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

3

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24 **Abstract**

25

26 Consumption of diets rich in fruits and vegetables, which provide some fat-soluble vitamins  
27 and many phytochemicals, is associated with a lower risk of developing certain degenerative  
28 diseases. It is well accepted that not only the parent compounds, but also their derivatives formed  
29 upon enzymatic or nonenzymatic transformations, can produce protective biological effects. These  
30 derivatives can be formed during food storage, processing, or cooking. They can also be formed in  
31 the lumen of the upper digestive tract during digestion, or via metabolism by microbiota in the colon.  
32 This review compiles the known metabolites of fat-soluble vitamins and fat-soluble phytochemicals  
33 (FSV and FSP) that have been identified in food and in the human digestive tract, or could  
34 potentially be present based on the known reactivity of the parent compounds in normal or  
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  
39 absorption, and probing their putative health effects, much research remains to be conducted to  
40 understand and capitalize on the potential of these molecules to preserve health.

41

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

## 43 **Introduction**

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

59           The biological roles of FSV metabolites, e.g. retinoic acid and 1,25-dihydroxycholecalciferol  
60 on maintaining health are well established. In contrast, the biological roles of FSP metabolites are  
61 much less well known, although their potential beneficial health effects are supported by the fact that  
62 some are antioxidants [17, 18], have anti-inflammatory effects [19-22], modulate gene expression  
63 [23, 24] or affect the epigenome [25-27]. It is also likely that some of these compounds exert several  
64 effects simultaneously, e.g. lycopene which acts with different molecular and cellular mechanisms  
65 [28].

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

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

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

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

97

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

99 Because FSV and FSP are closely related to lipids, there is some overlap in the process of  
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  
102 NPC1L1, facilitate the absorption of some FSV, e.g., vitamins D and E, and that of some FSP, e.g.  
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  
108 amphipathic and polar metabolites, e.g. some derivatives of FSV and FSP, are released directly into  
109 the blood, and travel from the portal vein to the liver for “first pass” metabolism. This often includes  
110 oxidation by cytochrome P450 enzymes, regardless of the compound in question. Routes of  
111 excretion, including release of the parent FSV and FSP, as well as their phase I and phase II  
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<sub>1</sub>) this occurs in the liver, thanks to  $\alpha$ -

118 tocopherol transfer protein [50]. In contrast, it is assumed that most FSP are non-specifically bound  
119 to unknown proteins, in order to remain soluble in the cytosol. Another important distinction is the  
120 regulation of active vitamin concentrations in the blood stream following a meal. Vitamins A, D,  
121 and K are primarily found in foods as non-active “provitamin” forms, which require additional  
122 transformation via metabolism to produce the active forms. Recent evidence suggests that dietary  
123 forms of vitamin E may also serve as provitamins for some functions [51]. This additional step  
124 permits great fluctuations in circulating concentrations of the provitamin forms following a meal,  
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  
127 dosing over a given window of time to reach and maintain a concentration within the biological  
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  
133 nuclear receptors [53, 54]. Vitamin K has a clear role in converting glutamate into  $\gamma$ -  
134 carboxyglutamate – a required step in the blood coagulation cascade, which may also be important  
135 in bone mineralization [55]. Furthermore, a total of 17 vitamin K-dependent proteins have been  
136 identified to date and involved in bone and cardiovascular health [56]. In contrast, diverse  
137 mechanism(s) of action are proposed for many FSP metabolites, e.g. direct antioxidant effects,  
138 regulation of gene expression, effect on inflammation.

139

## 140 **2. Derivatives of FSV and FSP found in foods**

141 Upon storage food is subject to various physical and chemical agents, e.g. UV radiation or  
142 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  
144 or industrial processing may enzymatically or nonenzymatically, i.e. physically or chemically,  
145 produce derivatives of FSV and FSP. Chopping or grinding food for preparation can cleave cell  
146 walls and allow enzymes to come into contact with substrates previously located in different cells  
147 or sub-cellular compartments. Mixing or blending can accelerate this process and also introduce  
148 dioxygen, which can serve as an essential cofactor for many enzymes, as well as a chemical  
149 oxidant. Heat can also rupture cell tissue and increase the reaction rate for most chemical  
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  
152 result in intakes of FSV and FSP metabolites produced by microbial species, the animal, or the  
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  
158 that the same metabolites that play a biological role in visual function and in gene expression in  
159 humans, namely 11-*cis*-retinal and retinoic acid respectively, are synthesized from the pro-vitamin  
160 A carotenoids by the main animals that we eat, i.e. beef, pork and chicken. These metabolites are  
161 therefore theoretically present in the meat produced from these animals. Nevertheless, 11-*cis*-retinal  
162 is present in the eyes, which are generally not consumed, and retinoic acid is present in very low  
163 concentrations in tissues. The main form of vitamin A present in food from farm animals is  
164 primarily retinyl palmitate, which can be present in very high, even toxic, concentrations in the  
165 liver of certain animals (e.g. polar bears) [57]. To our knowledge, there is no data on the human  
166 consumption of endogenously synthesized vitamin E metabolites present in tissues from livestock.  
167 Vitamin E is intentionally supplemented to livestock to reduce lipid peroxidation in meat products



168 post-slaughter [58]. The resulting metabolites are presumed to be regenerated via intracellular  
169 reducing reagents [58], although to the best of our knowledge this has not been studied directly.  
170 Vitamin D, as either vitamin D<sub>2</sub> or D<sub>3</sub> isoforms in foods, undergoes hydroxylation in the  
171 mammalian and avian liver to produce 25-hydroxyvitamin D<sub>2</sub> and D<sub>3</sub>, respectively [59, 60]. These  
172 25-hydroxy metabolites are found in beef, pork, chicken, and eggs, [61, 62], as well as in milk,  
173 cream, and butter [63], in concentrations on the same order of magnitude as the vitamin D<sub>2</sub> and D<sub>3</sub>  
174 precursors. Trace quantities of 25-hydroxyvitamin D<sub>3</sub> have also been reported in salmon, tilapia,  
175 and mahi-mahi [61]. Like most sterols, 25-hydroxyvitamin D is robust to various methods of  
176 cooking [64]. Although not systematically measured in the food supply, the most potent vitamin D  
177 metabolite, 1,25-dihydroxyvitamin D, is especially rich in beef kidney and liver, with  
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  
180 is present in food either as vitamin K<sub>1</sub> (phylloquinone) or as vitamin K<sub>2</sub> (menaquinones).  
181 Menaquinones are actually a cluster of K<sub>2</sub> isoforms produced either by mammalian metabolism of  
182 vitamin K<sub>1</sub> or by bacteria such as the lactic acid bacteria (the most common form of bacteria in  
183 fermented foods). Menaquinones can have 5-10 isoprenyl units and are found in the human colon  
184 (see section 7), as well as in food sources (e.g. buttermilk, whole-fat milk, various cheeses,  
185 sauerkraut) [68]. The most common menaquinone, menaquinone-4 (MK-4), is a mammalian  
186 metabolite of phylloquinone (vitamin K<sub>1</sub>), 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,  
188 like sauerkraut and natto [70, 71]. Vitamin K<sub>1</sub> in plant oils is robust to high heat processing  
189 conditions, but sensitive to degradation by daylight [72]. Chemically, it has no clear structural  
190 vulnerabilities to autoxidation or hydrolysis.

191 Provitamin A carotenoids (i.e. mainly  $\beta$ -carotene,  $\alpha$ -carotene, and  $\beta$ -cryptoxanthin) as well as  
192 xanthophyll carotenoids (e.g. lutein and zeaxanthin) are consumed by grazing beef, dairy cattle and

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

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

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

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  
220 extraction or cooking process), or UV-light, and in fried products (i.e. potato chips, French fries)  
221 [87, 89]. They are also found in coffee silverskin, a roasting byproduct [90]. Food products  
222 “enriched” with phytosterols, including heat-treated milk products [86, 91] and dark chocolate [92],  
223 have also been reported to contain oxidized metabolites. Although it has been shown that thermal  
224 treatment of foods containing phytosterols acylated by a PUFA chain leads to phytosterol oxidation  
225 [93] (**Fig. 2**), co-heating of phytosterols with a saturated lipid induced a greater concentration of  
226 oxidized metabolites than with unsaturated lipid [94]. Phytostanols, another type of plant sterols,  
227 are largely protected from oxidation, likely due to the absence of a double bond on the B-ring [89,  
228 94].

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

236

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

238 The metabolism of FSV and FSP likely starts in the mouth as chewing produces mechanical  
239 grinding and partial breakdown of food matrices. Indeed, this process disrupts a fraction of the plant  
240 cell walls, and disrupts intracellular organelles in which the FSV and FSP are located. This puts FSV  
241 and FSP into contact with enzymes and other molecules located in other organelles and tissues for  
242 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  
244 (e.g. ferrous iron, dioxygen). Saliva also comes into contact with food in the oral cavity, and  
245 provides food lubrication, antimicrobial defense, assistance with taste and early digestion [96].  
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 alpha-  
248 amylase) and macro- and micronutrients and phytochemicals. Salivary lactoperoxidase and  
249 myeloperoxidase catalyze the reaction of hydrogen peroxide with thiocyanate to produce the highly  
250 reactive hypothiocyanous acid, which has antimicrobial activity and can also react with FSV and  
251 FSP. Activated phagocytes in saliva can also release a series of toxic oxidants [99, 100] which could  
252 oxidize redox-sensitive molecules. Theoretically, the hydrophobic parent molecules of FSV and FSP  
253 remain within lipid phases through the oral cavity, which can confer protection (if the lipids are not  
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  
256 FSV and FSP and their derivatives will depend on the proportion of prooxidants (e.g. ferrous iron,  
257 hydrogen peroxide, hypothiocyanous acid) and oxidation-sensitive nutrients (e.g. polyunsaturated  
258 fatty acids) to antioxidants (e.g. polyphenols, carotenoids, vitamin C), simultaneously present in the  
259 mouth. The risk of oxidation also depends on the location of the molecules of interest in the different  
260 phases, which depends both on hydrophobicity and on their physical state. For example, it is  
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.

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

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

272

#### 273 **4. Metabolism of FSV and FSP in the stomach**

274 The stomach of mono-gastric animals could have two main roles on the digestion of FSV and  
275 FSP. The first, for which we have the most data is to amplify the digestion of food [105]. This  
276 process leads to the release of FSV and FSP from their matrices, transfer to the lipid phase of the  
277 digestate, and possible chemical transformations dependent upon physicochemical structures and  
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 O<sub>2</sub> [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  
281 conditions can promote varied chemical reactions ranging from association, e.g. binding of the  
282 water-soluble carotenoid crocin to starch [110], to chemical modifications, e.g. autoxidation of  
283 carotenoids [108, 109, 111, 112].

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

289

##### 290 ***4.1 Distribution of FSV and FSP between the different matrices coexisting in the stomach***

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

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

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

#### 329 330 **4.2 Formation of FSV and FSP derivatives in the stomach lumen**

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

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

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

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

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



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

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

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

393 (rather low, compared to *in vivo* conditions), the stability of lycopene, the carotenoid most sensitive  
394 to oxidation, was extremely high in tomato (~ 92% recovery) [136]. This stability was probably due  
395 to the fact that lycopene was protected within the food matrix. Indeed, another study showed that  $\beta$ -  
396 carotene and retinyl-palmitate standards, i.e. pure molecules, were strongly degraded at the end of  
397 the gastric phase, while  $\beta$ -carotene was largely spared when provided by carrot juice [137]. In  
398 addition,  $\beta$ -carotene and violaxanthin provided by raw spinach were highly degraded, suggesting  
399 that not all food matrices provide the same level of carotenoid protection. By contrast, lutein was  
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  
402 model (TIM-1, assumed to better mimic *in vivo* conditions than static *in vitro* models) showed that  
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.  
408 Furthermore, these results highlight the importance of accurately reproducing gastric  
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  
411 containing 20 - 30  $\mu\text{g}$  of total iron [140]. Dietary iron is a potential initiator of oxidative processes  
412 called autoxidation (non-enzymatic oxidation by  $\text{O}_2$ ). Oxidizable (electron-rich) FSV and FSP,  
413 such as vitamin E and carotenoids, are intrinsically vulnerable to autoxidation in the stomach  
414 following an iron-rich meal. Sy et al. [109] studied the autoxidation of pure  $\beta$ -carotene at pH 4.0,  
415 corresponding to the mid-digestion of meals rich in fruits and vegetables [106]. Under these  
416 conditions,  $\text{Fe}^{2+}$  and metmyoglobin induced the isomerization and oxidation of  $\beta$ -carotene to  
417 epoxides and cleavage products of various chain lengths [109] (**Fig. 4**). *In vitro* work by Kopec et

418 al. [112] with the inclusion of gastric enzymes found more attenuated effects of gastric digestion on  
419  $\beta$ -carotene, with a ~20% drop from the initial dose observed when  $\beta$ -carotene was digested alone,  
420 and a ~50-60% drop when digested with metmyoglobin or  $\text{Fe}^{2+}$ . In the same study, no statistically  
421 significant drop in concentrations of lutein or lycopene during the gastric phase when digested  
422 alone, or with the addition of metmyoglobin or  $\text{Fe}^{2+}$ . *In vivo*, both increased time of sampling and  
423 the presence of  $\text{FeSO}_4$  consumed with a lycopene-rich beverage resulted in less lycopene in the  
424 stomach than the lycopene-rich beverage alone [108]. Free retinol itself is also known to be highly  
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  
427 of prooxidant agents.

428 In addition to iron, all lipid-rich foods contain traces of lipid hydroperoxides (LOOH) with  
429 peroxide values typically in the range of 1 – 5  $\mu\text{mol/g}$  [142, 143]. The Fenton reaction between  $\text{Fe}^{\text{II}}$   
430 and LOOH is a source of highly reactive oxyl radicals ( $\text{LO}^\bullet$ ), while heme- $\text{Fe}^{\text{III}}$  reacting with  
431 hydroperoxides also leads to hypervalent iron forms (heme- $\text{Fe}^{\text{IV}}$ ) that are efficient initiators of lipid  
432 peroxidation through the propagating lipid peroxy radicals ( $\text{LOO}^\bullet$ ) [144] (**Fig. 5**). The prooxidant  
433 character of a meal rich in iron and oxidizable (polyunsaturated) lipids may be mitigated by plant  
434 antioxidants. Hydrophilic antioxidants, such as phenolic compounds, either bind non-heme iron  
435 under inert complexes or reduce hypervalent heme iron, while lipophilic antioxidants, such as  
436 vitamin E and carotenoids, reduce the lipid oxyl and peroxy radicals, or trap them as stabilized  
437 radical adducts. Under model gastric conditions using micelles and emulsions, this chemistry is  
438 well-established [145-150], and shows that the co-oxidation of electron-rich FSV and FSP with  
439 polyunsaturated lipids is much faster than their direct autoxidation. For instance, both  $\alpha$ -tocopherol  
440 and  $\beta$ -carotene are rapidly consumed via co-oxidation when incubated with heated turkey muscle in  
441 a simulated gastric fluid at pH 3, 37°C., but protected upon addition of red wine polyphenols [107,  
442 151]. It is also noteworthy that apo-carotenoids (possibly present in plant food or formed in the

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

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

467           Regeneration of the amphiphilic antioxidant  $\alpha$ -tocopherol (TocOH) from its oxidized forms is  
468 key to prolonging its lipid-protecting activity while avoiding the prooxidant activity of the  
469 corresponding aryloxy radical (TocO<sup>•</sup>) (**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<sup>•</sup> 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.**  
473 **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,  
475 alcohol seems to lower the stability of some FSV and FSP in the gastric lumen, as it was observed  
476 that alcohol consumers had significantly lower antral mucosal and gastric juice concentrations of  $\beta$ -  
477 carotene, compared to non-consumers [122]. The physicochemical and enzymatic conditions in the  
478 gastric compartment can also be altered under certain pathological states or during aging, which is  
479 associated with a higher prevalence of atrophic gastritis [126], or during infection by *Helicobacter*  
480 *pylori*. For example, it has been shown that infection with *H. pylori* decreases the concentration of  $\beta$ -  
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  $\beta$ -carotene concentration in gastric juice  
483 [122] or on the (*E*)-(*Z*) isomerization of  $\beta$ -carotene during absorption were observed.

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

492

#### 493 ***4.3 Potential uptake of FSV and FSP and their derivatives by the gastric mucosa***

494 Some FSV and FSP, i.e.  $\alpha$ -tocopherol and  $\beta$ -carotene [122], as well as other carotenoids  
495 (lutein, zeaxanthin and  $\beta$ -cryptoxanthin) [160], have been found in the gastric mucosa. Moreover,  
496 in the same study it was reported that the concentration of certain carotenoids was lower in  
497 cancerous gastric mucosal tissues than in non-cancerous ones. Although it is likely that a  
498 significant fraction of the compounds present in the gastric mucosa are derived from the blood  
499 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.  
507 Polyunsaturated fatty acids (PUFA) are the main class of oxidizable essential fatty acids. PUFA  
508 oxidation lowers the nutritional quality of the meal, not only through loss of essential lipids but also  
509 by the alteration of dietary proteins [161], which are vulnerable to electrophilic and/or oxidizing  
510 lipid peroxidation products (e.g. lipid hydroperoxides, malondialdehyde, 4-hydroxy-2-alkenals).  
511 Moreover, the delivery of these potentially toxic products to intestinal cells or their incorporation  
512 into the circulating lipoproteins may be risk factors in atherosclerosis [98] and colon cancer [162].

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

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

531 After being pre-digested in the stomach, the food, mixed with the digestive juices secreted in  
532 the mouth and in the stomach, is poured into the duodenum via the pylorus. The physicochemical  
533 and enzymatic conditions then radically change. The partial pressure of oxygen decreases [171], the  
534 pH increases to about 6.5 [172, 173], and bile and pancreatic secretions arrive bringing new  
535 molecules and enzymes, e.g. bile salts, pancreatic lipase, that can induce chemical and biochemical  
536 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***

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

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

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

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



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

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

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

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

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

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

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

605

## 606 *5.2 Metabolism of FSV and FSP in the upper intestinal lumen and identified metabolites.*

607 The most easily identified duodenal products of FSV / FSP metabolism are those arising from  
608 the hydrolysis of fatty acid esters, e.g. retinyl esters and xanthophyll esters. Three pancreatic  
609 enzymes are able to hydrolyse these esters. Carboxyl ester lipase, also called bile salt-stimulated  
610 lipase, which is able to hydrolyse the esters of xanthophylls [186] and  $\alpha$ -tocopherol [179], but also  
611 pancreatic lipase and pancreatic lipase-related protein 2, which are able to hydrolyse retinyl esters  
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.  
614 This hydrolysis is important for the bioavailability of these compounds, assumed to be effectively  
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  
617 the combined influence of lipases and other enzymes present in pancreatic secretions, as well as  
618 interactions with other co-consumed species (e.g. iron). Regardless of the absence or presence of  
619 digestive enzymes (i.e. mimicking chemical and biochemical degradation, respectively), *in vitro*  
620 digestion experiments revealed no significant change in lutein or  $\beta$ -carotene as digestion progressed  
621 from the gastric to the duodenal phase [112]. However, in the absence of enzymes, a ~13% loss was  
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  $\beta$ -carotene  
625 concentrations, causing a ~25% loss between the gastric and duodenal compartments in the absence  
626 of enzymes, and a ~35% loss in the presence of enzymes [112]. Follow-up studies in healthy males  
627 with isotopically labelled  $\beta$ -carotene demonstrated the presence of labelled  $\beta$ -apo-carotenals  
628 (aldehyde catabolites) in the oral dose provided [111]. Increased concentrations of most  $\beta$ -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,  $\beta$ -apo-carotenals  
631 remained ~1000 times less abundant than  $\beta$ -carotene in the same samples, and were not detected in  
632 the newly-absorbed lyophilic fraction of blood (nor the plasma itself) afterward. Thus, the data does  
633 not support  $\beta$ -carotene conversion to apo-products in the enterocyte. However,  $\beta$ -apo-13-carotenone  
634 and  $\beta$ -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  $\beta$ -apo-carotenals in the blood stream, this activity most  
636 plausibly could occur in enterocytes.

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

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

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

### 656

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

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

666 involved in the absorption and efflux of vitamin D [47]. ABCB1 has also been shown to participate  
667 in the efflux of vitamins D and K [48, 191]; SR-BI in the uptake of phytoene, phytofluene [192] and  
668 vitamin K<sub>1</sub> [193]; CD36 in the uptake of vitamin E [194] and vitamin K1 [193]; ABCG1 in the efflux  
669 of vitamin E [195]. Overall, these proteins are able to interact with the uptake of FSV and FSP  
670 having very different structures. This observation suggests that it is the more homogenous lipid  
671 components of mixed micelles that are recognized by these transporter proteins. Thus, FSV and FSP  
672 incorporated into these micelles are inadvertently driven to areas of the enterocyte membrane, e.g.  
673 lipid rafts, in which they are more easily solubilized. To our knowledge, there is no data on specific  
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*

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

685 Concerning vitamin D, 24 h after intravenous administration of the metabolite 25-  
686 hydroxyvitamin D<sub>3</sub> in humans, ~30% of the radioactivity could be measured in the duodenum, thus  
687 demonstrating biliary secretion. Moreover, ~85% of this secreted dose was reabsorbed [201, 202]  
688 [203, 204]. A series of experiments by Avioli et al. [205], supported by follow-up studies [206, 207],  
689 shows that the inactive phase II metabolites comprise the bulk of the radioactivity recovered in bile  
690 following an intravenous injection. These products were recently confirmed to be sulfates and

691 glucuronides of 25-hydroxyvitamin D<sub>3</sub> [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<sub>3</sub> may  
694 provide a source of vitamin D for intestinal cells.

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

706 Intravenous administration of either <sup>14</sup>C-labeled vitamin K<sub>1</sub>, K<sub>2</sub>, or K<sub>3</sub>, to rodents resulted in  
707 8.5, 74 and 37% of the isotope in bile after 12 h of collection, respectively [212], demonstrating a  
708 high propensity for biliary elimination. An elegant series of cannulation experiments in rodents by  
709 Hirota et al. [213] reported no secretion of labeled phylloquinone or its menaquinone-4 metabolite in  
710 bile following controlled dosing, implying that the excreted biliary dose is exclusively comprised of  
711 metabolites. Finally, humans intravenously injected with isotopically labeled vitamin K<sub>1</sub> secreted  
712 slightly more polar labeled metabolites (relative to the parent compound) into the bile duct [214].  
713 However, the structures were not identified and the possibility for these metabolites to be taken up  
714 from the small intestine is unknown.

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

720 Very little data is available regarding the potential enterohepatic cycling of FSP. Regarding  
721 phytosterols, we hypothesize that since their initial absorption is very low ( $\leq 2\%$  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- $\beta$ -OH-campesterol, 7- $\beta$ -OH-sitosterol) has  
724 been reported following a second meal (after initial phytosterol dosing). However, it's not clear if  
725 these oxyphytosterol metabolites were produced in intestinal cells, so that their presence in serum  
726 reflects delayed absorption, or whether true enterohepatic recycling occurred [216]. Two studies in  
727 humans and rabbits suggest that the chlorophyll metabolites pheophytin and pheophorbide can  
728 undergo enterohepatic recycling [217]. Finally, to the best of our knowledge, the enterohepatic  
729 recycling of non-provitamin A metabolites of carotenoids, e.g. lycopene and lutein, has not been  
730 explored.

731

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

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

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  
742 of retinyl esters) is also absorbed throughout the jejunum, with less uptake in the ileum [219]. It can  
743 be transported within the cells via cellular retinol binding protein [220], and reduced to retinal via  
744 aldehyde dehydrogenases like retinol dehydrogenase 11 (RDH11) [220]. Retinal is further converted  
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  
749 attack [223, 224]. It also stimulates gap junction growth and tight junction formation between  
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.

755 Vitamin D metabolism within the jejunum and ileum is largely driven by cytochrome P450  
756 enzymes (CYPs), of which many have shown activity, as extensively reviewed elsewhere [227, 228].  
757 Hydroxylation of the 25<sup>th</sup> carbon occurs primarily by CYP27A1 and CYP2R1 expressed throughout  
758 the small intestine [228]. The resulting 25-OH vitamin D metabolite could be released into the blood  
759 stream, or metabolized further by CYP27B1, which performs 1 $\alpha$ -hydroxylation to produce bioactive  
760 1,25-dihydroxyvitamin D. CYP27B1 is expressed in the fetal small intestine at highly regulated  
761 levels, which are measurable but considerably lower than in the colon [229]. CYP24 is believed to be  
762 the primary enzyme responsible for inactivation of 1,25-dihydroxyvitamin D via hydroxylation of  
763 the 23rd or 24th carbon, producing metabolites with ~10 times less bioactivity [228]. CYP3A4, an  
764 enzyme catalyzing the hydroxylation of the 4 $\beta$ -position of 25-hydroxyvitamin D or 1,25-



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

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

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

791         Following enterocyte uptake of vitamin K<sub>1</sub>, a portion of the administered dose can have the  
792 phytol tail cleaved to produce vitamin K<sub>3</sub>, followed by prenylation catalyzed by the enzyme UbiA  
793 prenyltransferase domain-containing 1 (UBIAD1/TERE1) to produce bioactive vitamin K<sub>2</sub> [213,  
794 237] (**Fig. 9**). Insufficient evidence is available to determine if UBIAD1/TERE1 is the only enzyme  
795 involved in this two-step conversion to K<sub>2</sub>, and the relative proportion of conversion occurring in the  
796 intestine vs. other tissues [55, 238]. However, it is known that a murine knockout of UBIAD1 is  
797 embryonically lethal [239], highlighting the potent bioactivity conferred by the vitamin K<sub>2</sub>  
798 metabolite, which is the primary isoform of vitamin K found in extra-hepatic tissues. For vitamin K<sub>1</sub>,  
799 the metabolites remaining after  $\beta$ -oxidation in the enterocyte (as discussed above) can be  
800 glucuronidated for urinary excretion [40]. The  $\gamma$ -carboxylation activity (the primary role of vitamin  
801 K in blood clotting) of these phase I and II metabolites has not been completely characterized,  
802 although anecdotal evidence suggests it is highly diminished [40].

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

812

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

814           Because only a portion of the dietary FSV and FSP (and likely their derivatives), are absorbed  
815 in the small intestine, and because enterohepatic circulation occurs, a substantial percentage of the  
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  
818 transporters NPC1L1, CD-36, and SR-BI [244, 245]. These transporters could permit localized FSV  
819 uptake to this tissue (and subsequent metabolism), analogous to the mechanisms detailed in the  
820 previous section. This hypothesis is supported by numerous *in vitro* studies, which directly apply  
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  
831 the intestinal mucosa, which in turn suppress production of cytokines associated with autoimmune  
832 responses [248, 249]. The influence of FSV on immune function also has relevance to colorectal  
833 cancer, as discussed in the following section.

834           Beyond maintenance of the host gastrointestinal barrier, recent research has revealed that the  
835 colon microbiome composition and abundance of specific species are correlated with, or directly  
836 influenced by, the intake of each of the FSV [246, 250-252]. These observations reflect the  
837 importance of FSV for the microbiota itself, and likely highlight an inability of many species to  
838 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  
840 species, or to elicit a pathogenic phenotype from otherwise innocuous species based upon dietary  
841 intake alone, highlights the importance of better understanding the relation between host dietary  
842 behavior and microflora growth. As an example, some microbial species have lost the ability to  
843 produce menaquinones, but data suggests they rely on neighboring species or dietary intakes to  
844 obtain vitamin K necessary for respiration [252]. This reliance was proposed to be the cause of lower  
845 cecal abundance of vitamin K-requiring species on a vitamin K-deficient diet, simultaneously  
846 permitting increased abundance of other non-vitamin K-dependent species in the same animals  
847 [252].

848           Unique to vitamin K, some menaquinone isoforms are synthesized by the colonic microflora.  
849 However, very little is known about their subsequent metabolism. *In vitro* culturing of human feces  
850 with labeled vitamins K<sub>1</sub>, K<sub>2</sub>, and K<sub>3</sub> demonstrated that the gut microflora was able to metabolize  
851 vitamin K<sub>3</sub> to produce bioactive vitamin K<sub>2</sub> (i.e. menaquinone 4), as well as menaquinones with  
852 longer chain lengths [252]. These results suggest the possibility that mammalian cleavage of vitamin  
853 K<sub>1</sub> in the small intestine provides a source of vitamin K<sub>3</sub> to be further metabolized to K<sub>2</sub> via the  
854 colonic microbiota. This K<sub>2</sub> could be used by colonic species directly and/or absorbed by the host.

855           Several FSP have been shown to influence colon health via host-derived mechanisms, as well  
856 as through enhanced or diminished growth of specific microbial species in the colon, as recently  
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  
859 thought to be more potent. For example, the microbiota of the colon is hypothesized to be the  
860 primary driver behind the conversion of saponins to sapogenins, and recent research suggests that  
861 sapogenins behave like prebiotics [254]. Likewise, murine studies have shown that phytosterols  
862 appear to rescue colon metabolism under conditions of colitis, alleviating symptoms and colon  
863 damage [255], which may be at least partially driven by changes in bile acid metabolism [256]. In

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

866

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

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

873

### 874 ***8.1 Oesophageal cancer***

875 Limited metabolism of FSV and FSP is expected in the oral cavity and the oesophagus (see  
876 **section 3**), thus the effects of oesophageal cancer are also expected to be limited. Some studies have  
877 reported that individuals with some types of oesophageal cancer have lower circulating  
878 concentrations of  $\alpha$ -tocopherol [257] and retinol [258], compared to controls. Likewise, upper  
879 gastrointestinal cancer (including both oesophageal and gastric cancer) subjects of East Asian  
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  
883 make swallowing (and thus eating) difficult.

884

### 885 ***8.2 Gastric cancer***

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

889 retinol [258] and 25-hydroxyvitamin D [259] have been associated with increased incidence of  
890 gastric cancer in individuals of East Asian ancestry. Although these correlations are generally  
891 interpreted by assuming that these FSV reduce the risk of developing gastric cancer, it can also be  
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  
894 risk of gastric cancer [262]. Since this microbe causes the loss of acid-producing parietal cells, we  
895 would expect a higher susceptibility of some FSV and FSP (e.g. vitamin E) to autoxidation because  
896 of the higher pH. In contrast, the increased pH may favor the growth of additional gastric microbial  
897 species, which would also be expected to influence the production of FSV and FSP metabolites. In  
898 summary, it is likely that infection with this bacterium is responsible for changes in the absorption  
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**).  
906 Recycling of FSP metabolites, if it occurs, would also be predicted to be limited. In more severe  
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  
909 even more pronounced, with patients often presenting with symptoms of deficiency [263]. Under  
910 these conditions, it would be expected that localized metabolism of these vitamins would be  
911 upregulated in target tissues (including the GI tract itself) that do not receive sufficient quantities of  
912 metabolites from the liver. Furthermore, due to limited bile release, production of micelles is greatly  
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,  $\alpha$ -tocopherol, and commonly  
915 consumed carotenoids are reduced in subjects with even early stages of cholestasis, relative to  
916 healthy controls [264]. Fortunately, treatment with the bile salt ursodeoxycholic acid proves to be  
917 highly effective at earlier stages of the disease, and limits the severity of FSV deficiency in this  
918 population [265].

919

#### 920 *8.4 Alcoholic fatty Liver, non-alcoholic fatty Liver, non-alcoholic steatohepatitis, and hepatic* 921 *cirrhosis*

922 Both alcoholic fatty liver (driven by excess alcohol consumption) and non-alcoholic fatty  
923 liver (driven primarily by obesity) are characterized by hepatic steatosis, which impairs liver  
924 functioning [266]. Data suggests that the bioactive metabolites of FSV and carotenoids themselves  
925 may both be influenced by, and may directly influence, fatty liver disease progression, especially in  
926 younger individuals and/or earlier stages of condition development [266-269]. Fatty liver disease  
927 upregulates utilization of FSV vitamin stores found there, increases synthesis of bioactive FSV  
928 isoforms, and increases phase I metabolism for excretion. Impaired functioning of the “classical” bile  
929 acid synthesis pathway leads to increased metabolism by a secondary pathway involving CYP27A1,  
930 the same enzyme that produces 25-hydroxyvitamin D [270]. Likewise, in a murine model of alcohol-  
931 induced hepatic steatosis, increased expression of hepatic CYP26A1 and CYP26B1, which convert  
932 retinoic acid to phase I metabolites for excretion, as well as broad-spectrum phase I CYPs, i.e.  
933 CYP2C29, CYP2C39 and CYP3A11, were observed [271]. In the same study, liver vitamin A stores  
934 were also simultaneously depleted. Thus, we would expect increased enterohepatic recycling of  
935 vitamin A and D metabolites, and increased concentrations in the intestinal lumen of these  
936 metabolites in patients with fatty liver. The change in the composition of bile acids released may also  
937 influence microbiota composition/abundance, and thus FSV and FSP metabolism in the distal small  
938 intestine and colon [270]. Increased plasma concentrations of the oxidized vitamin E metabolite  $\alpha$ -

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

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

949

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

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

958

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

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



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

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

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

973

#### 974 *8.7 Celiac disease*

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

983

#### 984 *8.8 Cystic fibrosis*

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

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

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

999

## 1000 ***8.9 Intestinal failure***

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

1008 Previous studies have reported limited re-sectioning success under conditions of vitamin A  
1009 deficiency [291]. Intestinal failure also causes deficiencies in vitamins D and E [292, 293], while  
1010 vitamin K remains unstudied in this population. Historical oils used to produce the intravenous lipid  
1011 emulsions provided to this population (e.g. Intralipid®) primarily containing soybean oil naturally  
1012 rich in  $\gamma$ -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),  $\alpha$ -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  
1022 (classified as class I), 3) an accelerated catabolism of these lipoproteins in the blood (classified as  
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  
1026 supplementation (likely because they are not considered essential). There are also no data on the FSV  
1027 metabolites present in the enterocyte of subjects with this pathology, but due to increased FSV  
1028 retention, increased FSV metabolites would be anticipated. From here, it is not clear whether these  
1029 metabolites would be secreted in the portal vein, returned to the intestinal lumen, or released into the  
1030 lymphatic system. While not yet known, such subjects could potentially serve as excellent models to  
1031 further study enterocyte FSV and FSP metabolism.

1032

### 1033 ***8.11 Inflammatory bowel disease***

1034 Overall, subjects with Crohn's disease and ulcerative colitis have reduced circulating  
1035 concentrations of vitamins A, D, and E, relative to healthy controls [296, 297]. Results on vitamin K  
1036 are mixed, with some studies demonstrating higher concentrations in inflammatory bowel disease  
1037 subjects, and others demonstrating a deficiency [296, 297]. Oral supplementation in this population

1038 has been rather disappointing, but is still often prescribed [297]. Changes in the mucosal membrane  
1039 of the colon, which exacerbates the symptoms of inflammatory bowel disease, should stimulate  
1040 bacterial growth. This might cause unique production of FSV / FSP metabolites in this cohort.

1041 In summary, we can conclude that most of the digestive tract diseases probably reduce, to a  
1042 greater or lesser extent, the absorption and metabolism of FSV and FSP. However, nothing is known  
1043 about the consequences this may have on the biliary re-secretion of the FSV / FSP metabolites, on  
1044 the microbiota, and on the FSV / FSP metabolism by the microbiota.

1045

## 1046 **9. Effects of surgery of the gastrointestinal tract on FSV and FSP metabolism in this organ**

1047 Surgeons may have to operate on certain parts of the digestive tract following various  
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  
1051 lower FSV and FSP intake due to the lower amount of food consumed/day. This can also decrease  
1052 absorptive surface areas and thus the number of proteins involved in FSV and FSP uptake by  
1053 intestinal cell (**section 5.3**). It is also likely that some of these surgeries alter the intraluminal  
1054 metabolism of certain FSV / FSP and consequently the production of metabolites. Surgical  
1055 interventions might require correcting the FSV [298-301] or carotenoid [302-304] status of patients.  
1056 It is also interesting for the physiologist to better understand the key factors that modulate the  
1057 bioavailability of these compounds [305]. Very little is known about the effects of different surgical  
1058 procedures on the production and uptake of FSV / FSP metabolites, thus we postulate the  
1059 consequences of these interventions based on our knowledge of metabolism in the healthy digestive  
1060 tract.

1061

### 1062 ***9.1 Gastrectomy / gastric resection***

1063           The first part of the digestive tract that may be partially or totally removed is the stomach, as  
1064 frequently observed with stomach cancer. Malabsorption of lipids, and therefore of FSV / FSP and  
1065 their fat-soluble metabolites, can occur after total gastrectomy [306, 307]. For example, following  
1066 surgical treatment, gastric cancer patients are at risk of vitamin A and E deficiencies [308]. The  
1067 cause is apparently either excessively rapid intestinal transit or bacterial overgrowth [309].  
1068 Malabsorption also depends on the portion of the intestine that has been resected together with the  
1069 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  
1072 supported by a recent review showing that these subjects are at higher risk of vitamin E deficiency  
1073 [301]. Nevertheless, it is difficult to conclude that this is due to a lower absorption efficiency of the  
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  
1078 consequences of bariatric surgery on vitamin absorption have measured the concentrations of  
1079 vitamins in the blood of fasting subjects several weeks or months after surgery. Although this does  
1080 not make it possible to conclude the effect of surgery on absorption, it gives an indication of the  
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  
1083 surgery, specifically Roux-en-Y gastric bypass surgery, on absorption efficiency of the FSV. In the  
1084 first study, [313] cholecalciferol absorption was decreased by 25% after the surgery. In the second  
1085 study, despite the fact that vitamin A intakes remained unchanged pre- vs. post-surgery, and despite  
1086 post-surgical supplementation of retinol palmitate, serum vitamin A concentrations were lower  
1087 following surgery [314]. Thus, bariatric surgery appears to decrease FSV / FSP absorption, but a

1088 comparison remains to be made between the effects of different bariatric surgery techniques on the  
1089 absorption efficiency of FSV / FSP. Nothing is known about the consequences of bariatric surgery on  
1090 the production of metabolites in the digestive lumen.

1091

## 1092 ***9.2 Intestinal failure***

1093 Vitamin D deficiency is highly prevalent in children with a history of intestinal failure, who  
1094 have achieved enteral autonomy despite enteral supplementation with higher than standard doses of  
1095 vitamin D. Shorter remnant small-bowel length and longer duration of parenteral nutrition were the  
1096 main parameters associated with vitamin D deficiency [315]. This suggests that this pathology has  
1097 more consequences on the absorption of FSV and FSP than stomach diseases. This result is logical  
1098 since these compounds are absorbed in the intestine, but it does not provide information on the  
1099 production of degradation compounds or metabolites in the intestine vs. stomach.

1100

## 1101 ***9.3 Pancreatic resection***

1102 The key role of pancreatic secretions on the absorption of vitamins A and D, and most likely  
1103 also on the absorption of other FSV / FSP and their derivatives, is supported by the observation of a  
1104 severe deficiency of these vitamins in a 12-year-old girl, who had undergone pancreatic resection for  
1105 chronic calcific pancreatitis [305].

1106 Nevertheless, two studies suggest that the digestive tract can, in the long term, adapt to  
1107 compensate for the loss of absorption capacities. In the first one, shortening of rat jejunum by an  
1108 end-to-end anastomosis (jejunum-bypass operation) [316] increased the ileal concentration of  
1109 CRBP(II) by a factor 2, which would be an adaptation of the body to compensate for the loss of  
1110 vitamin A absorption capacity. In the second one, a rat model of short bowel syndrome [317] pointed  
1111 to an increase in the expression of genes involved in the intestinal metabolism of vitamin A, in that

1112 case *Rbp2* and *Apoa4*. It remains to be seen whether the intestine is also able to adapt for lower  
1113 absorption of other FSV and FSP after GI tract surgery.

1114

## 1115 **10. Effect of xenobiotics that impair lipid absorption**

1116 Many strategies have been developed to combat obesity. Among these are administrations of  
1117 compounds and drugs that decrease lipid absorption. An obvious question is the impact on FSV  
1118 absorption and numerous studies have been carried out to address it. Concerning olestra, a zero-  
1119 calorie fat replacement manufactured by Proctor & Gamble under the name olean, it has been shown  
1120 that, as expected, it reduces the absorption of FSV and FSP with a logP (P: water-octanol partition  
1121 coefficient) > 7.5 [318]. Thus, this additive has been banned in Canada and Europe, although it  
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  
1125 compounds that interfere with the absorption of very hydrophobic molecules [319].

1126 Mineral oil, an indigestible lipid, has been used for many decades as a remedy to treat  
1127 constipation, and as a placebo in some randomized, controlled trials. As long as the mineral oil is  
1128 administered between meals, the impact on FSV / FSP status is limited [320, 321]. In the best  
1129 controlled study to date, children treated for up to 4 months with mineral oil had a drop in serum  $\beta$ -  
1130 carotene, but an increase in retinol (and no change in  $\alpha$ -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  
1132 [322]. With more sophisticated methods of FSV / FSP delivery in new foods and supplements (e.g.  
1133 encapsulation and nanoemulsion), *in vitro* evidence suggests that mineral oil negatively impacts  
1134 vitamin D bioaccessibility [323]. Thus, further evaluation is warranted.

1135 Finally, the anti-obesity drug orlistat, a lipase inhibitor, has been shown to reduce both  
1136 postprandial absorption and circulating plasma concentrations of FSV and provitamin A, following

1137 prospective dosing [324]. The favourable effects of orlistat on carbohydrate metabolism and non-  
1138 alcoholic fatty liver disease will probably override concerns on FSV / FSP uptake in the short-term in  
1139 adults, but these effects have also been reported in children, for whom ensuring sufficient FSV status  
1140 is critical for growth and development [324]. Additionally, some evidence suggests that a greater  
1141 percentage of provitamin A is metabolized to vitamin A in the intestine when the meal is consumed  
1142 with digestible lipid. Thus, reducing digestible lipid may also influence FSV metabolism [325].

1143 In summary, xenobiotics aiming to decrease the absorption of lipids also decrease the  
1144 absorption of some FSV and carotenoids. However, the effects on the absorption of other FSP / FSV  
1145 and their metabolites are unknown, as well as the consequences of these xenobiotics on the biliary  
1146 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  
1150 metabolite production, absorption, and potential bioactivity in digestive tract. We have also  
1151 identified many areas where FSV / FSP metabolism remains unknown or poorly documented. In  
1152 these instances, we have relied upon what is known about the parent FSV / FSP. Technological  
1153 developments in analytical chemistry (e.g. metabolomics) have increased the capacity to identify and  
1154 quantify a larger number of FSV and FSP metabolites in biological samples simultaneously. When  
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  
1157 physiopathology, many more FSV / FSP metabolites are likely to be identified and correlated with  
1158 various bioactivities.

1159

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1161 Agriculture [Hatch project W4122].



1162

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1164 **Table 1.** Vitamins and phytochemicals with computed octanol-water partition coefficients ( $\log_{10} P >$   
 1165 5).

<b>Compound</b>	<b>Compound Class</b>	<b>Computed <math>\log_{10} P^1</math></b>
menaquinone 8-14 (vitamin K <sub>2</sub> 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 <sub>2</sub> isoform)	vitamin	14.5
chlorophyll b	tetrapyrrole	13.9
$\alpha$ -carotene (provitamin A)	carotenoid	13.6
$\beta$ -carotene (provitamin A)	carotenoid	13.3
chlorophyll a	tetrapyrrole	12.9
menaquinone-6 (vitamin K <sub>2</sub> isoform)	vitamin	12.6
$\beta$ -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 <sub>1</sub> )	vitamin	10.9
menaquinone-5 (vitamin K <sub>2</sub> isoform)	vitamin	10.9
$\alpha$ -tocopherol (vitamin E)	vitamin	10.7

$\beta$ -tocopherol (vitamin E isoform)	vitamin	10.3
$\gamma$ -tocopherol (vitamin E isoform)	vitamin	10.3
astaxanthin	carotenoid	10.3
24-methylenecycloartanol	phytosterol	10.3
$\delta$ -tocopherol (vitamin E isoform)	vitamin	10.0
cycloartenol	phytosterol	9.8
$\alpha$ -tocotrienol (vitamin E isoform)	vitamin	9.3
$\beta$ -sitosterol	phytosterol	9.3
$\beta$ -tocotrienol (vitamin E isoform)	vitamin	8.9
$\gamma$ -tocotrienol (vitamin E isoform)	vitamin	8.9
menaquinone-4 (vitamin K <sub>2</sub> )	vitamin	8.9
campesterol	phytosterol	8.8
stigmasterol	phytosterol	8.6
$\delta$ -tocotrienol (vitamin E isoform)	vitamin	8.6
brassicasterol	phytosterol	8.0
cholecalciferol (vitamin D <sub>3</sub> )	vitamin	7.9
ergocalciferol (vitamin D <sub>2</sub> )	vitamin	7.4
ergosterol	phytosterol	7.4
soyasapogenol B	phytosterol	7.0
calcifediol (25-hydroxyvitamin D <sub>3</sub> )	vitamin	6.2
solanidine	steroidal alkaloid	6.1
tomatidine	steroidal alkaloid	6.0
falcarinone	polyacetylene	6.0
ercalcidiol (25-hydroxyvitamin D <sub>2</sub> )	vitamin	6.0
rosmaridiphenol	other	5.9

falcarinol

polyacetylene

5.5

1166

---

1167

<sup>1</sup>Value computed by XLOGP3 version 3.0 [326].

1168

1169 **Figure legends**

1170

1171 **Figure 1: Vitamin D derivatives and possible mechanisms of formation.** Left panel,  
1172 physicochemical mechanisms for the degradation of  $1\alpha,25$ -dihydroxycholecalciferol [66]. **A)**  
1173 Thermal degradation in DMSO, possibly occurring during thermal processing. **B)** Acid-catalyzed  
1174 degradation in a 1:1 pH 3 phosphate buffer – MeCN mixture, possibly occurring in stomach. Middle  
1175 panel, biochemical mechanisms for metabolism in the liver and intestine. Right panel, hypothesized  
1176 deconjugation by the microbiota.

1177

1178 **Figure 2: Phytosterol derivatives and possible mechanisms of formation.** Left panel,  
1179 physicochemical mechanisms for the formation of phytosterol oxidation products upon thermal  
1180 treatment of fat-rich food containing phytosterols acylated by polyunsaturated fatty acids [93]. Upon  
1181 thermal treatment of lipid food (e.g. phytosterol-enriched margarine), phytosterols acylated by fatty  
1182 acids are more vulnerable to oxidation when the unsaturation degree of the acyl chain increases.  
1183 Autoxidation of a PUFA chain leads to highly reactive peroxy radicals that efficiently oxidize the  
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.

1186

1187 **Figure 3: Gastric phases / structures in which parent FSV / FSP and their derivatives can be**  
1188 **distributed during digestion.** Derivatives (**D**) mean compounds formed upon either  
1189 physicochemical or enzymatic modification of the parent molecule (**P**); *filled arrow*: known transfer  
1190 route; *dotted arrows*: some hypothesized transfer routes.

1191

1192 **Figure 4: Vitamin A derivatives and possible mechanisms of formation.** Left panel,  
1193 physicochemical mechanisms for the iron-induced autoxidation of carotenoids [109, 327]. Dioxygen

1194 activation involves non-heme Fe<sup>II</sup> traces. The reaction with Fe<sup>III</sup> is slower as it requires a first rate-  
1195 limiting step of Fe<sup>III</sup> reduction by carotenoids. Such mechanisms may occur during food processing  
1196 and digestion, especially when dietary carotenoids are transferred from emulsions to mixed micelles  
1197 along lipid digestion. Middle panel, metabolism of the main dietary source of preformed vitamin A  
1198 by human gastrointestinal enzymes. Right panel, hypothesized deconjugation by the microbiota.

1199

1200 **Figure 5: Prooxidant effect of polyunsaturated fatty acids on FSV and FSP.** Upper panel: Co-  
1201 oxidation of polyunsaturated fatty acids (LH) and antioxidants during iron-induced lipid peroxidation  
1202 [145-148]. LH = polyunsaturated fatty acids; AO1 = water-soluble antioxidant, e.g. phenolic  
1203 compounds, vitamin C, short-chain apocarotenoids; AO2 = fat-soluble antioxidant, e.g. vitamin E,  
1204 carotenoids, long-chain apocarotenoids; LOOH = lipid hydroperoxides. A) Initiation by heme iron  
1205 (Fe<sup>III</sup>). Lower panel: initiation by non-heme iron (Fe<sup>II</sup>). Such mechanisms may occur in the gastric  
1206 compartment where dietary iron and traces of hydroperoxides from lipid food can initiate PUFA  
1207 peroxidation under vigorous mixing, favorable acidic conditions and non-limiting O<sub>2</sub> concentrations.

1208

1209 **Figure 6: Derivatives of the fat-soluble phenols of rosemary.** Upon autoxidation (during food  
1210 processing or in the GI tract) or in the course of its antioxidant activity, carnosic acid (**1**), one of the  
1211 main antioxidant diterpenes of rosemary, is converted into carnosol (**2**), then into rosmanol (**3**) [154].  
1212 Through its electron-rich catechol ring, rosmanol itself can undergo additional two-electron  
1213 oxidation. These electron transfer sequences sustain the strong antioxidant activity of rosemary  
1214 extracts

1215

1216 **Figure 7: Derivatives of the fat-soluble phenols of olive oil.** A) Some olive phenols (except parent  
1217 glucosides, which are only present in the non-oily part of the olive fruit) are present in substantial  
1218 concentration in virgin olive oil (up to ca. one gram / kg) [155, 156]. They are known to contribute to

1219 the nutritional benefits of olive oil consumption, which is emphasized by a EFSA health claim [328].  
1220 **B)** Hydroxytyrosol (HT), the typical phenolic antioxidant of olive oil, inhibits lipid peroxidation in  
1221 synergy with  $\alpha$ -tocopherol [157]. While acting as an antioxidant, HT is converted in dimers and  
1222 higher oligomers that undergo further oxidation. Some incorporate water molecules [158].

1223

1224 **Figure 8: Vitamin E derivatives and possible mechanisms of formation.** Left panel,  
1225 physicochemical mechanisms with the example of interplay between  $\alpha$ -tocopherol and other dietary  
1226 antioxidants [329-334].  $\alpha$ -Tocopherol regeneration by other antioxidants is important to prolong  
1227 tocopherol activity and avoid tocopherol-mediated lipid peroxidation within lipid-rich phases. This  
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  
1231 metabolism of vitamin E by the microbiota.

1232

1233 **Figure 9: Vitamin K derivatives and possible mechanisms of formation.** Left panel,  
1234 physicochemical mechanisms with the example of the possible interplay between menaquinone MQ-  
1235 7 (R = hepta-isoprenyl chain) and carotenoids in the presence of heme or non-heme iron [335].  
1236 Carotenoids are spared in the process. MQ-7, naturally present in cocktails of bacterial carotenoids,  
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  
1239 carotenoids against autoxidation and potentiates their antioxidant activity. Middle panel, biochemical  
1240 mechanisms for the metabolism of phylloquinone in the small intestine. Right panel, vitamin K  
1241 metabolite produced by the microbiota.

1242

1243 **Figure 10: Upper intestinal phases / structures in which parent molecules and their derivatives**  
1244 **can be distributed during digestion.** In the upper intestine FSV and FSP and their derivatives are  
1245 assumed to distribute between the phases / structures present in the gastric lumen (see **Fig. 3**) and  
1246 secreted into the duodenum through the pylorus plus additional phases / structures coming from  
1247 biliary secretion and the digestion of dietary lipids, i.e. mainly triglycerides and phospholipids. **P**:  
1248 parent molecule; **D**: derivative; **P\***: parent molecule previously absorbed, then secreted in the bile;  
1249 **D\***: derivative previously absorbed, or resulting from metabolism of **P**, then secreted in the bile;  
1250 **filled arrows**: known transfer routes; **doted arrows**: some hypothesized transfer routes.



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