Fat-soluble vitamin and phytochemical metabolites: Production, gastrointestinal absorption, and health effects

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Abstract

Consumption of diets rich in fruits and vegetables, which provide some fat-soluble vitamins and many phytochemicals, is associated with a lower risk of developing certain degenerative diseases. It is well accepted that not only the parent compounds, but also their derivatives formed upon enzymatic or nonenzymatic transformations, can produce protective biological effects. These derivatives can be formed during food storage, processing, or cooking. They can also be formed in the lumen of the upper digestive tract during digestion, or via metabolism by microbiota in the colon. This review compiles the known metabolites of fat-soluble vitamins and fat-soluble phytochemicals (FSV and FSP) that have been identified in food and in the human digestive tract, or could potentially be present based on the known reactivity of the parent compounds in normal or pathological conditions, or following surgical interventions of the digestive tract or consumption of xenobiotics known to impair lipid absorption. It also covers the very limited data available on the bioavailability (absorption, intestinal mucosa metabolism) and summarizes their effects on health. Notably, despite great interest in identifying bioactive derivatives of FSV and FSP, studying their absorption, and probing their putative health effects, much research remains to be conducted to understand and capitalize on the potential of these molecules to preserve health.

Keywords: carotenoids, cholecalciferol, phylloquinone, phytosterols, retinol, tocopherol.

Introduction

Of the thousands of different molecules consumed through plant foods in our diet, the best known are macronutrients (proteins, fats, carbohydrates) and micronutrients (vitamins and trace elements). However, we also ingest a multitude of compounds called "phytochemicals", plant secondary metabolites with great chemical diversity. Phytochemicals are classified into large families, e.g. terpenoids and phenolics, which are thought to be at least partially involved in the prevention of numerous pathologies [1-4]. Until now, research on fat-soluble phytochemicals (FSP) has primarily focused on the parent molecules originally found in plant foods [5-8]. This review will focus on metabolites of fat-soluble vitamins (FSV) and FSP, i.e. metabolites of food components that are insoluble in water and typically associated with lipids in oils, emulsions or cell membranes. These metabolites may be derived from the chemical degradation of these molecules during culinary preparation or food processing [9-11], or phase I and phase II metabolism in the intestinal mucosa or within the liver (from previously absorbed FSV and FSP whose metabolites can be secreted into the intestinal lumen via bile). It is also now appreciated that these metabolites could be produced by microbiota [12, 13], elicit effects on the intestinal microbiota [14, 15], or even be absorbed [16], although research in this area is nascent.

The biological roles of FSV metabolites, e.g. retinoic acid and 1,25-dihydroxycholecalciferol on maintaining health are well established. In contrast, the biological roles of FSP metabolites are much less well known, although their potential beneficial health effects are supported by the fact that some are antioxidants [17, 18], have anti-inflammatory effects [19-22], modulate gene expression [23, 24] or affect the epigenome [25-27]. It is also likely that some of these compounds exert several effects simultaneously, e.g. lycopene which acts with different molecular and cellular mechanisms [28].

Likewise, certain carotenoid metabolites with a structure analogous, but not identical to, retinoic acid have effects on gene expression, while their parent precursors do not [29]. Thus, this review

68 focuses on chemical transformations of FSV and FSP during the technological and culinary
69 transformation of food, as well as molecules resulting from the chemical degradation and metabolism
70 of these compounds in all compartments of the human digestive tract. Known, or hypothesized
71 absorption and health effects will also be discussed. This review also highlights gaps in knowledge
72 regarding microbial metabolism of FSV & FSP. Indeed, it is plausible that the very limited
73 understanding of FSV & FSP microbial transformations have limited appreciation for the full range of
74 biological effects elicited by these compounds, analogous to the field of polyphenols, for which the
75 critical role of microbial transformation is now appreciated [30-32].

76 Out of the 13 vitamins essential to humans, vitamins A, D, E and K are fat-soluble. The
77 basics of their digestion, absorption and metabolism have been widely discussed in previous books
78 and review papers: vitamin A [33-35]; vitamin D [36], vitamin E [37, 38], vitamin K [39, 40].
79 Unlike FSV, FSP are nonessential compounds and there is no pathology associated with a
80 deficiency. However, they can elicit significant biological effects and their long-term consumption
81 has been associated with beneficial effects on pathologies linked to aging. Terpenoids are the main
82 class of FSP. They are biosynthesized through the assembly of a variable number (N) of a 5-carbon
83 (isoprene) unit, and subdivided accordingly: monoterpenes (N = 2, e.g. limonene, menthol and
84 vanillin), diterpenes (N = 4), tetraterpenes (N = 8), including the carotenoid pigments. In plants,
85 carotenoids play an essential role in photosynthesis, and in mammals some serve as provitamin A
86 (i.e. α- and β-carotenes, β-cryptoxanthin, γ-carotene). Some xanthophyll carotenoids (i.e. lutein and
87 zeaxanthin) appear to play a role in visual function and in the prevention of age-related macular
88 degeneration. The carotenoid lycopene (i.e., the red pigment of tomato) has anti-inflammatory
89 effects [20], which may explain partly its association with a reduced risk of cardiometabolic disease
90 [41-43]. Triterpenes (N = 6) have also aroused much scientific interest, in particular their sterol
91 derivatives, e.g. β-sitosterol, stigmasterol, sitostanol. These so-called phytosterols have a structure
92 analogous to cholesterol and serve a similar biological function in plants. They have been observed

to decrease the capacity and the rate of cholesterol absorption in humans [44]. Thus, they have garnered interest in reducing hypercholesterolemia [45], and ultimately the risk of cardiovascular disease. In addition to carotenoids and phytosterols, a selection of FSP having interesting *in vitro* properties, for example antioxidant or antimicrobial, will be mentioned.

1. Commonalities and differences between FSV vs. FSP metabolism and biological effects

Because FSV and FSP are closely related to lipids, there is some overlap in the process of absorption and metabolism and the that of triacylglycerols, phospholipids and sterols. At dietary doses of FSV, it is well established that apical membrane proteins of the enterocyte, e.g. SR-BI and NPC1L1, facilitate the absorption of some FSV, e.g., vitamins D and E, and that of some FSP, e.g. some carotenoids [46]. However, at supplemental/pharmacological doses, both FSV and FSP are assumed to enter the enterocyte via passive diffusion. Once taken up, some FSV and FSP can be phase I metabolized within the enterocyte. It has been shown that some FSV can also be effluxed back into the intestinal lumen via specific transporters [47-49]. Following uptake, lipophilic compounds, e.g. parent molecules of FSV & FSP, are packaged into the chylomicron particle, while amphipathic and polar metabolites, e.g. some derivatives of FSV and FSP, are released directly into the blood, and travel from the portal vein to the liver for "first pass" metabolism. This often includes oxidation by cytochrome P450 enzymes, regardless of the compound in question. Routes of excretion, including release of the parent FSV and FSP, as well as their phase I and phase II metabolites, occur in the liver and the kidney, respectively.

Despite these shared pathways, there are many fundamental points of difference in the handling of FSV absorption and metabolism, as compared to FSP. Once shuttled into the enterocyte, the FSV are often chaperoned around via specific binding proteins, which again recognize particular structures or functional groups. For vitamins A and D, this shuttling begins in the enterocyte of the small intestine, while for vitamin E (and potentially vitamin K_1) this occurs in the liver, thanks to α-

tocopherol transfer protein [50]. In contrast, it is assumed that most FSP are non-specifically bound to unknown proteins, in order to remain soluble in the cytosol. Another important distinction is the regulation of active vitamin concentrations in the blood stream following a meal. Vitamins A, D, and K are primarily found in foods as non-active "provitamin" forms, which require additional transformation via metabolism to produce the active forms. Recent evidence suggests that dietary forms of vitamin E may also serve as provitamins for some functions [51]. This additional step permits great fluctuations in circulating concentrations of the provitamin forms following a meal, without disrupting the highly regulated steady-state concentrations of the active forms. In contrast, many FSP are rapidly and non-specifically metabolized for excretion. Thus, they require repeated dosing over a given window of time to reach and maintain a concentration within the biological window of effect [52]. An additional point of difference between FSV and FSP is high specificity in mechanisms of action. Vitamins A and D metabolites, i.e. retinoic acid and 1,25-dihydrocholecalciferol, are nuclear receptor agonists with high specificity in binding to the retinoic acid receptors (RAR) and to the vitamin D receptors (VDR), respectively. Vitamin E can act as a direct antioxidant to inhibit lipid peroxidation, and some of its metabolites may also directly bind nuclear receptors [53, 54]. Vitamin K has a clear role in converting glutamate into γ-carboxyglutamate – a required step in the blood coagulation cascade, which may also be important in bone mineralization [55]. Furthermore, a total of 17 vitamin K-dependent proteins have been identified to date and involved in bone and cardiovascular health [56]. In contrast, diverse mechanism(s) of action are proposed for many FSP metabolites, e.g. direct antioxidant effects, regulation of gene expression, effect on inflammation.

2. Derivatives of FSV and FSP found in foods

Upon storage food is subject to various physical and chemical agents, e.g. UV radiation or dioxygen, which can start altering the most labile molecules. Microorganisms growth can also

begin to metabolize many molecules including FSV and FSP. Transformation of foods via cooking or industrial processing may enzymatically or nonenzymatically, i.e. physically or chemically, produce derivatives of FSV and FSP. Chopping or grinding food for preparation can cleave cell walls and allow enzymes to come into contact with substrates previously located in different cells or sub-cellular compartments. Mixing or blending can accelerate this process and also introduce dioxygen, which can serve as an essential cofactor for many enzymes, as well as a chemical oxidant. Heat can also rupture cell tissue and increase the reaction rate for most chemical transformations in foods. Additionally, consumption of products transformed by yeasts, bacteria, and fungi (e.g. cheese, yogurt, kimchi, sauerkraut), or mammals (e.g. dairy products, meat), can result in intakes of FSV and FSP metabolites produced by microbial species, the animal, or the microbiome within the animal. These metabolites are likely present at trace levels in all transformed products, but can be especially rich in organs known to concentrate metabolites (e.g. mammalian liver, kidney), or in animal byproducts consumed by humans.

Mechanisms of production of FSV metabolites by the main animal species that we consume, i.e. cattle, poultry and pigs, are similar to those in humans. Concerning vitamin A, it is accepted that the same metabolites that play a biological role in visual function and in gene expression in humans, namely 11-*cis*-retinal and retinoic acid respectively, are synthesized from the pro-vitamin A carotenoids by the main animals that we eat, i.e. beef, pork and chicken. These metabolites are therefore theoretically present in the meat produced from these animals. Nevertheless, 11-*cis*-retinal is present in the eyes, which are generally not consumed, and retinoic acid is present in very low concentrations in tissues. The main form of vitamin A present in food from farm animals is primarily retinyl palmitate, which can be present in very high, even toxic, concentrations in the liver of certain animals (e.g. polar bears) [57]. To our knowledge, there is no data on the human consumption of endogenously synthesized vitamin E metabolites present in tissues from livestock. Vitamin E is intentionally supplemented to livestock to reduce lipid peroxidation in meat products

post-slaughter [58]. The resulting metabolites are presumed to be regenerated via intracellular reducing reagents [58], although to the best of our knowledge this has not been studied directly. Vitamin D, as either vitamin D_2 or D_3 isoforms in foods, undergoes hydroxylation in the mammalian and avian liver to produce 25-hydroxyvitamin D_2 and D_3, respectively [59, 60]. These 25-hydroxy metabolites are found in beef, pork, chicken, and eggs, [61, 62], as well as in milk, cream, and butter [63], in concentrations on the same order of magnitude as the vitamin D_2 and D_3 precursors. Trace quantities of 25-hydroxyvitamin D_3 have also been reported in salmon, tilapia, and mahi-mahi [61]. Like most sterols, 25-hydroxyvitamin D is robust to various methods of cooking [64]. Although not systematically measured in the food supply, the most potent vitamin D metabolite, 1,25-dihydroxyvitamin D, is especially rich in beef kidney and liver, with concentrations ~5-10 times lower in beef muscle tissue [65]. Data suggests that it can be significantly isomerized and degraded by food processing, notably heat [66][67](**Fig. 1**). Vitamin K is present in food either as vitamin K_1 (phylloquinone) or as vitamin K_2 (menaquinones). Menaquinones are actually a cluster of K_2 isoforms produced either by mammalian metabolism of vitamin K_1 or by bacteria such as the lactic acid bacteria (the most common form of bacteria in fermented foods). Menaquinones can have 5-10 isoprenyl units and are found in the human colon (see section 7), as well as in food sources (e.g. buttermilk, whole-fat milk, various cheeses, sauerkraut) [68]. The most common menaquinone, menaquinone-4 (MK-4), is a mammalian metabolite of phylloquinone (vitamin K_1), and is found in whole-fat milk, cheeses, salami, beef, pork, and chicken [68, 69]. Small quantities of MK-4 have also been reported in fermented foods, like sauerkraut and natto [70, 71]. Vitamin K_1 in plant oils is robust to high heat processing conditions, but sensitive to degradation by daylight [72]. Chemically, it has no clear structural vulnerabilities to autoxidation or hydrolysis.

Provitamin A carotenoids (i.e. mainly β-carotene, α-carotene, and β-cryptoxanthin) as well as xanthophyll carotenoids (e.g. lutein and zeaxanthin) are consumed by grazing beef, dairy cattle and

193 sheep, and are thus found in tissues and milk [73]. Ruminants cleave a significant fraction of
194 provitamin A into vitamin A (retinal) in the intestine, which is stored primarily in the liver as
195 retinol esters. Thus, vitamin A, as a metabolite of provitamin A carotenoids, is found in dairy and
196 cuts of beef, goats, lamb, and especially liver tissue [74]. Although lutein metabolites have been
197 previously reported in human breastmilk [75], their presence in meat or dairy has not been
198 investigated.

199 There is apparently little degradation of carotenoids in foods. Lycopene, one of the most
200 chemically labile carotenoids, only undergoes mild (*Z*)-(*E*) isomerization following traditional
201 thermal processing of tomato products [76]. Likewise, β-carotene and lutein have also been
202 reported to be quite stable in a variety of foods following domestic or industrial thermal processing
203 [77-79]. Shorter-chain metabolites of β-carotene and lycopene, respectively termed "β-apo-
204 carotenoids" and "apo-lycopenoids", have also been reported in both raw and processed fruits and
205 vegetables [80-83]. However, their origins are unknown. Carotenoid cleavage enzymes within the
206 plant can produce these apo-carotenoids [84]. It is also likely that at least a portion of these apo-
207 carotenoids are enzymatically or chemically produced during food storage, food processing and
208 food preparation/cooking, although studies are lacking. In supplements, high carotenoid
209 concentrations and presence of oil (for which co-oxidation can occur) would be expected to
210 produce higher concentrations of apo-carotenoids. Lutein extract from marigold following was
211 found to degrade following 10 days of exposure to mid-day heat (31°C) + sunlight (5.89 kW h m^{-2})
212 to produce derivatives with shorter carbon chains which elicit PPAR-γ activity [85]. The presence
213 of these products in lutein containing foods or supplements has not been reported, but may merit
214 further investigation due to the pronounced biological effects.

215 Phytosterols in foods are susceptible to oxidation of the B ring, via free radical or UV-exposure,
216 with oxidation product concentrations positively increasing with storage time [86]. Their diversity
217 in structures and occurrence in a wide array of foods has been nicely summarized previously [87,

88]. Following oxidation, an epoxide, keto, mono- or di-hydroxyl group is added to the B-ring. These phytosterol oxidation products primarily occur in plant oils exposed to heat (during the extraction or cooking process), or UV-light, and in fried products (i.e. potato chips, French fries) [87, 89]. They are also found in coffee silverskin, a roasting byproduct [90]. Food products "enriched" with phytosterols, including heat-treated milk products [86, 91] and dark chocolate [92], have also been reported to contain oxidized metabolites. Although it has been shown that thermal treatment of foods containing phytosterols acylated by a PUFA chain leads to phytosterol oxidation [93] (**Fig. 2**), co-heating of phytosterols with a saturated lipid induced a greater concentration of oxidized metabolites than with unsaturated lipid [94]. Phytostanols, another type of plant sterols, are largely protected from oxidation, likely due to the absence of a double bond on the B-ring [89, 94].

Finally, there are a few studies on the degradation of chlorophyll during food processing. Thermal processing and acids added to some foods (e.g. pickling cucumbers) cause the magnesium ion to be released from the porphyrin ring, thus producing olive-green pheophytin [95]. Further heating converts the pheophytin into pyropheophytin, with loss of the carboxymethyl group but retention of the lipophilic phytol tail. Alternatively, rapid blanching causes enzymatic cleavage of the phytol tail to produce water-soluble metabolites (i.e. chlorophyllides) and their breakdown products (i.e. pheophorbides).

3. Possible transformations of FSV and FSP in the oral cavity

The metabolism of FSV and FSP likely starts in the mouth as chewing produces mechanical grinding and partial breakdown of food matrices. Indeed, this process disrupts a fraction of the plant cell walls, and disrupts intracellular organelles in which the FSV and FSP are located. This puts FSV and FSP into contact with enzymes and other molecules located in other organelles and tissues for the first time, and can completely change the fate of these molecules. For example, carotenoids may

be exposed to known oxidants or prooxidants within the plant tissue itself or from the atmosphere (e.g. ferrous iron, dioxygen). Saliva also comes into contact with food in the oral cavity, and provides food lubrication, antimicrobial defense, assistance with taste and early digestion [96]. Indeed, the oral cavity has been considered a "bioreactor" [97, 98] in which multiple interactions occur between salivary components (e.g. ions, proteins, including digestive enzymes, such as alpha-amylase) and macro- and micronutrients and phytochemicals. Salivary lactoperoxidase and myeloperoxidase catalyze the reaction of hydrogen peroxide with thiocyanate to produce the highly reactive hypothiocyanous acid, which has antimicrobial activity and can also react with FSV and FSP. Activated phagocytes in saliva can also release a series of toxic oxidants [99, 100] which could oxidize redox-sensitive molecules. Theoretically, the hydrophobic parent molecules of FSV and FSP remain within lipid phases through the oral cavity, which can confer protection (if the lipids are not oxidized). In contrast, we hypothesize that some of their less apolar derivatives might bind to salivary proteins, analogous to what occurs with polyphenols [101, 102]. The risk of oxidation of FSV and FSP and their derivatives will depend on the proportion of prooxidants (e.g. ferrous iron, hydrogen peroxide, hypothiocyanous acid) and oxidation-sensitive nutrients (e.g. polyunsaturated fatty acids) to antioxidants (e.g. polyphenols, carotenoids, vitamin C), simultaneously present in the mouth. The risk of oxidation also depends on the location of the molecules of interest in the different phases, which depends both on hydrophobicity and on their physical state. For example, it is probable that crystallized carotenoids (like those found in carrots or tomatoes) are less sensitive to oxidation. Finally, the oral microbiome, comprised of different bacterial and yeast species, also produces enzymes that likely metabolize certain FSV and FSP.

Surprisingly, no data exists on the metabolites of FSV and FSP that are potentially produced in the oral cavity. Nevertheless, based on data obtained on the role of saliva in oxidation processes possibly taking place in the stomach [103] and inhibited by dietary antioxidants, we can imagine certain scenarios resulting in metabolite production. For example, we know that the oral microbiota

reduces nitrate secreted by saliva to nitrite, a precursor of nitric oxide. We also know that apple polyphenols, by inhibiting nitrosation/nitration [104], form nitrated and oxidized polyphenols. Such pathway could also apply to some oxidizable or nucleophilic FSV and FSP (e.g. carotenoids), thus generating nitrated or oxidized metabolites as end-products.

4. Metabolism of FSV and FSP in the stomach

The stomach of mono-gastric animals could have two main roles on the digestion of FSV and FSP. The first, for which we have the most data is to amplify the digestion of food [105]. This process leads to the release of FSV and FSP from their matrices, transfer to the lipid phase of the digestate, and possible chemical transformations dependent upon physicochemical structures and gastric enzymes. The typical gastric conditions are: 37 °C, pH from weakly to fairly acidic [106], the presence of a significant partial pressure of O_2 [107] and of digestive enzymes, e.g. pepsin and gastric lipase, and the presence of potentially prooxidant agents (e.g. ferrous iron) [108, 109]. These conditions can promote varied chemical reactions ranging from association, e.g. binding of the water-soluble carotenoid crocin to starch [110], to chemical modifications, e.g. autoxidation of carotenoids [108, 109, 111, 112].

The second hypothetical role of the stomach could be to secrete proteins that facilitate FSV and FSP and/or their derivatives, parallel to intrinsic factor released in the stomach to facilitate vitamin B_{12} intestinal absorption, This hypothesis is supported by the observation that the glandular stomach secretes 2-3 glycoproteins which are able to bind retinol [113], and could influence uptake in the lower intestine.

4.1 Distribution of FSV and FSP between the different matrices coexisting in the stomach

The formation of FSV and FSP derivatives of in the stomach depends on the ability to interact with agents (i.e. physical, chemical or enzymatic) which are likely to transform them. It is

293 therefore important to determine in which phase(s) or interface(s) these molecules are distributed.
294 Initially, these molecules are located in the food matrices in which they are ingested, but during
295 digestion they are gradually released and distribute themselves between the different phases present
296 in the digestive tract. For FSV and FSP to be freed from the structural barriers which impede
297 release from the food matrices, [114, 115], the biochemical action of gastric juice and the peristaltic
298 movements are required. The importance of the peristaltic movements in freeing FSP was
299 confirmed by a study showing that β-carotene was better released from sweet potatoes when
300 mechanical forces were applied [105, 116]. A small number of studies have also been devoted to
301 measuring the transfer of FSV and FSP between the different phases present in the stomach during
302 digestion (**Fig. 3**). Tyssandier et al. [106] fed human volunteers with test meals that contained
303 vegetable purees and sunflower oil, then separated the gastric contents into 3 phases: a lipid phase,
304 an aqueous phase, and a pellet of insoluble plant debris. A significant fraction of carotenoids was
305 recovered in the lipid phase, showing that they were transferred from the vegetable purees to this
306 phase during the oral and/or gastric phase(s). Interestingly, the percentage of carotenoid transferred
307 was very different depending on the food matrix and carotenoid subclasses. This result suggests
308 that the percentage of carotenoid transferred depends on the carotenoids' physicochemical
309 properties, as well as on their location in, and interactions with, the plant matrix. *In vitro* studies
310 have further deciphered the factors involved. Rich et al. suggested that carotenoids incorporated
311 into cell membranes are more difficult to transfer than carotenoids in crystalline form [117]. Then,
312 Goupy et al. conducted a study to specify the respective roles of the carotenoid structure, the
313 presence and nature of emulsifiers covering lipid droplets, and the effect of the food matrix on the
314 transfer efficiency of carotenoids from vegetable matrices to lipid droplets [118]. The results
315 confirmed what was deduced from the clinical study [106], i.e. that the transfer of carotenoids
316 between plant foods and lipid emulsions depends on all of these factors. Additionally, Yuan et al.
317 reported that carotenoid transfer was greater when the lipid droplets were emulsified with caseinate

than with Tween 20 or modified starch [119]. They hypothesized that this was because caseinate was partially hydrolysed by pepsin to facilitate carotenoid transfer. This hypothesis was reinforced by the results of another study in which Tween 20-stabilized emulsions had a lower rate and extent of lipid digestion than those of protein-stabilized emulsions [120]. Furthermore, β-carotene was more easily released from emulsions when they were coated with β-lactoglobulin, as compared to other milk proteins [121]. Thus, the type of proteins that cover the interface also has an influence on the transfer. In summary, the presence and nature of emulsifiers is a key factor that governs the transfer of carotenoids from the food matrix to lipid emulsions in the stomach during digestion. With regard to the transfer of other FSV and FSP or their derivatives between the different phases present in the stomach, there is, to our knowledge, no data available. It can nevertheless be assumed that transfer also depends on the parameters mentioned above.

4.2 Formation of FSV and FSP derivatives in the stomach lumen

The physicochemical conditions that exist in the stomach, e.g. acidic pH, presence of dioxygen, prooxidants and digestive enzymes, can lead to chemical and/or enzymatic changes of FSV and FSP, especially those sensitive to oxidation. However, because these modifications first require FSV and FSP to be accessible to factors likely to modify them, they are very difficult to predict. Likewise, pathologies, including microbial infection (e.g. by *Helicobacter pylori*), aging, and alcohol ingestion can also affect FSV and FSP concentrations [122]. The rest of this chapter discusses the state-of-the-art knowledge regarding these factors.

The first factor of influence in the stomach is the acidic pH. To our knowledge, its effect on the potential degradation of FSV and FSP has only been studied on a vitamin D and vitamin D analogues in simplified chemical models [66, 67] (**Fig. 1**), suggesting possible isomerization in the stomach. It would therefore be interesting to systematically study the effect of pH on the potential degradation of other FSV & FSP, considering the fact that they are not absorbed in pure forms but

incorporated in food matrices or in excipients (case of nutritional supplements), which will probably protect them significantly from this acidity.

Concerning carotenoids, there is no data on the effect of pH on the molecules themselves, but only a clinical study on the effect of pH on the bioavailability of β-carotene. Tang and her colleagues [123] questioned the role of gastric acidity on the bioavailability of a pharmacological dose of *all-trans* β-carotene incorporated in a gelatine capsule. Using omeprazole to inhibit gastric secretions (HCl and digestive enzymes), they observed that the bioavailability of β-carotene was approximately halved, as compared to control without omeprazole (low gastric pH). They hypothesized that the relatively high pH produced more negatively charged β-carotene-containing micelles, which reduced their absorption. We put forth an alternative hypothesis: the higher pH, together with the absence of gastric enzymes, e.g. gastric lipase [124, 125] and pepsin, could cause a large fraction of β-carotene to remain trapped within the undigested lipids of the meal. Consequently, the decreased gastric secretion, which can occur with ageing o disease [126], could affect the bioavailability of β-carotene, and by extension, that of other FSV and FSP. Nevertheless, this likely happens in subjects with clinical signs of decreased gastric secretion, since studies in apparently healthy elderly people did not show a significant effect of age on carotenoid bioavailability [127, 128] or on vitamin E response to supplementation [129].

Another factor important for metabolism of FSV and FSP in the gastric lumen is the presence of salivary or gastric enzymes that could hydrolyse some of these compounds. Gastric lipase is one of the two main digestive enzymes secreted by the stomach. Rabbit gastric lipase, which has been used as a model for the human version [125, 130], is able to hydrolyse a fraction of cryptoxanthin esters with concomitant release of free cryptoxanthin [130]. We hypothesize that this lipase is also capable of hydrolysing other xanthophyll esters and perhaps other FSV and FSP esters, e.g. phytosterol esters. As the bioaccessibility of free cryptoxanthin is superior to that of esterified cryptoxanthin [130], and assuming that it is the same for other FSV and FSP, we also hypothesize

368 that the hydrolysis of any FSV or FSP ester by gastric lipase could enhance its overall
369 bioavailability.

370 The second main digestive enzyme secreted by the stomach is the protease pepsin, which is
371 not assumed to directly interact with FSV and FSP. However, by hydrolysing proteins located at
372 the interface of lipid droplets [131], pepsin might facilitate the release of FSV and FSP solubilized
373 into the triglyceride core of lipid droplets, which in turn could enhance their bioavailability.

374 Derivatives resulting from the degradation or modification of certain FSV and FSP in the
375 stomach have been detected, for example, carotenoid (*Z*)-isomers were observed following
376 exposure to cation or dication radicals, or to triplet oxygen [132]. *In vitro* incubation of lycopene
377 from tomato puree in gastric juice resulted in ≤10% (*Z*)-(*E*) isomerization, and pure encapsulated
378 lycopene ≤20% over 3h, as compared to controls [133]. Surprisingly, the isomerization percentage
379 was not different between 1 min and 3 h of incubation [133], suggesting that gastric isomerization
380 is a rapid and primarily chemical process. Additionally, no unidentified products (which could be
381 shorter-chain metabolites) were reported [133, 134]. In contrast, incubating different (*Z*)-isomers of
382 lycopene emulsified with tributyrin for up to 3 h led to significant lycopene breakdown [134]. It's
383 not clear if the artificial tributyrin micelle or the artificially low gastric pH ~2 (only observed on an
384 empty stomach) [126, 135] drove these differences. Interestingly, the acidic conditions appeared to
385 drive 13-(*Z*)-lycopene to convert back to the all-(*E*) form during digestion, which was unexpected
386 [134]. *In vivo* studies, in which the concentrations of carotenoid derivatives were measured in
387 gastric samples collected at different time points during digestion, do not show a significant
388 increase in the concentration of (*Z*)-isomers [106, 108, 111] nor apo-carotenoids, previously
389 predicted to be major *in vitro* metabolites [108, 111]. Kopec et al. [111] found that in healthy men,
390 [^{13}C]-β-apo-carotenal levels remained ~3 orders of magnitude lower than that of [^{13}C]-β-carotene
391 throughout digestion, and neither [^{13}C]-β-apo-carotenols, nor [^{13}C]-β-apo-carotenoic acids were
392 observed in the gastric digesta. In an *in vitro* study using gastric human juices adjusted to pH 2.5

(rather low, compared to *in vivo* conditions), the stability of lycopene, the carotenoid most sensitive to oxidation, was extremely high in tomato (~ 92% recovery) [136]. This stability was probably due to the fact that lycopene was protected within the food matrix. Indeed, another study showed that β-carotene and retinyl-palmitate standards, i.e. pure molecules, were strongly degraded at the end of the gastric phase, while β-carotene was largely spared when provided by carrot juice [137]. In addition, β-carotene and violaxanthin provided by raw spinach were highly degraded, suggesting that not all food matrices provide the same level of carotenoid protection. By contrast, lutein was largely spared, when provided by the same matrix [137], suggesting that the different carotenoids do not have the same sensitivity to degradation. Another study, using a dynamic gastrointestinal model (TIM-1, assumed to better mimic *in vivo* conditions than static *in vitro* models) showed that egg xanthophylls were stable (average recovery of about 90%) and that no (*Z*)-(*E*) isomerization occurred during *in vitro* digestion [138]. A lack of significant (*Z*)-(*E*) isomerization of lycopene was also observed in another study using the same model [139]. Collectively, the majority of *in vitro* and *in vivo* evidence suggests that limited isomerization and loss occurs for most carotenoids when embedded in a food matrix, or when provided in a form that is highly insoluble in the digesta. Furthermore, these results highlight the importance of accurately reproducing gastric physicochemical conditions and their evolution during digestion.

Iron, both heme or non-heme, is abundant in animal muscle tissue, with 1 g of beef containing 20 - 30 μg of total iron [140]. Dietary iron is a potential initiator of oxidative processes called autoxidation (non-enzymatic oxidation by O_2). Oxidizable (electron-rich) FSV and FSP, such as vitamin E and carotenoids, are intrinsically vulnerable to autoxidation in the stomach following an iron-rich meal. Sy et al. [109] studied the autoxidation of pure β-carotene at pH 4.0, corresponding to the mid-digestion of meals rich in fruits and vegetables [106]. Under these conditions, Fe^{2+} and metmyoglobin induced the isomerization and oxidation of β-carotene to epoxides and cleavage products of various chain lengths [109] (**Fig. 4**). *In vitro* work by Kopec et

al. [112] with the inclusion of gastric enzymes found more attenuated effects of gastric digestion on β-carotene, with a ~20% drop from the initial dose observed when β-carotene was digested alone, and a ~50-60% drop when digested with metmyoglobin or Fe^{2+}. In the same study, no statistically significant drop in concentrations of lutein or lycopene during the gastric phase when digested alone, or with the addition of metmyoglobin or Fe^{2+}. *In vivo*, both increased time of sampling and the presence of $FeSO_4$ consumed with a lycopene-rich beverage resulted in less lycopene in the stomach than the lycopene-rich beverage alone [108]. Free retinol itself is also known to be highly susceptible to autoxidation [141]. Collectively, these results highlight that contrasting results can be obtained depending on meal composition, pH, the presence of digestive enzymes, and the presence of prooxidant agents.

In addition to iron, all lipid-rich foods contain traces of lipid hydroperoxides (LOOH) with peroxide values typically in the range of 1 – 5 μmol/g [142, 143]. The Fenton reaction between Fe^{II} and LOOH is a source of highly reactive oxyl radicals ($LO^{\bullet}$), while heme-Fe^{III} reacting with hydroperoxides also leads to hypervalent iron forms (heme-Fe^{IV}) that are efficient initiators of lipid peroxidation through the propagating lipid peroxyl radicals ($LOO^{\bullet}$) [144] (**Fig. 5**). The prooxidant character of a meal rich in iron and oxidizable (polyunsaturated) lipids may be mitigated by plant antioxidants. Hydrophilic antioxidants, such as phenolic compounds, either bind non-heme iron under inert complexes or reduce hypervalent heme iron, while lipophilic antioxidants, such as vitamin E and carotenoids, reduce the lipid oxyl and peroxyl radicals, or trap them as stabilized radical adducts. Under model gastric conditions using micelles and emulsions, this chemistry is well-established [145-150], and shows that the co-oxidation of electron-rich FSV and FSP with polyunsaturated lipids is much faster than their direct autoxidation. For instance, both α-tocopherol and β-carotene are rapidly consumed via co-oxidation when incubated with heated turkey muscle in a simulated gastric fluid at pH 3, 37°C., but protected upon addition of red wine polyphenols [107, 151]. It is also noteworthy that apo-carotenoids (possibly present in plant food or formed in the

443 course of carotenoid – polyunsaturated fatty acids co-oxidation during food processing or in the
444 gastric phase of digestion) are themselves antioxidants [147]. In a simple model using micelles of
445 linoleic acid, apo-6'-lycopenal and apo-8'-lycopenal were even better inhibitors of metmyoglobin-
446 induced lipid peroxidation than (all-*E*)-lycopene itself [147]. In general, a long unsaturated chain
447 and a terminal carboxylic acid group both favor the antioxidant activity of apo-lycopenoids. The
448 short-chain apo-14'-lycopenoic acid was also shown to directly reduce the hypervalent iron form of
449 metmyoglobin, thus behaving as a hydrophilic antioxidant [147]. Of course, the *in vivo* relevance of
450 this chemistry is much more difficult to demonstrate. As an example, in minipigs equipped with a
451 canula for uptake of gastrointestinal fluids, end-markers of lipid peroxidation (TBARs) following a
452 meal combining sunflower oil and beef meat were found in lower concentrations when the meal
453 also included fruit and vegetable purées [152].

454 Other electron-rich FSP that could also undergo autoxidation and co-oxidation with
455 polyunsaturated fatty acids along the gastric digestion are the fat-soluble catechols of rosemary and
456 olives. Indeed, the catechol ring (1,2-dihydroxybenzene) is a critical moiety conferring electro-
457 donating capacity on phenolic compounds. It can be involved in one- and two-electron transfers
458 with concomitant formation of a semiquinone and an *ortho*-quinone, respectively. For instance, the
459 rosemary diterpene carnosic acid is a potent antioxidant and its oxidized derivatives retain the
460 catechol ring [153] (**Fig. 6**). These antioxidant diterpenes, as well as a decarboxylated derivative,
461 were also detected in the meat of lambs fed diets supplemented with rosemary extracts. They confer
462 higher oxidative stability to the meat [154]. Hydroxytyrosol and its derivatives are present in
463 substantial concentration in virgin olive oil (up to ca. one gram / kg, **Fig. 7A**) [155, 156].
464 Hydroxytyrosol inhibits lipid peroxidation in synergy with α-tocopherol under model gastric
465 conditions [157]. While acting as an antioxidant, it is converted into dimers and higher oligomers,
466 which undergo further oxidation, thus prolonging the antioxidant activity [158](**Fig. 7B**).

Regeneration of the amphiphilic antioxidant α-tocopherol (TocOH) from its oxidized forms is key to prolonging its lipid-protecting activity while avoiding the prooxidant activity of the corresponding aryloxyl radical (TocO$^{\bullet}$) (**Fig. 8**). The reduced forms of coenzyme Q and vitamin K, as well as vitamin C and a variety of polyphenols may play this role. This regeneration may occur from TocO$^{\bullet}$ upon one-electron reduction, but also from some non-radical two-electron oxidized forms of TocOH (e.g., *o*-methylenequinones, the *p*-quinone form and its hemiketal tautomer, **Fig. 8**). Similarly, oxidation and metabolism of vitamin K is shown in **Fig. 9**.

Many other factors may lead to chemical modifications of certain FSV and FSP. For instance, alcohol seems to lower the stability of some FSV and FSP in the gastric lumen, as it was observed that alcohol consumers had significantly lower antral mucosal and gastric juice concentrations of β-carotene, compared to non-consumers [122]. The physicochemical and enzymatic conditions in the gastric compartment can also be altered under certain pathological states or during aging, which is associated with a higher prevalence of atrophic gastritis [126], or during infection by *Helicobacter pylori*. For example, it has been shown that infection with *H. pylori* decreases the concentration of β-carotene in gastric juice [122], suggesting that a fraction of this provitamin A carotenoid was converted to metabolites. No significant effects of age on β-carotene concentration in gastric juice [122] or on the (*E*)-(*Z*) isomerization of β-carotene during absorption were observed.

Gastric metabolism of carotenoids has largely been focused on the lumen because it is presumed that the absorption of these compounds by the mucosa (as well as that of the other FSV / FSP, and their metabolites) is low or negligible. However, when β-carotene was incubated with gastric mucosal homogenates or with soy lipoxygenase, the production of known β-carotene metabolites, i.e. apo-carotenals, β-apo-13-carotenone, retinoic acid and retinal, were successfully detected [159]. The authors suggested that a mucosa lipoxygenase is responsible for the metabolism of β-carotene. However, it is not known whether metabolites produced in the mucosa can be re-secreted in the gastric lumen or directly enter the systemic circulation. Further work is required.

4.3 Potential uptake of FSV and FSP and their derivatives by the gastric mucosa

Some FSV and FSP, i.e. α-tocopherol and β-carotene [122], as well as other carotenoids (lutein, zeaxanthin and β-cryptoxanthin) [160], have been found in the gastric mucosa. Moreover, in the same study it was reported that the concentration of certain carotenoids was lower in cancerous gastric mucosal tissues than in non-cancerous ones. Although it is likely that a significant fraction of the compounds present in the gastric mucosa are derived from the blood circulation, it is possible that a fraction was absorbed from the gastric lumen.

4.4 Potential health effects of FSV and FSP in the gastric lumen and mucosa

Several FSV and FSP, e.g. vitamin E and carotenoids, are known to be important antioxidants in cell membranes and plasma lipoproteins. Others (e.g., the lipophilic phenols from olives and rosemary, and generally all dietary phenolic compounds) are more likely to exert their antioxidant effects in the lumen of the digestive tract, where they can reach millimolar concentrations under postprandial conditions as compared to the nano-micromolar concentrations in certain cells. Polyunsaturated fatty acids (PUFA) are the main class of oxidizable essential fatty acids. PUFA oxidation lowers the nutritional quality of the meal, not only through loss of essential lipids but also by the alteration of dietary proteins [161], which are vulnerable to electrophilic and/or oxidizing lipid peroxidation products (e.g. lipid hydroperoxides, malondialdehyde, 4-hydroxy-2-alkenals). Moreover, the delivery of these potentially toxic products to intestinal cells or their incorporation into the circulating lipoproteins may be risk factors in atherosclerosis [98] and colon cancer [162].

Some FSV and FSP and/or their metabolites could also have beneficial effects on the gastric mucosa, not only through their antioxidant activity, but also by scavenging nitrite, as some polyphenols do [163, 164], thus participating in the prevention of stomach cancer [165]. This hypothesis is supported by a study showing that lycopene was capable of inhibiting nitrite-induced

gastric carcinogenesis in rats [166]. A fraction of FSV and FSP and/or their metabolites could also be absorbed by the gastric mucosa where they could modulate inflammation. Indeed, it has been shown that retinoic acid, which is present in some foods of animal origin, can inhibit mucosal inflammation [167], possibly by an NF-kappa B-driving mechanism, as has been shown in adipose tissue [168].

Furthermore, it has been shown that apo-carotenals, possibly produced by carotenoid – PUFA co-oxidation in the stomach, have anti-inflammatory and antioxidant properties in cells through the respective down- and up-regulation of the NF-κB and nrf2 (antioxidant/electrophile response element) pathways, while the corresponding apo-carotenoic acids are inactive [169, 170]. This is explained by the fact that apo-carotenals are electrophilic unsaturated aldehydes capable of reacting with key nucleophilic thiols (Cys residues) of proteins controlling the activity of these transcription factors.

5. Metabolism of FSV and FSP in the upper intestine, i.e. duodenum, jejunum and ileum.

After being pre-digested in the stomach, the food, mixed with the digestive juices secreted in the mouth and in the stomach, is poured into the duodenum via the pylorus. The physicochemical and enzymatic conditions then radically change. The partial pressure of oxygen decreases [171], the pH increases to about 6.5 [172, 173], and bile and pancreatic secretions arrive bringing new molecules and enzymes, e.g. bile salts, pancreatic lipase, that can induce chemical and biochemical modifications of FSV and FSP and their derivatives.

5.1 Distribution of FSV and FSP between the different matrices coexisting in the upper intestine

After exiting the stomach, the FSV and FSP and their derivatives potentially have the ability to be transferred in two new phases resulting from bile secretion: mixed micelles, which results from the interaction of bile micelles with the lipolysis products of dietary triglycerides, and lipid vesicles,

542 which consist mainly of uni- and multilamellar liposomes [174, 175]. Note that bile micelles can
543 contain FSV and FSP [176-178], as well as some of their derivatives, because enterohepatic
544 recycling of some of these molecules may occur [177]. Thus, there are several phases in the upper
545 intestine between which the FSV and FSP and their derivatives can theoretically be distributed: the
546 food matrix being digested, the lipid phase, which is transformed during digestion into emulsified
547 lipid droplets, the micellar phase, which contains both mixed micelles and lipid vesicles, i.e.
548 liposome-like structures, and the aqueous phase, which can contain food-borne or salivary proteins
549 (**Fig. 10**). However, there is little data on the distribution or transfer of FSV and FSP or their
550 derivatives between these different phases during digestion. Thus, only hypotheses can be
551 formulated.

552 When entering the duodenum, a fraction of the parent FSV and FSP and derivatives are still
553 in the partially digested food matrix and a fraction transferred into lipid emulsions following gastric
554 processing (**see section 4.1**). At least a portion of the more hydrophilic derivatives may have
555 associated with aqueous soluble proteins or peptides of partially digested dietary proteins. Some
556 derivatives may also be water-soluble. Of course, this distribution is dynamic and evolves during
557 digestion, with FSV and FSP and their derivatives transferred to the other phases as lipolysis
558 continues. It has been shown *in vitro* that parent FSV and FSP are transferred partly to lipid
559 emulsions and partly to micelles [117, 179, 180], but it is likely that a fraction is also transferred to
560 vesicles and another binds to soluble proteins [181]. Some limited *in vivo* data are available for
561 retinyl palmitate, α-tocopherol and the major carotenoids [106, 179, 182]. However, the distribution
562 of these molecules between all the phases mentioned above has not been assessed, and nothing is
563 known about the derivatives.

564 The distribution of these molecules between the different phases is governed by two key
565 parameters, i.e. their intrinsic solubility in the different phases, and their capacity to transfer between
566 the different phases. Indeed, when a liquid/liquid extraction is performed, the distribution between

567 the two phases occurs based upon relative solubility alone. In contrast, in the lumen of the digestive
568 tract, the transfer is prevented by the very weak mixing of the different phases and by the presence of
569 many molecules, located within the phases or at the interface, and acting as barriers against free
570 transfer [114].

571 To date, only data on the intrinsic solubility of the parent molecules in emulsified lipid
572 droplets and micelles is available. Data on carotenoids show differential distribution between the
573 triglyceride core and the phospholipid interface of emulsified lipid droplets. β-Carotene is
574 preferentially localized in the core, whereas zeaxanthin, which has two polar hydroxyl groups, is
575 preferentially localized at the lipid droplet surface [183].Scattered data exists concerning the
576 solubility of FSV and FSP and their derivatives in mixed micelles [184]. A comparative study of the
577 intrinsic solubility of FSV and FSP in micelles whose composition mimics those formed *in vivo* is
578 lacking, but this is probably a key parameter to explain the very different absorption rates of these
579 molecules.

580 **Fig. 10** details what is known regarding the factors that drive interphase transfer of FSV and
581 FSP and their derivatives. The first step, the transfer between food matrices and emulsified lipid
582 droplets, was recently been studied for carotenoids [118]. This transfer is basically governed by van
583 der Waals interactions occurring between carotenoids and triglycerides. It has also been shown that
584 amphiphilic molecules that coat triglyceride droplets in the gut, e.g. phospholipids and proteins,
585 strongly impair the transfer of pure carotenoids to triglyceride droplets [118], suggesting that they act
586 as a barrier that impair the transfer. However, carotenoids incorporated in plant matrices were better
587 transferred to triglyceride droplets coated with emulsifiers than to uncoated ones [118].

588 The second and arguably best-studied step is the FSV + FSP transfer between lipid emulsions
589 and micelles [185]. For example, the transfer of carotenoids is inversely related to carotenoid
590 hydrophobicity with maximal transfer occurring: between pH 6 and 7, with ≥ 2 mmol/L bile salts.
591 Carotene transfer, but not xanthophyll transfer, was impaired by the presence of other carotenoids.

In the absence of pathologies of the digestive tract during digestion, the pH in the duodenum is very stable at ~ 6.5 [185], and the concentration of bile salts is ~10 mmol/L (with bile salt concentrations falling to ≥5 mmol/L in a fasted stat) [173]. Therefore, as the pH is very stable in the pH zone in which the transfer is maximal, and the concentration of bile salts is always much higher than the concentration which allows a maximal transfer, we hypothesize that, in vivo, pH and bile salt concentration do not influence transfer efficiency.

Finally, no data exist regarding the possible presence of FSV / FSP derivatives in the aqueous phase, nor on the potential association of FSV / FSP and their derivatives with proteins or vesicles.

In summary, much remains to be discovered about the distribution of FSV / FSP and their derivatives between the different intestinal phases, and on the underlying mechanisms that govern phase transfer. This information would be very useful to better understand the distribution, and therefore the absorption efficiency, of these molecules, especially if we plan to improve their bioavailability.

5.2 Metabolism of FSV and FSP in the upper intestinal lumen and identified metabolites.

The most easily identified duodenal products of FSV / FSP metabolism are those arising from the hydrolysis of fatty acid esters, e.g. retinyl esters and xanthophyll esters. Three pancreatic enzymes are able to hydrolyse these esters. Carboxyl ester lipase, also called bile salt-stimulated lipase, which is able to hydrolyse the esters of xanthophylls [186] and α-tocopherol [179], but also pancreatic lipase and pancreatic lipase-related protein 2, which are able to hydrolyse retinyl esters [187, 188]. It is likely that these enzymes, given their low substrate specificity, are also capable of hydrolysing other FSV and FSP esters (e.g. phytosterol esters), but this remains to be demonstrated. This hydrolysis is important for the bioavailability of these compounds, assumed to be effectively absorbed only in their non-esterified form.

It is very likely that derivatives of FSV and FSP are produced in the upper intestine following the combined influence of lipases and other enzymes present in pancreatic secretions, as well as interactions with other co-consumed species (e.g. iron). Regardless of the absence or presence of digestive enzymes (i.e. mimicking chemical and biochemical degradation, respectively), *in vitro* digestion experiments revealed no significant change in lutein or β-carotene as digestion progressed from the gastric to the duodenal phase [112]. However, in the absence of enzymes, a ~13% loss was observed for lycopene, the carotenoid most sensitive to oxidation (no change in the presence of enzymes).

The addition of myoglobin (heme iron) most dramatically influenced β-carotene concentrations, causing a ~25% loss between the gastric and duodenal compartments in the absence of enzymes, and a ~35% loss in the presence of enzymes [112]. Follow-up studies in healthy males with isotopically labelled β-carotene demonstrated the presence of labelled β-apo-carotenals (aldehyde catabolites) in the oral dose provided [111]. Increased concentrations of most β-apo-carotenals were observed over time in the duodenal digesta, with duodenal concentrations of the shorter chain products increasing relative to the longer chain ones. However, β-apo-carotenals remained ~1000 times less abundant than β-carotene in the same samples, and were not detected in the newly-absorbed lyophilic fraction of blood (nor the plasma itself) afterward. Thus, the data does not support β-carotene conversion to apo-products in the enterocyte. However, β-apo-13-carotenone and β-apo-14'-carotenal were shown to act as antagonists of the retinoic acid receptor *in vitro* [189]. Based on the lack of uptake of labelled β-apo-carotenals in the blood stream, this activity most plausibly could occur in enterocytes.

The effect of iron (as ferrous sulfate) on lycopene metabolism in the lumen of the digestive tract was tested in a clinically. The orally administered dose was relatively rich in apo-lycopenals (although ~200 times less abundant than lycopene). When the dose was given in the absence of iron, the apo-lycopenal concentrations in the digesta increased over 4 h. By contrast, in the presence of

641 iron, the concentrations of most apo-lycopenals decreased, probably because of autoxidation to
642 shorter-chain products [108]. Moreover, apo-lycopenals were detected in the newly-absorbed lipid
643 fraction of blood, suggesting that at least a portion was absorbed from the diet [108]. In contrast to
644 these results, the feeding of isotopically labelled lycopene (with undetectable apo-lycopenals in the
645 dose) to healthy subjects resulted in no labelled apo-lycopenals in the plasma (the digesta was not
646 tested). However, the appearance of labelled lycopene 1,2-epoxide in the plasma, fairly rapidly after
647 administration (~2 h after dosing), suggests oxygenation in the gastrointestinal tract during digestion
648 or shortly after absorption [190].

649 In conclusion, these data clearly show that there is production of β-carotene and lycopene
650 metabolites in the lumen of the upper intestine and that this production is modulated by iron.
651 Additionally, the proportions of β-carotene and lycopene transformed into metabolites are relatively
652 low. Nevertheless, it is important to remember that some FSV / FSP metabolites can be very active at
653 very low concentrations (e.g. retinoic acid and 1,25-dihydroxyvitamin D) and it is not known in what
654 proportions are metabolized the other FSV and FSP, and what are their derivatives produced
655 upstream, i.e. in food or in the stomach. Thus, many studies remain to be conducted.

656

657 ***5.3 Uptake of FSV and FSP and their derivatives by enterocytes***

658 The understanding of the molecular mechanisms of uptake of several FSV and FSP by the
659 intestinal cell has considerably advanced over the past decade. Indeed, while it was thought that all
660 these molecules were absorbed by passive diffusion, Borel and co-workers, as well as other teams,
661 have identified enterocyte proteins that are involved in both apical uptake and efflux back to the
662 intestinal lumen, as well as through the basolateral membrane. For further details, we refer the reader
663 to a review published in the same journal [46]. Since this previous publication, new proteins involved
664 in uptake and basolateral efflux of FSV and FSP have been identified. The ABCG5/G8 complex,
665 well known for its key role in the efflux of phytosterols back to the intestinal lumen, has also been

involved in the absorption and efflux of vitamin D [47]. ABCB1 has also been shown to participate in the efflux of vitamins D and K [48, 191]; SR-BI in the uptake of phytoene, phytofluene [192] and vitamin K_1 [193]; CD36 in the uptake of vitamin E [194] and vitamin K1 [193]; ABCG1 in the efflux of vitamin E [195]. Overall, these proteins are able to interact with the uptake of FSV and FSP having very different structures. This observation suggests that it is the more homogenous lipid components of mixed micelles that are recognized by these transporter proteins. Thus, FSV and FSP incorporated into these micelles are inadvertently driven to areas of the enterocyte membrane, e.g. lipid rafts, in which they are more easily solubilized. To our knowledge, there is no data on specific proteins that would facilitate the capture, or efflux, of FSV / FSP derivatives, but it is possible that the same transporter proteins are involved.

5.4 Bile secretion and enterohepatic circulation of FSV and FSP derivatives

Unlike the enterohepatic cycle of bile salts, the enterohepatic circulation of FSV and FSP derivatives is poorly documented. Regarding vitamin A, injection of ^{14}C-retinol and ^{14}C-retinoic acid directly into the duodenum of rats led to release of ~40% of the dose in the bile within 24 h. This bile fraction was placed into the intestinal loop of another rat, and ~30% of the radioactivity re-excreted over a 24 h period, confirming enterohepatic circulation [196, 197]. Retinoic acid esters and retinoyl-β-glucuronic acid were identified as the primary bile components [198, 199]. Studies of ^{3}H-retinoic acid in rats confirmed the previous metabolites, as well as the presence of retinotaurine [200].

Concerning vitamin D, 24 h after intravenous administration of the metabolite 25-hydroxyvitamin D_3 in humans, ~30% of the radioactivity could be measured in the duodenum, thus demonstrating biliary secretion. Moreover, ~85% of this secreted dose was reabsorbed [201, 202] [203, 204]. A series of experiments by Avioli et al. [205], supported by follow-up studies [206, 207], shows that the inactive phase II metabolites comprise the bulk of the radioactivity recovered in bile following an intravenous injection. These products were recently confirmed to be sulfates and

691 glucuronides of 25-hydroxyvitamin D_3 [208]. However, it is unexpected that phase II metabolites
692 would be released in bile instead of urine. The authors speculated that once released back into the
693 gastrointestinal lumen, deconjugation of these metabolites into free 25-hydroxyvitamin D_3 may
694 provide a source of vitamin D for intestinal cells.

695 Data in rodents suggests that vitamin E undergoes enterohepatic recycling following
696 metabolism. Indeed, rodents release ~20% of labeled α-tocopherol into bile in the first 24 h post-
697 consumption, with only ~3% as α-tocopherol, and the remaining portion as biliary metabolites
698 [202][203, 204]. In humans, intravenous injection of labeled α-tocopherol (bypassing first-pass
699 metabolism in the liver), results in only ~6% of the label in the bile [209, 210], suggesting that
700 enterohepatic recycling is low. Furthermore, biliary metabolites of γ- and δ-tocopherol were
701 observed at greater concentrations relative to α-tocopherol, following mixed tocopherol consumption
702 in humans and mice [204]. This effect is due to the high relative affinity of hepatic α-tocopherol
703 transfer protein for RRR α-tocopherol relative to other vitamin E isoforms [211]. To date, the
704 intestinal absorption of long-chain metabolites of tocopherols and tocotrienols, either following
705 secretion from the bile or from direct feeding with the metabolites, has not been studied.

706 Intravenous administration of either ^{14}C-labeled vitamin K_1, K_2, or K_3, to rodents resulted in
707 8.5, 74 and 37% of the isotope in bile after 12 h of collection, respectively [212], demonstrating a
708 high propensity for biliary elimination. An elegant series of cannulation experiments in rodents by
709 Hirota et al. [213] reported no secretion of labeled phylloquinone or its menaquinone-4 metabolite in
710 bile following controlled dosing, implying that the excreted biliary dose is exclusively comprised of
711 metabolites. Finally, humans intravenously injected with isotopically labeled vitamin K_1 secreted
712 slightly more polar labeled metabolites (relative to the parent compound) into the bile duct [214].
713 However, the structures were not identified and the possibility for these metabolites to be taken up
714 from the small intestine is unknown.

715 In summary, secretions of metabolites of the four essential FSV have been observed, but it has
716 not been elucidated if these metabolites are reabsorbed by the intestinal cell and further metabolized
717 back to parent structures (to exert biological effects), or whether additional metabolism into other
718 species occurs. A better understanding of this process could demonstrate whether true enterohepatic
719 cycling occurs (analogous to bile salts), and whether this contributes to whole-body FSV intakes.
720 Very little data is available regarding the potential enterohepatic cycling of FSP. Regarding
721 phytosterols, we hypothesize that since their initial absorption is very low (≤ 2% for sterols, ≤ 0.2%
722 for stanols) [215], it is unlikely that there is a significant enterohepatic cycle. Furthermore, an
723 increase in serum oxyphytosterol concentrations (i.e. 7-β-OH-campesterol, 7-β-OH-sitosterol) has
724 been reported following a second meal (after initial phytosterol dosing). However, it's not clear if
725 these oxyphytosterol metabolites were produced in intestinal cells, so that their presence in serum
726 reflects delayed absorption, or whether true enterohepatic recycling occurred [216]. Two studies in
727 humans and rabbits suggest that the chlorophyll metabolites pheophytin and pheophorbide can
728 undergo enterohepatic recycling [217]. Finally, to the best of our knowledge, the enterohepatic
729 recycling of non-provitamin A metabolites of carotenoids, e.g. lycopene and lutein, has not been
730 explored.
731
732 **6. Metabolism of FSV and FSP in the mucosa of the upper intestine and biological effects**
733 **of metabolites in this tissue.**
734 Metabolic pathways, based upon localized expression of enzymes active in the jejunum and
735 ileum, and whose specific activity toward FSV and FSP has been studied in other tissues, are detailed
736 below. While much is understood about vitamin A, limited work on vitamins D, E, and especially K
737 has been conducted so far to determine the role of these enzymes in influencing local or whole-body
738 FSV and FSP metabolite concentrations, maintaining FSV homeostasis, and in eliciting local
739 bioactivity.

Provitamin A is absorbed and converted to the vitamin A metabolite retinal via BCO1 in the small intestine [218] (**Fig. 1**). Preformed vitamin A (as retinol alone or produced from the cleavage of retinyl esters) is also absorbed throughout the jejunum, with less uptake in the ileum [219]. It can be transported within the cells via cellular retinol binding protein [220], and reduced to retinal via aldehyde dehydrogenases like retinol dehydrogenase 11 (RDH11) [220]. Retinal is further converted to the bioactive vitamin A metabolite all-*trans*-retinoic acid by retinaldehyde dehydrogenase I (RALDH1), for local utilization both by enterocytes and by mucosal dendritic cells involved in immune homeostasis [221, 222]. Indeed, retinoic acid synthesized by gut-associated lymphoid tissues imprints gut tropism, ultimately providing regional immunity and preventing autoimmune attack [223, 224]. It also stimulates gap junction growth and tight junction formation between epithelial cells to keep pathogens out, and stimulates cell repair following damage [225, 226]. Intestinal deactivation of retinoic acid occurs via conversion to oxo- and hydroxy-metabolites by cytochromes CYP1A1 and CYP3A, CYP26 [221], which might be transported directly into the blood, followed by phase II metabolized for urinary excretion, or directly effluxed back into the intestinal lumen for fecal excretion.

Vitamin D metabolism within the jejunum and ileum is largely driven by cytochrome P450 enzymes (CYPs), of which many have shown activity, as extensively reviewed elsewhere [227, 228]. Hydroxylation of the 25^{th} carbon occurs primarily by CYP27A1 and CYP2R1 expressed throughout the small intestine [228]. The resulting 25-OH vitamin D metabolite could be released into the blood stream, or metabolized further by CYP27B1, which performs 1α-hydroxylation to produce bioactive 1,25-dihydroxyvitamin D. CYP27B1 is expressed in the fetal small intestine at highly regulated levels, which are measurable but considerably lower than in the colon [229]. CYP24 is believed to be the primary enzyme responsible for inactivation of 1,25-dihydroxyvitamin D via hydroxylation of the 23rd or 24th carbon, producing metabolites with ~10 times less bioactivity [228]. CYP3A4, an enzyme catalyzing the hydroxylation of the 4β-position of 25-hydroxyvitamin D or 1,25-

765 dihydroxyvitamin D for clearance, is also expressed in the small intestine [230]. Collectively, the
766 presence of each of these enzymes in the small intestine supports a role for locally controlled
767 production, and subsequent inactivation, of bioactive vitamin D.

768 Vitamin E metabolism is largely driven by cytochrome P450s, whose upregulation may be at
769 least partially driven following binding of tocotrienols to the steroid and xenobiotic (SXR) nuclear
770 receptor [231], also known as the pregnane X receptor (PXR). Cytochrome P450 4F2 (CYP4F2),
771 responsible for the ω-hydroxylation of multiple vitamin E isoforms (**Fig. 8**) and vitamin K_1 (the
772 initial step required for β-oxidation of the phytyl tail), is more highly expressed in the human
773 jejunum and ileum relative to the duodenum [232, 233]. Rodent studies suggest that the jejunum is
774 particularly important for metabolism of isoforms of vitamin E distinct from α-tocopherol. Selective
775 knockdown of murine hepatic equivalent of CYP4F2 (i.e. CYP4F14) only reduced γ- and δ-
776 tocopherol metabolism by 70% [203]. Similarly, oral feeding of γ-tocopherol or a mixture of
777 tocotrienols (including γ-tocotrienol) to rats resulted in γ-CEHC in the jejunum 3 h afterward [234].
778 Importantly, jejunal γ-CEHC concentration was significantly diminished when the CYP4F inhibitor
779 ketoconazole was co-administered [234]. Co-administration of α-tocopherol with ketoconazole did
780 not significantly alter jejunal concentrations relative to administration α-tocopherol alone, echoing
781 previous reports of limited CYP4F2 activity toward α-tocopherol [235]. CYP4F11, expressed in the
782 same location, can also catalyze ω-hydroxylation of vitamin K [236]. β-Oxidation may continue in
783 the intestine or in other tissues as long as the aliphatic chain contains at least 5 carbons. The jejunum
784 and ileum likely resorb α-tocopherol metabolites produced in the liver and released into bile (e.g. α-
785 13′-hydroxytocopherol, α-13′-carboxytocopherol, etc.), although this hasn't been tested. The anti-
786 inflammatory bioactivity of these vitamin E metabolites has recently been reviewed in great detail
787 [54]. In summary, they inhibit 5-lipoxygenase, cycloxygenases 1 and 2, and reduce nitric oxide
788 production in *in vitro* models. It has also been speculated that the dietary isoforms of vitamin E may

789 be provitamins with metabolism conferring binding activity toward nuclear receptors like PXR
790 and/or PPAR-γ [51], although this has not been proven.

791 Following enterocyte uptake of vitamin K_1, a portion of the administered dose can have the
792 phytol tail cleaved to produce vitamin K_3, followed by prenylation catalyzed by the enzyme UbiA
793 prenyltransferase domain-containing 1 (UBIAD1/TERE1) to produce bioactive vitamin K_2 [213,
794 237] (**Fig. 9**). Insufficient evidence is available to determine if UBIAD1/TERE1 is the only enzyme
795 involved in this two-step conversion to K_2, and the relative proportion of conversion occurring in the
796 intestine vs. other tissues [55, 238]. However, it is known that a murine knockout of UBIAD1 is
797 embryonically lethal [239], highlighting the potent bioactivity conferred by the vitamin K_2
798 metabolite, which is the primary isoform of vitamin K found in extra-hepatic tissues. For vitamin K_1,
799 the metabolites remaining after β-oxidation in the enterocyte (as discussed above) can be
800 glucuronidated for urinary excretion [40]. The γ-carboxylation activity (the primary role of vitamin
801 K in blood clotting) of these phase I and II metabolites has not been completely characterized,
802 although anecdotal evidence suggests it is highly diminished [40].

803 Data suggests that at least some cholesterol-like FSP, including phytosterols and triterpenoids
804 (e.g. stigmasterol, enoxolone), influence CYP3A activity [240, 241]. This cytochrome is also heavily
805 involved in the metabolism of vitamins A & D and drugs, setting up the possibility of competition
806 for metabolism of these compounds. Human data also suggests that solanidine (a steroidal
807 glycoalkaloid) is preferentially metabolized via CYP2D6, a CYP which metabolizes ~25% of all
808 drugs currently in use [242], and likewise solanadine metabolism may further limit metabolism and
809 excretion of other compounds. Phytosterols have also been shown to be effluxed via ABC
810 transporters back into the intestinal lumen, and to facilitate trans-intestinal cholesterol excretion via
811 another as-yet unidentified mechanism [243].

812

813 **7. Metabolism and health effects of FSV and FSP and their metabolites in the colon.**

Because only a portion of the dietary FSV and FSP (and likely their derivatives), are absorbed in the small intestine, and because enterohepatic circulation occurs, a substantial percentage of the ingested dose is available for colonic or microbial metabolism. While certainly the bulk of FSV transport occurs in the small intestine, the colon also expresses (lower levels) of the apical transporters NPC1L1, CD-36, and SR-BI [244, 245]. These transporters could permit localized FSV uptake to this tissue (and subsequent metabolism), analogous to the mechanisms detailed in the previous section. This hypothesis is supported by numerous *in vitro* studies, which directly apply FSV to cultured colon tissues and assess uptake. *Ex vivo* evidence from the murine intestinal tract has also demonstrated that incubation of the tissue with at least one isoform of each FSV resulted in small, but measurable, quantities taken up by the colon [219].

Both vitamins A and D play key roles in colon health, largely mediated by the immune system, as extensively reviewed [246]. The bioactive vitamin A metabolite retinoic acid is critical for the adaptive and innate immune functions of the intestinal mucosa [247], and these biological activities are equally relevant in the colon. Vitamin D appears to play a more active role in the health of colonocytes and other colon cell types relative to the small intestine. Elimination of the receptor for 1,25-dihydroxyvitamin D increases susceptibility to colitis via increased tight junction membrane permeability [225]. 1,25-Dihydroxyvitamin D has also been shown to induce regulatory T-cells of the intestinal mucosa, which in turn suppress production of cytokines associated with autoimmune responses [248, 249]. The influence of FSV on immune function also has relevance to colorectal cancer, as discussed in the following section.

Beyond maintenance of the host gastrointestinal barrier, recent research has revealed that the colon microbiome composition and abundance of specific species are correlated with, or directly influenced by, the intake of each of the FSV [246, 250-252]. These observations reflect the importance of FSV for the microbiota itself, and likely highlight an inability of many species to synthesize them. In most instances, it is not clear if the parent FSV, bioactive FSV derivatives, or

both, drive taxa changes. Regardless, the ability to modulate the relative abundance of pathogenic species, or to elicit a pathogenic phenotype from otherwise innocuous species based upon dietary intake alone, highlights the importance of better understanding the relation between host dietary behavior and microflora growth. As an example, some microbial species have lost the ability to produce menaquinones, but data suggests they rely on neighboring species or dietary intakes to obtain vitamin K necessary for respiration [252]. This reliance was proposed to be the cause of lower cecal abundance of vitamin K-requiring species on a vitamin K-deficient diet, simultaneously permitting increased abundance of other non-vitamin K-dependent species in the same animals [252].

Unique to vitamin K, some menaquinone isoforms are synthesized by the colonic microflora. However, very little is known about their subsequent metabolism. *In vitro* culturing of human feces with labeled vitamins $K_{1,}$ $K_{2,}$ and K_3 demonstrated that the gut microflora was able to metabolize vitamin K_3 to produce bioactive vitamin K_2 (i.e. menaquinone 4), as well as menaquinones with longer chain lengths [252]. These results suggest the possibility that mammalian cleavage of vitamin K_1 in the small intestine provides a source of vitamin K_3 to be further metabolized to K_2 via the colonic microbiota. This K_2 could be used by colonic species directly and/or absorbed by the host.

Several FSP have been shown to influence colon health via host-derived mechanisms, as well as through enhanced or diminished growth of specific microbial species in the colon, as recently reviewed in detail [253]. Importantly, some microbial species contain enzymes having the ability to hydrolyze glycosides, permitting FSP aglycones to be absorbed. The aglycone form is generally thought to be more potent. For example, the microbiota of the colon is hypothesized to be the primary driver behind the conversion of saponins to sapogenins, and recent research suggests that sapogenins behave like prebiotics [254]. Likewise, murine studies have shown that phytosterols appear to rescue colon metabolism under conditions of colitis, alleviating symptoms and colon damage [255], which may be at least partially driven by changes in bile acid metabolism [256]. In

rodents, the growth of some microbial species also appears to be driven by phytosterol concentrations, and evidence suggests some microbial species produce phytosterol metabolites [253].

8. Effect of diseases of the gastrointestinal tract on FSV and FSP metabolism

Looking at the effect of different diseases of the digestive tract on the concentrations of FSV and FSP and their derivatives in the digestive tract can be very interesting. Indeed, variations in concentrations compared to normal, i.e. healthy subjects, or the appearance or disappearance of certain derivatives, can give us information on the normal transformations that take place in the healthy subject and on the factors responsible for these transformations.

8.1 Oesophageal cancer

Limited metabolism of FSV and FSP is expected in the oral cavity and the oesophagus (see **section 3**), thus the effects of oesophageal cancer are also expected to be limited. Some studies have reported that individuals with some types of oesophageal cancer have lower circulating concentrations of α-tocopherol [257] and retinol [258], compared to controls. Likewise, upper gastrointestinal cancer (including both oesophageal and gastric cancer) subjects of East Asian ancestry, but not those of European ancestry, had lower circulating 25-hydroxy-vitamin D concentrations [259]. Although these differences could be due to altered metabolism of these FSV in the oesophagus area, it is likely that they are mostly due to lower FSV intakes, as the disease can make swallowing (and thus eating) difficult.

8.2 Gastric cancer

Because some FSV have been suggested to be protective against different types of cancer, a number of historical studies have correlated gastric cancer risk with FSV intakes and/or circulating FSV or FSV metabolite concentrations [260, 261]. For example, lower blood concentrations of both

retinol [258] and 25-hydroxyvitamin D [259] have been associated with increased incidence of gastric cancer in individuals of East Asian ancestry. Although these correlations are generally interpreted by assuming that these FSV reduce the risk of developing gastric cancer, it can also be hypothesized that this cancer leads to a lower absorption and/or a higher use of these vitamins by the body. Another contributing factor is the bacterium *H. Pylori*, which is well known to increase the risk of gastric cancer [262]. Since this microbe causes the loss of acid-producing parietal cells, we would expect a higher susceptibility of some FSV and FSP (e.g. vitamin E) to autoxidation because of the higher pH. In contrast, the increased pH may favor the growth of additional gastric microbial species, which would also be expected to influence the production of FSV and FSP metabolites. In summary, it is likely that infection with this bacterium is responsible for changes in the absorption and metabolism of FSV and FSP, which would explain altered blood concentrations of the corresponding metabolites in patients with gastric cancer.

8.3 Biliary atresia/cholangitis, cholestasis

Blockage of the bile duct, due either to congenital defects (i.e. atresia) or to autoimmune-induced damage (i.e. cholangitis/cirrhosis) limits enterohepatic circulation of compounds commonly found in this digestive fluid, including bile salts and some FSV metabolites [263] (**see section 5.4**). Recycling of FSP metabolites, if it occurs, would also be predicted to be limited. In more severe and/or untreated cases when liver disease accompanies biliary cholangitis, active FSV metabolite production (in the case of vitamins A and D) and retention (in the case of vitamin E) by the liver are even more pronounced, with patients often presenting with symptoms of deficiency [263]. Under these conditions, it would be expected that localized metabolism of these vitamins would be upregulated in target tissues (including the GI tract itself) that do not receive sufficient quantities of metabolites from the liver. Furthermore, due to limited bile release, production of micelles is greatly diminished (as evidenced by steatorrhea) and thus limited FSV and FSP uptake is expected, further

914 exacerbating the problem. Indeed, plasma concentrations of retinol, α-tocopherol, and commonly
915 consumed carotenoids are reduced in subjects with even early stages of cholestasis, relative to
916 healthy controls [264]. Fortunately, treatment with the bile salt ursodeoxycholic acid proves to be
917 highly effective at earlier stages of the disease, and limits the severity of FSV deficiency in this
918 population [265].
919
920 ***8.4 Alcoholic fatty Liver, non-alcoholic fatty Liver, non-alcoholic steatohepatitis, and hepatic***
921 ***cirrhosis***
922 Both alcoholic fatty liver (driven by excess alcohol consumption) and non-alcoholic fatty
923 liver (driven primarily by obesity) are characterized by hepatic steatosis, which impairs liver
924 functioning [266]. Data suggests that the bioactive metabolites of FSV and carotenoids themselves
925 may both be influenced by, and may directly influence, fatty liver disease progression, especially in
926 younger individuals and/or earlier stages of condition development [266-269]. Fatty liver disease
927 upregulates utilization of FSV vitamin stores found there, increases synthesis of bioactive FSV
928 isoforms, and increases phase I metabolism for excretion. Impaired functioning of the "classical" bile
929 acid synthesis pathway leads to increased metabolism by a secondary pathway involving CYP27A1,
930 the same enzyme that produces 25-hydroxyvitamin D [270]. Likewise, in a murine model of alcohol-
931 induced hepatic steatosis, increased expression of hepatic CYP26A1 and CYP26B1, which convert
932 retinoic acid to phase I metabolites for excretion, as well as broad-spectrum phase I CYPs, i.e.
933 CYP2C29, CYP2C39 and CYP3A11, were observed [271]. In the same study, liver vitamin A stores
934 were also simultaneously depleted. Thus, we would expect increased enterohepatic recycling of
935 vitamin A and D metabolites, and increased concentrations in the intestinal lumen of these
936 metabolites in patients with fatty liver. The change in the composition of bile acids released may also
937 influence microbiota composition/abundance, and thus FSV and FSP metabolism in the distal small
938 intestine and colon [270]. Increased plasma concentrations of the oxidized vitamin E metabolite α-

939 tocopheryl quinone have also been reported in human subjects with non-alcoholic fatty liver disease
940 [272], with a fraction likely released into the bile.

941 Over time, non-alcoholic fatty liver disease can progress to non-alcoholic steatohepatitis,
942 with up to ~20% evolving into cirrhosis [273]. Liver cirrhosis is a severe form of liver disease
943 characterized by accumulated fibrous scar tissue that greatly hinders cell functioning. Multiple
944 studies have demonstrated that the majority (~70%) of adults with liver cirrhosis undergoing
945 evaluation for organ transplant present with deficient concentrations of circulating vitamin A and D
946 metabolites, while ~40% have vitamin E deficiency [274-276]. There is no clear link between
947 cirrhosis etiology and the severity of FSV deficiency, but there is correlation with albumin
948 concentrations, as a surrogate biomarker reflective of liver function [274].

949

950 ***8.5 Cholestatic liver diseases, cholestasis, chronic liver disease***

951 Cholestatic liver diseases produce the same phenotype as biliary cholangitis. However, the
952 changes are driven by insufficient bile production by the liver itself (as opposed to impaired bile and
953 FSV metabolite release into the intestinal lumen). Thus, these patients experience lipid
954 malabsorption, leaving more FSV and FSP in the gastrointestinal lumen (and likely their derivatives)
955 available for interactions with the colonic microbiota. Like liver cirrhosis, other forms of chronic
956 liver disease in both children and adults reduce liver functioning (and thus metabolism) and produce
957 FSV deficiencies [277].

958

959 ***8.6 Chronic pancreatitis, pancreatic insufficiency, Shwachman-Diamond syndrome (SDS)***

960 Because the pancreas is responsible for lipase production and release necessary for FSV and
961 FSP absorption, it is no surprise that chronic pancreatitis is associated with an increased prevalence
962 in FSV deficiencies relative to healthy controls [278]. Similarly, studies have demonstrated that

963 chronic pancreatitis patients have significantly lower blood carotenoid concentrations, relative to
964 healthy controls [279][280].

965 Shwachman-Diamond syndrome, a rare inherited disorder diagnosed in childhood and
966 characterized by pancreatic insufficiency, severely limits lipid and FSV / FSP absorption [281].
967 Treatment commonly includes pancreatic enzyme replacement therapy and micronutrient
968 supplementation. However, data in children shows that this treatment still leaves half of them
969 deficient in vitamins A and E [282].

970 Collectively, data suggests that chronic pancreatitis, pancreatic insufficiency, and
971 Shwachman-Diamond syndrome cause increased FSV / FSP concentrations to remain in the
972 intestinal lumen, and provide higher concentrations for metabolism by the colonic microbiota.

973

974 ***8.7 Celiac disease***

975 The dramatically reduced small intestinal luminal surface area typical of celiac subjects
976 would be expected to reduce FSV and FSP absorption and localized metabolism, again leaving
977 higher concentrations in the intestinal lumen for microbial metabolism. Surprisingly, only a few FSV
978 and FSP studies have been performed in this population. A case-control study in children reported
979 reduced circulating concentrations of the metabolite status markers of vitamin A and D in a majority
980 of those newly diagnosed with celiac disease [283]. Nevertheless, mixed results have been reported
981 in relation to deficiencies in vitamins E and K, with some studies showing little prevalence [284],
982 and others showing high prevalence [283, 285, 286].

983

984 ***8.8 Cystic fibrosis***

985 Patients with cystic fibrosis display malfunction in the transporter responsible for sodium and
986 chloride exchange (i.e. the cystic fibrosis transmembrane conductance regulator, CFTR), leading to
987 excess mucus secretion throughout the gastrointestinal tract [287]. CFTR also influences the ability

988 to secrete pancreatic digestive enzymes, and limits the ability of the liver to produce bile salts,
989 leading to lipid (and FSV) malabsorption. Indeed, FSV deficiency is common at diagnosis, with FSV
990 supplementation included with treatment [288]. Reduced circulating concentrations of FSP have also
991 been reported in patients with cystic fibrosis, including carotenoids and phytosterols, relative to
992 healthy controls [289, 290]. For these reasons, one would expect cystic fibrosis patients to have
993 reduced enterohepatic circulation of FSV and FSP metabolites.

994 Increased nutrient retention in the small intestinal lumen, as well as reduced gut motility,
995 provide a rich environment for small intestinal bacterial overgrowth and colonic dysbiosis [288].
996 Changes in microbiota would certainly be expected to influence microbial FSV / FSP metabolism,
997 thus producing metabolites and/or metabolite concentrations not typically observed in healthy
998 subjects, although to date this point remains undocumented.

999

1000 ***8.9 Intestinal failure***

1001 Intestinal failure presents a host of digestive challenges, especially when the disease is
1002 diagnosed in growing children, whose bodies demand adequate macro- and micronutrient absorption
1003 to thrive. Treatment typically involves re-sectioning of the damaged tissue, producing short-bowel
1004 syndrome and accompanying side-effects (e.g. bile acid malabsorption, steatorrhea, reduced number
1005 of transporters for uptake, etc.) [291]. Besides obvious challenges in absorption, re-sectioning
1006 increases the risk of luminal contents leaking through the intestinal barrier. Tissue transplantation is
1007 an alternative option in very severe cases [292].

1008 Previous studies have reported limited re-sectioning success under conditions of vitamin A
1009 deficiency [291]. Intestinal failure also causes deficiencies in vitamins D and E [292, 293], while
1010 vitamin K remains unstudied in this population. Historical oils used to produce the intravenous lipid
1011 emulsions provided to this population (e.g. Intralipid®) primarily containing soybean oil naturally
1012 rich in γ-tocopherol and phytosterols (as well as omega-6 long chain polyunsaturated fatty acids),

which would be expected to be metabolized by the liver and excreted back into the intestinal lumen. In contrast, more contemporary formulations contain fish oil (rich in omega-3 long chain polyunsaturated fatty acids), α-tocopherol and less phytosterols [294]. Like the other diseases mentioned above, a higher percentage of FSV and FSP remaining in the gastrointestinal tract would permit greater colonic metabolism.

8.10 Familial Hypobetalipoproteinemia

Familial hypobetalipoproteinemia is a genetic disease that may be due to 1) a defect in the assembly of lipoproteins in the intestine, 2) in the secretion of these lipoproteins by the intestine (classified as class I), 3) an accelerated catabolism of these lipoproteins in the blood (classified as class II) [295]. We focus here on class I because this category would be expected to modify the production of FSV and FSP metabolites in the intestine. It is known that individuals with this disease absorb FSV poorly and are thus treated with high doses of these vitamins, but no data exists on FSP supplementation (likely because they are not considered essential). There are also no data on the FSV metabolites present in the enterocyte of subjects with this pathology, but due to increased FSV retention, increased FSV metabolites would be anticipated. From here, it is not clear whether these metabolites would be secreted in the portal vein, returned to the intestinal lumen, or released into the lymphatic system. While not yet known, such subjects could potentially serve as excellent models to further study enterocyte FSV and FSP metabolism.

8.11 Inflammatory bowel disease

Overall, subjects with Crohn's disease and ulcerative colitis have reduced circulating concentrations of vitamins A, D, and E, relative to healthy controls [296, 297]. Results on vitamin K are mixed, with some studies demonstrating higher concentrations in inflammatory bowel disease subjects, and others demonstrating a deficiency [296, 297]. Oral supplementation in this population

has been rather disappointing, but is still often prescribed [297]. Changes in the mucosal membrane of the colon, which exacerbates the symptoms of inflammatory bowel disease, should stimulate bacterial growth. This might cause unique production of FSV / FSP metabolites in this cohort.

In summary, we can conclude that most of the digestive tract diseases probably reduce, to a greater or lesser extent, the absorption and metabolism of FSV and FSP. However, nothing is known about the consequences this may have on the biliary re-secretion of the FSV / FSP metabolites, on the microbiota, and on the FSV / FSP metabolism by the microbiota.

9. Effects of surgery of the gastrointestinal tract on FSV and FSP metabolism in this organ

Surgeons may have to operate on certain parts of the digestive tract following various diseases, e.g. stomach or colon cancer, but also to treat obesity and the diseases associated with it, e.g. bariatric surgery. These surgical procedures can result in the removal of certain parts of the digestive tract and/or changes in the normal course of food, e.g. after gastric bypass. This can lead to lower FSV and FSP intake due to the lower amount of food consumed/day. This can also decrease absorptive surface areas and thus the number of proteins involved in FSV and FSP uptake by intestinal cell (**section 5.3**). It is also likely that some of these surgeries alter the intraluminal metabolism of certain FSV / FSP and consequently the production of metabolites. Surgical interventions might require correcting the FSV [298-301] or carotenoid [302-304] status of patients. It is also interesting for the physiologist to better understand the key factors that modulate the bioavailability of these compounds [305]. Very little is known about the effects of different surgical procedures on the production and uptake of FSV / FSP metabolites, thus we postulate the consequences of these interventions based on our knowledge of metabolism in the healthy digestive tract.

9.1 Gastrectomy / gastric resection

The first part of the digestive tract that may be partially or totally removed is the stomach, as frequently observed with stomach cancer. Malabsorption of lipids, and therefore of FSV / FSP and their fat-soluble metabolites, can occur after total gastrectomy [306, 307]. For example, following surgical treatment, gastric cancer patients are at risk of vitamin A and E deficiencies [308]. The cause is apparently either excessively rapid intestinal transit or bacterial overgrowth [309]. Malabsorption also depends on the portion of the intestine that has been resected together with the stomach, e.g. duodenum vs. jejunum [310].

Patients who undergo bariatric surgery are assumed to be at greater risk of developing FSV deficiencies, as well as lower blood and tissue concentrations of FSP and their metabolites. This is supported by a recent review showing that these subjects are at higher risk of vitamin E deficiency [301]. Nevertheless, it is difficult to conclude that this is due to a lower absorption efficiency of the FSV of interest for two main reasons. First, most subjects who have undergone bariatric surgery are supplemented with vitamins and minerals following the operation to compensate for anticipated deficiencies [311]. Thus, blood concentrations of vitamin E can be higher after Roux-en-Y gastric bypass than prior to the surgery [312]. Second, most studies that have claimed to assess the consequences of bariatric surgery on vitamin absorption have measured the concentrations of vitamins in the blood of fasting subjects several weeks or months after surgery. Although this does not make it possible to conclude the effect of surgery on absorption, it gives an indication of the vitamin status after surgery, which is modulated by absorption but also by the vitamin intake and use/elimination by the body. To our knowledge, only two studies have reported the effect of bariatric surgery, specifically Roux-en-Y gastric bypass surgery, on absorption efficiency of the FSV. In the first study, [313] cholecalciferol absorption was decreased by 25% after the surgery. In the second study, despite the fact that vitamin A intakes remained unchanged pre- vs. post-surgery, and despite post-surgical supplementation of retinol palmitate, serum vitamin A concentrations were lower following surgery [314]. Thus, bariatric surgery appears to decrease FSV / FSP absorption, but a

comparison remains to be made between the effects of different bariatric surgery techniques on the absorption efficiency of FSV / FSP. Nothing is known about the consequences of bariatric surgery on the production of metabolites in the digestive lumen.

9.2 Intestinal failure

Vitamin D deficiency is highly prevalent in children with a history of intestinal failure, who have achieved enteral autonomy despite enteral supplementation with higher than standard doses of vitamin D. Shorter remnant small-bowel length and longer duration of parenteral nutrition were the main parameters associated with vitamin D deficiency [315]. This suggests that this pathology has more consequences on the absorption of FSV and FSP than stomach diseases. This result is logical since these compounds are absorbed in the intestine, but it does not provide information on the production of degradation compounds or metabolites in the intestine vs. stomach.

9.3 Pancreatic resection

The key role of pancreatic secretions on the absorption of vitamins A and D, and most likely also on the absorption of other FSV / FSP and their derivatives, is supported by the observation of a severe deficiency of these vitamins in a 12-year-old girl, who had undergone pancreatic resection for chronic calcific pancreatitis [305].

Nevertheless, two studies suggest that the digestive tract can, in the long term, adapt to compensate for the loss of absorption capacities. In the first one, shortening of rat jejunum by an end-to-end anastomosis (jejunum-bypass operation) [316] increased the ileal concentration of CRBP(II) by a factor 2, which would be an adaptation of the body to compensate for the loss of vitamin A absorption capacity. In the second one, a rat model of short bowel syndrome [317] pointed to an increase in the expression of genes involved in the intestinal metabolism of vitamin A, in that

case *Rbp2* and *Apoa4*. It remains to be seen whether the intestine is also able to adapt for lower absorption of other FSV and FSP after GI tract surgery.

10. Effect of xenobiotics that impair lipid absorption

Many strategies have been developed to combat obesity. Among these are administrations of compounds and drugs that decrease lipid absorption. An obvious question is the impact on FSV absorption and numerous studies have been carried out to address it. Concerning olestra, a zero-calorie fat replacement manufactured by Proctor & Gamble under the name olean, it has been shown that, as expected, it reduces the absorption of FSV and FSP with a logP (P: water-octanol partition coefficient) > 7.5 [318]. Thus, this additive has been banned in Canada and Europe, although it remains approved for use in snack foods in the USA. Interestingly, olestra has recently been shown to decrease plasma concentrations of lipid-soluble persistent organic pollutants, following 6 months of randomized, controlled administration, highlighting both the risks and benefits of consuming compounds that interfere with the absorption of very hydrophobic molecules [319].

Mineral oil, an indigestible lipid, has been used for many decades as a remedy to treat constipation, and as a placebo in some randomized, controlled trials. As long as the mineral oil is administered between meals, the impact on FSV / FSP status is limited [320, 321]. In the best controlled study to date, children treated for up to 4 months with mineral oil had a drop in serum β-carotene, but an increase in retinol (and no change in α-tocopherol) during the study period [322]. It is not clear whether the mineral oil has a direct effect on the provitamin-to-vitamin A conversion [322]. With more sophisticated methods of FSV / FSP delivery in new foods and supplements (e.g. encapsulation and nanoemulsion), *in vitro* evidence suggests that mineral oil negatively impacts vitamin D bioaccessibility [323]. Thus, further evaluation is warranted.

Finally, the anti-obesity drug orlistat, a lipase inhibitor, has been shown to reduce both postprandial absorption and circulating plasma concentrations of FSV and provitamin A, following

prospective dosing [324]. The favourable effects of orlistat on carbohydrate metabolism and non-alcoholic fatty liver disease will probably override concerns on FSV / FSP uptake in the short-term in adults, but these effects have also been reported in children, for whom ensuring sufficient FSV status is critical for growth and development [324]. Additionally, some evidence suggests that a greater percentage of provitamin A is metabolized to vitamin A in the intestine when the meal is consumed with digestible lipid. Thus, reducing digestible lipid may also influence FSV metabolism [325].

In summary, xenobiotics aiming to decrease the absorption of lipids also decrease the absorption of some FSV and carotenoids. However, the effects on the absorption of other FSP / FSV and their metabolites are unknown, as well as the consequences of these xenobiotics on the biliary secretion of FSV / FSP metabolites, and on the metabolism of FSV / FSP by the microbiota.

Conclusions

Overall, we have highlighted several recent developments in the understanding of FSV / FSP metabolite production, absorption, and potential bioactivity in digestive tract. We have also identified many areas where FSV / FSP metabolism remains unknown or poorly documented. In these instances, we have relied upon what is known about the parent FSV / FSP. Technological developments in analytical chemistry (e.g. metabolomics) have increased the capacity to identify and quantify a larger number of FSV and FSP metabolites in biological samples simultaneously. When paired with multi-omic integration (e.g. considering genetic, epigenetic, proteomic, exposomic, and microbiome factors) and the current knowledge on the gastrointestinal physiology and physiopathology, many more FSV / FSP metabolites are likely to be identified and correlated with various bioactivities.

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Table 1. Vitamins and phytochemicals with computed octanol-water partition coefficients ($\log_{10}$ P > 5).

Compound	Compound Class	Computed $\log_{10}$ P[1]
menaquinone 8-14 (vitamin K_2 isoforms)	vitamin	16.4-27.5
lycopene	carotenoid	15.6
neurosporene	carotenoid	15.5
phytofluene	carotenoid	15.4
phytoene	carotenoid	15.3
menaquinone-7 (vitamin K_2 isoform)	vitamin	14.5
chlorophyll b	tetrapyrrole	13.9
α-carotene (provitamin A)	carotenoid	13.6
β-carotene (provitamin A)	carotenoid	13.3
chlorophyll a	tetrapyrrole	12.9
menaquinone-6 (vitamin K_2 isoform)	vitamin	12.6
β-cryptoxanthin (provitamin A)	carotenoid	12.3
pheophytin a	tetrapyrrole	11.7
cafestol palmitate	diterpene ester	11.2
kahweol palmitate	diterpene ester	11.2
pheophytin b	tetrapyrrole	11.0
lutein	carotenoid	11.0
zeaxanthin	carotenoid	10.9
phylloquinone (vitamin K_1)	vitamin	10.9
menaquinone-5 (vitamin K_2 isoform)	vitamin	10.9
α-tocopherol (vitamin E)	vitamin	10.7

β-tocopherol (vitamin E isoform)	vitamin	10.3
γ-tocopherol (vitamin E isoform)	vitamin	10.3
astaxanthin	carotenoid	10.3
24-methylenecycloartanol	phytosterol	10.3
δ-tocopherol (vitamin E isoform)	vitamin	10.0
cycloartenol	phytosterol	9.8
α-tocotrienol (vitamin E isoform)	vitamin	9.3
β-sitosterol	phytosterol	9.3
β-tocotrienol (vitamin E isoform)	vitamin	8.9
γ-tocotrienol (vitamin E isoform)	vitamin	8.9
menaquinone-4 (vitamin K_2)	vitamin	8.9
campesterol	phytosterol	8.8
stigmasterol	phytosterol	8.6
δ-tocotrienol (vitamin E isoform)	vitamin	8.6
brassicasterol	phytosterol	8.0
cholecalciferol (vitamin D_3)	vitamin	7.9
ergocalciferol (vitamin D_2)	vitamin	7.4
ergosterol	phytosterol	7.4
soyasapogenol B	phytosterol	7.0
calcifediol (25-hydroxyvitamin D_3)	vitamin	6.2
solanidine	steroidal alkaloid	6.1
tomatidine	steroidal alkaloid	6.0
falcarinone	polyacetylene	6.0
ercalcidiol (25-hydroxyvitamin D_2)	vitamin	6.0
rosmaridiphenol	other	5.9

falcarinol	polyacetylene	5.5

[1]Value computed by XLOGP3 version 3.0 [326].

Figure legends

Figure 1: Vitamin D derivatives and possible mechanisms of formation. Left panel, physicochemical mechanisms for the degradation of 1α,25-dihydroxycholecalciferol [66]. **A)** Thermal degradation in DMSO, possibly occurring during thermal processing. **B)** Acid-catalyzed degradation in a 1:1 pH 3 phosphate buffer – MeCN mixture, possibly occurring in stomach. Middle panel, biochemical mechanisms for metabolism in the liver and intestine. Right panel, hypothesized deconjugation by the microbiota.

Figure 2: Phytosterol derivatives and possible mechanisms of formation. Left panel, physicochemical mechanisms for the formation of phytosterol oxidation products upon thermal treatment of fat-rich food containing phytosterols acylated by polyunsaturated fatty acids [93]. Upon thermal treatment of lipid food (e.g. phytosterol-enriched margarine), phytosterols acylated by fatty acids are more vulnerable to oxidation when the unsaturation degree of the acyl chain increases. Autoxidation of a PUFA chain leads to highly reactive peroxyl radicals that efficiently oxidize the nearby phytosterol moiety. Middle panel, biochemical mechanisms that can happen in the stomach and intestine. Right panel, no data available on the metabolism of phytosterols by the microbiota.

Figure 3: Gastric phases / structures in which parent FSV / FSP and their derivatives can be distributed during digestion. Derivatives (**D**) mean compounds formed upon either physicochemical or enzymatic modification of the parent molecule (**P**); *filled arrow*: known transfer route; *doted arrows*: some hypothesized transfer routes.

Figure 4: Vitamin A derivatives and possible mechanisms of formation. Left panel, physicochemical mechanisms for the iron-induced autoxidation of carotenoids [109, 327]. Dioxygen

activation involves non-heme Fe^{II} traces. The reaction with Fe^{III} is slower as it requires a first rate-limiting step of Fe^{III} reduction by carotenoids. Such mechanisms may occur during food processing and digestion, especially when dietary carotenoids are transferred from emulsions to mixed micelles along lipid digestion. Middle panel, metabolism of the main dietary source of preformed vitamin A by human gastrointestinal enzymes. Right panel, hypothesized deconjugation by the microbiota.

Figure 5: Prooxidant effect of polyunsaturated fatty acids on FSV and FSP. Upper panel: Co-oxidation of polyunsaturated fatty acids (LH) and antioxidants during iron-induced lipid peroxidation [145-148]. LH = polyunsaturated fatty acids; AO1 = water-soluble antioxidant, e.g. phenolic compounds, vitamin C, short-chain apocarotenoids; AO2 = fat-soluble antioxidant, e.g. vitamin E, carotenoids, long-chain apocarotenoids; LOOH = lipid hydroperoxides. A) Initiation by heme iron (Fe^{III}). Lower panel: initiation by non-heme iron (Fe^{II}). Such mechanisms may occur in the gastric compartment where dietary iron and traces of hydroperoxides from lipid food can initiate PUFA peroxidation under vigorous mixing, favorable acidic conditions and non-limiting O_2 concentrations.

Figure 6: Derivatives of the fat-soluble phenols of rosemary. Upon autoxidation (during food processing or in the GI tract) or in the course of its antioxidant activity, carnosic acid (**1**), one of the main antioxidant diterpenes of rosemary, is converted into carnosol (**2**), then into rosmanol (**3**) [154]. Through its electron-rich catechol ring, rosmanol itself can undergo additional two-electron oxidation. These electron transfer sequences sustain the strong antioxidant activity of rosemary extracts

Figure 7: Derivatives of the fat-soluble phenols of olive oil. A) Some olive phenols (except parent glucosides, which are only present in the non-oily part of the olive fruit) are present in substantial concentration in virgin olive oil (up to ca. one gram / kg) [155, 156]. They are known to contribute to

the nutritional benefits of olive oil consumption, which is emphasized by a EFSA health claim [328]. **B)** Hydroxytyrosol (HT), the typical phenolic antioxidant of olive oil, inhibits lipid peroxidation in synergy with α-tocopherol [157]. While acting as an antioxidant, HT is converted in dimers and higher oligomers that undergo further oxidation. Some incorporate water molecules [158].

Figure 8: Vitamin E derivatives and possible mechanisms of formation. Left panel, physicochemical mechanisms with the example of interplay between α-tocopherol and other dietary antioxidants [329-334]. α-Tocopherol regeneration by other antioxidants is important to prolong tocopherol activity and avoid tocopherol-mediated lipid peroxidation within lipid-rich phases. This interplay between tocopherol and other dietary antioxidants may also apply with vitamin K. Vitamin K itself (through its reduced form) inhibits lipid peroxidation. Middle panel, biochemical mechanisms for the metabolism of vitamin E in the liver. Right panel, no data available on the metabolism of vitamin E by the microbiota.

Figure 9: Vitamin K derivatives and possible mechanisms of formation. Left panel, physicochemical mechanisms with the example of the possible interplay between menaquinone MQ-7 (R = hepta-isoprenyl chain) and carotenoids in the presence of heme or non-heme iron [335]. Carotenoids are spared in the process. MQ-7, naturally present in cocktails of bacterial carotenoids, is insensitive to iron-induced autoxidation and a poor antioxidant in the inhibition of iron-induced lipid peroxidation. However, in the presence of heme or non-heme iron, MQ-7 efficiently protects carotenoids against autoxidation and potentiates their antioxidant activity. Middle panel, biochemical mechanisms for the metabolism of phylloquinone in the small intestine. Right panel, vitamin K metabolite produced by the microbiota.

Figure 10: Upper intestinal phases / structures in which parent molecules and their derivatives can be distributed during digestion. In the upper intestine FSV and FSP and their derivatives are assumed to distribute between the phases / structures present in the gastric lumen (see **Fig. 3**) and secreted into the duodenum through the pylorus plus additional phases / structures coming from biliary secretion and the digestion of dietary lipids, i.e. mainly triglycerides and phospholipids. **P**: parent molecule; **D**: derivative; **P***: parent molecule previously absorbed, then secreted in the bile; **D***: derivative previously absorbed, or resulting from metabolism of **P**, then secreted in the bile; **filled arrows**: known transfer routes; **doted arrows**: some hypothesized transfer routes.

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