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Anthony Fardet, Jean-Michel Chardigny

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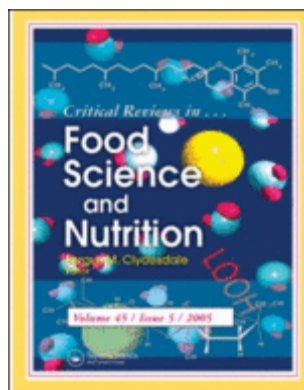
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Plant-Based Foods As a Source of Lipotropes for Human Nutrition: a Survey of In Vivo Studies

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Only

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2 1 **Plant-Based Foods As a Source of Lipotropes for Human Nutrition: a Survey of**
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5 2 ***In Vivo* Studies**
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10 4 ANTHONY FARDET, PhD,^a and JEAN-MICHEL CHARDIGNY, PhD^a
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31 13 ^aINRA, UMR 1019 Nutrition Humaine, F-63122 Saint Genès Champanelle, France ; Clermont
32
33 14 Université, UFR Médecine, UMR 1019 Nutrition Humaine, F-63000, Clermont-Ferrand, France ;
34
35 15 CRNH Auvergne, F-63000 Clermont-Ferrand, France.
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38 16
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43 18 Address correspondence to Anthony Fardet, INRA, UMR 1019 Nutrition Humaine, F-63122 Saint
44
45 19 Genès Champanelle, France ; Clermont Université, UFR Médecine, UMR 1019 Nutrition Humaine,
46
47 20 F-63000, Clermont-Ferrand, France ; CRNH Auvergne, F-63000 Clermont-Ferrand, France, Tel.
48
49 21 +33(0)4 73 62 47 04, Fax. +33(0)4 73 62 47 55. E-mail: anthony.fardet@clermont.inra.fr
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1 Abstract

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

18
19 **Keywords:** Phytochemicals, lipotrope, hepatic steatosis, humans, rats

1 *PLANT-BASED FOOD CONSUMPTION, CHRONIC DISEASE RISK AND* 2 3 4 5 2 *PHYTOCHEMICALS*

3 *Epidemiological and observational studies*

4 Increased consumption of plant-based foods (PBF), mainly whole-grain cereals, legumes,
5 vegetables and fruits, is generally associated with a lower prevalence of all-cause mortality and of
6 the major chronic diseases that are cardiovascular diseases (CVD), obesity, diabetes and cancers.
7 However, more specifically, the effects seem to vary according to the botanical origin of the PBF
8 with more or less conclusive results from prospective studies. Thus, while whole-grain cereals have
9 been convincingly shown to be protective against all main chronic diseases or disorders (Chan et
10 al., 2007; Chatenoud et al., 1998; De Munter et al., 2007; Flight and Clifton, 2006; Jacobs et al.,
11 2007; Jacobs et al., 1998; Koh-Banerjee et al., 2004; Koh-Banerjee and Rimm, 2003; Larsson et al.,
12 2005; Mellen et al., 2008; Murtaugh et al., 2007; Sahyoun et al., 2006; Schatzkin et al., 2008; Van
13 De Vijver et al., 2009; Venn and Mann, 2004; Williams et al., 2008), the effects of legumes, fruits
14 and/or vegetables are less obvious with both either no or positive effects reported that depends on
15 the variety used, the population studied, the targeted disease or the age of the subjects. For example,
16 the protective role of PBF and plant-based diets against childhood obesity has been recently
17 reviewed: it clearly appears that, except for ready-to-eat cereals, there is a lack of evidence to
18 conclude for an association between PBF and childhood obesity in relation with fruit and vegetable,
19 grain other than cereal, and legume intake (Newby, 2009).

20 To summarize, the most conclusive associations are observed with whole-grain cereals for
21 all diseases, with legumes on mortality risk (all-cause, CVD or cancers) (Nagura et al., 2009;
22 Noethlings et al., 2008), with fruits on CVD (Hung et al., 2004; Nagura et al., 2009) and weight
23 gain/obesity (Buijsse et al., 2009; He et al., 2004), with vegetables on CVD (Hung et al., 2004;
24 Nagura et al., 2009), weight gain/obesity (Buijsse et al., 2009; He et al., 2004) and type 2 diabetes
25 (Bazzano et al., 2008; Villegas et al., 2008), and with both fruits and vegetables on all-cause
26 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

1 et al., 2003; Wu et al., 2004a), (2) the stimulation/modulation of the immune function (Barr et al.,
2 1998; Mantovani et al., 2008), (3) the regulation of glucose homeostasis (*e.g.* magnesium stimulates
3 the glucose uptake by insulin) (Venn and Mann, 2004), (4) the lowering of circulating or liver
4 damaging lipid fractions (*e.g.* LDL-cholesterol) (Lee et al., 2005; Okazaki and Katayama, 2008),
5 (5) the reduction of hyperhomocysteinemia recognized as a risk factor for CVD (Graham et al.,
6 1997; Samman et al., 2002) and for carcinogenesis (Wu and Wu, 2002), (6) the anti-carcinogenicity
7 or the capacity to induce apoptosis (Azzi and Stocker, 2000; Rubis et al., 2008; Shamsuddin, 2002),
8 and/or (7) the anti-aggregability (Shechter et al., 1999) and anti-inflammatory (Liu et al., 2004;
9 Rahman et al., 2006) properties of polyphenols and other micronutrients richly contained in the bran
10 and germ fractions of cereals but also in whole-grain legumes, fruits and vegetables (Azzi and
11 Stocker, 2000; Eastwood, 1999; Fardet, 2009; Lotito and Frei, 2006; Prior, 2003; Thompson et al.,
12 2005). As demonstrated more recently, the up- or down-regulation of cell redox status *via*
13 signalling-related mechanisms, of glutathione synthesis and/or of genes involved in the
14 development of chronic diseases (Azzi and Stocker, 2000; Moskaug et al., 2005; Rahman et al.,
15 2006), notably through the action of polyphenols and/or their metabolites (Horev-Azaria et al.,
16 2009; Hsu and Yen, 2008), would also be involved. Today, one agrees to advance that several
17 phytochemicals are involved in each of these physiological mechanisms through a synergetic effect.
18 For example, the antioxidant capacity of fruits, vegetables and whole-grain cereals is attributed to
19 very different compounds such as polyphenols, vitamins E and C, selenium, phytic acid... In other
20 words, one compound may exert several protective functions and several phytochemicals may act
21 synergistically to counteract the development of one damaging physiological process as we have
22 recently reviewed it for the protective mechanisms associated with whole-grain cereal consumption
23 (Fardet, 2009).

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

1
2 1 vegetables and fruits with a modest antioxidant effect or 5 botanical families with a high reported *in*
3
4 2 *vivo* antioxidant activity (Thompson et al., 2006). Moreover, similarly to the increased oxidative
5
6 3 stress that has been shown to be involved in most of the previously cited chronic diseases (Bartsch
7
8 4 and Nair, 2006, Castelao and Gago-Dominguez, 2008; Keaney et al., 2002; Maiese et al., 2007),
9
10 5 other impaired physiological mechanisms may be common to different metabolic disorders, such as
11
12 6 increased inflammation, immuno- or glucose homeostasis dysregulation, and/or hyperlipidemia in
13
14 7 plasma or liver. However, the number of different phytochemicals contained in PBF is so high that
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16 8 the elucidation of all the mechanisms involved will be a long lasting and difficult task.
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26 11 ***PLANT-BASED FOODS AS DIETARY SOURCES OF LIPOTROPES***

27 28 29 30 31 13 ***The main lipotropes: betaine, choline, myo-inositol and methionine***

32 33 34 35 15 ***Betaine, choline, myo-inositol and methionine in plants***

36 16 Although discovered a very long time ago in plants, some of them have been rather neglected when
37
38 17 compared to studies related to health potential of minerals, trace elements, vitamins and more
39
40 18 recently polyphenols. These compounds are choline, betaine and *myo*-inositol, this latter being a
41
42 19 natural isomer of glucose that belongs to the cyclitol family (Figure 1). They have been mostly
43
44 20 studied as isolated compounds and often at non-nutritional doses. In plants, betaine has choline as
45
46 21 precursor. Betaine and choline are water soluble cytoplasmic osmolytes and thermoprotectants that
47
48 22 play a regulatory role in situation of stress for the plant, notably in water-depressed (drought), saline
49
50 23 and temperature-stressed environments (Caldas et al., 1999; Hanson and Hitz, 1982; Hanson and
51
52 24 Wyse, 1982; Hitz et al., 1982; Ladyman et al., 1980; Nolte et al., 1997; Summers and Weretilnyk,
53
54 25 1993). Among PBF, beetroot (*Beta vulgaris*), *Chenopodiaceae*- (e.g. spinach, lambsquarters and
55
56 26 whole-grain pseudocereals such as amaranth and quinoa) and *Gramineae*- (i.e. whole-grain cereals)

1 derived plants are well recognized for their high betaine content, as a result of an adaptation to
2 environmental stress (Craig, 2004; Hanson and Hitz, 1982; Hanson et al., 1985; Hanson and Wyse,
3 1982; Hitz et al., 1982; Yokoishi and Tanimoto, 1994). The database recently released by USDA
4 for betaine and choline contents confirmed these observations (USDA, 2008). Except fruits, PBF
5 are generally a good source of choline, particularly whole-grain cereals, wheat bran and germ, leafy
6 vegetables and soybean (USDA, 2008).

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

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

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

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

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

12 Betaine, choline and *myo*-inositol have been first very early shown to have the particularity
13 to exert lipotropic effect within animal liver (Best, 1934; Best and Huntsman, 1932; Best and
14 Huntsman, 1935; Gavin and Mchenry, 1941a; Owens, 1942; Perrault and Dormard, 1966; Thuillier,
15 1956) (Supplemental Table 1). Although betaine and choline were discovered during the 19th
16 century in respectively beet juice and ox bile (1862) - *chole* is bile in greek (Li and Vance, 2008),
17 the term “lipotropic” was first used only in 1935 by Best et al. who showed that choline is able to
18 prevent and cure fatty livers in rats and that increased liver fat infiltration and accumulation was
19 primarily due to deficiency in some essentials factors whose the principal role is to assure lipid
20 transport and turnover (Best, 1935). Today, one defines lipotropes as compounds that act on lipid
21 metabolism by preventing fat accumulation within the liver through hastening fat removal or by
22 preventing excessive fat deposits (*e.g.* accumulation of cholesterol).

23 The prevalence of NAFL and NASH in the general population of the United States is estimated at 20% and 3%
24 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}.

25 Excessive hepatic fat deposits indeed leads to fatty liver or steatosis, a metabolic dysregulation
26 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 transfer 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)

1
2 1 Otherwise, in humans with non-alcoholic fatty liver diseases (NAFLD), increased long-
3
4 2 chain poly-unsaturated FA (PUFA) n-6/n-3 ratio was also observed and authors concluded that such
5
6 3 “condition may favour lipid synthesis over oxidation and secretion” (Araya et al., 2004). Indeed,
7
8 4 imbalanced diets generally lead to increased PUFA n-6/n-3 ratio that reduces PPAR α activation and
9
10 5 increases SREBP-1 (sterol regulatory element binding protein) expression, both mechanisms
11
12 6 leading to respectively decreased peroxisomal/mitochondrial β -oxidation and increased ApoB-100
13
14 7 degradation (that means a reduction of TG exportation from liver *via* VLDL), and to enhanced FA
15
16 8 and TG synthesis (Araya et al., 2004). The depletion in long-chain PUFA of the n-3 and n-6 series
17
18 9 might notably result from both their increased peroxidation in situation of increased oxidative stress
19
20 10 and inadequate intake (Araya et al., 2004). In obese patients, higher hepatic mRNA levels of
21
22 11 SREBP-1c (+33%) and fatty acid synthase (FAS) (+70%), higher SREBP-1c/PPAR α ratio (+62%)
23
24 12 with a concomitant reduced level of hepatic long-chain PUFA n-3 (-53%) and insulino-resistance,
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26 13 as compared to non-obese subjects, were reported and proposed as conditions that would favour
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28 14 lipogenesis to the detriment of FA oxidation (Pettinelli et al., 2009).

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35 15 In the case of NAFL associated with insulin resistance, the increased hepatic free fatty acid
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37 16 (FFA) synthesis from glucose not uptook by peripheral adipocytes is also involved; while, in the
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39 17 case of obesity, increased amounts of FFA simply enter the liver (Patrick, 2002). In presence of
40
41 18 excess FA, the mitochondrial β -oxidation pathway thus becomes an insufficient way of degrading
42
43 19 excess fat that accumulates in TG stored within cytoplasm. Excess TG may be also secreted in
44
45 20 plasma *via* VLDL leading to hypertriglyceridemia (Pagano et al., 2002). In the end, the increased
46
47 21 level of lipid peroxidation in hepatosteatosis generates more free radicals that may lead to
48
49 22 mitochondrial DNA damages and inhibit further lipid β -oxydation (Patrick, 2002). Thus, in a rat
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51 23 nutritional model of hepatic steatosis with inflammation (following a 4-week methionine-choline-
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53 24 deficient diet) - that is morphologically similar to non-alcoholic steatohepatitis in humans -
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55 25 significant increased in hepatic microsomal CYP2E1 (cytochrome P450 2E1) content was reported,
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1 this effect generating more reactive oxygen species that may damage liver cells (Weltman et al.,
2 1996).

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

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

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

10 Fatty liver or hepatic steatosis models

11 In animals - mainly rats and mice, fatty liver is generally provoked by using lipotrope-deficient
12 diets (Lombardi et al., 1968; Olson et al., 1958a), high-fat diet (\approx 20-40%) (Borgschulte et al.,
13 2008; Olson et al., 1958a; Ryu and Cha, 2003; Singal and Eckstein, 1939), high-cholesterol diet
14 (Felmlee et al., 2009), high-fructose/glucose/sucrose diet (\approx 60%) (Hammond et al., 2003; Olson et
15 al., 1958a; Rosenfeld, 1973; Ryu and Cha, 2003; Sanchez-Lozada et al., 2010), low-PUFA diet
16 (Goheen et al., 1983; Keim and Mares-Perlman, 1984), orotic acid-supplemented diet (fatty liver
17 resulting from ApoB synthesis impairment) (Fukuwatari et al., 2002; Nagiel-Ostaszewski and Lau-
18 Cam, 1990; Vaishwanar et al., 1972) or ethanol-rich diet (Balkan et al., 2004; Barak et al., 1997;
19 Song et al., 2008). Fatty liver may be also provoked by single ethanol (Baker et al., 1973), carbone
20 tetrachloride (CCl₄) (Vaishwanar et al., 1972) or DDT (1,1,1-trichloro-2,2-bis (p-chlorophenyl)
21 ethane) (Okazaki et al., 2006) injections, *via* depleting hepatic carnitine levels by using chemicals
22 such as mildronate or THP (trimethylhydraziniumpropionate) (Degrace et al., 2007; Spaniol et al.,
23 2003) or *via* hypercaloric and fat-free parenteral nutrition (Keim and Mares-Perlman, 1984). The
24 use of specific mice strains that mimic choline-deficient diet has also been reported (Dumas et al.,
25 2006). There are still other animal models of steatosis, notably in relation with naturally occurring
26 mutations in rats (*e.g.* obese *fa/fa* Zucker rats) and mice (*db/db* mice - diabetic dyslipidemia - or

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

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

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

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

22 The lipotropic efficiency of betaine, choline and *myo*-inositol towards fatty liver has thus been
23 demonstrated since a long time by using lipotrope-deficient, high-fat/high-sucrose or ethanol-
24 enriched diets in rats as exhaustively reviewed in Supplemental Table 1 (Barak et al., 1997; Barak
25 et al., 1996a; Barak et al., 1996b; Best et al., 1950; Carroll and Williams, 1982; Chahl and Kratzing,
26


1 1966a; Gavin and Mchenry, 1940; Halliday, 1938; Hayashi et al., 1974a). The efficiency was
2 notably determined through dose-response curves, choline being 3-fold the potency of betaine and
3 methionine and betaine being more efficient than *myo*-inositol (Best et al., 1950; Young et al.,
4 1965). Microscopical observations confirmed the lower lipotropic potential of betaine compared to
5 choline (Ball, 1964). However, Andersen and Holub showed that, on a same molar basis of 5.4
6 mmol/kg of diet, choline and *myo*-inositol had the same lipotropic effect towards hepatic TG
7 accumulation in rats fed a basal diet not supplemented with choline or *myo*-inositol suggesting that
8 previously reported efficiency ratios would differ according to the experimental scheme (Andersen
9 and Holub, 1980).



10 In humans, published results were scarcer. The first results reported in a scientific journal, to
11 our knowledge, were those of Broun and Muether in 1942: authors apparently based on the results
12 of Griffith and Mulford - obtained in rats and released one year before (Griffith and Mulford,
13 1941b) - to test choline chloride for more than 2 years in humans (1 g daily) with hepatic cirrhosis
14 (Broun and Meuther, 1942). They notably observed decreases in blood bilirubin and cholesterol,
15 elimination of ascites – *i.e.* accumulation of fluid into peritoneal cavity that may be TG-rich - and
16 decreased liver size (Broun and Meuther, 1942). Three years latter, Barclay and Cooke reported the
17 case of a 27 years-old man who had developed severe liver dysfunction (and renal failure) after
18 receiving large doses of barbiturates for anxiety state; and who was treated both orally (2-5 g for
19 one day) and intravenously (6-8 g) with high doses of choline chloride, then methionine (6 g) and
20 choline chloride during more than one month: recovery of the patient was noted despite important
21 side-effects related to the choline treatment (*i.e.* fall in red cells - anemia, severe sweating,
22 bronchial secretion and painful abdominal cramps,...), probably due to the high doses used (Barclay
23 and Cooke, 1945). In 1946-1948, improvement of liver functions, notably ascite clearance and
24 decreased liver size, were reported in patient with cirrhosis of the liver with ascites and that were
25 administered a low fat, high-protein/carbohydrate diet supplemented with choline (1 g daily)
26 (Broun, 1948) or a combination of choline and cystine (1-3 g daily each) (Beams, 1946). In the

1
2 1 latter study, hepatic fatty changes were suspected based on the agreement that such treatment is
3
4 2 more effective “when there are fatty changes in the liver” and when there is an enlarged liver rather
5
6 3 than when livers are small and probably contracted by fibrous tissue: a lipotropic action of choline
7
8 4 and cystine was therefore proposed (Beams, 1946). Prolonged hepatic fatty infiltration was indeed
9
10 5 emphasized in the development of cirrhosis associated with diabetes and chronic alcoholism
11
12 6 (Russakoff and Blumberg, 1944). Latter, the positive effects of a lipotropic therapy were reported in
13
14 7 humans exhibiting various hepatic dysfunctions and/or atherosclerosis (Colson and Gally, 1964;
15
16 8 Nadeau et al., 1954; Navarranne et al., 1964; Warembourg and Bertrand, 1964). Thus, in 1954,
17
18 9 Nadeau et al. suggested that fatty liver in alcoholic patients may result from a dietary carence that
19
20 10 has lead to choline deficiency, and they observed that the administration of lipotrope tablets lead to
21
22 11 rapid improvement of hepatic function - by decreasing values of the bromosulphalein test, this latter
23
24 12 being notably shown in dogs to be tightly related to hepatic fatty overload (Hough et al., 1943;
25
26 13 Popper and Schaffner, 1952) - and might be a significant supplement to an adequate diet (Nadeau et
27
28 14 al., 1954). In 1964, several authors reported improvements of hepatic function and atherosclerotic
29
30 15 markers in humans with hepatic and/or cardiovascular dysfunctions following admisnitration of
31
32 16 Ornitain[®] (10.045 formula, Jacques Logeais laboratory, Issy-Les-Moulineaux), a cocktail
33
34 17 containing ornithine chlorhydrate and other associated substances such as pyridoxine chlorhydrate,
35
36 18 sorbitol and 2 lipotropes that are betaine and magnesium citrate (Navarranne et al., 1964;
37
38 19 Warembourg and Bertrand, 1964). In 1991, Zeisel et al. reported that choline-deficient subjects
39
40 20 developed upon 3 weeks symptoms of incipient liver dysfunction, notably an increased in serum
41
42 21 alanin aminotransferase (ALT) and a decrease in plasma phosphatidylcholine (Zeisel et al., 1991).
43
44 22 More recently, it was shown (*via* the use of computed tomography, a non-invasive method for
45
46 23 estimating hepatic fat content) in patients receiving parenteral nutrition that dietary choline
47
48 24 deficiency lead to the development of hepatosteatosis, as it was reported in animal models
49
50 25 (Buchman et al., 2001; Zeisel et al., 1991). However, it was also shown that plasma level of free
51
52 26 choline and PL-bound choline were not different between patients with and without severe liver
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1 fibrosis, and was not correlated with the degree of fat infiltration within liver (Nehra et al., 2001).
2 More recently, men (40% of the 20 tested) and postmenopausal women (80% of the 15 tested)
3 deprived of dietary choline have been reported to develop hepatic steatosis, the most common sign
4 of choline deficiency (Fischer et al., 2007).

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

14 Methionine has been also early recognized as a lipotrope compound (Best and Ridout, 1940;
15 Caballero et al., 2008; Chahl and Kratzing, 1966b; Shils and Stewart, 1954; Tucker and Eckstein,
16 1937) and would directly account for the lipotropic effect of proteins (Eckstein, 1952). The
17 lipotropic effect of methionine was demonstrated to be notably based on methyl supply for choline
18 synthesis (see Figure 2A) (Du Vigneaud et al., 1940; Du Vigneaud et al., 1941). This was latter
19 confirmed that methionine does not directly act upon lipid metabolism but as a precursor of choline
20 through methyl donation to phosphatidylethanolamine (Figure 2A) (Labadie, 1974). Its lipotropic
21 potency would be weaker than that of choline at equivalent quantities (Chahl and Kratzing, 1966b),
22 up to 3-fold lower as shown in weanling rats (Griffith and Mulford, 1941a). Methionine is also the
23 product of homocysteine methylation by betaine (Figure 2A). Although partial deficiencies of some
24 amino-acid (*e.g.* threonine) may lead to fat accumulation into rat liver (Harper et al., 1954a) and
25 although protein play a role in controlling liver fat content (Channon and Wilkinson, 1935), only
26 methionine among the essential amino-acids appears to exert a direct lipotropic effect (Eckstein,

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

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

7
8 *Detailed physiological mechanisms associated with the lipotropic effect of betaine, choline,*
9 *methionine and myo-inositol*

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

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

1
2 1 Thus, choline participates in and accelerates the synthesis of fat into PL from
3
4 2 phosphatidylethanolamine - notably of lecithin type like phosphatidylcholine (Figure 2A) (Mchenry
5
6 3 and Patterson, 1944; Mookerjea, 1971; Nadeau et al., 1954; Tokmakjian and Haines, 1979), this
7
8 4 latter being indispensable to export fat outside hepatocytes and methionine indirectly contribute to
9
10 5 fat exportation from liver by allowing formation of choline. Accordingly, phosphatidylcholine has
11
12 6 been shown to limit excess TG in cultured rat hepatocytes by favouring their exportation *via*
13
14 7 lipoproteins (Yao and Vance, 1988, 1989). As choline, betaine was early shown to accelerate PL
15
16 8 turnover but the effect would be less than choline in doses up to 50 mg per rat and the increase not
17
18 9 directly proportional to doses ingested (Perlman and Chaikoff, 1939).

19
20
21 10 In culture hepatocytes from rats fed a choline-deficient diet, Yao and Vance unravelled
22
23 11 important mechanisms that are involved in the lipotropic effect of choline, betaine and methionine,
24
25 12 *i.e.*: normal hepatic secretion of VLDL (a TG-rich lipoprotein) requires phosphatidylcholine
26
27 13 synthesis - *i.e.* a choline head group moiety -, choline and methionine stimulate the synthesis of
28
29 14 phosphatidylcholine, choline favours TG excretion from hepatocytes and betaine may correct
30
31 15 VLDL secretion inhibition initiated by choline deficiency (Yao and Vance, 1988, 1989).
32
33 16 Accordingly, the impairment of lipoprotein and TG secretions from liver, the subsequent increase in
34
35 17 hepatic TG synthesis - *i.e.* increased activity of FAS (Rosenfeld, 1973) - and the decreased plasma
36
37 18 PL levels (lecithins and sphingomyelins) of chylomicrons, VLDL and LDL have been reported in
38
39 19 rats deprived of choline (Lombardi et al., 1968; Mookerjea, 1971; Mookerjea et al., 1975; Olson et
40
41 20 al., 1958a), TG being characterized by increased palmitic acid (16:0) content (Rosenfeld, 1973) -
42
43 21 this latter being the first FA produced during lipogenesis and from which longer FA are generated.
44
45 22 In the absence of adequate phosphatidylcholine, cholesterol and TG are likely to move towards
46
47 23 cytosol, leading to fatty liver as shown in choline-deficient rats (Da Costa et al., 1995). Latter, in
48
49 24 choline-deficient rats, Yao and Vance observed hepatic TG accumulation, plasmatic TG and VLDL
50
51 25 reduction, decrease in phosphatidylcholine and TG content of VLDL but no change in plasmatic
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1 HDL level (Yao and Vance, 1990). Choline may also prevent from an increased phospholipases A₂
2 and C activity, the enzymes that releases FFA from membrane PL (Singh et al., 1990).

3 To go further, KO mice for the hepatic enzyme that allow transformation of
4 phosphatidylethanolamine into phosphatidylcholine (*i.e.* phosphatidylethanolamine *N*-
5 methyltransferase: *Pemt*^{-/-} mice) and/or for the hepatic enzyme that allow phosphatidylcholine to be
6 secreted within bile (*i.e.* phosphatidylcholine-specific flippase, multiple drug-resistant protein 2:
7 *Mdr2*^{-/-}/*Pemt*^{-/-} mice) were produced by breeding (Li et al., 2005). It was clearly shown that choline-
8 deficient *Pemt*^{-/-} mice died within 5 days after an hepatic phosphatidyl depletion of 50% but that
9 choline-deficient *Mdr2*^{-/-}/*Pemt*^{-/-} mice survived until more than 90 days with the same 50%
10 phosphatidylcholine depletion, effect being attributed to an important adaptation of the
11 phosphatidylcholine homeostasis that is activation of various hepatic choline recycling pathway
12 (*e.g.* up regulation of phospholipase A₂, choline kinase and phosphocholine cytidyltransferase
13 activities and decreased expression of choline oxidase) and the lack of phosphatidylcholine
14 depletion *via* biliary secretion (Li et al., 2005).

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

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

3 In the end, another unexpected cellular mechanism might be involved in the lipotropic effect
4 of betaine, choline and *myo*-inositol. Indeed, as small hydrosoluble molecules that do not interfere
5 with cellular protein functions - even at high concentrations -, betaine, choline and *myo*-inositol are
6 all osmolytes and may participate in cell volume regulation, the level of cellular hydration affecting
7 cellular metabolism *via* gene expression modifications (Häussinger, 1996). Thus, increased cell
8 swelling in rat hepatocytes was shown to increase lipogenesis and to activate ACC (Baquet et al.,
9 1991; Hue, 1994), this enzyme allowing formation of the metabolic intermediate malonyl-CoA that
10 plays a major role in FA synthesis. In the same way, hypo-osmotic incubation of hepatocytes - *i.e.*
11 that increases their volume - was shown to inhibit CPT-1 (carnitine palmitoyltransferase-1) (allows
12 lipid transfer within mitochondria) whose deficit lead to defective FA oxidation (Figure 2B)
13 (Guzmán et al., 1994). Conversely, transfert of osmolytes into cell will lead to cell shrinkage and
14 inverse effects (Häussinger, 1996). We may therefore hypothesized that increased cellular content
15 of betaine, choline and *myo*-inositol might contribute to cell shrinkage with possible potential
16 positive effects upon lipid metabolism and fat liver content (Figure 2A).

18 *Lipotropes or methyl donors?*

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

1 also characterized by DNA hypomethylation in mammary tissues that was associated with the
2 highest number of tumors (Moon et al., 1998). More generally, a decrease in the amount of methyl
3 groups within organism would favour an increased sensibility towards cancers by altering immune
4 function and xenobiotic (*e.g.* carcinogens) metabolism (Nauss et al., 1982; Newberne and Rogers,
5 1986).

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

14 *Are proteins lipotropic?*

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

16 The lipotropic effect of proteins has been very early discussed and reviewed (McHenry and
17 Patterson, 1944). In 1935, it has been notably suggested that hepatic fat deposits was influenced by
18 and linked to protein metabolism (Best and Huntsman, 1935). Thus, the same year, it was shown
19 that increasing the protein content (caseinogen, from 0 to 50%) of a high-fat diet (40%) containing
20 17.5 mg choline/100 g at the expense of carbohydrates (glucose hydrate, from 50 to 0%)
21 counteracted the development of fatty liver in rats, and the effect was apparently dose-dependent
22 (Channon and Wilkinson, 1935). In the same study, authors also showed that the quality of liver
23 lipids was altered upon high-protein diet with phosphatide and free cholesterol percentage
24 increasing while TG percentage decreasing; and they finally suggested that some aminoacids of
25 caseinogen may be converted within choline and betaine (Channon and Wilkinson, 1935). Their
26 results were further criticized by Best et al. that found higher liver fat percentages in rats within

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

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

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

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

1 27% after 6 weeks (Osumi et al., 1969). The lipotropic action of proteins was further underlined in
2 rats and woodchucks for which the effect of lipotropic factors (choline, methionine, folic acid and
3 vitamin B12) varied according to the amount of soy protein isolate in the diet (*i.e.* 10 vs 20%)
4 Study by Iritani et al. (1986): lipotropic effect of gluten and soybean protein vs casein and fish protein towards TG content in liver
5 (Boyd et al., 1986). Lipotropic effect of proteins has also been emphasized in rats fed a high-fat plus
6 cholesterol vs high-fat and fish proteins plus cholesterol diet, results showing a significantly lower
7 level of hepatic total cholesterol and TG with the fish protein-containing diet (Hosomi et al., 2009).
8 Both an increased expression of hepatic CYP7A1 (cholesterol 7 α -hydroxylase) - *via* activation of
9 the transcription factor liver receptor homologue-1 - and an inhibition of cholesterol and bile acid
10 absorption within small intestine are notably involved (Hosomi et al., 2009). Similarly, compared to
11 casein, rats fed pork protein had lower hepatic levels of TG (-46%) *via* decreased mRNA SREBP-
12 1c (sterol regulatory element binding protein) and G6PDH concentrations, *i.e.* *via* a reduced FA
13 synthesis (Brandsch et al., 2006). In rats receiving cholesterol intravenously and intragastrically,
14 soy protein compared to casein was shown to be antihypercholesterolemic *via* stimulation of hepatic
15 cholesterol synthesis in response to increased faecal steroid excretion (Nagata et al., 1982). Such an
16 effect may be attributable to the lower digestibility of soybean protein compared to casein,
17 hydrophobic peptides of soybean protein binding bile acids and consequently stimulating hepatic
18 cholesterol turnover (Iwami et al., 1986). Moreover, it was shown in rats that highly purified
19 soybean proteins affect enzymes involved in cholesterol metabolism (Madani et al., 1998).
20 Compared to casein, rice and soy proteins were also shown to exert lipotropic effect in both
21 growing and adults rats fed or not with high-cholesterol diet, protective mechanisms involving a
22 reduced secretion of hepatic cholesterol into circulation, an increased excretion of biliary bile acids
23 and reduced hepatic TG accumulation (Yang and Kadowaki, 2009; Yang et al., 2007). Compared to
24 casein, soybean proteins were also shown to significantly reduce cholesterol, TG and ApoA-1
25 (apolipoprotein A-1) secretion from isolated rat liver, and cholesterol and TG contents in liver;
26 difference in secretion being not observed with corresponding equivalent amino acid mixtures
(Sugano et al., 1982).


1
2 1 Lipotropic effect of proteins seems therefore to depend on protein origin - and probably also
3
4 2 methionine content. Thus, in rats fed 25% either casein or proteins from lactalbumin, whole egg,
5
6 3 egg albumin, sardine, soybean and wheat gluten, its has been shown significant variations in hepatic
7
8 4 cholesterol, TG and PL concentrations, wheat gluten proteins leading to the highest lipid
9
10 5 accumulation while soybean proteins leading to the lowest TG accumulation (Sugiyama et al.,
11
12 6 1996). In addition, authors reported that lactalbumine and whole egg proteins lead to the highest
13
14 7 methionine concentration in rat liver, that casein lead to around 10% more phosphatidylcholine
15
16 8 relative to total PL than soybean proteins, and that methionine content of dietary proteins was
17
18 9 correlated with the liver microsomal phosphatidylcholine/phosphatidylethanolamine ratio
19
20 10 (Sugiyama et al., 1996).

21
22 11 In humans, the lipotropic effect of proteins was apparently very little studied. A report was
23
24 12 made with a mildly hypercholesterolemic and healthy middle-aged alcoholic woman upon either a
25
26 13 normal diet containing 100 g protein or a low-protein diet of 25 g: liver biopsies did not reveal any
27
28 14 fatty material accumulation upon the low-protein diet but it was observed in serum important
29
30 15 decreases in lipid (cholesterol, PL and TG) and lipoprotein concentrations suggesting impairment of
31
32 16 lipid metabolism within liver, notably for cholesterol (Olson et al., 1958b). Then the administration
33
34 17 of a supplement of lipotropic factors (choline, methionine, inositol, vitamin B12 and liver
35
36 18 concentrate) restaured serum cholesterol to its normal level (Olson et al., 1958b). The lipotropic
37
38 19 effect of proteins has been recently confirmed in healthy humans fed a high-fat vs a high-fat and
39
40 20 high-animal protein diet by measuring the intrahepatocellular lipids by ¹H-magnetic resonance
41
42 21 spectroscopy: a blunting effect of proteins upon liver lipids ($\approx -22\%$) was observed (Bortolotti et al.,
43
44 22 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.

23 24 25 *The lipotropic effect of inositol isomers and phytate*

1 Besides *myo*-inositol, inositol possess 8 other isomers, notably *chiro*- and *scyllo*-inositol that are
2 also present in PBF, but at a largely lower levels than *myo*-inositol (Kim et al., 2005; Sanz et al.,
3 2004). However, to our knowledge, only *myo*-inositol was shown to have lipotropic properties
4 (Andersen and Holub, 1980; Beach and Flick, 1982; Okazaki et al., 2006; Yagi and Kotaki, 1969).
5 Conversely, *chiro*-inositol consumption has been reported to increase fat deposits in rat liver
6 (Okazaki et al., 2006). Actually, *chiro*-inositol is recognized for its ability to improve insulin
7 regulation and is used in diabetes management (Kim et al., 2005).

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

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

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

11 Yet, phytate was shown very early to be degraded in humans based on a 20-60% recovery of
12 ingested phytin (calcium-magnesium salt of phytate) in faeces (McCance and Widdowson, 1935). A
13 60% degradation of wheat bran phytate into *myo*-inositol penta-, tetra- and triphosphates has also
14 been reported in ileostomates (Sandberg et al., 1987). Although mucosal phytases and alkaline
15 phosphatases are present in humans (Bitar and Reinhold, 1972), the degradation of phytate appears
16 to be mainly due to dietary phytases of plant and/or microbial origins that could be activated at the
17 low pH encountered in the stomach (as *e.g.* for cereal phytases), as shown in healthy ileostomates
18 with phytase-deactivated wheat bran (Sandberg and Andersson, 1988), but also due to endogenous
19 microbial phytases within the colon (Sandberg and Andlid, 2002). Another *in vitro* study lead
20 within 3 cell lines (*i.e.* mouse T cell leukemia, human erythroleukemia and human colon
21 adenocarcinoma) showed that phytic acid may be uptook as such and/or partly dephosphorylated
22 (Vucenik and Shamsuddin, 1994). However, no human studies have reported increased hepatic free
23 *myo*-inositol content or improved liver FA metabolism following high-phytate consumption. Up
24 today, results are therefore not sufficiently convincing to consider *myo*-inositol phosphates as a
25 source of lipotropes in humans; and the extrapolation of the lipotropic effect of *myo*-inositol
26 phosphates from rats to human remains highly uncertain or prematured.

3 *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}

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

16 As choline, betaine and *myo*-inositol, the lipotropic effect of carnitine can be also simply
 17 unravelled in carnitine-deficient rats that notably develop an important increase in hepatic TG
 18 content (> +250%) and a significant decrease in PL content (-22 and -36%; Supplemental Table 2)
 19 (Degrace et al., 2007). However, at equimolar amounts, lipotropic effect of carnitine was
 20 demonstrated to be significantly lower in rat than that of choline (Hu, 1975; Khairallah and Wolf,
 21 1965). In addition, in rats fed a 20%-protein and choline deficient diet, carnitine surprisingly did not
 22 allow preventing fatty liver whereas choline did, probably since methyl group of carnitine is not
 23 labile and cannot be transferred to form methionine from homocysteine (Fritz and Dupont, 1957).
 24 Such apparent contradictory results have probably to be attributed to experimental conditions,
 25 notably diet composition.

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

8 Body carnitine results from both synthesis from dietary lysine and methionine contents
9 (Figure 2C) and from natural carnitine found in low amount in PBF such as avocado, *tempeh*
10 (fermented soya), some nuts, seeds, legumes, vegetables, fruits et cereals (*e.g.* pumpkin, sunflower,
11 sesame, cabbage, common bean, apricots and banana). Compared to animal tissues, the carnitine
12 and acylcarnitine (2% of the total carnitine pool) contents in plant tissues is around a hundred and
13 thousand times lower (Bourdin et al., 2007) and best sources are of animal origin such as red meat
14 and, to a lesser extent, milk products (Seline and Johein, 2007). Values of respectively 0.32, 0.51
15 and 0.27 mg/100 g dry weight (dw) have been reported for rapessed, flax and tobacco (Bourdin et
16 al., 2007), values that are closer to ranges found for B vitamins in PBF than those found for betaine,
17 choline, *myo*-inositol and methionine. More generally, Seline and Johein determined total carnitine
18 contents of 74 food products and obtained the following ranges on a fresh weight-basis: 3.2 (breast
19 pheasant) – 166.0 (kangaroo steak) mg/100 g for 20 animal products, 0.64 (Babybel®) - 14.9
20 (Norwegian goat cheese) mg/100 g for 20 cheeses, 2.2 (yogurt) - 42.8 (condensed milk) mg/100 g
21 for 17 liquid dairy products, and 0.014 (orange) - 4.98 (oyster mushroom) mg/100 g for 13 plant-
22 based foods (Seline and Johein, 2007), thus confirming conclusions of Bourdin et al. when
23 comparing animal- and plant-based foods (Bourdin et al., 2007). Among PBF, mushrooms (1.32,
24 2.62 and 4.98 mg/100 g for respectively chanterelle, mushroom and oyster mushroom) appears as
25 the best source of carnitine both on a 100 g fresh food- and dry weight-basis followed by avocado

1 (0.43 mg/100 g), carrot (0.40 mg/100 g), cauliflower (0.36 mg/100 g), cucumber (0.19 mg/100 g),
2 banana (0.10 mg/100 g) and apple (0.05 mg/100 g) (Seline and Johein, 2007)

3 4 5 ***The contribution of magnesium and vitamins B to the overall lipotropic effect***

6 7 ***Magnesium and B vitamins***

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


23 Lipotrope effect has also been reported for vitamin B12 (cobalamine) either alone (Drill,
24 1954; Quan and Le Breton, 1973; St. Greif and Wenning, 1954; Shils and Stewart, 1954) or in
25 combination with choline and folates (Laird and Drill, 1971), this B vitamin being only present in
26 animal-based food (ABF) products, and to a lesser extent in some fermented cereals (*e.g.* beer)

1 where it is supplied by yeast. It is notably involved within the process of transmethylation that
2 corresponds to the transfert of a methyl group from 5-methyl tetrahydrofolates to homocysteine
3 allowing methionine formation in a way similar to the action of betaine with homocysteine (Figure
4 2A) (Gillis and Norris, 1951; Jaenicke and Rudiger, 1971; Newberne and Rogers, 1986).
5 Accordingly, carcinogenic lipotrope-deficient or methyl donor-deficient diets generally include
6 vitamin B12 deficiency (Christman et al., 1993; Moon et al., 1998; Newberne et al., 1971; Rogers
7 and Newberne, 1969; Wu et al., 1998).

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

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

13 Folates (vitamin B9)

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

1 it appears to be effective only when adequate amounts of other lipotropes, notably choline, are
2 initially present in the diet (Laird et al., 1965). This supportive lipotropic effect of folates is
3 concomitant with their ability to reduce hyperhomocysteinemia (Brouwer et al., 1999; Moat et al.,
4 2003), a CVD risk factor.

6 Niacin (vitamin B3)

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

1 and hypothesized that nicotinic acid may have depress the mobilization of non-esterified FA from
2 adipose tissue that was induced by ethanol (Baker et al., 1973). Nicotinic acid was also shown to
3 importantly reduce different lipid fractions (total lipids, cholesterol, lipid phosphorus and TG) in rat
4 fatty livers induced with CCl₄ and orotic acid: competitiveness with CoA synthesis (involved in
5 lipogenesis) and a possible inhibition of fat depot mobilization and TG/FFA availability for lipid
6 synthesis have been hypothesized in this study (Vaishwanar et al., 1972). And in laying hens
7 supplemented with niacin, 50 mg niacin/kg reduced fat infiltration in liver by around 29%, but
8 effect was not significant due to a high variability in data (Hartfiel and Kirchner, 1973). Conversely,
9 excess fat deposits in high-fat- or normal-diet-fed rats supplemented with niacin at a high level of
10 0.1% have been observed despite the presence of choline (Baker et al., 1977; Rikans et al., 1965). In
11 the study of Baker et al., the 0.1% niacin-supplementation of rats fed a choline-deficient diet lead to
12 -40, +94, -14, +116 and +33% changes in respectively hepatic PL, TG, free cholesterol, cholesterol
13 esters and non-esterified FA contents but effects were not significant (Baker et al., 1977). Adding
14 0.5% choline dihydrogen citrate to the 0.1% nicotinic acid lead to reduction for all lipid classes,
15 effect becoming significant for TG (-26%) and cholesterol ester (-7%) contents, but surprisingly
16 also for PL content (-52%), also indicating “that niacin interferes with choline-induced lipotropism”
17 (Baker et al., 1977). Although 0.1% niacin-supplementation was not nutritionally realistic, Baker et
18 al. interestingly showed by using the *in vitro* models *Escherichia coli* (requiring vitamin B12 or
19 methionine) and thermophilic yeast *Torulopsis pintolopessi* (requiring choline or methionine) that
20 the potentiated hepatic steatosis induced by high doses of nicotinic acid (Sorrell et al., 1976) -
21 although plasma TG level is generally decreased - may be ascribed to its interference in the
22 transmethylation process by preventing methionine to provide methyl groups for choline synthesis
23 and by blocking vitamin B12 from acting as a co-factor in the methylation of homocysteine in
24 methionine (Baker et al., 1977; Rikans et al., 1964). Accordingly, it had been previously
25 hypothesized that the antilipotropic effect of nicotinic acid at high doses (from 1 to 4%) might be
26 due to the important need in methyl groups of its detoxification products (Schön, 1958) - notably

1
2 1 nicotinamide that requires more methyl groups for excretion than nicotinic acid (Miller et al., 1960),
3
4 2 excess niacin being methylated in the liver to *N*-methyl-nicotinamide then excreted in urine
5
6 3 (Institute of Medicine, 1998); which lead to assimilate nicotinic acid to a “methyl trap that drains
7
8 4 off methyl groups from choline and/or methionine synthesis leading to a functional choline
9
10 5 deficiency” and leading to impaired secretion of lipids from the liver (Baker et al., 1977; Cantoni,
11
12 6 1951, Handler, 1944; Perlzweig et al., 1943). Indeed, addition of choline generally reverses the fatty
13
14 7 liver induced by excess niacin (Baker et al., 1977; Rikans et al., 1965).
15
16
17

18
19 8 More specifically, concerning liver cholesterol, nicotinic acid has been shown by different
20
21 9 authors to significantly reduce its content and its rate of biosynthesis (Merrill and Lemley-Stone,
22
23 10 1957; Perry, 1960; Schade and Saltman, 1959; Schön, 1958), an effect attributed to a lack of acetyl-
24
25 11 CoA needed for cholesterol synthesis, CoA competing with detoxication systems - notably towards
26
27 12 nicotinuric acid at high doses of nicotinic acid - and lipid synthesis (Schade and Saltman, 1959).
28
29 13 Other advanced that nicotinic acid would divert cholesterol precursors towards oxidation rather than
30
31 14 in the cholesterol synthesis pathway, as for FA formation (Perry, 1960). In another study, different
32
33 15 rate of acetate incorporation into cholesterol synthesis were obtained with rat liver slices incubated
34
35 16 in 2-¹⁴C sodium acetate according to the mode of administration of nicotinic acid, either chronically
36
37 17 injected in rats during 21 days before killing at a level of 20 mg/kg b.w. or directly added to
38
39 18 incubation medium of liver slices at a concentration of 10⁻³ M (Orbetsova et al., 1976). In the
40
41 19 former case no changes were observed while a stimulation of acetate incorporation was reported in
42
43 20 the latter case. Authors suggested that chronic administration of nicotinic acid vs direct incubation
44
45 21 or single injection would not influence cholesterol synthesis at the same level of the metabolic chain
46
47 22 (Orbetsova et al., 1976). Accordingly, they observed in rats injected with nicotinic acid (250 mg/kg
48
49 23 b.w.) a decreased hepatic cholesterol and TG content after 6 hours with increase after 3 hours
50
51 24 (Orbetsova, 1977). In humans, nicotinic acid administration - from 1 to 2 g 3 times daily - lead to
52
53 25 lowered serum cholesterol levels (Miller et al., 1960; Parsons, 1961b), such reduction being likely
54
55 26 to partly result from marked reduction in hepatic cholesterol synthesis (Parsons, 1961b). Thus, from
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1 these studies, it seems that nicotinic acid induces fatty liver only at high doses and in absence of one
2 or more other lipotropes with variations according to animal species and modes of administration,
3 *i.e.* single injection *vs* chronic administration. That would partly explain apparent contradictory
4 results between studies.

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

1 Recent studies allowed unravelling new mechanisms that may contribute to the overall
2 positive effect of niacin on hepatic lipid metabolism (Figure 2C). Thus, results obtained with
3 HepG2 cells showed that niacin may: 1°) inhibit TG production and FA synthesis combined with
4 accelerated ApoB (a TG-rich lipoprotein) degradation (Jin et al., 1999; Jin et al., 1996; Kashyap et
5 al., 1997; Van Der Hoorn et al., 2008); 2°) increase efflux of HDL ApoA-1 (Jin et al., 1997); 3°)
6 reduce intracellular cholesterol (total, free and esters); 4°) induce expression of PPAR α mRNA
7 (PPAR α regulates FA oxidation and stimulates peroxysome proliferation) (Siripurkpong and Na-
8 Bangehang, 2009); 5°) up-regulate ABCA1 (ATP-Binding Cassette Transporter 1) mRNA
9 expression (Siripurkpong and Na-Bangehang, 2009) - ABCA1 effluxes excess cellular cholesterol
10 to ApoA-1 to form nascent HDL; 6°) reduce expression of CETP (Cholesteryl Ester Transfer
11 Protein) mRNA (Van Der Hoorn et al., 2008) - CETP mediates the transfer of cholesteryl esters
12 from HDL to pro-atherogenic apoB-lipoproteins; 7°) inhibit hepatocyte DGAT (diacylglycerol
13 acyltransferase), the key enzyme for the synthesis of triglycerides, finally resulting in a potential
14 reduction of hepatic atherogenic lipoprotein secretion (Ganji et al., 2002); and 8°) inhibit surface
15 expression of ATP synthase β chain - this latter mediating hepatic HDL endocytose (Martinez et al.,
16 2003); and consequently 9°) reduce HDL uptake by HepG2 cell (Zhang et al., 2008).

17 In the fifties, Niacin was otherwise reported to be hypolipidemic in humans, notably
18 hypocholesterolemic (Altschul et al., 1955, Parsons and Flinn, 1959), and is today widely used
19 clinically as a drug at high doses (generally 3-6 g daily) in the treatment of lipid disorders such as
20 hyperlipidemia (Figge et al., 1988; Grundy et al., 1981) by notably reducing plasma TG and
21 cholesterol levels and raising plasma HDL cholesterol level (Chapman et al., 2010; Shepherd et al.,
22 1979). The effect of nicotinic acid was also tested in healthy women at the high dose of 2 g/day and
23 was shown to decrease both acutely and chronically VLDL-TG production rate from liver (Wang et
24 al., 2001). A similar reduction was observed with hyperlipidemic patients given 1 g three time daily
25 of niacin (Grundy et al., 1981). However, within clinical therapy context, such high-dose of niacin
26 (around 1-3 g daily) may be hepatotoxic - and also lead to various undesirable, but generally

1 reversible, side-effects like blushing/flushing, itching, gastrointestinal irritation,... -, notably with
2 slow/sustained-release niacin as compared to immediate-release niacin (Dalton and Berry, 1992;
3 Etchason et al., 1991; Lawrence, 1993; Pardue, 1961; Rader et al., 1992; Reimund and Ramos,
4 1994; Schwenk and Fisher, 1994; Stern, 2007); but the co-administration of betaine (McCarty, 2000)
5 or methionine (Aronov et al., 1999) decreased hepatotoxic risk. Others reported the beneficial use
6 of *myo*-inositol hexanicotinate instead of niacin alone, *myo*-inositol hexanicotinate being free from
7 side effects (Welsh and Ede, 1961); and Baggenstos et al. (1967), *via* liver biopsies in
8 hypercholesterolemic humans chronically administered 1.5 to 6 g nicotinic acid, observed minor
9 histological alterations that were also reported in healthy patients, and concluded that the use of
10 nicotinic acid is not contraindicated in carefully supervised patients. Similarly, after one year of
11 nicotinic acid therapy in 17 patients, no significant hepatic alteration was found *via* the use of
12 several liver tests, and needle biopsies did not show any fatty changes or abnormalities (Parsons and
13 Flinn, 1959) although significant alterations in hepatic function tests were reported in another
14 studies 2 years later in 10 hypercholesterolemic patients among 36 (Parsons, 1961a). Recently,
15 lower doses of niacin up to 50.1 mg daily have been tested in healthy volunteers and it has been
16 observed that a 16.7 mg-dose niacin does not cause flushing symptoms, that are sporadic at a 50.1
17 mg-dose (Schweikart et al., 2009). In addition, no change occurs concerning blood pressure, pulse
18 and skin temperature (Schweikart et al., 2009). In addition, niacin may reduce the release of FFA in
19 plasma through inhibition of catecholamine stimulation of TG lipolysis in adipose tissue (Arner,
20 1999), as notably shown *in vitro* (Carlson, 1963), leading to reduction of hepatic VLDL-TG
21 production (Chapman et al., 2010; Figge et al., 1988) and resulting in decreased plasma VLDL-TG
22 concentrations (Grundy et al., 1981). This may occur *via* either a reduced transport of FFA to the
23 liver or a direct inhibition of hepatic secretion/synthesis of ApoB-containing lipoproteins (Tato et
24 al., 1998). Others have shown in nondiabetic patients that the administration of 2 g daily of
25 nicotinic acid during 2 weeks reduces cholesterol synthesis by around 50% (Nunn et al., 1961). And
26 a study in hyperlipidemic subjects that were administered 1 to 2 g daily nicotinic acid has lead to

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

3 Compared to other lipotropes, physiological mechanisms involved in the lipotropic effect of
4 niacin therefore appear multifactorial as we have tentatively summarized and illustrated it in Figure
5 2C based on references cited previously and on those from Supplemental Table 1.

6 Pantothenic acid (vitamin B5)

7 As for niacin, apparent contradictory results have been also reported for pantothenic acid (Carter
8 and Hockaday, 1962; Griffith and Mulford, 1941b; Morgan and Lewis, 1953; Schaefer et al., 1942).
9 First, it was found that feeding rats with a B vitamin- (including thiamine, riboflavin, pantothenic
10 acid and pyridoxine) or a pantothenic acid-deficient diet prevented the development of fatty liver
11 (Engel, 1942; Morgan and Lewis, 1953), notably an increased cholesterol content in high-
12 cholesterol fed rats (Guehring et al., 1952), pantothenic acid being indirectly involved in the
13 transformation of acetate into cholesterol (Bloch and Rittenberg, 1942) *via* acetyl-CoA action and
14 being constitutive of the coenzyme. A 2-fold decreased food intake has been notably proposed as an
15 explanation for the observed reduced liver fat content of pantothenic acid-deficient rats
16 (Guggenheim and Olson, 1952). Others suggested that adrenal hormone production is reduced and
17 fat metabolism seriously impaired in pantothenic acid-deficient rats, adrenal hormone being
18 synthesized from cholesterol and pantothenic acid being involved in cholesterol synthesis (Morgan
19 and Lewis, 1953). However, fatty liver was reduced to normal level in rats when adding adequate
20 amounts of both inositol and choline to diets containing B vitamins thus moderating and relativising
21 the role that pantothenic acid may play in fatty liver development (Engel, 1942). The same year, it
22 was shown that pantothenic acid deficiency may lead to fatty liver in dogs (Schaefer et al., 1942)
23 and progressive increase in lipid globules in rat liver (Wirtschafter and Walsh, 1962). It was also
24 observed in pantothenic acid-deficient and high-fat fed rats a reduced hepatic neutral fat content
25 compared to pantothenic acid-supplemented and high-fat fed rats, with no difference for hepatic
26

1 total cholesterol, free cholesterol and PL contents (Carter and Hockaday, 1962). The same
2 tendencies were reported with low-fat diets (Carter and Hockaday, 1962). Conversely, in the fifties,
3 Italian research teams reported lipotropic action of pantothenic acid in rats (Catolla Cavalcanti and
4 Levis, 1950, Turchetto et al., 1955). In pantothenic acid-deficient cats (only 0 to 3 mg/kg diet), some
5 hepatic fatty metamorphosis and fine and coarse vacuolar formation with lipids evenly deposited
6 were reported, no histological changes being observed when increasing pantothenic acid content of
7 the diet from 5 to 20 mg despite a largely higher weight gain (Gershoff and Gottlieb, 1964). In
8 1968, Williams et al. showed that supplementing low-fat or high-fat fed rats with pantothenic acid
9 increased liver weight and FA contents but not that of PL with variations according to the FA
10 considered, *e.g.* higher levels of stearate and arachidonate in PL and higher proportion of linoleate
11 in TG (Williams et al., 1968). In 1969, Osumi et al. showed in rats that Ca-pantothenate partly
12 reduced the high hepatic TG content initially developed through a low-protein diet (Osumi et al.,
13 1969) while no change in hepatic lipid content was observed with pantothenic-deficient- vs normal-
14 fed rats (Fidanza et al., 1970). Latter, pantothenic acid carence has been shown to increase, but not
15 significantly, the total lipid content of liver in ducklings (Saheb and Demers, 1972). In pantothenic
16 acid-deficient rats kept on diet for more than 75 days, significantly lower phosphatidylcholine
17 content of 40% compared to non-deficient rats was also observed (Mahboob, 1975). In mice with
18 hypothalamic obesity induced by aurothioglucose, pantothenic acid derivatives
19 (phosphopantothenate, pantethine and panthenol) importantly and significantly reduced hepatic TG
20 content with no effect on total PL and free cholesterol, and significant effect upon total cholesterol
21 and cholesterol ester reduction by panthenol, reduced resistance to insulin and lipolysis activation
22 being hypothesized as possible mechanisms (Naruta and Buko, 2001).

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

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

22
23 Such results emphasized different pantothenic acid effects on hepatic lipid metabolism (see
24 Supplemental Table 1 that reports most relevant studies). We believe that the contradictory results
25 obtained with both niacin and pantothenic acid probably depends on the presence or not of the other
26 main lipotropes - choline, betaine, methionine and *myo*-inositol - or other B vitamins, but also on

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

7 8 Magnesium

9 Concerning magnesium, its depletion has been associated with cirrhosis (Koivisto et al., 2002), and
10 hypomagnesemia associated with NAFLD and non-alcoholic steatohepatitis (Hanje et al., 2006). A
11 low plasma level of magnesium has also been associated with insulin resistance (Rosolova et al.,
12 1997), and a low magnesium diet was otherwise shown to decrease insulin sensitivity (Nadler et al.,
13 1993). Magnesium has been also shown to reduce hyperlipidemia (Kisters et al., 1993).

14 More specifically, magnesium is well known as antioxidant (Freedman et al., 1992). It is
15 also particularly involved in the reaction of CoA with ATP (Mg-ATP complex) and FFA to yield
16 acyl-CoA (Figure 2B), and it activates CoA synthesis from pantothenic acid proportionally to the
17 presence of ATP. It is also required by mitochondria for oxidative phosphorylations that produce
18 ATP. All of these properties of magnesium play a role in the overall FA β -oxidation process (Figure
19 2B) (Andrieux-Domont and Le Van, 1970; Berg, 1959; Garfinkel and Garfinkel, 1985; Ingraham
20 and Green, 1958). The role of magnesium on FA oxidation was well illustrated by the dramatic
21 increase of palmitate oxidation reached in heart muscle mitochondria when increasing magnesium
22 concentration from 0.01 to 5 mM in presence of carnitine ($\approx +800\%$) or acetylcarnitine ($\approx +950\%$;
23 Supplemental Table 1) (Fritz, 1959).

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

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

6 *Other phytochemicals and plant extracts*

8 Lipotropic effect of choline, betaine, methionine and *myo*-inositol has been unravelled in rats quite
9 early between 1932 and 1941 (Best and Huntsman, 1932; Gavin and Mchenry, 1941b; Tucker and
10 Eckstein, 1937); then, always in rats, the lipotropic potential of vitamins B was apparently first
11 emphasized around 1950 (Catolla Cavalcanti and Levis, 1950; Kelley et al., 1950; Tyner et al.,
12 1950). The effect of carnitine on FA oxidation was reported in rat liver slice in 1959 (Fritz, 1959)
13 and carnitine was shown to importantly reduce hepatic TG content in choline-methionine-deficient
14 and high-fat (30%) fed rats (see Supplemental Tables 1 and 2) (Khairallah and Wolf, 1965).

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

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2 1 Now, we therefore consider all phytochemicals - other than betaine, choline, methionine,
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4 2 *myo*-inositol, vitamins B, magnesium, carnitine and phytate - for which at least one significant
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6 3 positive effect on lipid metabolism has been reported, be on total lipid, TG or cholesterol contents,
7
8 4 on lipogenic enzyme activities, FA oxidation enzyme activities, gene expression of PPAR α and
9
10 5 SREBP, or rate of lipogenesis (Supplemental Tables 1-4). However, in the following section will be
11
12 6 considered as lipotropic compounds *sensu stricto* only those that significantly reduce hepatic total
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14 7 lipid or TG contents. Those decreasing only hepatic cholesterol content may not be considered as
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16 8 lipotrope since steatosis is mostly concerned by TG accumulation or retention within hepatocytes
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18 9 (Adams et al., 2005).
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26 11 *Specific plant compounds: hydroxycitric acid and organosulfur compounds*

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28 12 Besides the 8 previously defined lipotropes that are betaine, choline, *myo*-inositol, methionine,
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30 13 magnesium, niacin, pantothenic acid and folates and that are quite ubiquitous in plants, other
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32 14 phytochemicals that come from specific botanical families have been cited as having positive
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34 15 effects on hepatic lipid metabolism: they were HCA (Lowenstein, 1971; Sullivan et al., 1972)
35
36 16 mainly isolated from fruits of the *Garcinia* family, notably *Garcinia cambogia* (Heymsfield et al.,
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38 17 1998; Lewis and Neelakantan, 1965) and used in commercial nutritional supplements that aim at
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40 18 losing weight, and cysteine-containing compounds as the organosulfured compounds found in
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42 19 *Allium* species (*e.g.* *s*-ethyl cysteine and *s*-methyl cysteine in onion or garlic) (Supplemental Table
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44 20 2).
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52 22 Hydroxycitric acid

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54 23 The lipotropic effect of HCA may however appear controversial as illustrated by the apparent
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56 24 contradictory results obtained, as the increased post-prandial hepatic lipid content of chronically
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58 25 high-fructose fed rat supplemented with HCA (Brandt et al., 2006), the decreased rate of
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60 26 lipogenesis in rat liver following either i.v./i.p. HCA injection or orally ingested HCA (Lowenstein,

1 1971, Sullivan et al., 1974b, Sullivan et al., 1972), the absence of effect on liver lipid content
2 following HCA supplementation in normal rats (Sullivan et al., 1974a) or in rats with
3 experimentally induced obesity (Sullivan and Triscari, 1977), the important increase in hepatic post-
4 prandial lipid content ($\approx +67\%$) in high-fructose fed rats (Brandt et al., 2006) or the significant
5 reduction of hepatic FA synthesis rate by HCA in high-fructose and high-glucose fed rats (Sullivan
6 et al., 1974b; Sullivan et al., 1977) (Table 2 and Supplemental Table 2). In addition, HCA was
7 shown *in vitro* to inhibit ATPCL/CCE (ATP-citrate lyase/citrate cleavage enzyme) activity, the
8 enzyme that catalyzes the split of citrate to oxaloacetate and acetyl CoA, the construction material
9 for FA: this inhibition of the conversion of carbohydrate metabolites into fat favours glycogen
10 accumulation within muscles and liver (Supplemental Table 2) (Watson et al., 1969).

11 Conversely, HCA was convincingly shown to significantly reduce weight gain or regain in
12 rats (Brandt et al., 2006; Greenwood et al., 1981; Kang et al., 2007; Leonhardt and Langhans, 2002;
13 Nageswara Rao and Sakariah, 1988; Shara et al., 2004; Shara et al., 2003). This effect might be
14 notably attributed to the anorectic property of HCA in relation with an increased FA β -oxidation
15 (Leonhardt and Langhans, 2002) that would result from reduction in malonyl CoA production (*via*
16 inhibition of ATPCL) (McCarty, 1994), an inhibitor of CPT-1 (Figure 1b), and to the role that plays
17 FA oxidation in the metabolic control of food intake at high fat dose (Scharrer and Langhans,
18 1986).

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

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2 1 Some of the mechanisms involved - notably as unravelled by using rat hepatocytes - are probably in
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4 2 relation with a decreased activity of two lipogenic enzymes that are ME and FAS, a decreased
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6 3 activity of HMG-CoA reductase and a reduced rate of acetate or mevalonate incorporation into
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8 4 lipids (Supplemental Table 2) (Gebhardt and Beck, 1996; Kumari and Augusti, 2007; Kumari et al.,
9
10 5 1995; Lin et al., 2008; Lin and Yin, 2008; Lin et al., 2004; Liu and Yeh, 2000; Yeh and Yeh, 1994).
11
12 6 This has been linked to significant depressed mRNA expressions for ME, FAS, HMG-CoA
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14 7 reductase and SREBP-2 (Supplemental Table 2) (Lin and Yin, 2008). In addition, studies lead in
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16 8 HepG2 cells suggest that the concerted action of several organosulfur compounds would allow
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18 9 reaching a higher inhibition of acetate incorporation into cholesterol as compared to isolated
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20 10 organosulfur compounds (*i.e.* *s*-allyl or *s*-propyl cysteine) (Lee and Yeh, 2003) and that inhibition
21
22 11 of hepatic cholesterol synthesis would mainly result from water-soluble organosulfur compounds
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24 12 not lipid-soluble compounds that may become toxic at high doses (*i.e.* 1-4 mM) (Yeh and Liu,
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26 13 2001). One may therefore conclude that results convincingly support lipotropic effect of
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28 14 organosulfur compounds.
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16 *Unsaturated and short-chain fatty acids, melatonin and para-aminobenzoic acid*

17 Mono-unsaturated and poly-unsaturated fatty acids 

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

21 Most of studies were lead in rats or mice (Supplemental Table 2). The only human studies
22 concerns patient with NAFLD who were administered 1-2 g daily of PUFA for 6-12 months
23 (Capanni et al., 2006; Spadaro et al., 2008). Results clearly showed a significant decrease in the
24 degree of steatosis with 24-30% of subjects having no more steatosis diagnosed (Capanni et al.,
25 2006; Spadaro et al., 2008). However, PUFA were either of animal origin (Capanni et al., 2006) or
26 no precision were given (Spadaro et al., 2008). Accordingly, n-3 PUFA have been recently

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

5 Among mechanisms involved, PUFA are known to inhibit the expression of FAS (Moon et
6 al., 2002) as shown with conjugated linoleic acid (CLA) in high-fat-fed rats (Choi et al., 2007), with
7 dietary long-chain n-3 FA-containing krill oil in high-fat-fed mice (Tandy et al., 2009), with PUFA
8 from safflower oil in high-fructose/glucose fed rats (Toussant et al., 1981), with methyl esters of
9 polyunsaturated vs long-chain saturated FA given to rats fed fat-free diet for 7 days (Clarke et al.,
10 1977) and with α -linolenic acid (18:3 n-3)-rich diet in both wild type and PPAR α -null (KO) mice
11 (Supplemental Table 2) (Morise et al., 2009). And several authors have described n-3 PUFA as
12 “negative regulator of hepatic lipogenesis” (Alwayn et al., 2005; Sekiya et al., 2003; Spadaro et al.,
13 2008). PUFA were also shown to increase PPAR α mRNA expression (Choi et al., 2007; Morise et
14 al., 2009) and to decrease SREBP mRNA expression (Sekiya et al., 2003) or activity (Di Nunzio et
15 al., 2010), to inhibit activities of several lipogenic (TG and cholesterol) enzymes that are ACC,
16 G6PDH, HMG-CoA reductase and ME and to increase activities of FA oxidation enzymes that are
17 CPT and acyl-CoA oxidase (ACO) (Supplemental Table 2). Cellular and nuclear mechanisms by
18 which PUFA may favour peroxisomal and mitochondrial FA β -oxidation *via* PPAR up-regulation
19 and inhibit TG and FA synthesis *via* SREBP1 down-regulation have been described and reviewed
20 by Clarke (Clarke, 2001). However, concerning SREBP, results are not always consistent since
21 some studies reported no effect or increased expression of SREBP (Gotoh et al., 2009; Morise et al.,
22 2009) but this may be explained by the specific strains of mice used in these studies, *i.e.* *db/db* mice
23 (with hyperlipidemic, diabetic and obese symptoms) (Gotoh et al., 2009) and PPAR α -null (KO)
24 mice (Morise et al., 2009). In addition to these mechanisms, it was shown in ethanol-fed rats that
25 DHA and AA prevent from fatty liver development, and that protection of some mitochondrial
26 enzymes (aldehyde dehydrogenase, ATP synthase, and 3-ketoacyl-CoA thiolase) from oxidation by

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

5 As shown recently in mice fed synthetic diet containing lard (low in PUFA and highly
6 unsaturated FA, HUFA), canola oil (high in PUFA, *i.e.* linoleic and linolenic acids) or a mixture of
7 menhaden and fish/fungal oils (high in HUFA, *i.e.* AA, EPA and DHA), it seems that HUFA from
8 animal origin (menhaden/fish/fungal oil) are more efficient in preventing from steatosis than PUFA
9 from plant origin (canola oil) although linoleic and linolenic acids are both precursors *in vivo* of
10 HUFA (Sealls et al., 2008). Yet, MUFA-rich olive oil was shown to be more efficient in reducing
11 degree of steatosis in methionine-choline-deficient rats than PUFA-rich fish oil; and while olive oil
12 consumption significantly reduced hepatic TG content by around 29%, fish oil failed to
13 (Supplemental Table 5) (Hussein et al., 2007). Accordingly, the role of oleic acid in olive oil to
14 prevent steatosis in NAFLD patients has been latter discussed (Assy et al., 2009). Indeed, oleic acid
15 is able to decrease NF- κ B activation and LDL oxidation while increasing insulin resistance that in
16 the end lead to dow- and up-regulation of respectively SREBP and PPAR α and PPAR γ and
17 increased hepatic FA oxidation (Assy et al., 2009). However, several other phytochemicals would
18 also contribute to the overall lipotropic effect of olive oil, such as phenolic compounds, squalene,
19 lignans and hydroxytyrosol, which prompted Assy et al. to suggest that olive oil and, more
20 generally MUFA-rich foods, is a main contributor of the beneficial effect of the Mediterranean diet
21 in the primary prevention of NAFLD (Assy et al., 2009). Besides olive oil, PUFA/n-3 rich/low-
22 *trans* structured fat synthesized from flaxseed oil, butter fat and palm stearin was also shown to exert
23 significant lipotropic effects, among which a decreased hepatic TG content of 16%, an increased β -
24 oxidation of 96% and an increased CPT activity of 88% in ApoE^{-/-} mice compared to ApoE^{-/-} mice
25 fed a 10%-fat (commercial shortening, 53.4% *trans* FA) diet (Supplemental Table 5) (Cho et al.,
26 2009). However, results do not appear always consistent. Thus, the respective efficacy of different

1 oils in improving various markers of hepatic lipid metabolism has been tested in rats fed initially a
2 10%-fat diet rich in saturated lipids: while sunflower (n-6 PUFA-rich), linseed (enriched with α -
3 linolenic acid) or sardine (n-3 PUFA-rich) oils importantly decreased TG content, and ACC and
4 G6PDH activities, olive oil (oleic acid-rich) failed to (Supplemental Table 5) (Takeuchi et al.,
5 2001). However, all oils importantly and significantly increased β -oxidation and CPT activity (at
6 least +100%), olive oil remaining the less efficient (Takeuchi et al., 2001). These results appear
7 somewhat contradictory with those of Hussein et al. reported above with olive and fish oils
8 (Hussein et al., 2007). Discrepancies may be ascribed to the different models tested, *i.e.* methionine-
9 choline deficient vs 10%-fat fed rats.

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

20 In the end, one may first wonder whether all unsaturated FA of plant origin are lipotropic or
21 not: if results appear still insufficient to definitively conclude, those reported in Supplemental Table
22 2 in both animals and humans tend to support a lipotropic effect whose significance vary according
23 to models and FA chosen. Secondly, one may wonder whether n-6 (*e.g.* arachidonic acid, C20:4 n-
24 6) and n-3 (*e.g.* α -linolenic acid, C18:3 n-3) would have the same lipotropic potential. In humans,
25 only n-3 PUFA have been proposed to treat patients with NAFLD (Xin et al., 2008), excess n-6
26 consumption being pro-inflammatory (Lee et al., 2007a) and being likely to be involved in the

1 promotion of hepatic necro-inflammation (Cortez-Pinto et al., 2006) that may transform NAFLD
2 into non-alcoholic steatohepatitis.
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9 Short-chain fatty acids

10 Short-chain fatty acids (SCFA) mainly result in humans and animals from fiber fermentation and
11 the most important are acetate, propionate and butyrate. As for the previously PBF compounds, they
12 have been shown, either as isolated compound or in mixture, to exert positive and significant effects
13 on hepatic lipid metabolism (Supplemental Table 2). But only one study reported a significant
14 decrease in hepatic TG content (around 16%) with acetic acid in high-fat fed mice (Kondo et al.,
15 2009). Among mechanisms involved, up-regulation of PPAR α , ACO and CPT-1, and down-
16 regulation of FAS gene expression were demonstrated (Kondo et al., 2009). Consequently, SCFA
17 being produced *via* fiber fermentation within colon, fiber may be considered as possibly indirectly
18 playing a role in these mechanisms.
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33 Other studies mainly reported the inhibition effect of SCFA upon rate of cholesterol
34 synthesis as shown in isolated hepatocytes with propionic acid (Wright et al., 1990) or in liver slices
35 with SCFA mixture of acetic, propionic and butyric acids (Hara et al., 1999) (Supplemental Table
36 2). And hepatic acetate and propionate concentrations were shown to be negatively correlated with
37 hepatic cholesterol content in rats (Koseki et al., 1991).
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47 Melatonin

48 In human, melatonin is synthesized from serotonin in pineal gland and is before all known as being
49 the central hormone that regulates chronobiological rhythms, notably sleeping. In plants, melatonin
50 is a strong antioxidant and also plays a role in its growth. To our knowledge, there is no database
51 for the melatonin content of PBF, and melatonin content of some PBF still remains unknown.
52 However, hazelnuts and walnuts are considered as good vegetable sources of melatonin; and
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1 melatonin is also found in algae, ginger, grape, cocoa, cereals (e.g. maize, rice and wheat),
2 tomatoes, potatoes and green vegetables.

3 Several studies have reported a protective effect of melatonin against liver injury in relation
4 with its antioxidant property and its effect on gene expression in relation with antioxidant status
5 (Catala et al., 2007; Leon et al., 2004; Sener et al., 2004; Subramanian et al., 2007; Taysi et al.,
6 2003). More specifically, although studies are scarce, melatonin has been reported in rats, mice and
7 minks to importantly reduce hepatic TG contents and to improve grade for steatosis (Supplemental
8 Table 2) (Kuzu et al., 2007; Nieminen et al., 2001; Pan et al., 2006; Sener et al., 2004; Shieh et al.,
9 2009; Subramanian et al., 2007). However, doses used in rat and mice studies were high and un-
10 physiological (i.e. from 0.5-10 mg/kg b.w. injected i.p. and 10 mg/L of drinking water) (Pan et al.,
11 2006; Sener et al., 2004). The study lead in minks used more physiological doses around 10 μ g
12 daily (Nieminen et al., 2001).

13 Mechanisms involved in this lipotrope effect might notably include a reduced oxidative stress
14 - increased oxidative stress and lipid peroxidation being associated with steatosis - and decreased
15 insulin resistance (Kuzu et al., 2007; Sener et al., 2004). Increased insuline resistance is an
16 important parameter in the ethiology of fatty liver. Indeed, such decreased insulin sensitivity may
17 accelerate TG hydrolysis within adipose tissues releasing FFA within bloodstream, this latter being
18 then uptook in great amount by the liver and re-synthesized in TG forming excess fat deposits.
19 Deficiency in MTP and decreased synthesis of ApoB that are involved in VLDL assembly to export
20 TG from liver are notably mainly involved in such an impaired metabolic context (Adams et al.,
21 2005).

22 23 Para-aminobenzoic acid

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

1 lipotropic effect. Indeed, PABA has been shown to decrease serum cholesterol level in men (Failey
2 and Childress, 1962), to play a role in folate formation (Barbieri et al., 1995), notably as
3 intermediate in the bacterial synthesis of folates (Wegkamp et al., 2007) and has been recognized as
4 stimulating bacteria growth (Briggs and Daft, 1955; Pfiffner and Bird, 1956). In addition, bacteria
5 are found in human intestine, folates are lipotropes, and PABA omission in the diet of guinea pig
6 was shown to lead to folic acid deficiency (Woodruff et al., 1953). Yet, although used in
7 commercial lipotropic complexes, the lipotropic effect of PABA, notably a reduced hepatic TG or
8 lipid content, has never been demonstrated, neither in animals nor in humans. It has only been
9 shown in rats that steatosis was associated with an increased level of acetylation due to inhibition of
10 FA oxidation, this being reflected with increased level of acetylated PABA in rat urine (Van Hung,
11 1953).

12 13 *Fiber-type and polyphenol-type compounds*

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

18 19 Soluble and insoluble fiber

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

1
2 1 Concerning cholesterol, apparent contradictory results - *i.e.* lower hepatic content together
3
4 2 with higher HMG-CoA reductase activity and higher rate of synthesis - were also reported (Thomas
5
6 3 et al., 1983). This may be attributed to an adaptation resulting from the higher release of cholesterol
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8 4 and its precursors (*i.e.* bile acids) within intestine *via* hydrophobic binding to insoluble fiber or
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10 5 trapping within soluble and viscous fiber. Consequently, the liver compensates losses in cholesterol
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12 6 by increasing its synthesis and turnover through an enhanced HMG-CoA reductase activity and rate
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14 7 of cholesterol synthesis (Figure 2D). Thus, Thomas et al. have notably shown on liver slices of rats
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16 8 fed for 1 month a 11%-fat diet supplemented with 30% of neutral detergent fiber from blackgram
17
18 9 that incorporation of [U-¹⁴C]glucose or [1,2-¹⁴C]Na-acetate into cholesterol was increased by
19
20 10 respectively 80 and 258% (Thomas et al., 1983).

21
22
23 11 Physico-chemical properties of fiber have therefore to be considered to explain their hepatic
24
25 12 lipid-lowering effect. For exemple, fiber, especially hydrophobic lignin (including in the fiber
26
27 13 definition), have been early shown to adsorb and/or sequester bile acid conjugates *via*
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29 14 hydrophobic bounds (Eastwood and Mowbray, 1976; Eastwood, 1975; Eastwood and Girdwood,
30
31 15 1968; Eastwood and Hamilton, 1968) thus potentially stimulating cholesterol efflux from liver.
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33 16 Latter, Mongeau and Brassard evaluated the bile salt binding capacity of various cereal products
34
35 17 ranging from 16.2 μ mol glycocholate/0.2 g of neutral detergent fiber (NDF) for wheat germ to 34.2
36
37 18 μ mol glycocholate/0.2 g NDF for spoon-size shredded wheat (Mongeau and Brassard, 1982).

38
39 19 Thanks to new technical tools, the effect of fiber on hepatic gene expression can be now
40
41 20 studied. Thus, recently, it has been shown in mice fed a 10% husk diet that genes encoding for FA
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43 21 oxidation and lipogenesis were respectively up- and down-regulated after 3 weeks but the inverse
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45 22 was observed after 10 weeks suggesting a “regulatory mechanism to restore the lowered plasma
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47 23 cholesterol and TG levels” (Chan and Heng, 2008). However, at the hepatic cellular level, it is
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49 24 unlikely that fiber compounds act directly on gene and explanations have probably to be found in
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51 25 fiber-associated compounds like polyphenols and their resulting conjugated and metabolized forms
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1 and/or fiber fermentation products that are SCFA, especially propionic acid, all of them being able
2 to reach liver and directly impact cellular metabolism and gene expression.
3

4 Oligosaccharides

5 Oligosaccharides from PBF are considered as fiber-type compounds that are completely fermented
6 within colon and that include oligofructoses and galactosides like verbascose, stachyose and
7 raffinose; but, to our knowledge, hepatic lipid-lowering effect has been mainly reported for
8 oligofructoses like fructans (*e.g.* inulin) in rats fed standard, high-sucrose or high-fructose diet and
9 in obese Zucker rats (Supplemental Table 3) (Busserolles et al., 2003; Daubioul et al., 2002;
10 Daubioul et al., 2000; Kok et al., 1996a; Kok et al., 1996b; Sugatani et al., 2006). The action of
11 inulin-type fructans on TG and cholesterol metabolism has been recently reviewed by Beylot
12 (Beylot, 2005). Among mechanisms involved, fructans have been notably shown to decrease gene
13 expression and/or resulting activities of lipogenic enzymes that are ME, FAS, ACC, ATPCL/CCE
14 and G6PDH (Figure 2D, Table 3 and Supplemental Table 3) (Aghelli et al., 1998; Delzenne and
15 Kok, 1999). Such data tend to explain that the reduction of TG-rich lipoproteins (*i.e.* VLDL)
16 secretion observed in rats would be in relation with a decreased hepatic lipogenesis (Delzenne and
17 Daubioul, 2000). Other mechanism possibly include the production of propionate - through
18 colonic fermentation of fructans - that was shown to inhibit lipogenesis in rat hepatocytes *in vitro*
19 (Supplemental Table 2) (Demigné et al., 1995, Wright et al., 1990). Beylot otherwise suggests that
20 “hypotriglyceridaemic action of fructans results rather from a decrease in the hepatic TG synthesis
21 than from a higher clearance of TG-rich lipoproteins” (Beylot, 2005). In their review, Delzenne and
22 Daubioul also proposed that 1°) fructans, by affecting glycemic and insulinemic responses,
23 indirectly modulate TG levels, insulin participating in the regulation of TG synthesis; and/or that
24 2°) since oligofructose may increase GLP-1 caecal concentration in rats fed oligofructose (Kok et
25 al., 1998) and since GLP-1 may increase insulin sensitivity, this hormone is likely to be a modulator
26 of lipid metabolism as well (Delzenne and Daubioul, 2000). This last hypothesis is supported by a

1 recent study showing in hyperinsulinaemic subjects fed +20 g/d of wheat fiber a significant increase
2 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

3
4 Polyphenols

5 Polyphenols in

6 compounds), li

7 positive effects

8 quite recent and

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

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

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

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

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

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

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

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

14 Curcumin

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

20 Saponins

21 As curcumin, saponins are not *sensu stricto* polyphenols but possess a polyphenol-like chemical
22 structure (Figure 1). They are generally included in the fiber fraction. Studies are less recent than
23 with polyphenols (Supplemental Table 4). Their consumption or injection may lead to reduced
24 hepatic fat deposits or lipid contents (TG and cholesterol) (Khanal et al., 2009; Onning and Asp,
25 1995). For example, plant saponins from *Aralia mandshurica* and commercial white saponins
26 reduced hepatic TG contents by respectively -40/-35% and -39/-20% in high-fat (Wojcicki et al.,

1 1977) and high-cholesterol (Oakenfull et al., 1979) fed rats (Supplemental Table 4). Paradoxically,
2 saponin supplementation also lead to an increased rate of liver cholesterol synthesis as shown with
3 ginsenosides purified from ginseng in rats (Supplemental Table 4) (Sakakibara et al., 1975). This
4 has probably to be attributed to the same effect as for fiber, *i.e.* the adsorption of bile salts by
5 saponins within digestive tract that thereafter stimulates cholesterol turnover and hepatic synthesis
6 (Figure 2D). Indeed, saponins are most of the time associated with fiber within food matrix.

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

8 Alkylresorcinols

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

18 *Cholesterol-lowering phytochemicals*

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

22 Gamma-oryzanol

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

-37%

significantly

Chandrasekhara, 1988, 1993). In the two other studies, γ -oryzanol was reported to significantly 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.

Policosanols

Policosanols 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

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

11 12 Phytosterols

13 As early as 1956, it was shown that β -sitosterol (20 to 25 g daily) could reduce serum cholesterol in
14 patients with hypothyroidism by around 20% (Best and Duncan, 1956). But, to our knowledge,
15 there is no studies lead in humans to investigate the effect of phytosterol consumption on steatosis.
16 In animal models, phytosterols have no significant effects on hepatic TG content contrary to
17 cholesterol content (Supplemental Table 4). Yet, phytosterols were shown to increase HMG-CoA
18 reductase, CYP7A1 and sterol 27-hydroxylase activities: such enhanced activities may be explained
19 by the increased cholesterol release within small intestine under the action of phytosterols, which in
20 turn stimulates cholesterol synthesis to compensate such intestinal losses (Moghadasian et al.,
21 2001), similarly to what occurs with fiber or saponins. Mechanisms underlying the cholesterol-
22 lowering properties of phytosterols have been otherwise thoroughly described by Brufau et al.
23 (Brufau et al., 2008). Besides, phytosterols were shown to importantly decrease hepatic ACC, ME
24 and G6PDH activities in high-cholesterol fed rats (Figure 2D) (Laraki et al., 1993). Although these
25 enzymes are directly involved in FA synthesis, we lack studies demonstrating a significant reduced
26 hepatic TG and/or lipid contents to conclude that phytosterols are lipotropic.

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2 *Plant or plant-based food extracts*

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

6 Thus, some authors focused on various plant extracts rather than on a particular compound.
7 Studies are numerous and all could not have been cited in Supplemental Table 5. It is interesting to
8 note that complex foods or food extracts may lead to similar or enhanced lipotrope-like effects than
9 isolated compounds, *i.e.* mainly decreased hepatic TG and TC contents, increased activities of
10 enzymes involved in FA oxidation, decreased activities of enzymes involved in FA and cholesterol
11 synthesis. For exemple, plant extract from *Platycodi radix* was more efficient in reducing TG (-
12 44%) than crude saponins (-17%, NS) from the food extract (Supplemental Table 5) (Kwon et al.,
13 2009b); and while tomato powder significantly reduced by 22% hepatic TG content in rats fed
14 standard diet, lycopene alone in the same amount than in tomato powder had no effect (Alshatwi et
15 al., 2010). Literature survey also unravels that foods tested cover a large range of PBF that are
16 cereal products, vegetable oils, fruits, seeds, vegetables, beverages or leaf extracts (Supplemental
17 Table 5).

18 However, the whole *food package* is not always more efficient towards liver steatosis or
19 associated lipid metabolism parameters than the isolated compound. For example, purified
20 polyphenols from *Hibiscus sabdariffa* (74% content) had more marked effect on hepatic cholesterol
21 and TG contents than the corresponding plant-extract containing 2% polyphenols (Yang et al.,
22 2010). Some antinutrients from leaf extracts like tannins and saponins may be involved in impaired
23 hepatic functions as suggested by de Melo et al. who observed in rat liver higher levels of lipids and
24 cholesterol following cassava leaves flour consumption compared to control (De Melo et al., 2008).
25 Otherwise, it was shown with *Ziziphus Mauritania* leaf extract that pre-treatment (30 min before
26 alcohol administration) was more efficient than co- or post-administration in reducing hepatic

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

11 **COMPARISON OF THE POTENTIAL LIPOTROPIC EFFECT OF THE** 12 **DIFFERENT CLASSES OF PLANT COMPOUNDS AS UNRAVELLED FROM** 13 **RAT STUDIES**



16 **Study selection**

18 The lipotropic potential of each plant compound have been evaluated by selecting studies from
19 supplemental Tables 1-4. To allow relevant comparisons, only studies lead in rats fed steatogen
20 diet supplemented with phytochemicals have been considered. Selected steatogen diets are those
21 involving excess fat, sucrose, glucose and fructose percentages, alcohol and lipotrope deficiencies.
22 We therefore chose to select only steatogenic diets of nutritional origin; fatty liver provoked by
23 chemicals or drugs like CCl₄ or DDT were not considered. Finally, 3 studies using obese *falpa*
24 Zucker rats were also selected since these rats developed fatty liver (Daubioul et al., 2002) and
25 since many of its metabolic abnormalities, including leptin and insuline resistance and
26 hyperlipidemia, are observed in human obesity (Kurtz et al., 1989; Marchesini et al., 1999; Sharabi

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

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24
25 ***Influence of phytochemicals on hepatic total lipid, TG and cholesterol contents following***
26 ***steatogen diet consumption by rats***

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4 2 First, concerning hepatic lipid contents, the most striking reductions, *i.e.* > 80%, are reached for
5
6 3 total lipid and TG contents with choline, methionine, *myo*-inositol, fiber (lignin) and phytic acid.
7
8 4 Although only one study could have been selected, unsaturated FA (*i.e.* arachidonic acid in the
9
10 5 study concerned) may also lead to important reduction in total lipid/fat (-63%) and TG contents (-
11
12 6 83%) (Goheen et al., 1983). Conversely, increases in hepatic lipid percentages ranged between +1%
13
14 7 for cholesterol content with phenolic acids and +136% for TG content with lignans with significant
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16 8 effects reached only for fiber and lignans on cholesterol content (resp. +17 and +21%), and lignans
17
18 9 on TG content (+136%). (Table 3).
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23 10 If increased cholesterol contents are not unexpected with fiber since they may stimulate
24
25 11 hepatic cholesterol turnover consequently to an increase faecal excretion, that of TG content with
26
27 12 lignans is very surprising. However, the effect has been reported for fish oil only (at a level of 8%)
28
29 13 not with palm and safflower oils (resp. -68 and -23% TG content reduction, $p < 0.05$) (Ide et al.,
30
31 14 2004). As an explanation, authors suggested that the interaction of sesamin with fish oil may have
32
33 15 change expression of genes involved in VLDL assembly and production, impairing hepatic TG
34
35 16 excretion (Ide et al., 2004). Concerning other studies with lignans, TG content modifications were
36
37 17 all ≤ 0 within the range [$\approx 0/-68\%$] (Figure 3B and Supplemental Table 4). It is interesting to note
38
39 18 that the sole increase was obtained with the only oil rich in HUFA (10% of 20:5n-3 and 32.6% of
40
41 19 22:6n-3) that is fish oil, oils used in other studies being all vegetable oils (safflower, palm and
42
43 20 coconut oil) with largely less HUFA contents: indeed, palm oil is characterized by a high level of
44
45 21 16:0 ($\approx 45\%$) and 18:1n-9 ($\approx 39\%$) (Ide et al., 2004), safflower oil by a high level of 18:2n-6 (\approx
46
47 22 78%) and 18:1n-9 ($\approx 13\%$) (Ide et al., 2004) and coconut oil by a high level of saturated FA ($\approx 87\%$)
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49 23 (USDA, 2005e). Another explanation for the high increased TG content of +136% might therefore
50
51 24 rely on the fact that fish oil is a n-3 PUFA-rich oil contrary to palm (saturated and MUFA-rich) and
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53 25 safflower (n-6 PUFA-rich) oils. Indeed, PUFA are known to be lipotropic (see above) which may
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55 26 have lead to the absence of TG reduction effect by sesamin: otherwise, in this study, palm and
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1 safflower oils alone lead to respectively 5.8- and 3.2-fold more hepatic TG accumulation than fish
2 oil for which level of hepatic TG is quite low (14 $\mu\text{mol/g}$ liver) (Ide et al., 2004). This means that
3 the 10%-fish oil diet was not steatogen.

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

14 Concerning hepatic cholesterol content reduction, it tends to be less important than TG
15 content reduction with choline, *myo*-inositol, carnitine, phytic acid and oligofructose, while
16 opposite tendency may be observed with phytosterols (Tables 2 and 3). Finally, maximal hepatic
17 cholesterol content reduction reached are quite high for choline (-56%), folates (-51%), carnitine (-
18 60%), fiber (-75%), saponins (-52%) and phytosterols (-76%) (Tables 2 and 3).

21 *Influence of phytochemicals on hepatic lipogenic enzyme activities following steatogen diet* 22 *consumption by rats*

23
24 *Myo*-inositol, unsaturated FA, phytic acid, oligofructose and lignans were the compounds the most
25 often tested for their ability to reduce lipogenic enzyme activities in rats, and results showed that
26 these compounds may be all efficient depressors of them (Figures 4 A-E). The most important

1 reductions ($\geq 50\%$) are obtained with unsaturated FA and lignans on FAS, ME, G6PDH,
2 ACC/CBX and/or ATPCL/CCE activities (Tables 2 and 3; Figures 4 A-E). However, unsaturated
3 FA tested here were all either methylated or ethylated, and therefore they did not correspond to the
4 natural form found in PBF (Supplemental Table 2) (Clarke et al., 1977; Toussant et al., 1981). A
5 65%-decrease has been also obtained with phytic acid on FAS (Figures 4A) activity (Katayama,
6 1997a). One unexpected result as regards with effect on other lipogenic enzymes is the tendency of
7 lignans to increase ME activity (up to +125%, Table 3). However, in the study reporting this result,
8 *i.e.* by Ashakumary et al., ME activity was first reduced by 50% at 0.1% sesamin level then
9 increased by 25 and 125% at respectively 0.2 and 0.5% level of the diet, and this was paralleled by
10 increasing mRNA levels for the enzyme (Ashakumary et al., 1999). These results were later
11 confirmed in rats with quite the same conditions (Supplemental Table 4) (Ide et al., 2001). One
12 explanation may be based on the PPAR-dependent regulation of ME gene expression unlike other
13 other lipogenic enzymes like FAS or G6PDH (Castelein et al., 1994). Thus, lipotropes, by inducing
14 increased PPAR mRNA expression may increase in the same time ME activity: this underlined the
15 dual role played by the transcription factor PPAR that both favour FA β -oxidation and ME activity
16 (Castelein et al., 1994).

17
18
19 ***Influence of phytochemicals on hepatic PPAR and SREBP mRNA expression following***
20 ***steatogen diet consumption by rats***

21
22 Concerning changes in the levels of both transcription factors PPAR α and SREBP, data collected
23 are scarce, but they indicate that flavonoids importantly increase PPAR α mRNA levels, and that
24 lignan importantly reduce that of SREBP, both results being in agreement with a lipotropic effect,
25 *i.e.* a reduction of hepatic lipid content (Tables 2 and 3).
26

1 2 3 4 2 **THE WHOLE LIPOTROPE VS ANTIOXODANT “PACKAGE”**

5 6 7 3 8 9 4 **The antioxidant “package”**

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14 6 The lipotropic potential of PBF has quite interesting similarities with the concept of antioxidant
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16 7 capacity of PBF. Indeed, lipotropes and antioxidants both include several phytochemicals with
17
18 8 different physiological modes of action dedicated to reach a same physiological effect: either a
19
20 9 decreased fatty liver or a decreased oxidative stress. Indeed, it is today more and more assumed
21
22 10 that it is preferable to consume several antioxidants in a limited amount than only one at high dose
23
24 11 (Murakami et al., 2003, Stanner et al., 2004), as the ATBC (Alpha-Tocopherol, Beta-Carotene
25
26 12 Cancer) study has dramatically showed it, with a 8% increased mortality and 18% increase in lung
27
28 13 cancer registered in the group of male smokers consuming a supplemented dose of 20 mg/day β -
29
30 14 carotene (The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994). This
31
32 15 underlines that high dose of only one substance may be pro-oxidative and harmful. As stated by
33
34 16 Stanner et al., “The most prudent public health advice remains to increase the consumption of plant
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36 17 foods, as such dietary patterns are associated with reduced risk of chronic diseases” (Stanner et al.,
37
38 18 2004). The synergy between antioxidants appears therefore essential since one antioxidant may
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40 19 regenerate the other after being oxidized. This is well illustrated by vitamin C that regenerates
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42 20 oxidized vitamin E and glutathione that regenerates oxidized vitamin C. This has also been
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44 21 demonstrated with various combinations of antioxidants, *e.g.* green tea extract, quercetin and folic
45
46 22 acid protect better against H₂O₂-induced cellular damages than compound alone (Jeong et al.,
47
48 23 2005), combinations of various antioxidants (*i.e.* ascorbic acid, caffeic acid, quercetin and urate)
49
50 24 have been shown *in vitro* to have a higher antioxidant potential than the sum of their components
51
52 25 (Parker et al., 2010), and tomato powder is more protective against elevated serum MDA levels in
53
54 26 rats receiving H₂O₂ than isolated lycopene (Alshatwi et al., 2010). Thus, at least 30 phytochemicals

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

11 ***The lipotropic “package”***

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

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

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

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

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

16 ***Several phytochemical properties to improve fatty liver***

17
18 In addition, since increased oxidative stress is also generally associated with fatty liver, both
19 lipotropes and antioxidants may synergistically contribute to alleviate hepatic steatosis. This is well
20 illustrated by the unrefined/virgin olive oil phytochemical *package* that is composed of several
21 compounds with complementary properties that all may contribute to protect from impaired
22 physiological functions associated with fatty liver: thus, Assy et al. proposed that the potential
23 protective role of olive oil towards NAFLD may be attributed to the combined actions of phenolic
24 compounds (hydroxytyrosol, oleuropein, caffeic acid, o-coumaric acid, vanillic acid and 3,4-
25 dihydroxyphenylethanol), oleic acid and squalene that exert anti-inflammatory, antioxidant and
26 immunomodulatory actions, that modulate transduction pathways, that regulate gene expression in

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

7 **CONCLUSIONS AND PERSPECTIVES**

9 ***What compound should be considered as lipotropes?***

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

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

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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 confirm 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

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

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

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

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

8 *The contribution of metabolomics*

10 Metabolomics is a quite recent set of
 11 biological fluids like urine, plasma
 12 soluble, like from liver homogenate

{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}: metabolomics for studying steatosis of liver
 {Griffin, 2004 #25160}: metabolomics 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 metabolomics
 The lipotropic effect of caloric restriction (30%) in humans {Elias, 2010 #25149}
 {Kim, 2010 #26157}: metabolomics of high-fat fed mice

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

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

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2 1 glucose level and that serum lactate level tended to be lower at the limit of significance
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4 2 (Subramanian et al., 2008). Based on these two markers, they have accurately classified 118/120
5
6 3 patients as control or NAFLD subjects (Subramanian et al., 2008). One may understand that by
7
8 4 unravelling new biomarkers in serum or urine through metabolomics, it will become quite
9
10 5 effective, easy and rapid to diagnose hepatic steatosis with a 100%-reliability.
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14 6 Otherwise, the few studies lead in animal models have allowed better understanding how
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16 7 hepatic lipid metabolic pathways are involved in steatosis, which one are activated or depressed
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18 8 and how lipidome or lipid profiles are modified compared to controls (Ginneken et al., 2007;
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20 9 Griffin et al., 2007; Pilvi et al., 2008; Zivkovic et al., 2009). In these four studies, steatosis has
21
22 10 and also how liver metabolite profiling changes upon high-cholesterol diet from simple steatosis to steatohepatitis (Vinaixa et al (2010))
23
24 11 been provoked by starvation, high-fat diet, 1% orotic acid supplementation and alcohol excess in
25
26 12 respectively mice (Ginneken et al., 2007; Pilvi et al., 2008), rats (Griffin et al., 2007) and minipigs
27
28 13 (Zivkovic et al., 2009). For example, in mice, while hepatic phosphatidylcholine content was
29
30 14 importantly reduced after 24 hours starvation, the appearance of a new putative biomarker of
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32 15 steatosis was also observed; and it was identified as a 49:4-TG with an odd number of C atoms,
33
34 16 such odd TG being rare compounds (Ginneken et al., 2007). In the study with minipigs, Zivkovic
35
36 17 et al. showed that alcoholic steatosis is likely to notably result from alcohol suppressive effect on
37
38 18 the phosphatidylethanolamine-*N*-methyltransferase pathway (Figure 2A) (Zivkovic et al., 2009).
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42 20 Metabolomics appears therefore as a suitable complementary technic for studying effect of
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44 21 phytochemicals on hepatic steatosis development or finding associations between levels of
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46 22 phytochemical consumption and risk/prevalence or degree of NAFLD. That should allow leading
47
48 23 more human studies based on the simple measurement of new serum and/or urinary NAFLD
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50 24 biomarkers.
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54 25 ***Databases for the lipotrope contents of plant-based foods***
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1 Last but not least issue is the absence of official database available for some of the lipotropic
2 compounds found PBF, notably free *myo*-inositol, carnitine, melatonin, organosulfur compounds,
3 acetic acid, oligofructose, curcumin and saponins. Data has to be found article by article - when
4 they exist! Concerning *myo*-inositol, the sole database is that of Clements and Darnell for total
5 *myo*-inositol (Clements and Darnell, 1980); however, it includes *myo*-inositol moieties from all
6 *myo*-inositol-derived compounds, notably phytic acid (*myo*-inositol hexakisphosphates) for which
7 the lipotropic effect has not been demonstrated in humans.

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

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

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

1
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- 1
- 2 1 **ABBREVIATIONS**
- 3
- 4 2 ABCA: ATP-Binding Cassette transporter
- 5
- 6 3 ACC: Acetyl-CoA Carboxylase
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- 8 4 ACO: Acyl-CoA Oxidase
- 9
- 10 5 ALT: Alanin aminotransferase
- 11
- 12 6 ApoA/ApoB: Apolipoprotein A or B
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- 14 7 ATP: Adenosine Triphosphate
- 15
- 16 8 ATPCL/CCE: ATP-Citrate Lyase or Citrate Cleavage Enzyme
- 17
- 18 9 BHMT: Betaine Homocysteine S-Methyltransferase
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- 20 10 CETP: Cholesteryl Ester Transfer Protein
- 21
- 22 11 CoA: Coenzyme A
- 23
- 24 12 CPT: Carnitine Palmitoyltransferase
- 25
- 26 13 CVD: Cardiovascular Diseases
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- 28 14 CYP2E1: Cytochrome P450 2E1
- 29
- 30 15 CYP7A1: CYtochrome P450, family 7, subfamily A, polypeptide 1 or cholesterol 7 α -hydroxylase
- 31
- 32 16 DGAT: Diacylglycerol Acyltransferase
- 33
- 34 17 DNA: Deoxyribonucleic Acid
- 35
- 36 18 FA: Fatty Acid
- 37
- 38 19 FAS: Fatty Acid Synthase/Synthetase
- 39
- 40 20 FFA: Free Fatty Acid
- 41
- 42 21 G6PDH: Glucose-6-Phosphate Dehydrogenase
- 43
- 44 22 HDL: High-Density Lipoprotein
- 45
- 46 23 HUFA: Highly Unsaturated Fatty Acid
- 47
- 48 24 i.p.: intraperitoneally
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- 50 25 LDL: Low Density Lipoprotein
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- 52 26 ME: Malic Enzyme
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2 1 mRNA: Messenger Ribonucleic Acid
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4 2 mtGPAT: mitochondrial Glycerol-3-Phosphate Acyltransferase
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6 3 MTP: Microsomal triglyceride Transfert Protein
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8 4 NAFL: Non-Alcoholic Fatty Liver
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10 5 NAFLD: Non-Alcoholic Fatty Liver Disease
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12 6 PABA: Para-Aminobenzoic Acid
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14 7 PBF: Plant Based Foods
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16 8 PL: Phospholipid
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18 9 PPAR: Peroxisome Proliferator Activated Receptor
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20 10 PUFA: Poly-Unsaturated Fatty Acid
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22 **RS: Resistant Starch**
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24 11 SREBP: Sterol Regulatory Element Binding Protein
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26 12 TG: Triglyceride
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28 13 USDA: United States Department of Agriculture
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30 14 VLDL: Very Low Density Lipoprotein
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1 **Figure captions**

2 **Figure 1** Molecular structure of main lipotropes and of phytochemicals for which at least one
3 significant hepatic total lipids/fat or triglyceride content reduction has been reported in animal
4 studies. Gamma (γ)-oryzanol is a mixture of ferulic acid esters of triterpene alcohols and sterols.
5 **ABBREVIATIONS:** SCFA, Short-Chain Fatty Acid; PUFA: Poly-Unsaturated Fatty Acid.

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7 **Figures 2 A-D.** The different potential mechanisms by which lipotropes may prevent excess fat
8 deposits in the liver: A - The lipotropic action of choline, betaine, *myo*-inositol, methionine and
9 folate (vitamin B9) as methyl donors in the transmethylation pathway for methionine synthesis, as
10 phospholipids precursors for triglyceride-rich lipoprotein formation and as osmolytes possibly
11 participating in cell volume regulation, cell shrinkage being a catabolic signal likely to decreased
12 lipogenesis; B - The lipotropic action of pantothenic acid (vitamin B5), magnesium and carnitine in
13 the β -oxidation pathway: pantothenic acid is precursor and constitutive of coenzyme A, magnesium
14 is cofactor of the enzymatic reaction that allows transformation of free fatty acids into acyl-CoA
15 while carnitine allows acyl-CoA to be transferred into mitochondria for β -oxidation; C - The multi-
16 factorial lipotropic action of niacin that may exert by 1°) favouring carnitine synthesis from its two
17 precursors lysine and methionine, 2°) inhibiting activity of enzymes involved in FA and TG
18 syntheses (*i.e.* ACC and DGAT), 3°) up-regulating expression of genes that code for PPAR α , and
19 4°) reducing the release of FFA in plasma through inhibition of catecholamine stimulation of TG
20 lipolysis in adipose tissue; mechanisms by which niacin may inhibit cholesterol synthesis and
21 favour and reduce efflux of respectively Apo A (HDL)- and Apo B (LDL and VLDL)-containing
22 lipoproteins outside livers are also presented. D - The lipotropic effects of other phytochemicals
23 which is mainly based on the up- and down-regulation of gene expression for enzymes and/or
24 transcription factors involved respectively in FA oxidation and synthesis, but which is also based
25 on the specific actions of fiber on incorporation of acetate into cholesterol and FA, of HCA on
26 CCE activity inhibition, of melatonin on decreased oxidative stress and insulino-resistance and of

1 oligofructose on FA re-esterification inhibition. Figures 1 A-D have been mainly elaborated from
2 results presented in Supplemental Tables 1-4. *ABBREVIATIONS*: ABCA, ATP-Binding Cassette
3 Transporter; ACC, Acetyl-CoA Carboxylase; ACO, Acyl-CoA Oxidase; AMP, Adenosine
4 MonoPhosphate; Apo A, Apolipoprotein A; Apo B, Apolipoprotein B; ATP, Adenosine
5 TriPhosphate; ATPCL/CCE, ATP-Citrate Lyase/Citrate Cleavage Enzyme; BHMT, Betaine
6 Homocysteine MethylTransferase; CE, Cholesteryl Ester; CETP, Cholesteryl Ester Transfer
7 Protein; CoA, Coenzyme A; CPT, Carnitine Palmitoyl Transferase; DGAT, Diacylglycerol O-
8 AcylTransferase; FA, Fatty Acid; FAS, Fatty Acid Synthase; FC, Free Cholesterol; FFA, Free
9 Fatty Acid; Glycerol 3-P, Glycerol 3-Phosphate; G6PDH, Glucose-6-Phosphate-DesHydrogenase;
10 GSH, reduced glutathione; HCA, HydroxyCitric Acid; HDL, High Density Lipoprotein; LDL, Low
11 Density Lipoprotein; ME, Malic Enzyme; Mg, Magnesium; MS, Methionine Synthetase; MUFA,
12 Mono-Unsaturated Fatty Acid; NF- κ B, Nuclear Factor Kappa B; PEMT,
13 PhosphatidylEthanolamine-N-MethylTransferase; PP, PyroPhosphate; PPAR α , Peroxisome
14 Proliferator Activated Receptor alpha; PUFA, PolyUnsaturated fatty Acid; SREBP, Sterol
15 Regulatory Element Binding Protein; TC, Total Cholesterol; TG, triglyceride; THF,
16 TetraHydroFolate; VLDL, Very Low Density Lipoprotein.

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18 **Figures 3 A-C.** Percentage changes for: A - hepatic total lipids/fat content, B – triglyceride content
19 and C - cholesterol content following lipotrope consumption by rats initially fed steatogen diet
20 (control group). Ranges for duration of the feeding periods and percentages of lipotrope
21 supplementation are presented in Tables 2 and 3. Red crosses and horizontal bars respectively
22 indicate the means and the median. Concerning unsaturated FA, reductions of total/lipid and
23 triglyceride levels have been obtained with arachidonic acid only (Supplemental Table 2).
24 *ABBREVIATIONS*: HCA, Hydroxycitric Acid; PUFA, Poly-Unsaturated Fatty Acid

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2 1 **Figures 4 A-E.** Percentage changes for lipogenic enzyme activities following lipotrope
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4 2 consumption by rats initially fed steatogen diet (control group): A – Fatty Acid Synthase (FAS); B
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6 3 – Malic Enzyme (ME); C – Glucose-6-Phosphate dehydrogenase (G6PDH); D – Acetyl-CoA
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8 4 Carboxylase (ACC), E – ATP-Citrate Lyase/Citrate Cleavage Enzyme (ATP-CL/CCE). Enzymes
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10 5 are those directly involved in FA synthesis, *i.e.* FAS (Fatty Acid Synthase), ACC (Acetyl-CoA
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12 6 Carboxylase) and ATP-CL/CCE (ATP-Citrate Lyase or Citrate Cleavage Enzyme) and those
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14 7 yielding NADPH,H⁺ directly used for FA synthesis, *i.e.* ME (Malic Enzyme) and G6PDH
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16 8 (Glucose-6-Phosphaphate DeHydrogenase). Concerning unsaturated FA, reductions of FAS, ME
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18 9 and G6PDH activities have been obtained with methyl linolenate, methyl linoleate, methyl oleate
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20 10 and ethyl linoleate; and reduction of ACC activity with ethyl linoleate only (Supplemental Table
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26 11 2). **ABBREVIATIONS:** PUFA, Poly-Unsaturated Fatty Acid
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Table 1 Protective effect of PBF against chronic disease and all-cause mortality risks¹

| | 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 | <i>Myo</i> -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, %) ^c | -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 | - |

Comment cite 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

URL: <http://mc.manuscriptcentral.com/bfsn> Email: fergc@foodsci.umass.edu

| | | | | | | | | | | | | | | |
|----------------|-------------------|---|---|-----------|---|---|---|---|---|---|---|-----|---------|---|
| | 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 | - | - | - | - | - | - | - | - | - | - |

^aNumber of references extracted from Supplemental Tables 1 and 2

^bNo data found

^cThe 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

^dppm = 10⁶, i.e. 1 mg/kg

^eMax- and min-values for reduced and/or increased percentages are given: they include both significant and insignificant 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

Comment cite as 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

URL: <http://mc.manuscriptcentral.com/bfsn> Email: fergc@foodsci.umass.edu

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 | \approx 0.005-1 ^d | 0.1-2 | 0.2-1.2 | \approx 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 | \approx 0.005-1 ^d | 0.1-5 | 0.01-1.2 | \approx 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 | - | \approx 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 | - | - | - | - | - |

Comment cite 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

URL: <http://mc.manuscriptcentral.com/bfsn> Email: fergc@foodsci.umass.edu

| | | | | | | | | | | | | |
|--------------------------|-------------------|---|---------|-------|---|-----------------------|-----------|---|---|---|---|---|
| | 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 | - | - | - | - | - |
| PPAR α 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 | - | - | - | - | - |

^aNumber of references extracted from Supplemental Tables 3 and 4

^bNo data found

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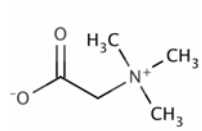
*Max- and min-values for reduced and/or increased percentages are given: they include both significant and insignificant results since an absence of effect (notably 0 change) deserves to be mentioned (for significance of results, see corresponding Supplemental Tables)

^dThe 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

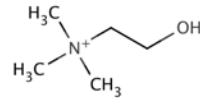
*Range of the compound percentage is that of 2 references among the three selected since one reference did not give the percentage; the upper limit was evaluated from percentage in drinking water assuming that an adult rat consumes around 20 mL water daily

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; PPAR α , Peroxisome Proliferator Activated Receptor *alpha*; SREBP, Sterol Regulatory Element-Binding Proteins; TG, TriGlyceride; TL, Total Lipids

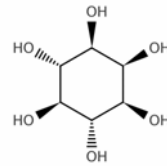
Figure 1



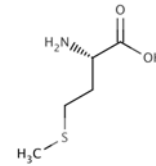
Betaine



Choline

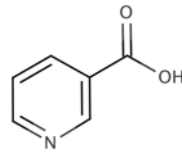


Myo-inositol

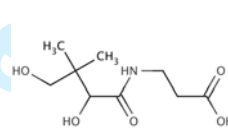


Methionine

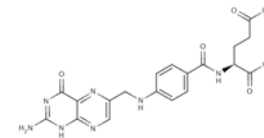
Mg²⁺



Niacin

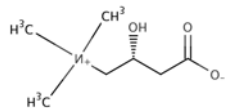


Pantothenic acid

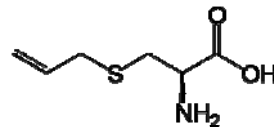


Folates

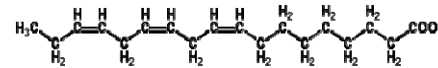
Magnesium



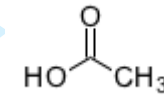
Carnitine



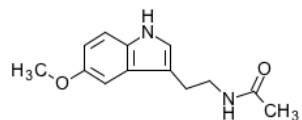
s-allyl cysteine (organosulfur compound)



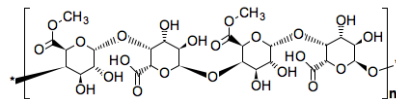
Acide α-linolenic (PUFA)



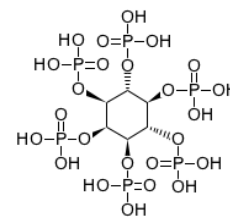
Acetic acid (SCFA)



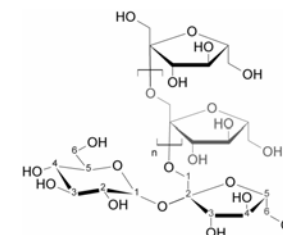
Melatonin



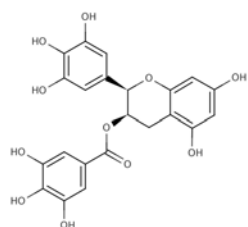
Pectin (soluble fiber)



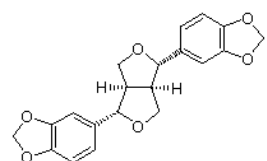
Phytic acid



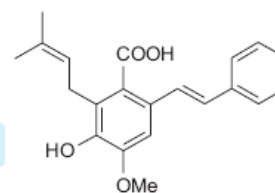
Fructans (oligofructose)



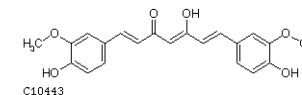
Epigallocatechin gallate (flavonoid)



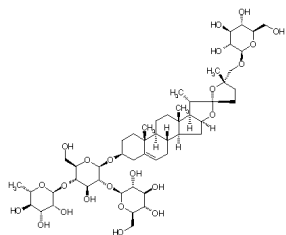
Sesamin (lignan)



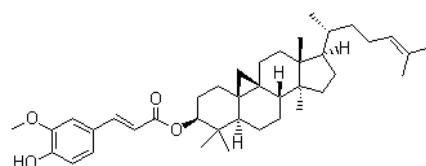
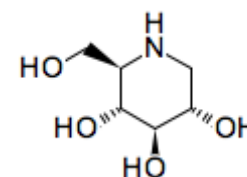
Cajanin (stilbene)



Curcumin



Avenacoside A (saponin)

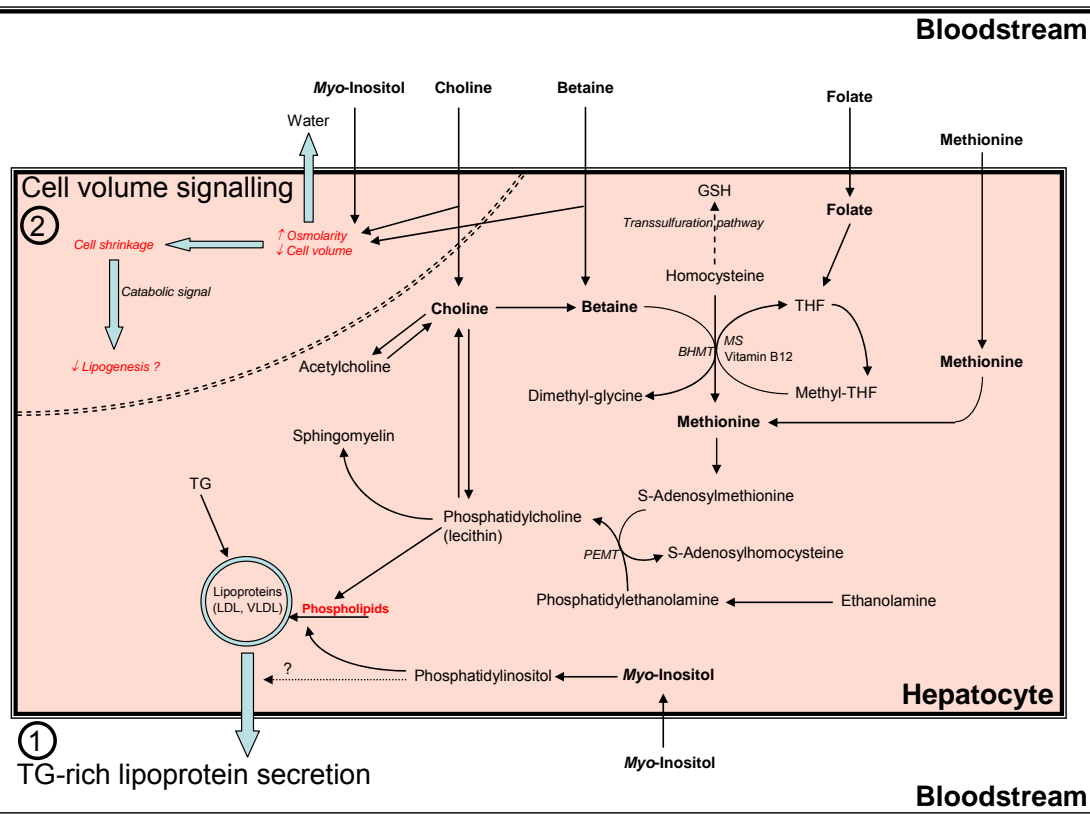
 γ -oryzanol

1-Deoxynojirimycin

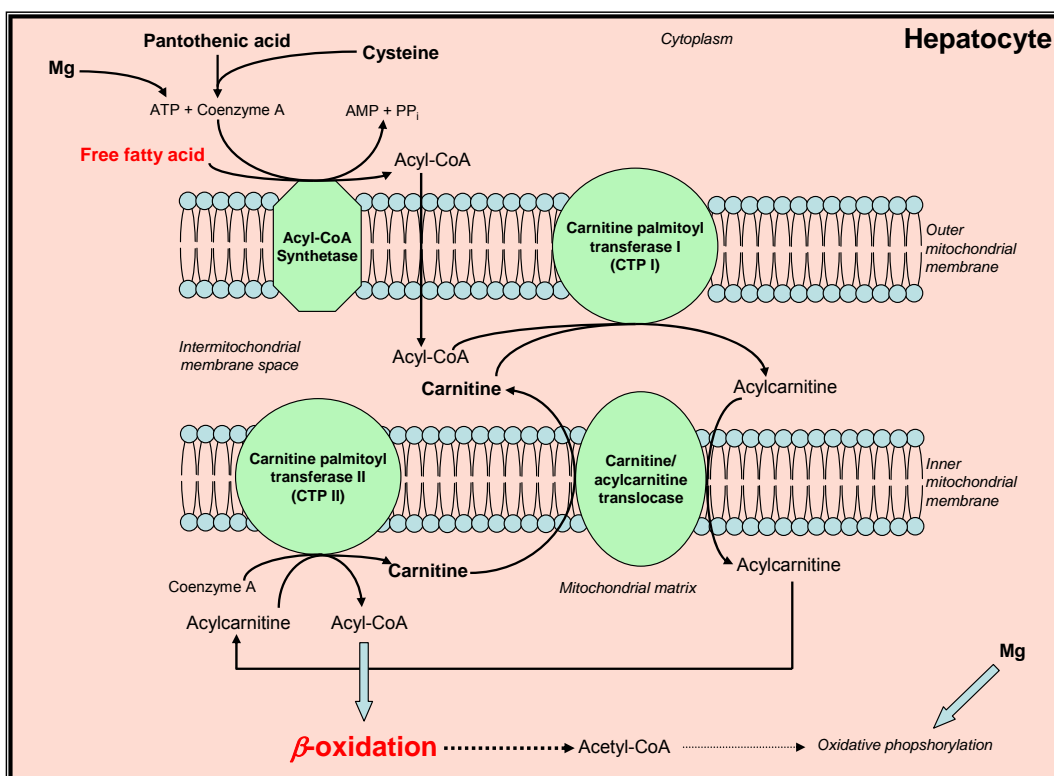
Comment cite as document:

Figure 2 A-D

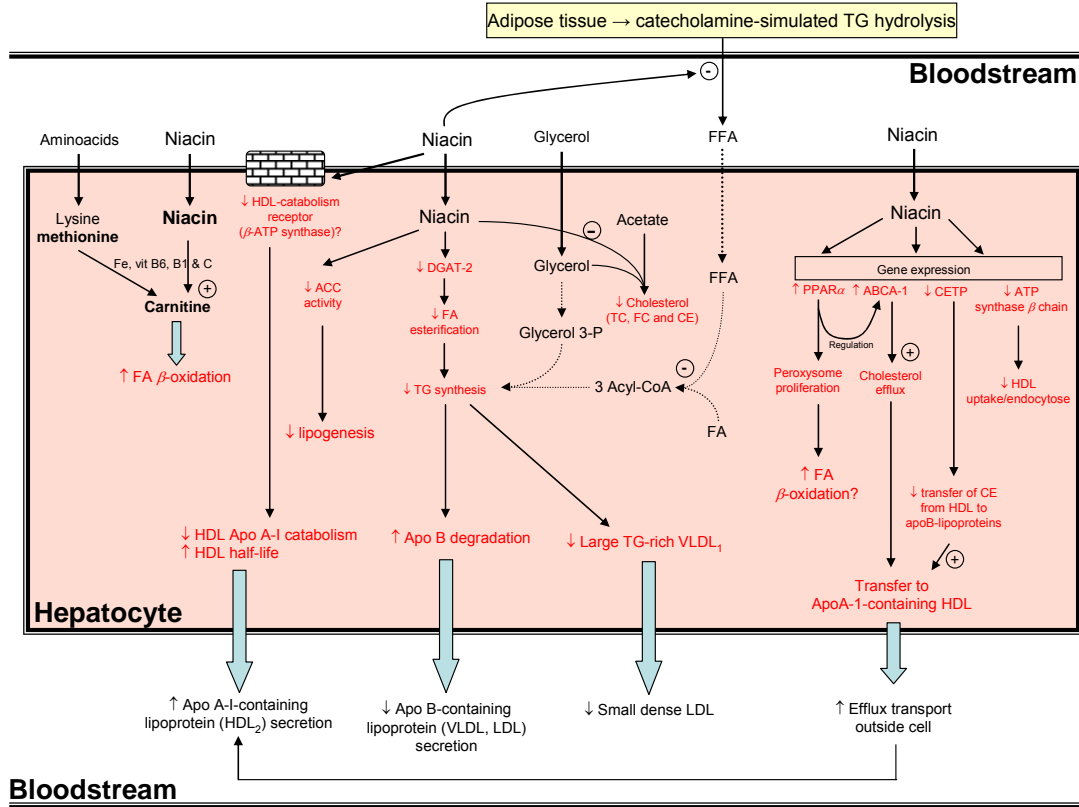
A)



B)



C)



D)

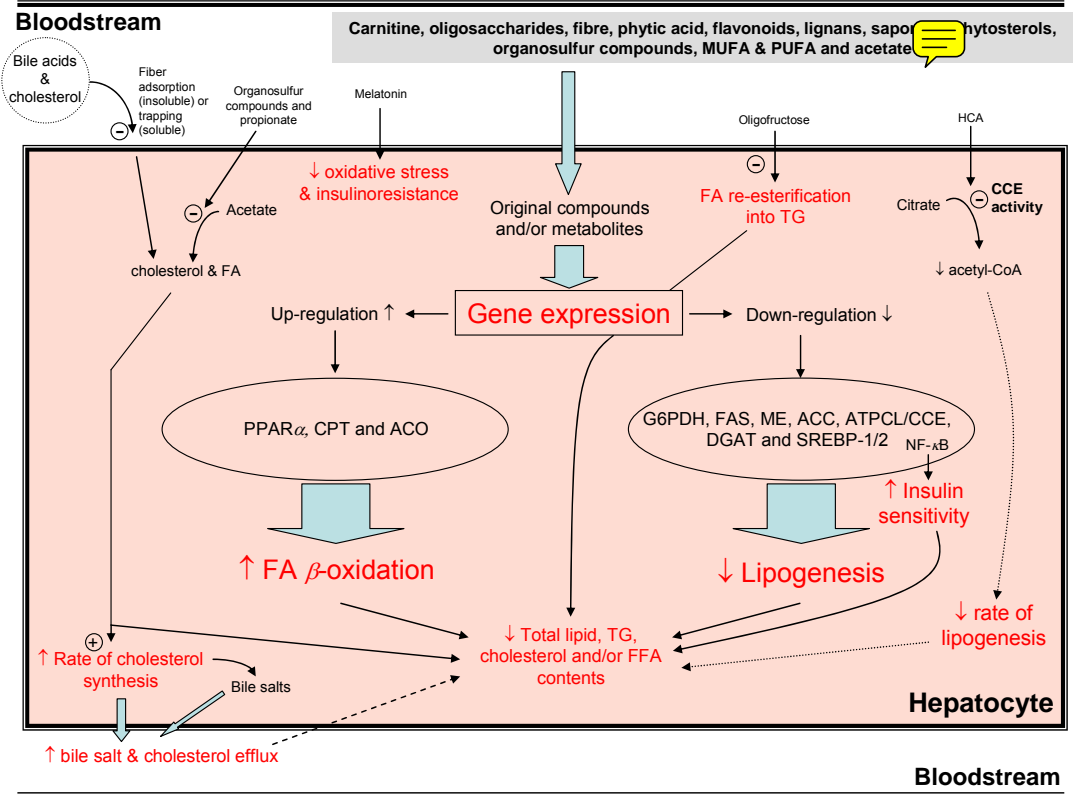
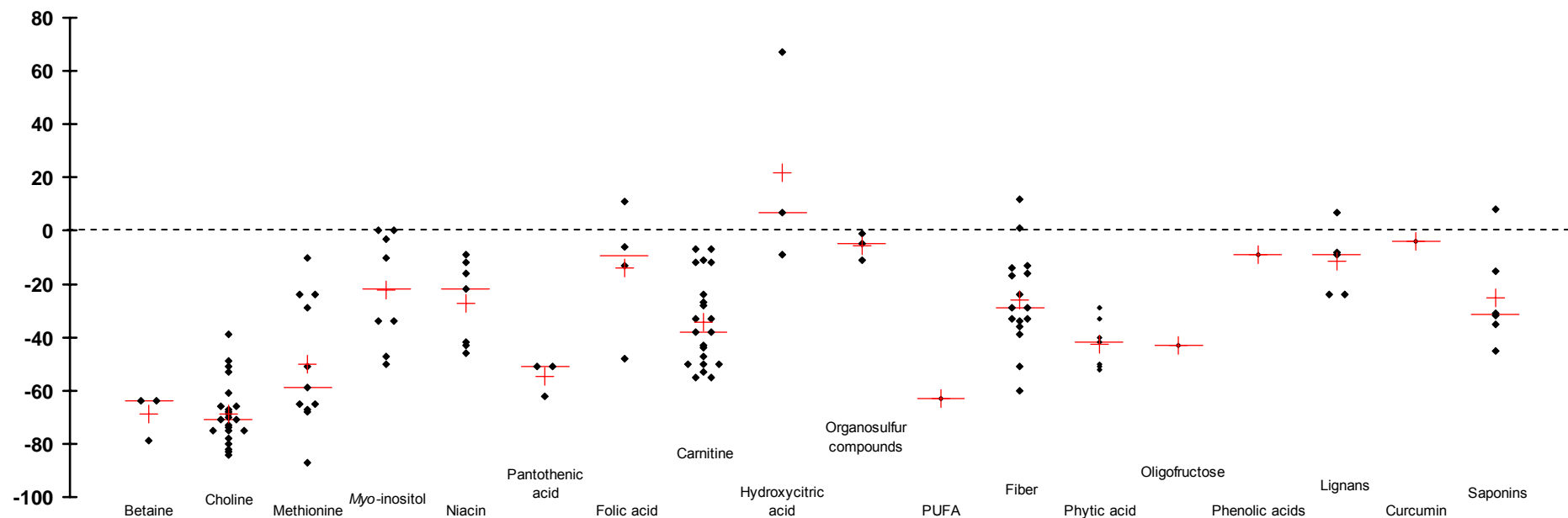


Figure 3 A-C



TL

A)



Retirer valeurs de Schön (1958) et les mettre dans Total Cholesterol.

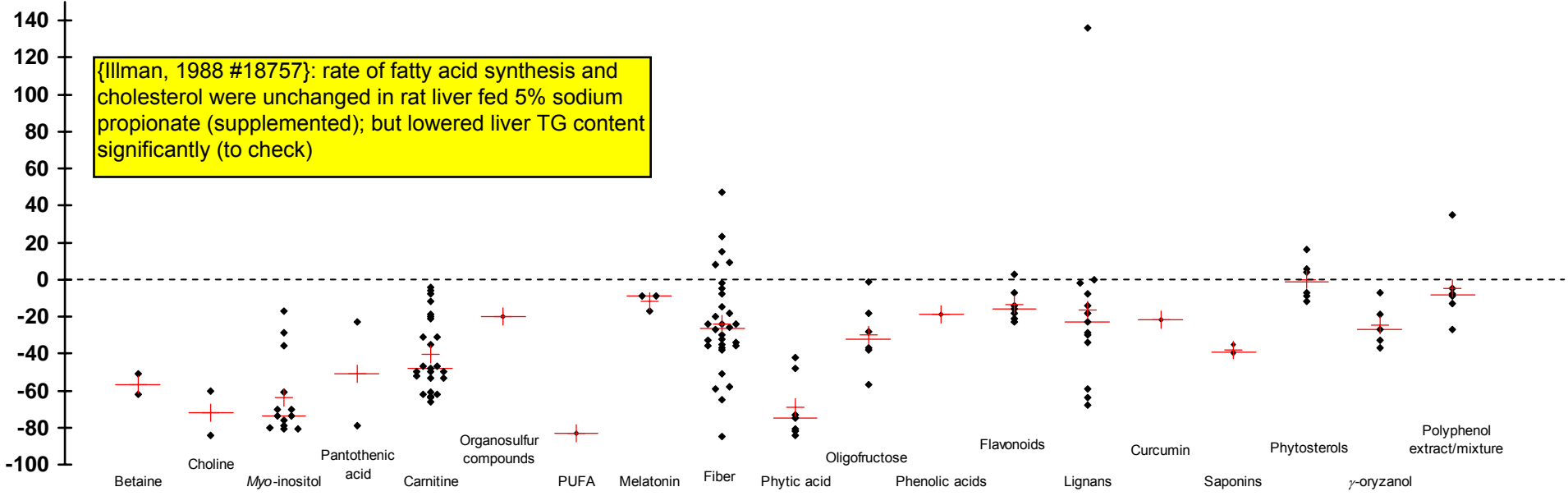
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B)

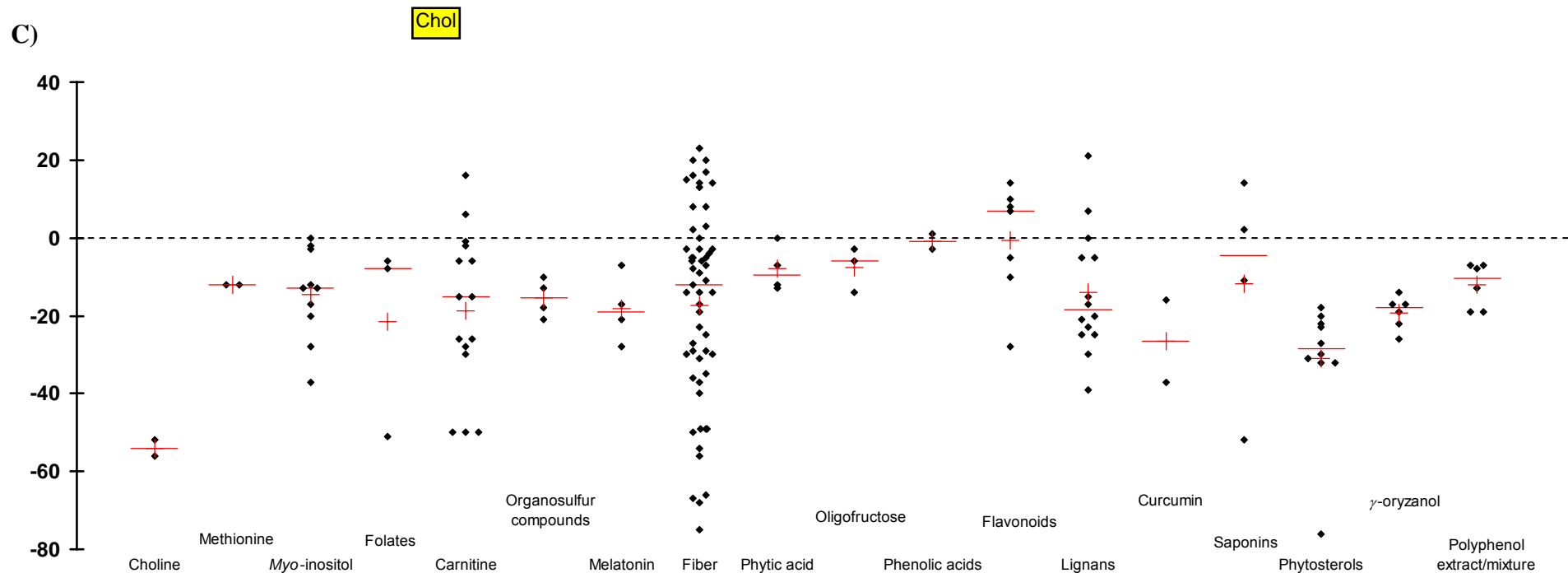
TG: vérifier pour resistant starch si valeurs à ajouter

{Illman, 1988 #18757}: rate of fatty acid synthesis and cholesterol were unchanged in rat liver fed 5% sodium propionate (supplemented); but lowered liver TG content significantly (to check)



Coumarin: auraptene reduced hepatic TG in long evan fatty rats {Nagao, 2010 #22917}

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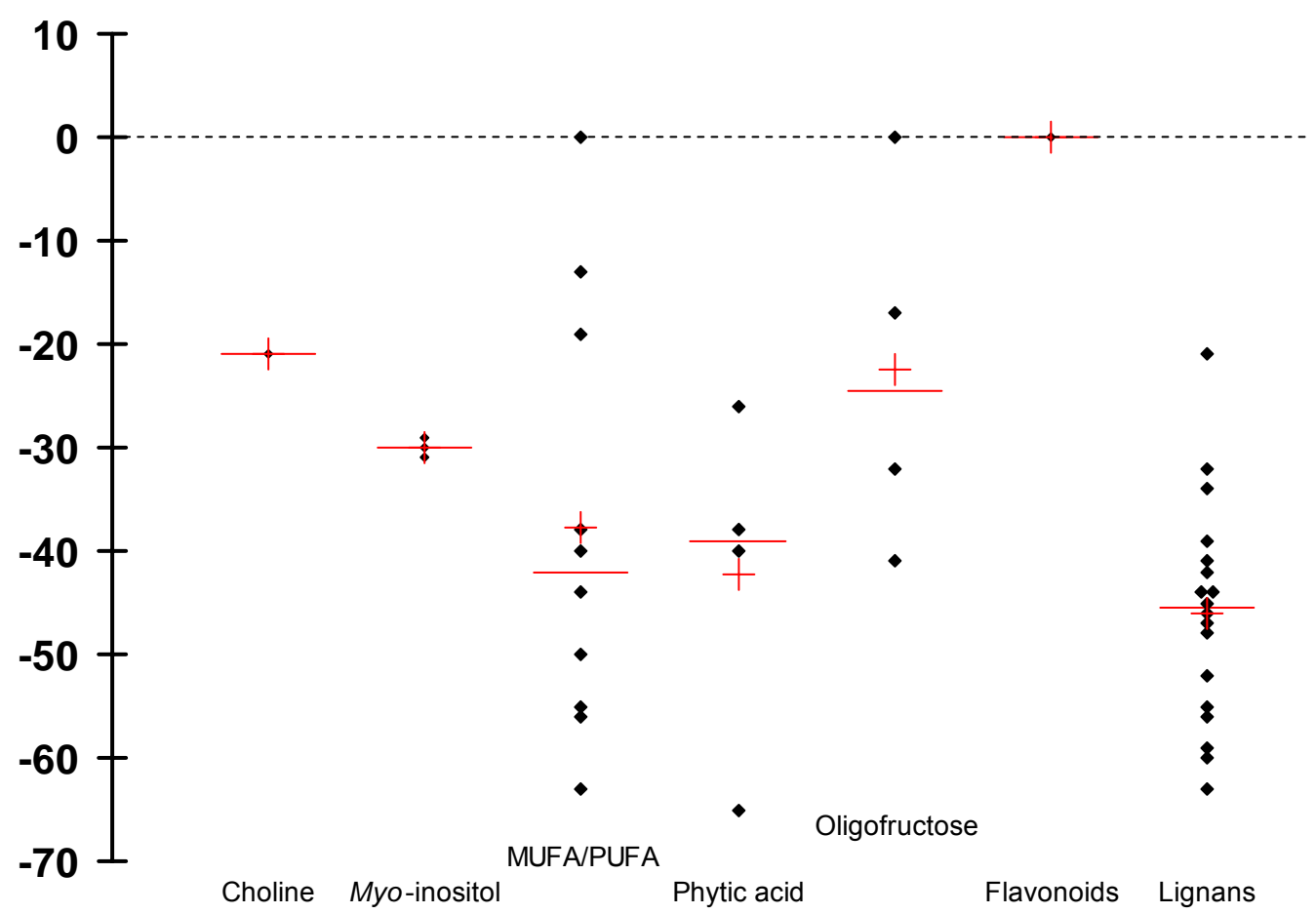


Ajouter valeurs de Schön (1958) pour Total Cholesterol / Niacine

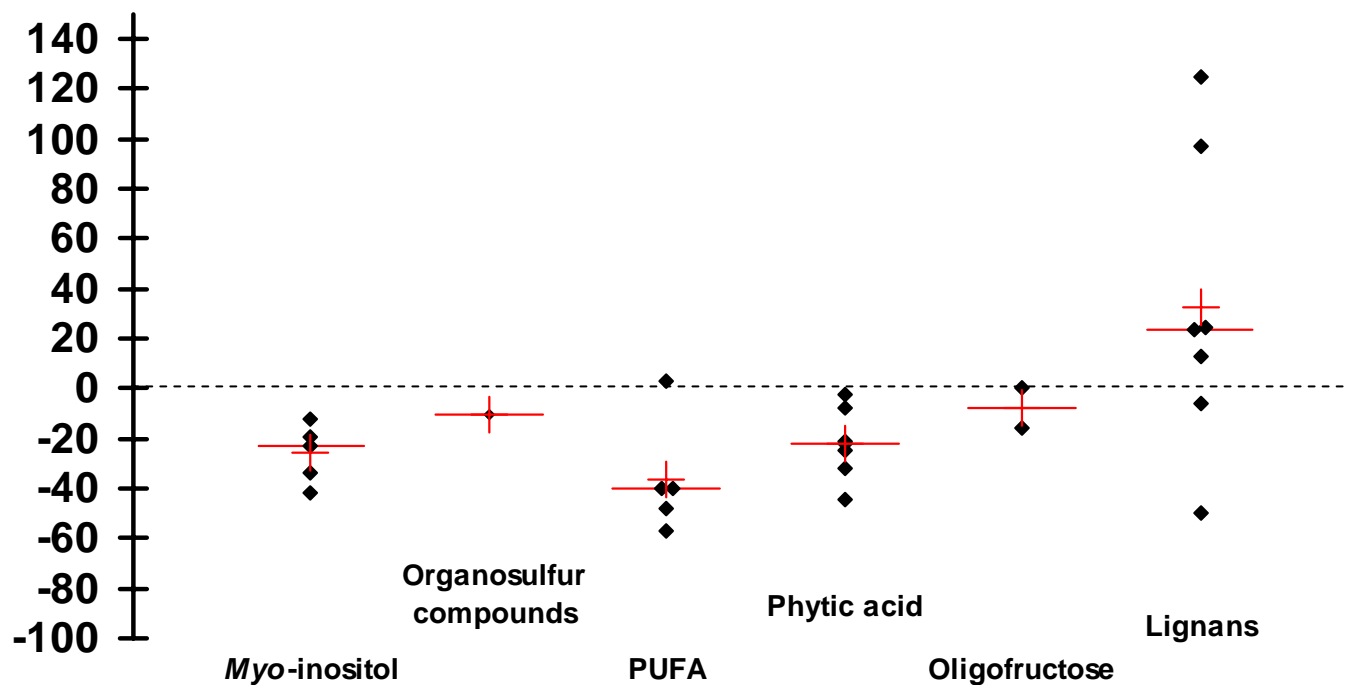
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Figure 4 A-E

A)



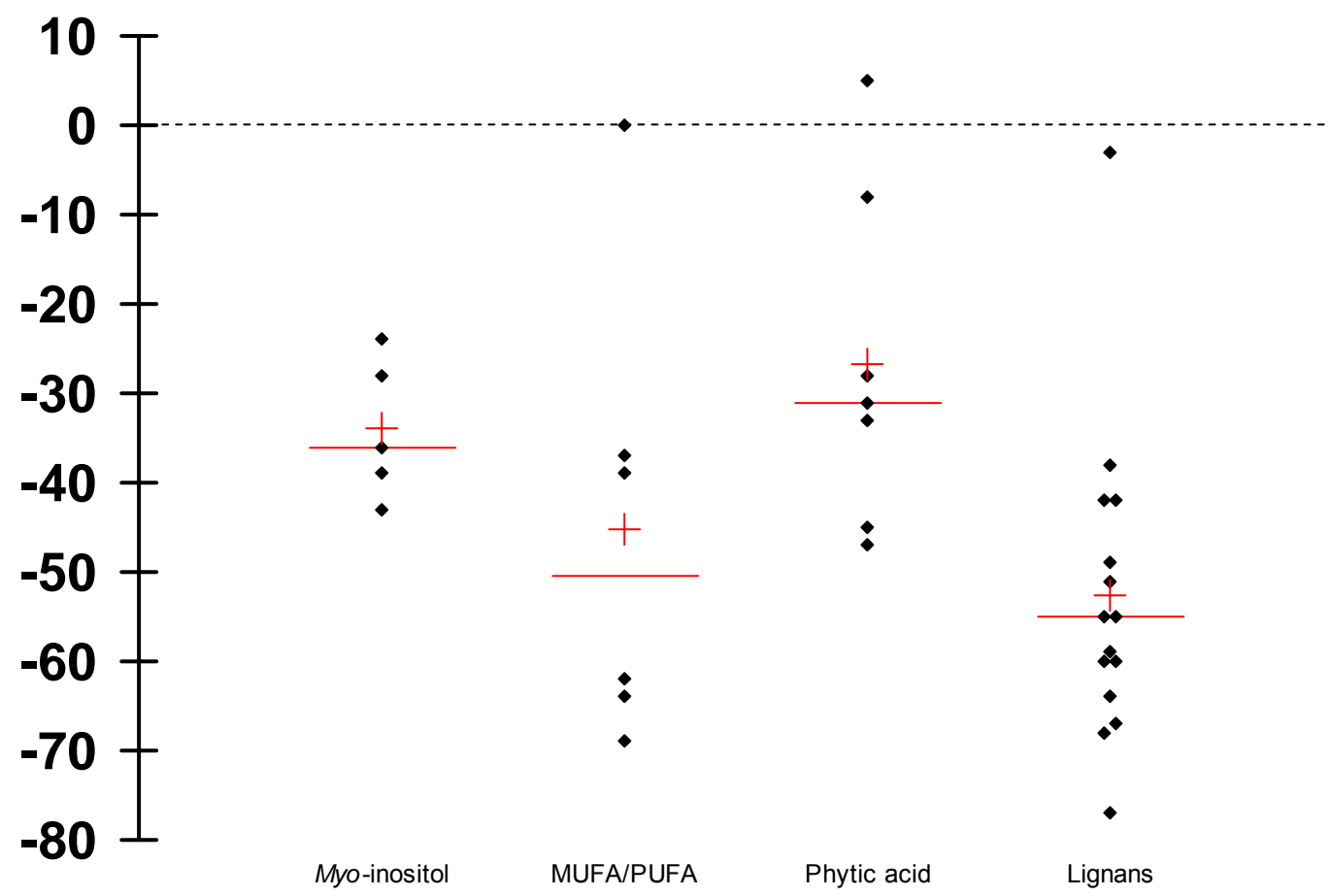
B)



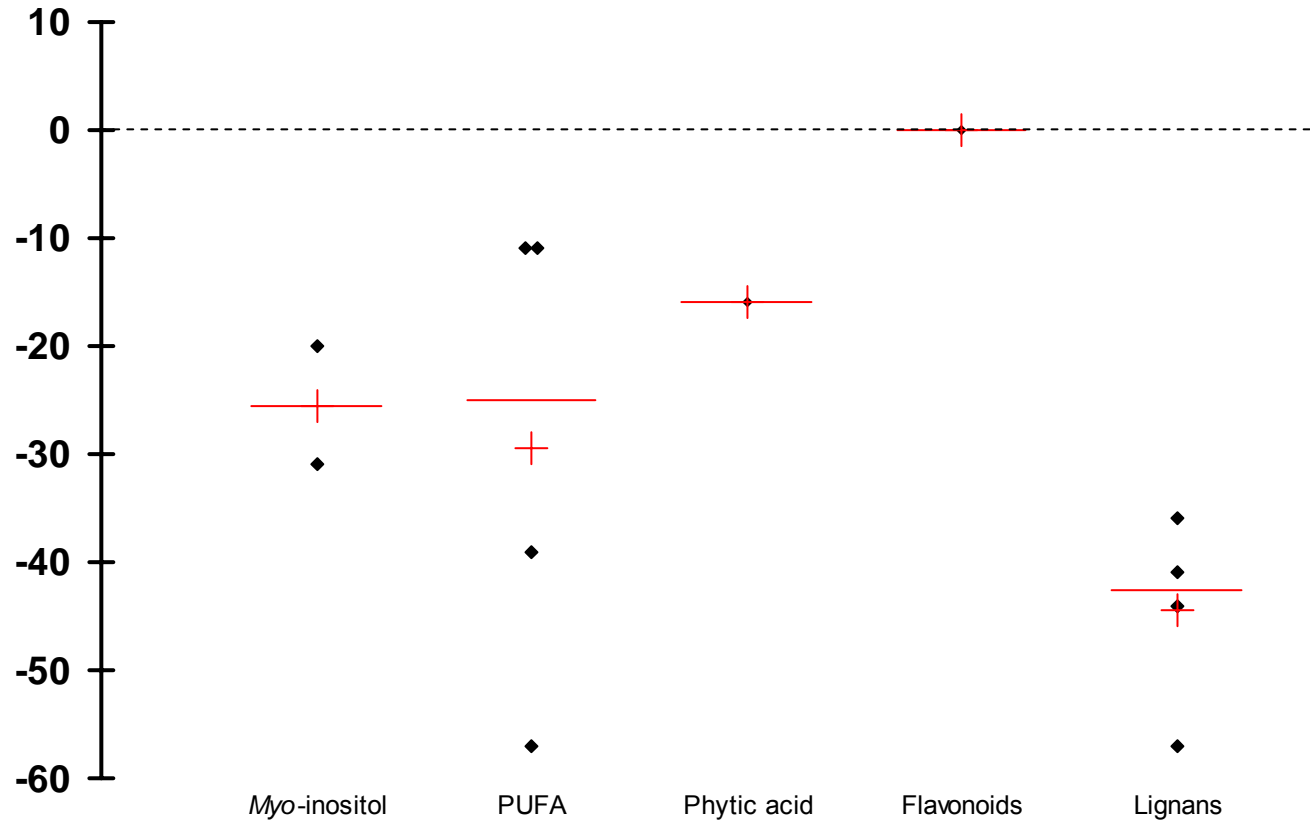
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C)

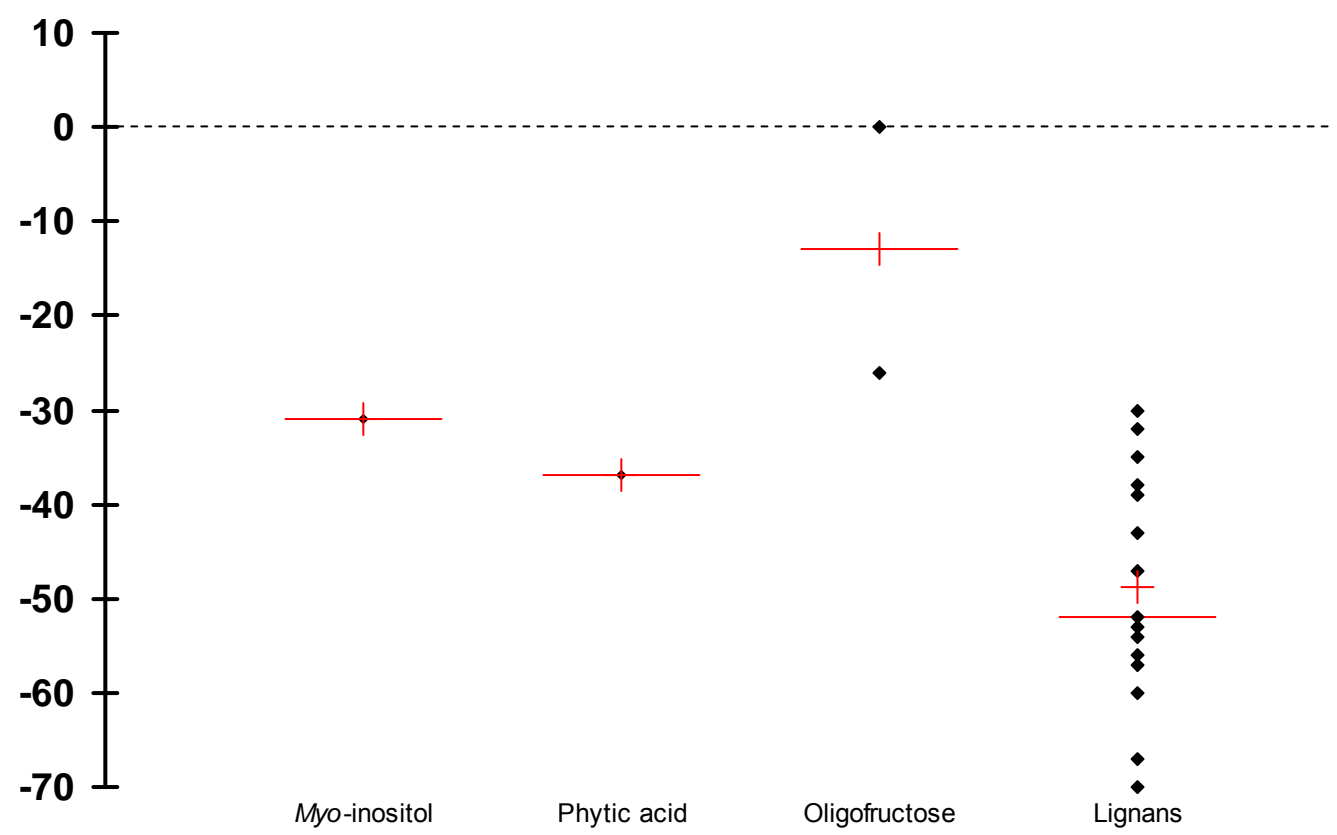


D)



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E)



1 Supplemental Tables

2 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 folate:

| 3 Lipotropic compounds | 4 <i>In vivo</i> or <i>in vitro</i> models | 5 Supplemented daily dose | 6 Duration of lipotrope exposition | 7 Hepatic effect(s) | 8 References |
|--|---|--------------------------------|------------------------------------|--|--------------------------------|
| 9 A - Main lipotropes | | | | | |
| 10 A1 - Betaine | | | | | |
| 11 Betaine | Rats fed high-fat (40%) diet | 120 mg | 21 days | ↓ FA percentage (-59%) ^b | (Best and Huntsman, 1932) |
| 12 Betaine | Rats fed high-fat (40%) diet | 100 mg | 21 days | ↓ FA percentage (-82%) | (Best, 1934) |
| 13 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) |
| 14 Betaine hydrochloride | 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%) | |
| 15 Betaine hydrochloride | Rats fed fat-free and methionine-restricted diet | 0.16% free betaine | 21 days | ↓ TL percentage (≈ -64%) | (Best et al., 1950) |
| 16 Betaine hydrochloride | Rats fed high-fat (30%) and methionine-restricted diet | 0.32% free betaine | 21 days | ↓ TL percentage (≈ -64%) | |
| 17 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) |
| 18 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) |
| 19 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) |
| 20 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) |
| 21 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) |
| 22 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 days without betaine (resp. -62, -59 and -71%) | (Hayes et al., 2003) |
| 23 Betaine | 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%) | |
| 24 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) |
| 25 Betaine | Ethanol-treated guinea pigs for the last 10 days | 2% of diet | 30 days | ↓ TG level (-43%) | (Balkan et al., 2004) |
| 26 Betaine | Isolated hepatocytes from ethanol-fed rats for 4 weeks | 1 mM | 4 hrs | ↓ TG content (≈ -20%) | (Kharbanda et al., 2005) |
| 27 Betaine | Mice fed high-fat (20% energy) diet | 1.5% of diet | 8 months | ↓ histologic liver injury (0.7 vs 3.5, <i>p</i> < 0.01) | (Borgschulte et al., 2008) |
| 28 A2 - Choline | | | | | |
| 29 Choline | Rats fed high-fat (40%) diet | 70 mg | 21 days | ↓ FA percentage (-64%) | (Best and Huntsman, 1932) |
| 30 Choline | Rats fed high-fat (40%) diet | From 10 to 117 mg | 21 days | ↓ FA percentage (from -40 to -69%) | |
| 31 Choline | Rats fed high-fat (40%) diet | 75 mg | 21 days | ↓ FA percentage (-68%) | (Best, 1934) |
| 32 Choline chloride | Rats fed high-fat (40%) diet | 70 mg | 21 days | ↓ FA percentage (-66%) | (Best and Huntsman, 1935) |
| 33 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) |
| 34 Choline chloride | 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%) | |
| 35 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) |

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

Commentaire [A.F.]

| | | | | | | |
|----|-------------------------------|--|----------------------------------|--------------------------|--|------------------------------|
| 1 | | | | | | |
| 2 | | 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 | |
| 3 | | | 4.5 g | ≈ 9 months | Case 5: marked improvement (e.g. ↓ ascites) | |
| 4 | | | | | | |
| 5 | | | 6 g then 4.5 g | ≈ 6 months then 6 months | Case 7: improvements (e.g. less abdominal paracenteses required) | |
| 6 | | | | | | |
| 7 | | | 4-6 g | 45 days | Case 8: steadily improvement (e.g. ascites disappeared) | |
| 8 | | | 1.5 g thrice | ≥ 4 weeks | Case 9: continued improvement (e.g. ↓ ascites and ↓ icterus index) | |
| 9 | | | 6 g | ≥ 10 days | Case 10: considerable improvements (e.g. ↓ ascites) | |
| 10 | Choline chloride (dessicated) | Rats fed fat-free and methionine-restricted diet | 0.16% free choline | 21 days | [Cases 1, 4 and 6: death or no improvement] ↓ TL percentage (≈ -75%), ↓ CE (≈ -69%) | (Best et al., 1950) |
| 11 | | | | | | |
| 12 | | Rats fed high-fat (30%) and methionine-restricted diet | 0.32% free choline | 21 days | ↓ TL percentage (≈ -73%) | |
| 13 | | | | | | |
| 14 | 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) |
| 15 | | | | | | |
| 16 | Choline chloride | Rats fed 20% protein choline-deficient diet | 0.26% of diet | 3 weeks | ↓ lipid percentage (-68%) | (Fritz and Dupont, 1957) |
| 17 | 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) |
| 18 | | | | | | |
| 19 | | Rats fed high-sucrose (69%) and casein (adequate methionine) diet → moderate fatty liver | 0.3% of diet | 14 days | ↓ lipid percentage (-51%) | |
| 20 | | | | | | |
| 21 | | Rats fed high-fat (lard: 39.9%) and soy protein (low methionine) diet | 0.3% of diet | 14 days | ↓ lipid percentage (-83%) | |
| 22 | | | | | | |
| 23 | | Rats fed high-fat (lard: 39.9%) and casein (adequate methionine) diet | 0.3% of diet | 14 days | ↓ lipid percentage (-75%) | |
| 24 | | | | | | |
| 25 | | Rats fed high-fat (butter fat: 39.9%) and soy protein (low methionine) diet | 0.3% of diet | 14 days | ↓ lipid percentage (-71%) | |
| 26 | | | | | | |
| 27 | | Rats fed high-fat (corn oil: 39.9%) and soy protein (low methionine) diet | 0.3% of diet | 14 days | ↓ lipid percentage (-66%) | |
| 28 | | | | | | |
| 29 | | 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%) | |
| 30 | | | | | | |
| 31 | | 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%) | |
| 32 | | | | | | |
| 33 | | | | | | |
| 34 | 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) |
| 35 | | | | | | |
| 36 | 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) |
| 37 | | | | | | |
| 38 | Choline chloride | Rats fed basal hypolipotropic and choline-deficient diet | 0.6% of diet | - ^c | ↓ total esterified FA content (-89%) | (Haines and Mookerjee, 1965) |
| 39 | | | | | | |
| 40 | | 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%) | |
| 41 | | | | | | |
| 42 | 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) |
| 43 | | | | | | |
| 44 | | | 0.75 or 1.00% of diet | 14 days | ↓ fat percentage for 1% choline only (-36%) compared to 0.50% choline + 0.1% niacin | |
| 45 | | | | | | |
| 46 | | | 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 | |
| 47 | 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) |
| 48 | | | | | | |
| 49 | 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) |
| 50 | | | | | | |
| 51 | | 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%) | |
| 52 | 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) |
| 53 | | | | | | |

| | | | | | | |
|----|----------------------------|--|---|-----------------|---|-------------------------------|
| 1 | | | | | ↑TG content in plasma VLDL (+85%) | |
| 2 | 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) |
| 3 | | | | | | |
| 4 | 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) |
| 5 | | | | | | |
| 6 | 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) |
| 7 | | | | | | |
| 8 | 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) |
| 9 | | | | | | |
| 10 | 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) |
| 11 | | | | | | |
| 12 | | 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) | |
| 13 | | | | | ↓ cholesterol content (-56%/beef tallow or -52%/safflower oil) | |
| 14 | | | | | ↓ PL content (-21%/beef tallow or -16%/safflower oil) | |
| 15 | | | | | ↑ % cholesterol of total lipid (+47%/beef tallow or no change/safflower oil) | |
| 16 | | | | | ↑ % PL of total lipid (+143%/beef tallow or +72%/safflower oil) | |
| 17 | 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) |
| 18 | | | | | | |
| 19 | | | | | | |
| 20 | 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 | (Singh et al., 1990) |
| 21 | | | | | No significant effect on protein kinase C activity | |
| 22 | | | | | | |
| 23 | Choline | Rats fed choline-deficient then re-fed with choline-supplemented diet | 0.48% of diet | 16 weeks | ↓ FFA (-87%), ↑ DRG (+915%) | (Da Costa et al., 1995) |
| 24 | | | | | | |
| 25 | 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 ±16.5 HU) | (Buchman et al., 1995) |
| 26 | 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) |
| 27 | | | | | | |
| 28 | | | | | | |
| 29 | | | | | | |
| 30 | | | | | | |
| 31 | | | | | | |
| 32 | | | | | | |
| 33 | | | | | | |
| 34 | | | | | | |
| 35 | 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) |
| 36 | | | | | | |
| 37 | | | | | | |
| 38 | | | | | | |
| 39 | A3 - Methionine | | | | | |
| 40 | | | | | | |
| 41 | Methionine | Rats fed high-fat (40%) diet | 0.5% of diet | 18-19 days | ↓ TL (-87%) | (Tucker and Eckstein, 1937) |
| 42 | <i>dl</i> -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) |
| 43 | | | | | | |
| 44 | <i>dl</i> -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) |
| 45 | | | | | | |
| 46 | | | | | | |
| 47 | <i>d</i> -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%) | |
| 48 | | | | | | |
| 49 | <i>l</i> -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%) | |
| 50 | | | | | | |
| 51 | 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) |
| 52 | <i>dl</i> -Methionine | Rats fed high-fat (20%) and high-sucrose | From 75 to 300 | 8 days | ↓ fat percentage (-64%) | (Griffith and Mulford, 1941) |
| 53 | | | | | | |
| 54 | | | | | | |
| 55 | | | | | | |
| 56 | | | | | | |
| 57 | | | | | | |
| 58 | | | | | | |
| 59 | | | | | | |
| 60 | | | | | | |

| | | | | | | |
|----|-------------------|---|----------------------------|---------------|---|----------------------------------|
| 1 | | (48.9%) diet | mg | | | |
| 2 | Methionine | Rats fed high-fat (40%) and 35% gelatin diet | 0.774% of diet | 21 days | ↓ crude FA content (-69%) | (Beveridge et al., 1945) |
| 3 | DL-Methionine | Rats fed high-fat (35%) and low casein (5%) diet | 1.02% of diet | 21 days | ↓ TL percentage (-63%) | (Eckstein, 1952) |
| 4 | | | | | | |
| 5 | 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) |
| 6 | | | | | | |
| 7 | 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) |
| 8 | | | | 65 days | ↓ fat percentage (mean decrease of -59%) | |
| 9 | | | 1.0% of diet | 65 days | ↓ fat percentage (mean decrease of -64%) | |
| 10 | 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) |
| 11 | | | | | | |
| 12 | | 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%) | |
| 13 | L-Methionine | Rats fed high-sucrose (69%), casein and choline-deficient diet at 21°C | 0.34 % of diet | 21 days | ↓ lipid percentage (-67%) | (Chahl and Kratzing, 1966b) |
| 14 | | | 0.68 % of diet | | ↓ lipid percentage (-68%) | |
| 15 | 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) |
| 16 | | | | | | |
| 17 | | Rats fed low-protein diet (5% casein) | 0.5% of diet | 3 weeks | ↑ total-coenzyme A (+17%) and acyl-coenzyme A (+6%) activities | |
| 18 | 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) |
| 19 | 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) |
| 20 | | | | | | |
| 21 | | | | | | |
| 22 | A4 - Myo-Inositol | | | | | |
| 23 | (free) | | | | | |
| 24 | | | | | | |
| 25 | 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) |
| 26 | | | | | | |
| 27 | 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) |
| 28 | | | | | | |
| 29 | Inositol | Depancreatized dogs | - | - | Small lipotropic activity but no so marked than a preparation of lipocaic | (Owens, 1942) |
| 30 | | | | | | |
| 31 | Inositol | Rats fed high-fat and cholesterol diet | - | - | Moderate lipotropic action | (Mchenry and Patterson, 1944) |
| 32 | | Rats fed fat-free diet, thiamine, riboflavin, pyridoxine and pantothenic acid and/or cholesterol | | | Moderate lipotropic action | |
| 33 | | | | | | |
| 34 | | | | | | |
| 35 | 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) |
| 36 | | Rats fed 12%-fat and methionine-restricted diet | 0.32% of diet | 21 days | No effect on TL percentage | |
| 37 | | Rats fed high-fat (30%) and methionine-restricted diet | 0.32% of diet | 21 days | No effect on TL percentage | |
| 38 | Inositol | Humans with hepatic dysfunctions | 1 g dissolved in 100 mL | - | ↓ cholesterolemia | (Gargini, 1951) |
| 39 | | | | | | |
| 40 | Inositol | Rats fed high-fat (51%) diet | 2.0 mg (3 x week) | 64 days | ↓ fat content (-17%) | (Drill, 1954) |
| 41 | | | | | | |
| 42 | | | 4.0 mg (3 x week) | 64 days | ↓ fat content (-24%) | |
| 43 | | | | | | |
| 44 | 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) |
| 45 | | | | | | |
| 46 | 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) |
| 47 | | | | | | |
| 48 | 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) |
| 49 | Inositol | Rats fed high-fat (51%) diet | 3 x 2 mg per week | 33 days | ↓ fat percentage (-17%, NS) | (Laird and Drill, 1971) |
| 50 | | | | | | |
| 51 | | | 3 x 4 mg per week | 33 days | ↓ fat percentage (-24%) | |
| 52 | | | | | | |
| 53 | | Rats fed high-fat (51%) diet and administered 3 | 3 x 2 mg per | 71 days | No significant change | |

| | | | | | |
|----|----------------------|---|------------------------|----------------|---|
| 1 | | x 2 mg choline, 1 µg cobalamin (B12) and 2.5 | week | | |
| 2 | | µg folic acid per week | | | |
| 3 | <i>Myo</i> -inositol | Rats fed a high-sucrose (65.5%), 10%-fat | 0.5% of diet | 1 week | ↓ TG (-61%), cholesterol (-13%), non-esterified FA (-16%) and PL (no significant change) contents (Hayashi et al., 1974a) |
| 4 | | (hydrogenated cottonseed oil) and <i>myo</i> - | | | |
| 5 | | inositol-deficient diet | | | |
| 6 | | Rats fed a high-sucrose (65.5%), 10%-fat | 0.5% of diet | 2 weeks | ↓ TG (-81%), cholesterol (-28%) and non-esterified fatty acid (no significant change) contents, ↑ PL content (+14%) |
| 7 | | (hydrogenated cottonseed oil) and <i>myo</i> - | | | |
| 8 | | inositol-deficient diet | | | |
| 9 | | Rats fed a high-sucrose (65.5%), 10%-fat | 0.5% of diet | 1 week | Natural vs hydrogenated cottonseed oil: no effect on TG and cholesterol contents |
| 10 | | (natural cottonseed oil) and <i>myo</i> -inositol- | | | |
| 11 | | deficient diet | | | |
| 12 | | Rats fed a high-sucrose (65.5%), 10%-fat | 0.5% of diet | 1 week | ↓ TG (-79%) and cholesterol (-17%) contents |
| 13 | | (hydrogenated soybean oil) and <i>myo</i> -inositol- | | | |
| 14 | | deficient diet | | | |
| 15 | | Rats fed a high-sucrose (65.5%), 10%-fat | 0.5% of diet | 1 week | ↓ TG (-36%) and cholesterol (-12%, NS) contents |
| 16 | <i>Myo</i> -inositol | (coconut oil) and <i>myo</i> -inositol-deficient diet | No | 1 week + 24 hr | ↑ 2.7 times the rate of [¹⁴ C]palmitate incorporation into liver lipids from labelled epididymal fat pads → ↑ FA mobilization from adipose tissues to the liver (Hayashi et al., 1974b) |
| 17 | | Rats fed a high-sucrose (65.5%) and <i>myo</i> - | | after | |
| 18 | | inositol-deficient diet | | palmitate | |
| 19 | | | | incubation | |
| 20 | | | | of | |
| 21 | | | | epididymal | |
| 22 | | | | fat pads | |
| 23 | | Rats fed a high-sucrose (65.5%) and <i>myo</i> - | No | 1 week + 24 hr | ↑ 2.5 times the level of [¹⁴ C]palmitate incorporation into liver lipids → ↓ disappearance (by transport and degradation) rate of FA from the liver |
| 24 | | inositol-deficient diet | | after | |
| 25 | | | | palmitate | |
| 26 | | | | injection in | |
| 27 | | | | tail vein | |
| 28 | <i>Myo</i> -inositol | Rats fed a high-sucrose (65.5%) and <i>myo</i> - | No | 2 weeks | ↓ L-glycerol 3-phosphate (direct precursor of TG) content (-62%) |
| 29 | | inositol-deficient diet | | | |
| 30 | | Lactating rat dams fed <i>myo</i> -inositol-deficient | 0.5% of diet | 21 days | ↓ TG (≈ -96%) and CE (≈ -95%) contents, ↑ PL (≈ +93%) content, no change in free cholesterol content; numerous large intracellular droplets in <i>myo</i> -inositol deficient 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) |
| 31 | | and high-sucrose (62.1%) diet + 0.5% | | lactation | |
| 32 | | phthalylsulfathiazole | | | |
| 33 | | | | | |
| 34 | | Lactating rat dams fed <i>myo</i> -inositol-deficient | 0.01, 0.05 and | 14 days | ↓ 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 (Andersen and Holub, 1980a) |
| 35 | | and high-sucrose (62.1%) diet + 0.5% | 0.5% of diet | lactation | |
| 36 | | phthalylsulfathiazole | | | |
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| 40 | <i>Myo</i> -inositol | Young rats fed high-glucose (60%) and <i>myo</i> - | 0.5% of diet | 7-14 days | ↓ TG level (-70%, n = 2 experiments, NS) (Andersen and Holub, 1980a) |
| 41 | | inositol-deficient diet | | | |
| 42 | | Old rats fed high-glucose (60%) and <i>myo</i> - | 0.5% of diet | 14 days | ↓ TG level (-6%, NS) |
| 43 | | inositol-deficient diet | | | |
| 44 | <i>Myo</i> -inositol | Rats fed high-glucose (60%) diet not | 0.075 and 0.5% | 7 days | ↓ TG level (respectively -48 and -76%) (Andersen and Holub, 1980b) |
| 45 | | supplemented with <i>myo</i> -inositol | of diet | | |
| 46 | | Rats fed high-glucose (60%) and <i>myo</i> -inositol- | ≈ 0.072 % of diet | 7 days | ↓ TG level (-71%) |
| 47 | | and choline-deficient diet | ≈ 0.072 % <i>myo</i> - | 7 days | ↓ TG level (-77%) |
| 48 | | | inositol % + ≈ | | |
| 49 | | | 0.015% | | |
| 50 | | | choline | | |
| 51 | | | 0.5 % of diet | 7 days | ↓ TG level (-74%) |
| 52 | | | 0.5 % <i>myo</i> - | 7 days | ↓ TG level (-92%) |
| 53 | | | inositol % + | | |

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| 1 | | | | | | |
| 2 | | | 0.056% | | | |
| 3 | | | choline | | | |
| 4 | <i>Myo</i> -inositol | Rats fed <i>myo</i> -inositol-deficient and balanced diet | 0.5% of diet | 14 days | ↓ TG level (≈-70%) | (Beach and Flick, 1982) |
| 5 | | | | 3 days | ↓ FAS (≈-31%: maximum reached) and ACC/CBX (≈-31%) specific activity | |
| 6 | | | | 12 hours | ↓ rate of FAS synthesis (≈-40%: maximum reached) | |
| 7 | <i>Myo</i> -inositol | Rat dam fed <i>myo</i> -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) |
| 8 | | | | | | |
| 9 | | Rat dam fed <i>myo</i> -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 | |
| 10 | | | | | | |
| 11 | Inositol | Mice (germ-free <i>vs</i> conventional) fed inositol-deficient and high-sucrose (60%) diet | No | 23 days | Degree of fatty liver more evident in conventional mice | (Ikeda et al., 1992) |
| 12 | | | | | ↓ ME activity/ g protein (≈-50% in germ-free <i>vs</i> ≈-27% in conventional mice) | |
| 13 | | | | | ↓ G6PDH activity/g protein (≈-45% in germ-free <i>vs</i> ≈-32% in conventional mice) | |
| 14 | | | | | ↓ ACC activity/g protein (≈-32% in germ-free <i>vs</i> no change in conventional mice) | |
| 15 | | | | | ↑ plasma TG (+29%, NS), FFA (+38%) and total cholesterol (+15%, NS) levels in germ-free mice | |
| 16 | | | | | ↑ plasma TG (+42%), FFA (+4%, NS) and total cholesterol (+6%, NS) levels in conventional mice | |
| 17 | | | | | ↓ TL (-38%), cholesterol (-34%) and TG (-66%) contents | (Katayama, 1993) |
| 18 | <i>Myo</i> -inositol | Rats fed AIN formula diet supplemented with 0.1% DDT | 0.2% of diet | 13-14 days | ↑ PL content (+8%) | |
| 19 | | | | | | |
| 20 | <i>Myo</i> -inositol | Rats fed high-starch/high-sucrose (65%) and <i>myo</i> -inositol-deficient diet | 0.1% of diet | 16-17 days | <u>Starch</u> : ↓ TL (-2%, NS), cholesterol (-2%, NS), and TG (-22%, NS) contents; ↑ PL content (+9%, NS); ↓ G6PDH (-26%, NS) and ME (-13%, NS) activities | (Katayama, 1994) |
| 21 | | | | | <u>Sucrose</u> : ↓ TL (-47%), cholesterol (-20%), and TG (-74%) contents; ↑ PL content (+6%, NS); ↓ G6PDH (-43%) and ME (-34%) activities | |
| 22 | | | | | | |
| 23 | <i>Myo</i> -inositol | Rats fed high-starch/high-sucrose (65%) and <i>myo</i> -inositol-deficient diet | 0.1% of diet | 12-13 days | <u>Starch</u> : ↓ 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 | (Katayama, 1997 ^b) |
| 24 | | | | | <u>Sucrose</u> : ↓ 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 | |
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| 28 | <i>Myo</i> -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) |
| 29 | | | | | | |
| 30 | | 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 | |
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| 37 | <i>Myo</i> -inositol | Rats fed high-starch/high-sucrose (50.2%) and <i>myo</i> -inositol-deficient diet | 0.2% of diet | 14-15 days | <u>Starch</u> : ↓ 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) | (Okazaki and Katayama, 2003) |
| 38 | | | | | <u>Sucrose</u> : ↓ 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) | |
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| 49 | | | 0.2% +0.07% | 14-15 days | <u>Starch</u> : ↓ 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 | |
| 50 | | | DDT | | <u>Sucrose</u> : ↓ total lipid (-40%), TG (-40%S), cholesterol (-33%) and | |
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| 1 | | | | | PL (-5%, NS) levels; no change in plasma TG, cholesterol and PL levels; ↓ ME (-37%), G6PDH (-44%) and FAS (-21%, NS) activity/mg protein | |
| 2 | | | | | ↓ 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) |
| 3 | | | | | ↓ 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 | |
| 4 | <i>Myo-, D-chiro- and L-chiro- inositol</i> | Rats fed high-sucrose (50.2%) and <i>myo</i> -inositol-deficient diet with 0.07% DDT | 0.2% <i>myo</i> -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 | |
| 5 | | | 0.2% D- <i>chiro</i> -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) |
| 6 | | | 0.2% L- <i>chiro</i> -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%) | |
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| 18 | <i>Myo</i> -inositol | Rats fed high-sucrose (50.3%) and <i>myo</i> -inositol-deficient diet | 0.2% <i>myo</i> -inositol | 14 days | | |
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| 30 | B - Magnesium and vitamins B | | | | | |
| 31 | vitamins B | | | | | |
| 32 | | | | | | |
| 33 | B1 - Magnesium | | | | | |
| 34 | | | | | | |
| 35 | 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) |
| 36 | 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) |
| 37 | | | 1.13 mM ATP + 0.67 mM Mg | 1 hour | ↑ CoA content (≈ +149%) and ↓ pantothenic acid content (≈ -69%) as compared with ATP alone | |
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| 40 | B2 - Niacin (vitamin B3) | | | | | |
| 41 | B3) | | | | | |
| 42 | | | | | | |
| 43 | 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) |
| 44 | Nicotinic acid | Rabbits fed high-cholesterol (2%) diet | 0.4% of diet | 8 weeks | ↓ cholesterol content (-77%) | (Merrill and Lemley-Stone, 1957) |
| 45 | 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) |
| 46 | | | | | | |
| 47 | 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) |
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| 51 | Nicotinic acid | 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%) | |
| 52 | 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) |
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| 1 | Nicotinic acid | Nondiabetic patients injected with C ¹⁴ -acetate | 3 to 6 g | 2 weeks | ↓ plasma cholesterol (-32%) | (Nunn et al., 1961) |
| 2 | Nicotinic acid | Hypercholesterolemic patients | 1 to 2 g three times | - | ↓ serum cholesterol suggesting marked reduction in hepatic synthesis | (Parsons, 1961) |
| 3 | | | | | | |
| 4 | 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) |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | 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%) | |
| 8 | 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) |
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| 12 | Nicotinamide | 33 weeks-old laying hens fed diet without nicotinamide | 0.002% of diet | - | ↓ fat percentage (-12%) | (Hartfiel and Kirchner, 1973) |
| 13 | | | | | | |
| 14 | | 41 weeks-old laying hens fed diet without nicotinamide | 0.002 and 0.005 % of diet | - | ↓ fat percentage (resp. -16 and -29%) | |
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| 16 | | 45 weeks-old laying hens fed diet without nicotinamide | 0.005 and 0.01 % of diet | - | ↓ fat percentage (resp. -8 and no change) | |
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| 18 | 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 <i>via</i> β-oxidation | (Yeh, 1979) |
| 19 | Nicotinic acid | Partially purified ACC from chicken liver incubated <i>in vitro</i> | 10, 20, 50 and 100 mkmoles/0.9 mL | - | ↓ ACC activity (resp. -19, -45, -70 and -100%) | (Fomenko et al., 1979) |
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| 23 | Nicotinic acid | Hyperlipidemic male patients | 1 g thrice | 5 weeks | ↑ biliary output of cholesterol (+26%) and lecithin (phospholipids, +17%, NS); | (Grundy et al., 1981) |
| 24 | | | | | | |
| 25 | | | | 48 hours | ↓ plasma VLDL-TG activity | |
| 26 | 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) |
| 27 | | | | | | |
| 28 | | 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 | |
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| 32 | 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) |
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| 36 | | HepG2 cells incubated with 0.4 mmol/L oleic acid (inhibits 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) | |
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| 41 | | 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%) | |
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| 45 | 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) |
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| 49 | | 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) | |
| 50 | | | | | | |
| 51 | 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) |
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| 2 | | <i>sn</i> -1,2-dioleoylglycerol | | | selectively ↓ DGAT-2 activity (-100%), not DGAT-1 activity (no change) | |
| 3 | Copper nicotinic acid complex | Rats fed high-carbohydrate (40% starch and 40% sucrose) and fat-free semi-synthetic 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) |
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| 7 | Niacin | <i>APOE*3Leiden.CETP</i> 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 ($\mu\text{g}/\text{mg}$ protein); ↓ CETP mRNA expression (-74% at 0.1% niacin and -88% at 1% niacin) | (Van Der Hoorn et al., 2008) |
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| 11 | 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%) <u>Plasma ApoA-I</u> : ↑ concentration (+16%) and production rate (+21%); no significant effect upon fractional catabolic rate <u>Plasma ApoA-II</u> : no effect upon concentration, production rate and fractional catabolic rate <u>Plasma ApoB-100 in TG-rich lipoprotein</u> : ↓ concentration (+-39%) and ↑ fractional catabolic rate (+48%); no significant effect upon production rate <u>Plasma ApoB-48 in TG-rich lipoprotein</u> : ↓ concentration (+-28%) and ↑ fractional catabolic rate (+46%); no significant effect upon production rate | (Lamon-Fava et al., 2008) |
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| 23 | Niacin | HepG2 cells preincubated with or without niacin for 48 hours, then incubated 16 hours with ^{125}I -labeled HDL (5-10 $\mu\text{g}/\text{mL}$) | 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) |
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| 25 | | | | | | |
| 26 | Niacin | HepG2 cells | 1 and 5 mM | 48 hours | ↑ ABCA1 (resp. \approx 1.35 and 1.45-fold) and PPAR α (resp. \approx 1.35 and 1.95-fold) gene expression; no significant effect upon ApoA-1 transcription levels | (Siripurkpong and Na-Bangehang, 2009) |
| 27 | | | | | | |
| 28 | | HepG2 cells first loaded 24 h with cholesterol | 1, 3 and 5 mM | 48 hours | ↓ intracellular cholesterol (resp. \approx -20, -36 and -32%) | |
| 29 | | | | | | |
| 30 | B3 - Pantothenic acid (vitamin B5) | | | | | |
| 31 | | | | | | |
| 32 | | | | | | |
| 33 | Pantothenic acid | Dogs fed high-sucrose (66%) and pantothenic acid-deficient diet | No | \geq 4 weeks | ↑ fat percentage (+202%); necropsy reveals fatty livers | (Schaefer et al., 1942) |
| 34 | | | | | | |
| 35 | 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) |
| 36 | | | | | | |
| 37 | | | | | | |
| 38 | 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) |
| 39 | | | | | | |
| 40 | 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) |
| 41 | | | | | | |
| 42 | 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) |
| 43 | | | | | | |
| 44 | | | | | | |
| 45 | 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) |
| 46 | | | | | | |
| 47 | Ca-pantothenate | Rats fed pantothenate-deficient diet | 0.002% of diet | 10 weeks | ↑ CoA content (+39%) | (Aiyar et al., 1959) |
| 48 | 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) |
| 49 | | | | | | |
| 50 | 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) |
| 51 | | | | | | |
| 52 | 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) |
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| 1 | | 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 | Killed at birth: ↑ fat percentage (resp. ≈ +35, +18 and +25%); ↓ fat percentage (-21%)/6 th week deficiency Killed at 7 days: ↑ fat percentage (resp. ≈ +33, +260 and +13%); ↓ fat percentage (-7%)/7 th week deficiency | |
| 2 | 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 | (Williams et al., 1968) |
| 3 | 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) |
| 4 | | 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 | |
| 5 | 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) |
| 6 | 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) |
| 7 | 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) |
| 8 | 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 (pantothenic acid) | 12 or 24 hours | Pantethine: 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 Pantothenic acid: 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) |
| 9 | 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) |
| 10 | 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) |
| 11 | 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 restoration upon pantothenic acid supplementation | (Youssef et al., 1994) |
| 12 | 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 | Phosphopantothenate: ↓ 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%) Pantethine: ↓ 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)

| | | | | | | |
|----|-------------------|---|---|----------------------|---|---------------------------|
| 8 | 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) |
| 9 | | Rats fed high-sucrose (56%), 10% glycine and 2% ribonucleic acid diet | 0.0005% of diet | 60 days | ↓ total FA content (-56%) | |
| 10 | | 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) | |
| 11 | | 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) | |
| 12 | | 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) | |
| 13 | Folic acid | Rats fed high-fat (51%) diet | 2.5 µg (3 x week) | 64 days | ↓ fat content (-13%) | (Drill, 1954) |
| 14 | | | 25.0 µg (3 x week) | 64 days | ↑ fat content (+11%) | |
| 15 | 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%) | |
| 16 | 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) |
| 17 | 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 | <u>Liver histology:</u> abnormal histopathology demonstrating features of steatosis, necrosis and inflammation compared to other 3 groups (normal folates, folate deficient and normal folate +ethanol) <u>Ethanol + folate vs normal + folates:</u> ↓ methionine level (-39%) <u>Ethanol - folate vs normal + folates:</u> ↓ methionine level (-68%) <u>Normal vs normal - folates:</u> ↓ methionine level (-25%) No significant effect of folate deficiency on MS activity <u>Ethanol - folates vs ethanol + folates:</u> ↑ BHMT (+14%) | (Halsted et al., 2002) |
| 18 | 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): • <u>Standard diet - folates:</u> ↓ long-chain acyl-coenzyme A dehydrogenase (2.10-fold) and farnesyl diphosphate synthase (3.60-fold) gene expression • <u>Ethanol diet - folates:</u> ↓ long-chain acyl-coenzyme A dehydrogenase (2.50-fold) and farnesyl diphosphate synthase (7.39-fold) gene expression <u>Without ethanol:</u> 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 <u>With ethanol:</u> 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) |
| 19 | Folic acid | Fetal liver from female rats fed folic acid-deficient (AIN)-76 formula diet | No | 21 days of gestation | <u>Affects fat metabolism:</u> ↑ PEBP (+36%), 4-trimethylaminobutyraldehyde dehydrogenase (+44%) and dienoyl-CoA isomerase (+44%) relative abundance (<i>i.e.</i> up-regulation); ↑ L-CPT-1 (+174%) and ↓ CD36 (-40%) gene expression | (Mcneil et al., 2009) |

{Christensen, 2010 #23801}: folate deficiency in mice

1 ^aAll terms used in the Table are precisely those of the article considered: for example, 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
2 relevant interpretations
3 ^bIndicates 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)
4 ^cNo data given in the reference
5 ^dValproate 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)
6 **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, Adenosine TriPh
7 Betaine Homocysteine MethyTransferase; b.w., body weight; CCE, Citrate Cleavage Enzyme (or ATP-Citrate Lyase, ATPCL); CCl₄, 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
8 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,
9 (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
10 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, PhosphatidylEtha
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For Peer Review Only

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 short-chain fatty acids, melatonin, tocotrienol, policosanol and *para*-aminobenzoic acid^a

| Lipotropic compounds | <i>In vivo</i> or <i>in vitro</i> models | Supplemented daily dose | Duration of lipotrope exposition | Hepatic effect(s) | References |
|--|--|---|----------------------------------|--|-----------------------------|
| Carnitine | | | | | |
| <i>dl</i> -carnitine hydrochloride | Rat liver slices incubated with C ¹⁴ long-chain FA (from 63 to 142 μ M), <i>i.e.</i> 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 μ M) <i>i.e.</i> 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. \approx +50 and \approx +7%) | (Fritz, 1964) |
| | Liver slices from rat | 0.1 or 1 mM | 30 min | ↑ palmitate conversion into CO ₂ (resp. \approx +30 and \approx +37%) and ketones (resp. \approx +260 and \approx +400%); no effect on plmitate conversion into lipids (free of FFA); ↓ palmitate conversion into FFA (\approx 0 and \approx -50%) | |
| | Liver homogenates (from rats) | 0.5 mM | 30 min | ↑ palmitate conversion into CO ₂ (\approx +22%); ↓ palmitate conversion into neutral glycerides (\approx -47%) and PL (\approx -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 (\approx -50%), TG (\approx -50%), cholesterol (\approx -50%) and PL (\approx -50%) | (Rhew and Sachan, 1983) |
| DL-Carnitine-HCl | Rats fed ethanol-rich (36% of calories) diet | 1% of diet (\pm 0.5% L-lysine-HCl and 0.2% L-methionine, 2 | 56 days | <u>Ethanol vs ethanol+carnitine:</u> ↓ TL (-28%), TG (-62%), CE (-28%), FC (-14%), TC (-26%), PL (-20%) and FFA (+9%, NS) <u>Ethanol vs ethanol+lysine+methionine:</u> ↓ TL (-24%), TG (-46%), CE (-24%), FC (-11%), TC (-22%), PL (- | (Sachan et al., 1984) |

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|----|------------------------|---|---|------------------------------|--|------------------------------|
| 1 | | | | | | |
| 2 | | | carnitine precursors) | | 13%, NS) and FFA (+32%) | |
| 3 | | | | | <u>Ethanol vs ethanol+carnitine+lysine+methionine:</u> | |
| 4 | | | | | ↓ TL (-27%), TG (-47%), CE (-31%), FC (-14%), TC (-28%), PL (-2%, NS) and FFA (+24%, NS) | |
| 5 | 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) |
| 6 | L-Carnitine | Pregnant rats fed wheat gluten (unsupplemented, <i>i.e.</i> 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 | <u>Low protein level:</u> ↓ TG content for nonpregnant rats (resp. -48 and -34%, NS) and pregnant rats (resp. -45%, NS, and -32%, NS) No significant 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 | (Ortega, 1989) |
| 7 | Carnitine deficiency | | | | <u>High protein level:</u> No significant effect on TG, PI and cholesterol contents for both un- and pregnant rats | |
| 8 | | | | | <u>TL:</u> resp. -11 (NS), -33, -55, -47 and -38% | (Rhew and Sachan, 1986) |
| 9 | 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 | <u>TG:</u> resp. -4 (NS), -31, -64, -61 and -52% <u>FC:</u> resp. -1 (NS), -10 (NS), -14 (NS), -7 (NS), and -2% (NS), <u>CE:</u> resp. -3 (NS), -4 (NS), -15 (NS), -5 (NS) and +9% (NS) <u>TC:</u> resp. -2 (NS), -6 (NS), -15, -6 (NS) and +6% (NS) <u>PL:</u> resp. +5 (NS), -8 (NS), -6 (NS), -4 (NS) and -16 (NS) ↑ nonesterified FA concentrations (NS): resp. +0.3, +16, +19, +19 and +25% | |
| 10 | | | | | <u>Liver histology (light microscopy):</u> no significant change in the grade of steatosis | (Bowyer et al., 1988) |
| 11 | L-Carnitine | 3 females on home parenteral nutrition (carnitine deficiency) with abnormalities in standard liver function tests (notably moderate or severe steatosis, <i>i.e.</i> grade ≥2) | 1 g daily i.v. | 1 month | No significant effect on TG content (resp. +4, +34 and +25%) | |
| 12 | 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 | <u>High-fat vs high-fat+carnitine:</u> 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 <u>Control vs Carnitine (3 weeks):</u> ↓ TL (-3%, NS), TG (-10%, NS) and cholesterol (-22%) levels <u>Cholesterol vs chol+carnitine (10 days):</u> ↓ TL (-7%, NS) and TG (-8%, NS) levels; ↑ cholesterol level (+16%, NS) | (Shimura and Hasegawa, 1993) |
| 13 | | | | | ↓ 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) |
| 14 | L-Carnitine-HCl | <i>jvs/jvs</i> 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 | | |
| 15 | | | | | Normal rats: ↓ TG (-57%) and cholesterol (-32%) contents Cirrhotic rats: ↓ TG (-51%) and cholesterol (-22%) contents | (Liang et al., 1999) |
| 16 | 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 | | |
| 17 | Carnitine-deficiency | Rats fed vegetarian food poor in carnitine and fed THP (20 mg/100 g/day) | - | 6 weeks | <u>Histological observations:</u> ↓ severity of steatosis ↓ 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) |
| 18 | | | | | ↓ total TG content (-38%) | (Clark et al., 2007) |
| 19 | L-Carnitine L-tartrate | Ovariectomized rats fed AIN-93M diet | 0.015% of diet | 8 weeks | <u>Fed state:</u> ↑ TG content (+275%); ↓ PL (-22%), FFA -7%, NS, total acyl-CoA (-11%, NS) and malonyl-CoA (-17%, NS) contents | (Degrace et al., 2007) |
| 20 | Carnitine-deficiency | Mildronate (that yields carnitine depletion)-treated rats (fed vs fasted state) | - | 10 days | <u>Fasted (18 hours) state:</u> ↑ TG (+815%) and FFA (+70%) contents; ↓ PL (-36%), total acyl-CoA (-4%, NS) and malonyl-CoA (-33%, NS) contents | |
| 21 | | | | | <u>Fasted state:</u> ↓ palmitate oxidation/metabolisation level (≈ -50%); ↑ | |
| 22 | | Perfused livers from mildronate-treated rat (fed | - | 90 min | | |

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| 2 | | 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 PPAR ₂ mRNA levels; ↑ DGAT1 (≈ +90%), LDLR (≈ +120%), FAT/CD36 (≈ +40%), FABpm (≈ +40%), ACO (≈ +335%) and PPAR _α (≈ +20%, NS) mRNA levels | |
| 3 | | | | | <u>Fed state</u> : no change for levels of oxidation and esterification; ↓ FABPpm (≈ -50%); no change in CPT I _α and CPT I _β isoforms, mRNA, mtGPAT, microsomal DGAT1, CTPpct, ApoB, LDLR, LPL and FAT/CD36 mRNA levels | |
| 4 | 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>i.e.</i> 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) |
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| 18 | Hydroxycitric acid (HCA) | | | | | |
| 19 | | | | | | |
| 20 | (-)-Hydroxycitrate (from <i>Garcinia cambogia</i>) | 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) |
| 21 | | | | | | |
| 22 | | | | | | |
| 23 | (-)-Allo-hydroxycitrate (from <i>Hibiscus sabdariffa</i>) | 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) | |
| 24 | | | | | | |
| 25 | | | | | | |
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| 27 | | | | | | |
| 28 | Sodium (-)-hydroxycitrate | Rats fed 10-15 days with high-glucose/high-fructose (58%) diet, then i.v. injected with ³ H ₂ O 45 min after i.p. HCA injection and killed 45-60 min after ³ H ₂ O injection | From 0.1 to 4.0 mmoles/kg b.w. | i.p. injection 45 min before ³ H ₂ O injection | ↓ FA synthesis (-25-30% at 0.1 mmole/kg b.w.) <u>High-fructose</u> : ↓ FA synthesis (≈ -67, -73, -77 and -82% at resp. = 0.6, 1.3, 2.3 and 4.0 mmoles/kg b.w.) <u>High-glucose</u> : ↓ FA synthesis (≈ -55, -74 and -85% at resp. = 0.3, 0.8 and 1.5 mmoles/kg b.w.) | (Lowenstein, 1971) |
| 29 | | | | | | |
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| 32 | | | | | | |
| 33 | (-)-Hydroxycitrate lactone (from <i>Garcinia cambogia</i>) | 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) |
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| 1 | | | | | |
| 2 | | b.w. fed orally | (stomach | | |
| 3 | | (by stomach | tube) | | |
| 4 | (-)-Hydroxycitrate | Liver high-speed supernatants collected 13 days | 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) |
| 5 | | after feeding rats with a high-glucose (70%) | | | |
| 6 | (+)-Hydroxycitrate | diet, and added with 5 or 10 μmol/mL of [1,5- | | | ↑ 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%) |
| 7 | | ¹⁴ C]citrate | | | |
| 8 | | | | | |
| 9 | (-)-Allo- | | | | ↓ rate of lipogenesis (resp. -10 and -6% at 5 mM citrate; -12 and -2% at 10 mM citrate) |
| 10 | Hydroxycitrate | | | | |
| 11 | (+)-Allo- | | | | ↑ rate of lipogenesis (resp. +31 and +4% at 5 mM citrate; +8 and +3% at 10 mM citrate) |
| 12 | Hydroxycitrate | | | | |
| 13 | (-)-Hydroxycitrate | Rats fed 13 days with high-glucose (70%) diet, | 2.63 mmoles/kg | 60 min | ↓ rate of lipogenesis (-42%) |
| 14 | (+)-Hydroxycitrate | then i.v. injected with [¹⁴ C]alanine and killed 3 | b.w. (by | before | ↑ rate of lipogenesis (+16%) |
| 15 | (-)-Allo- | hours after beginning of feeding | stomach tube) | feeding | ↓ rate of lipogenesis (-2%) |
| 16 | Hydroxycitrate | | | | |
| 17 | (+)-Allo- | | | | ↑ rate of lipogenesis (+4%) |
| 18 | Hydroxycitrate | | | | |
| 19 | (+)-Hydroxycitrate | Liver from rats fed 70% glucose diet for 7 days | 2.63 mmoles/kg | 2, 4, 6, 8, | <u>Rate of lipogenesis from [¹⁴C]alanine:</u> ≈ -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 |
| 20 | | and killed 30 min after i.v. injection of | b.w. (orally) | 10, 12, 15, | (Sullivan et al., 1974b) |
| 21 | | [¹⁴ C]alanine or ³ H ₂ O | the last day | 18, 21 or | |
| 22 | | | before killing | 24 hours | <u>Rate of lipogenesis from ³H₂O:</u> ≈ -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) |
| 23 | | | | | |
| 24 | | | | | |
| 25 | | Rats fed 70% glucose diet for 9 days and killed | 2.63, 5.26 or | 4 hours | ↓ rate of lipogenesis (resp. -42, -78 and -89%) |
| 26 | | 30 min after i.v. injection of [¹⁴ C]alanine | 10.52 | before | |
| 27 | | | mmol/kg b.w. | killing | |
| 28 | | | (orally) the | | |
| 29 | | | last day | | |
| 30 | | Liver from rats fed 70% glucose diet for 30 days, | 0.17, 0.33, 0.66, | 30 days | <u>Without 10 mM hydroxycitric acid added:</u> ↑ rate of lipogenesis (resp. ≈ +13, NS, ≈ +25%, NS, ≈ +56, ≈ +104 and ≈ +108%) |
| 31 | | then incubated <i>in vitro</i> with 10 mM [¹⁴ C]citrate | 1.32 or 2.63 | | <u>With 10 mM hydroxycitric acid added:</u> ↑ rate of lipogenesis (resp. ≈ 0, ≈ +18%, NS, ≈ +55, ≈ +105 and ≈ +118%) |
| 32 | | | mmol/kg b.w. | | Rate of lipogenesis was lower when adding 1 mM hydroxycitric acid <i>in vitro</i> (from ≈ -54 to ≈ -53%) |
| 33 | | | (orally) ±1 | | |
| 34 | | | mM added <i>in vitro</i> after | | |
| 35 | | | killing | | |
| 36 | | Rats fed 70% glucose diet for 9 days and killed | 0.33, 0.66, 1.32 | 11 days | ↓ rate of lipogenesis from [¹⁴ C]alanine (resp. -27, NS, -21, NS, -76 and -43%) |
| 37 | | 30 min after i.v. injection of [¹⁴ C]alanine or | or 2.63 | | |
| 38 | | ³ H ₂ O | mmol/kg b.w. | | ↓ rate of lipogenesis from ³ H ₂ O (resp. -22, NS, -13, NS, -49 and -37%) |
| 39 | | | (via stomach | | |
| 40 | | | tube) | | |
| 41 | | Rats fed 70% glucose diet for 30 days and killed | 0.66, 1.32 or | 30 days | ↓ rate of lipogenesis from [¹⁴ C]alanine (resp. -6, NS, -29 and -49%) |
| 42 | | 30 min after i.v. injection of [¹⁴ C]alanine or | 2.63 mmol/kg | | ↓ rate of lipogenesis from ³ H ₂ O (resp. 0, -20 and -32%) |
| 43 | (-)-Hydroxycitrate | ³ H ₂ O | b.w. (orally) | | |
| 44 | (Na) ₃ | Rats fed 70% glucose diet | 1.32 mmol/kg | 11 days | ↓ lipid content (-9%, NS) |
| 45 | (-)-Hydroxycitrate | | b.w. | | (Sullivan et al., 1974a) |
| 46 | | 3-hr meal-fed rats | - | 24 hours | ↓ significantly the rate of FA synthesis over 8-hr period when control animals had elevated rates |
| 47 | | | | | (Sullivan et al., 1974c) |
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| 1 | | | | | | |
| 2 | | i.v. injected with Triton WR 1339 ⁴⁰⁰ (250 | 2.63 mmol/kg | 6 hours | ↓ FA synthesis rate from ³ H ₂ O (-43%) | |
| 3 | | mg/kg) | b.w. (oral | | | |
| 4 | (-)-Hydroxycitrate | Hep G2 cells incubated with [1,5- ¹⁴ C]citrate | ≥0.01 and ≤10 | 2.5 hour | ↓ incorporation of [1,5- ¹⁴ C]citrate into FA and cholesterol: IC ₅₀ | (Berkhout et al., 1990) |
| 5 | | | mM | preincubati | (concentration given 50% inhibition) = 0.01-0.5 mM | |
| 6 | | | | on | | |
| 7 | | Hep G2 cells incubated with ³ H ₂ O | 1 mM | 18 hours | ↓ cholesterol (-73%) and FA (-34%, NS) syntheses | |
| 8 | | Hep G2 cells incubated 3 hours with ¹²⁵ I-LDL (10 | 2.5 mM | 18 hours | ↑ LDL-receptor-mediated association (=+49%) and degradation (= | |
| 9 | | μg/mL) | | preincubati | +107%) | |
| 10 | | | | on | | |
| 11 | | Hep G2 cells incubated 2.5 hours with ¹²⁵ I-LDL | 2 mM | 16 hours | ↑ receptor-mediated binding of LDL to Hep G2 cells (= +64% at = 4 | |
| 12 | | (from = 4 to = 38 μg/mL) | | preincubati | μg/mL ¹²⁵ I-LDL and =+41% at = 38 μg/mL ¹²⁵ I-LDL) | |
| 13 | Hydroxycitrate | Hyperinsulinemic obese subjects fed controlled | 6 g | 6 days | No decrease in hepatic <i>de novo</i> lipogenesis measured after fasting | (Schwarz et al., 1999) |
| 14 | | high carbohydrate diet (68% energy) | | | or fructose infusion | |
| 15 | (-)-Hydroxycitrate | Overweight subjects | 750 mg | 8 weeks | ↓ blood TG (-7%), VLDL (-15%, NS) and LDL (-6%) levels | (Badmaev et al., 2002) |
| 16 | (-)-Hydroxycitrate | Obese subjects | 2800 mg | Middle time | ↓ blood LDL (resp. -4%, NS, and -12%), TG (resp. -4%, NS, and - | (Preuss et al., 2004b) |
| 17 | (from a calcium- | | | (0 < time < | 9%) and TC (resp. -3%, NS, and -6%) concentrations; ↑ HDL | |
| 18 | potassium salt of | | | 8 weeks) | concentration (resp. +0.3%, NS, and +11%); ↓ VLDL | |
| 19 | 60% HCA extract | | | and 8 | concentration (resp. -3%, NS, and -3%, NS) | |
| 20 | from <i>Garcinia</i> | | | weeks | | |
| 21 | (-)-Hydroxycitrate | Obese subjects | 2800 mg | 4 and 8 | ↓ blood LDL (resp. -7 and -13%), TG (resp. -3%, NS, and -6%, NS) | (Preuss et al., 2004a) |
| 22 | (from a calcium- | | | weeks | and TC (resp. -3%, NS, and -7%) concentrations; ↑ blood HDL | |
| 23 | potassium salt of | | | | (resp. +5 and +8%) and VLDL (resp. +7%, NS, and +4%, NS) | |
| 24 | 60% HCA extract | | | | concentrations | |
| 25 | from <i>Garcinia</i> | | | | | |
| 26 | from <i>Garcinia</i> | | | | | |
| 27 | SuperCitriMax-600- | Rats fed high-fructose (48%) diet | 0.018% of diet | 26 days | ↑ post-prandial lipid content (= +67%) | (Brandt et al., 2006) |
| 28 | SXG* (60% HCA) | | | | | |
| 29 | Hydroxycitric acid | Rats fed high-carbohydrate or high-fat diet | 1.6 or 3.2% of | 8 weeks | Tends to ↓ ATPCL/CCE activity and ↑ CPT activities | (Hong et al., 2007) |
| 30 | | | diet | | | |
| 31 | Calcium- | Obese women | 1.15 g <i>Garcinia</i> | 2 months | ↓ serum TG (-23%) and TC (-5%, NS) contents; ↑ serum HDL level | (Roongpisuthipong et al., 2007) |
| 32 | hydroxycitrate | | <i>atrovitridis</i> 3 | | (+3%, NS) | |
| 33 | (water soluble) | | times | | | |
| 34 | from <i>Garcinia</i> | | | | | |
| 35 | <i>atroviridis</i> | | | | | |
| 36 | Organosulfur | | | | | |
| 37 | compounds | | | | | |
| 38 | Sulfur-containing | Rats fed high-cholesterol (1%) diet | 0.5% of diet | 2 weeks | <u><i>s</i>-methyl-L-cysteine sulfoxide</u> : ↓ TL (-11%, NS), TC (-18%), FC (- | (Itokawa et al., 1973) |
| 39 | amino acids | | | | 24%) and cholesterol/PL (-18%); no effect on PL content | |
| 40 | | | | | <u><i>s</i>-allyl-L-cysteine sulfoxide</u> : ↓ TL (-5%, NS), TC (-21%), FC (-24%) | |
| 41 | | | | | and cholesterol/PL (-18%); no effect on PL content | |
| 42 | | | | | <u><i>s</i>-methyl-cysteine</u> : ↓ TL (-1%, NS), TC (-10%, NS), FC (-9%, NS) | |
| 43 | | | | | and cholesterol/PL (-11%, NS); no effect on PL content | |
| 44 | <i>S</i> -allyl cysteine | Hepatocytes isolated from rat liver and incubated | 0.05, 0.1, 0.5, | 4 hours | ↓ rate of [1- ¹⁴ C]acetate incorporation into cholesterol at 2.0 (-21%) | (Yeh and Yeh, 1994) |
| 45 | | with 0.5 mM [1- ¹⁴ C]acetate | 1.0, 2.0 and | | and 4.0 (-27%) mM; no significant changes at other | |
| 46 | | | 4.0 mM | | concentrations | |
| 47 | | | | | No significant reduction in rate of FA synthesis from [1- ¹⁴ C]acetate | |
| 48 | Petroleum ether-, | Hepatocytes isolated from rat liver and incubated | 1x or 5x (≅ 0.25 | 4 hours | <u>At 1x concentration</u> : ↓ [1- ¹⁴ C]acetate incorporation into cholesterol | |
| 49 | methanol- and | with 0.5 mM [1- ¹⁴ C]acetate or 0.1 mM [2- | and 1.25 mg | | (resp. -10%, NS, -15%, NS, and -53%) and FA (resp. -9%, NS, - | |
| 50 | water-extractable | ³ H]glycerol (-oleic acid or +acetic acid) | dry garlic | | 62 and -64%) | |
| 51 | fractions of fresh | | powder added | | <u>At 5x concentration</u> : | |
| 52 | garlic | | to 2 mL | | - ↓ [1- ¹⁴ C]acetate incorporation rate into cholesterol (resp. -36, -44 | |
| 53 | | | incubation | | and -64%) and FA (resp. -29, -59 and -62%); | |
| 54 | | | medium) | | - ↑ [2- ³ H]glycerol incorporation rate into TG (resp. +8%, NS, +15% | |

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|----|--------------------------------|--|------------------|---------|--|---------------------------|
| 1 | | | | | and +9%, NS) and PL (resp. = 0, +9 and +28%) in presence of | |
| 2 | | | | | oleic acid | |
| 3 | | | | | - ↓ [2- ³ H]glycerol incorporation rate into TG (resp. -14, -9 and - | |
| 4 | | | | | 12%), diacylglycerols (resp. -21, -9 and -20%) and PL (resp. -26, | |
| 5 | | | | | -21 and -21%) in presence of acetic acid | |
| 6 | S-methyl cysteine | Diabetic (alloxan-treated) rats | 200 mg/kg b.w. | 45 days | ↓ TC (-10%), TG (-13%) and PL (-6%) contents | (Kumari et al., 1995) |
| 7 | sulphoxide (from | | (by stomach | | | |
| 8 | <i>Allium cepa</i>) | | tube) | | | |
| 9 | Organosulfur | Hepatocytes (from rats fed a standardized diet) | From 0.1 to 1000 | 2 hours | ↓ biosynthesis of nonsaponifiable neutral lipids from [¹⁴ C]acetate: | (Gebhardt and Beck, 1996) |
| 10 | compounds (from | incubated with [¹⁴ C]acetate or [¹⁴ C]mevalonate | μM | | - allicin: -11% (NS) at 50 mM and -32% at 500 mM | |
| 11 | <i>Allium sativum</i>) | | | | - diallyl disulfide: -3% (NS) at 100 mM, -9% at 250 mM and -15% | |
| 12 | | | | | at 500 mM | |
| 13 | | | | | - allyl mercaptan: -4% (NS) at 100 mM, -8% at 250 mM and -13% | |
| 14 | | | | | at 500 mM | |
| 15 | | | | | ↓ incorporation of [¹⁴ C]mevalonate into nonsaponifiable neutral | |
| 16 | | | | | lipids (= -38%); 1,2-vinyl-dithiin at 1000 μM | |
| 17 | | | | | ↓ incorporation of [¹⁴ C]acetate into cholesterol: | |
| 18 | | | | | - diallyl disulfide: -22 (10 μM), -56 (100 μM), -93 (200 μM) and - | |
| 19 | Organosulfur | Hepatocytes isolated from rats fed a standard non | 0.05-4.0 mM | 4 hours | -99% (1000 μM) | |
| 20 | compounds (from | purified diet and incubated with sodium salt of | | | - allyl mercaptan: -10 (100 μM), -16 (200 μM) and -77% (1000 μM) | (Liu and Yeh, 2000) |
| 21 | <i>Allium sativum</i>) | [2- ¹⁴ C]acetate | | | <u>Water-soluble compounds</u> (s-allyl-cysteine, s-ethyl-cysteine, s- | |
| 22 | | | | | propyl-cysteine, γ-glutamyl-s-allyl cysteine, γ-glutamyl-s-methyl | |
| 23 | | | | | cysteine, γ-glutamyl-s-propyl cysteine and s-allyl | |
| 24 | | | | | mercaptocysteine): ↓ incorporation of [¹⁴ C]acetate into FA from | |
| 25 | | | | | 42 to 55% maximal inhibition (IC ₅₀ from 0.58 for s-methyl | |
| 26 | | | | | cysteine to 1.72 mM for γ-glutamyl-s-propyl cysteine) | |
| 27 | | | | | <u>Lipid-soluble compounds</u> (diallyl sulphide, diallyl disulfide, diallyl | |
| 28 | Water- (WEF), | HepG2 cells incubated with [2- ¹⁴ C]acetate or [2- | 0.05-4.0 mM | - | trisulfide, dipropyl sulphide and dipropyl disulfide): ↓ | (Yeh and Liu, 2001) |
| 29 | methanol- (MEF) | ³ H]glycerol and garlic extracts (MEF, PEF and | | | incorporation of [¹⁴ C]acetate into FA from 0 to ≈ 25% at 0.05 mM | |
| 30 | and petroleum | WEF at 1.25 g/L) or organosulfur compounds | | | and from ≈ 42 to 100% at 4 mM | |
| 31 | ether-(PEF) | | | | ↓ incorporation of [2- ¹⁴ C]acetate into cholesterol (-44% for MEF, - | |
| 32 | extractable | | | | 36% for PEF, -64% for WEF, -77% for Kyolic - ≈ 0.4 mM s-allyl | |
| 33 | fractions of garlic, | | | | cysteine - and ≈ -22% for s-allyl cysteine at 2 mM) | |
| 34 | Kyolic ⁵ , water- | | | | ↓ incorporation of [2- ³ H]glycerol into TG (from -9 to -14% for | |
| 35 | and lipid-soluble | | | | WEF, MEF and PEF), but only in presence of acetate, not FA | |
| 36 | organosulfur | | | | <u>Water-soluble compounds</u> (s-allyl, s-ethyl and s-propyl cysteine): ↓ | |
| 37 | comounds (from | | | | dose-dependently incorporation of [2- ¹⁴ C]acetate into cholesterol | |
| 38 | <i>Allium sativum</i>) | | | | (maximal inhibition of 40-60% at 2.0-4.0 mM) | |
| 39 | | | | | <u>Water-soluble glutamate derivatives</u> (γ-glutamyl s- | |
| 40 | | | | | allyl/methyl/propyl cysteine): ↓ incorporation of [2- ¹⁴ C]acetate | |
| 41 | | | | | into cholesterol (from -20 to -35%) | |
| 42 | | | | | <u>Water-soluble alliin, s-allyl acetylcysteine and s-allyl</u> | |
| 43 | | | | | sulfonylalanine: no effect on incorporation of [2- ¹⁴ C]acetate into | |
| 44 | | | | | cholesterol | |
| 45 | | | | | <u>Lipid soluble compounds</u> (diallyl sulphide/trisulfide, dipropyl | |
| 46 | Kyolic ^d and water- | HepG2 cells incubated with [2- ¹⁴ C]acetate | 0.05-0.8 mM | - | sulphide/disulfide and methyl allylsulfide): ↓ incorporation of [2- | (Lee and Yeh, 2003) |
| 47 | soluble | | | | ¹⁴ C]acetate into cholesterol (from -10 to -15% at 0.05-0.5 mm); | |
| 48 | organosulfur | | | | cytotoxic at 1.0-4.0 mM | |
| 49 | comounds (from | | | | IC ₅₀ of water-soluble compounds: from 0.34 (S-propyl cysteine) to | |
| 50 | <i>Allium sativum</i>) | | | | 1.88 (γ-glutamyl s- propylcysteine) mM | |
| 51 | | | | | <u>Kyolic</u> : ↓ incorporation of [2- ¹⁴ C]acetate into cholesterol (-30% at | |
| 52 | | | | | 0.2 mM and -55% at 0.4 mM: equivalent to 0.2 and 0.4 mM of s- | |
| 53 | | | | | allyl-cysteine) | |
| 54 | | | | | <u>s-allyl- and s-propyl cysteine</u> : no effect at 0.05-0.2 mM | |
| 55 | | | | | <u>Kyolic (≈ 0.3 mM S-allyl-cysteine) + s-allyl-cysteine (0.4 and 0.8</u> | |
| 56 | | | | | <u>mM)</u> : further ↓ incorporation of [2- ¹⁴ C]acetate into cholesterol | |
| 57 | | | | | <u>Kyolic + s-propyl cysteine (0.4 mM)</u> : similar additive effect on ↓ | |
| 58 | | | | | incorporation of [2- ¹⁴ C]acetate into cholesterol | |
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| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 |
| Organosulfur compounds | Mice fed high-fat (18%) diet | 1 g/L of drinking water | 4 weeks | <i>N</i> -acetyl cysteine: ↓ TG (-5%) and cholesterol (-23%) contents; ↓ ME (-19%) and FAS (-24%) activities <i>s</i> -allyl cysteine: ↓ TG (-11%) and cholesterol (-24%) contents; ↓ ME (-11%) and FAS (-29%) activities <i>s</i> -ethyl cysteine: ↓ TG (-7%) and cholesterol (-11%, NS) contents; ↓ ME (-12%) and FAS (-22%) activities <i>s</i> -methyl-cysteine: ↓ TG (-15%) and cholesterol (-24%) contents; ↓ ME (-18%) and FAS (-26%) activities <i>s</i> -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 | <i>N</i> -acetyl cysteine: ↓ TG (-33%) and cholesterol (-25%) contents <i>s</i> -allyl cysteine: ↓ TG (-37%) and cholesterol (-23%) contents <i>s</i> -ethyl cysteine: ↓ TG (-30%) and cholesterol (-11%, NS) contents <i>s</i> -methyl-cysteine: ↓ TG (-25%) and cholesterol (-9%, NS) contents <i>s</i> -propyl-cysteine: ↓ TG (-43%) and cholesterol (-28%) contents | (Hsu et al., 2004) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <i>s</i> -methyl cysteine sulfoxide (from <i>Allium cepa</i> 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 | <i>n</i> -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%) <i>s</i> -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%) <i>s</i> -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 | <i>s</i> -allyl-cysteine: ↓ TG content (≈ -47%); ↓ FAS activity (-30%); no significant effect upon TC content and malic enzyme and HMG-CoA reductase activities <i>s</i> -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) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 39 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 | <u>Linolenate</u> : ↓ FAS (-55%), G6PDH (-62%) and ME (-40%, NS) activities, and rate of FA synthesis from [U- ¹⁴ C]glucose (-50%) <u>Stearate</u> : ↑ 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 | <u>Linolenate</u> : ↓ FAS (-40%, NS), G6PDH (-37%) and ME (-40%) activities, and rate of FA synthesis from [U- ¹⁴ C]glucose (-24%, NS) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

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| 4 | Methyl linoleate (C18:2) vs methyl oleate (C18:1) | Rats fed fat-free and high-glucose (72%) diet | 3% of diet | 7 days | <p>Palmitate: ↑ G6PDH (+15%, NS) and ME (+8%, NS) activities, and ↓ FAS activity (-20%, NS) and rate of FA synthesis from [U-¹⁴C]glucose (-18%, NS)</p> <p>Linoleate: ↓ FAS activity (-13%, NS) and rate of FA synthesis from [U-¹⁴C]glucose (-24%, NS) and ³H₂O (-6%, NS); no effect on G6PDH (0%) and ME (+3%, NS) activities</p> <p>Oleate: ↓ FAS (-38%), G6PDH (-39%) and ME (-31%) activities, and rate of FA synthesis from [U-¹⁴C]glucose (-26%) and ³H₂O (-16%)</p> | |
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| 9 | 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 | <p>Linoleate: ↓ FAS (-50%), GPDH (-64%) and ME (-48%) activities, and ↓ rate of FA synthesis from ³H₂O (-54%)</p> <p>Linolenate: ↓ FAS (-63%), GPDH (-69%) and ME (-57%) activities, and ↓ rate of FA synthesis from ³H₂O (-60%)</p> <p>Palmitate: ↑ FAS (+6%, NS), GPDH (+30%) and ME (+17%, NS) activities, and ↑ rate of FA synthesis from ³H₂O (+8%, NS)</p> | |
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| 15 | Ethyl linoleate (C18:2) | Rats fed fat-free and high-glucose (72%) diet for 7 days then supplemented with PUFA, injected with ³ H ₂ O and killed 20 min after injection | 5% of diet | 1, 2, 3 or 4 days | <p>↓ FA synthesis (resp. 0, -25, 41 and -59%)</p> <p>↓ FAS (resp. 0, -19%, NS, -44 and -56%) and ACC (resp. -11%, NS, -11%, NS, -39 and -57%) activities</p> | (Toussant et al., 1981) |
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| 17 | | | | | | |
| 18 | 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) |
| 19 | 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 | <p>↓ TG (-42%), cholesterol (-10%, NS) and PL (-3%, NS) contents</p> <p>↑ mitochondrial (+37% with palmitoyl-CoA as substrate and +35% with palmitoyl-L-carnitine as substrate) and peroxisomal β-oxidation</p> <p>↑ 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</p> <p>↑ relative mRNA levels of CPT-II (+69%), 2,4-dienoyl-CoA reductase (+191%) and ACO (+72%)</p> <p>↑ FA oxidation (≈ +142%)</p> | (Willumsen et al., 1997) |
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| 28 | | Rat hepatocytes incubated with [1- ¹⁴ C]oleic acid | Ratio methyl 3-thia-TODT:BSA = 2.5:1 | 4 hours | | |
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| 32 | 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) |
| 33 | | | | | | |
| 34 | EPA ethyl ester | Leptin-deficient <i>ob/ob</i> mice (obesity model) fed high-carbohydrate and fat-free diet | 15% triolein+5% EPA or 20% tuna fish oil | 7 days | <p>↓ SREBP-1 nuclear form expression (≈ 3-fold lower)</p> <p>Suppress expression of SREBP-1-target lipogenic genes (FAS and SCD1) and of <i>S₁₄</i> gene</p> <p>Induced expression of PPARα and ACO</p> <p>↓ TG (resp. ≈ -26 and ≈ -44%) and TC (resp. ≈ -11%, NS and ≈ -15%, NS) contents</p> | (Sekiya et al., 2003) |
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| 39 | 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) |
| 40 | | | | | | |
| 41 | | Leptin-deficient B6.V- <i>Lep^{ob}</i> mice fed standard chow | 2.4 g/kg b.w. | 30 days | No difference in fat percentage | |
| 42 | Omega-3 fatty acids (from fish oil) | Mice fed fat-free and high-carbohydrate diet | 600 μ L (oral or i.v.) | 19 days | <p>↓ macrovesicular steatosis (-10%, digital image analysis)</p> <p>↓ fat content (resp. -70 and -62%)</p> <p>Had only minor micro-vesicular steatosis</p> | (Alwayn et al., 2005b) |
| 43 | | | | | | |
| 44 | 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) |
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| 49 | 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 | <p>Females: ↑ PL content (+3%); no effect on TC, FC, CE and TG contents</p> <p>Males: ↓ TC (-25%), FC (-13%), CE (-26%) and TG (-20%) contents; no effect on PL content</p> | (Morise et al., 2006) |
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| 1 | 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>i.e.</i> ↓ hepatocellular vacuolation and fat content from ≈ 51-75% to ≈ >25% ↓ TG (≈ -29%) and cholesterol (≈ -25%) levels | (Song et al., 2008) |
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| 5 | 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) |
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| 9 | EPA, DPA and DHA | <i>db/db</i> 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) |
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| 16 | Linseed oil (ALA-rich) | Wild-type (WT) and PPAR α -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; ↑ PPAR α expression (≈ +98%) and no effect on PPAR γ , 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%); ↑ PPAR α expression (+61%) and no effect on PPAR γ , 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 PPAR α and SREBP2 expressions; ↓ PPAR γ 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 PPAR α , PPAR γ and SREBP2 expressions | (Morise et al., 2009) |
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| 34 | LA (18:2 n-6), DPA | HepG2 cells | 6, 60 or 120 μ M | 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) |
| 35 | 22:5 n-6, OA | | | | | |
| 36 | 18:1 n-9, AA | | | | | |
| 37 | 20:4 n-6, ALA | | | | | |
| 38 | (18:3 n-3), EPA | | | | | |
| 39 | (20:5 n-3) and | | | | | |
| 40 | DHA (22:6 n-3) | | | | | |
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| 43 | Short-chain fatty acids | | | | | |
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| 46 | 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 ₂ O (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 ₂ O; 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) |
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| 51 | SCFA | Isolated liver cells from rats fed standard chow diet and incubated with ³ H ₂ O 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) |
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| 2 | | substrates in near-physiological concentration | and butyrate) | | (\approx -55%) and cholesterol (\approx -30%) synthesis from $^3\text{H}_2\text{O}$; \downarrow FA (\approx - | |
| 3 | | of glucose, glutamine and acetate | and 2 mM | | 51-70% for 0.3-2.5 mM acetate/0.6 mM propionate and \approx -62- | |
| 4 | | | (acetate) | | 70% for 0.3-2.5 mM acetate/1.2 mM propionate) and cholesterol | |
| 5 | | | | | (\approx -27-64% for 0.3-2.5 mM acetate/0.6 mM propionate and \approx -33- | |
| 6 | | | | | 55% for 0.3-2.5 mM acetate/1.2 mM propionate) synthesis from | |
| 7 | | | | | 1- ^{14}C acetate; no inhibition of FA and cholesterol synthesis from | |
| 8 | | | | | 1- ^{14}C butyrate | |
| 9 | | | | | <u>Acetate</u> : \uparrow intracellular citrate (+19%, NS) and ketone body (+25%, | |
| 10 | | | | | NS, for β -HB and +14%, NS, for acetoacetate) concentrations | |
| 11 | | | | | <u>Butyrate</u> : \uparrow intracellular citrate (+89%) and ketone body (+275% for | |
| 12 | | | | | β -HB and +121% for acetoacetate) concentrations | |
| 13 | | | | | <u>Propionate + acetate</u> : \downarrow intracellular citrate (-2%, NS) and ketone | |
| 14 | | | | | body (0% for β -HB and -14%, NS, for acetoacetate) | |
| 15 | | | | | concentrations; \downarrow FA (\approx -50%) and cholesterol (\approx -30%) synthesis | |
| 16 | | | | | from $^3\text{H}_2\text{O}$ | |
| 17 | | | | | <u>Propionate + butyrate</u> : \uparrow intracellular citrate (-80%) and ketone body | |
| 18 | | | | | (+200% for β -HB and +93% for acetoacetate) concentrations; \uparrow | |
| 19 | SCFA mixture | Liver slices from rats fed 14 days sucrose-based | 3.5% acetate, | 1.5 hours | \uparrow cholesterol synthesis rate vs fibre-free diet (\approx +60%, NS) | (Hara et al., 1999) |
| 20 | sodium salts of | diet (\approx 65%) or sugar beet fiber-base diet | 2.2% | | \downarrow cholesterol synthesis rate vs sugar beet fibre diet (\approx -14%, NS) | |
| 21 | acetic, propionic | (10%) and incubated with $^3\text{H}_2\text{O}$ | propionate | | | |
| 22 | and butyric acids | | and 9% | | | |
| 23 | simulating | | butyrate in rat | | | |
| 24 | fermentation | | diet (14 days) | | | |
| 25 | products of SBF | Rats fed fibre-free and sucrose-based or sugar | | 14 days | \downarrow cholesterol synthesis rate vs fibre-free diet or sugar beet fibre diet | |
| 26 | produced by cecal | beet fibre (10%) diets and i.v. injected $^3\text{H}_2\text{O}$ | | | (\approx -36%) | |
| 27 | bacteria) | the last day | | | | |
| 28 | Propionate | Hepatocytes isolated from Zucker <i>fa/fa</i> rats fed | 0.3 and 0.6 mM | 180 min | \downarrow TL (intracellular + extracellular) synthesis (resp. -30%, NS, and - | (Daubioul et al., 2002) |
| 29 | | control diet, and incubated with [1- ^{14}C]- | | | 35%); no effect on TG synthesis | |
| 30 | | acetate (2 mM) or [1- ^{14}C]-palmitate (0.2 mM) | | | | |
| 31 | | and with propionate at higher and mean | | | | |
| 32 | | concentrations found in portal vein of fructan- | | | | |
| 33 | Acetic acid | treated (10% of diet) Zucker rats (resp. 0.3 | | | | |
| 34 | | and 0.6 mM) | | | | |
| 35 | | Mice fed high-fat (27.1%) diet | 0.3 or 1.5% | 42 days | \downarrow TG (resp. -15 and -17%) and TC contents (resp. -13 and -14%) | (Kondo et al., 2009) |
| 36 | | | solution at 10 | | \uparrow PPAR α (resp. 1.15- and 1.16-fold), ACO (resp. 1.78- and 1.60- | |
| 37 | | | mL/kg b.w. | | fold), CPT-1 (resp. 1.42- and 1.28-fold) and ACC (resp. 1.03- and | |
| 38 | | | administered | | 1.03-fold, NS) mRNA levels/expression; no effect on SREBP-1 | |
| 39 | | | via a stomach | | mRNA level/expression; \downarrow mRNA level/expression of FAS (resp. | |
| 40 | | | tube | | 0.73- and 0.79-fold, NS) | |
| 41 | | HepG2 cells transfected with a negative-control | 100, 200 or 500 | 3 hours | \uparrow PPAR α (resp. \approx 1.45-, \approx 1.7- and \approx 1.65-fold), ACO (resp. \approx 1.2-, | |
| 42 | | number 1 siRNA or validated siRNAs targeting | μM | | NS, \approx 1.65- and \approx 1.9-fold) and CPT-1 (resp. \approx 1.4-, \approx 1.6- and \approx | |
| 43 | | human $\alpha 2$ (catalytic subunit) AMPK | | | 1.85-fold) mRNA levels in HepG2 cells transfected with a | |
| 44 | | | | | negative-control | |
| 45 | Melatonin | | | | No change in HepG2 cells transfected with a validated siRNAs | |
| 46 | | | | | targeting human $\alpha 2$ AMPK | |
| 47 | Melatonin | Rats fed high-cholesterol (1% +0.5% bile salts) | 12.5 mg/kg b.w. | 30 days | \downarrow cholesterol level (-21%) | (Chan and Tang, 1995) |
| 48 | | diet | i.p. | | | |
| 49 | Melatonin | Mink (<i>Mustela vison</i>) fed diet with 33% energy | Subcutaneous | \approx 2-3 months | <u>Males</u> : \downarrow polar lipid (-3%, NS), cholesterol (-5%, NS), TG levels (- | (Nieminen et al., 2001) |
| 50 | | coming from fat, 46% from proteins and 21% | 2.7-mg | | 65%) and FFA (-10%, NS) contents; \downarrow lipase esterase activity (- | |
| 51 | | from carbohydrates | implant, i.e. \approx | | 30%) | |
| 52 | | | 10 μg daily | | <u>Females</u> : \downarrow cholesterol (-29%), TG levels (-87%) and FFA (-25%, | |
| 53 | | | | 4 months | NS) contents; no change in polar lipid content (+0.3%, NS); \downarrow | |
| 54 | | | | | lipase esterase activity (-1%, NS) | |

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|----|--|--|--------------------------------------|--------------|---|------------------------------|
| 1 | 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) |
| 2 | Melatonin | Rats fed high-cholesterol (2%) diet | 2.5, 5 and 10 mg/kg i.p. injected | 12 weeks | ↓ 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) |
| 3 | Melatonin | Rats fed standard pellets | 0.5 and 1.0 mg/kg b.w. i.p. injected | 45 days | ↓ TC (resp. -7%, NS, -17 and -28%) and TG (resp. -9%, NS, -9%, NS, and -17%) contents | (Subramanian et al., 2007) |
| 4 | Melatonin | Rats fed high-fat diet | 10 and 50 mg/kg b.w. injected i.p. | 8 weeks | ↓ cholesterol (resp. ≈ -71 and -71%), PL (resp. ≈ -36 and -37%), TG (resp. ≈ -57 and -58%) and FFA (resp. ≈ -34 and -36%) levels | (Kuzu et al., 2007) |
| 5 | Melatonin | Mice fed high-fat (34.9%) diet | 10 mg/kg i.p. injected | 12 weeks | <u>Histological analyses</u> : ameliorates liver steatosis | (Shieh et al., 2009) |
| 6 | Tocotrienols | | | | | |
| 7 | <i>d</i> -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) |
| 8 | <i>γ</i> -tocotrienols | 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%) | (Parker et al., 1993) |
| 9 | <i>γ</i> -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) |
| 10 | <i>α</i> -tocotrienols | 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) | (Parker et al., 1993) |
| 11 | <i>α</i> -tocotrienols | HepG2 cells | 10 μM | 16 hours | ↓ HMG-CoA reductase protein level (≈ -75%) and LDL receptor protein level (≈ +75%) | (Parker et al., 1993) |
| 12 | <i>α</i> -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) | (Parker et al., 1993) |
| 13 | Tocotrienols | Male guinea pigs fed 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) |
| 14 | Tocotrienols (isolated from palm oil FA distillate) ^a | 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) |
| 15 | Policosanols ^b | | | | | |
| 16 | Policosanols | Rats fed standard diet | 500 mg/kg b.w. | 4 weeks | ↓ cholesterol biosynthesis from ³ H ₂ O (-26%) | (Menendez et al., 1996) |
| 17 | Policosanols | Liver microsomes | 5 or 50 μg/mL | 60 min | No significant effect on HMG-CoA reductase activity | (Menendez et al., 1996) |
| 18 | Policosanols | Rabbits fed 27%-casein diet (hypercholesterolaemic diet) | 50 mg/kg b.w. | 30 days | ↓ cholesterol biosynthesis from ³ H ₂ O (≈ -48%) | (Menendez et al., 1997) |
| 19 | Policosanols or geraniol ^c | Mice fed for 7 days control diet and i.v. injected with Triton WR1339 ^d 3 hours before killing | 10 or 67 mg/kg b.w. | 7 days | ↓ newly synthesized cholesterol (resp. -24 and -28%) | (Wu et al., 2005) |
| 20 | <i>Para</i> -aminobenzoic acid | | | | | |
| 21 | <i>Para</i> -aminobenzoic acid | Man | 2 g 4 times | ≈ 5 days | ↓ serum cholesterol level (-12%) | (Failey and Childress, 1962) |

^aAll terms used in the Table are precisely those of the article considered: for example, 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 comparison relevant interpretations

^bIndicates the decreased or increased percentage induced by the lipotrope compared to the control, *i.e.* steatogen diet (NS - Not Significant - means absence of significance for the change observed; in other cases, the effect was either significant or no information was given in the article)

^cNo data given in the reference

^dKyolic is an aged garlic extract containing *s*-allyl cysteine, *s*-ethyl cysteine and *s*-propyl cysteine

^eContains 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

^fMixture of high-molecular-mass aliphatic alcohols isolated and purified from sugar cane wax (main component is octacosanol followed by triacontanol and hexacosanol; other alcohols – tetraacosanol, heptacosanol, nonacosanol, dodriacontanol and tetratriacontanol - are minor components)

1 ^aGeraniol is a monoterpene alcohol

2 ^bTriton WR1339 induces hyperlipidemia by inhibiting lipoprotein lipase and thus preventing catabolism of TG-rich lipoproteins

3 **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; BS, Albumine; b.w., body weight; CCE/ATPCL, Citrate Cleavage Enzyme (or ATP-Citrate Lyase, an important step in fatty acid biosynthesis; CCl₄, Carbon tetraChloride; CE, Cholesteryl Esters; CoA, Coenzyme A; CPT, Carnitine Palmitoyl Transferase; CTPpct, CTP:phosphocholine cytidyltransferase (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 reductase; MethylGlutaryl Coenzyme A reductase; IC₅₀, concentration required for 50% maximal inhibition; i.p., intraperitoneally; i.v., intravenously; 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 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, Peroxisome Proliferator-Activated Receptor (transcription factor of β lipogenesis); PUFA, Poly-Unsaturated Fatty Acid; RMI 14,514, (5-(tetradecyloxy)-2-furoic acid); 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); SCFA, Short-Chain Fatty Acid; SRE, Sterol Regulatory Element; 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

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2 **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**

| 3 Lipotropic compounds | 4 <i>In vivo</i> or <i>in vitro</i> models | 5 Supplemented daily dose | 6 Duration of lipotrope exposition | 7 Hepatic effect(s) | 8 References |
|--|--|---|------------------------------------|--|--------------------------------|
| 9 Fibre | | | | | |
| 10 Pectin (from citrus), gum arabic (from acacia powder) and agar | 11 <u>Exp. 1:</u> Rats fed once a day a 10%-fat and 0.2%-cholesterol diet with 0% cellulose 12 <u>Exp. 2:</u> Rats fed <i>ad libitum</i> 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 | 13 5.0% of diet | 14 14 days | 15 ↓ cholesterol (resp. -14, -5%, NS, and -3%, NS) ^b and long-chain FA (resp. -20, -11%, NS, and -20%) levels | 16 (Kelley and Tsai, 1978) |
| 17 Cellulose | 18 Rats fed 10% fat diet containing adequate amount of dietary copper with either marginal or abundant (0.12% of diet) dietary zinc | 19 8 or 16% of diet | 20 9 weeks | 21 <u>Marginal zinc content:</u> no significant effect on cholesterol (resp. -7 and -5%) and lipid (resp. -13 and -17%) concentration 22 <u>Abundant zinc content:</u> no significant effect on cholesterol (resp. +8 and +13%) and lipid (resp. -16 and +1%) concentration | 23 (Looney and Lei, 1978) |
| 24 Alfalfa, cellulose or lignin | 25 Rats fed 10% fat and 1% cholesterol diet | 26 5% of diet | 27 28 days | 28 <u>Alfalfa:</u> no significant effect on TC (-3%), FC (+2%) and TG (-15%) contents 29 <u>Cellulose:</u> no significant effect on TC (+15%), FC (+8%) and TG (+15%) contents 30 <u>Lignin:</u> no significant effect on TC (-19%) and FC (-1%) contents; ↓ TG content (-85%) | 31 (Story et al., 1981) |
| 32 Cellulose, lignin or pectin | 33 Rats fed 10% fat and 0.5% cholesterol diet | 34 5% of diet | 35 28 days | 36 <u>Cellulose:</u> ↓ TC (-30%, NS), FC (-22%, NS) and TG (-36%, NS) contents 37 <u>Lignin:</u> ↓ TC (-66%), FC (-18%, NS) and TG (-18%, NS) contents 38 <u>Pectin:</u> ↓ TC (-75%), FC (-27%, NS) and TG (-58%) contents | 39 |
| 40 Neutral detergent fiber (from blackgram) | 41 Rats fed a 11%-fat and fibre-free diet: 42 - liver slices incubated with [U- ¹⁴ C]glucose 10 mM (5 μCi) 43 - 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) | 44 30% of diet | 45 1 month | 46 ↓ cholesterol concentration (-9%); ↑ HMG-CoA reductase (<i>i.e.</i> ↓ HMG-CoA/mevalonate ratio by 36%) 47 ↑ incorporation of [U- ¹⁴ C]glucose into cholesterol (+80%) 48 ↑ incorporation of [1,2- ¹⁴ C]Na-acetate into cholesterol (+258%) | 49 (Thomas et al., 1983) |
| 50 Citrus pectin (purified) | 51 Rats fed standard diet containing 14% cellulose | 52 10% of diet | 53 5 weeks | 54 ↓ TL (-68%) and TC (-63%) contents | 55 (Rotenberg and Eggum, 1986) |
| 56 Neutral detergent fiber (from wheat bran) | 57 Rats fed diets with various contents in carbohydrate (C: 40-60%), lipid (L: 9-19%) and protein (P: 9-37%), <i>i.e.</i> n = 32 diets | 58 0-14% of diet | 59 28 days | 60 From 2.83 to 11.17% fiber, <i>i.e.</i> +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%) | 61 (Stewart et al., 1987) |
| 62 Methylcellulose (low, medium and high viscosity: LV, MV and HV) | 63 Rats fed sucrose-based diet | 64 8% of diet | 65 10 days | 66 <u>MV and HV:</u> ↓ 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 | 67 (Topping et al., 1988) |
| 68 Particulate (alfalfa, cellulose or wheat bran), soluble/ionic (pectin) and soluble/noionic fiber (guar gum or Metamucil®) | 69 Rats fed a 14%-fat diet | 70 5 (pectin and guar gum) or 10% (particulate fiber and Metamucil) of diet | 71 28 days | 72 ↑ cholesterol content (resp. +20, +16, 0, +20, +14 and +23%) 73 ↑ and ↓ TG content (resp. +23, -5, +8, -2, -32 and -26%) 74 ↓ PL content (resp. 0, -27, -5, 0, 0 and -11%) 75 ↑ PC content (resp. +25, +8, +10, +24, +13 and +11%) 76 ↓ PE (resp. -11, 0, -10, -14, -11 and -6%) and Sph (resp. -53, -23, -20, -39, -25 and -26%) contents 77 ↑ and ↓ LPC (resp. -8, +3, +7, -15, +8 and +15%) and PI+PS (resp. -5, 0, +17, -3, +8 and +4%) contents | 78 (Kritchevsky et al., 1988) |
| 79 Citrus pectin | 80 Rats fed fiber-free diet | 81 1, 3, 6 or 10% of diet | 82 26 days | 83 ↓ cholesterol (resp. ≈ -7%, NS, ≈ -9%, NS, ≈ -11%, NS, and ≈ -13%, NS) and TG (resp. ≈ -23%, NS, ≈ -41, ≈ -59 and ≈ -73%) concentrations | 84 (Ide and Horii, 1989) |
| 85 Wheat bran (GMD: | 86 Rats fed high-sucrose (49%) diet containing 5% | 87 5, 7.5 or 10% of | 88 6 weeks | 89 <u>Fine beet fiber:</u> ↓ TG (resp. -20, -34 and -37%) and cholesterol | 90 (Klopfenstein, 1990) |

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|----|-------------------------------|--|-----------------------|-----------------|---|--------------------------------|
| 1 | | | | | (resp. +2%, NS, -14 and -27%) levels | |
| 2 | 492 μm , or coarse | cellulose (GMD: 179 μm) | diet | | <u>Coarse beet fiber</u> : \downarrow TG (resp. -24, -35 and -51%) and cholesterol | |
| 3 | (436 μm) and fine | | | | (resp. -3%, NS, -12% and -37%) levels | |
| 4 | (185 μm) sugar | | | | <u>Wheat bran (5% only)</u> : \downarrow TG content (-8%, NS); no effect on | |
| 5 | beet fiber | | | | cholesterol level (+3%, NS) | |
| 6 | Oat bran, pectin or | Rats fed 10%-fat and 0.3%-cholesterol diet | 7.5% of diet | 3 weeks | \downarrow TL (resp. -33, -24 and -14%) and TC (resp. -68, -56 and -35%) | (Arjmandi et al., 1992a) |
| 7 | psyllium | containing 7.5% cellulose | | | levels | |
| 8 | Pectin, psyllium or | Rats fed 10%-fat and 0.3%-cholesterol diet | 10% of diet | 3 weeks | <u>Pectin and psyllium</u> : \downarrow TL (resp. -29 and -29%) and TC (resp. -54 | (Arjmandi et al., 1992b) |
| 9 | oat bran | containing 10% cellulose | | | and -40%) levels | |
| 10 | Guar gum | Quails fed 5% cellulose diet \pm 50 ppm of | 5% of diet | 4 or 44 weeks | <u>Oat bran</u> : \uparrow TL (+12%, NS) and TC (+17%) levels | |
| 11 | | tocotrienol-rich fraction (from palm oil) | | | <u>No tocotrienol-rich fraction</u> : \downarrow lipid percentage (resp. -14%, NS, | (Hood and Sidhu, 1992) |
| 12 | | | | | and -13%, NS); no effect on cholesterol content (resp. +1% and | |
| 13 | | | | | -21%); \downarrow cholesterol synthesis at 44 weeks (-18%, NS) | |
| 14 | | | | | <u>With tocotrienol-rich fraction</u> : \downarrow lipid percentage (resp. -28%, NS, | |
| 15 | | | | | and -17%, NS) and cholesterol content (resp. -6%, NS, and - | |
| 16 | Fiber from defatted | Rats fed hypercholesterolemic (1% cholesterol | Resp. 1.9, 2.8 | 9 days | <u>Soluble fiber</u> : \downarrow cholesterol (-31% for oat, -49% for barley, and - | (Oda et al., 1993) |
| 17 | oat, barley or | and 0.25% sodium cholate) diet containing | and 0.6 | | 11% for wheat, NS) concentration | |
| 18 | wheat | 5% cellulose | soluble fiber | | <u>Insoluble fiber</u> : \downarrow cholesterol (-4% for oat, NS, -5% for barley, NS, | |
| 19 | | | or 3.1, 2.2 and | | and -8% for wheat, NS) concentration | |
| 20 | | | 4.4% | | | |
| 21 | Wheat bran, psyllium | Rats fed basal diet containing 9.09% wheat bran, | 7.2-7.6% of fiber | 3.5, 10, 15 and | <u>Cholesterol</u> : no significant changes (except a tendency to \downarrow at 15 | (Schneeman and Richter, 1993) |
| 22 | husk or oat bran | 4.00% psyllium husk or 15.38% oat bran | | 18.5 months | and 18.5 months for wheat bran and psyllium) | |
| 23 | | | | | <u>CE</u> : no significant changes (except a slight tendency to \downarrow at 18.5 | |
| 24 | | | | | months) | |
| 25 | | | | | <u>TG</u> : no significant changes (except a slight tendency to \downarrow at 18.5 | |
| 26 | Oat bran, guar gum, | Hamsters fed hypercholesterolemic (0.1% | \approx 10% of diet | 4 weeks | months) \downarrow cholesterol (-18% for oat bran, NS, -24% for guar gum, NS, and - | (Jonnalagadda et al., 1993) |
| 27 | cellulose or xylan | cholesterol and 10% fat) diet | | | 29% for xylan, NS) concentration; \uparrow cholesterol (+44% for | |
| 28 | | | | | cellulose) concentration | |
| 29 | Prune fiber or pectin | Rats fed high cholesterol (1% + 0.1% cholic | 3 or 6% of diet | 28 days | <u>3% prune fiber</u> : \downarrow cholesterol (-25%) and TG (-27%) contents; no | (Tinker et al., 1994) |
| 30 | | acid) AIN-76 diet | | | effect on CE:TC | |
| 31 | | | | | <u>6% prune fiber</u> : \downarrow cholesterol (-29%), CE:TC (-11%, NS) and TG (- | |
| 32 | | | | | 24%) contents | |
| 33 | | | | | <u>3% pectin</u> : \downarrow cholesterol (-36%), CE:TC (-5%, NS) and TG (-33%) | |
| 34 | Oat bran | Rats fed high cholesterol (1% + 0.1% cholic | 7.5% of NSP + | 14 days | contents | |
| 35 | | acid) AIN 76 diet | lignin | | \downarrow cholesterol pool (-23%) | (Jackson et al., 1994) |
| 36 | Rice bran, oat bran, | Rats fed 0.25%-cholesterol diet containing 5% | 5% of diet | 4 weeks | \downarrow TC content (resp. -21, -41 and -47%) | (Chezem et al., 1996) |
| 37 | or psyllium | cellulose | | | \uparrow bile acid synthesis (resp. +65, +118, +60% and no effect) | |
| 38 | Guar gum | Rats and gerbils fed high-fat (40%) and 6.5% | 6.5% of diet | 21 (gerbils) | <u>Gerbils</u> : \downarrow TC (-47%) and FC (-10%) contents, and \uparrow TL content | (Onning and Asp, 1995) |
| 39 | | cellulose diet | | and 19 | (+5%, NS) | |
| 40 | | | | (rats) days | <u>Rats</u> : \downarrow TL (-39%), and \uparrow TC (-50%) and FC (0%) contents | (Tsai and Tsai, 1999) |
| 41 | Cellulose, guar gum, | Rats fed high-fat (15% fish oil) diet | 10% of diet | 8 weeks | \downarrow TL (resp. -36, -60, -51, -34 and -33%), TG (resp. \approx -30, \approx -65, \approx - | |
| 42 | pectin, konjac | | | | 59, \approx -38 and \approx -36%) and cholesterol (resp. \approx -30, \approx -67, \approx -49, \approx - | |
| 43 | mannan or gum | | | | 29% and \approx -17%, NS) contents | |
| 44 | arabic | | | | <u>Histological observations</u> : \downarrow size of lipid vacuoles with pectin and | |
| 45 | Psyllium and pectin | Male, female and ovariectomized guinea pigs | 5% + 5% of diet | - ^c | guar gum | |
| 46 | | fed control diet | | | \uparrow CYP7A1 activity (+45%) and mRNA level | (Roy et al., 2000) |
| 47 | Dietary fiber | Rats fed AIN-76A diet containing 10% cellulose | 10% of diet | 21 days | \downarrow cholesterol content (-17%); \uparrow TG content (+36%, NS) | (Kritchevsky and Tepper, 2005) |
| 48 | complex ^d | | | | | |
| 49 | β -glucan concentrate | Rats fed modified AIN-93G diet containing | 5% of diet | 28 days | \downarrow TC content (\approx -30%) | (Gallaher and Plate, 2005) |
| 50 | | 0.25% cholesterol | | | | |
| 51 | Psyllium husks | Mice fed standard AIN-93M diet | 10% of diet | 3 and 10 | <u>At week 3</u> : Up-regulation of genes involved in fatty acid β - | (Chan and Heng, 2008) |
| 52 | | | | weeks | oxidation (e.g. 1.6-fold for CPT1a) and down-regulation of | |
| 53 | | | | | genes involved in lipid biosynthesis (e.g. 3.7-fold for SREBF1 | |

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|----|--|--|---|------------|---|------------------------------|
| 1 | | | | | and 4-fold for FAS); up-regulation of genes involved in cholesterol synthesis pathway (between 1.5- and 1.9-fold) | |
| 2 | | | | | At week 10: Down-regulation of genes involved in fatty acid β -oxidation (e.g. CPT1a, CPT2 and DCI, and 2.3-fold for PPAR α) | |
| 3 | | | | | 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 | |
| 4 | | | | | | |
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| 7 | | | | | | |
| 8 | 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) |
| 9 | | | | | | |
| 10 | 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 <i>Gynostemma pentaphyllum</i> total glucoside tablet at 0.032 g/kg b.w. ↓ LI (resp. -10, NS, -4, NS, and -1%, NS) | (Wang et al., 2009b) |
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| 12 | | | | | | |
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| 14 | | | | | | |
| 15 | | | | | | |
| 16 | | | | | | |
| 17 | Phytic acid | | | | | |
| 18 | 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) |
| 19 | | | | | | |
| 20 | | | | | | |
| 21 | | | | | | |
| 22 | 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) |
| 23 | | | | | | |
| 24 | | 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) | |
| 25 | | | | | | |
| 26 | | | | | | |
| 27 | 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) |
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| 33 | | | | | | |
| 34 | 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) |
| 35 | | | | | | |
| 36 | | | | | | |
| 37 | 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) |
| 38 | | | | | | |
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| 40 | | | | | | |
| 41 | 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) |
| 42 | | | | | | |
| 43 | 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 | (Lee et al., 2007) |
| 44 | | | | | | |
| 45 | | | | | | |
| 46 | Inositol hexakisphosphate (IP6) | Rats fed high-sucrose (50.3%) and <i>myo</i> -inositol-deficient diet | 1.02% of diet | 14 days | Histology (light microscopy): ↓ severity of fatty liver ↓ 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) |
| 47 | | | | | | |
| 48 | | | | | | |
| 49 | | | | | | |
| 50 | | | | | | |
| 51 | | Rats fed high-sucrose (50.3%) and <i>myo</i> -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 | |
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| 53 | | | | | | |

Article Isken et al. (2010) montre que fibre insoluble (cereal) plus efficace que soluble (guar gum) pour réduire 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"

| | | | | | | |
|----|---|---|-----------------------------|---------------------------------|--|----------------------------|
| 1 | | | | | PL (-23%) concentrations; no significant change for PC, PE, PS, LPC and Sph percentages/total PL, ↑ PI/PC ratio (+8%), ↑ PI percentage (+0.7%) | |
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| 3 | | | | | | |
| 4 | | | | | | |
| 5 | Oligosaccharides | | | | | |
| 6 | | | | | | |
| 7 | 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%) | (Kok et al., 1996b) |
| 8 | | | | | ↓ FAS (-41%), PAP (-11%, NS), CPT I (-8%, NS) and GPAT (-11%) activities | |
| 9 | | | | | ↓ TG synthesis from ¹⁴ C-acetate (-53%) | |
| 10 | | Hepatocytes from rats fed standard or oligofructose-supplemented diet and incubated with 2 mM [1- ¹⁴ C]acetate | 10% of diet | 180 min | | |
| 11 | | | | | | |
| 12 | | | | | | |
| 13 | 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 | <u>Water</u> : ↓ 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 | (Kok et al., 1996a) |
| 14 | | | | | <u>Fructose</u> : ↓ 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 | |
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| 16 | | | | | | |
| 17 | | | | | | |
| 18 | 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%) | (Aghelli et al., 1998) |
| 19 | | | | | ↓ FAS activity (-32% in mU/mg protein and -36% in mU/g tissue) | |
| 20 | Oligofructose | Rats fed high-fat (14% +0.15% cholesterol) diet | 10% of diet | 19 days | <u>Histological examination</u> : only microvacuolar accumulation of fat was present, not macrovacuolar as in the high-fat diet only | (Kok et al., 1998) |
| 21 | | | | | No effect on TG (-1%, NS), PL (-5%, NS) and TC (-3%, NS) contents | |
| 22 | | | | | | |
| 23 | | | | | | |
| 24 | 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 | (Delzenne and Kok, 1999) |
| 25 | | | | | ↓ ME (-51%), ATPCL (-45%), G6PDH (-46%) and ACC (-40%) activities; ↓ FAS mRNA/18S rRNA ratio (-42%) | |
| 26 | | | | | | |
| 27 | | 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 (-57%) | |
| 28 | | | | | | |
| 29 | | | | | | |
| 30 | Inulin (from <i>Platycodi radix</i>) | 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) |
| 31 | | | | | | |
| 32 | Oligofructose ^e | Obese Zucker <i>fa/fa</i> rats fed control diet | 10% of diet | 10 weeks | ↓ TG (-57%) and PL (-30%) levels | (Daubioul et al., 2000) |
| 33 | | | | | ↓ fatty degeneration of hepatocytes (histological observations) | |
| 34 | | | | | ↓ FAS (-17%, NS), ME (-16%), ATPCL (-26%, NS) and PAP (-8%) activities; ↓ FAS mRNA (-9%, NS) | |
| 35 | Fructans or cellulose ^e | Obese Zucker <i>fa/fa</i> rats fed control diet | 10% of diet | 6 (for NMR analyses) or 8 weeks | <u>Fructans</u> : ↓ 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 (<i>via</i> histology); no effect on FAS, ME, ATPCL/CCE and phosphatidate phosphohydrolase activities (key enzymes in fatty acid synthesis) | (Daubioul et al., 2002) |
| 36 | | | | | <u>Cellulose</u> : ↓ fat content (≈ -2%, NS); ↑ TG content (+21%, NS) | |
| 37 | | | | | ↓ TG concentration (-28%) | (Busserolles et al., 2003) |
| 38 | | | | | ↓ lipid droplet accumulation (histological observations) | (Sugatani et al., 2006) |
| 39 | | | | | <u>Vehicle</u> : ↓ TG (-38%), TC (-14%, NS) and FFA (-12%) levels | |
| 40 | | | | | <u>Phenobarbital</u> : ↓ TG level (-9%, NS); ↑ TC (+20%, NS) and FFA (+13%, NS) levels | |
| 41 | Oligofructose ^e | Rats fed high-fructose (65%) diet | 10% of diet | 4 weeks | | |
| 42 | Inulin ^e | 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 | ↓ LI (-1%, NS, -6 and -10%) | (Chen et al., 2010a) |
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| 46 | Oligosaccharides (from soybean) | Rats fed high-fat (16%) diet | 150, 300 and 450 mg/kg b.w. | 45 days | | |
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| 49 | | | | | | |
| 50 | Other compounds | | | | | |
| 51 | | | | | | |
| 52 | 1-Deoxynojirimycin ^h (from mulberry) | Rats fed standard diet | 1 mg/kg b.w. (direct) | 4 weeks | ↓ TG level (-21%) | (Tsuduki et al., 2009) |
| 53 | | | | | No effect on TC and PL levels | |
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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

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|---|----------------------|-------------|--|
| 1 | | | |
| 2 | leaves, <i>Morus</i> | stomach | ↑ FAS ($\approx +13\%$, NS), CPT ($\approx +56\%$) and ACO ($\approx +45\%$) activities; ↓ |
| 3 | <i>alba</i>) | intubation) | ME ($\approx -12\%$, NS) |
| 4 | | | ↑ CPTI ($\approx +50\%$), ACO ($\approx +110\%$) and AMPK ($\approx +145\%$) mRNA |
| 5 | | | expressions; ↓ PPAR α mRNA expression ($\approx -25\%$, NS) |

^aAll terms used in the Table are precisely those of the article considered: for example, 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

^bIndicates the decreased or increased percentage induced by the lipotrope compared to the control, *i.e.* steatogen diet (NS - Not Significant - means absence of significance for the change observed; in other cases, the effect was either significant or no information was given in the article)

^cNo data given in the reference

^dContained oat bran, citrus pectin, guar gum, cellulose, apple pulp fiber, rice fiber, locust bean gum, date fiber, prune fiber, and fructo oligosaccharides

^eOligofructose 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

^fFructans 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

^gIs synthesized enzymatically from sucrose by inulin-producing enzyme and consists of a linear polymer (average ratio of glucose/fructose, 1:17) having $\beta(2-1)$ linkages of D-fructose with one terminal glucose and

^hD-glucose analogue in which the oxygen atom of the pyranose ring is substituted by an NH group

ⁱABBREVIATIONS: ACC/CBX, Acetyl-CoA Carboxylase (involved in FA synthesis; is inhibited 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 7 α Hydroxylase (enzyme for the initial rate-limiting step of bile acid synthesis from c

^jDodecenoyl-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

^kGlucose-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

^lLysophosphatidylCholine; 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 Significant; PC, PhosphatidylCholine; PE, PhosphatidylEthanolamine; PI, Phosphat

^mPhosphoLipid; resp., respectively; PPAR, Peroxisome 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

ⁿTC, Total Cholesterol; TG, TriGlyceride; TL, Total Lipids

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For Peer Review Only

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2 **Supplemental Table 4** *In vivo, ex vivo* and *in vitro* studies reporting effects on hepatic lipid metabolism following supplementation of carotenoids, polyphenols and polyphenol-derived compounds^a

| 3 Lipotropic compounds | 4 <i>In vivo</i> or <i>in vitro</i> models | 5 Supplemented daily dose | 6 Duration of lipotrope exposition | 7 Hepatic effect(s) | 8 References |
|---|--|---|------------------------------------|---|---|
| 9 A - Carotenoids | | | | | |
| 10 Astaxanthin and canthaxanthin | 11 Rainbow trouts fed commercial extruded basal diet | 12 0.01% of diet | 13 21 days | 14 ↓ TL (resp. -41 and -39%) ^b and unsaturated lipid (resp. -5%, NS, and -34%, NS) level (as evaluated by image analysis, <i>i.e.</i> mean grey-scale values for differential hepatic histochemical staining) | 15 (Page et al., 2005) |
| 16 Lycopene | 17 Rats fed standard AIN-93M-based diet | 18 0.65% of diet | 19 5 weeks | 20 ↓ cholesterol level (≈ -34%) and ↑ TG level (≈ +6%, NS) | 21 (Alshatwi et al., 2010) |
| 22 B - Polyphenols | | | | | |
| 23 B1 - Undefined, mixture or extracts | | | | | |
| 24 Oryzanol ^c from rice bran oil | 25 Rats fed high-cholesterol (1% +0.15% bile salts) diet | 26 0.2, 0.5, 1.0 or 1.2% of diet | 27 7 weeks | 28 ↓ 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%) | 29 (Seetharamaiah and Chandrasekhara, 1988) |
| 30 Oryzanol ^c | 31 Rats fed high-cholesterol (1% +0.15% bile salts) diet | 32 0.5% of diet | 33 7 weeks | 34 ↓ TC (-26%), FC (-5%), CE (-31%), TG (-19%, NS) and PL (-26%) contents | 35 (Seetharamaiah and Chandrasekhara, 1993) |
| 36 Oryzanol ^c | 37 Hamsters fed hypercholesterolemic (0.1% +5% coconut oil) diet | 38 1% of diet | 39 8.5 weeks | 40 ↓ HMG-CoA reductase activity (-15%, NS) | 41 (Rong et al., 1997) |
| 42 Grape skin and seed polyphenols (≈ 12%) | 43 Rats fed liquid ethanol-rich (36% as energy) diet (Lieber-DeCarli diet) | 44 50 mg/L | 45 2 months | 46 <u>Histological assessment</u> : significantly less hepatic damages, <i>i.e.</i> no evidence of steatosis, a highly organized structure comparable to that observed in liver of rats fed basal diet, and absence of a large number of lipid vacuoles with a large extent of distribution | 47 (Sun et al., 1999) |
| 48 Polyphenon-100 nd (green tea polyphenols) | 49 Male rats fed standard diet | 50 0.01, 0.05, 0.1, 0.2 and 0.5 g/kg b.w. | 51 23 days | 52 No effect on TG and PL levels 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) | 53 (Nakamura et al., 2001) |
| 54 Polyphenols from virgin olive oil | 55 Rats fed 1%-cholesterol diet | 56 ≈ quantity extracted from 30% virgin olive | 57 5 weeks | 58 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) | 59 (Benkhalti et al., 2002) |
| 60 Polyphenol-rich ethylacetate extract (from defatted safflower seed powder) | 61 Ovariectomized rats fed standard diet (11.5% fat) | 62 1% of diet | 63 4 weeks | 64 ↓ cholesterol (-15%) and TG (-8%, NS) levels | 65 (Cho et al., 2004) |
| 66 γ -oryzanol ^c (normal vs microencapsulated) | 67 Rats fed high-cholesterol diet (10% heat-treated lard, 1% cholesterol and 0.5% cholic acid) | 68 0.01% of diet | 69 4 weeks | 70 ↓ LI (resp. -19%, NS, and -23%) and cholesterol level (resp. -19 and -15%) | 71 (Suh et al., 2005) |
| 72 Oligonol [®] (oligomerized polyphenols from lychee fruit and green tea) | 73 Mice fed choline deficient and L-amino acid defined diet | 74 0.02% of diet | 75 4 weeks | 76 ↓ fat deposit; up-regulation of PPAR γ coactivator-1 α (promotes β -oxidation) and ↑ β -oxidation enzyme expression | 77 (Tojo et al., 2008) |
| 78 Green tea extract (30% catechin) ^c | 79 Male leptin-deficient (<i>ob/ob</i>) mice fed standard AIN-93G diet | 80 1 or 2% of diet | 81 6 weeks | 82 <u>Hepatic histologic evaluation</u> : marked reduction in the degree of steatosis; 4/16 obese mice responded maximally to green tea | 83 (Bruno et al., 2008) |

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|----|--|---|---|----------|--|--------------------------------|
| 1 | | | | | extract, resulting in grade 1 histologic score; for most, effect was dramatic | |
| 2 | | | | | <u>Hepatic steatosis grading</u> : 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; <i>ob/ob</i> mice are graded 3) | |
| 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%) | |
| 4 | Provinol [®] (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 | <u>Histological examination</u> : 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) |
| 5 | Polyphenol-rich extract (45%) from walnut (<i>Juglans regia</i> 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) |
| 6 | | | | | ↑ TG accumulation within cells (resp. +47, +42 and +43%) | |
| 7 | | HepG2 cells | 10, 30 or 100 μg/mL | 48 hours | ↑ 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 | |
| 8 | | | 1, 10 or 100 μg/mL | | ↓ cholesterol (resp. -27 and -40%) and TG (resp. -10 and -39%) levels | (Lin et al., 2009) |
| 9 | Polyphenol extract from <i>Nelumbo nucifera</i> 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 | <u>Histological examinations</u> : significantly and dose-dependently ↓ number of lipid vesicles increased by the high-fat diet | |
| 10 | Silymarin (extract from milk thistle seeds, <i>Silybum marianum</i>) | | 0.01% of diet | 10 weeks | ↓ cholesterol (-22%) and TG (-25%) levels <u>Histological examinations</u> : significantly ↓ number of lipid vesicles increased by the high-fat diet | |
| 11 | Polyphenol-rich extract from <i>Hibiscus sabdariffa</i> (≈ 74% polyphenols) [§] | 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) |
| 12 | | 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 | |
| 13 | | HepG2 cells | 0.05 or 0.5 mg/mL | 18 hours | ↑ LDL uptake (resp. ≈ +10 and 65%) | |
| 14 | Polyphenol-rich longan (<i>Dimocarpus longans</i> 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) |
| 15 | 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) |

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|----|---|---|---------------------------------|---------------------|---|---|
| 1 | extract (from | rats | mg/kg b.w. i.g. | | 9 and -13%) levels | |
| 2 | black rice) | | injected | | <u>Histopathological examinations:</u> ↓ alterations (apparently in |  |
| 3 | | | | | relation with lipid accumulation) | |
| 4 | | | | | | |
| 5 | B2 - Phenolic acids | | | | | |
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| 7 | 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) |
| 8 | 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) |
| 9 | Ferulic acid, <i>m</i> -hydroxycinnamic acid or 3,4-dihydroxyphenyl-propionic acid ¹ | 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) |
| 10 | | | | | | |
| 11 | Gallic acid | FAS from chicken liver | 0.5 mM | 3 hours | FAS residual activity ≈ 97% | (Wang et al., 2003) |
| 12 | 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) |
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| 22 | 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) |
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| 26 | B3 - Flavonoids | | | | | |
| 27 | | | | | |  |
| 28 | 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) |
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| 31 | 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) |
| 32 | | | | | | |
| 33 | 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) |
| 34 | | | | | | |
| 35 | 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) |
| 36 | | | | | | |
| 37 | 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) |
| 38 | | | | | | |
| 39 | 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) |
| 40 | | | | | | |
| 41 | Naringenin or hesperetin | HepG2 cells | 10-200 or 50-200 μM | 24 hours | ↓ dose-dependently ApoB accumulation into the media: <u>Naringenin</u> : from ≈ -7% (10 μM), NS, to ≈ -83% (200 μM) <u>Hesperetin</u> : from ≈ -39% (50 μM), NS, to ≈ -75% (200 μM) | (Wilcox et al., 2001) |
| 42 | | | | | | |
| 43 | 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 | |
| 44 | | | | | | |
| 45 | Naringenin or hesperetin | HepG2 cells | 50 or 200 μM | 24 hours | ↓ cellular CE mass: <u>Naringenin</u> : resp. ≈ -8%, NS, and ≈ -26% <u>Hesperetin</u> : resp. ≈ -17%, NS, and ≈ -21% ↑ cellular FC mass: <u>Naringenin</u> : resp. ≈ +4%, NS, and ≈ +7%, NS <u>Hesperetin</u> : resp. ≈ +3%, NS, and ≈ +3%, NS ↑ cellular TG mass: | |
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| 3 | 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 μ M | 5 hours | <u>Naringenin</u> : resp. \approx +14%, NS, and \approx +34%, NS <u>Hesperetin</u> : resp. \approx +3%, NS, and \approx +50%, NS <u>Without 19 hours-preincubation with flavonoids</u> : Naringenin: \downarrow rate of incorporation of oleate into CE (resp. -37 and -70%); \uparrow rate of incorporation of oleate into TG (resp. +13%, NS, and +29%) and PL (resp. +4%, NS, and +2%, NS) Hesperetin: \downarrow rate of incorporation of oleate into CE (resp. -22%, NS, and -57%); \uparrow rate of incorporation of oleate into TG (resp. +21%, NS, and +35%, NS) and PL (resp. +20%, NS, and +16%, NS) <u>With 19 hours-preincubation with flavonoids</u> : Naringenin: \downarrow rate of incorporation of oleate into CE (resp. -60 and -84%); \uparrow rate of incorporation of oleate into TG (resp. +4%, NS, and +27%); no effect on rate of incorporation of oleate into PL Hesperetin: \downarrow rate of incorporation of oleate into CE (resp. -31%, NS, and -70%) and PL (resp. -7%, NS, and -12%, NS); \uparrow rate of incorporation of oleate into TG (resp. \approx 0 and +9%, NS) \downarrow rate of CE hydrolysis (resp. -34 and -36%) |
| 16 | Naringenin or hesperetin | HepG2 cells incubated with [1- ¹⁴ C]oleic acid in presence of 10 μ M ACAT inhibitor | 200 μ M | 24 hours | |
| 17 | Naringenin | HepG2 cells | 200 μ M | 24 hours or 5 days | <u>24 hours</u> : no significant effect on MTP large subunit expression <u>5 days</u> : nearly complete depletion of MTP large subunit expression \downarrow MTP activity: |
| 18 | Naringenin or hesperetin | HepG2 cells | 50, 100 or 200 μ M | 24 hours | - Naringenin: resp. -19, -32 and -40% - Hesperetin: resp. -8%, NS, -33 and -22% |
| 19 | Naringenin | HepG2 cells | 200 μ M | 24 hours | \uparrow LDL receptor activity: \uparrow ¹²⁵ I-LDL cell binding (resp. \approx 0 and \approx +200%), uptake (resp. \approx +67 and \approx +150%) and degradation (resp. \approx +18%, NS, and \approx +164%) |
| 20 | Naringenin or hesperetin | HepG2 cells | 50 or 200 μ M | 24 hours | <u>Naringenin</u> : \uparrow and \downarrow 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 \approx 0) and GAPDH (resp. +30%, NS, and -15%, NS) mRNA levels <u>Hesperetin</u> : \uparrow and \downarrow 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 |
| 21 | Naringenin or hesperetin | HepG2 cells | 50 or 200 μ M | 24 hours | |
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| 23 | Naringenin or hesperetin | HepG2 cells | 200 μ M | 24 hours | |
| 24 | | | | | |
| 25 | Naringenin or hesperetin | HepG2 cells | 50 or 200 μ M | 24 hours | |
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| 35 | 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. | 28 days | <u>Normal diet</u> : (Nakamura and Tonogai, 2002) - \downarrow LI (-12% at 0.5 g/kg) - \downarrow cholesterol (-25% at 1 g/kg, NS), TG (-25% at 1 g/kg, NS) and PL (-32% at 1 g/kg) contents (mg/liver) |
| 36 | | | 0.1, 0.2, 0.5 or 1 g/kg b.w. | | <u>Lithogenic diet</u> : - \downarrow 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 |
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| 44 | Taxifolin | HepG2 cells | - | 24 hours | \downarrow dose-dependently TG synthesis and secretion (resp. -59 and -68% at optimum concentration of 200 μ M); \downarrow PL synthesis and secretion (resp. -15 and -57%) \downarrow dose-dependently DGAT activity (-60%), but no effect of quercetin and genistein; \downarrow MTP activity (-27%) Shifted metabolic pathway from Tg to PL synthesis |
| 45 | | | | | (Therjault et al., 2002) |
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| 49 | Flavonoid glycoside fraction from <i>Salix matsudana</i> leaves | Female ICR mice fed high-fat (40%) diet | 2% or 5% | 9 weeks | \downarrow TG (resp. -13%, NS, and -16%) and TC (resp. -27 and -30%) contents; no effect on LI (Han et al., 2003) |
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| 1 | 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) |
| 2 | | | | | | |
| 3 | Epicatechin gallate (ECG) | FAS from chicken liver | - | - | IC ₅₀ = 42 μM | (Wang et al., 2003) |
| 4 | (+)-catechin | FAS from chicken liver | 0.5 mM | 3 hours | FAS residual activity ≈ 21% | |
| 5 | | | - | - | IC ₅₀ = 1.6 mM | |
| 6 | (-)-epicatechin | FAS from chicken liver | 0.5 mM | 3 hours | FAS residual activity ≈ 100% | |
| 7 | | | - | - | IC ₅₀ = 3.8 mM | |
| 8 | | | 0.5 mM | 3 hours | FAS residual activity ≈ 93% | |
| 9 | Epigallocatechin gallate (EGCG) | FAS from chicken liver | 0.5 mM | 3 hours | FAS residual activity ≈ 21% | |
| 10 | Epigallocatechin (EGC) | FAS from chicken liver | 0.5 mM | 3 hours | FAS residual activity ≈ 91% | |
| 11 | | | | | | |
| 12 | 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) |
| 13 | | | | | | |
| 14 | Taxifolin | HepG2 cells | 75-200 μM | 24 hours | ↓ dose-dependently ApoB secretion (≈ -62% at 200 μM) | (Casaschi et al., 2004) |
| 15 | | HepG2 cells preincubated 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%) | |
| 16 | | | | | | |
| 17 | | HepG2 cells | 200 μM | 24 hours | ↓ non-competitively DGAT activity (-35%), and MTP activity (≈ -41%); post-transcriptional regulation of DGAT activity | |
| 18 | | | | | | |
| 19 | | 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 | |
| 20 | 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) |
| 21 | | 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 | |
| 22 | 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) |
| 23 | | | | | | |
| 24 | Daidzein + glycitein ^k | Enzyme assay: 5.3 μg of HMG-CoA reductase/150 μL | 4.5 μg/150 μL | - | ↓ HMG-CoA reductase (-64%) | (Sung et al., 2004) |
| 25 | Genistein ^k | | 3.8 μg/150 μL | - | ↓ HMG-CoA reductase (-50%) | |
| 26 | Soy extract ^t | HepG2 cells | 10 mg/L | 24 hours | ↑ mature SREBP-2 form and HMG-CoA reductase levels, and HMG-CoA synthase mRNA level; no effect on SREBP-1 | (Mullen et al., 2004) |
| 27 | | | | | ↑ SRE-regulated expression of HMG-CoA synthase (≈ +315%) and LDL receptor (≈ +55%, NS) | |
| 28 | 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 synthase mRNA level; no effect on SREBP-1 | |
| 29 | | | | | ↑ SRE-regulated expression of HMG-CoA synthase (resp. ≈ +370, ≈ +25%, NS, and ≈ +280%) and LDL receptor (resp. ≈ +25%, NS, ≈ -30%, NS, and ≈ +80%, NS) | |
| 30 | 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) | (Kim et al., 2004) |
| 31 | | | | | ↑ 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) | |
| 32 | | 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 | |
| 33 | | HepG2 cells | 1, 10 or 100 μM | 24 hours | ↑ PPAR _α mRNA level (resp. ≈ +80, ≈ +280 and ≈ +240%) | |
| 34 | | | 10 μM | 6, 24 or 48 hours | ↑ PPAR _α mRNA level: maximum at 24 hours (3.9-fold) | |
| 35 | | | | | ↑ PPAR _α protein level: maximum at 24 hours | |
| 36 | | HepG2 cells | 0.1, 1 or 5 μM | 24 hours | ↑ PPAR _α transcriptional activity (resp. ≈ +150, ≈ +169 and ≈ +200%) | |

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| 1 | Isoflavone aglycone- | 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 | (Kawakami et al., 2005) |
| 2 | or glucoside-rich powder (resp. 26.3 or 32.0% aglycone moieties) | | | | ↓ and ↑ CYP7A1 (resp. ≈ +20%, NS, and ≈ +30%, NS) and Δ6 desaturase ^m (resp. ≈ -40 and ≈ -38%) activities | |
| 3 | | | | | ↓ linoleic acid saturation index of liver PL, <i>i.e.</i> (20:3n-6 + 20:4n-6)/(18:2n-6): resp. ≈ -15 and ≈ -15% for PC, and ≈ -24 and ≈ -24% for PE | |
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| 7 | C-iso ^a , U-iso ^a , daidzein, glycitein and genistein (from soy) | HepG2 cells | 10 ng/L | 24 hours | ↑ PPAR α (resp. ≈ +40, ≈ +150, ≈ +45, ≈ -20 and ≈ +45%) and PPAR γ (resp. ≈ +105, ≈ +325, ≈ +375, ≈ +235 and ≈ +130%) | (Ricketts et al., 2005) |
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| 11 | 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 | (Kim et al., 2005) |
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| 13 | | | | | <u>Gene expression of cholesterol biosynthetic pathway enzymes:</u> | |
| 14 | | | | | - farnesyl diphosphate farnesyl transferase 1: from 0.35- to 1.10-fold | |
| 15 | | | | | - squalene epoxidase: from 0.19- to 1.12-fold | |
| 16 | | | | | - ACAT 1: from 3.90- to 4.20-fold | |
| 17 | | | | | - 7-dehydrocholesterol reductase: from 1.05- to 0.25-fold | |
| 18 | | | | | <u>Gene expression of FA metabolism:</u> | |
| 19 | | | | | - FAS: from 0.32- to 1.17-fold | |
| 20 | | | | | - ACO: from 1.70- to 3.05-fold | |
| 21 | | | | | - carnitine <i>O</i> -octanoyltransferase: from 1.15- to 4.40-fold | |
| 22 | | | | | - CPT1: from 2.3- to 2.5-fold | |
| 23 | | | | | - CPT2: from 2.6- to 3.5-fold | |
| 24 | | | | | - PPAR α : from 2.2- to 5.3-fold | |
| 25 | | | | | - PPAR γ : from 3.4- to 4.9-fold | |
| 26 | 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 | (Odbayar et al., 2006) |
| 27 | | | | | ↓ 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 | |
| 28 | | | | | ↓ 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) | |
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| 34 | Green tea extract Catechin gallate ((-)-CG) | FAS from duck liver | ≈ 3.5-60 μ g/mL | - | IC ₅₀ ≈ 12.2 μ g/mL (< IC ₅₀ of EGCG and ECG) | (Zhang et al., 2006) |
| 35 | | | ≈ 1-42 μ M | - | IC ₅₀ = 1.5 μ g/mL (16-fold and 12-fold higher than EGCG and ECG) | |
| 36 | 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) | (Doan Thi Thanh et al., 2006) |
| 37 | | | | | 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 | |
| 38 | | | | | No effect on TG, cholesterol and PL levels | |
| 39 | | | | | ↑ LDL receptor binding activity (resp. ≈ +50%, NS, ≈ +20%, NS, ≈ +28%, NS, ≈ +118 and +86%) at 100 μ M | (Bursill and Roach, 2006) |
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| 47 | Catechins (from green tea) and green tea extract (≥ 58% catechins) | HepG2 cells | 0-200 μ M | 24 hours | ↑ LDL receptor binding activity (≈ +220%), LDL receptor protein (≈ +146%), medium cholesterol (≈ +27%) and cell lathosterol (≈ +46%) concentrations (max. at 200 μ M); No effect on FC and chenodeoxycholic acid concentrations | |
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| 1 | | | | | ↓ TC concentration (≈ -28%) | |
| 2 | | | | | ↑ 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 | |
| 3 | | | | | ↑ PC (resp. no effect, ≈ +92 and ≈ +92%) and SM (resp. no effect, ≈ +26 and ≈ +75%) contents | (Babenko and Shakhova, 2006) |
| 4 | | | | | ↓ ceramide (precursor of SM) content (resp. no effect, ≈ -46 and ≈ -70%) | |
| 5 | Chamiloflan ^o | 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 | | |
| 6 | (flavonoids from <i>Chamomilla recutita</i>) | | | | | |
| 7 | | | 160 mg/kg b.w. | 1 week | ↓ ceramide production from [¹⁴ C]palmitic acid pre-labeled Sph (-28%); no effect on sphingoside production | |
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| 10 | 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 | |
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| 13 | (-)-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%) | (Bose et al., 2008) |
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| 16 | | | | | <u>Gross examination</u> : around 3-fold less in size/volume and similar to control group (4.3% fat) | |
| 17 | | | | | <u>Histological/microscopic examinations</u> : marked ↓ in liver lipid accumulation similar to control group (4.3% fat) | |
| 18 | | | | | | |
| 19 | 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 | (Guo et al., 2009) |
| 20 | | | | | | |
| 21 | | | | | | |
| 22 | | | | | | |
| 23 | | | | | | |
| 24 | | | | | ↓ LPL activity (resp. ≈ 0, -17 and -46%) | |
| 25 | Total flavonoids ^o from the dried leaves of <i>Litsea coreana</i> leave (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 | <u>Morphological evaluation</u> : 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) | (Wang et al., 2009a) |
| 26 | | | | | | |
| 27 | | | | | | |
| 28 | | | | | ↓ TG (resp. ≈ -14, -20 and -27%), TC (resp. ≈ -22, -33 and -44%) and FFA (resp. ≈ -20, -41 and -62%) contents | |
| 29 | | | | | ↑ PPAR α protein expression (≈ +89%) | |
| 30 | | | | | | |
| 31 | 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 | ↑ PPAR α gene expression (≈ +160%); no effect on CPT-1, ACO, SREBP-1, MCD, FAS and ACC gene expressions | (Chen et al., 2009) |
| 32 | | | | | No effect on TG content | |
| 33 | | | | | | |
| 34 | | | | | | |
| 35 | | | | | | |
| 36 | Pedunculagin (tannin) | HepG2 cells | 1, 3 or 10 μg/mL | 24 hours | ↓ PPAR α (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 ↑ PPAR α (1.31-fold) and ACOX1 (1.20-fold) mRNA expression at 10 μg/mL | (Shimoda et al., 2009) |
| 37 | | | | | | |
| 38 | | | | | | |
| 39 | | | | | | |
| 40 | | | | | | |
| 41 | Tellimagrandin I (tannin) | HepG2 cells | 1, 3 or 10 μg/mL | 24 hours | ↑ PPAR α (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); ↓ PPAR α mRNA expression at 1 μg/mL (0.84-fold) | |
| 42 | | | | | | |
| 43 | | | | | | |
| 44 | | | | | | |
| 45 | Tellimagrandin II (tannin) | HepG2 cells | 1, 3 or 10 μg/mL | 24 hours | No effect on PPAR α 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) | |
| 46 | | | | | | |
| 47 | | | | | | |
| 48 | | | | | | |
| 49 | Green tea extract (29.2% total catechins) ^o | 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 | (Shrestha et al., 2009) |
| 50 | | | | | | |
| 51 | | | | | | |
| 52 | | | | | ↓ SREBP1c (resp. ≈ -50 and ≈ -75%), FAS (resp. ≈ -50 and ≈ -68%), SCD1 (resp. ≈ -48 and ≈ -62%), HMG-CoA reductase (resp. ≈ - | |
| 53 | | | | | | |

69 and \approx -56%), ABCA1 (resp. \approx -52 and \approx -33%) and SR-B1 (resp. \approx -29%, NS, and \approx -43%, NS) relative mRNA abundance; no effect on ACAT1, ACAT2 and MTP relative mRNA abundance



B4 - Lignans

| | | | | | | |
|----|--|---|---------------------------|---|---|----------------------------|
| 8 | Silybin-dihemisuccinate (derived from the flavonolignan silybin) | Postmitochondrial supernatant of rat liver homogenates and rat liver slice incubated with [1- ¹⁴ C]acetate or ³ H ₂ O | 150.6 mg/kg b.w. | i.v. injection 30 and 60 min before killing | ↓ incorporation of [1- ¹⁴ C]acetate or ³ H ₂ O in FA (\approx -25%) | (Schriewer et al., 1979) |
| 9 | | <i>In vitro</i> incubation mixture of liver homogenates | 0.45-0.6 mM | | ↓ linearly and dose-dependently incorporation of [1- ¹⁴ C]acetate or ³ H ₂ O in FA (\approx -25%) | |
| 10 | | | 0.1 mM | | ↓ ACC, ATPCL and FAS activities (\approx -50%) | |
| 11 | | | 1 mM | | ↓ NADP-malate-dehydrogenase ^a (-20%) | |
| 12 | Sesamin | Liver from rats fed standard chow \pm sesamin, and perfused 4 h with exogenous oleic acid (100 μ M) | 0.2% of diet | 14-16 days + 4 hour liver perfusion | No significant effect on TG and cholesterol content of postperfused liver | (Fukuda et al., 1998) |
| 13 | | | | | ↑ PL content of postperfused liver (+49%) | |
| 14 | | | | | ↑ cumulative production of ketone bodies (+21%) | |
| 15 | | | | | ↓ β -hydroxybutyrate/acetoacetate ratio (-24%, NS) | |
| 16 | | | | | ↓ cumulative secretion of TG (-40%) and cholesterol (-2%, NS) | |
| 17 | | | | | ↓ TC (-39%) and lipid (-9%, NS) contents | |
| 18 | Sesamin | Liver from rats fed standard chow \pm sesamin, and perfused 4 h with an exogenous di- <i>trans</i> isomer (to differentiate from relative contribution of endogenous linoleic acid) of linoleic acid (linoleic acid, <i>trans</i> , <i>trans</i> -9,12-octadecadienoic acid)(100 μ M) | 0.2% of diet | 14 days | No significant effect on TG and cholesterol content of postperfused liver | (Fukuda et al., 1999) |
| 19 | | | | | ↑ PL content of postperfused liver (+20%) | |
| 20 | | | | | ↑ cumulative production of ketone bodies (+46%) | |
| 21 | | | | | ↓ β -hydroxybutyrate/acetoacetate ratio (-34%) | |
| 22 | | | | | ↓ cumulative secretion of TG (-56%), cholesterol (-16%, NS) and PL (-37%) | |
| 23 | 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 (\approx +87% at 0.5% sesamin) and peroxisomal (\approx +1300% at 0.5% sesamin) palmitoyl-CoA oxidation rate | (Ashakumary et al., 1999) |
| 24 | | | | | ↑ dose-dependently hepatic FA oxidation enzyme activity: CPT I (\approx +143% in mitochondria and \approx +280% in whole homogenate at 0.5% sesamin), acyl-CoA dehydrogenase (\approx +130%), acyl-CoA oxidase (\approx +1050%), enoyl-CoA hydratase (\approx +106%), 3-hydroxyacyl-CoA dehydrogenase (\approx 380%), 3-ketoacyl-CoA thiolase (\approx +360-650%), 2,4-dienoyl-CoA reductase (\approx +534%) and Δ^3,Δ^2 -enoyl-CoA isomerase (\approx +550%) | |
| 25 | | | | | ↑ dose-dependently gene expression of mitochondrial FA oxidation enzymes: CPT I (\approx +95% at 0.5% sesamin), CPT II (\approx +275%), long-chain acyl-CoA dehydrogenase (\approx +160%), mitochondrial trifunctional enzyme subunits α (\approx +300%) and β (\approx +240%), mitochondrial 3-ketoacyl-CoA thiolase (\approx +360%), 2,4-dienoyl-CoA reductase (\approx +450%) and Δ^3,Δ^2 -enoyl-CoA isomerase (\approx +835%) | |
| 26 | | | | | ↑ dose-dependently gene expression of peroxisomal FA oxidation enzymes: acyl-CoA oxidase (\approx +1400% at 0.5% sesamin), peroxisomal bifunctional enzyme (\approx +4800%) and peroxisomal 3-ketoacyl-CoA thiolase (\approx +480%) | |
| 27 | | | | | ↓ FAS and L-pyruvate kinase activities (resp. -44 and -62% at 0.5% sesamin) and gene expression (resp. \approx -42 and \approx -67% at 0.5% sesamin); ↑ ME activity (\approx +125% at 0.5% sesamin) and gene expression (\approx +100% at 0.5% sesamin) | |
| 28 | | | | | ↓ 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 | |
| 29 | 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) |

| | | | | | | |
|----|----------------------|--|-----------------|---------|---|------------------------|
| 1 | | | | | | |
| 2 | of sesamin and | | | | | |
| 3 | episesamin) | | | | | |
| 4 | Sesamin (1:1 mixture | Rats fed sesamin-free and 10%-fat diet | 0.1 and 0.2% of | 15 days | ↑ dose-dependently hepatic FA oxidation enzyme activity: | (Ide et al., 2001) |
| 5 | of sesamin and | | diet | | peroxisomal oxidation (resp. +22 and +130%), acyl-CoA | |
| 6 | episesamin) | | | | oxidase (resp. +38 and +112%), CPT (resp. +61 and +135%), 3- | |
| 7 | | | | | hydroxyacyl-CoA dehydrogenase (resp. +56 and +90%) and 3- | |
| 8 | | | | | ketoacyl-CoA thiolase (resp. +72 and +116%) | |
| 9 | | | | | ↓ dose-dependently ACC, FAS, ATPCL, G6PDH and pyruvate | |
| 10 | | | | | kinase activities (resp. -36, -32, -30, -42 and -19% at 0.1%, and | |
| 11 | | | | | resp. -57, -46, -47, -59 and -44% at 0.2% sesamin) and gene | |
| 12 | | | | | expression (resp. -35, -36, -28, -36 and -25% at 0.1%, and resp. | |
| 13 | | | | | -52, -50, -48, -64 and -55% at 0.2% sesamin); no effect on ME | |
| 14 | | | | | activity (resp. -6 and +13%) and gene expression (resp. +2 and - | |
| 15 | | | | | 7%) | |
| 16 | | | | | ↓ dose-dependently activity of hepatic enzymes involved in | |
| 17 | | | | | cholesterol synthesis: farnesyl pyrophosphate synthase (resp. - | |
| 18 | | | | | 20 and -29%) and squalene synthetase (resp. -32 and -39%); no | |
| 19 | | | | | effect on HMG-CoA synthase | |
| 20 | | | | | ↓ dose-dependently gene expression (mRNA levels) of hepatic | |
| 21 | | | | | enzymes involved in cholesterol synthesis: HMG-CoA | |
| 22 | | | | | reductase (resp. -23 and -30%), farnesyl pyrophosphate | |
| 23 | | | | | synthase (resp. -21 and -35%), squalene synthetase (resp. -30 | |
| 24 | | | | | and -44%) and of LDL receptor (resp. -22 and -28%); ↑ mRNA | |
| 25 | | | | | level of HMG-CoA synthase (resp. +9%, NS, and +31%) | |
| 26 | | | | | ↓ mRNA level of SREBP-1 (resp. ≈ -30 and -35%) | |
| 27 | | | | | ↓ dose-dependently protein level of precursor and mature forms of | |
| 28 | | | | | SREBP-1 (resp. ≈ -13%, NS, and -37%) | |
| 29 | | | 0.2 and 0.4% of | 15 days | ↑ dose-dependently hepatic FA oxidation enzyme activity: | |
| 30 | | | diet | | peroxisomal oxidation (resp. +207 and +600%), acyl-CoA | |
| 31 | | | | | oxidase (resp. +260 and +768%), CPT (resp. +127 and +232%), | |
| 32 | | | | | 3-hydroxyacyl-CoA dehydrogenase (resp. +148 and +329%) | |
| 33 | | | | | and 3-ketoacyl-CoA thiolase (resp. +139 and +275%) | |
| 34 | | | | | ↓ ACC, FAS, ATPCL, G6PDH and pyruvate kinase activities (resp. | |
| 35 | | | | | -44, -47, -43, -60 and -50% at 0.2% sesamin, and resp. -41, -39, | |
| 36 | | | | | -46, -55 and -56% at 0.4% sesamin) and gene expression (resp. | |
| 37 | | | | | -49, -59, -44, -48 and -66% at 0.2%, and resp. -47, -57, -40, -49 | |
| 38 | | | | | and -65% at 0.4% sesamin) with plateau reached at 0.2% | |
| 39 | | | | | sesamin; ↑ dose-dependently ME activity (resp. +24%, NS, and | |
| 40 | | | | | +97%) and gene expression (resp. +16%, NS, and +92%) | |
| 41 | | | | | ↓ activity of hepatic enzymes involved in cholesterol synthesis: | |
| 42 | | | | | farnesyl pyrophosphate synthase (-27% at 0.2% sesamin and no | |
| 43 | | | | | significant effect at 0.4% sesamin) and squalene synthetase (- | |
| 44 | | | | | 37% at 0.2% sesamin and no significant effect at 0.4% | |
| 45 | | | | | sesamin); ↑ dose-dependently HMG-CoA synthase activity | |
| 46 | | | | | (resp. +66 and +189%) | |
| 47 | | | | | ↓ dose-dependently gene expression (mRNA levels) of HMG-CoA | |
| 48 | | | | | reductase (resp. -26 and -42%), farnesyl pyrophosphate | |
| 49 | | | | | synthase (-37% at 0.2% sesamin), squalene synthase (-34% at | |
| 50 | | | | | 0.1% sesamin) and of LDL receptor (resp. -30 and -47%); ↑ | |
| 51 | | | | | dose-dependently mRNA level of HMG-CoA synthase (+172% | |
| 52 | Sesamin or | Rats fed sesamin-free and 10%-fat diet | 0.2% of diet | 15 days | at 0.4% sesamin); no effect on mRNA level of farnesyl | |
| 53 | episesamin | | | | pyrophosphate synthase at 0.4% sesamin | |
| 54 | | | | | ↓ dose-dependently mRNA level of SREBP-1 (resp. ≈ -37 and - | |
| 55 | | | | | 55%) | |
| 56 | | | | | ↓ protein level of precursor and mature forms of SREBP-1 (resp. ≈ - | |
| 57 | | | | | 84 and -88%) | |
| 58 | | | | | ↑ FA oxidation enzyme activity: mitochondrial (resp. +73 and | (Kushiro et al., 2002) |
| 59 | | | | | +129%) and peroxisomal (resp. +63 and +407%) palmitoyl- | |
| 60 | | | | | | |

| | | | | | | |
|----|------------------------------|--|---------------------------------|---------|--|------------------------|
| 1 | | | | | 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%) | |
| 2 | | | | | ↑ 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 reductase (resp. +180 and +213%) | |
| 3 | | | | | ↑ 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%) | |
| 4 | | | | | ↓ 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%) | |
| 5 | | | | | ↓ 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%) | |
| 6 | | | | | ↓ 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%) | |
| 7 | 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 dehydrogenase (-14%, NS), 3-ketoacyl-CoA thiolase (-13%, NS), FAS (-2%, NS), ATPCL (-26%, NS), G6PDH (-37%, NS) and pyruvate kinase (-4%, NS) activities | (Kushiro et al., 2004) |
| 8 | | | | | ↑ peroxisomal fatty acid oxidation (+18%, NS) and ACO activity (+15%, NS) | |
| 9 | | | | | ↓ mRNA levels of mitochondrial trifunctional enzyme subunits α (-6%, NS) and β (-27%, NS) and 3-ketoacyl-CoA thiolase (-8%, NS) | |
| 10 | | | | | ↑ 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) | |
| 11 | | 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 | |
| 12 | | | | | ↑ peroxisomal FA oxidation (+11%, NS), and 3-hydroxyacyl-CoA dehydrogenase (+16%, NS) and 3-ketoacyl-CoA thiolase (+14%, NS) activity | |
| 13 | | | | | ↑ 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%) | |
| 14 | | | | | ↓ mRNA levels of FAS (-63%), ATPCL (-45%) and L-pyruvate kinase (-64%) | |
| 15 | | 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 dehydrogenase (+89%) and 3-ketoacyl-CoA thiolase (+80%) activity | |
| 16 | | | | | ↓ FAS (-57%), ATPCL (-55%), G6PDH (-66%) and pyruvate kinase (-64%) activities | |
| 17 | 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) |

| | | | | | | |
|----|---|---|-------------------------------|---------|--|--|
| 1 | | | | | | |
| 2 | of sesamin and | | | | | (resp. \approx +150, +87 and +58%; \approx -33% for safflower oil and -52% |
| 3 | episesamin) | | | | | for fish oil vs palm oil+sesamin) and peroxisomal (resp. \approx +325, |
| 4 | | | | | | +320 and +300%; \approx +10% for safflower oil, NS, and +110% for |
| 5 | | | | | | fish oil vs palm oil+sesamin) palmytoyl CoA oxidation, ACO |
| 6 | | | | | | (resp. \approx +200, +325 and +400%; \approx +50% for safflower oil, NS, |
| 7 | | | | | | and +290% for fish oil vs palm oil+sesamin), CPT (resp. \approx |
| 8 | | | | | | +233, +140 and +78%; \approx +10% for safflower oil, NS, and +40% |
| 9 | | | | | | for fish oil vs palm oil+sesamin), 3-ketoacyl-CoA thiolase |
| 10 | | | | | | (resp. \approx +163, +200 and +196%; \approx +15% for safflower oil, NS, |
| 11 | | | | | | and +60% for fish oil vs palm oil+sesamin), and 2,4-dienoyl- |
| 12 | | | | | | CoA reductase (resp. \approx +247, +177 and +71%; \approx +1% for |
| 13 | | | | | | safflower oil, NS, and -22% for fish oil vs palm oil+sesamin) |
| 14 | | | | | | ↑ mRNA levels of hepatic peroxisomal proteins (carnitine |
| 15 | | | | | | octanoyltransferase, ACO, bifunctional enzyme, 3-ketoacyl- |
| 16 | | | | | | CoA thiolase, and PEX11 α) and of mitochondrial enzymes |
| 17 | | | | | | involved in hepatic fatty acid oxidation (CPT II, medium-chain |
| 18 | | | | | | acyl-CoA dehydrogenase, trifunctional enzyme subunits α and |
| 19 | | | | | | β , 3-ketoacyl-CoA thiolase, 2,4-dienoyl-CoA reductase and |
| 20 | | | | | | short-chain Δ^3, Δ^2 -enoyl-CoA isomerase) |
| 21 | | | | | | ↓ FAS (resp. -45, -63 and -48, NS, %), ATPCL (resp. -53, -60 and |
| 22 | | | | | | -70%) and G6PDH (resp. -60, -77 and -38, NS, %) activities |
| 23 | | | | | | ↓ mRNA levels of enzymes involved in hepatic fatty acid synthesis |
| 24 | | | | | | (ACO, FAS, ATPCL and spot 14) |
| 25 | Matairesinol | Ovariectomized rats fed standard diet (11.5% fat) | 0.02% of diet | 4 weeks | | TG level: resp. -68, -23 and +136% |
| 26 | | HepG2 cells | 0.01, 0.1 and 1 μ M | 3 days | | Cholesterol level: resp. -20, -21 and +21% |
| 27 | | | | | | PL level: resp. +19, +30 and +19% |
| 28 | Sesamin | Male rats fed standard diet | 250 mg/5 mL olive oil/kg b.w. | 3 days | | ↓ cholesterol (-6%, NS) and TG (-12%, NS) levels (Cho et al., 2004) |
| 29 | | | | | | ↓ cholesterol (resp. -30, -27 and -19%, NS) and TG (resp. \approx 0, -15 |
| 30 | | | | | | and -12%, NS) contents |
| 31 | | | | | | Significantly up-regulated expression of genes encoding for |
| 32 | | | | | | proteins with a lipid-metabolizing function: acyl-CoA hydrolase |
| 33 | | | | | | (114.6-fold), very-long-chain acyl-CoA thioesterase (14.2- and |
| 34 | | | | | | 4.7-fold: different probe position in rat genome), acyl-CoA |
| 35 | | | | | | hydrolase-like protein (3.4-fold), acyl-CoA hydrolase (2.1- |
| 36 | | | | | | fold), peroxisomal 3-ketoacyl-CoA thiolase (8.3- and 3.4-fold), |
| 37 | | | | | | peroxisomal bifunctional enzyme (4.5-fold), 3,2- <i>trans</i> -enoyl- |
| 38 | | | | | | CoA isomerase (3.4-fold), enoyl CoA hydratase (3.0-fold), |
| 39 | | | | | | Δ^3, Δ^2 -enoyl-CoA isomerase (3.0-fold), 2,4-dienoyl-CoA |
| 40 | | | | | | reductase I (2.6- and 2.2-fold), ACO (2.1-fold) and ME (2.8- |
| 41 | | | | | | and 2.2-fold) |
| 42 | | | | | | Significantly up-regulated gene expression of early-stage |
| 43 | | | | | | mitochondrial (CPT I like protein and CPT II) and peroxisomal |
| 44 | | | | | | (carnitine octanoyltransferase) β -oxidation enzymes |
| 45 | | | | | | Significantly up-regulated gene expression of late-stage |
| 46 | | | | | | mitochondrial (very-long-chain acyl-CoA dehydrogenase, |
| 47 | | | | | | trifunctional enzyme β , 2,4-dienoyl-CoA reductase I, Δ^3, Δ^2 - |
| 48 | | | | | | enoyl-CoA isomerase and 3,2- <i>trans</i> -enoyl-CoA isomerase) and |
| 49 | | | | | | peroxisomal (ACO, enoyl CoA hydratase, bifunctional enzyme, |
| 50 | | | | | | 3-ketoacyl-CoA thiolase and 2,4-dienoyl-CoA reductase) β - |
| 51 | Sesamin (1:1 mixture of sesamin and episesamin) | Rats fed 10%-fat (palm oil) diet | 0.2 or 0.4% of diet | 15 days | | oxidation enzymes |
| 52 | | | | | | Significantly down-regulated gene expression of early-stage |
| 53 | | | | | | mitochondrial (acyl-CoA syntahse 5) β -oxidation enzymes |
| 54 | | | | | | Significantly down-regulated gene expression of L-type pyruvate |
| 55 | | | | | | kinase (0.37-fold) and Apo A-IV (0.48-fold) |
| 56 | | | | | | ↑ activity of the hepatic fatty acid oxidation enzymes: peroxisomal |
| 57 | | | | | | palmytoyl-CoA- oxidation (resp. \approx +550 and +1150%), ACO |
| 58 | | | | | | (resp. \approx +267 and +667%), CPT (resp. \approx +214 and +343%), 3- |

| | | | | | |
|----|---------------------|--|----------------------|---------|---|
| 1 | | | | | hydroxyacyl-CoA dehydrogenase (resp. \approx +175 and 263%) and 3-ketoacyl-CoA thiolase (resp. \approx +146 and +242%) |
| 2 | | | | | |
| 3 | | Rats fed 10%-fat (8% palm oil + 2% DHA ethyl ester) diet | 0.2% of diet | 15 days | \uparrow activity of the hepatic FA oxidation enzymes: peroxisomal palmytoyl-CoA oxidation (\approx +500%), ACO (\approx +575%), CPT (\approx +211%), 3-hydroxyacyl-CoA dehydrogenase (\approx +183%) and 3-ketoacyl-CoA thiolase (\approx +151%) |
| 4 | | | | | |
| 5 | | Rats fed 10%-fat (palm oil) diet | 0.2% of diet | 15 days | \uparrow activity of the hepatic FA oxidation enzymes: peroxisomal palmytoyl-CoA-oxidation (\approx +300%), ACO (\approx +300%), CPT (\approx +250%), enoyl-CoA hydratase (\approx +48%), 3-hydroxyacyl-CoA dehydrogenase (\approx +141%) and 3-ketoacyl-CoA thiolase (\approx +312%) |
| 6 | | | | | |
| 7 | | Rats fed 10%-fat (8% palm oil + 2% EPA ethyl ester) diet | 0.2% of diet | 15 days | \uparrow activity of the hepatic FA oxidation enzymes: peroxisomal palmytoyl-CoA oxidation (\approx +420%), ACO (\approx +540%), CPT (\approx +140%), enoyl-CoA hydratase (\approx +73%), 3-hydroxyacyl-CoA dehydrogenase (\approx +188%) and 3-ketoacyl-CoA thiolase (\approx +333%) |
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| 17 | | | | | <u>4 experiments:</u> |
| 18 | | | | | \uparrow mRNA levels of hepatic peroxisomal proteins (carnitine octanoyltransferase, ACO, bifunctional enzyme, 3-ketoacyl-CoA thiolase, and PEX11 α) 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) |
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| 23 | Sesamin | Rats fed 10%-fat (palm oil) diet | 0.06 or 0.2% of diet | 10 days | \uparrow 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 |
| 24 | | | | | (Lim et al., 2007) |
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| 30 | | | | | \downarrow FAS (resp. -41 and -60%), ATPCL (resp. -38 and -57%), G6PDH (resp. -49 and -64%) and pyruvate kinase (resp. -15%, NS, and -39%) activities |
| 31 | | | | | |
| 32 | | | | | \downarrow TG (resp. -59 and -64%) and cholesterol (resp. -25 and -25%) levels; \uparrow PL level (resp. 0 and +6%, NS) |
| 33 | | | | | |
| 34 | Sesamolol | Rats fed 10%-fat (palm oil) diet | 0.06 or 0.2% of diet | 10 days | \uparrow 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 |
| 35 | | | | | |
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| 38 | | | | | |
| 39 | | | | | \downarrow FAS (resp. -34 and -55%), ATPCL (resp. -35 and -67%), G6PDH (resp. -51 and -68%) and pyruvate kinase (resp. -20 and -51%) activities |
| 40 | | | | | |
| 41 | | | | | |
| 42 | | | | | \downarrow TG (resp. -18 and -30%) and cholesterol (resp. -17 and -30%) levels; \uparrow PL level (resp. +6%, NS, and +37%) |
| 43 | Sesamin + sesamolol | Rats fed 10%-fat (palm oil) diet | 0.14+0.06% of diet | 10 days | \uparrow 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 |
| 44 | | | | | |
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| 47 | | | | | |
| 48 | | | | | \downarrow FAS (-56%), ATPCL (-56%), G6PDH (-67%) and pyruvate kinase (-45%) activities |
| 49 | | | | | |
| 50 | | | | | \downarrow TG (-34%) and cholesterol (-23%) levels; \uparrow PL level (+42%) |
| 51 | | | | | <u>All experiments:</u> |
| 52 | | | | | \uparrow mRNA abundance of enzymes involved in FA oxidation (from +10% at 0.06% sesamin for trifunctional enzyme subunit β to |
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| 1 | | | | | +544% at 0.2% sesamol for peroxisomal carnitine octanoyltransferase): | |
| 2 | | | | | - peroxisomal carnitine octanoyltransferase, ACO, bifunctional enzyme, 3-ketoacyl-CoA thiolase and P11 α | |
| 3 | | | | | - mitochondrial CPT II, bifunctional enzyme subunits α and β , 3-ketoacyl-CoA thiolase, Δ^3, Δ^2 -enoyl-CoA isomerase and 2,4-dienoyl-CoA reductase | |
| 4 | | | | | ↓ mRNA abundance of proteins involved in lipogenesis in almost all cases (from 0% for mixture of sesamin+sesamol to -69% at 0.2% sesamol 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 | |
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| 13 | 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 PPAR γ (+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), PPAR γ (-14%, NS, at 3 mg/kg) and SREBP-2 (-27%, NS, and -19%, NS) mRNA expression levels | (Felmlee et al., 2009) |
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| 24 | | 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 PPA γ (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 | |
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| 35 | Secoisolariciresinol diglucoside (SDG) | Hypertriacylglycerolaemic rats (10% fructose in drinking water) | 3 and 6 mg/kg b.w. | 2 weeks | ↑ PPAR α mRNA expression level (resp. +36 and +31%) ↓ SREBP-1c mRNA expression level (resp. -9 and -38%) | |
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| 38 | B5 - Stilbenes | | | | | |
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| 40 | Stilbenes containing extract-fraction (from <i>Cajanus cajan</i> 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. \approx +14%, NS, and \approx +61%), CYP7A1 (resp. \approx +20%, NS, and \approx +48%) and LDL-receptor (resp. \approx +28 and \approx +84%) mRNA expressions | (Luo et al., 2008) |
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| 47 | C - Phenolic-derived compounds | | | | | |
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| 50 | C1 - Curcumin | | | | | |
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| 52 | 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) |
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| 1 | Curcumin | Rats fed 10%-fat diet | 0.2% of diet | 4 weeks | ↓ TC (-37%) and lipid (-4%, NS) contents | (Kamal-Eldin et al., 2000) |
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| 3 | C2 - Saponins | | | | | |
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| 5 | Ginsenosides (Rb ₁ , Rc, Rg ₁ , Rd and Re) purified from ginseng (<i>Panax ginseng</i>) | 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%) <u>Rb₁:</u> ↑ 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) |
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| 14 | Purified saponosides from <i>Aralia mandshurica</i> (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 | <u>0.005 g/kg:</u> ↑ and ↓ TL (+8%), TG (-40%) and TC (+14%) contents <u>0.01 g/kg:</u> ↓ TL (-35%), TG (-35%) and TC (-11%) contents | (Wojcicki et al., 1977) |
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| 19 | Commercial white saponins (probably from European Soapwort, <i>Saponaria officinalis</i>) | 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) |
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| 25 | Commercial white saponins (probably from European Soapwort, <i>Saponaria officinalis</i>) | Rats fed standard diet containing methionine-supplemented sodium isolates of soybean or casein (25% energy) | 1% of diet | 56 days | <u>Soybean-based diet:</u> ↑ cholesterol content (+41%) <u>Casein-based diet:</u> ↓ cholesterol content (-4%) | (Pathirana et al., 1980) |
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| 31 | Saponins (purified) | Laying hens (brown and white Leghorn) fed standard diet | 0.1 or 0.5% of diet | 5 or 8 weeks | ↓ lipid content (resp. -16%, NS, and -26%) No effect on cholesterol content (resp. -3%, NS, and +8%, NS) | (Whitehead et al., 1981) |
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| 37 | Steroid saponins (from <i>Gypsophila</i> 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 | <u>Compared to standard diet without citrus pectin:</u> ↓ TL (-68%) and TC (-65%) contents <u>Compared to standard diet with 10% citrus pectin:</u> ↑ TL (+6%, NS) and TC (+13%, NS) contents | (Rotenberg and Eggum, 1986) |
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| 42 | Mixture of avcanosides 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 | <u>Gerbils:</u> ↓ TL (-4%, NS), TC (-6%, NS) and FC (-6%, NS) contents <u>Rats:</u> ↓ TL (-31%), and ↑ TC (+2%, NS) and FC (+6%, NS) contents | (Onning and Asp, 1995) |
| 43 | | | | | | |
| 44 | | | | | | |
| 45 | Soy saponins | HepG2 cells | 10 ng/L | 24 hours | ↑ PPAR α (≈ +60%) and PPAR γ (≈ +80%) | (Ricketts et al., 2005) |
| 46 | Changkil saponins (from root of <i>Platycodon grandiflorum</i>) | 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) |
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| 50 | Changkil saponins (from root of <i>Platycodon grandiflorum</i>) | 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) |
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| 1 | | | | | ↑ phosphorylated-ACC level (resp. +10%, NS, +40 and +70%) | |
| 2 | Saponins (from | 90% pancreatectomized diabetic rats fed high-fat | 0.2 g/kg b.w. | 8 weeks | ↓ TG content (≈ -17%, NS) | (Kwon et al., 2009) |
| 3 | <i>Platycodi radix</i>) | (40% as energy) diet | | | | |
| 4 | | | | | | |
| 5 | C3 - Phyto- | | | | | |
| 6 | sterols/stanols | | | | | |
| 7 | | | | | | |
| 8 | β -sitosterol | Mice fed high-cholesterol (1%) diet with 0.25, | 2.5% of diet | 3 weeks | ↓ TC (resp. -27, -47 and -7% with $p \leq 0.05$ at 1.0% cholic acid) | (Beher and Anthony, 1955) |
| 9 | | 0.5 or 1.0% of cholic acid | | | | |
| 10 | β -sitosterol | Normal and hypothyroid rats fed high- | 5% of diet | 13 days | ↓ TC content (-76% for normal rats and -83% for hypothyroid rats) | (Best and Duncan, 1956) |
| 11 | | cholesterol (1%) diet | | | Prevented the increase in stainable lipids (microscopic observations) | |
| 12 | Sterols (from soy) | Male (M) and female (F) mice fed cholesterol | 1% of diet | 12 days | ↓ neutral lipid (M: -7%, NS; F: -53%) and cholesterol (M: -48%; F: | (Katz et al., 1970) |
| 13 | | (0.5%) diet | | | -68%) contents | |
| 14 | | | 1% of diet | 1, 3 and 5 days | ↓ cholesterol content (resp. -23%, NS, -50 and -65%) | |
| 15 | | | | | | |
| 16 | | | 1% of diet | 5 days | <u>β-sitosterol</u> : ↓ cholesterol content (-67%, n = 2 experiments) | |
| 17 | | | | | <u>Stigmasterol</u> : ↓ cholesterol content (-57%, n = 2 experiments) | |
| 18 | | | | | <u>Ergosterol</u> : ↓ cholesterol content (-53%, n = 2 experiments) | |
| 19 | | | | | <u>Campesterol</u> : ↓ cholesterol content (-53%, n = 2 experiments) | |
| 20 | | | | | <u>Steryl glucoside</u> : ↓ cholesterol content (-18%, NS) | |
| 21 | β -sitosterol | Rats fed diet containing combination of | 0.1, 0.5 or 2.0% | 31 days | <u>9.5% butter fat, 0.5% safflower oil and 0.5% β-sitosterol</u> : ↓ | (Sugano et al., 1982) |
| 22 | | safflower oil (0 or 0.5%) and butter fat (9.5 | of diet | | cholesterol content (-27%), and ↑ TG (+6%, NS) and PL (+2%, | |
| 23 | | or 10% containing ≈ 0.004% campesterol, ≈ | | 35 days | NS) contents | |
| 24 | | 0.005% β -sitosterol and ≈ 0.28% cholesterol) | | | <u>10% butter fat, 0% safflower oil and 0.5% β-sitosterol</u> : ↓ cholesterol | |
| 25 | | | | | (-31%), TG (-9%, NS) and PL (-2%, NS) contents; ↑ ApoA-I | |
| 26 | | | | 33 days | serum concentration (+40%) | |
| 27 | | | | | <u>10% butter fat and 0% safflower oil</u> : | |
| 28 | | | | | 0.1% β -sitosterol: ↓ cholesterol (-18%, NS) and TG (-7%, NS) | |
| 29 | | | | | contents; no effect on PL content; ↑ ApoA-I (+22%) and ApoB | |
| 30 | | | | | (+7%, NS) serum concentrations | |
| 31 | | | | | 0.5% β -sitosterol: ↓ cholesterol content (-23%), and ↑ TG (+16%, | |
| 32 | | | | | NS) and PL (+6%, NS) contents; ↑ ApoA-I (+19%, NS) and ↓ | |
| 33 | | | | | ApoB (-9%, NS) serum concentrations | |
| 34 | | | | | 2.0% β -sitosterol: ↓ cholesterol content (-32%), and ↑ TG (+4%, NS) | |
| 35 | | | | | and PL (+4%, NS) contents; ↑ ApoA-I (+7%, NS) and ApoB | |
| 36 | | | | | (+38%) serum concentrations | |
| 37 | | | | | ↓ cholesterol (-54%) and TG (-44%) contents | |
| 38 | Sitosterol and | Mice fed diet containing safflower oil (0.5%) | 0.5% of diet | 40 days | | |
| 39 | spinasterol | and butter fat (9.5 containing ≈ 0.004% | | | | |
| 40 | Sitosterol | campesterol, ≈ 0.005% β -sitosterol and ≈ | | | | |
| 41 | | 0.28% cholesterol) | | | | |
| 42 | Sitosterol and | Mice fed ordinary powder diet | 1% of diet | 15 days | ↓ cholesterol (resp. -26 and -22%) and PL (resp. -4%, NS, and -3%, | (Uchida et al., 1983) |
| 43 | spinasterol | | | | NS) levels | |
| 44 | Sitosterol | Hamsters fed standard chow | 2% of diet | 7 weeks | ↓ cholesterol concentration (-32%) and steroid 12 α -hydroxylase | (Kuroki et al., 1983) |
| 45 | | | | | activity (-30%) | |
| 46 | Phytosterol mixture | Rats fed high-cholesterol (1%) diet | 3% of diet | 7 days | ↓ cholesterol level (-52%) | (Katagiri and Shimizu, 1992) |
| 47 | (57% β -sitosterol | | | | | |
| 48 | and 35% | | | | | |
| 49 | campesterol) | | | | | |
| 50 | Phytosterols from | Rats fed cholesterol diets (12 or 24 mg daily) for | 12, 24 or 48 mg | 3 last weeks | <u>12 mg cholesterol daily</u> : | (Laraki et al., 1993) |
| 51 | maize (72.5% β - | 4 weeks | | | No significant effect on ACC (0 and -3%), ME (≈ 0) and G6PDH | |
| 52 | sitosterol, 20.5% | | | | (resp. 0, -5 and +11%) activities except for ACC at 48 mg | |
| 53 | campesterol and | | | | phytosterol daily (+23%) | |
| 54 | 7% stigmasterol) | | | | No significant effect on FA content (resp. +13, +16 and -3%); ↓ | |
| 55 | | | | | cholesterol content (resp. +1%, NS, and -3 and -8%) | |
| 56 | | | 24, 48 or 96 mg | 3 last weeks | <u>24 mg cholesterol daily</u> : | |
| 57 | | | | | ↓ ACC (resp. -68, -70 and -69%), ME (resp. -63, -63 and -63%) and | |
| 58 | | | | | G6PDH (resp. -81, -76 and -74%) activities | |
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| 1 | | | | | ↓ FA (resp. -64, -65 and -62%) and cholesterol (resp. -20, -30 and -32%) contents | |
| 2 | | | | | ↑ HMG-CoA reductase activity (+148%) and mRNA level (≈ +150%) | (Shefer et al., 1994) |
| 3 | Plant sterol mixture | Rats fed standard diet | 2% of diet | 7 days | | |
| 4 | (82% sitosterol, | Rats i.v. injected with liposomes | 1% of liposomes | 42 hours | | |
| 5 | 12% sitostanol | | (to mimic | | No significant effect on HMG-CoA reductase activity (-3%), and ↑ | |
| 6 | and 6% | | sisterolemia | | HMG-CoA mRNA level (≈ +160%) | |
| 7 | campesterol) | | as found in | | ↓ CYP7A1 activity (-26%) | |
| 8 | | | humans) | | | |
| 9 | Phytosterol mixtures | Rats fed high-cholesterol (1%) diet | 1% of diet | 10 days | ↑ serum HDL cholesterol (+49%) for phytosterol mixtures naturally | (Ling and Jones, 1995) |
| 10 | naturally | | | | containing sitostanol (≈ 16 or 20% content); no effect with | |
| 11 | containing | | | | sitostanol-free soybean phytosterol material (only unsaturated | |
| 12 | sitostanol ¹ (from | | | | phytosterols) | |
| 13 | tall-oil) and | | | | | |
| 14 | sitostanol-free | | | | | |
| 15 | soybean | | | | | |
| 16 | phytosterol | | | | | |
| 17 | material | | | | | |
| 18 | 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 | (Ntanios and Jones, 1998a) |
| 19 | Plant sterol mixtures | Rabbits fed atherogenic diet (0.5% cholesterol) | 1% of diet | 50 days | ↓ median cholesterol level (-10%, NS) | (Ntanios et al., 1998a) |
| 20 | from soybean | | | | <u>Soybean sterols</u> (0.01% sitostanol): | |
| 21 | (0.01% sitostanol) | | | | <u>Tall oil sterols</u> (0.2% sitostanol): ↑ median cholesterol level (+24%, | |
| 22 | and tall oil (0.2 | | | | NS) | |
| 23 | and 0.8% | | | | <u>Tall oil sterols</u> (0.8% sitostanol): ↓ median cholesterol level (-31%, | |
| 24 | sitostanol) | | | | NS) | |
| 25 | Plant sterol mixtures | Rabbits fed cholesterol-enriched (0.25%) diet | 1% of diet | 45 days | ↓ cholesterol (≈ -74%, NS, for soybean sterols, and ≈ -92% for tall | (Ntanios and Jones, 1998b) |
| 26 | from soybean | | | | oil sterols and pure sitostanol) content | |
| 27 | (0.01% sitostanol) | | | | | |
| 28 | and tall oil (0.2% | | | | | |
| 29 | sitostanol), and | | | | | |
| 30 | pure sitostanol | | | | | |
| 31 | Phytosterols (from | Hamsters fed cholesterol-enriched (0.25%) diet | 0.5 or 1% | 90 days | <u>Tall oil phytosterols</u> : ↑ hepatic cholesterol fractional synthetic rate | (Ntanios et al., 1998b) |
| 32 | tall oil or soybean) | | | | (in % per day) (resp. +41%, NS, and +35%, NS) | |
| 33 | | | | | <u>Soybean phytosterols</u> : ↓ hepatic cholesterol fractional synthetic rate | |
| 34 | Phytosterol mixture | ApoE-KO mice (model of atherogenesis) fed | 2% of diet | 20 weeks | in % per day (resp. -39%, NS, and -16%, NS) | |
| 35 | (69% β-sitosterol, | mouse diet | | | ↓ cholesterol level (-54%) | (Moghadasian et al., 2001) |
| 36 | 16%, sitostanol | | | | ↑ HMG-CoA reductase (+184%), cholesterol 7α-hydroxylase ¹¹ | |
| 37 | and 15% | | | | (+18%, NS) and sterol 27-hydroxylase ¹¹ (+3%, NS) activities | |
| 38 | campesterol) | | | | | |
| 39 | Free phytosterol, | Gerbils fed 0.15%-cholesterol diet | 0.75% of diet | - | ↓ TC (resp. -80, -76 and -76%) and CE (resp. -91, -88 and -88%) | (Wijendran et al., 2002) |
| 40 | esterified sterols | | | | contents | |
| 41 | or stanols | | | | | |
| 42 | Nonesterified (free) | Gerbils fed high-fat (13.7%) diet containing | 0.5% of diet | 4-5 weeks | ↓ TC (resp. -57, -71 and -39%), FC (resp. 0, -38 and -11%, NS) and | (Hayes et al., 2002) |
| 43 | phytosterols | 0.05, 0.10 or 0.5% cholesterol | | | CE (resp. -72, -82 and -40%, NS) concentrations | |
| 44 | (80%)/stanols | | | | | |
| 45 | (20%) from tall oil | | | | | |
| 46 | Nonesterified (free) | Gerbils fed high-fat (13.7%) diet containing | 0.75% of diet | 4 weeks | <u>Phytosterols consumed with each dietary serving of cholesterol</u> : ↓ | |
| 47 | phytosterols | 0.15% cholesterol | | | TC (-78%), FC (-19%, NS) and CE (-89%) concentrations | |
| 48 | (80%)/stanols | | | | <u>Phytosterol consumed in a way alternated between diet without</u> | |
| 49 | (20%) from tall oil | | | | <u>phytosterols and diet with 0.15% of free phytosterol every other</u> | |
| 50 | | | | | <u>days</u> : ↓ TC (-66%), FC (-19%, NS) and CE (-74%) concentrations | |
| 51 | Free phytosterol from | Gerbils fed high-fat (13.7%) diet containing | 0.75% of diet | 5 weeks | Free phytosterols: ↓ TC (-80%), FC (-11%, NS) and CE (-91%) | |
| 52 | tall oil and | 0.15% cholesterol | | | concentrations | |
| 53 | esterified | | | | Sterol esters: ↓ TC (-77%), FC (-11%, NS) and CE (-88%) | |
| 54 | phytosterols | | | | concentrations | |
| 55 | (sterols and | | | | Stanol esters: ↓ TC (-76%), FC (0) and CE (-88%) concentrations | |
| 56 | stanols) from | | | | | |

| | | | | | | |
|----|-----------------------------|---|--------------------------|--------------------------|---|--|
| 1 | commercial | | | | | |
| 2 | margarines | | | | | |
| 3 | Phytosterol mixture | 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 | (Shin et al., 2004) |
| 4 | ±soy lecithin | | | | | |
| 5 | | | | | ↓ HMG-CoA reductase (-1%, NS, and -4%, NS, plus lecithin) and ACAT (-12% and -12% plus lecithin) activities | |
| 6 | | | | | ↓ LI (-14%), and TC (-44%) and TG (-40%) levels | (Li et al., 2010) |
| 7 | Conjugated linoleyl | Mice fed 2 weeks with hyperlipidemic diet then | 0.04% of diet | 2 last weeks | | |
| 8 | β-sitosterol | 2 weeks with basal diet | | with hyperlipidemic diet | | |
| 9 | | | | | | |
| 10 | Phytosterols and | <i>Inbred</i> rats with a mutation in the <i>Abcg5</i> gene | 0.2% of diet | 5 weeks | ↓ cholesterol levels (resp. -40 and -16%) | (Chen et al., 2010b) |
| 11 | phytosterols* | (<i>i.e.</i> over absorb phytosterols and phytosterols) | | | | |
| 12 | | | | | | |
| 13 | C4 - Alkylresorcinols | | | | | |
| 14 | | | | | | |
| 15 | 5- <i>n</i> - | Enzyme assays: methanolic solutions of | From 4 to 50 μM | Changes in | <u>5-<i>n</i>-pentadecylresorcinol:</u> | (Rejman and Kozubek, 2003) |
| 16 | alk(en)ylresorcinol | resorcinolic lipids with enzyme (2 U/mL) | | absorbance for 15 min | - from 50 (4 μM) to 100% (11 μM) inhibition fro GPDH activity | |
| 17 | 1 (resorcinolic | | | | - from 0 (4 μM) to 30% (50 μM) inhibition for ADH and LDH activities | |
| 18 | lipid homologues | | | | - from 0 (4 μM) to 20% (50 μM) inhibition for G6PDH activity | |
| 19 | from wheat and | | | | - 0% inhibition from 4 μM to 50 μM for IDH | |
| 20 | rye brans) | | | | ↓ TG content/accumulation: | |
| 21 | | 3T3-L1 cells (model to study adipocyte differentiation) | From 2.5 to 12.5 μM | 7 days | - from ~ -15 to ~ -59% for pentadecylresorcinol (C 15:0, IC ₅₀ = 10.7 μM) | |
| 22 | | | | | - from ~ -35 to ~ -93% for heneicosylresorcinol (C 21:0, IC ₅₀ = 5.0 μM) | |
| 23 | | | | | - 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) | |
| 24 | | | | | - from ~ -32 to ~ -80% for Cardanol | |
| 25 | | | | | - from ~ -25 to ~ -70% for Cardol | |
| 26 | | | | | - from ~ -5 to ~ -50% for anacardic acid | |
| 27 | Cardol, Cardanol and | 3T3-L1 cells (model to study adipocyte differentiation) | From 2.5 to 12.5 μM | | | |
| 28 | Anacardic acid ^d | | | | | |
| 29 | | | | | | |
| 30 | Alkylresorcinols | 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 | (Ross et al., 2004) |
| 31 | (from rye bran) | | | | 0.4%: ↓ TL (-18%, NS), TC (-47%) and cholesterol in liver lipids (-35%) concentrations | C5 - Coumarin Auraptene {Nagao, 2010 #22917} |
| 32 | | | | | | |
| 33 | | | | | | |

³⁴All terms used in the Table are precisely those of the article considered: for example, 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-lipotrope effects (*i.e.* an increase in hepatic lipid content and/or lipogenic enzyme activities) are also presented to allow comparisons and further relevant interpretations

³⁵Indicates the decreased or increased percentage induced by the lipotrope compared to the control, *i.e.* steatogen diet (NS - Not Significant - means absence of significance for the change observed; in other cases, the effect was either significant or no information was given in the article)

³⁶Mixture of ferulic acid esters of triterpene alcohols and sterols (isolated from rice bran oil)

³⁷Polyphenon-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

³⁸Catechins from green tea extract are composed of 48% EGCG, 31% EGC, 13% ECG and 8% EC

³⁹Provinol[®] 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 anthocyanes 0.095%)

⁴⁰Contains protocatechuic acid (24.24%), catechin (2.67%), gallic acid (2.44%), caffeic acid (19.85%) and gallic acid gallates (27.98%)

⁴¹1.25% 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

⁴²Metabolites of hesperetin

⁴³No data given in the reference

⁴⁴Isolated from fermented Korean soybean paste

⁴⁵Contains 40, 1 and 18% of respectively genistein, glycitein and daidzein

⁴⁶Δ⁶ 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

⁴⁷C-iso and U-iso are mixtures of respectively conjugated or unconjugated isoflavones

⁴⁸Contains flavones (apigenin, luteolin, apigenin-7-glucoside - AP7Glu, luteolin-7-glucoside - LU7Glu) and flavonols (isorhamnetin and quercetin)

⁴⁹Mainly 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%)

⁵⁰Contains 48% EGCG, 31% EGC, 13% ECG and 8% EC

⁵¹5-α-saturated derivative of sitosterol

⁵²Phytosterols are composed of 22% of brassicasterol, 31.9% campesterol, 43.2% β-sitosterol and 2.9% others; phytosterols are composed of 54.7% campestanol and 44.8% sitostanol

⁵³Cardol: natural mixture of unsaturated C15 alkylphenolic congeners, Cardanol: natural mixture of unsaturated C15 alkylphenolic acid congeners

⁵⁴ABBREVIATIONS: ABCA, ATP-Binding Cassette transporter (also known as the cholesterol efflux regulatory protein that is encoded by ABCA1 gene); ACAT, Acetyl/ Acyl-CoA:Cholesterol Acetyl/ AcylTransferase (forms CE from cholesterol); ACC/CBX, Acetyl-CoA Carboxylase (involved in FA synthesis; is inhibited when phosphorylated); ACO/ACOX, Acyl-CoA

⁵⁵oxidase (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; AMPK α, AMP-activated protein Kinase α (AMPK regulates several intracellular systems including β-

⁵⁶oxidation 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,

⁵⁷Coenzyme A; CPT, Carnitine PalmytoylTransferase (allows transfer of long-chain FA across mitochondrial 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

⁵⁸diacylglycerol and Acyl-CoA); EC, EpiCatechin; ECG, EpiCatechin Gallate; ECH1, Enoyl-CoA Hydratase/3-hydroxyacyl-CoA dehydrogenase (catalyzes 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

⁵⁹cholesterol; FFA, Free Fatty Acids; GAPDH, GlycerAldehyde-3-Phosphate DeHydrogenase (involved in glycolysis); G6PDH, Glucose-6-Phosphate DeHydrogenase (NADPH⁺-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-

⁶⁰MethylGlutaryl-Coenzyme A Synthase 2; *i.p.*, intraperitoneally; IC₅₀, concentration required for 50% inhibition; ICR, Imprinting Control Region; IDH, Isocitrate DeHydrogenase; *i.v.*, intravenously; LDH, L-Lactate DeHydrogenase; LDL, Low-Density Lipoprotein; LDLR, Low-Density Lipoprotein Receptor (involved in transfer of lipids into hepatocytes); LI, Liver Index

1 (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 ($IC_{50} > 1$
2 mM); NS, Not Significant; PC, PhosphatidylCholine; PE, PhosphatidylEthanolamine; PEX11 α , peroxisomal membrane protein; PL, PhosphoLipid; resp., respectively; PPAR, Peroxisome Proliferator-Activated Receptor (transcription factor of genes involved in lipogenesis); PPAR α -null KO (Knock Out) mice, homozygous mice for deletion of PPAR α gene; resp.,
3 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
4 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)

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1
2 **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**

| 3 Plant extract or plant-based foods | 4 <i>In vivo</i> or <i>in vitro</i> models | 5 Supplemented daily dose | 6 Duration of lipotrope exposition | 7 Hepatic effect(s) | 8 References |
|---|---|--|------------------------------------|--|--|
| 9 Corn oil vs hydrogenated coconut oil (control) | 10 Healthy male subjects fed <i>ad libitum</i> institutional American type diet | 11 One ounce (24-33 g) | 12 1 month | 13 <u>Corn oil</u> : ↓ liver cholesterol (-25%) ^b upon 1 month <u>Hydrogenated coconut oil</u> : ↓ liver cholesterol (+9%, NS) upon 1 month | 14 (Frantz and Carey, 1961) |
| 15 Cottonseed vs coconut oils | 16 Rats fed 10%-fat diet ±1% cholesterol | 17 10% of diet | 18 7 weeks | 19 <u>Males</u> : adding cholesterol ↑ TL (+475 vs +110%) ^c , TC (+1916 vs +600%), FC (+95 vs +27%) and PL (+227 vs -3%) contents <u>Females</u> : adding cholesterol ↑ TL (+218 vs +75%), TC (+2436 vs +493%), FC (+93 vs +80%) and PL (+26 vs +14%) contents | 20 (Okey et al., 1961) |
| 21 Arachis oil, 3 margarines ^d and butter | 22 Rabbits fed 20%-fat diet (no control group) | 23 20% of diet | 24 42 weeks | 25 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%) | 26 (Krogh et al., 1961) |
| 27 Whole wheat breads or rye breads | 28 Rats fed white breads | 29 - ^d | 30 16 weeks | 31 <u>Whole wheat breads</u> : ↓ TG (NS) and cholesterol levels <u>Rye breads</u> : ↓ TG level (NS) | 32 (Yacowitz et al., 1976) |
| 33 Safflower oil | 34 Rats fed fat-free and high-fructose/glucose (72%) diet for 7 days then supplemented with PUFA, injected with ³ H ₂ O and killed 20 min after injection | 35 5% or 10% of diet | 36 3 or 4 days | 37 <u>Fructose</u> : ↓ 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) <u>Glucose</u> : ↓ FAS (-71% at 5% fat level) and phosphofructokinase (-7%, NS at 5% fat level) activities; ↓ FA synthesis (-53% at 5% fat level) | 38 (Toussant et al., 1981) |
| 39 Rice bran oil | 40 Rats fed high-cholesterol (1% +0.5% cholic acid) diet | 41 10% of diet | 42 8 weeks | 43 ↓ TC (-22%, NS) and TG (-32%, NS) contents | 44 (Sharma and Rukmini, 1986) |
| 45 Safflower or menhaden fish oil | 46 Rats trained 10 days with high-glucose (58.43%) and fat-free diet, then supplemented 7 days with PUFA-rich oils or tripalmitin (control) | 47 20% digestible energy of diet | 48 - | 49 ↓ FAS mRNA abundance (≈ -69% for n-6-rich safflower oil and ≈ -87% for n-3-rich menhaden fish oil) | 50 (Clarke et al., 1990) |
| 51 Menhaden fish oil | 52 Rats trained 10 days with high-glucose (58.43%) and fat-free diet, then supplemented 7 days with PUFA-rich oil or tripalmitin (control) | 53 20% digestible energy of diet | 54 7 days | 55 ↓ transcription rate of FAS (-94%) and S ₁₄ protein (putative lipogenic protein, -79%) | 56 (Blake and Clarke, 1990) |
| 57 Rice bran oil (RBO), defatted rice bran oil (DRB), RBO + DRB, and 4 levels of rice brans | 58 Male hamsters fed 0.3%-cholesterol diets (all contains 10% fiber and 9% fat) | 59 Resp. 9, 35, 35 + 8.9, and 43.7, 32.8, 21.8 and 10.9% | 60 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) | ↓ LI (resp. -11, -4%, NS, -9, -11, -9, -9 and -7%) (Kahlon et al., 1992a) |
| 61 Rice bran, defatted rice bran ^e , rice bran oils (n = 2), and rice bran oil gum and wax | 62 Hypercholesterolemic hamsters (control diet contains 0.3% cholesterol, 10% cellulose and 9% corn oil): all diets contain 10% fiber, 9% fat and 3% nitrogen | 63 Resp. 50.2, 41.3-41.5, 7.9-9.0, 0.9 and 0.2% of diet | 64 21 days | 65 ↓ 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 | 66 (Kahlon et al., 1992b) |
| 67 Wheat and oat brans, barley and malted barley | 68 Rats fed AIN 76-based and high-cholesterol (1% + 0.1% cholic acid) diet | 69 7.5% (NSP and lignin) of diet | 70 14 days | 71 ↓ 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) | 72 (Jackson et al., 1994) |
| 73 Liquid aged garlic extract (Kyolic [®]) | 74 Hepatocytes isolated from rat liver and incubated with 0.5 mM [1- ¹⁴ C]acetate | 75 0.01, 0.05, 0.1, 0.2 and 0.4 mM | 76 4 hours | 77 ↓ 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 | 78 (Yeh and Yeh, 1994) |
| 79 Oatmeal or its ethanol extract | 80 Rats and gerbils fed high-fat (40%) and 6.5% cellulose diet | 81 6.5% of diet | 82 21 (gerbils) and 19 (rats) days | 83 <u>Gerbils</u> : ↓ TL (resp. -2%, NS, and -1%, NS), TC (-38 and -34%) and FC (resp. -10 and -15%) <u>Rats</u> : ↓ TL (resp. -8%, NS, and -10%, NS), TC (-52 and -55%) and FC (resp. -10 and -24%) | 84 (Onning and Asp, 1995) |

| | | | | | | |
|----|---|---|---------------------------------|----------|--|--------------------------------|
| 1 | Tangerine-peel extract ¹ | Rats fed high-cholesterol (1%) diet | 16.7% of diet | 6 weeks | ↓ HMG-CoA reductase (-36%) and ACAT (-38%) activities | (Bok et al., 1999) |
| 2 | | | | | | |
| 3 | Soy protein enriched with isoflavones ⁸ (low or high levels) | Lean and obese (<i>fafa</i>) Zucker rats fed standard AIN-76-based diet | 20% of diet | 70 days | <u>Lean Zucker</u> : no effect on LI; ↓ TG (resp. ≈ -54%, NS, and ≈ -54%, NS), TC (resp. ≈ -18%, NS, and ≈ -35%) and CE (resp. ≈ -51 and ≈ -88%) concentrations | (Peluso et al., 2000) |
| 4 | | | | | | |
| 5 | | | | | <u>Obese Zucker</u> : ↓ LI (resp. ≈ -26 and ≈ -43%), and TG (resp. ≈ -33 and ≈ -49%, NS), TC (resp. ≈ -34 and ≈ -48%) and CE (resp. ≈ -46 and ≈ -77%) concentrations | |
| 6 | | | | | | |
| 7 | | 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%) | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | 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 | |
| 11 | | | | | | |
| 12 | | | | | | |
| 13 | | | | | | |
| 14 | <i>Platycodi radix</i> 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) |
| 15 | | | | | | |
| 16 | | | | | | |
| 17 | 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) | (Cheng and Lai, 2000) |
| 18 | | | | | | |
| 19 | | | | | ↓ TG concentrations (resp. -17, NS, -21, NS, -24, NS, and -28% compared to 0%-rice starch content) | |
| 20 | | | | | ↓ TC concentrations (resp. -1, NS, -10, -7 and -7% compared to 0%-rice starch content) | |
| 21 | | | | | | |
| 22 | 10% (w/v) brewed green tea | HepG2 cells | 0-200 μL | 24 hours | ↑ LDLR binding activity (≈ +80% at 200 μL) | (Bursill et al., 2001) |
| 23 | | | | | ↓ cholesterol (≈ -30% at 200 μL) and FC (≈ -25% at 200 μL) concentrations | |
| 24 | | | | | | |
| 25 | | | | | ↑ transcription factor form of SREBP-1 (+62-65% at 200 μL) | |
| 26 | | | | | ↓ (≈ -29% at 50 μL) and ↑ (≈ +107% at 200 μL) cholesterol synthesis | |
| 27 | | | | | ↑ extracellular media cholesterol concentration at 200 μL (≈ +25%) and tended to ↓ media chenodeoxycholic acid concentration (NS) | |
| 28 | 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 | |
| 29 | | | | | | |
| 30 | | | | | | |
| 31 | | | | | | |
| 32 | | | | | <u>Ethyl acetate extract</u> : ↑ dose-dependently LDLR activity (+312% at 100 μM equivalence of EGC), protein (+2100%) and mRNA (+2166%), and HMG-CoA reductase mRNA (+1335%) | |
| 33 | | | | | ↓ cholesterol concentration (resp. -54, -61 and -66%) | |
| 34 | | | | | No effect on TG concentration | (Adam et al., 2001) |
| 35 | 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 | | |
| 36 | | | | | | |
| 37 | | | | | | |
| 38 | | | | | | |
| 39 | | | | | | |
| 40 | | | | | | |
| 41 | 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%) | (Sirato-Yasumoto et al., 2001) |
| 42 | | | | | | |
| 43 | | | | | ↓ 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%) | |
| 44 | | | | | | |
| 45 | | | | | | |
| 46 | | | | | ↑ mitochondrial (resp. ≈ +44, +83 and +61%) and peroxisomal (resp. +33%, NS, +261 and +356%) FA oxidation rate | |
| 47 | | | | | | |
| 48 | | | | | ↓ 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%) | |
| 49 | | | | | | |
| 50 | | | | | | |
| 51 | Olive (oleic acid-rich), sunflower | Rats fed 10% fat (mixture of 64% tripalmitin, 16% tristearin and 20% corn oil; <i>i.e.</i> ≈ 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) |
| 52 | | | | | | |
| 53 | | | | | | |

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|----|-------------------------------|--|-------------------|-------------|--|--------------------------|
| 1 | | | | | | |
| 2 | (n-6 PUFA-rich), | saturated FA) diet | oil) | | 8%, NS, and +1%, NS) concentrations | |
| 3 | linseed (enriched | | | | ↓ ACC (resp. ≈ 0, ≈ -50, ≈ -64 and ≈ -70%) and DGAT (resp. ≈ -14%, | |
| 4 | with α-linolenic | | | | NS, ≈ -14%, NS, ≈ -16%, NS, and ≈ -23%) activities | |
| 5 | acid) or sardine oil | | | | ↓ and ↑ G6PDH (resp. ≈ +11%, NS, ≈ -31, ≈ -23 and ≈ -65%), PAP | |
| 6 | (n-3 PUFA-rich) | | | | (resp. ≈ +12%, NS, ≈ +16%, NS, ≈ -2%, NS, and ≈ -16%) and | |
| 7 | | | | | PCDGT (resp. ≈ -4%, NS, ≈ +46%, NS, ≈ +35%, NS, and ≈ 0) | |
| 8 | | | | | activities | |
| 9 | | | | | ↑ AST (resp. ≈ +46, ≈ +64, ≈ +90 and ≈ +95%) and CPT (resp. ≈ | |
| 10 | Wheat bran | Rats fed semi-purified diet (76% starch) | 21.4% of diet | 21 days | +156, ≈ +167, ≈ +222 and ≈ +222%) activities, and peroxisomal | |
| 11 | Whole wheat flour | | 70.0% of diet | | β-oxidation (resp. ≈ +100, ≈ +367, ≈ +633 and ≈ +567%) | (Adam et al., 2002) |
| 12 | White wheat flour | | 48.6% of diet | | ↓ TG (-40%) and cholesterol (-23%) concentrations | |
| 13 | Whole wheat flour | Rats fed semi-purified diet (71.75% starch) | 70% of diet | 21 days | ↓ TG (-45%) and cholesterol (-30%) concentrations | |
| 14 | and whole wheat | | | | ↓ TG (-32%) and cholesterol (-54%) concentrations | (Adam et al., 2003) |
| 15 | bread | | | | ↓ TG (resp. -39 and -32%) and cholesterol (resp. -48 and -54%) | |
| 16 | Soy protein enriched | Obese Zucker rats fed AIN-93-based diet | 20% of diet | 8 weeks | ↓ liver weight (resp. -12%, NS, and -26%), and cholesterol (resp. - | (Mezei et al., 2003) |
| 17 | with isoflavones ^b | | | (males) | 2%, NS, and -39%) and TG (-5%, NS, and -47%) concentrations | |
| 18 | (low or high | | | 11 weeks | ↓ liver weight (resp. -1%, NS, and -28%), and cholesterol (resp. -27 | |
| 19 | levels) | | | (females) | and -350%) and TG (≈ 0 and -38%) concentrations | |
| 20 | Sea buckhorn | Mice fed for 7 days control diet and i.v. injected | 2.79 ± 0.067 g/kg | 7 days | ↓ newly synthesized cholesterol (resp. -44 and -45% with geraniol) | (Wu et al., 2005) |
| 21 | ±geraniol ⁱ | with Triton WR1339 3 hours before killing | b.w. | | | |
| 22 | Olive or sunflower | Rats fed 1 month with high-fat (14% olive or | 14% then 5% of | 1 month + 1 | <u>Light micrography</u> : ↓ degree of liver steatosis (accumulation of fat | (Hernandez et al., 2005) |
| 23 | oil | sunflower oil) then 1 month with normal-fat | diet | month | droplets): apparent complete steatosis disappearance with olive | |
| 24 | Olive oil, fish oil or | Rats fed methionine-choline deficient diet | 0.45 mg/g rat | 2 months | oil and less important effect with sunflower oil | |
| 25 | butter fat | | | | <u>Histology</u> : ≈ 3, ≈ 3, 33 and 88% of rats had severe fatty infiltration | (Hussein et al., 2007) |
| 26 | | | | | (>60% hepatocytes affected) with methionine-choline deficient, | |
| 27 | | | | | olive oil, fish oil and butter fat diet, resp.; resp. 93, 90, 67 and | |
| 28 | | | | | 17% had mild-moderate fatty infiltration (<60% hepatocytes | |
| 29 | | | | | affected) | |
| 30 | | | | | ↓ and ↑ TG content (resp. ≈ -29%, ≈ +12%, NS, and ≈ +6%) | |
| 31 | Dried apricot | CCl ₄ -treated (1 mL/kg b.w. injected | 10 or 20% of diet | 5 months | Hepatic cholesterol (<i>r</i> = -0.8) and TG (<i>r</i> = -0.4) contents correlated | |
| 32 | | subcutaneously for 3 days at the end of the 5 | | | with MDA | |
| 33 | | months) rats | | | <u>Ultrastructural observations (transmission electrom microscopy)</u> : ↓ | (Ozturk et al., 2009) |
| 34 | Green and black tea | Rats fed high-fat (≈ 15%) diet | 100% of fluid | 26 weeks | volume and number of lipid globules | |
| 35 | | | intake | | ↑ PPARα (≈ +400 and ≈ +400%), CPT-1 (resp. ≈ +150 and ≈ +650%), | (Chen et al., 2009) |
| 36 | | | | | ACO (resp. ≈ +1950 and ≈ +1300%), SREBP-1 (resp. ≈ +770 and | |
| 37 | | | | | ≈ +400%), MCD (resp. ≈ +1100 and ≈ +1230%), FAS (resp. ≈ | |
| 38 | | | | | +480 and ≈ +260%) and ACC (resp. ≈ +400 and ≈ +570%) gene | |
| 39 | Diluted beverages | Specific-pathogen-free female mice fed standard | 100% of fluid | 6 weeks | expressions | |
| 40 | from tomato and | commercial diet | intake | | No effect on TG content | (Aizawa et al., 2009) |
| 41 | paprika | | | | <u>Tomato</u> : | |
| 42 | | | | | - up-regulation of genes involved in fatty acid degradation | |
| 43 | | | | | (cytochrome P450, CPT-1a, acyl-CoA synthetase long-chain | |
| 44 | | | | | family member) and cholesterol synthesis (HMG-CoA | |
| 45 | | | | | reductase) | |
| 46 | | | | | - down-regulation of genes involved in FA synthesis (elongation of | |
| 47 | | | | | long-chain fatty acid, FAS, steroyl-CoA desaturase 1, ME, | |
| 48 | | | | | SREBP-1, ATPCL and ACCα) and degradation (acyl-CoA | |
| 49 | | | | | dehydrogenase, enoyl-CoA hydratase/3-hydroxyacyl-CoA | |
| 50 | | | | | dehydrogenase and acyl-CoA oxidase 2 branched chain), and in | |
| 51 | | | | | cholesterol synthesis and catabolism | |
| 52 | | | | | <u>Paprika</u> : | |
| 53 | | | | | - up-regulation of genes involved in FA synthesis (ME, FAS, | |
| 54 | | | | | ATPCL and ACCα) and degradation (acyl-CoA synthetase | |
| 55 | | | | | long-chain family member and CPT-1a), and in cholesterol | |
| 56 | | | | | synthesis (acetoacetyl-CoA synthetase) and lipid circulation | |

| | | | | | | |
|----|------------------------------|---|-----------------|---------------|---|---------------------------|
| 1 | | | | | (LDL receptor) | |
| 2 | | | | | - down-regulation of genes involved in cholesterol synthesis and | |
| 3 | | | | | catabolism (bile acid biosynthesis) | |
| 4 | Mulberry extract | Rats fed standard diet | 100 or 200 | 4 weeks | ↓ TG level (resp. -10%, NS, and -23%); no effect on TC and PL | (Tsuduki et al., 2009) |
| 5 | (0.53% of 1- | | mg/kg b.w. | | levels | |
| 6 | deoxynojirimycin) | | (direct | | ↑ FAS (resp. ≈+31%, NS, and ≈+19%, NS), CPT (resp. ≈+45% and ≈ | |
| 7 | | | stomach | | +45%) and ACO (≈+36% at 200 mg/kg b.w. at 100 mg/kg b.w.) | |
| 8 | | | intubation) | | activities; ↓ ME (resp. ≈-25%, NS, and ≈-2%, NS) and ACO (≈- | |
| 9 | | | | | 8%, NS, at 100 mg/kg b.w.) activities | |
| 10 | | | | | ↑ CPTI (resp. ≈+50 and ≈+60%), ACO (resp. ≈+5%, NS, and ≈ | |
| 11 | | | | | +85%), PPARα (≈+15%, NS, at 100 mg/kg b.w.) and AMPK | |
| 12 | | | | | (resp. ≈+60%, NS, and ≈+145%) mRNA expressions; ↓ PPARα | |
| 13 | <i>Monascus</i> -fermented | Rats fed hypelipidemic (10% pig oil, 10% | 200 or 400 | 40 days | <u>Unfermented</u> : ↓ HMG-CoA reductase/mevalonate ratio (-16%) | (Pyo and Seong, 2009) |
| 14 | soybean or | powdered egg yolk and 1% cholesterol) diet | mg/kg b.w. | | <u>Fermented</u> : ↑ HMG-CoA reductase/mevalonate ratio (+8%, NS, at | |
| 15 | unfermented | | | | 200 mg/kg b.w. and +39%) | |
| 16 | soybean ^t ethanol | | | | ↓ TC (resp; -16%, NS, -23 and -35%) and TG (resp. -16, -29 and - | |
| 17 | extracts | | | | 32%) levels | |
| 18 | Freezed dried melon | Male hamsters fed high-fat (24%) diet | 0.7, 2.8 or 5.6 | 12 weeks | <u>Histological analysis</u> : improved (at 2.8 mg) and disappearance (at | (Décordé et al., 2009) |
| 19 | juice extract | | mg (aqueous | | 5.6 mg) hepatocellular ballooning degeneration | |
| 20 | | | solution by | | ↓ lipid content (resp. -42, -71 and -73%) | |
| 21 | Freezed-dried 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 | (Fukushima et al., 2009) |
| 22 | (3% caffeine) or | | | | content | |
| 23 | decaffeinated | | | | | |
| 24 | coffee | | | | | |
| 25 | Coconut oil, butter | Hamsters fed standard diet | 7% of diet | 6 weeks | ↑ LI (resp. +21, +15 and +15%) | (Yang et al., 2009) |
| 26 | and flaxseed oil | | | | ↑ cholesterol (resp. +193, +373 and +123%) and TG (resp. +37, +56 | |
| 27 | | | | | and +26%) contents: lower increases (<i>vs</i> control) with flaxseed | |
| 28 | <i>Sophora japonica</i> L. | 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) |
| 29 | powder (from | | | | | |
| 30 | dried mature fruits | | | | | |
| 31 | including pericarp | | | | | |
| 32 | and seed) | | | | | |
| 33 | <i>Ginkgo biloba</i> leaf | Rats fed high-fat (8% lard, 7% egg yolk powder | 0.2% of diet | 19 weeks | ↓ TC content (-20%, NS) | (Gu et al., 2009) |
| 34 | extract | and 0.5% sodium chocolate) | | | <u>Histopathological detection</u> : ↓ lipid accumulation (lipid droplets | |
| 35 | | | | | occupied a smaller area) | |
| 36 | | | | | Down- and up-regulation of gene involved in lipid metabolism: ↓ | |
| 37 | | | | | FA and cholesterol biosynthesis, ↓ conversion of cholesterol into | |
| 38 | Cauliflower | Genetically obese (<i>ob/ob</i>) mice fed standard diet | 100 or 300 | 10 weeks | ↓ liver weight (resp. -28 and -28%), TG (resp. -43 and -42%) and | (Park et al., 2009a) |
| 39 | mushroom water | | mg/kg b.w. | | TC (resp. -35 and -38%) contents | |
| 40 | extract | | | | | |
| 41 | Cinnamon bark | Mice fed standard diet for 4 days, and killed on | 0.5 mL/kg b.w. | 4 days before | <u>Microscopic and image analyses</u> : | (Kanuri et al., 2009) |
| 42 | alcoholic extract | day 5 12 hours after i.g. ethanol injection (6 | (in drinking | ethanol | - blunted ethanol-induced hepatic steatosis by ≈ 45% | |
| 43 | | g/kg b.w.) | water) | injection | - ↓ fat (≈ -36%, measured as % of microscopic field) and TG (≈ - | |
| 44 | Garlic aqueous | Rabbits fed high-cholesterol (0.5 g/kg b.w. i.g.) | 1.5 mL/kg b.w. | 3 last months | 58%, NS) accumulation | (Arhan et al., 2009) |
| 45 | extract (20%, w/v) | diet for 4 months (GI), then standard diet for 3 | | | <u>Histological examinations</u> : | |
| 46 | | months (GII) | | | ↓ mean steatosis grade (only 1/8 rat with steatosis of grade 1: <33% | |
| 47 | | | | | of hepatocytes were involved) compared to GI and GII | |
| 48 | | | | | ↓ cholesterol (-86% <i>vs</i> GI and -78% <i>vs</i> GII) and TG (-46% <i>vs</i> GI | |
| 49 | <i>Ziziphus Mauritania</i> | Chronic alcohol (40% ethanol <i>via</i> gastric | 400 mg/kg b.w. | 6 or 2 weeks | and -27% <i>vs</i> GII) levels | |
| 50 | aqueous leaf | intubation, 1 mL/100 g b.w.) administered rats | | | <u>Pre-administration <i>via</i> gastric intubation (30 min before alcohol)</u> : ↓ | (Dahiru and Obidoa, 2009) |
| 51 | extract <i>vs</i> | for 6 weeks | | | cholesterol (resp. -47 and -43%) and TG (resp. -42 and -38%) | |
| 52 | syllimarin | | | | contents | |
| 53 | | | | | <u>Co-administration with alcohol</u> : ↓ cholesterol (resp. -9%, NS, and - | |
| 54 | | | | | 21%) and TG (resp. -16%, NS, and -44%) contents | |

| 1 | | | | | Post-administration (2 weeks without alcohol) after 6 weeks | |
|----|---------------------------|---|-------------------|--------------|---|-----------------------------|
| 2 | | | | | alcohol: ↓ cholesterol (resp. -15 and -35%) and TG (resp. -30 and | |
| 3 | | | | | -38%) contents | |
| 4 | <i>Platycodi radix</i> | 90% pancreatectomized diabetic rats fed high-fat | 2 g/kg b.w. | 8 weeks | ↓ TG content (≈ -44%) | (Kwon et al., 2009) |
| 5 | extract | (40% as energy) diet | | | | |
| 6 | <i>Codonopsis</i> | Rats fed liquid ethanol (36% of energy) diet | 0.5% of liquid | 8 weeks | ↓ TG (≈ -33%) and cholesterol (≈ -36%) levels | (Cho et al., 2009a) |
| 7 | <i>lanceolata</i> root | | diet | | <u>Liver histology</u> : enlargement of the hepatocytes and increase in the | |
| 8 | water extract | | | | number of lipid droplets were normalized | |
| 9 | | | | | ↓ TNF α (≈ -37%), LXR α (≈ -17%), SREBP-1c (≈ -21%), HMG-CoA | |
| 10 | | | | | reductase (≈ -41%) and LDLR (≈ -31%) mRNA levels | |
| 11 | | | | | ↑ AMPK α (≈ +6%, NS), ACC (≈ +48%), FAS (+29%) and SCD1 (≈ | |
| 12 | | | | | +10%, NS) mRNA levels | |
| 13 | | | | | ↑ phosphorylated/total ratio of AMPK (≈ +133%) and ACC (↑ | |
| 14 | Commercial low- | Apo E ^{-/-} mice fed a 10%-fat (commercial | 10% of diet | 12 weeks | ↓ LI (resp. -34 and -44%), and cholesterol (resp. -31 and -41%) and | (Cho et al., 2009b) |
| 15 | <i>trans</i> fat or n-3- | shortening, 53.4% <i>trans</i> FA) diet | | | TG (resp. -22 and -16%) levels | |
| 16 | rich/low- <i>trans</i> | | | | ↓ HMG-CoA reductase (resp. -12%, NS, and -51%), ACAT (resp. - | |
| 17 | structured fat | | | | 6%, NS, and -18%), G6PDH (resp. -52 and -66%), ME (resp. -25 | |
| 18 | (synthesized | | | | and -47%) and PAP (resp. 0 and -12%) activities | |
| 19 | from flaxseed oil, | | | | ↑ β -oxidation (resp. -4%, NS, and +96%) and CPT (resp. +17%, NS, | |
| 20 | anhydrous | | | | and +88%) activity | |
| 21 | butterfat and palm | | | | <u>Hepatic tissue morphology</u> : low- <i>trans</i> structured fat importantly ↓ | |
| 22 | stearin) | | | | accumulation of hepatic lipid droplets | |
| 23 | Fermented ginseng | HepG2 cells | 500 μ g/mL | From 1 to 24 | ↑ phosphorylation of AMPK (max.: ≈ 2.7-fold at 12 hours) and ACC | (Kim et al., 2009) |
| 24 | radix ethanol | | | hours | (max.: ≈ 2.7-fold at 24 hours) | |
| 25 | extract | | | | ↓ time-dependently SREBP1c, SCD1 and FAS gene expression; ↑ | |
| 26 | | | | | time-dependently PPAR α gene expression | |
| 27 | | | 100, 250 or 500 | 24 hours | ↓ TG accumulation (resp. ≈ -80, ≈ -80 and ≈ -95%) | |
| 28 | | | μ g/mL | | | |
| 29 | | <i>db/db</i> mice fed standard chow diet | 100 or 200 | 10 weeks | ↑ gene expression of pAMPK and pACC (↑ phosphorylation of | |
| 30 | | | mg/kg b.w. | | AMPK and ACC), and of CD36 and PPAR α ; ↓ gene expression of | |
| 31 | Garlic + medicinal | Rats fed ethanol (10 mL of 20% ethanol/kg | (0.5 + 1.0%) or | 4 weeks | ↓ TL (resp. -14 and -28%), TC (resp. -17 and -23%) and TG (resp. - | (Soo-Jung et al., 2009) |
| 32 | plant extracts | b.w./day) diet | (1.0 + 1.0)% | | 9%, NS, and -30%) levels | |
| 33 | | | of diet | | | |
| 34 | Refined rice bran oil, | 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 | (Chopra and Sambaiah, 2009) |
| 35 | alone or blended | | | | TG (resp. -9, -19 and -26%) contents | |
| 36 | with refined | | | | | |
| 37 | linseed oil (3:2, | | | | | |
| 38 | w/w) or cod liver | | | | | |
| 39 | oil (1:1) | | | | | |
| 40 | Safflower oil or | Rats fed standard chow (4% fat) | 29.5 or 29% of | 3 days | ↑ TG (resp. ≈ +59 and ≈ +60%) and cholesterol (resp. ≈ +21%, NS, | (Gustavsson et al., 2009) |
| 41 | cocoa butter ¹ | | diet ¹ | | and ≈ +71%) levels | |
| 42 | | | | | ↓ SCD-1 mRNA expression (resp. ≈ -62 and ≈ -81%) | |
| 43 | | | | | <u>Cocoa butter</u> : | |
| 44 | | | | | ↑ ATPCL (4.00-fold), ME 1 (1.81-fold), pyruvate kinase (1.59- | |
| 45 | | | | | fold), farnesyl diphosphate farnesyl transferase 1 (2.69-fold), | |
| 46 | | | | | mevalonate (diphospho) decarboxylase (2.12-fold), cholate-CoA | |
| 47 | | | | | ligase (2.01-fold), HMG-CoA synthase (1.89-fold), squalene | |
| 48 | | | | | epoxidase (1.87-fold), 7-dehydrocholesterol reductase (1.72-fold), | |
| 49 | | | | | lanosterol synthase (1.72-fold), farnesyl diphosphate synthase | |
| 50 | | | | | (1.66-fold), bile acid-CoA ligase (1.63-fold), ACAT 2 (2.00- | |
| 51 | | | | | fold), ACAT 1 (1.63-fold), FAD 1 (1.71-fold), FAD 2 (1.57-fold) | |
| 52 | | | | | and FAD 3 (1.69-fold) mRNA expression; ↓ GPDH 1 (0.63-fold), | |
| 53 | | | | | ABC subfamily A (0.46-fold), mitochondrial acyl-CoA | |
| 54 | | | | | thioesterase 1 (0.63-fold), peroxisomal acyl-CoA thioesterase 2B | |
| 55 | | | | | (0.63-fold), CPTpc (0.48-fold), SCD 2 (0.27-fold) and SCD 1 | |
| 56 | | | | | (0.22-fold) mRNA expression | |

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|---|--|--|----------|--|---|---------------------------|
| | | | | | ↑ 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%) ↓ intrahepatocellular lipids (≈ -22%) as calculated from ¹ H-MR spectra | |
| 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 | | | (Bortolotti et al., 2009) |
| <i>Hibiscus sabdariffa</i> 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 ↑ AMPK phosphorylated (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 ↑ 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 (methanol extract that contains 2 coumarins, <i>i.e.</i> 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 microvesicular 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) |

45^aAll terms used in the Table are precisely those of the article considered: for example, 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-lipotrope effects (*i.e.* an increase in hepatic lipid content and/or lipogenic enzyme activities) are also presented to allow comparisons and further relevant interpretations

46^bIndicates the decreased or increased percentage induced by the lipotrope compared to the control, *i.e.* steatogen diet (NS - Not Significant - means absence of significance for the change observed; in other cases, the effect was either significant or no information was given in the article)

47^cMargarines 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)

48^dNo data given in the reference

49^eOil extracted at 54°C

50^fContains 0.6% hesperidin and 0.03% naringin

51^gLow 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

52^hLow- 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

53ⁱGeraniol is a monoterpenoid alcohol

54^jTriton WR1339 induces hyperlipidemia by inhibiting lipoprotein lipase and thus preventing catabolism of TG-rich lipoproteins

55^kEnriched with bioactive mevinolins (natural statins) and aglycone isoflavones (daidzein, glycitein and genistein)

56^lSafflower 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

1 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 inhibited
2 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
3 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); CCl₄, Carbon tetrachloride; CD36, , fatty acid translocase (long chain fatty acid transporter); CE, Cholesteryl Esters; CoA, Coenzyme A; CPT,
4 Carnitine Palmitoyl Transferase; CPTpc, CTP:phosphocholine cytidyltransferase; CYP51, Sterol 14 α -demethylase (involved in first step of cholesterol synthesis); CYP7A1, Cholesterol 7 α Hydroxylase (enzyme for the initial rate-limiting step of bile acid synthesis from cholesterol); DGAT, Diacylglycerol Acetyltransferase; EGC, Epigallocatechin; FA, Fatty Acid;
5 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
6 Lipoprotein; LDLR, Low-Density Lipoprotein Receptor (involved in transfer of lipids into hepatocytes); LI, Liver Index (liver weight/body weight); LXR α , 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
7 RiboNucleotic Acid; NS, Not Significant; PCDGT, Phosphocholine Diacylglycerol Transferase; PL, Phospholipid; resp., respectively; PPAR, Peroxisome 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-
8 Binding Proteins; TC, Total Cholesterol; TG, TriGlyceride; TL, Total Lipids; TNF α , Tumor Necrosis Factor alpha (involved in the development of fatty liver)

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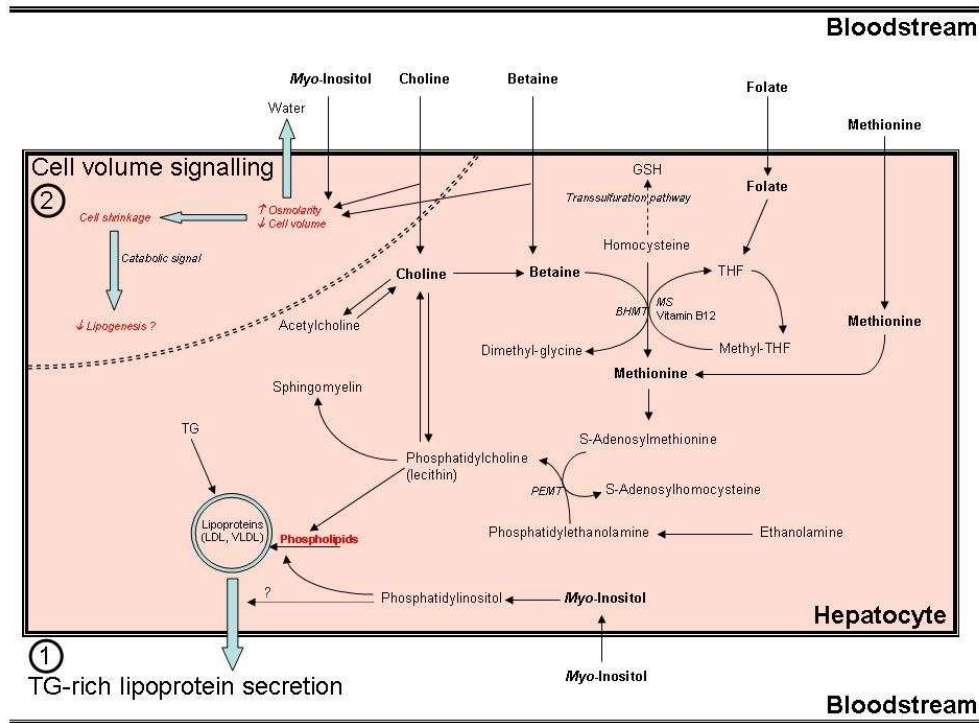


Figure 2A
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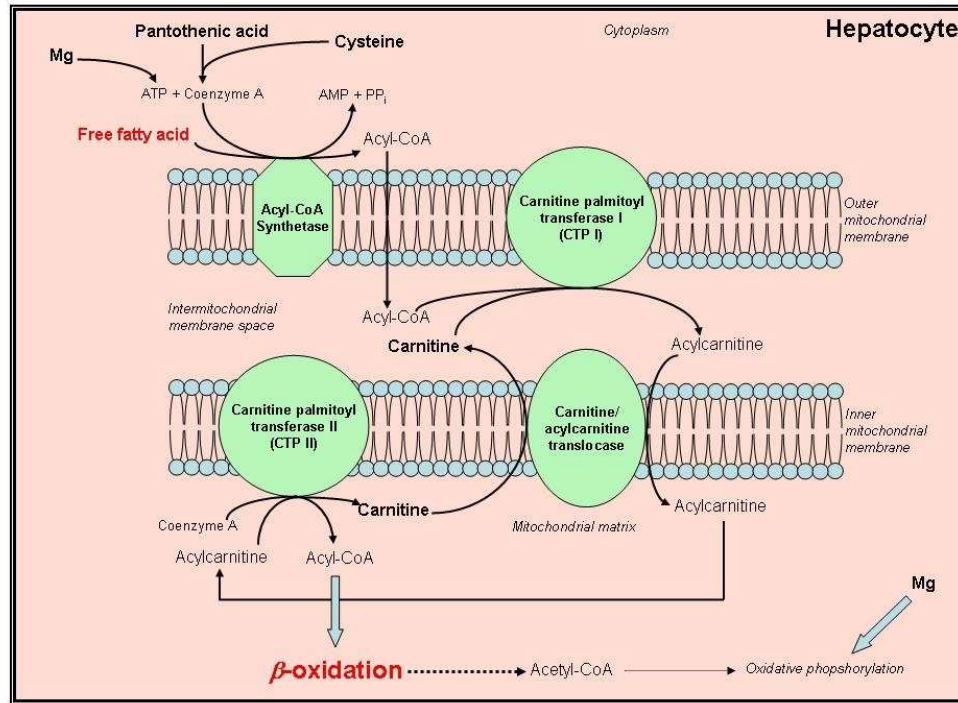


Figure 2B
254x190mm (96 x 96 DPI)

new Only

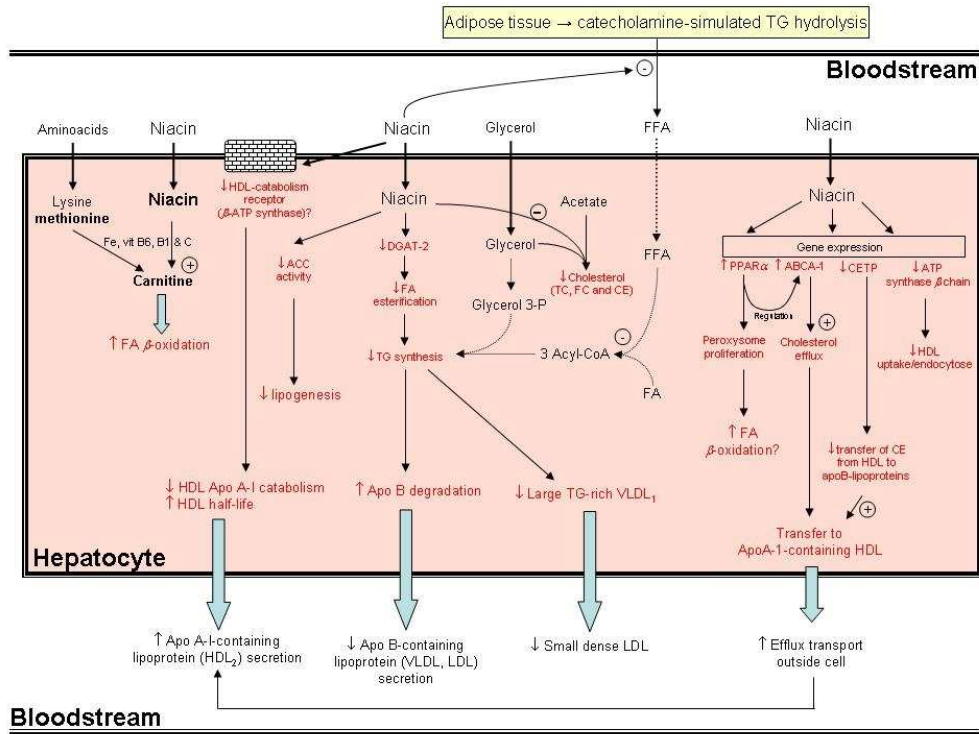


Figure 2C
254x190mm (96 x 96 DPI)

new Only

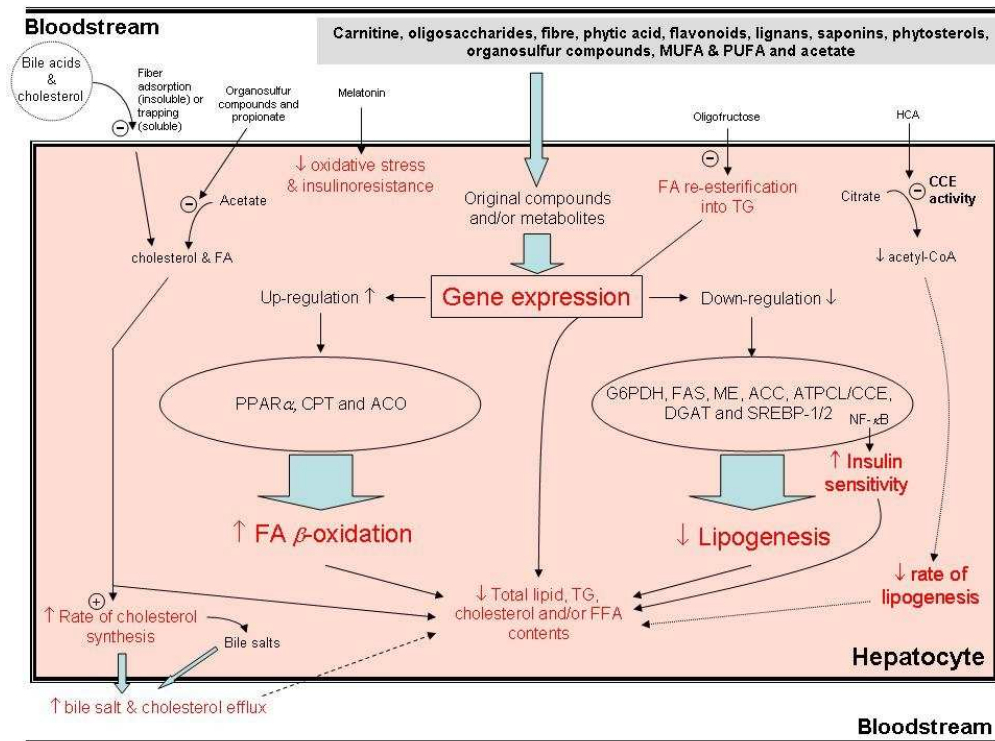


Figure 2D
254x190mm (96 x 96 DPI)