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1	Fat-soluble vitamin and phytochemical metabolites: production, gastrointestinal
2	absorption, and health effects.
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- 24 Abstract
- 25

Consumption of diets rich in fruits and vegetables, which provide some fat-soluble vitamins 26 27 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 28 upon enzymatic or nonenzymatic transformations, can produce protective biological effects. These 29 30 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. 31 32 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 33 potentially be present based on the known reactivity of the parent compounds in normal or 34 35 pathological conditions, or following surgical interventions of the digestive tract or consumption of 36 xenobiotics known to impair lipid absorption. It also covers the very limited data available on the 37 bioavailability (absorption, intestinal mucosa metabolism) and summarizes their effects on health. 38 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 39 40 understand and capitalize on the potential of these molecules to preserve health.

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

43 Introduction

Of the thousands of different molecules consumed through plant foods in our diet, the best 44 known are macronutrients (proteins, fats, carbohydrates) and micronutrients (vitamins and trace 45 46 elements). However, we also ingest a multitude of compounds called "phytochemicals", plant secondary metabolites with great chemical diversity. Phytochemicals are classified into large 47 families, e.g. terpenoids and phenolics, which are thought to be at least partially involved in the 48 49 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 50 51 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. 52 These metabolites may be derived from the chemical degradation of these molecules during culinary 53 54 preparation or food processing [9-11], or phase I and phase II metabolism in the intestinal mucosa or 55 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 56 57 microbiota [12, 13], elicit effects on the intestinal microbiota [14, 15], or even be absorbed [16], although research in this area is nascent. 58

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, retinoicacid 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 of these compounds in all compartments of the human digestive tract. Known, or hypothesized 70 71 absorption and health effects will also be discussed. This review also highlights gaps in knowledge regarding microbial metabolism of FSV & FSP. Indeed, it is plausible that the very limited 72 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 basics of their digestion, absorption and metabolism have been widely discussed in previous books 77 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 has been associated with beneficial effects on pathologies linked to aging. Terpenoids are the main 81 82 class of FSP. They are biosynthesized through the assembly of a variable number (N) of a 5-carbon (isoprene) unit, and subdivided accordingly: monoterpenes (N = 2, e.g. limonene, menthol and 83 vanillin), diterpenes (N = 4), tetraterpenes (N = 8), including the carotenoid pigments. In plants, 84 carotenoids play an essential role in photosynthesis, and in mammals some serve as provitamin A 85 (i.e. α - and β -carotenes, β -cryptoxanthin, γ -carotene). Some xanthophyll carotenoids (i.e. lutein and 86 87 zeaxanthin) appear to play a role in visual function and in the prevention of age-related macular degeneration. The carotenoid lycopene (i.e., the red pigment of tomato) has anti-inflammatory 88 effects [20], which may explain partly its association with a reduced risk of cardiometabolic disease 89 90 [41-43]. Triterpenes (N = 6) have also aroused much scientific interest, in particular their sterol derivatives, e.g. β-sitosterol, stigmasterol, sitostanol. These so-called phytosterols have a structure 91 analogous to cholesterol and serve a similar biological function in plants. They have been observed 92

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.

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98 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 99 100 absorption and metabolism and the that of triacylglycerols, phospholipids and sterols. At dietary 101 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. 102 103 some carotenoids [46]. However, at supplemental/pharmacological doses, both FSV and FSP are 104 assumed to enter the enterocyte via passive diffusion. Once taken up, some FSV and FSP can be 105 phase I metabolized within the enterocyte. It has been shown that some FSV can also be effluxed 106 back into the intestinal lumen via specific transporters [47-49]. Following uptake, lipophilic 107 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 108 the blood, and travel from the portal vein to the liver for "first pass" metabolism. This often includes 109 oxidation by cytochrome P450 enzymes, regardless of the compound in question. Routes of 110 excretion, including release of the parent FSV and FSP, as well as their phase I and phase II 111 112 metabolites, occur in the liver and the kidney, respectively.

113 Despite these shared pathways, there are many fundamental points of difference in the handling 114 of FSV absorption and metabolism, as compared to FSP. Once shuttled into the enterocyte, the FSV 115 are often chaperoned around via specific binding proteins, which again recognize particular 116 structures or functional groups. For vitamins A and D, this shuttling begins in the enterocyte of the 117 small intestine, while for vitamin E (and potentially vitamin K_1) this occurs in the liver, thanks to α -

118 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 119 120 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 121 transformation via metabolism to produce the active forms. Recent evidence suggests that dietary 122 123 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, 124 125 without disrupting the highly regulated steady-state concentrations of the active forms. In contrast, 126 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 127 128 window of effect [52]. An additional point of difference between FSV and FSP is high specificity 129 in mechanisms of action. Vitamins A and D metabolites, i.e. retinoic acid and 1,25-130 dihydrocholecalciferol, are nuclear receptor agonists with high specificity in binding to the retinoic 131 acid receptors (RAR) and to the vitamin D receptors (VDR), respectively. Vitamin E can act as a 132 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 -133 carboxyglutamate – a required step in the blood coagulation cascade, which may also be important 134 in bone mineralization [55]. Furthermore, a total of 17 vitamin K-dependent proteins have been 135 identified to date and involved in bone and cardiovascular health [56]. In contrast, diverse 136 137 mechanism(s) of action are proposed for many FSP metabolites, e.g. direct antioxidant effects, regulation of gene expression, effect on inflammation. 138

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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

143 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, 144 produce derivatives of FSV and FSP. Chopping or grinding food for preparation can cleave cell 145 146 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 147 148 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 149 150 transformations in foods. Additionally, consumption of products transformed by yeasts, bacteria, 151 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 152 153 microbiome within the animal. These metabolites are likely present at trace levels in all 154 transformed products, but can be especially rich in organs known to concentrate metabolites (e.g. 155 mammalian liver, kidney), or in animal byproducts consumed by humans.

156 Mechanisms of production of FSV metabolites by the main animal species that we consume, 157 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 158 humans, namely 11-cis-retinal and retinoic acid respectively, are synthesized from the pro-vitamin 159 160 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 161 162 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 163 primarily retinyl palmitate, which can be present in very high, even toxic, concentrations in the 164 165 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. 166 Vitamin E is intentionally supplemented to livestock to reduce lipid peroxidation in meat products 167

168 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. 169 Vitamin D, as either vitamin D_2 or D_3 isoforms in foods, undergoes hydroxylation in the 170 171 mammalian and avian liver to produce 25-hydroxyvitamin D₂ and D₃, respectively [59, 60]. These 25-hydroxy metabolites are found in beef, pork, chicken, and eggs, [61, 62], as well as in milk, 172 cream, and butter [63], in concentrations on the same order of magnitude as the vitamin D_2 and D_3 173 precursors. Trace quantities of 25-hydroxyvitamin D₃ have also been reported in salmon, tilapia, 174 and mahi-mahi [61]. Like most sterols, 25-hydroxyvitamin D is robust to various methods of 175 176 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 177 178 concentrations ~5-10 times lower in beef muscle tissue [65]. Data suggests that it can be 179 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). 180 181 Menaquinones are actually a cluster of K₂ isoforms produced either by mammalian metabolism of 182 vitamin K₁ 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 183 184 (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 185 186 metabolite of phylloquinone (vitamin K₁), and is found in whole-fat milk, cheeses, salami, beef, 187 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 188 conditions, but sensitive to degradation by daylight [72]. Chemically, it has no clear structural 189 190 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

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

There is apparently little degradation of carotenoids in foods. Lycopene, one of the most 199 200 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 reported to be quite stable in a variety of foods following domestic or industrial thermal processing 202 203 [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 vegetables [80-83]. However, their origins are unknown. Carotenoid cleavage enzymes within the 205 206 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 food preparation/cooking, although studies are lacking. In supplements, high carotenoid 208 209 concentrations and presence of oil (for which co-oxidation can occur) would be expected to produce higher concentrations of apo-carotenoids. Lutein extract from marigold following was 210 found to degrade following 10 days of exposure to mid-day heat $(31^{\circ}C)$ + sunlight (5.89 kW h m⁻²) 211 212 to produce derivatives with shorter carbon chains which elicit PPAR- γ activity [85]. The presence of these products in lutein containing foods or supplements has not been reported, but may merit 213 further investigation due to the pronounced biological effects. 214

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

218 88]. Following oxidation, an epoxide, keto, mono- or di-hydroxyl group is added to the B-ring. 219 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) 220 221 [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], 222 223 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 224 [93] (Fig. 2), co-heating of phytosterols with a saturated lipid induced a greater concentration of 225 226 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, 227 228 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).

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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

243 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 244 provides food lubrication, antimicrobial defense, assistance with taste and early digestion [96]. 245 246 Indeed, the oral cavity has been considered a "bioreactor" [97, 98] in which multiple interactions 247 occur between salivary components (e.g. ions, proteins, including digestive enzymes, such as alphaamylase) and macro- and micronutrients and phytochemicals. Salivary lactoperoxidase and 248 249 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 250 251 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 252 remain within lipid phases through the oral cavity, which can confer protection (if the lipids are not 253 254 oxidized). In contrast, we hypothesize that some of their less apolar derivatives might bind to 255 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, 256 hydrogen peroxide, hypothiocyanous acid) and oxidation-sensitive nutrients (e.g. polyunsaturated 257 fatty acids) to antioxidants (e.g. polyphenols, carotenoids, vitamin C), simultaneously present in the 258 259 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 260 261 probable that crystallized carotenoids (like those found in carrots or tomatoes) are less sensitive to 262 oxidation. Finally, the oral microbiome, comprised of different bacterial and yeast species, also 263 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.

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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 274 FSP. The first, for which we have the most data is to amplify the digestion of food [105]. This 275 276 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 277 278 gastric enzymes. The typical gastric conditions are: 37 °C, pH from weakly to fairly acidic [106], 279 the presence of a significant partial pressure of O₂ [107] and of digestive enzymes, e.g. pepsin and 280 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 281 282 water-soluble carotenoid crocin to starch [110], to chemical modifications, e.g. autoxidation of carotenoids [108, 109, 111, 112]. 283

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 B₁₂ 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.

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290 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 digestion they are gradually released and distribute themselves between the different phases present 295 296 in the digestive tract. For FSV and FSP to be freed from the structural barriers which impede release from the food matrices, [114, 115], the biochemical action of gastric juice and the peristaltic 297 298 movements are required. The importance of the peristaltic movements in freeing FSP was confirmed by a study showing that β -carotene was better released from sweet potatoes when 299 300 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 digestion (Fig. 3). Tyssandier et al. [106] fed human volunteers with test meals that contained 302 303 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 that the percentage of carotenoid transferred depends on the carotenoids' physicochemical 308 309 properties, as well as on their location in, and interactions with, the plant matrix. In vitro studies have further deciphered the factors involved. Rich et al. suggested that carotenoids incorporated 310 311 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 presence and nature of emulsifiers covering lipid droplets, and the effect of the food matrix on the 313 transfer efficiency of carotenoids from vegetable matrices to lipid droplets [118]. The results 314 315 confirmed what was deduced from the clinical study [106], i.e. that the transfer of carotenoids between plant foods and lipid emulsions depends on all of these factors. Additionally, Yuan et al. 316 reported that carotenoid transfer was greater when the lipid droplets were emulsified with caseinate 317

318 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 319 by the results of another study in which Tween 20-stabilized emulsions had a lower rate and extent 320 321 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 322 323 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 324 transfer of carotenoids from the food matrix to lipid emulsions in the stomach during digestion. 325 326 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 327 328 that transfer also depends on the parameters mentioned above.

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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 willprobably protect them significantly from this acidity.

Concerning carotenoids, there is no data on the effect of pH on the molecules themselves, but 345 346 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 347 348 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 349 350 approximately halved, as compared to control without omeprazole (low gastric pH). They 351 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, 352 353 together with the absence of gastric enzymes, e.g. gastric lipase [124, 125] and pepsin, could cause 354 a large fraction of β -carotene to remain trapped within the undigested lipids of the meal. 355 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, 356 357 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 358 359 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 360 of salivary or gastric enzymes that could hydrolyse some of these compounds. Gastric lipase is one 361 362 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 363 esters with concomitant release of free cryptoxanthin [130]. We hypothesize that this lipase is also 364 capable of hydrolysing other xanthophyll esters and perhaps other FSV and FSP esters, e.g. 365 phytosterol esters. As the bioaccessibility of free cryptoxanthin is superior to that of esterified 366 cryptoxanthin [130], and assuming that it is the same for other FSV and FSP, we also hypothesize 367

that the hydrolysis of any FSV or FSP ester by gastric lipase could enhance its overallbioavailability.

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

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

393 (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 394 to the fact that lycopene was protected within the food matrix. Indeed, another study showed that β -395 396 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 397 398 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 399 400 largely spared, when provided by the same matrix [137], suggesting that the different carotenoids 401 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 402 403 egg xanthophylls were stable (average recovery of about 90%) and that no (Z)-(E) isomerization 404 occurred during *in vitro* digestion [138]. A lack of significant (Z)-(E) isomerization of lycopene 405 was also observed in another study using the same model [139]. Collectively, the majority of in 406 vitro and in vivo evidence suggests that limited isomerization and loss occurs for most carotenoids 407 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 408 409 physicochemical conditions and their evolution during digestion.

410 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 411 412 called autoxidation (non-enzymatic oxidation by O₂). Oxidizable (electron-rich) FSV and FSP, such as vitamin E and carotenoids, are intrinsically vulnerable to autoxidation in the stomach 413 414 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 415 conditions, Fe^{2+} and metmyoglobin induced the isomerization and oxidation of β -carotene to 416 epoxides and cleavage products of various chain lengths [109] (Fig. 4). In vitro work by Kopec et 417

418 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, 419 and a ~50-60% drop when digested with metmyoglobin or Fe^{2+} . In the same study, no statistically 420 significant drop in concentrations of lutein or lycopene during the gastric phase when digested 421 alone, or with the addition of metmyoglobin or Fe²⁺. In vivo, both increased time of sampling and 422 the presence of FeSO₄ consumed with a lycopene-rich beverage resulted in less lycopene in the 423 stomach than the lycopene-rich beverage alone [108]. Free retinol itself is also known to be highly 424 425 susceptible to autoxidation [141]. Collectively, these results highlight that contrasting results can be 426 obtained depending on meal composition, pH, the presence of digestive enzymes, and the presence of prooxidant agents. 427

428 In addition to iron, all lipid-rich foods contain traces of lipid hydroperoxides (LOOH) with peroxide values typically in the range of $1 - 5 \mu mol/g$ [142, 143]. The Fenton reaction between Fe^{II} 429 and LOOH is a source of highly reactive oxyl radicals (LO[•]), while heme-Fe^{III} reacting with 430 hydroperoxides also leads to hypervalent iron forms (heme-Fe^{IV}) that are efficient initiators of lipid 431 peroxidation through the propagating lipid peroxyl radicals (LOO[•]) [144] (**Fig. 5**). The prooxidant 432 character of a meal rich in iron and oxidizable (polyunsaturated) lipids may be mitigated by plant 433 antioxidants. Hydrophilic antioxidants, such as phenolic compounds, either bind non-heme iron 434 under inert complexes or reduce hypervalent heme iron, while lipophilic antioxidants, such as 435 vitamin E and carotenoids, reduce the lipid oxyl and peroxyl radicals, or trap them as stabilized 436 437 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 438 439 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 440 a simulated gastric fluid at pH 3, 37°C., but protected upon addition of red wine polyphenols [107, 441 151]. It is also noteworthy that apo-carotenoids (possibly present in plant food or formed in the 442

443 course of carotenoid – polyunsaturated fatty acids co-oxidation during food processing or in the gastric phase of digestion) are themselves antioxidants [147]. In a simple model using micelles of 444 linoleic acid, apo-6'-lycopenal and apo-8'-lycopenal were even better inhibitors of metmyoglobin-445 446 induced lipid peroxidation than (all-*E*)-lycopene itself [147]. In general, a long unsaturated chain and a terminal carboxylic acid group both favor the antioxidant activity of apo-lycopenoids. The 447 448 short-chain apo-14'-lycopenoic acid was also shown to directly reduce the hypervalent iron form of metmyoglobin, thus behaving as a hydrophilic antioxidant [147]. Of course, the in vivo relevance of 449 450 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 meal combining sunflower oil and beef meat were found in lower concentrations when the meal 452 453 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 semiguinone and an *ortho*-quinone, respectively. For instance, the 459 rosemary diterpene carnosic acid is a potent antioxidant and its oxidized derivatives retain the catechol ring [153] (Fig. 6). These antioxidant diterpenes, as well as a decarboxylated derivative, 460 were also detected in the meat of lambs fed diets supplemented with rosemary extracts. They confer 461 462 higher oxidative stability to the meat [154]. Hydroxytyrosol and its derivatives are present in substantial concentration in virgin olive oil (up to ca. one gram / kg, Fig. 7A) [155, 156]. 463 464 Hydroxytyrosol inhibits lipid peroxidation in synergy with α -tocopherol under model gastric conditions [157]. While acting as an antioxidant, it is converted into dimers and higher oligomers, 465 which undergo further oxidation, thus prolonging the antioxidant activity [158](Fig. 7B). 466

467 Regeneration of the amphiphilic antioxidant α-tocopherol (TocOH) from its oxidized forms is 468 key to prolonging its lipid-protecting activity while avoiding the prooxidant activity of the 469 corresponding aryloxyl radical (TocO[•]) (**Fig. 8**). The reduced forms of coenzyme Q and vitamin K, 470 as well as vitamin C and a variety of polyphenols may play this role. This regeneration may occur 471 from TocO[•] upon one-electron reduction, but also from some non-radical two-electron oxidized 472 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**.

474 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 475 476 that alcohol consumers had significantly lower antral mucosal and gastric juice concentrations of β-477 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 478 associated with a higher prevalence of atrophic gastritis [126], or during infection by Helicobacter 479 *pylori*. For example, it has been shown that infection with *H. pylori* decreases the concentration of β -480 481 carotene in gastric juice [122], suggesting that a fraction of this provitamin A carotenoid was 482 converted to metabolites. No significant effects of age on β -carotene concentration in gastric juice 483 [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 484 485 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 486 487 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 488 489 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-490 secreted in the gastric lumen or directly enter the systemic circulation. Further work is required. 491

493 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.

500

501 4.4 Potential health effects of FSV and FSP in the gastric lumen and mucosa

502 Several FSV and FSP, e.g. vitamin E and carotenoids, are known to be important antioxidants 503 in cell membranes and plasma lipoproteins. Others (e.g., the lipophilic phenols from olives and 504 rosemary, and generally all dietary phenolic compounds) are more likely to exert their antioxidant 505 effects in the lumen of the digestive tract, where they can reach millimolar concentrations under 506 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 507 oxidation lowers the nutritional quality of the meal, not only through loss of essential lipids but also 508 by the alteration of dietary proteins [161], which are vulnerable to electrophilic and/or oxidizing 509 lipid peroxidation products (e.g. lipid hydroperoxides, malondialdehyde, 4-hydroxy-2-alkenals). 510 511 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]. 512

513 Some FSV and FSP and/or their metabolites could also have beneficial effects on the gastric 514 mucosa, not only through their antioxidant activity, but also by scavenging nitrite, as some 515 polyphenols do [163, 164], thus participating in the prevention of stomach cancer [165]. This 516 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].

522 Furthermore, it has been shown that apo-carotenals, possibly produced by carotenoid – PUFA 523 co-oxidation in the stomach, have anti-inflammatory and antioxidant properties in cells through the 524 respective down- and up-regulation of the NF- κ B and nrf2 (antioxidant/electrophile response 525 element) pathways, while the corresponding apo-carotenoic acids are inactive [169, 170]. This is 526 explained by the fact that apo-carotenals are electrophilic unsaturated aldehydes capable of reacting 527 with key nucleophilic thiols (Cys residues) of proteins controlling the activity of these transcription 528 factors.

529

530 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.

537

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

When entering the duodenum, a fraction of the parent FSV and FSP and derivatives are still 552 553 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 associated with aqueous soluble proteins or peptides of partially digested dietary proteins. Some 555 556 derivatives may also be water-soluble. Of course, this distribution is dynamic and evolves during digestion, with FSV and FSP and their derivatives transferred to the other phases as lipolysis 557 continues. It has been shown in vitro that parent FSV and FSP are transferred partly to lipid 558 emulsions and partly to micelles [117, 179, 180], but it is likely that a fraction is also transferred to 559 560 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 of these molecules between all the phases mentioned above has not been assessed, and nothing is 562 known about the derivatives. 563

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

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

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

Fig. 10 details what is known regarding the factors that drive interphase transfer of FSV and 580 FSP and their derivatives. The first step, the transfer between food matrices and emulsified lipid 581 582 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 amphiphilic molecules that coat triglyceride droplets in the gut, e.g. phospholipids and proteins, 584 585 strongly impair the transfer of pure carotenoids to triglyceride droplets [118], suggesting that they act as a barrier that impair the transfer. However, carotenoids incorporated in plant matrices were better 586 transferred to triglyceride droplets coated with emulsifiers than to uncoated ones [118]. 587

The second and arguably best-studied step is the FSV + FSP transfer between lipid emulsions and micelles [185]. For example, the transfer of carotenoids is inversely related to carotenoid hydrophobicity with maximal transfer occurring: between pH 6 and 7, with ≥ 2 mmol/L bile salts. 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 \geq 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.

605

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 607 the hydrolysis of fatty acid esters, e.g. retinyl esters and xanthophyll esters. Three pancreatic 608 609 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 610 pancreatic lipase and pancreatic lipase-related protein 2, which are able to hydrolyse retinyl esters 611 612 [187, 188]. It is likely that these enzymes, given their low substrate specificity, are also capable of 613 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 614 615 absorbed only in their non-esterified form.

616 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 617 interactions with other co-consumed species (e.g. iron). Regardless of the absence or presence of 618 619 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 620 from the gastric to the duodenal phase [112]. However, in the absence of enzymes, a ~13% loss was 621 622 observed for lycopene, the carotenoid most sensitive to oxidation (no change in the presence of 623 enzymes).

624 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 625 626 of enzymes, and a ~35% loss in the presence of enzymes [112]. Follow-up studies in healthy males 627 with isotopically labelled β -carotene demonstrated the presence of labelled β -apo-carotenals 628 (aldehyde catabolites) in the oral dose provided [111]. Increased concentrations of most β -apo-629 carotenals were observed over time in the duodenal digesta, with duodenal concentrations of the 630 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 631 the newly-absorbed lyophilic fraction of blood (nor the plasma itself) afterward. Thus, the data does 632 not support β -carotene conversion to apo-products in the enterocyte. However, β -apo-13-carotenone 633 634 and β -apo-14'-carotenal were shown to act as antagonists of the retinoic acid receptor *in vitro* [189]. 635 Based on the lack of uptake of labelled β -apo-carotenals in the blood stream, this activity most plausibly could occur in enterocytes. 636

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

In conclusion, these data clearly show that there is production of β -carotene and lycopene metabolites in the lumen of the upper intestine and that this production is modulated by iron. Additionally, the proportions of β -carotene and lycopene transformed into metabolites are relatively low. Nevertheless, it is important to remember that some FSV / FSP metabolites can be very active at very low concentrations (e.g. retinoic acid and 1,25-dihydroxyvitamin D) and it is not known in what proportions are metabolized the other FSV and FSP, and what are their derivatives produced 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 intestinal cell has considerably advanced over the past decade. Indeed, while it was thought that all 659 these molecules were absorbed by passive diffusion, Borel and co-workers, as well as other teams, 660 661 have identified enterocyte proteins that are involved in both apical uptake and efflux back to the intestinal lumen, as well as through the basolateral membrane. For further details, we refer the reader 662 663 to a review published in the same journal [46]. Since this previous publication, new proteins involved in uptake and basolateral efflux of FSV and FSP have been identified. The ABCG5/G8 complex, 664 well known for its key role in the efflux of phytosterols back to the intestinal lumen, has also been 665

666 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 667 vitamin K₁ [193]; CD36 in the uptake of vitamin E [194] and vitamin K1 [193]; ABCG1 in the efflux 668 669 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 670 components of mixed micelles that are recognized by these transporter proteins. Thus, FSV and FSP 671 672 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 673 674 proteins that would facilitate the capture, or efflux, of FSV / FSP derivatives, but it is possible that 675 the same transporter proteins are involved.

676

677 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 ¹⁴C-retinol and ¹⁴C-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 ³H-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 25hydroxyvitamin D₃ 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.

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

Intravenous administration of either ¹⁴C-labeled vitamin K_1 , K_2 , or K_3 , to rodents resulted in 706 707 8.5, 74 and 37% of the isotope in bile after 12 h of collection, respectively [212], demonstrating a high propensity for biliary elimination. An elegant series of cannulation experiments in rodents by 708 709 Hirota et al. [213] reported no secretion of labeled phylloquinone or its menaquinone-4 metabolite in bile following controlled dosing, implying that the excreted biliary dose is exclusively comprised of 710 metabolites. Finally, humans intravenously injected with isotopically labeled vitamin K₁ secreted 711 slightly more polar labeled metabolites (relative to the parent compound) into the bile duct [214]. 712 713 However, the structures were not identified and the possibility for these metabolites to be taken up from the small intestine is unknown. 714

715 In summary, secretions of metabolites of the four essential FSV have been observed, but it has not been elucidated if these metabolites are reabsorbed by the intestinal cell and further metabolized 716 back to parent structures (to exert biological effects), or whether additional metabolism into other 717 718 species occurs. A better understanding of this process could demonstrate whether true enterohepatic cycling occurs (analogous to bile salts), and whether this contributes to whole-body FSV intakes. 719

Very little data is available regarding the potential enterohepatic cycling of FSP. Regarding 720 721 phytosterols, we hypothesize that since their initial absorption is very low ($\leq 2\%$ for sterols, $\leq 0.2\%$ 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 been reported following a second meal (after initial phytosterol dosing). However, it's not clear if 724 725 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 undergo enterohepatic recycling [217]. Finally, to the best of our knowledge, the enterohepatic 728 729 recycling of non-provitamin A metabolites of carotenoids, e.g. lycopene and lutein, has not been 730 explored.

731

6. Metabolism of FSV and FSP in the mucosa of the upper intestine and biological effects 732 733 of metabolites in this tissue.

734 Metabolic pathways, based upon localized expression of enzymes active in the jejunum and ileum, and whose specific activity toward FSV and FSP has been studied in other tissues, are detailed 735 below. While much is understood about vitamin A, limited work on vitamins D, E, and especially K 736 737 has been conducted so far to determine the role of these enzymes in influencing local or whole-body FSV and FSP metabolite concentrations, maintaining FSV homeostasis, and in eliciting local 738 bioactivity. 739

740 Provitamin A is absorbed and converted to the vitamin A metabolite retinal via BCO1 in the 741 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 742 743 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 744 745 to the bioactive vitamin A metabolite all-trans-retinoic acid by retinaldehyde dehydrogenase I 746 (RALDH1), for local utilization both by enterocytes and by mucosal dendritic cells involved in 747 immune homeostasis [221, 222]. Indeed, retinoic acid synthesized by gut-associated lymphoid 748 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 749 750 epithelial cells to keep pathogens out, and stimulates cell repair following damage [225, 226]. 751 Intestinal deactivation of retinoic acid occurs via conversion to oxo- and hydroxy-metabolites by 752 cytochromes CYP1A1 and CYP3A, CYP26 [221], which might be transported directly into the 753 blood, followed by phase II metabolized for urinary excretion, or directly effluxed back into the 754 intestinal lumen for fecal excretion.

Vitamin D metabolism within the jejunum and ileum is largely driven by cytochrome P450 755 enzymes (CYPs), of which many have shown activity, as extensively reviewed elsewhere [227, 228]. 756 Hydroxylation of the 25th carbon occurs primarily by CYP27A1 and CYP2R1 expressed throughout 757 the small intestine [228]. The resulting 25-OH vitamin D metabolite could be released into the blood 758 759 stream, or metabolized further by CYP27B1, which performs 1a-hydroxylation to produce bioactive 1,25-dihydroxyvitamin D. CYP27B1 is expressed in the fetal small intestine at highly regulated 760 levels, which are measurable but considerably lower than in the colon [229]. CYP24 is believed to be 761 762 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 763 enzyme catalyzing the hydroxylation of the 4 β -position of 25-hydroxyvitamin D or 1,25-764

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

768 Vitamin E metabolism is largely driven by cytochrome P450s, whose upregulation may be at least partially driven following binding of tocotrienols to the steroid and xenobiotic (SXR) nuclear 769 770 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 K₁ (the initial step required for β -oxidation of the phytyl tail), is more highly expressed in the human 772 jejunum and ileum relative to the duodenum [232, 233]. Rodent studies suggest that the jejunum is 773 774 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 tocopherol metabolism by 70% [203]. Similarly, oral feeding of y-tocopherol or a mixture of 776 tocotrienols (including γ -tocotrienol) to rats resulted in γ -CEHC in the jejunum 3 h afterward [234]. 777 Importantly, jejunal y-CEHC concentration was significantly diminished when the CYP4F inhibitor 778 779 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 previous reports of limited CYP4F2 activity toward α-tocopherol [235]. CYP4F11, expressed in the 781 same location, can also catalyze ω-hydroxylation of vitamin K [236]. β-Oxidation may continue in 782 783 the intestine or in other tissues as long as the aliphatic chain contains at least 5 carbons. The jejunum and ileum likely resorb α -tocopherol metabolites produced in the liver and released into bile (e.g. α -784 785 13'-hydroxytocopherol, α -13'-carboxytocopherol, etc.), although this hasn't been tested. The antiinflammatory bioactivity of these vitamin E metabolites has recently been reviewed in great detail 786 787 [54]. In summary, they inhibit 5-lipoxygenase, cycloxygenases 1 and 2, and reduce nitric oxide production in *in vitro* models. It has also been speculated that the dietary isoforms of vitamin E may 788

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

Following enterocyte uptake of vitamin K₁, a portion of the administered dose can have the 791 792 phytol tail cleaved to produce vitamin K₃, followed by prenylation catalyzed by the enzyme UbiA 793 prenyltransferase domain-containing 1 (UBIAD1/TERE1) to produce bioactive vitamin K₂ [213, 237] (Fig. 9). Insufficient evidence is available to determine if UBIAD1/TERE1 is the only enzyme 794 795 involved in this two-step conversion to K₂, and the relative proportion of conversion occurring in the intestine vs. other tissues [55, 238]. However, it is known that a murine knockout of UBIAD1 is 796 797 embryonically lethal [239], highlighting the potent bioactivity conferred by the vitamin K_2 metabolite, which is the primary isoform of vitamin K found in extra-hepatic tissues. For vitamin K_1 , 798 799 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, although anecdotal evidence suggests it is highly diminished [40]. 802

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

812

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

814 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 815 816 ingested dose is available for colonic or microbial metabolism. While certainly the bulk of FSV 817 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 818 uptake to this tissue (and subsequent metabolism), analogous to the mechanisms detailed in the 819 previous section. This hypothesis is supported by numerous in vitro studies, which directly apply 820 821 FSV to cultured colon tissues and assess uptake. Ex vivo evidence from the murine intestinal tract 822 has also demonstrated that incubation of the tissue with at least one isoform of each FSV resulted in 823 small, but measurable, quantities taken up by the colon [219].

824 Both vitamins A and D play key roles in colon health, largely mediated by the immune 825 system, as extensively reviewed [246]. The bioactive vitamin A metabolite retinoic acid is critical for 826 the adaptive and innate immune functions of the intestinal mucosa [247], and these biological 827 activities are equally relevant in the colon. Vitamin D appears to play a more active role in the health 828 of colonocytes and other colon cell types relative to the small intestine. Elimination of the receptor 829 for 1,25-dihydroxyvitamin D increases susceptibility to colitis via increased tight junction membrane 830 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 831 responses [248, 249]. The influence of FSV on immune function also has relevance to colorectal 832 833 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

839 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 840 intake alone, highlights the importance of better understanding the relation between host dietary 841 842 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 843 obtain vitamin K necessary for respiration [252]. This reliance was proposed to be the cause of lower 844 845 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 846 847 [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 855 as through enhanced or diminished growth of specific microbial species in the colon, as recently 856 857 reviewed in detail [253]. Importantly, some microbial species contain enzymes having the ability to 858 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 859 primary driver behind the conversion of saponins to sapogenins, and recent research suggests that 860 861 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 862 863 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].

867

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.

873

874 8.1 Oesophageal cancer

Limited metabolism of FSV and FSP is expected in the oral cavity and the oesophagus (see 875 section 3), thus the effects of oesophageal cancer are also expected to be limited. Some studies have 876 reported that individuals with some types of oesophageal cancer have lower circulating 877 concentrations of a-tocopherol [257] and retinol [258], compared to controls. Likewise, upper 878 gastrointestinal cancer (including both oesophageal and gastric cancer) subjects of East Asian 879 880 ancestry, but not those of European ancestry, had lower circulating 25-hydroxy-vitamin D 881 concentrations [259]. Although these differences could be due to altered metabolism of these FSV in 882 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. 883

884

885 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 889 gastric cancer in individuals of East Asian ancestry. Although these correlations are generally 890 interpreted by assuming that these FSV reduce the risk of developing gastric cancer, it can also be 891 892 hypothesized that this cancer leads to a lower absorption and/or a higher use of these vitamins by the 893 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 894 895 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 896 897 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 898 899 and metabolism of FSV and FSP, which would explain altered blood concentrations of the 900 corresponding metabolites in patients with gastric cancer.

901

902

8.3 Biliary atresia/cholangitis, cholestasis

903 Blockage of the bile duct, due either to congenital defects (i.e. atresia) or to autoimmune-904 induced damage (i.e. cholangitis/cirrhosis) limits enterohepatic circulation of compounds commonly 905 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 906 907 and/or untreated cases when liver disease accompanies biliary cholangitis, active FSV metabolite 908 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 909 these conditions, it would be expected that localized metabolism of these vitamins would be 910 911 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 912 913 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 liver (driven primarily by obesity) are characterized by hepatic steatosis, which impairs liver 923 924 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 acid synthesis pathway leads to increased metabolism by a secondary pathway involving CYP27A1, 929 930 the same enzyme that produces 25-hydroxyvitamin D [270]. Likewise, in a murine model of alcoholinduced hepatic steatosis, increased expression of hepatic CYP26A1 and CYP26B1, which convert 931 932 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 were also simultaneously depleted. Thus, we would expect increased enterohepatic recycling of 934 vitamin A and D metabolites, and increased concentrations in the intestinal lumen of these 935 936 metabolites in patients with fatty liver. The change in the composition of bile acids released may also influence microbiota composition/abundance, and thus FSV and FSP metabolism in the distal small 937 938 intestine and colon [270]. Increased plasma concentrations of the oxidized vitamin E metabolite α - tocopheryl quinone have also been reported in human subjects with non-alcoholic fatty liver disease[272], with a fraction likely released into the bile.

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

949

950 8.5 Cholestatic liver diseases, cholestasis, chronic liver disease

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

958

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

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

963 chronic pancreatitis patients have significantly lower blood carotenoid concentrations, relative to964 healthy controls [279][280].

Shwachman-Diamond syndrome, a rare inherited disorder diagnosed in childhood and characterized by pancreatic insufficiency, severely limits lipid and FSV / FSP absorption [281]. Treatment commonly includes pancreatic enzyme replacement therapy and micronutrient supplementation. However, data in children shows that this treatment still leaves half of them 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 would be expected to reduce FSV and FSP absorption and localized metabolism, again leaving 976 977 higher concentrations in the intestinal lumen for microbial metabolism. Surprisingly, only a few FSV and FSP studies have been performed in this population. A case-control study in children reported 978 979 reduced circulating concentrations of the metabolite status markers of vitamin A and D in a majority of those newly diagnosed with celiac disease [283]. Nevertheless, mixed results have been reported 980 981 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

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

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

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

999

1000 8.9 Intestinal failure

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

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

1013 which would be expected to be metabolized by the liver and excreted back into the intestinal lumen. 1014 In contrast, more contemporary formulations contain fish oil (rich in omega-3 long chain 1015 polyunsaturated fatty acids), α -tocopherol and less phytosterols [294]. Like the other diseases 1016 mentioned above, a higher percentage of FSV and FSP remaining in the gastrointestinal tract would 1017 permit greater colonic metabolism.

1018

1019 8.10 Familial Hypobetalipoproteinemia

1020 Familial hypobetalipoproteinemia is a genetic disease that may be due to 1) a defect in the 1021 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 1022 1023 class II) [295]. We focus here on class I because this category would be expected to modify the 1024 production of FSV and FSP metabolites in the intestine. It is known that individuals with this disease 1025 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 1026 1027 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 1028 1029 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 1030 1031 further study enterocyte FSV and FSP metabolism.

1032

1033 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.

1045

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 1047 1048 diseases, e.g. stomach or colon cancer, but also to treat obesity and the diseases associated with it, 1049 e.g. bariatric surgery. These surgical procedures can result in the removal of certain parts of the 1050 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 1051 1052 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 1053 metabolism of certain FSV / FSP and consequently the production of metabolites. Surgical 1054 interventions might require correcting the FSV [298-301] or carotenoid [302-304] status of patients. 1055 It is also interesting for the physiologist to better understand the key factors that modulate the 1056 1057 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 1058 consequences of these interventions based on our knowledge of metabolism in the healthy digestive 1059 1060 tract.

1061

1062 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].

1070 Patients who undergo bariatric surgery are assumed to be at greater risk of developing FSV 1071 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 1072 [301]. Nevertheless, it is difficult to conclude that this is due to a lower absorption efficiency of the 1073 1074 FSV of interest for two main reasons. First, most subjects who have undergone bariatric surgery are 1075 supplemented with vitamins and minerals following the operation to compensate for anticipated 1076 deficiencies [311]. Thus, blood concentrations of vitamin E can be higher after Roux-en-Y gastric 1077 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 1078 1079 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 1080 1081 vitamin status after surgery, which is modulated by absorption but also by the vitamin intake and 1082 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 1083 first study, [313] cholecalciferol absorption was decreased by 25% after the surgery. In the second 1084 1085 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 1086 following surgery [314]. Thus, bariatric surgery appears to decrease FSV / FSP absorption, but a 1087

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.

1091

1092 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.

1100

1101 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 lowerabsorption of other FSV and FSP after GI tract surgery.

- 1114
- 1115

10. Effect of xenobiotics that impair lipid absorption

Many strategies have been developed to combat obesity. Among these are administrations of 1116 compounds and drugs that decrease lipid absorption. An obvious question is the impact on FSV 1117 absorption and numerous studies have been carried out to address it. Concerning olestra, a zero-1118 calorie fat replacement manufactured by Proctor & Gamble under the name olean, it has been shown 1119 1120 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 1121 1122 remains approved for use in snack foods in the USA. Interestingly, olestra has recently been shown 1123 to decrease plasma concentrations of lipid-soluble persistent organic pollutants, following 6 months 1124 of randomized, controlled administration, highlighting both the risks and benefits of consuming compounds that interfere with the absorption of very hydrophobic molecules [319]. 1125

Mineral oil, an indigestible lipid, has been used for many decades as a remedy to treat 1126 constipation, and as a placebo in some randomized, controlled trials. As long as the mineral oil is 1127 administered between meals, the impact on FSV / FSP status is limited [320, 321]. In the best 1128 controlled study to date, children treated for up to 4 months with mineral oil had a drop in serum β-1129 1130 carotene, but an increase in retinol (and no change in α -tocopherol) during the study period [322]. It 1131 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. 1132 1133 encapsulation and nanoemulsion), in vitro evidence suggests that mineral oil negatively impacts 1134 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 nonalcoholic 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.

1147

1148 Conclusions

1149 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 1150 1151 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 1152 1153 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 1154 1155 paired with multi-omic integration (e.g. considering genetic, epigenetic, proteomic, exposomic, and 1156 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 1157 various bioactivities. 1158

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Table 1. Vitamins and phytochemicals with computed octanol-water partition coefficients (log₁₀ P >
5).

		Computed
Compound	Compound Class	$\log_{10} \mathbf{P}^1$
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 K2 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	
1166				-
1167	¹ Value computed by XLOGP3 version 3.0 [326].			
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1169 **Figure legends**

1170

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.

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Figure 2: Phytosterol derivatives and possible mechanisms of formation. Left panel, 1178 1179 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 1180 thermal treatment of lipid food (e.g. phytosterol-enriched margarine), phytosterols acylated by fatty 1181 acids are more vulnerable to oxidation when the unsaturation degree of the acyl chain increases. 1182 Autoxidation of a PUFA chain leads to highly reactive peroxyl radicals that efficiently oxidize the 1183 1184 nearby phytosterol moiety. Middle panel, biochemical mechanisms that can happen in the stomach 1185 and intestine. Right panel, no data available on the metabolism of phytosterols by the microbiota.

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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.

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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 ratelimiting 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.

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Figure 5: Prooxidant effect of polyunsaturated fatty acids on FSV and FSP. Upper panel: Co-1200 oxidation of polyunsaturated fatty acids (LH) and antioxidants during iron-induced lipid peroxidation 1201 [145-148]. LH = polyunsaturated fatty acids; AO1 = water-soluble antioxidant, e.g. phenolic 1202 compounds, vitamin C, short-chain apocarotenoids; AO2 = fat-soluble antioxidant, e.g. vitamin E, 1203 1204 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 1205 compartment where dietary iron and traces of hydroperoxides from lipid food can initiate PUFA 1206 peroxidation under vigorous mixing, favorable acidic conditions and non-limiting O₂ concentrations. 1207 1208

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

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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].

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Figure 8: Vitamin E derivatives and possible mechanisms of formation. Left panel, 1224 physicochemical mechanisms with the example of interplay between α -tocopherol and other dietary 1225 antioxidants [329-334]. α -Tocopherol regeneration by other antioxidants is important to prolong 1226 tocopherol activity and avoid tocopherol-mediated lipid peroxidation within lipid-rich phases. This 1227 1228 interplay between tocopherol and other dietary antioxidants may also apply with vitamin K. Vitamin 1229 K itself (through its reduced form) inhibits lipid peroxidation. Middle panel, biochemical 1230 mechanisms for the metabolism of vitamin E in the liver. Right panel, no data available on the metabolism of vitamin E by the microbiota. 1231

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Figure 9: Vitamin K derivatives and possible mechanisms of formation. Left panel, 1233 physicochemical mechanisms with the example of the possible interplay between menaguinone MQ-1234 7 (R = hepta-isoprenyl chain) and carotenoids in the presence of heme or non-heme iron [335]. 1235 Carotenoids are spared in the process. MQ-7, naturally present in cocktails of bacterial carotenoids, 1236 1237 is insensitive to iron-induced autoxidation and a poor antioxidant in the inhibition of iron-induced 1238 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 1239 1240 mechanisms for the metabolism of phylloquinone in the small intestine. Right panel, vitamin K metabolite produced by the microbiota. 1241

1243 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 1244 assumed to distribute between the phases / structures present in the gastric lumen (see Fig. 3) and 1245 secreted into the duodenum through the pylorus plus additional phases / structures coming from 1246 biliary secretion and the digestion of dietary lipids, i.e. mainly triglycerides and phospholipids. P: 1247 parent molecule; **D**: derivative; **P***: parent molecule previously absorbed, then secreted in the bile; 1248 **D***: derivative previously absorbed, or resulting from metabolism of **P**, then secreted in the bile; 1249 filled arrows: known transfer routes; doted arrows: some hypothesized transfer routes. 1250

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