hepatic de novo lipogenesis, gluconeogenesis and glucose production in obese hyperinsulinemic subjects. *Circulation* **100 (Suppl. I)**: A1015 (pages 1195-1196).

Seetharamaiah, G. S. and Chandrasekhara, N. (1988). Hypocholesterolemic activity of oryzanol in rats. *Nutrition Reports International* **38**: 927-935.

Seetharamaiah, G. S. and Chandrasekhara, N. (1993). Comparative hypocholesterolemic activities of oryzanol, curcumin and ferulic acid in rats. *Journal of Food Science and Technology-Mysore* **30**: 249-252.

Sekiya, M., Yahagi, N., Matsuzaka, T., Najima, Y., Nakakuki, M., Nagai, R., Ishibashi, S., Osuga, J.-i., Yamada, N. and Shimano, H. (2003). Polyunsaturated fatty acids ameliorate hepatic steatosis in obese mice by SREBP-1 suppression. *Hepatology* **38**: 1529-1539.

Sener, G., Balkan, J., Cevikbas, U., Keyer-Uysal, M. and Uysal, M. (2004). Melatonin reduces cholesterol accumulation and prooxidant state induced by high cholesterol diet in the plasma, the liver and probably in the aorta of C57BL/6J mice. *Journal of Pineal Research* **36**: 212-216.

Sharma, R. and Rukmini, C. (1986). Rice bran oil and hypocholesterolemia in rats. *Lipids* **21**: 715-717.

Shefer, S., Salen, G., Bullock, J., Nguyen, L. B., Ness, G. C., Vhao, Z. H., Belamarich, P. F., Chowdhary, I., Lerner, S., Batta, A. K. and Tint, G. S. (1994). The effect of increased hepatic sitosterol on the regulation of 3-hydroxy-3-methylglutaryl-CoA reductase and cholesterol 7-alpha-hydroxylase in the rat and sitosterolemic homozygotes. *Hepatology* **20**: 213-219.

Shieh, J., Wu, H., Cheng, K. and Cheng, J. (2009). Melatonin ameliorates high fat diet-induced diabetes and stimulates glycogen synthesis via a PKCζ-Akt-GSK3β pathway in hepatic cells. *Journal of Pineal Research* **47**: 339-344.

Shils, M. E. and Stewart, W. B. (1954). Development of portal fatty liver in rats on corn diets - response to lipotropic agents. *Proceedings of the Society for Experimental Biology and Medicine* **85**: 298-303.

Shimoda, H., Tanaka, J., Kikuchi, M., Fukuda, T., Ito, H., Hatano, T. and Yoshidao, T. (2009). Effect of polyphenol-rich extract from walnut on diet-induced hypertriglyceridemia in mice *via* enhancement of fatty acid oxidation in the liver. *Journal of Agricultural and Food Chemistry* **57**: 1786-1792.

Shimura, S. and Hasegawa, T. (1993). Changes of lipid concentrations in liver and serum by administration of carnitine added diets in rats. *Journal of Veterinary Medical Science* **55**: 845-847.

Shin, J., Kim, Y. J., Choi, M. S., Woo, D. H. and Park, T. (2004). Phytosterols and lecithin do not have an additive effect in lowering plasma and hepatic cholesterol levels in diet-induced hypercholesterolemic rats. *Biofactors* **22**: 173-175.

Shrestha, S., Ehlers, S. J., Lee, J.-Y., Fernandez, M.-L. and Koo, S. I. (2009). Dietary green tea extract lowers plasma and hepatic triglycerides and decreases the expression of sterol regulatory element-binding protein-1c mRNA and its responsive genes in fructose-fed, ovariectomized rats. *Journal of Nutrition* **139**: 640-645.

Singal, S. A. and Eckstein, H. C. (1941). The lipotropic action of some sulfur-containing amino acids and related substances. *Journal of Biological Chemistry* **140**: 27-34.

Singh, U., Yokota, K., Gupta, C. and Shinozuka, H. (1990). Choline deficiency activates phospholipases A2 and C in rat liver without affecting the activity of protein kinase C. *Journal of Nutritional Biochemistry* **1**: 434-439.

Sirato-Yasumoto, S., Katsuta, M., Okuyama, Y., Takahashi, Y. and Ide, T. (2001). Effect of sesame seeds rich in sesamin and sesamolin on fatty acid oxidation in rat liver. *Journal of Agricultural and Food Chemistry* **49**: 2647-2651.

Siripurkpong, P. and Na-Bangehang, K. (2009). Effects of niacin and chromium on the expression of ATP-binding cassette transporter A1 and apolipoprotein A-1 genes in HepG2 cells. *Journal of Nutritional Biochemistry* **20**: 261-268.

Song, B. J., Moon, K. H., Olsson, N. U. and Salem, N. (2008). Prevention of alcoholic fatty liver and mitochondrial dysfunction in the rat by long-chain poly unsaturated fatty acids. *Journal of Hepatology* **49**: 262-273.

Soo-Jung, L., Min-Jung, K., Jung-Hye, S., Jeong-Gyun, K., Shin-Kwon, K. and Nak-Ju, S. (2009). The effect of garlic and medicinal plants extracts on the liver function and lipid metabolism of rats administered with alcohol. *Journal of the Korean Society of Food Science and Nutrition* **38**: 561-568.

Spadaro, L., Magliocco, O., Spampinato, D., Piro, S., Oliveri, C., Alagona, C., Papa, G., Rabuazzo, A. M. and Purrello, F. (2008). Effects of n-3 polyunsaturated fatty acids in subjects with nonalcoholic fatty liver disease. *Digestive and Liver Disease* **40**: 194-199.

Spaniol, M., Kaufmann, P., Beier, K., Wuthrich, J., Torok, M., Scharnagl, H., Marz, W. and Krahenbuhl, S. (2003). Mechanisms of liver steatosis in rats with systemic carnitine deficiency due to treatment with trimethylhydraziniumpropionate. *Journal of Lipid Research* **44**: 144-153.

Stewart, J. R., Fryer, E. B. and Fryer, H. C. (1987). Effects of dietary fiber, carbohydrate, lipid and protein-levels on serum and liver lipids in rats. *Journal of Nutrition* **117**: 650-659.

Story, J. A., Baldino, A., Czarnecki, S. K. and Kritchevsky, D. (1981). Modification of liver cholesterol accumulation by dietary fiber in rats. *Nutrition Reports International* **24**: 1213-1219.

Subramanian, P., Mirunalini, S., Pandi-Perumal, S. R., Trakht, I. and Cardinali, D. P. (2007). Melatonin treatment improves the antioxidant status and decreases lipid content in brain and liver of rats. *European Journal of Pharmacology* **571**: 116-119.

Sugano, M., Ikeda, I., Imaizumi, K., Watanabe, M. and Andoh, M. (1982). Effects of β-sitosterol on the concentrations of serum and liver cholesterol and serum apolipoproteins in rats fed butter fat. *Journal of Nutritional Science and Vitaminology* **28**: 117-126.

Sugatani, J., Wada, T., Osabe, M., Yamakawa, K., Yoshinari, K. and Miwa, M. (2006). Dietary inulin alleviates hepatic steatosis and xenobiotics-induced liver injury in rats fed a high-fat and

high-sucrose diet: Association with the suppression of hepatic cytochrome P450 and hepatocyte nuclear factor 4 alpha expression. *Drug Metabolism and Disposition* **34**: 1677-1687.

Suh, M. H., Yoo, S. H., Chang, P. S. and Lee, H. G. (2005). Antioxidative activity of microencapsulated γ-oryzanol on high cholesterol-fed rats. *Journal of Agricultural and Food Chemistry* **53**: 9747-9750.

Sullivan, A., Triscari, J., Hamilton, J. and Miller, O. (1974a). Effect of (-)-hydroxycitrate upon the accumulation of lipid in the rat: II. Appetite. *Lipids* **9**: 129-134.

Sullivan, A., Triscari, J., Hamilton, J., Miller, O. and Wheatley, V. (1974b). Effect of (-)-hydroxycitrate upon the accumulation of lipid in the rat: I. Lipogenesis. *Lipids* **9**: 121-128.

Sullivan, A., Triscari, J. and Miller, O. (1974c). The influence of (-)-hydroxycitrate on *in vivo* rates of hepatic glycogenesis, lipogenesis and cholesterogenesis. *Federation Proceedings* **33**: 656.

Sullivan, A., Triscari, J. and Spiegel, J. (1977). Metabolic regulation as a control for lipid disorders. II. Influence of (-)-hydroxycitrate on genetically and experimentally induced hypertriglyceridemia in the rat. *American Journal of Clinical Nutrition* **30**: 777-784.

Sullivan, A. C., Hamilton, J. G., Miller, O. N. and Wheatley, V. R. (1972). Inhibition of lipogenesis in rat liver by (-)-hydroxycitrate. *Archives of Biochemistry and Biophysics* **150**: 183-190.

Sun, G. Y., Xia, J. M., Xu, J. F., Allenbrand, B., Simonyi, A., Rudeen, P. K. and Sun, A. Y. (1999). Dietary supplementation of grape polyphenols to rats ameliorates chronic ethanol-induced changes in hepatic morphology without altering changes in hepatic lipids. *Journal of Nutrition* **129**: 1814-1819.

Sung, J. H., Choi, S. J., Lee, S. W., Park, K. H. and Moon, T. W. (2004). Isoflavones found in korean soybean paste as 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Bioscience, Biotechnology, and Biochemistry* **68**: 1051-1058.

Takeuchi, H., Nakamoto, T., Mori, Y., Kawakami, M., Mabuchi, H., Ohishi, Y., Ichikawa, N., Koike, A. and Masuda, K. (2001). Comparative effects of dietary fat types on hepatic enzyme

activities related to the synthesis and oxidation of fatty acid and to lipogenesis in rats. *Bioscience, Biotechnology, and Biochemistry* **65**: 1748-1754.

Tao, R. C., Peck, G. K. and Yoshimura, N. N. (1981). Effect of carnitine on liver fat and nitrogen-balance in intravenously fed growing-rats. *Journal of Nutrition* **111**: 171-177.

Theriault, A., Casaschi, A. and Ota, D. (2002). Secretion of hepatic triglyceride-rich lipoprotein is inhibited by the flavonoid, taxifolin, *via* reduced DGAT and MTP activity. *Arteriosclerosis Thrombosis and Vascular Biology* **22**: P423.

Thomas, M., Leelamma, S. and Kurup, P. A. (1983). Effect of blackgram fiber (*Phaseolus mungo*) on hepatic hydroxymethylglutaryl-CoA eeductase-activity, cholesterogenesis and cholesterol degradation in Rats. *Journal of Nutrition* **113**: 1104-1108.

Thurston, J. H., Carroll, J. E., Hauhart, R. E. and Schiro, J. A. (1985). A single therapeutic dose of valproate affects liver carbohydrate, fat, adenylate, amino-acid, coenzyme A, and carnitine metabolism in infant mice: possible clinical-significance. *Life Sciences* **36**: 1643-1651.

Thurston, J. H. and Hauhart, R. E. (1992). Amelioration of adverse effects of valproic acid on ketogenesis and liver coenzyme A metabolism by cotreatment with pantothenate and carnitine in developing mice: possible clinical significance. *Pediatric Research* **31**: 419-423.

Tinker, L. F., Davis, P. A. and Schneeman, B. O. (1994). Prune fiber or pectin compared with cellulose lowers plasma and liver lipids in rats with diet-induced hyperlipidemia. *Journal of Nutrition* **124**: 31-40.

Tojo, H., Igura, T., Nonomura, S., Sumi, R., Bando, Y. and Ito, T. (2008). A beneficial effect of polyphenol oligomers, oligonol, on choline deficiency-induced fatty liver in mice. *Chemistry and Physics of Lipids* **154**: S15-S15.

Tokmakjian, S. and Haines, D. S. M. (1979). Influence of dietary choline intake upon liver ethanolamine metabolism. *Canadian Journal of Biochemistry* **57**: 566-572.

Topping, D. L., Oakenfull, D., Trimble, R. P. and Illman, R. J. (1988). A viscous fiber (methylcellulose) lowers blood-glucose and plasma triacylglycerols and increases liver-glycogen independently of volatile fatty-acid production in the rat. *British Journal of Nutrition* **59**: 21-30.

Toussant, M. J., Wilson, M. D. and Clarke, S. D. (1981). Coordinate suppression of liver acetyl-CoA carboxylase and fatty acid synthetase by polyunsaturated fat. *Journal of Nutrition* **111**: 146-153.

Tsai, C. E. and Tsai, Y. (1999). Effect of dietary fiber on the prevention of liver lipid accumulation induced by high polyunsaturated oil. *Journal of Food Lipids* **6**: 75-89.

Tsuduki, T., Nakamura, Y., Honma, T., Nakagawa, K., Kimura, T., Ikeda, I. and Miyazawa, T. (2009). Intake of 1-deoxynojirimycin suppresses lipid accumulation through activation of the β-oxidation system in rat liver. *Journal of Agricultural and Food Chemistry* **57**: 11024-11029.

Tsuruoka, N., Kidokoro, A., Matsumoto, I., Abe, K. and Kiso, Y. (2005). Modulating effect of sesamin, a functional lignan in sesame seeds, on the transcription levels of lipid- and alcohol-metabolizing enzymes in rat liver: A DNA microarray study. *Bioscience, Biotechnology and Biochemistry* **69**: 179-188.

Tucker, H. F. and Eckstein, H. C. (1937). The effect of supplementary methionine and cystine on the production of fatty livers by diet. *Journal of Biological Chemistry* **121**: 479-484.

Tucker, H. F. and Eckstein, H. C. (1938). The effect of supplementary lysine, methionine, and cystine on the production of fatty livers by high fat diets containing gliadin. *Journal of Biological Chemistry* **126**: 117-123.

Turchetto, E., Infante, R. and Sechi, A. M. (1955). Effect of thyroxin on lipotropic activity of pantothenic acid. *Bollettino- Societa Italiana Biologia Sperimentale (Napoli)* **31**: 233-234.

Tyner, E. P., Lewis, H. B. and Eckstein, H. C. (1950). Niacin and the ability of cystine to augment deposition of liver fat. *Journal of Biological Chemistry* **187**: 651-654.

Uchida, K., Mizuno, H., Hirota, K., Takeda, K., Takeuchi, N. and Ishikawa, Y. (1983). Effects of spinasterol and sitosterol on plasma and liver cholesterol levels and biliary and fecal sterol and bile-acid excretions in mice. *Japanese Journal of Pharmacology* **33**: 103-112.

Ueshima, T., Shigata, Y., Wada, M., Oji, K. and Yoshida, T. (1956). Studies on the metabolism of pantothenic acid in liver damage. I. Urinary excretion of pantothenic acid in patients with various liver diseases and its correlation with liver function. *Journal of Vitaminology* **2**: 299-306.

Vaishwanar, I., Jiddewar, G. G., Shukla, R. D. and Kowale, C. N. (1972). Effect of nicotinic-acid on serum and hepatic lipids in experimentally induced fatty liver. *Indian Journal of Experimental Biology* **10**: 428-430.

van der Hoorn, J. W. A., de Haan, W., Berbee, J. F. P., Havekes, L. M., Jukema, J. W., Rensen, P. C. N. and Princen, H. M. G. (2008). Niacin increases HDL by reducing hepatic expression and plasma levels of cholesteryl ester transfer protein in APOE*3Leiden.CETP mice. *Arteriosclerosis Thrombosis and Vascular Biology* **28**: 2016-2022.

Wang, J. Q., Li, J., Zou, Y. H., Cheng, W. M., Lu, C., Zhang, L., Ge, J. F., Huang, C., Jin, Y., Lv, X. W., Hu, C. M. and Liu, L. P. (2009a). Preventive effects of total flavonoids of *Litsea coreana* leve on hepatic steatosis in rats fed with high fat diet. *Journal of Ethnopharmacology* **121**: 54-60.

Wang, M., Liu, J.-R., Gao, J.-M., Parry, J. W. and Wei, Y.-M. (2009b). Antioxidant activity of tartary buckwheat bran extract and its effect on the lipid profile of hyperlipidemic rats. *Journal of Agricultural and Food Chemistry* **57**: 5106-5112.

Wang, W., Basinger, A., Neese, R. A., Shane, B., Myong, S. A., Christiansen, M. and Hellerstein, M. K. (2001). Effect of nicotinic acid administration on hepatic very low density lipoprotein-triglyceride production. *American Journal of Physiology-Endocrinology and Metabolism* **280**: E540-E547.

Wang, X., Song, K.-S., Guo, Q.-X. and Tian, W.-X. (2003). The galloyl moiety of green tea catechins is the critical structural feature to inhibit fatty-acid synthase. *Biochemical Pharmacology* **66**: 2039-2047.

Wang, X. and Tian, W. (2001). Green tea epigallocatechin gallate: a natural inhibitor of fatty-acid synthase. *Biochemical and Biophysical Research Communications* **288**: 1200-1206.

Watson, J. A., Fang, M. and Lowenstein, J. M. (1969). Tricarballylate and hydroxycitrate: substrate and inhibitor of ATP:citrate oxaloacetate lyase. *Archives of Biochemistry and Biophysics* **135**: 209-217.

Whitehead, C. C., McNab, J. M. and Griffin, H. D. (1981). The effects of low dietary concentrations of saponin on liver lipid-accumulation and performance in laying hens. *British Poultry Science* **22**: 281-288.

Wijendran, V., Pronczuk, A., Beer, M. and Hayes, K. C. (2002). Free phytosterols lower plasma and liver lipids and increases fecal cholesterol excretion comparable to esterified sterols and stanols. *FASEB Journal* **16**: A242-A242.

Wilcox, L. J., Borradaile, N. M., de Dreu, L. E. and Huff, M. W. (2001). Secretion of hepatocyte apoB is inhibited by the flavonoids, naringenin and hesperetin, via reduced activity and expression of ACAT2 and MTP. *Journal of Lipid Research* **42**: 725-734.

Williams, M. A., Chu, L. C., McIntosh, D. J. and Hincenbe.I (1968). Effects of dietary fat level on pantothenate depletion and liver fatty acid composition in rat. *Journal of Nutrition* **94**: 377-382.

Willumsen, N., Vaagenes, H., Rustan, A. C., Grav, H., Lundquist, M., Skattebol, L., Songstad, J. and Berge, R. K. (1997). Enhanced hepatic fatty acid oxidation and upregulated carnitine palmitoyltransferase II gene expression by methyl 3-thiaoctadeca-6,9,12,15-tetraenoate in rats. *Journal of Lipid Mediators and Cell Signalling* **17**: 115-134.

Wirtschafter, Z. T. and Walsh, J. R. (1962). Hepatocellular lipoid changes in pantothenic acid deficiency. *American Journal of Clinical Nutrition* **10**: 525-530.

Wojcicki, J., Samochowiec, L., Kadlubowska, D. and Lutomski, J. (1977). Studies on saponin fraction from root of *Aralia mandshurica* Rupr. et Maxim. Part IV. Influence of saponosides on content of lipids in blood serum and liver in experimental hyperlipemia. *Herba Polonica* **23**: 285-289.

Wright, R. S., Anderson, J. W. and Bridges, S. R. (1990). Propionate inhibits hepatocyte lipid-synthesis. *Proceedings of the Society for Experimental Biology and Medicine* **195**: 26-29.

Wu, Z. M., Zhang, Y., Qi, Y., Lu, J. H., Tan, N. Z., Yin, W. T. and Zhu, J. S. (2005). Geraniol, policosanol, and SB formula: discrepant inhibitory expressions of liver cholesterol synthesis and serum lipids. *FASEB Journal* **19**: A972-A972.

Yacowitz, H., Fleischman, A. I. and Kritchevsky, D. (1976). Does fiber in bread affect serum and liver lipids in rats. *Journal of Nutrition* **106**: R26-R26.

Yagi, K. and Kotaki, A. (1969). The effect of massive doses of *myo*-inositol on hepatic phospholipid metabolism. *Annals of the New York Academy of Sciences* **165**: 710-725.

Yang, D.-J., Chang, Y.-Y., Hsu, C.-L., Liu, C.-W., Lin, Y.-L., Lin, Y.-H., Liu, K.-C. and Chen, Y.-C. (2010a). Antiobesity and hypolipidemic effects of polyphenol-rich longan (*Dimocarpus longans* Lour.) flower water extract in hypercaloric-dietary rats. *Journal of Agricultural and Food Chemistry* **58**: 2020-2027.

Yang, M.-Y., Peng, C.-H., Chan, K.-C., Yang, Y.-S., Huang, C.-N. and Wang, C.-J. (2010b). The hypolipidemic effect of *Hibiscus sabdariffa* polyphenols via inhibiting lipogenesis and promoting hepatic lipid clearance. *Journal of Agricultural and Food Chemistry* **58**: 850-859.

Yang, S., Tseng, J., Chang, Y. and Chen, Y. (2009). Flaxseed oil attenuates nonalcoholic fatty liver of hyperlipidemic hamsters. *Journal of Agricultural and Food Chemistry* **57**.

Yeh, Y. Y. (1979). The opposing effects of nicotinic-acid and dibutyryl cyclic adenosine-3',5'-monophosphate on ketogenesis in isolated rat hepatocytes. *Journal of Nutrition* **109**: 110-118.

Yeh, Y.-Y. and Liu, L. (2001). Cholesterol-lowering effect of garlic extracts and organosulfur compounds: human and animal studies. *Journal of Nutrition* **131**: 989S-993.

Yeh, Y.-Y. and Yeh, S.-M. (1994). Garlic reduces plasma lipids by inhibiting hepatic cholesterol and triacylglycerol synthesis. *Lipids* **29**: 189-193.

Yokota, F., Esashi, T., Takahash.S and Suzue, R. (1974). Effects of excess methionine and glycine on incorporation of sodium acetate-1-^{14}C into lipid of rat liver. *Nutrition Reports International* **10**: 405-408.

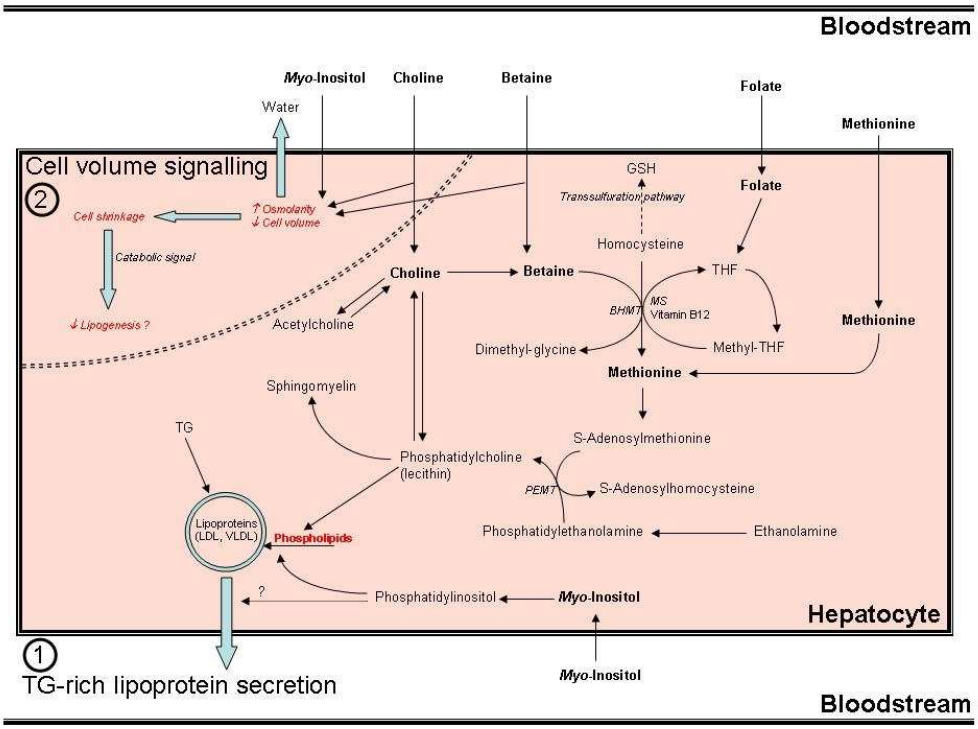
Young, R. J., Lucas, C. C., Patterson, J. M. and Best, C. H. (1965). Lipotropic dose-response studies in rats: comparisons of choline, betaine, and methionine. *Canadian Journal of Biochemistry and Physiology* **34**: 713.

Youssef, J., Cunningham, M. L. and Badr, M. (1994). Down-regulation of hepatic peroxisomal beta-oxidation due to pantothenic acid-deficiency. *FASEB Journal* **8**: A736-A736.

Zeisel, S., Da Costa, K., Franklin, P., Alexander, E., Lamont, J., Sheard, N. and Beiser, A. (1991). Choline, an essential nutrient for humans. *FASEB J* **5**: 2093-2098.

Zhang, L.-H., Kamanna, V. S., Zhang, M. C. and Kashyap, M. L. (2008). Niacin inhibits surface expression of ATP synthase β chain in HepG2 cells: implications for raising HDL. *Journal of Lipid Research* **49**: 1195-1201.

Zhang, R., Xiao, W., Wang, X., Wu, X. and Tian, W. (2006). Novel inhibitors of fatty-acid synthase from green tea (*Camellia sinensis* Xihu Longjing) with high activity and a new reacting site. *Biotechnology and Applied Biochemistry* **43**: 1-7.



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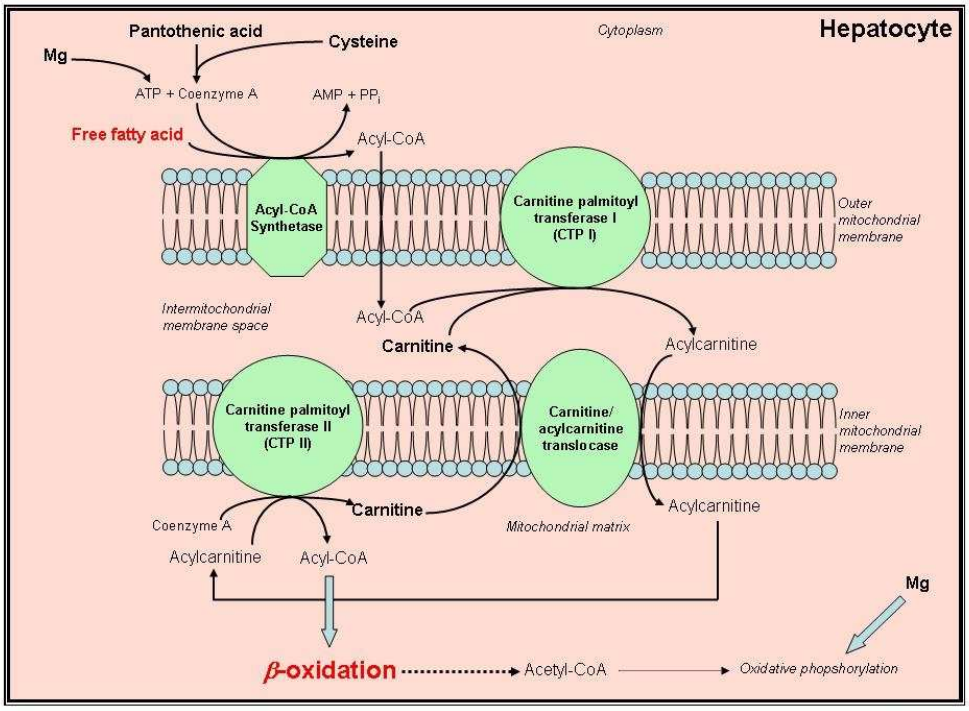

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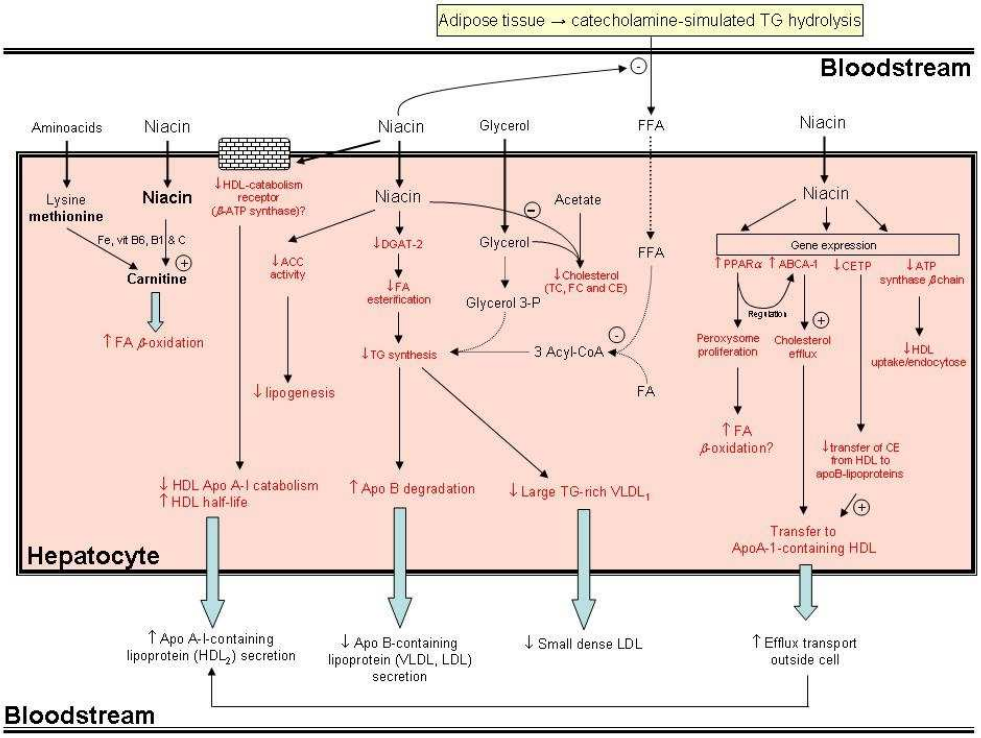

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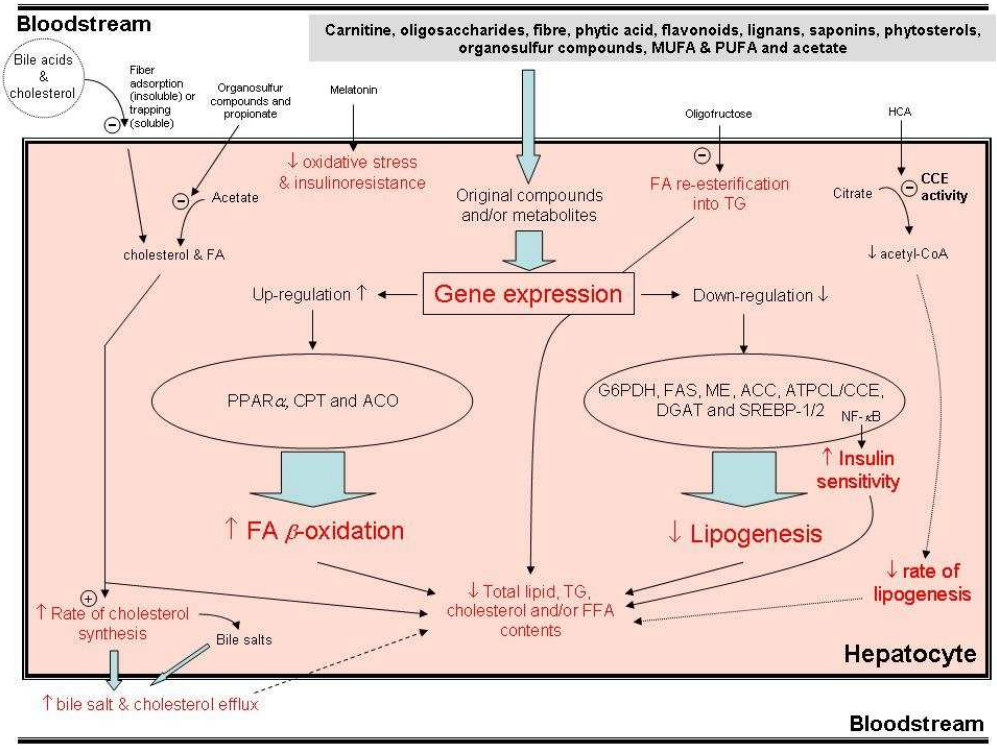

Figure 2D
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