



**HAL**  
open science

## Overview of carotenoid bioavailability determinants: From dietary factors to host genetic variations

Charles Desmarchelier, Patrick Borel

### ► To cite this version:

Charles Desmarchelier, Patrick Borel. Overview of carotenoid bioavailability determinants: From dietary factors to host genetic variations: Carotenoid bioavailability determinants. Trends in Food Science and Technology, 2017, 69 (B), Epub ahead of print. 10.1016/j.tifs.2017.03.002 . inserm-01499484

**HAL Id: inserm-01499484**

**<https://inserm.hal.science/inserm-01499484>**

Submitted on 1 Oct 2017

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0  
International License

# Accepted Manuscript

Overview of carotenoid bioavailability determinants: From dietary factors to host genetic variations

Charles Desmarchelier, Patrick Borel

PII: S0924-2244(16)30523-4

DOI: [10.1016/j.tifs.2017.03.002](https://doi.org/10.1016/j.tifs.2017.03.002)

Reference: TIFS 1977

To appear in: *Trends in Food Science & Technology*

Received Date: 16 November 2016

Revised Date: 11 January 2017

Accepted Date: 10 March 2017

Please cite this article as: Desmarchelier, C., Borel, P., Overview of carotenoid bioavailability determinants: From dietary factors to host genetic variations, *Trends in Food Science & Technology* (2017), doi: 10.1016/j.tifs.2017.03.002.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



**Overview of carotenoid bioavailability determinants: from dietary factors to host genetic variations<sup>1,2</sup>**

Charles Desmarchelier,<sup>3\*</sup> Patrick Borel,<sup>3\*</sup>

<sup>3</sup>NORT, Aix-Marseille Université, INRA, INSERM, 13005, Marseille, France

**Authors' last names for PubMed indexing:** Desmarchelier, Borel

**Number of figures:** 2

**Number of tables:** 0

**Running title:** Carotenoid bioavailability determinants

**Abbreviations:** ABCA1, ATP binding cassette AI; BCO1, beta-carotene oxygenase 1; BCO2, beta-carotene oxygenase 2; CD36, cluster of differentiation 36; NPC1L1, Niemann–Pick C1-Like 1; SNP, single nucleotide polymorphism; SR-BI, scavenger receptor class B member 1.

---

<sup>1</sup> Author disclosures: *C Desmarchelier, P Borel*, no conflicts of interest.

\* To whom correspondence should be addressed: Charles.Desmarchelier@univ-amu.fr; Patrick.Borel@univ-amu.fr  
UMR 1260 INRA/1062 INSERM/Aix-Marseille University  
"Nutrition, Obesity and Risk of Thrombosis"  
Faculté de Médecine  
27, boulevard Jean Moulin  
13005 Marseille  
France  
Phone: +33 (0)4 91 32 42 82; +33 (0)4 91 32 42 77  
Fax: +33 (0)4 91 78 21 01

## 1 **Abstract**

2 **Background:** Carotenoids are C-30 or C-40 based pigments with antioxidant/anti-  
3 inflammatory properties, some possessing vitamin A activity. Their dietary intake, especially  
4 within fruits and vegetables, has been associated with a decreased risk of chronic diseases,  
5 including type-2 diabetes, cardiovascular diseases, age-related macular degeneration, and  
6 several types of cancer. However, their bioavailability is wide ranging and is affected by  
7 numerous factors. Recent findings showing that the intestinal absorption of carotenoids  
8 involves proteins have raised new relevant questions about factors that can affect their  
9 bioavailability. It is therefore opportune to present a current overview of this topic.

10 **Scope and Approach:** This review begins by exploring what is known, as well as what is  
11 unknown, about the metabolism of carotenoids in the human upper gastrointestinal tract and  
12 then presents a methodical evaluation of factors assumed to affect carotenoid bioavailability.

13 **Key Findings and Conclusions:** Numerous unanswered questions remain about the  
14 metabolism of carotenoids in the intestinal lumen and about the factors affecting their  
15 absorption efficiency. These gaps need to be filled to be able to better understand individual,  
16 variable responses to these compounds so as to promote guidelines towards personalized  
17 dietary recommendation in order to increase carotenoid absorption efficiency and hence their  
18 health effects. Two main conclusions can be drawn. First, the efficiency of carotenoid  
19 absorption is affected by several dietary factors (*e.g.* food matrix, fat, and fat-soluble  
20 micronutrients). Second, carotenoid bioavailability also depends on host-related factors, *e.g.*  
21 diseases, life-style habits, gender and age, as well as genetic variations including single  
22 nucleotide polymorphisms.

23  
24 **Key words:** Lutein, beta-carotene, lycopene, food matrix, single nucleotide polymorphism,  
25 absorption.

26

## 27 Introduction

28

29 Carotenoids are natural pigments produced in many fruits and vegetables, mushrooms  
30 and algae and are responsible for colours ranging from red to yellow, although colorless  
31 carotenoids are also found (*e.g.* phytoene, phytofluene). Carotenoids are lipids and most of  
32 them can be described by the chemical formula  $C_{40}H_{56}O_n$ , with  $n$  ranging from 0 to 6. They  
33 are split into 2 classes:

34 - carotenes are non-oxygenated carotenoids (*i.e.*  $n=0$ ).

35 - xanthophylls are oxygenated carotenoids (*i.e.*  $n>0$ ).

36 To date, more than 750 different carotenoids have been identified but only about 40 are  
37 consumed in significant amounts in the human diet, of which the most abundant are  $\beta$ -  
38 carotene, lycopene, lutein,  $\beta$ -cryptoxanthin,  $\alpha$ -carotene, and zeaxanthin. Around 20 different  
39 carotenoids have been identified in human blood (Khachik, Beecher, Goli, Lusby, & Smith,  
40 1992). The 6 most concentrated carotenoids are those found at the highest quantities in the  
41 human diet. Astaxanthin and canthaxanthin are only found in the blood of subjects with an  
42 elevated intake of foods rich in these carotenoids (*i.e.* some fish and seashells for the former,  
43 some mushrooms for the latter). Carotenoids are ~~potent antioxidant~~ molecules with  
44 antioxidant properties and their dietary intake and plasma levels have been associated with a  
45 decreased risk of chronic diseases, including type-2 diabetes (Akbaraly, Fontbonne, Favier, &  
46 Berr, 2008), cardiovascular diseases (Y. Wang, Chun, & Song, 2013) and several types of  
47 cancer (Tanaka, Shnimizu, & Moriwaki, 2012). Some exhibit provitamin A properties,  
48 although only a few of these are present in significant amounts in the human diet, namely  $\beta$ -  
49 and  $\alpha$ -carotene, and  $\beta$ -cryptoxanthin. The importance of carotenoids as a source of vitamin A  
50 largely depends on the diet: a recent meta-analysis has shown that provitamin A carotenoids  
51 represented 35% of total vitamin A intake ( $\beta$ -carotene: 86%,  $\alpha$ -carotene: 10%,  $\beta$ -  
52 cryptoxanthin: 4% thereof respectively) in developed countries (Weber & Grune, 2012). In  
53 vegans, 100% of vitamin A originates from provitamin A carotenoids. ~~In countries where~~  
54 ~~animal product consumption is low (e.g. in developing countries), 70 to 90% of vitamin A~~  
55 ~~originates from carotenoids.~~ The xanthophylls lutein and zeaxanthin, which are present at  
56 high concentrations in the macula, can absorb incident blue light and hence protect the retina  
57 from light-induced damages (Mares, 2016) and their consumption has been associated with  
58 protection from age-related macular degeneration (Aronow & Chew, 2014).

59 Carotenoids are lipid molecules: they are insoluble in water and partially soluble in  
60 plant oils, animal fat and biological membranes. They share common transport mechanisms

61 with other lipids: in the lumen of the human digestive tract, they are found in structures  
62 allowing the solubilisation of lipids, *i.e.* micelles and probably vesicles. They are transported  
63 in the blood via lipoproteins and are found in membranes and lipid droplets in cells. Their  
64 bioavailability, *i.e.* the proportion of carotenoids, or one of their metabolites, that is available  
65 for use or storage by the organism, is wide-ranging, *i.e.* values between 3.5 % and 90 % have  
66 been reported for  $\beta$ -carotene (Haskell, 2012), and very little data is available for other  
67 carotenoids. It depends on the extraction efficiency from their food matrix to mixed micelles  
68 (*i.e.* bioaccessibility), their uptake efficiency by enterocytes, their blood transport, their  
69 uptake efficiency by target tissues and their tissue elimination (through *e.g.* catabolism). The  
70 fundamental mechanisms that govern their absorption and the factors that influence their  
71 absorption efficiency and their postprandial blood concentrations are not accurately known.  
72 This review will present an overview of what is known/unknown about the fate of carotenoids  
73 in the human upper gastrointestinal tract and then list the factors hypothesized to affect  
74 carotenoid bioavailability following a methodical evaluation.

75

## 76 **2. Carotenoid fate in the human upper gastrointestinal tract**

77

78 It is very difficult to give an absorption efficiency value for carotenoids in humans.  
79 Indeed, values between 3.5 % and 90 % have been reported for  $\beta$ -carotene (Haskell, 2012),  
80 and very little data is available for other carotenoids. The high variability reported for  $\beta$ -  
81 carotene probably comes from the different methodological approaches used to evaluate it.  
82 Indeed, different formulations (food *vs* supplements, *see* section 6.3), doses (nutritional or  
83 pharmacological), and models (postprandial chylomicron response, stable isotopes,  
84 ileostomised subjects...) have been used.

85 Carotenoid metabolism starts in the stomach, where foods rich in these molecules  
86 (essentially fruits and vegetables) are submitted to an acidic pH (between 2 and 5 during  
87 digestion) and to the action of gastric secretions, which contain several enzymes (pepsin,  
88 amylase, gastric lipase...). In a clinical study where 10 healthy men were given liquid test  
89 meals intragastrically, some carotenoids (lutein and  $\beta$ -carotene) were shown to be partially  
90 released from their food matrix in the stomach and to be transferred to the oil phase of the  
91 meal (Tyssandier, et al., 2003). This suggests that the stomach plays a significant role in  
92 carotenoid bioavailability by participating in their release from the food matrix. The extent of  
93 this phenomenon depends most likely on the physico-chemical properties of the different  
94 carotenoids (lycopene only exhibited a very low transfer to the oil phase of the meal in the

95 same study), on the quantity and the nature of lipids present at the same time as carotenoids in  
96 the food bolus, and on the characteristics of the matrix in which carotenoids are incorporated.

97 Some carotenoids are consumed as esters, *e.g.*  $\beta$ -cryptoxanthin in some citruses, lutein  
98 in some supplements from Marigold and also in tropical fruits (Breithaupt & Bamedi, 2001).  
99 It is hence possible that a fraction of these esters are hydrolysed by gastric lipase (Carriere,  
100 Barrowman, Verger, & Laugier, 1993). There is no data on the role of this enzyme on the  
101 hydrolysis of carotenoid esters but it might affect their bioavailability in subjects exhibiting a  
102 sub-optimal intestinal lipolytic activity (*e.g.* new-born babies and patients with pancreatic  
103 insufficiency).

104 In the duodenum, digestive enzyme (proteases, amylases, lipases...) participate in the  
105 release of carotenoids from the food matrix by degrading it further. It is widely accepted that  
106 carotenoids are then transferred to the lipid phase and to mixed micelles. However, it is not  
107 known if carotenoids are also present in other structures that solubilise lipids in the  
108 duodenum, *i.e.* vesicles (Staggers, Hernell, Stafford, & Carey, 1990), and if this has an effect  
109 on their absorption. Pancreatic lipase has been shown to facilitate the transfer of carotenoids  
110 from emulsified lipid droplets towards mixed micelles (Borel, et al., 1996). This transfer  
111 depends among others on pH, bile acid concentration and carotenoid hydrophobicity  
112 (Tyssandier, Lyan, & Borel, 2001). As it is accepted that only free carotenoids are taken up by  
113 enterocytes, hydrolysis of carotenoid esters in the duodenum has been questioned. The  
114 enzyme responsible for this hydrolysis is apparently bile-salt dependent lipase, also known as  
115 cholesteryl ester hydrolase, cholesterol esterase or carboxyl ester lipase (Breithaupt, Bamedi,  
116 & Wirt, 2002), secreted by the exocrine pancreas, but it is not known if pancreatic lipase-  
117 related protein 2, which can hydrolyse retinyl esters (Reboul, Berton, et al., 2006), is also  
118 involved.

119

### 120 **3. Uptake, metabolism and secretion of carotenoids by enterocytes**

121

122 After their extraction from the food matrix and incorporation into mixed micelles,  
123 bioaccessible carotenoids can be taken up by enterocytes. The main absorption site of  
124 carotenoids is in the duodenum (upper part of the intestinal tract), as suggested by beta-  
125 carotene oxygenase 1 and 2 (BCO1 and BCO2) cellular localization (Raghuvanshi, Reed,  
126 Blaner, & Harrison, 2015). Carotenoids can then be metabolised in the enterocytes before  
127 their incorporation into chylomicron, and possibly also intestinal HDL, and secretion in the  
128 blood circulation via the lymph. These processes are summarized in **Figure 1**.

129

### 130 **3.1 Carotenoid uptake at the apical membrane of the enterocyte**

131 Carotenoids have long been thought to enter enterocytes by simple passive diffusion.  
132 This dogma was mostly based on one study carried out in rats with  $\beta$ -carotene (Hollander &  
133 Ruble, 1978). However, several apical membrane proteins have been shown to facilitate  
134 carotenoid uptake (Reboul & Borel, 2011). Niemann–Pick C1-Like 1 (NPC1L1) is involved  
135 in the uptake of lutein (Sato, et al., 2012). Cluster of differentiation 36 (CD36) facilitates  $\beta$ -  
136 carotene uptake (Borel, et al., 2013) and could also facilitate lycopene uptake (Moussa, et al.,  
137 2011). Scavenger receptor class B member 1 (SR-BI), which is encoded by *SCARB1*,  
138 participates in the uptake of  $\beta$ -carotene (Borel, et al., 2013; van Bennekum, et al., 2005),  
139 lutein (During, Dawson, & Harrison, 2005) and lycopene (Moussa, et al., 2008). Several  
140 SNPs in the genes encoding these proteins have been reported to be associated with the  
141 variability in carotenoid plasma concentrations and bioavailability (*see* section 6.6).

142

### 143 **3.2 Intracellular transport of carotenoids in the enterocyte**

144

145 There is no data on the transfer mechanism of carotenoids from the apical membrane  
146 of the enterocyte to the Golgi apparatus (assembling site of chylomicrons, in which a fraction  
147 of carotenoids are incorporated). However, it is unlikely that these hydrophobic molecules  
148 could cross the aqueous intracellular compartment without being bound to (a) transport  
149 protein(s). Liver fatty acid binding protein (L-FABP), which can transport large molecules in  
150 its hydrophobic pocket, or cellular retinol-binding protein (CRBP), which transport vitamin A  
151 (M. S. Levin, 1993) could be good candidates. It is also possible that SR-BI-associated  
152 carotenoids are transported together towards the cytoplasm (G. H. Hansen, Niels-  
153 Christiansen, Immerdal, & Danielsen, 2003).

154

### 155 **3.3 Carotenoid metabolism in the enterocyte**

156

157 Following their transport into the enterocyte, carotenoids can be metabolised by two  
158 enzymes: BCO1 (dela Sena, et al., 2014) and BCO2 (Amengual, et al., 2013). BCO1 cleaves  
159 carotenoids centrally and yields at least one retinal molecules (2 for  $\beta$ -carotene) while BCO2  
160 cleaves carotenoids eccentrically and yields apo-carotenals. BCO1 catalyses the oxidative  
161 cleavage of provitamin A carotenoids, beta-apocarotenals, and possibly also lycopene, but not  
162 that of lutein (dela Sena, et al., 2013). While BCO1 is thought to be the main cleaving-



163 enzyme for  $\beta$ -carotene (von Lintig, 2012), lycopene has been suggested to be mostly cleaved  
164 by BCO2 (Lindshield, Canene-Adams, & Erdman, 2007). BCO2 has also been shown to be  
165 involved in lutein metabolism (Amengual, et al., 2011). While BCO1 is a cytosolic enzyme,  
166 BCO2 localizes to the inner mitochondrial membrane which suggest the existence of a  
167 compartmentalization between provitamin A carotenoid and xanthophyll metabolism  
168 (Palczewski, Amengual, Hoppel, & von Lintig, 2014; Raghuvanshi, et al., 2015). Most  $\beta$ -  
169 carotene conversion (>70%) has been shown to take place in the intestine (Tang, Qin,  
170 Dolnikowski, & Russell, 2003; Z. Wang, Yin, Zhao, Russell, & Tang, 2004). Additionally,  
171 carotenoid isomerisation can occur in the enterocyte and it has actually been reported that this  
172 was the key site for lycopene isomerisation during absorption in human subjects, since no  
173 isomerisation was observed in the gastro-intestinal lumen (Richelle, et al., 2010).

174

### 175 **3.4 Carotenoid secretion from the basolateral side of the enterocyte to the blood** 176 **circulation**

177

178 It is widely accepted that carotenoids follow the fate of other newly absorbed lipid  
179 molecules (fatty acids, monoglycerides, cholesterol...) and that they are incorporated with  
180 them in chylomicrons in the Golgi apparatus before secretion in the lymph (apolipoprotein B-  
181 dependent route). Nevertheless, another secretion pathway could exist. Indeed, since some  
182 carotenoids are found in HDL and since the small intestine synthesizes HDL, which can  
183 transport other newly absorbed lipid molecules, namely cholesterol and vitamin E, it can be  
184 hypothesized that a fraction of carotenoids is secreted into the lymph in HDL (apolipoprotein  
185 A1-dependent route) involving the transporter ATP binding cassette AI (ABCA1). This has  
186 been confirmed *in vitro* and in a hamster model for lutein and zeaxanthin where up- and  
187 down-regulation of ABCA1 expression, via activation of the liver X receptor and statin  
188 treatment respectively, led to respectively increased and decreased HDL-lutein and -  
189 zeaxanthin concentrations (Niesor, et al., 2014). The metabolic pathways of carotenoid  
190 transport through the enterocyte are summarized in **Figure 1**.

191

## 192 **4. Blood transport of carotenoids**

193

194 Since some carotenoids (notably xanthophylls) are principally localized at the surface  
195 of chylomicrons (Borel, et al., 1996), a fraction of carotenoids is probably transferred to other  
196 classes of lipoproteins and/or to some tissues during intravascular metabolism of

197 chylomicrons (Tyssandier, Choubert, Grolier, & Borel, 2002). Carotenoids that reach the liver  
198 via chylomicrons are stored in this organ, or eliminated in the bile, or re-secreted into VLDL  
199 to be distributed to peripheral tissues. It can be hypothesized that a fraction of VLDL-  
200 carotenoids (notably xanthophylls for the above-mentioned reasons) is exchanged with some  
201 other classes of lipoproteins during the metabolism of these lipoproteins. A part of VLDL-  
202 carotenoids, notably carotenes which are preferentially located in the hydrophobic core of  
203 these triglyceride-rich lipoproteins (Borel, et al., 1996), is found in LDL, which originate  
204 from VLDL metabolism. LDL-carotenoids are probably taken up by tissues together with  
205 LDL. It can be hypothesized that a fraction of LDL-carotenoids, preferentially xanthophylls,  
206 is exchanged with other classes of lipoproteins. The origin of HDL-carotenoids is not known  
207 but they can come from peripheral tissues, which would be somehow a reverse metabolism of  
208 carotenoids, or from other lipoprotein classes (through the exchanges between lipoproteins  
209 described above), or from the intestine (*see* section 3.4), or from a combination of some of  
210 these factors. Following these exchanges, xanthophylls are transported mostly in HDL while  
211 carotenes are transported mostly in LDL (Thomas & Harrison, 2016). **Figure 2** summarizes  
212 the current knowledge on the blood transport of carotenoids in humans.

213

## 214 **5. Tissue distribution of carotenoids**

215

216 Carotenoids are found in numerous tissues but at ~~very~~ different concentrations  
217 (Schmitz, Poor, Wellman, & Erdman, 1991). The adipose tissue and the liver respectively  
218 contain 80 and 10% of total carotenoids in the body, although the highest concentrations are  
219 not found in these organs. Very little is known on the mechanisms governing carotenoid tissue  
220 distribution. It is accepted that these lipophilic pigments follow the fate of lipids. It is thus  
221 hypothesized that carotenoids incorporated into LDL are taken up by tissues together with  
222 these lipoproteins (*see* chapter 4). Moreover, since some putative membrane transporters of  
223 carotenoids (*i.e.* SR-BI, CD36~~ABCA1~~...) are found at the cell surface of some tissues  
224 (Moussa, et al., 2011; Rigotti, Miettinen, & Krieger, 2003), it is possible that the cell  
225 internalisation of some carotenoids present at the surface of lipoproteins (xanthophylls  
226 notably) is facilitated by these transporters. It is also possible that some membrane proteins  
227 are involved in the efflux of carotenoids from peripheral tissues to the blood circulation.

228 Carotenoid analysis in the eyes of dead bodies have shown that, although around 40  
229 carotenoids are consumed by humans, only very few are found in this organ, namely lutein,  
230 zeaxanthin, *meso*-zeaxanthin, and to a lesser extent lycopene and  $\beta$ -carotene (Bernstein, et al.,

231 2001). Since among dietary carotenoids, only lutein and zeaxanthin are found in the human  
232 lens and retina, these carotenoids are sometimes considered as the “carotenoids of vision”.  
233 The macular pigment density, *i.e.* the concentration of carotenoids present in the macula, is  
234 partly correlated to lutein+zeaxanthin and  $\beta$ -carotene consumption and serum lutein and  
235 zeaxanthin concentration (Curran-Celentano, et al., 2001), and dietary intakes of lutein  
236 increase macular pigment density (Landrum, et al., 1997). Regarding *meso*-zeaxanthin  
237 (3R,3'S-zeaxanthin), it comes from lutein metabolism, as it has been shown when monkeys  
238 were fed either lutein or zeaxanthin (Johnson, Neuringer, Russell, Schalch, & Snodderly,  
239 2005). These studies in monkeys have also shown that lutein and zeaxanthin in the macula  
240 cannot interconvert, which suggests it is necessary to have a dietary intake of both carotenoids  
241 to maintain a normal macular pigment composition. Recently, a mechanism has been  
242 proposed to explain the selective uptake of zeaxanthin and lutein in the retina, where  
243 zeaxanthin transport from HDL is facilitated by SR-BI while lutein transport from LDL is  
244 probably facilitated by the LDL receptor (Thomas & Harrison, 2016).

245 Xanthophylls, and more precisely esterified lutein, have been found in the skin  
246 (Wingerath, Sies, & Stahl, 1998), but it is not known if these esters are formed in this tissue,  
247 through esterification of free lutein, or if they are absorbed as such and then transported to the  
248 skin (*see* section 3.5). Lycopene and  $\beta$ -carotene are the main carotenoids found in the prostate  
249 (Clinton, et al., 1996) with concentrations ranging from 0 to 2.6 nmol/g for lycopene and from  
250 0.09 to 1.7 nmol/g for  $\beta$ -carotene. The presence of significant amounts of lycopene in this  
251 organ support the results of epidemiological studies which suggest this carotenoid plays a  
252 preventive role against the development of prostate cancer (Jian, Du, Lee, & Binns, 2005;  
253 Wertz, Siler, & Goralczyk, 2004).

254 Lutein and zeaxanthin have been found at relatively high concentrations in the human  
255 brains where they have been suggested to have a beneficial role on cognitive function  
256 (Johnson, 2012).

257

## 258 **6. Factors modulating the bioavailability of carotenoids**

259

260 To be absorbed, carotenoids have to be extracted from the food matrix in which they  
261 are ingested (usually a vegetable matrix, oil or a dietary supplement) and presented to  
262 enterocytes in a structure enabling their absorption, *i.e.* in mixed micelles. Carotenoid  
263 absorption depends on many variables: (i) food processing (raw, dehydrated, frozen,  
264 cooked...), (ii) meal composition, (iii) the activity of digestive enzymes, (iv) transport

265 efficiency across the enterocyte, etc. The mnemotechnic term “SLAMENGHI” has been  
266 proposed to list all factors susceptible to affect carotenoid bioavailability (West &  
267 Castenmiller, 1998). Each letter represents one factor:

268 – S for “**S**pecies of carotenoids” (referring to the relative bioavailability of the different  
269 carotenoids depending on their physico-chemical properties)

270 – L for “**L**inkage” (referring to additional functional groups sometimes linked to  
271 carotenoids: esters, aldehyde...)

272 – A for “**A**mount of carotenoid consumed in the meal” (referring to the relative absorption  
273 efficiency as a function of the quantity of carotenoids consumed in a meal)

274 – M for “**M**atrix in which the carotenoid is incorporated” (referring to the effect of the matrix  
275 in which carotenoids are incorporated)

276 – E for “**E**ffectors of absorption” (referring to the effect of nutrients and drugs on carotenoid  
277 absorption)

278 – N for “**N**utrient status of the host” (referring to the effect of the vitamin A status of the host)

279 – G for “**G**enetic factors” (representing the effect of genetic polymorphisms or epigenetic  
280 modifications)

281 – H for “**H**ost-related factors” (referring to individual characteristics such as age, gender,  
282 pathologies...)

283 – I for “**I**nteractions” (referring to the differences in effects observed when two  
284 of the above-mentioned factors play a joint role compared with the sum of their effects  
285 observed separately).

286

## 287 **6.1 Species of carotenoids and molecular Linkage**

288

289 The study of the effect of carotenoid species on their bioavailability is not  
290 straightforward due the variability of the matrices in which they are incorporated (*see* section  
291 6.3). To differentiate between these effects, it is necessary to measure the bioavailability of  
292 pure carotenoids. This was done in a study carried out in rats which showed that carotenoid  
293 bioavailability was inversely correlated with their hydrophobicity (*i.e.* the bioavailability of  
294 carotenoids was as follows: astaxanthin>lutein> $\beta$ -carotene>lycopene), which was mainly due  
295 to differences in their bioaccessibility according to the authors (Sy, et al., 2012).

296 Due to their many conjugated double bonds, each carotenoid can theoretically form  
297 many geometrical isomers. For example,  $\beta$ -carotene, with 9 double bonds in its polyene chain,  
298 can form 272 isomers while lycopene can theoretically form 1056 geometrical isomers.

299 However, the steric hindrance of some configurations limits the number of *cis* isomers to a  
300 few dozens. As a consequence, carotenoids are found in the human diet under 4 main  
301 chemical forms: all-*trans* carotenoids, all-*trans* esterified carotenoids (Weller & Breithaupt,  
302 2003), *cis* carotenoids and *cis* esterified carotenoids. However, most carotenoids are usually  
303 present as all-*trans* non-esterified carotenoids. The fraction of *cis* isomers present in our diet  
304 is usually produced by technological treatments, in particular elevated temperatures  
305 (Milanowska & Gruszecki, 2005; Rodriguez-Amaya, 1999; Updike & Schwartz, 2003). A  
306 “*trans* to *cis*” conversion in the acidic environment of the stomach has also been proposed  
307 (Mortensen & Skibsted, 2000), although it has not been observed *in vivo* (Richelle, et al.,  
308 2010; Tyssandier, et al., 2003). However, Richelle *et al.* reported lycopene conversion to  
309 occur within the enterocyte (Richelle, et al., 2010). *Cis* isomers have different physico-  
310 chemical properties compared to corresponding all-*trans* isomers: they are no longer linear,  
311 rigid molecules, which affect their capacity to solubilize into mixed micelles (Milanowska,  
312 Polit, Wasylewski, & Gruszecki, 2003). Their tendency to crystallise or aggregate is also  
313 diminished (Britton, 1995). As a consequence, it has been hypothesized that they have  
314 different absorption efficiency. This has been investigated in several studies. *Cis* lycopene  
315 isomers have been shown to display a higher bioavailability than the all-*trans* isomer  
316 (Boileau, Boileau, & Erdman, 2002; Cooperstone, et al., 2015), which would be due to a  
317 higher solubility in mixed micelles. *Cis*  $\beta$ -carotene isomers also display a higher solubility in  
318 mixed micelles compared to all-*trans*  $\beta$ -carotene (G. Levin & Mokady, 1995; Tyssandier, et  
319 al., 2003) but surprisingly, they have a lower absorption efficiency (Ben-Amotz & Levy,  
320 1996). This apparent discrepancy could originate from the fact that *cis*  $\beta$ -carotene isomers are  
321 isomerised to all-*trans*  $\beta$ -carotene in enterocytes (You, Parker, Goodman, Swanson, & Corso,  
322 1996), which leads to an underestimation of their absorption efficiency. Of note, whether all-  
323 *trans*  $\beta$ -carotene enterocyte uptake is favoured remains controversial since a study with  
324 synthetic mixed micelles has shown a greater uptake of all-*trans*  $\beta$ -carotene *vs cis*  $\beta$ -carotene  
325 (During, Hussain, Morel, & Harrison, 2002) while another study did not observe any  
326 difference using micelles produced following *in vitro* digestions (Ferruzzi, Lumpkin,  
327 Schwartz, & Failla, 2006).

328 As mentioned earlier, carotenoids are found in the diet either as free carotenoids (for  
329 carotenes and xanthophylls) or esterified (for xanthophylls only). However, it is estimated that  
330 in the usual French diet, more than 90% carotenoids are consumed as free. Since, by analogy  
331 with what is observed with cholesterol and retinyl esters, carotenoids are supposed to be  
332 absorbed only as free, the absorption efficiency of esterified carotenoids was thought to be

333 inexistent. However, it was shown in a clinical study that lutein esters had a bioavailability  
334 equivalent to that of free lutein (Bowen, Herbst-Espinosa, Hussain, & Stacewicz-Sapuntzakis,  
335 2002), and the bioavailability of zeaxanthin dipalmitate was even greater than that of free  
336 zeaxanthin in another clinical study (Breithaupt, Weller, Wolters, & Hahn, 2004). This has  
337 also been observed with another xanthophyll ester, namely esterified  $\beta$ -cryptoxanthin  
338 (Breithaupt, Weller, Wolters, & Hahn, 2003). These results suggest that the hydrolysis of  
339 xanthophyll esters in the intestinal lumen is a highly efficient process. It can also be  
340 hypothesized that the facilitated transport of xanthophyll esters ~~are more soluble in mixed~~  
341 ~~micelles than free xanthophylls or that their facilitated transport~~ by membrane proteins is  
342 more efficient than that of free xanthophylls.

343

## 344 **6.2 Amount of carotenoids consumed in a meal**

345

346 The absorption efficiency of carotenoids is thought to remain constant to amounts up  
347 to 20-30 mg and then decrease for greater amounts due to several factors: limited capacity of  
348 mixed micelles to solubilise carotenoids, saturation of membrane proteins involved in their  
349 intestinal transport (*see* section 3.1), saturation of the solubilisation capacity of the  
350 intracellular compartment and/or chylomicrons (Stahl, et al., 2002). This saturation of the  
351 absorptive capacity has been reported for lycopene (Diwadkar-Navsariwala, et al., 2003).

352

## 353 **6.3 Matrix in which carotenoids are incorporated**

354

355 This factor is considered to be the key factor governing carotenoid bioavailability  
356 because, to be absorbed, carotenoids first need to be extracted from their food matrix and to  
357 be incorporated into mixed micelles in the upper part of the digestive tract. In plants,  
358 carotenoids are found in different structures: they can be present in chloroplasts in the  
359 photosynthetic system (in particular in the leaves of green plants) or in chromoplasts,  
360 dissolved in lipid droplets (in some fruits), or in a semi-crystal state associated to membranes  
361 (in carrots and tomatoes for example) (Vishnevetsky, Ovadis, & Vainstein, 1999). These  
362 differences in their localization and physical form are supposed to significantly affect their  
363 extraction efficiency and hence their bioaccessibility (*i.e.* % found in micelles) (Reboul,  
364 Richelle, et al., 2006; Xia, McClements, & Xiao, 2015) and bioavailability (Schweiggert &  
365 Carle, 2015). To illustrate this point, lutein and  $\beta$ -carotene were more bioavailable from  
366 broccolis (a flower) or green peas (a seed) than from spinach (where carotenoids are found in

367 chloroplasts) (van het Hof, Tijburg, Pietrzik, & Weststrate, 1999). Likewise, the  
368 bioavailability of carotenoids present in food not from plant origin is usually higher than that  
369 of carotenoids present in food from plant origin, probably because they are then not trapped  
370 by plant membranes and dietary fibres. For example, lutein from eggs was more bioavailable  
371 than lutein from spinach and supplements (Chung, Rasmussen, & Johnson, 2004).

372 Technological treatments and cooking usually improve carotenoid bioavailability and  
373 can thus compensate, at least partly, for their degradation. This is explained by the fact that  
374 these treatments alter plant cell walls and lead to a higher carotenoid extraction. Several  
375 studies have thus shown a higher carotenoid bioaccessibility following thermal or non-thermal  
376 processing (Buniowska, Carbonell-Capella, Frigola, & Esteve, 2017; Gupta, Kopec,  
377 Schwartz, & Balasubramaniam, 2011; Reboul, Richelle, et al., 2006). These differences in  
378 bioaccessibility usually translate to differences in bioavailability. For example, lutein  
379 bioavailability from spinach is higher when the spinach matrix is altered (through chopping in  
380 this case) (van het Hof, et al., 1999) and it is higher in vegetable juices compared to raw or  
381 cooked vegetables (McEligot, et al., 1999). Likewise, the bioavailability of  $\beta$ -cryptoxanthin  
382 has been shown to be higher in pasteurized orange juice compared to fresh oranges (Aschoff,  
383 et al., 2015).

384

## 385 **6.4 Effectors of absorption**

386

### 387 **6.4.1 Lipids**

388

389 Dietary triglycerides have been shown to be necessary to promote carotenoid  
390 absorption. Lipids increase the bioavailability of both free (Unlu, Bohn, Clinton, & Schwartz,  
391 2005) and esterified lutein (Roodenburg, Leenen, Hof, Weststrate, & Tijburg, 2000). When  
392 raw vegetables were consumed together with cooked whole eggs (each egg provided 5 g  
393 lipids), lutein, zeaxanthin,  $\alpha$ -carotene,  $\beta$ -carotene, and lycopene bioavailability increased 3-8  
394 fold (Kim, Gordon, Ferruzzi, & Campbell, 2015). Similarly, consumption of avocado together  
395 with tomatoes or raw carrots has been shown to increase the bioavailability of  $\beta$ -carotene and  
396 its conversion efficiency to vitamin A (Kopec, et al., 2014). Lipids can modulate carotenoid  
397 absorption by several mechanisms:

398 - They can facilitate the extraction of carotenoids from their food matrix by providing a  
399 hydrophobic phase in which carotenoids can solubilise.

400 - They can stimulate biliary secretion and consequently, micelle production, which would  
401 increase the quantity of carotenoids solubilised in micelles and hence available for  
402 absorption.

403 - By promoting chylomicron secretion, triglycerides could increase carotenoid secretion  
404 outside the enterocyte and thus prevent their intracellular accumulation, which would in turn  
405 increase their absorption.

406

407 Several characteristics of dietary lipids are thought to affect carotenoid bioavailability:

408 - the species of fatty acids from triglycerides (Borel, et al., 1998; Gleize, et al., 2013;  
409 Schaeffer & Hamilton, 1990). For example, olive and coconut oils have been shown to  
410 increase similarly the intestinal absorption of lutein in mice when compared to groundnut,  
411 soybean, sunflower, rice bran, corn, palm and fish oil (Nidhi, Ramaprasad, & Baskaran,  
412 2014). In humans, canola oil, which is rich in monounsaturated fatty acids, was shown to  
413 trend to promote higher lutein and  $\alpha$ -carotene bioavailability compared to butter, which is  
414 rich in saturated fatty acids (Goltz, Campbell, Chitchumroonchokchai, Failla, & Ferruzzi,  
415 2012).

416 - the amount of amphiphilic lipids (mostly phospholipids).

417 - the species of amphiphilic lipids. It is supposed that, before its hydrolysis to  
418 lysophosphatidylcholine, phosphatidylcholine could affect carotenoid absorption by  
419 decreasing lipolysis speed and hence micelle formation speed. Phosphatidylcholine inhibits  
420 lutein absorption while lysophosphatidylcholine has the opposite effect (Sugawara, et al.,  
421 2001).

422 - the extent of lipid emulsification. For example, the use an excipient emulsion with  
423 decreasing droplet size has been shown to increase the bioaccessibility of  $\alpha$ - and  $\beta$ -carotene  
424 from carrot juice *in vitro* (Zhang, et al., 2016) and an emulsion with small droplet size  
425 increased enterocyte uptake of  $\beta$ -carotene in Caco-2 cells (Lu, et al., 2016).

426

#### 427 6.4.2 Dietary fibers

428

429 Dietary fibres could affect carotenoid absorption by several mechanisms:

430 - by sequestering micelle components (Eastwood & Mowbray, 1976).

431 - by inhibiting pancreatic lipase (W. E. Hansen, 1987), which would decrease carotenoid  
432 extraction from lipid droplets (Tyssandier, et al., 2001).



433 - by increasing the viscosity of the intestinal content (Gallagher, Hassel, Lee, & Gallagher,  
434 1993) which would impair the diffusion of carotenoid-rich micelles towards the brush  
435 border.

436 This was confirmed in a study showing that a diet rich in pectin, guar gum, alginate cellulose  
437 or wheat bran (0.15 g/kg body weight) decreased lutein bioavailability (Riedl, Linseisen,  
438 Hoffmann, & Wolfram, 1999).

439

#### 440 6.4.3 Fat absorption inhibitors

441

442 Since obesity is a major health problem, several drugs have been designed to decrease  
443 fat absorption. However, these drugs could decrease lipid micronutrient absorption as well.  
444 Orlistat, an inhibitor of gastric and pancreatic lipase, has been shown to decrease the  
445 absorption of  $\alpha$ - and  $\beta$ -carotene (McDuffie, Calis, Booth, Uwaifo, & Yanovski, 2002) while  
446 Olestra, a saccharose polyester used as a lipid substitute, has been shown to decrease the  
447 absorption of  $\beta$ -carotene and lycopene (Weststrate & Hof, 1995). Similarly, phytosterols,  
448 which are used to decrease cholesterol absorption efficiency, also decrease the absorption of  
449 some carotenoids ( $\alpha$ - and  $\beta$ -carotene and lycopene) (Clifton, et al., 2004; Richelle, et al.,  
450 2004) although no effect was observed on  $\beta$ -cryptoxanthin bioavailability following the  
451 consumption of a milk-based fruit drink with or without plant free sterols for 28 days  
452 (Granado-Lorencio, Donoso-Navarro, Sanchez-Siles, Blanco-Navarro, & Perez-Sacristan,  
453 2011).

454

#### 455 6.4.4 Micronutrients

456 Since carotenoids are consumed together with other micronutrients, and since common  
457 absorption mechanisms are involved, it is hypothesized that some micronutrients compete  
458 with carotenoids regarding their absorption. Some results support this hypothesis: indeed,  
459 carotenoids have been shown to compete together for their incorporation into mixed micelles  
460 and subsequent uptake by enterocytes (During, et al., 2002; Tyssandier, Cardinault, et al.,  
461 2002; Tyssandier, et al., 2001; van den Berg, 1999). However, the effect of such competition  
462 on long term carotenoid status is not yet certain (Tyssandier, Cardinault, et al., 2002). On the  
463 other hand, microconstituants such as vitamin C, polyphenols and vitamin E are thought to  
464 protect carotenoids against oxidative degradation in the gastro-intestinal tract, and thus  
465 increase their absorption efficiency. The results are here conflicting since vitamin C has been  
466 suggested to increase lutein absorption (Tanumihardjo, Li, & Dosti, 2005), but results from

467 our lab are in disagreement: the postprandial lutein response to a lutein-rich meal containing a  
468 mixture of antioxidants, including vitamin C, was not different compared to a lutein-rich meal  
469 only (Reboul, et al., 2007). Additionally, vitamin C had no effect on lutein uptake by Caco-2  
470 cells.

471

#### 472 6.4.5 Minerals

473

474 Divalent minerals have been suggested to impair the *in vitro* bioaccessibility of lutein,  
475 neoxanthin, lycopene and  $\beta$ -carotene, with calcium having the most pronounced effect (100%  
476 reduction when added at 1000 mg/l) (Corte-Real, et al., 2016). In agreement with these  
477 results, the bioavailability of lycopene in humans has recently been shown to be significantly  
478 diminished when calcium was added at a nutritional dose to a test meal (83% reduction)  
479 (Borel, et al., 2017). These results call for a thorough assessment of the effects of calcium, or  
480 other divalent minerals, on the bioavailability of carotenoids.

481

#### 482 6.5 Vitamin A (Nutrient) status of the host

483

484 The variability in  $\beta$ -carotene absorption has been associated with host vitamin A  
485 status: following its activation by retinoic acid, the intestinal transcription factor Intestine  
486 Specific Homeobox (ISX) has been shown to function as a repressor of *SCARBI* and *BCOI*  
487 expression (Lobo, et al., 2010). This mechanism is thought to serve as a negative feedback  
488 loop regulating retinol status through modulation of provitamin A carotenoid absorption and  
489 cleavage efficiencies. Moreover, the presence of a SNP in the ISX binding site in the *BCOI*  
490 promoter was associated with decreased conversion rates by 50% and increased fasting blood  
491 levels of  $\beta$ -carotene (Lobo, et al., 2013). Since lutein and lycopene are also absorbed via SR-  
492 BI, it can be hypothesized that the host vitamin A status also has an effect on the absorption of  
493 these carotenoids (Widjaja-Adhi, Lobo, Golczak, & Von Lintig, 2015).

494

#### 495 6.6 Genetic factors

496

497 The involvement of several proteins in the intestinal absorption of carotenoids (apical  
498 uptake) suggests that variations in the genes encoding these proteins could modulate  
499 carotenoid absorption efficiency. This has been confirmed in an association study by Borel *et*  
500 *al.* (2007) where the influence of candidate SNPs of genes involved in lipid metabolism on

501 the fasting blood concentration of several carotenoids was investigated. More specifically,  
502 SNPs in *SCARB1* were associated with  $\beta$ -carotene but not with lycopene concentrations.  
503 These SNPs explained differences in  $\beta$ -carotene plasma concentrations by up to 50%. Several  
504 additional SNPs have meanwhile been identified (Borel, 2012), including several in *BCO1* in  
505 genome-wide association studies (Ferrucci, et al., 2009; Wood, et al., 2013). Three recent  
506 studies have reported associations of combinations of SNPs involved in interindividual  
507 variability of the bioavailability of lutein (Borel, et al., 2014), lycopene (Borel,  
508 Desmarchelier, Nowicki, & Bott, 2015b) and  $\beta$ -carotene (Borel, Desmarchelier, Nowicki, &  
509 Bott, 2015a), employing a candidate gene approach in postprandial studies. In these studies,  
510 plasma chylomicron carotenoids, representing newly absorbed carotenoids, were measured in  
511 healthy male adults. These combinations were associated with 73, 72 and 69% of the  
512 interindividual variability of the bioavailability of lutein, lycopene and  $\beta$ -carotene,  
513 respectively. While some SNPs were located in genes expressed in other tissues or were  
514 closely involved in plasma chylomicron metabolism, others were involved with carotenoid  
515 transport or metabolism at the enterocyte level. These included *ABCA1*, *ABCG5*, *BCO1*,  
516 *CD36*, *ELOVL2* (*ELOVL fatty acid elongase 2*), and *ISX*. Interestingly, one SNP in *ELOVL2*  
517 (rs9468304) was very strongly associated with all three phenotypes, possibly due to the  
518 inhibitory effect of eicosapentaenoic acid, which is further elongated to docosapentaenoic  
519 acid and docosahexaenoic acid by *ELOVL2*, on carotenoid absorption, as has been shown  
520 with  $\beta$ -carotene (Mashurabad, et al., 2016).

521

## 522 **6.7 Host-related factors**

523

524 Several studies have shown that some host-related factors could modulate carotenoid  
525 absorption (*see* (Bohn, et al., 2017) for a recent review).

526

### 527 **6.7.1 Gender**

528

529 Females usually exhibit higher blood carotenoid concentrations than men (Brady,  
530 Maresperlman, Bowen, & Stacewiczapuntzakis, 1996). This can be due to several reasons:  
531 differences in fruit and vegetable consumption (which are the main sources of carotenoids),  
532 differences in carotenoid absorption efficiency, differences in total blood volume (which is  
533 lower in women and hence will lead to a higher blood carotenoid concentration following the  
534 consumption of a similar amount of carotenoids) and differences in metabolism. The second

535 hypothesis was ruled out by a study in which no differences in  $\beta$ -carotene bioavailability  
536 (including the corresponding appearance of retinyl palmitate in the chylomicron fraction) was  
537 observed between men and women following the consumption of 40 mg encapsulated  $\beta$ -  
538 carotene with a standard meal (O'Neill & Thurnham, 1998).

539

#### 540 6.7.2 Age

541

542 The observed deterioration of gastro-intestinal tract functions concomitant with aging  
543 (Ikuma, Hanai, Kaneko, Hayashi, & Hoshi, 1996; Vellas, Balas, & Albaredo, 1991) could  
544 affect carotenoid absorption efficiency. Although this has been shown in the case of lycopene,  
545 no differences in  $\alpha$ -,  $\beta$ -carotene and lutein absorption efficiency were observed between  
546 young and older subjects (Cardinault, et al., 2003).

547

#### 548 6.7.3 Diseases

549

550 Any disease that alter the intestinal mucosal surface area can potentially alter  
551 carotenoid absorption efficiency. As most studies do not directly measure carotenoid  
552 bioavailability but rather look at carotenoid status (usually their fasting blood concentration),  
553 it is of paramount importance to control for carotenoid dietary intake since indirect effects of  
554 the disease on carotenoid absorption can also occur (through dietary adaptations, *e.g.* high  
555 fibre or low fat diet). Patients with cystic fibrosis have been shown to have lower plasma  
556 lutein and zeaxanthin concentrations compared to healthy subjects (Homnick, Cox, DeLoof,  
557 & Ringer, 1993; Schupp, et al., 2004). Several studies have shown that patients with Crohn's  
558 disease also exhibited lower fasting blood carotenoid concentrations (Drai, et al., 2009;  
559 Geerling, Badart-Smook, Stockbrugger, & Brummer, 1998; Genser, Kang, Vogelsang, &  
560 Elmadfa, 1999). In another study, subjects with Celiac disease and Crohn's disease showed  
561 37% decreased levels of macular carotenoids compared to controls despite normal serum  
562 carotenoids levels (Ward, Zhao, & Bernstein, 2008).

563

564 Surgical removal of parts of the gastro-intestinal tract can also reduce carotenoid  
565 absorption efficiency. Patients undergoing bariatric surgery (Roux-en-Y gastric bypass and  
566 biliopancreatic diversion) have been reported to display lower blood carotenoid  
567 concentrations despite apparently normal fruit and vegetable consumption (Granado-  
568 Lorenzo, Simal-Anton, Blanco-Navarro, Gonzalez-Dominguez, & Perez-Sacristan, 2011).  
Short bowel syndrome, usually due to large resections of the small intestine to treat

569 pathologies such as Crohn's disease or gastrointestinal tumours, have also been associated  
570 with carotenoid malabsorption: Edes *et al.* (1991) reported undetectable  $\beta$ -carotene blood  
571 levels following supplementation, despite adequate fat absorption, in a patient with extensive  
572 small intestinal resection (serum vitamin A levels appeared normal) while in another study, no  
573 increase in blood carotenoid concentration were reported in patients given a 12-week-long  
574 supplementation with  $\beta$ -carotene, lutein and lycopene, most likely due to low fat absorption in  
575 these patients (about 30% vs >95% in healthy subjects) (Luo, et al., 2009).

576

577 Intestinal parasites and gastro-intestinal tract dysbiosis (*e.g.* bacterial overgrowth) can  
578 also damage mucosal cells and result in increased permeability and decreased absorption of  
579 nutrients. Indonesian children infected with intestinal helminths exhibited greater increase in  
580 serum retinol concentrations when they were dewormed following consumption of red sweet  
581 potato (Jalal, Nesheim, Agus, Sanjur, & Habicht, 1998), possibly due to improved fat  
582 absorption.

583

## 584 **6.8 Mathematical Interactions**

585

586 Several of the above-mentioned factors can interact together, with an additive,  
587 synergistic or antagonist effect. Albeit there are no dedicated studies, it can be hypothesized  
588 that, although there is no effect of lutein esterification on its bioavailability in healthy subjects  
589 (*see* section 6.1), it is likely that this effect will be significantly higher in patients with lipid  
590 malabsorption, *i.e.* with low pancreatic secretion and thus esterases which hydrolyse lutein  
591 esters.

592

## 593 **Conclusions**

594

595 The absorption mechanisms of carotenoids are complex. This review underlines the  
596 vast amount of work still needed to improve our knowledge of carotenoid absorption and its  
597 modulating factors ("SLAMENGHI") (*see* (Bohn, et al., 2015) for a recent review). Indeed,  
598 several key points still need to be investigated:

- 599 - Is a fraction of carotenoids solubilised in the vesicles present in the lumen of the duodenum  
600 during digestion and if so, how does this affect their absorption?  
601 - What are the best dietary sources of carotenoids as far as absorption efficiency is concerned?  
602 - What are the other membrane proteins involved in carotenoid absorption?

603 - What is the intracellular enterocyte metabolism of carotenoids?  
604 - Is a fraction of carotenoids secreted in intestinal HDL? If so, does it affect their metabolism  
605 or their tissue distribution?  
606 - How to explain carotenoid distribution between the different tissues?  
607 - Is there a reverse transport of carotenoids from peripheral tissues towards liver?  
608 Several strategies can be applied in order to improve carotenoid bioavailability, *e.g.* to modify  
609 technological treatments or to provide food preparation advice, to provide nutritional  
610 recommendations (*e.g.* to consume carotenoids with lipids), to create formulations protecting  
611 carotenoids or improving their absorption (*e.g.* nanoencapsulation). There is a high  
612 interindividual variability of carotenoid bioavailability, which is partly due to genetic  
613 polymorphisms. The identification of additional SNPs and epigenetic factors involved in this  
614 variability is a promising area of research which, together with the identification of other  
615 factors might lead to propose more personalised recommendations in order to increase the  
616 health effects of carotenoids.

**Figure 1.** Proteins involved in uptake, transport and secretion pathways of carotenoids and their metabolites across the enterocyte.

(A) Unidentified apical uptake transporter; (B) unidentified apical efflux transporter; (C) passive diffusion; (D) unidentified basolateral efflux transporter. The transport into the enterocyte of carotenoids incorporated into mixed micelles following digestion is facilitated by apical membrane proteins: SR-BI (scavenger receptor class B type I), CD36 (cluster of differentiation 36) and NPC1L1 (Niemann–Pick C1-Like 1) and possibly other transporters. A fraction thereof might be effluxed back to the intestinal lumen via apical membrane transporters (SR-BI and possibly other transporters) while the remaining fraction is transported to the site where they are incorporated into chylomicrons. Although some proteins are hypothesized to be involved in intracellular transport of carotenoids, none has been identified yet. However, CRBP II (cellular retinol binding protein II) has been shown to be involved in the intracellular transport of retinol. Carotenoids can be metabolized by BCO1 (beta-carotene oxygenase 1), which is located in the cytosol, and BCO2 (beta-carotene oxygenase 2), which is associated with the inner mitochondrial membrane, while non-metabolized carotenoids are secreted into the lymph in chylomicrons. A fraction of carotenoids could also be secreted into the lymph in HDL (apolipoprotein AI dependent route) involving the transporter ATP binding cassette AI (ABCA1), as has been shown for lutein and zeaxanthin. Carotenoid metabolites, *e.g.* apo-carotenoids, are assumed to be secreted into the portal vein by unknown mechanisms.

**Figure 2.** Blood transport of carotenoids in humans.

Following their uptake (see **Figure 1** for details), carotenoids are secreted into the blood circulation in chylomicrons (apolipoprotein B-dependent route) or also possibly in HDL (apolipoprotein A1-dependent route), as has been shown for lutein and zeaxanthin. Carotenoids that reach the liver can then be stored, or metabolised following BCO1 and BCO2 enzymatic cleavage, secreted in VLDL or excreted in the bile. A part of carotenoids secreted in VLDL are then found in LDL, following VLDL metabolism, and can then be exchanged with other lipoproteins and/or be taken up by target tissues. The blood transport of carotenoid metabolites is scarcely known and hence not depicted in this figure.



## References

- Akbaraly, T. N., Fontbonne, A., Favier, A., & Berr, C. (2008). Plasma carotenoids and onset of dysglycemia in an elderly population: results of the Epidemiology of Vascular Ageing Study. *Diabetes Care*, *31*, 1355-1359.
- Amengual, J., Lobo, G. P., Golczak, M., Li, H. N., Klimova, T., Hoppel, C. L., Wyss, A., Palczewski, K., & von Lintig, J. (2011). A mitochondrial enzyme degrades carotenoids and protects against oxidative stress. *Faseb J*, *25*, 948-959.
- Amengual, J., Widjaja-Adhi, M. A., Rodriguez-Santiago, S., Hessel, S., Golczak, M., Palczewski, K., & von Lintig, J. (2013). Two carotenoid oxygenases contribute to mammalian provitamin A metabolism. *J Biol Chem*, *288*, 34081-34096.
- Aronow, M. E., & Chew, E. Y. (2014). Age-related Eye Disease Study 2: perspectives, recommendations, and unanswered questions. *Curr Opin Ophthalmol*, *25*, 186-190.
- Aschoff, J. K., Rolke, C. L., Breusing, N., Bosy-Westphal, A., Hogel, J., Carle, R., & Schweiggert, R. M. (2015). Bioavailability of beta-cryptoxanthin is greater from pasteurized orange juice than from fresh oranges - a randomized cross-over study. *Mol Nutr Food Res*, *59*, 1896-1904.
- Ben-Amotz, A., & Levy, Y. (1996). Bioavailability of a natural isomer mixture compared with synthetic all-trans beta-carotene in human serum. *Am J Clin Nutr*, *63*, 729-734.
- Bernstein, P. S., Khachik, F., Carvalho, L. S., Muir, G. J., Zhao, D. Y., & Katz, N. B. (2001). Identification and quantitation of carotenoids and their metabolites in the tissues of the human eye. *Exp Eye Res*, *72*, 215-223.
- Bohn, T., Desmarchelier, C., Dragsted, L. O., Nielsen, C. S., Stahl, W., Rühl, R., Keijer, J., & Borel, P. (2017). Host-related Factors Explaining Interindividual Variability of Carotenoid Bioavailability and Tissue Concentrations in Humans. *Mol Nutr Food Res*, *In Press*.
- Bohn, T., McDougall, G. J., Alegria, A., Alminger, M., Arrigoni, E., Aura, A. M., Brito, C., Cilla, A., El, S. N., Karakaya, S., Martinez-Cuesta, M. C., & Santos, C. N. (2015). Mind the gap-deficits in our knowledge of aspects impacting the bioavailability of phytochemicals and their metabolites--a position paper focusing on carotenoids and polyphenols. *Mol Nutr Food Res*, *59*, 1307-1323.
- Boileau, T. W., Boileau, A. C., & Erdman, J. W. (2002). Bioavailability of all-trans and cis-isomers of lycopene. *Exp Biol Med (Maywood)*, *227*, 914-919.
- Borel, P. (2012). Genetic variations involved in interindividual variability in carotenoid status. *Mol Nutr Food Res*, *56*, 228-240.
- Borel, P., Desmarchelier, C., Dumont, U., Halimi, C., Lairon, D., Page, D., Sébédio, J. L., Buisson, C., Buffière, C., & Rémond, D. (2017). Dietary calcium impairs tomato lycopene bioavailability in healthy humans. *Br J Nutr*, *In Press*.
- Borel, P., Desmarchelier, C., Nowicki, M., & Bott, R. (2015a). A combination of single-nucleotide polymorphisms is associated with interindividual variability in dietary beta-carotene bioavailability in healthy men. *J Nutr*, *145*, 1740-1747.
- Borel, P., Desmarchelier, C., Nowicki, M., & Bott, R. (2015b). Lycopene bioavailability is associated with a combination of genetic variants. *Free Radic Biol Med*, *83*, 238-244.
- Borel, P., Desmarchelier, C., Nowicki, M., Bott, R., Morange, S., & Lesavre, N. (2014). Interindividual variability of lutein bioavailability in healthy men: characterization, genetic variants involved, and relation with fasting plasma lutein concentration. *Am J Clin Nutr*, *100*, 168-175.

- Borel, P., Grolier, P., Armand, M., Partier, A., Lafont, H., Lairon, D., & Azais-Braesco, V. (1996). Carotenoids in biological emulsions: solubility, surface-to-core distribution, and release from lipid droplets. *J Lipid Res*, *37*, 250-261.
- Borel, P., Lietz, G., Goncalves, A., Szabo de Edelenyi, F., Lecompte, S., Curtis, P., Goumidi, L., Caslake, M. J., Miles, E. A., Packard, C., Calder, P. C., Mathers, J. C., Minihaue, A. M., Tourniaire, F., Kesse-Guyot, E., Galan, P., Hercberg, S., Breidenassel, C., Gonzalez Gross, M., Moussa, M., Meirhaeghe, A., & Reboul, E. (2013). CD36 and SR-BI are involved in cellular uptake of provitamin A carotenoids by Caco-2 and HEK cells, and some of their genetic variants are associated with plasma concentrations of these micronutrients in humans. *J Nutr*, *143*, 448-456.
- Borel, P., Moussa, M., Reboul, E., Lyan, B., Defoort, C., Vincent-Baudry, S., Maillot, M., Gastaldi, M., Darmon, M., Portugal, H., Planells, R., & Lairon, D. (2007). Human plasma levels of vitamin E and carotenoids are associated with genetic polymorphisms in genes involved in lipid metabolism. *J Nutr*, *137*, 2653-2659.
- Borel, P., Tyssandier, V., Mekki, N., Grolier, P., Rochette, Y., Alexandre-Gouabau, M. C., Lairon, D., & Azais-Braesco, V. (1998). Chylomicron beta-carotene and retinyl palmitate responses are dramatically diminished when men ingest beta-carotene with medium-chain rather than long-chain triglycerides. *J Nutr*, *128*, 1361-1367.
- Bowen, P. E., Herbst-Espinosa, S. M., Hussain, E. A., & Stacewicz-Sapuntzakis, M. (2002). Esterification does not impair lutein bioavailability in humans. *J Nutr*, *132*, 3668-3673.
- Brady, W. E., Maresperlman, J. A., Bowen, P., & Stacewiczsapuntzakis, M. (1996). Human serum carotenoid concentrations are related to physiologic and lifestyle factors. *J Nutr*, *126*, 129-137.
- Breithaupt, D. E., & Bamedi, A. (2001). Carotenoid esters in vegetables and fruits: a screening with emphasis on beta-cryptoxanthin esters. *J Agric Food Chem*, *49*, 2064-2070.
- Breithaupt, D. E., Bamedi, A., & Wirt, U. (2002). Carotenol fatty acid esters: easy substrates for digestive enzymes? *Comp Biochem Physiol B Biochem Mol Biol*, *132*, 721-728.
- Breithaupt, D. E., Weller, P., Wolters, M., & Hahn, A. (2003). Plasma response to a single dose of dietary beta-cryptoxanthin esters from papaya (*Carica papaya* L.) or non-esterified beta-cryptoxanthin in adult human subjects: a comparative study. *Br J Nutr*, *90*, 795-801.
- Breithaupt, D. E., Weller, P., Wolters, M., & Hahn, A. (2004). Comparison of plasma responses in human subjects after the ingestion of 3R,3R'-zeaxanthin dipalmitate from wolfberry (*Lycium barbarum*) and non-esterified 3R,3R'-zeaxanthin using chiral high-performance liquid chromatography. *Br J Nutr*, *91*, 707-713.
- Britton, G. (1995). Structure and properties of carotenoids in relation to function. *Faseb J*, *9*, 1551-1558.
- Buniowska, M., Carbonell-Capella, J. M., Frigola, A., & Esteve, M. J. (2017). Bioaccessibility of bioactive compounds after non-thermal processing of an exotic fruit juice blend sweetened with *Stevia rebaudiana*. *Food Chem*, *221*, 1834-1842.
- Cardinault, N., Tyssandier, V., Grolier, P., Winklhofer-Roob, B. M., Ribalta, J., Bouteloup-Demange, C., Rock, E., & Borel, P. (2003). Comparison of the postprandial chylomicron carotenoid responses in young and older subjects. *Eur J Nutr*, *42*, 315-323.
- Carriere, F., Barrowman, J. A., Verger, R., & Laugier, R. (1993). Secretion and contribution to lipolysis of gastric and pancreatic lipases during a test meal in humans. *Gastroenterology*, *105*, 876-888.

- Chung, H. Y., Rasmussen, H. M., & Johnson, E. J. (2004). Lutein bioavailability is higher from lutein-enriched eggs than from supplements and spinach in men. *J Nutr*, *134*, 1887-1893.
- Clifton, P. M., Noakes, M., Ross, D., Fassoulakis, A., Cehun, M., & Nestel, P. (2004). High dietary intake of phytosterol esters decreases carotenoids and increases plasma plant sterol levels with no additional cholesterol lowering. *J Lipid Res*, *45*, 1493-1499.
- Clinton, S. K., Emenhiser, C., Schwartz, S. J., Bostwick, D. G., Williams, A. W., Moore, B. J., & Erdman, J. W., Jr. (1996). cis-trans lycopene isomers, carotenoids, and retinol in the human prostate. *Cancer Epidemiol Biomarkers Prev*, *5*, 823-833.
- Cooperstone, J. L., Ralston, R. A., Riedl, K. M., Haufe, T. C., Schweiggert, R. M., King, S. A., Timmers, C. D., Francis, D. M., Lesinski, G. B., Clinton, S. K., & Schwartz, S. J. (2015). Enhanced bioavailability of lycopene when consumed as cis-isomers from tangerine compared to red tomato juice, a randomized, cross-over clinical trial. *Mol Nutr Food Res*, *59*, 658-669.
- Corte-Real, J., Iddir, M., Soukoulis, C., Richling, E., Hoffmann, L., & Bohn, T. (2016). Effect of divalent minerals on the bioaccessibility of pure carotenoids and on physical properties of gastro-intestinal fluids. *Food Chem*, *197*, 546-553.
- Curran-Celentano, J., Hammond, B. R., Jr., Ciulla, T. A., Cooper, D. A., Pratt, L. M., & Danis, R. B. (2001). Relation between dietary intake, serum concentrations, and retinal concentrations of lutein and zeaxanthin in adults in a Midwest population. *Am J Clin Nutr*, *74*, 796-802.
- dela Sena, C., Narayanasamy, S., Riedl, K. M., Curley, R. W., Jr., Schwartz, S. J., & Harrison, E. H. (2013). Substrate specificity of purified recombinant human beta-carotene 15,15'-oxygenase (BCO1). *J Biol Chem*, *288*, 37094-37103.
- dela Sena, C., Riedl, K. M., Narayanasamy, S., Curley, R. W., Jr., Schwartz, S. J., & Harrison, E. H. (2014). The human enzyme that converts dietary provitamin A carotenoids to vitamin A is a dioxygenase. *J Biol Chem*, *289*, 13661-13666.
- Diwadkar-Navsariwala, V., Novotny, J. A., Gustin, D. M., Sosman, J. A., Rodvold, K. A., Crowell, J. A., Stacewicz-Sapuntzakis, M., & Bowen, P. E. (2003). A physiological pharmacokinetic model describing the disposition of lycopene in healthy men. *J Lipid Res*, *44*, 1927-1939.
- Drai, J., Borel, P., Faure, H., Galabert, C., Le Moel, G., Laromiguiere, M., & Fayol, V. (2009). Fasting plasma carotenoids concentrations in Crohn's and pancreatic cancer patients compared to control subjects. *Int J Vitam Nutr Res*, *79*, 87-94.
- During, A., Dawson, H. D., & Harrison, E. H. (2005). Carotenoid transport is decreased and expression of the lipid transporters SR-BI, NPC1L1, and ABCA1 is downregulated in Caco-2 cells treated with ezetimibe. *J Nutr*, *135*, 2305-2312.
- During, A., Hussain, M. M., Morel, D. W., & Harrison, E. H. (2002). Carotenoid uptake and secretion by Caco-2 cells: beta-carotene isomer selectivity and carotenoid interactions. *J Lipid Res*, *43*, 1086-1095.
- Eastwood, M., & Mowbray, L. (1976). The binding of the components of mixed micelle to dietary fiber. *Am J Clin Nutr*, *29*, 1461-1467.
- Edes, T. E., Walk, B. E., Thornton, W. H., Jr., & Fritsche, K. L. (1991). Essential fatty acid sufficiency does not preclude fat-soluble-vitamin deficiency in short-bowel syndrome. *Am J Clin Nutr*, *53*, 499-502.
- Ferrucci, L., Perry, J. R., Matteini, A., Perola, M., Tanaka, T., Silander, K., Rice, N., Melzer, D., Murray, A., Cluett, C., Fried, L. P., Albanes, D., Corsi, A. M., Cherubini, A., Guralnik, J., Bandinelli, S., Singleton, A., Virtamo, J., Walston, J., Semba, R. D., & Frayling, T. M. (2009). Common variation in the beta-carotene 15,15'-monooxygenase

- 1 gene affects circulating levels of carotenoids: a genome-wide association study. *Am J Hum Genet*, 84, 123-133.
- Ferruzzi, M. G., Lumpkin, J. L., Schwartz, S. J., & Failla, M. (2006). Digestive Stability, micellarization, and uptake of beta-carotene isomers by Caco-2 human intestinal cells. *J Agric Food Chem*, 54, 2780-2785.
- Gallaher, D. D., Hassel, C. A., Lee, K. J., & Gallaher, C. M. (1993). Viscosity and fermentability as attributes of dietary fiber responsible for the hypocholesterolemic effect in hamsters. *J Nutr*, 123, 244-252.
- Geerling, B. J., Badart-Smook, A., Stockbrugger, R. W., & Brummer, R. J. (1998). Comprehensive nutritional status in patients with long-standing Crohn disease currently in remission. *Am J Clin Nutr*, 67, 919-926.
- Genser, D., Kang, M. H., Vogelsang, H., & Elmadfa, I. (1999). Status of lipidsoluble antioxidants and TRAP in patients with Crohn's disease and healthy controls. *Eur J Clin Nutr*, 53, 675-679.
- Gleize, B., Tourniaire, F., Depeyay, L., Bott, R., Nowicki, M., Albino, L., Lairon, D., Kesse-Guyot, E., Galan, P., Hercberg, S., & Borel, P. (2013). Effect of type of TAG fatty acids on lutein and zeaxanthin bioavailability. *Br J Nutr*, 110, 1-10.
- Goltz, S. R., Campbell, W. W., Chitchumroonchokchai, C., Failla, M. L., & Ferruzzi, M. G. (2012). Meal triacylglycerol profile modulates postprandial absorption of carotenoids in humans. *Mol Nutr Food Res*, 56, 866-877.
- Granado-Lorencio, F., Donoso-Navarro, E., Sanchez-Siles, L. M., Blanco-Navarro, I., & Perez-Sacristan, B. (2011). Bioavailability of beta-cryptoxanthin in the presence of phytosterols: in vitro and in vivo studies. *J Agric Food Chem*, 59, 11819-11824.
- Granado-Lorencio, F., Simal-Anton, A., Blanco-Navarro, I., Gonzalez-Dominguez, T., & Perez-Sacristan, B. (2011). Depletion of serum carotenoid and other fat-soluble vitamin concentrations following obesity surgery. *Obes Surg*, 21, 1605-1611.
- Gupta, R., Kopec, R. E., Schwartz, S. J., & Balasubramaniam, V. M. (2011). Combined pressure-temperature effects on carotenoid retention and bioaccessibility in tomato juice. *J Agric Food Chem*, 59, 7808-7817.
- Hansen, G. H., Niels-Christiansen, L. L., Immerdal, L., & Danielsen, E. M. (2003). Scavenger receptor class B type I (SR-BI) in pig enterocytes: trafficking from the brush border to lipid droplets during fat absorption. *Gut*, 52, 1424-1431.
- Hansen, W. E. (1987). Effect of dietary fiber on pancreatic lipase activity in vitro. *Pancreas*, 2, 195-198.
- Haskell, M. J. (2012). The challenge to reach nutritional adequacy for vitamin A: beta-carotene bioavailability and conversion--evidence in humans. *Am J Clin Nutr*, 96, 1193s-1203s.
- Hollander, D., & Ruble, P. E. (1978). beta-carotene intestinal absorption: bile, fatty acid, pH, and flow rate effects on transport. *Am J Physiol*, 235, E686-691.
- Homnick, D. N., Cox, J. H., DeLoof, M. J., & Ringer, T. V. (1993). Carotenoid levels in normal children and in children with cystic fibrosis. *J Pediatr*, 122, 703-707.
- Ikuma, M., Hanai, H., Kaneko, E., Hayashi, H., & Hoshi, T. (1996). Effects of aging on the microclimate pH of the rat jejunum. *Biochim Biophys Acta*, 1280, 19-26.
- Jalal, F., Nesheim, M. C., Agus, Z., Sanjur, D., & Habicht, J. P. (1998). Serum retinol concentrations in children are affected by food sources of beta-carotene, fat intake, and anthelmintic drug treatment. *Am J Clin Nutr*, 68, 623-629.
- Jian, L., Du, C. J., Lee, A. H., & Binns, C. W. (2005). Do dietary lycopene and other carotenoids protect against prostate cancer? *Int J Cancer*, 113, 1010-1014.
- Johnson, E. J. (2012). A possible role for lutein and zeaxanthin in cognitive function in the elderly. *Am J Clin Nutr*, 96, 1161s-1165s.

- Johnson, E. J., Neuringer, M., Russell, R. M., Schalch, W., & Snodderly, D. M. (2005). Nutritional manipulation of primate retinas, III: Effects of lutein or zeaxanthin supplementation on adipose tissue and retina of xanthophyll-free monkeys. *Invest Ophthalmol Vis Sci*, *46*, 692-702.
- Khachik, F., Beecher, G. R., Goli, M., Lusby, W. R., & Smith, J. C. (1992). Separation and identification of carotenoids and their oxidation products in the extracts of human plasma. *Anal Chem*, *64*, 2111-2122.
- Kim, J. E., Gordon, S. L., Ferruzzi, M. G., & Campbell, W. W. (2015). Effects of egg consumption on carotenoid absorption from co-consumed, raw vegetables. *Am J Clin Nutr*, *102*, 75-83.
- Kopec, R. E., Cooperstone, J. L., Schweiggert, R. M., Young, G. S., Harrison, E. H., Francis, D. M., Clinton, S. K., & Schwartz, S. J. (2014). Avocado consumption enhances human postprandial provitamin A absorption and conversion from a novel high-beta-carotene tomato sauce and from carrots. *J Nutr*, *144*, 1158-1166.
- Landrum, J. T., Bone, R. A., Joa, H., Kilburn, M. D., Moore, L. L., & Sprague, K. E. (1997). A one year study of the macular pigment: the effect of 140 days of a lutein supplement. *Exp Eye Res*, *65*, 57-62.
- Levin, G., & Mokady, S. (1995). Incorporation of all-trans- or 9-cis-beta-carotene into mixed micelles in vitro. *Lipids*, *30*, 177-179.
- Levin, M. S. (1993). Cellular retinol-binding proteins are determinants of retinol uptake and metabolism in stably transfected caco-2 cells. *J Biol Chem*, *268*, 8267-8276.
- Lindshield, B. L., Canene-Adams, K., & Erdman, J. W., Jr. (2007). Lycopene metabolites bioactive? *Arch Biochem Biophys*, *458*, 136-140.
- Lobo, G. P., Amengual, J., Baus, D., Shivdasani, R. A., Taylor, D., & von Lintig, J. (2013). Genetics and diet regulate vitamin A production via the homeobox transcription factor ISX. *J Biol Chem*, *288*, 9017-9027.
- Lobo, G. P., Hessel, S., Eichinger, A., Noy, N., Moise, A. R., Wyss, A., Palczewski, K., & von Lintig, J. (2010). ISX is a retinoic acid-sensitive gatekeeper that controls intestinal beta,beta-carotene absorption and vitamin A production. *Faseb J*, *24*, 1656-1666.
- Lu, W., Kelly, A. L., Maguire, P., Zhang, H., Stanton, C., & Miao, S. (2016). Correlation of Emulsion Structure with Cellular Uptake Behavior of Encapsulated Bioactive Nutrients: Influence of Droplet Size and Interfacial Structure. *J Agric Food Chem*, *64*, 8659-8666.
- Luo, M., Estivariz, C. F., Schleicher, R. L., Bazargan, N., Leader, L. M., Galloway, J. R., & Ziegler, T. R. (2009). Prospective analysis of serum carotenoids, vitamin A, and tocopherols in adults with short bowel syndrome undergoing intestinal rehabilitation. *Nutrition*, *25*, 400-407.
- Mares, J. (2016). Lutein and Zeaxanthin Isomers in Eye Health and Disease. *Annu Rev Nutr*, *36*, 571-602.
- Mashurabad, P. C., Kondaiah, P., Palika, R., Ghosh, S., Nair, M. K., & Raghu, P. (2016). Eicosapentaenoic acid inhibits intestinal beta-carotene absorption by downregulation of lipid transporter expression via PPAR-alpha dependent mechanism. *Arch Biochem Biophys*, *590*, 118-124.
- McDuffie, J. R., Calis, K. A., Booth, S. L., Uwaifo, G. I., & Yanovski, J. A. (2002). Effects of orlistat on fat-soluble vitamins in obese adolescents. *Pharmacotherapy*, *22*, 814-822.
- McEligot, A. J., Rock, C. L., Shanks, T. G., Flatt, S. W., Newman, V., Faerber, S., & Pierce, J. P. (1999). Comparison of serum carotenoid responses between women consuming vegetable juice and women consuming raw or cooked vegetables. *Cancer Epidemiology Biomarkers & Prevention*, *8*, 227-231.

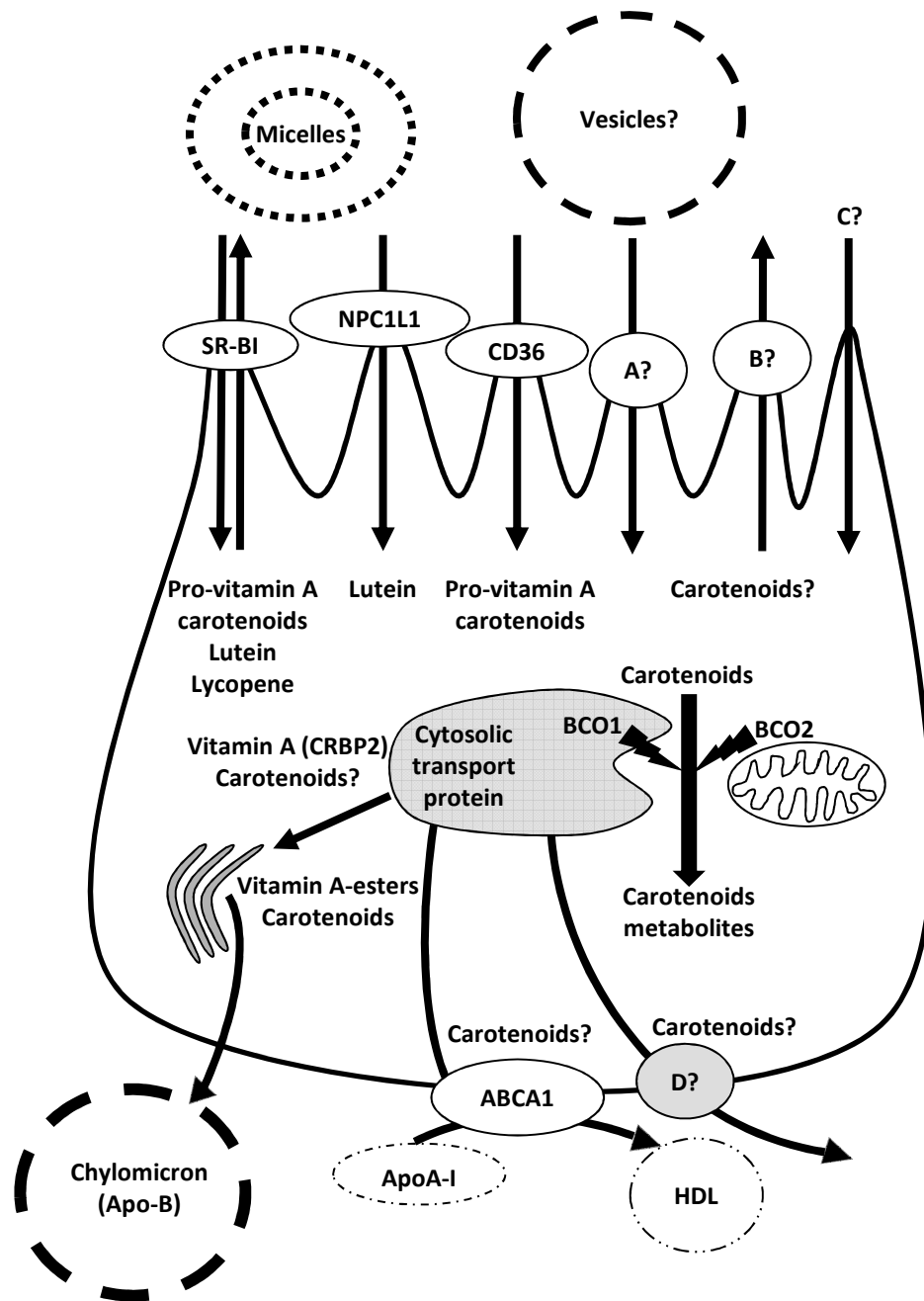
- Milanowska, J., & Gruszecki, W. I. (2005). Heat-induced and light-induced isomerization of the xanthophyll pigment zeaxanthin. *J Photochem Photobiol B*, *80*, 178-186.
- Milanowska, J., Polit, A., Wasylewski, Z., & Gruszecki, W. I. (2003). Interaction of isomeric forms of xanthophyll pigment zeaxanthin with dipalmitoylphosphatidylcholine studied in monomolecular layers. *J Photochem Photobiol B*, *72*, 1-9.
- Mortensen, A., & Skibsted, L. H. (2000). Kinetics and mechanism of the primary steps of degradation of carotenoids by acid in homogeneous solution. *J Agri Food Chem*, *48*, 279-286.
- Moussa, M., Gouranton, E., Gleize, B., Yazidi, C. E., Niot, I., Besnard, P., Borel, P., & Landrier, J. F. (2011). CD36 is involved in lycopene and lutein uptake by adipocytes and adipose tissue cultures. *Mol Nutr Food Res*, *55*, 578-584.
- Moussa, M., Landrier, J. F., Reboul, E., Ghiringhelli, O., Comera, C., Collet, X., Frohlich, K., Bohm, V., & Borel, P. (2008). Lycopene absorption in human intestinal cells and in mice involves scavenger receptor class B type I but not Niemann-Pick C1-like 1. *J Nutr*, *138*, 1432-1436.
- Nidhi, B., Ramaprasad, T. R., & Baskaran, V. (2014). Dietary fatty acid determines the intestinal absorption of lutein in lutein deficient mice. *Food Research International*, *64*, 256-263.
- Niesor, E. J., Chaput, E., Mary, J. L., Staempfli, A., Topp, A., Stauffer, A., Wang, H., & Durrwell, A. (2014). Effect of compounds affecting ABCA1 expression and CETP activity on the HDL pathway involved in intestinal absorption of lutein and zeaxanthin. *Lipids*, *49*, 1233-1243.
- O'Neill, M. E., & Thurnham, D. I. (1998). Intestinal absorption of beta-carotene, lycopene and lutein in men and women following a standard meal: response curves in the triacylglycerol-rich lipoprotein fraction. *Br J Nutr*, *79*, 149-159.
- Palczewski, G., Amengual, J., Hoppel, C. L., & von Lintig, J. (2014). Evidence for compartmentalization of mammalian carotenoid metabolism. *Faseb J*, *28*, 4457-4469.
- Raghuvanshi, S., Reed, V., Blaner, W. S., & Harrison, E. H. (2015). Cellular localization of beta-carotene 15,15' oxygenase-1 (BCO1) and beta-carotene 9',10' oxygenase-2 (BCO2) in rat liver and intestine. *Arch Biochem Biophys*, *572*, 19-27.
- Reboul, E., Berton, A., Moussa, M., Kreuzer, C., Crenon, I., & Borel, P. (2006). Pancreatic lipase and pancreatic lipase-related protein 2, but not pancreatic lipase-related protein 1, hydrolyze retinyl palmitate in physiological conditions. *Biochim Biophys Acta*, *1761*, 4-10.
- Reboul, E., & Borel, P. (2011). Proteins involved in uptake, intracellular transport and basolateral secretion of fat-soluble vitamins and carotenoids by mammalian enterocytes. *Prog Lipid Res*, *50*, 388-402.
- Reboul, E., Richelle, M., Perrot, E., Desmoulins-Malezet, C., Pirisi, V., & Borel, P. (2006). Bioaccessibility of Carotenoids and Vitamin E from Their Main Dietary Sources. *J Agric Food Chem*, *54*, 8749-8755.
- Reboul, E., Thap, S., Tourniaire, F., Andre, M., Juhel, C., Morange, S., Amiot, M. J., Lairon, D., & Borel, P. (2007). Differential effect of dietary antioxidant classes (carotenoids, polyphenols, vitamins C and E) on lutein absorption. *Br J Nutr*, *97*, 440-446.
- Richelle, M., Enslin, M., Hager, C., Groux, M., Tavazzi, I., Godin, J. P., Berger, A., Metairon, S., Quaile, S., Piguët-Welsch, C., Sagalowicz, L., Green, H., & Fay, L. B. (2004). Both free and esterified plant sterols reduce cholesterol absorption and the bioavailability of beta-carotene and alpha-tocopherol in normocholesterolemic humans. *Am J Clin Nutr*, *80*, 171-177.

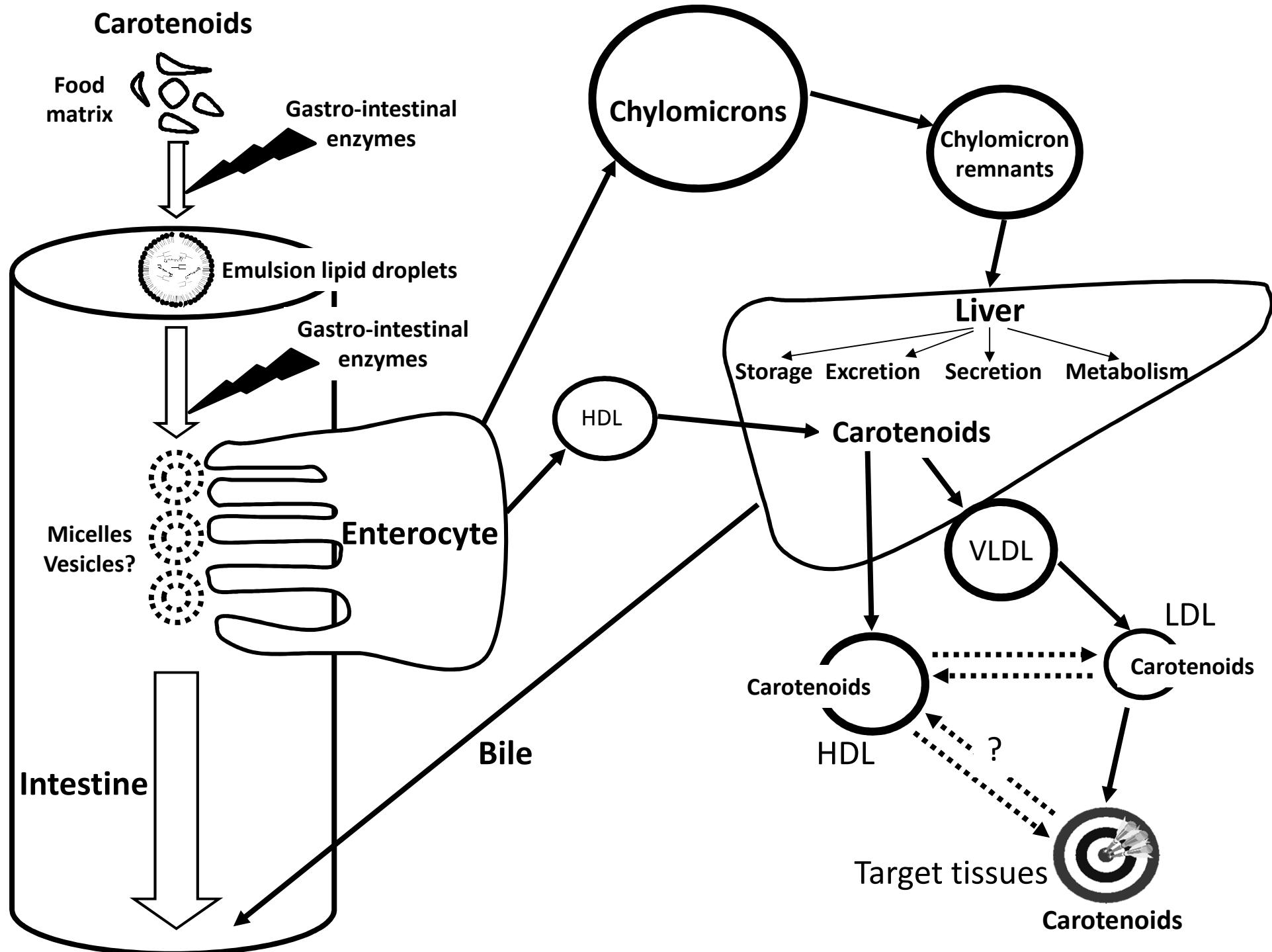
- Richelle, M., Sanchez, B., Tavazzi, I., Lambelet, P., Bortlik, K., & Williamson, G. (2010). Lycopene isomerisation takes place within enterocytes during absorption in human subjects. *Br J Nutr*, *103*, 1800-1807.
- Riedl, J., Linseisen, J., Hoffmann, J., & Wolfram, G. (1999). Some dietary fibers reduce the absorption of carotenoids in women. *J Nutr*, *129*, 2170-2176.
- Rigotti, A., Miettinen, H. E., & Krieger, M. (2003). The role of the high-density lipoprotein receptor SR-BI in the lipid metabolism of endocrine and other tissues. *Endocr Rev*, *24*, 357-387.
- Rodriguez-Amaya, D. B. (1999). Changes in carotenoids during processing and storage of foods. *Arch Latinoam Nutr*, *49*, 38S-47S.
- Roodenburg, A. J. C., Leenen, R., Hof, K. H. V., Weststrate, J. A., & Tijburg, L. B. M. (2000). Amount of fat in the diet affects bioavailability of lutein esters but not of alpha-carotene, beta-carotene, and vitamin E in humans. *Am J Clin Nutr*, *71*, 1187-1193.
- Sato, Y., Suzuki, R., Kobayashi, M., Itagaki, S., Hirano, T., Noda, T., Mizuno, S., Sugawara, M., & Iseki, K. (2012). Involvement of cholesterol membrane transporter Niemann-Pick C1-like 1 in the intestinal absorption of lutein. *J Pharm Pharm Sci*, *15*, 256-264.
- Schaeffer, J. L., & Hamilton, P. B. (1990). Effect of dietary lipid on lutein metabolism during aflatoxicosis in young broiler chickens. *Poult Sci*, *69*, 53-59.
- Schmitz, H. H., Poor, C. L., Wellman, R. B., & Erdman, J. W., Jr. (1991). Concentrations of selected carotenoids and vitamin A in human liver, kidney and lung tissue. *J Nutr*, *121*, 1613-1621.
- Schupp, C., Olano-Martin, E., Gerth, C., Morrissey, B. M., Cross, C. E., & Werner, J. S. (2004). Lutein, zeaxanthin, macular pigment, and visual function in adult cystic fibrosis patients. *Am J Clin Nutr*, *79*, 1045-1052.
- Schweiggert, R. M., & Carle, R. (2015). Carotenoid Deposition in Plant And Animal Foods and Its Impact on Bioavailability. *Crit Rev Food Sci Nutr*, *0*.
- Staggers, J. E., Hernell, O., Stafford, R. J., & Carey, M. C. (1990). Physical-chemical behavior of dietary and biliary lipids during intestinal digestion and absorption. 1. Phase behavior and aggregation states of model lipid systems patterned after aqueous duodenal contents of healthy adult human beings. *Biochemistry*, *29*, 2028-2040.
- Stahl, W., van den Berg, H., Arthur, J., Bast, A., Dainty, J., Faulks, R. M., Gartner, C., Haenen, G., Hollman, P., Holst, B., Kelly, F. J., Polidori, M. C., Rice-Evans, C., Southon, S., van Vliet, T., Vina-Ribes, J., Williamson, G., & Astley, S. B. (2002). Bioavailability and metabolism. *Mol Aspects Med*, *23*, 39-100.
- Sugawara, T., Kushi, M., Zhang, H., Nara, E., Ono, H., & Nagao, A. (2001). Lysophosphatidylcholine enhances carotenoid uptake from mixed micelles by Caco-2 human intestinal cells. *J Nutr*, *131*, 2921-2927.
- Sy, C., Gleize, B., Dangles, O., Landrier, J. F., Veyrat, C. C., & Borel, P. (2012). Effects of physicochemical properties of carotenoids on their bioaccessibility, intestinal cell uptake, and blood and tissue concentrations. *Mol Nutr Food Res*, *56*, 1385-1397.
- Tanaka, T., Shnimizu, M., & Moriwaki, H. (2012). Cancer chemoprevention by carotenoids. *Molecules*, *17*, 3202-3242.
- Tang, G., Qin, J., Dolnikowski, G. G., & Russell, R. M. (2003). Short-term (intestinal) and long-term (postintestinal) conversion of beta-carotene to retinol in adults as assessed by a stable-isotope reference method. *Am J Clin Nutr*, *78*, 259-266.
- Tanumihardjo, S. A., Li, J., & Dosti, M. P. (2005). Lutein absorption is facilitated with cosupplementation of ascorbic acid in young adults. *J Am Diet Assoc*, *105*, 114-118.
- Thomas, S. E., & Harrison, E. H. (2016). Mechanisms of selective delivery of xanthophylls to retinal pigment epithelial cells by human lipoproteins. *J Lipid Res*, *57*, 1865-1878.

- Tyssandier, V., Cardinault, N., Caris-Veyrat, C., Amiot, M. J., Grolier, P., Bouteloup, C., Azais-Braesco, V., & Borel, P. (2002). Vegetable-borne lutein, lycopene, and beta-carotene compete for incorporation into chylomicrons, with no adverse effect on the medium-term (3-wk) plasma status of carotenoids in humans. *Am J Clin Nutr*, *75*, 526-534.
- Tyssandier, V., Choubert, G., Grolier, P., & Borel, P. (2002). Carotenoids, mostly the xanthophylls, exchange between plasma lipoproteins. *Int J Vitam Nutr Res*, *72*, 300-308.
- Tyssandier, V., Lyan, B., & Borel, P. (2001). Main factors governing the transfer of carotenoids from emulsion lipid droplets to micelles. *Biochim Biophys Acta*, *1533*, 285-292.
- Tyssandier, V., Reboul, E., Dumas, J. F., Bouteloup-Demange, C., Armand, M., Marcand, J., Sallas, M., & Borel, P. (2003). Processing of vegetable-borne carotenoids in the human stomach and duodenum. *Am J Physiol Gastrointest Liver Physiol*, *284*, G913-923.
- Unlu, N. Z., Bohn, T., Clinton, S. K., & Schwartz, S. J. (2005). Carotenoid absorption from salad and salsa by humans is enhanced by the addition of avocado or avocado oil. *J Nutr*, *135*, 431-436.
- Updike, A. A., & Schwartz, S. J. (2003). Thermal processing of vegetables increases cis isomers of lutein and zeaxanthin. *J Agric Food Chem*, *51*, 6184-6190.
- van Bennekum, A., Werder, M., Thuahnai, S. T., Han, C. H., Duong, P., Williams, D. L., Wettstein, P., Schulthess, G., Phillips, M. C., & Hauser, H. (2005). Class B scavenger receptor-mediated intestinal absorption of dietary beta-carotene and cholesterol. *Biochemistry*, *44*, 4517-4525.
- van den Berg, H. (1999). Carotenoid interactions. *Nutr Rev*, *57*, 1-10.
- van het Hof, K. H., Tijburg, L. B. M., Pietrzik, K., & Weststrate, J. A. (1999). Influence of feeding different vegetables on plasma levels of carotenoids, folate and vitamin C. Effect of disruption of the vegetable matrix. *Br J Nutr*, *82*, 203-212.
- Vellas, B. J., Balas, D., & Albarede, J. L. (1991). Effects of aging process on digestive functions. *Compr Ther*, *17*, 46-52.
- Vishnevetsky, M., Ovadis, M., & Vainstein, A. (1999). Carotenoid sequestration in plants: the role of carotenoid-associated proteins. *Trends Plant Sci*, *4*, 232-235.
- von Lintig, J. (2012). Provitamin A metabolism and functions in mammalian biology. *Am J Clin Nutr*, *96*, 1234s-1244s.
- Wang, Y., Chun, O. K., & Song, W. O. (2013). Plasma and dietary antioxidant status as cardiovascular disease risk factors: a review of human studies. *Nutrients*, *5*, 2969-3004.
- Wang, Z., Yin, S., Zhao, X., Russell, R. M., & Tang, G. (2004). beta-Carotene-vitamin A equivalence in Chinese adults assessed by an isotope dilution technique. *Br J Nutr*, *91*, 121-131.
- Ward, M. S., Zhao, D. Y., & Bernstein, P. S. (2008). Macular and serum carotenoid concentrations in patients with malabsorption syndromes. *J Ocul Biol Dis Infor*, *1*, 12-18.
- Weber, D., & Grune, T. (2012). The contribution of beta-carotene to vitamin A supply of humans. *Mol Nutr Food Res*, *56*, 251-258.
- Weller, P., & Breithaupt, D. E. (2003). Identification and quantification of zeaxanthin esters in plants using liquid chromatography-mass spectrometry. *J Agric Food Chem*, *51*, 7044-7049.
- Wertz, K., Siler, U., & Goralczyk, R. (2004). Lycopene: modes of action to promote prostate health. *Arch Biochem Biophys*, *430*, 127-134.



- West, C. E., & Castenmiller, J. J. J. M. (1998). Quantification of the "SLAMENGGHI" factors for carotenoid bioavailability and bioconversion. *Internat J Vit Nutr Res*, *68*, 371-377.
- Weststrate, J. A., & Hof, K. H. V. (1995). Sucrose polyester and plasma carotenoid concentrations in healthy subjects. *Am J Clin Nutr*, *62*, 591-597.
- Widjaja-Adhi, M. A., Lobo, G. P., Golczak, M., & Von Lintig, J. (2015). A genetic dissection of intestinal fat-soluble vitamin and carotenoid absorption. *Hum Mol Genet*, *24*, 3206-3219.
- Wingerath, T., Sies, H., & Stahl, W. (1998). Xanthophyll esters in human skin. *Arch Biochem Biophys*, *355*, 271-274.
- Wood, A. R., Perry, J. R., Tanaka, T., Hernandez, D. G., Zheng, H. F., Melzer, D., Gibbs, J. R., Nalls, M. A., Weedon, M. N., Spector, T. D., Richards, J. B., Bandinelli, S., Ferrucci, L., Singleton, A. B., & Frayling, T. M. (2013). Imputation of variants from the 1000 Genomes Project modestly improves known associations and can identify low-frequency variant-phenotype associations undetected by HapMap based imputation. *PLoS One*, *8*, e64343.
- Xia, Z., McClements, D. J., & Xiao, H. (2015). Influence of physical state of beta-carotene (crystallized versus solubilized) on bioaccessibility. *J Agric Food Chem*, *63*, 990-997.
- You, C. S., Parker, R. S., Goodman, K. J., Swanson, J. E., & Corso, T. N. (1996). Evidence of cis-trans isomerization of 9-cis-beta-carotene during absorption in humans. *Am J Clin Nutr*, *64*, 177-183.
- Zhang, R., Zhang, Z., Zou, L., Xiao, H., Zhang, G., Decker, E. A., & McClements, D. J. (2016). Enhancement of carotenoid bioaccessibility from carrots using excipient emulsions: influence of particle size of digestible lipid droplets. *Food Funct*, *7*, 93-103.





- Carotenoid bioavailability displays a relatively high variability.
- The absorption mechanisms of carotenoids are complex and involve numerous steps.
- Carotenoid bioavailability is affected by dietary factors (*e.g.* food matrix, fat).
- It is also affected by host-related factors (*e.g.* diseases, genetic variations).
- A better knowledge thereof could lead to more personalised dietary recommendations.

ACCEPTED MANUSCRIPT