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# Nutraceutical nanodelivery; an insight into the bioaccessibility/bioavailability of different bioactive compounds loaded within nanocarriers

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## ABSTRACT

Nanofoods is a current concept that is based on the application of nanotechnologies in the preparation of safe foods, with superior nutritional and sensory characteristics, and capable of providing multiple health benefits. In line with the principles of this concept, food scientists have focused on developing new types of nano biosystems that can contribute to increasing the bioavailability of bioactive compounds used in food fortification. Numerous research teams have investigated the main factors limiting oral bioavailability including: bioaccessibility, absorption and transformation of bioactive compounds and bioactive-loaded nanocarriers. The physicochemical processes involved in the factors limiting oral bioavailability have been extensively studied, such as the release, solubility and interaction of bioactive compounds and nanocarriers during food digestion, transport mechanisms of bioactive compounds and nanoparticles through intestinal epithelial cells as well as the chemical and biochemical transformations in phase I and phase II reactions. In this comprehensive review, the physicochemical processes involved in the bioaccessibility/bioavailability of different encapsulated bioactive compounds, that play an important role in human health, will be explained including polyphenols, phytosterols, carotenoids, vitamins and minerals. In particular, the mechanisms involved in the cellular uptake of bioactive-loaded nanocarriers including transcellular transport (diffusion, endocytosis, pinocytosis, transcytosis, phagocytosis), paracellular transport (through the "tight junctions" between epithelial cells), and the active transport of bioactive compounds under the action of membrane transporters are highlighted.

## KEYWORDS

Bioavailability; carotenoids; minerals; nanocarriers; phytosterols; polyphenols; vitamins

## Introduction

If by the mid-twentieth century, foods were considered the materials that mainly satisfy the need for human nutrition to support the basic functions of the body, over the past 50 years, foods have been studied as complex systems that can bring multiple health benefits, like the medicines. Thus, different concepts have emerged that define food according to their role in the human body, such as: medical food (FDA 2020), food and dietary supplements (FDA 2019; DSHEA), functional foods and foods for particular nutritional uses—PARNUT (<http://data.europa.eu/eli/dir/2009/39/oj>). Some of these foods are aimed at all consumers and help maintain good health and prevent diseases, while other foods are recommended only for people with various diseases such as: digestive or metabolic diseases (lactose intolerance, gluten, celiac disease), diabetes, and cardiovascular diseases, and some foods are recommended for infants, young children or athletes.

A new concept that has emerged in the field of the agri-food sector is the "nanofood" concept, which includes the applications of nanotechnologies in the development of

innovative foods, with high sensory and nutritional attributes, prepared from safe and ecological raw materials (Beaudoin, Vandelac, and Papilloud 2013; Van der Meulen et al. 2014). Under these conditions, many objectives of the research strategy in the field of food science intersect with the research objectives in other fields such as medicine, pharmacy, biology, engineering, materials science, etc. Developed as an alternative to traditional technologies for functional food processing, the nanotechnologies have provided food scientists solutions for increasing the bioavailability ( $B_{AV}$ ) of nutrients used in fortifying foods (Jafari and McClements 2017), such as encapsulating them into different types of nanodelivery systems including: nanoemulsions/microemulsions, nanoliposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and polymeric nanocarriers (Katouzian and Jafari 2016; McClements 2017; Rostamabadi, Falsafi, and Jafari 2019; Salvia-Trujillo et al. 2013; de Souza Simões et al. 2017).

In recent years, more and more research teams have studied the factors that affect the  $B_{AV}$  of bioactive compounds and they have developed different methods for

improving it. For instance, studies by McClements and his colleagues have highlighted three main factors that affect the  $B_{AV}$ : i.e., bioaccessibility ( $B_{AC}$ ), absorption, and transformation that nutrients undergo during food passage through the gastrointestinal tract (GIT) (McClements 2015; Qin et al. 2017; Joye, Davidov-Pardo, and McClements 2014). Each of these factors includes processes that contribute to increasing or decreasing the oral  $B_{AV}$ . As an example, the  $B_{AC}$  of a bioactive compound, which refers to the fraction of an ingested bioactive accessible to the cellular uptake, is influenced by the release rate of the bioactive from the food matrix or nanocarriers, the solubility of the bioactive in the corresponding gastrointestinal (GI) fluid, and the possible interactions with other components from food or GI secretions (enzymes, bile acids, proteins, polysaccharides, lipids, minerals, etc.).

A factor that has a crucial influence on the oral  $B_{AV}$  is the intestinal absorption of bioactive compounds and nanoparticles (NPs). The reported results show that most biocomponents are absorbed in the small intestine, but the importance of the large intestine in the cellular uptake of biocomponents such as polyphenols was also highlighted (Tambe and Desai 2018; van Duynhoven et al. 2011). In order to be metabolized into cells or for entering into the systemic circulation, the soluble biocomponents in the mixed micelles or the undigested NPs must pass through two barriers: (i) the mucus layer, with a thickness from 120 to 480  $\mu\text{m}$ , and (ii) the cell membrane, formed by cells with different functionalities, such as: epithelial cells, goblet cells and M-cells (Ensign, Cone, and Hanes 2012). The mucus layer is made up of mucin and plays an important role in the protection of epithelial cells, in the bioadhesiveness and selective passage of compounds or NPs. The passage of biocomponents and NPs through the cell membrane has been the subject of study in many projects (Behzadi et al. 2017, Reinholtz, Landfester, and Mailänder 2018). The transport mechanisms described by all the researchers are based on the structure and composition of the cell membrane (fluid mosaic model) formed from a phospholipid bilayer with external and internal polar surfaces due to the phosphate groups (heads) of the phospholipid molecules and an inner nonpolar domain due to the hydrophobic tails of the phospholipids. In the cell membrane, there are other components that ensure cell homeostasis and functionality, such as cholesterol, proteins, glycolipids, and carbohydrates (Singer and Nicolson 1972).

According to published results, the cellular uptake of bioactive species (molecules, ions) and NPs is based on two general transport mechanisms: *passive transport*, when chemical species or NPs penetrate into the phospholipid bilayer through a spontaneous process, without energy consumption, in direct sense of the concentration gradient, and *active transport* which takes place in the opposite direction to the gradients, with energy consumption and with the involvement of specific transporters (Dima et al. 2020). In terms of the passage pathways of bioactive compounds or NPs from the lumen inside the cell and further into the systemic circulation, two types of transports are distinguished:

*transcellular transport*, when chemical species or NPs penetrate into the cell membrane and traffic epithelial cells, and *paracellular transport*, when chemical species or NPs pass through the spaces between the epithelial cells linked by tight junctions. Small and hydrophobic molecules can easily penetrate into the lipid bilayer by diffusion (passive transport), while polar molecules and NPs are internalized using the specific receptors (active transport), through a membrane process called *endocytosis*. The endocytic pathways are widely described in the literature and include: pinocytosis, macropinocytosis and phagocytosis (Behzadi et al. 2017).

The efficiency of cellular uptake, which takes place through one of the aforementioned pathways, is affected by a number of physicochemical characteristics, such as: charge, size, shape, functionality, and hydrophobicity/hydrophilicity of bioactive compounds and NPs (Murugan et al. 2015). The purpose of this work is to provide an overview of the physicochemical and biological processes involved in the  $B_{AV}$  of different encapsulated bioactive compounds and to highlight the cellular uptake mechanisms of common bioactive compounds important for human health, including polyphenols, phytosterols, carotenoids, vitamins and minerals.

## Bioavailability of encapsulated bioactive compounds: processes and mechanisms

The  $B_{AV}$  of free or encapsulated bioactive compounds in different types of nanocarriers has been extensively studied in recent years (Jain et al. 2018; Liu et al. 2019; Park, Rho, and Kim 2019; Rana et al. 2019; Wan et al. 2018; Yuan et al. 2019).  $B_{AV}$  is defined as the fraction of a biocomponent delivered to the body in different ways, which reaches the tissues and organs and manifests its therapeutic effects. Research has highlighted the complexity of the physicochemical and biochemical processes involved in the  $B_{AV}$  of biocomponents, such as: release, absorption, distribution, metabolism, and excretion, so called "RADME." Many food scientists have investigated the factors that limit the oral  $B_{AV}$  of biocomponents; e.g., the release from food matrices, solubility in GI fluids, digestion, and absorption in different compartments of GIT (Dima et al. 2020). Also, different methods have been tested to improve the oral  $B_{AV}$  of bioactives, such as the use of excipient foods (McClements et al. 2015) and nanocarriers (Esfanjani, Assadpour, and Jafari 2018).

## Bioaccessibility of encapsulated bioactive compounds

$B_{AC}$  is an important factor that positively or negatively affects the oral  $B_{AV}$  of biocomponents.  $B_{AC}$  represents the fraction of the swallowed biocomponent that reaches to the surface of the intestinal epithelial layer. To be absorbed, bioactive compounds are first released from food matrices or nanocarriers used for food functionalization. This process is influenced by different factors (Dima et al. 2020), including the matrix effect (aggregation state, texture, interactions), processing techniques, type of nanocarriers (lipid-based, polymeric, surfactant-based, etc.), physical forces (chewing,

motility, peristalsis), and characteristics of the GI fluids (pH, ionic strength, enzymatic activity, viscosity, etc.).

Food lipids and excipients used in food preparation contribute to the release of hydrophobic biocomponents from food matrices or nanocarriers. Bile salts and other biosurfactants in GI fluids emulsify the lipophilic compounds. The emulsions formed are subjected to the digestion process, when the triglycerides in the oil droplets are hydrolyzed by lipases into diacylglycerides (DAGs), monoacylglycerides (MAGs), and free fatty acids (FFAs) (McClements 2018; McClements et al. 2015). Lately, numerous studies have been published that investigated the influence of factors such as the type of oil (Ozturk et al. 2015; Zhang et al. 2015a), the type of biosurfactants (Yuan et al. 2019), and the presence of dietary fibers (Zhang et al. 2015b) on the stability, physico-chemical characteristics and digestibility of the emulsions formed in the GIT compartments. The released hydrophobic biocomponents are incorporated into the hydrophobic core of micelles, vesicles or other mesophasic structures formed by the self-assembly of the amphiphilic molecules of the bile salts, phospholipids, DAGs, MAGs, and FFAs. These mesophasic structures form the so-called mixed micellar phase, used to evaluate the  $B_{AC}$  of hydrophobic biocomponents (Hur et al. 2011).

### **Cellular uptake mechanisms of bioactive-loaded nanocarriers**

After digestion, biocomponents can exist in various forms, such as: hydrophobic components included in the small or large vesicles, ionic components (metal ions, salts), or strongly polar components (polyphenols, vitamins) solubilized in the appropriate biological fluids, and components loaded within nanocarriers that remain intact after digestion. Each of these biocomponents are absorbed by different mechanisms. For example, hydrophobic bioactives from the micellar phase can pass through the phospholipid bilayer of the cell membrane either due to the concentration gradient between the intestinal lumen and the inner compartment of the cell (passive transport), or under the action of membrane transporters, which, by energy consumption, ensures the entry or exit of the biomolecules from cells (active transport), as depicted in Figure 1.

The cellular uptake of free or encapsulated biomolecules, which cannot be diffused through the lipid hydrophobic bilayer, occurs mainly by endocytosis mechanisms; i.e., transcellular transport which consists of the recognition of biomolecules or NPs by certain receptors, followed by the invagination of the cell membrane and the formation of vesicles called endosomes, loaded with biomolecules or NPs. The detached endosomes are internalized and interact with

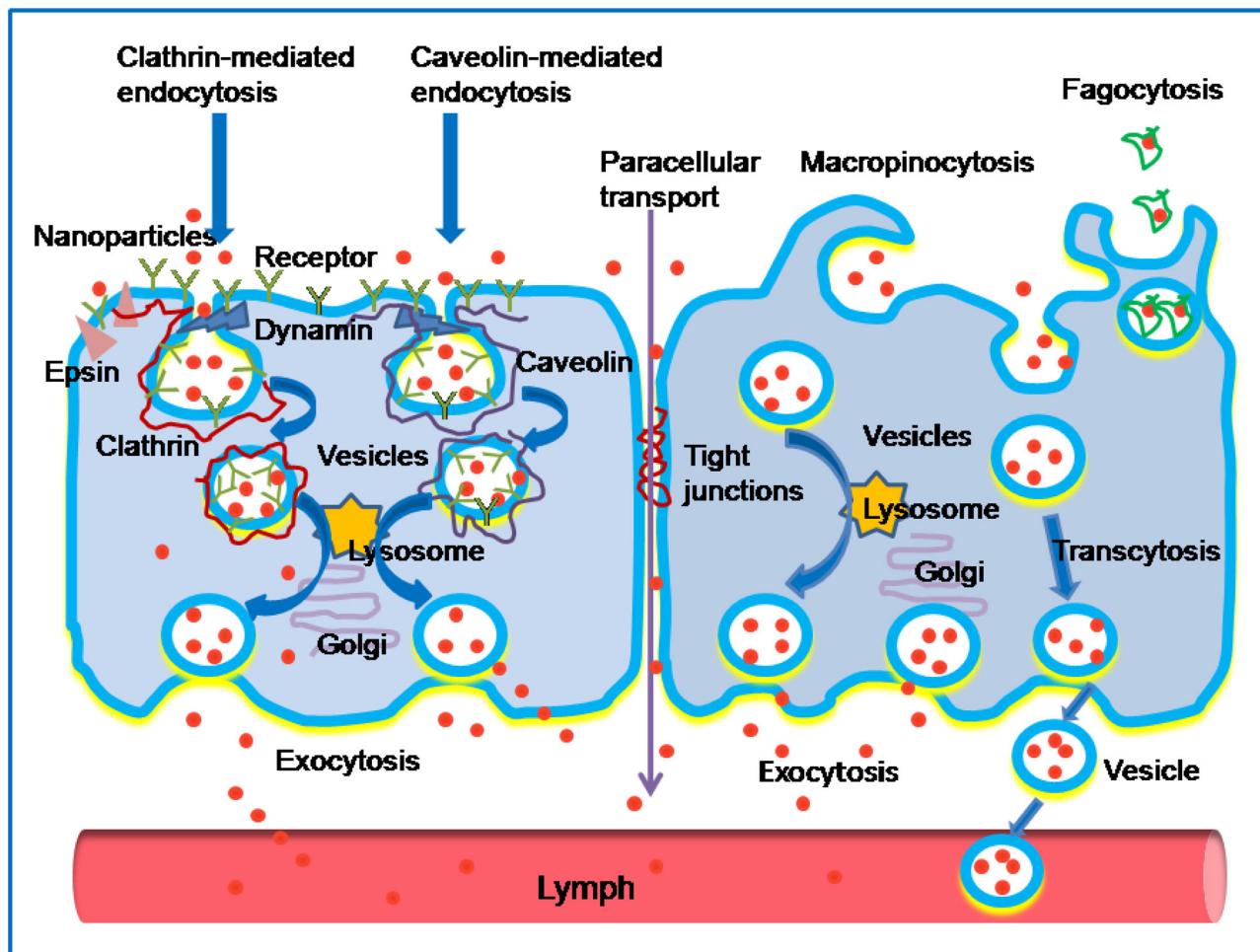
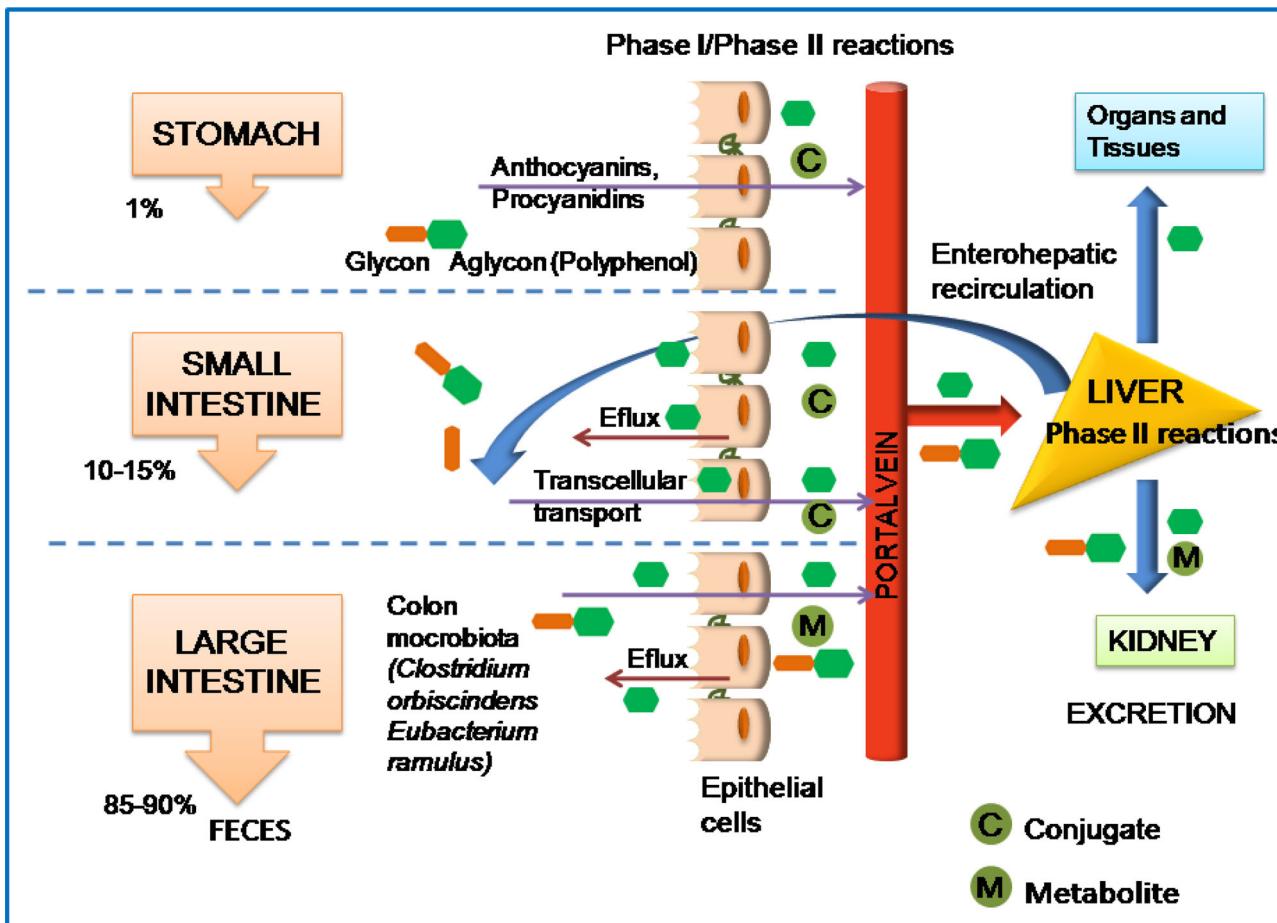


Figure 1. Cellular uptake of bioactive-loaded nanoparticles.



**Figure 2.** Absorption and metabolism of polyphenols.

organelles within epithelial cells (lysosomes, Golgi, mitochondria, endoplasmic reticulum) (Murugan et al. 2015). Hydrophilic molecules, minerals and some NPs can penetrate into the intestinal epithelial layer through the narrow gaps between cells, known as “paracellular transport” (Figure 1)

#### Transcellular transport: cellular uptake of NPs by endocytosis

The cellular uptake of NPs takes place through special mechanisms, included in transcellular transport and paracellular transport. The passage of molecules or NPs through epithelial cells can be done by diffusion and endocytosis. Endocytosis is a form of active transport and includes two different pathways: pinocytosis and phagocytosis. Pinocytosis is a pathway for the entry of NPs into cell through invagination of the cell membrane surface and formation of small vesicles that travel through the cell. Depending on the involvement or noninvolvement of membrane proteins in the cellular uptake of NPs, pinocytosis includes: clathrin-mediated endocytosis, caveolin-mediated endocytosis, clathrin and caveolin-independent endocytosis and macropinocytosis (Figure 1).

Clathrin-mediated endocytosis refers to the bending of the cell membrane under the action of an adapter protein (epsin) and the formation of pits in which the NPs are captured. On the inner surface of the curved cell membrane, the chains of a cytosol protein, called clathrin, are adsorbed.

Another protein, called dynamin, contributes to the “closing” of the pits and formation of clathrin-coated vesicles with a size of 100–150 nm, loaded within NPs (Foroozandeh and Aziz 2018). During cell trafficking, the clathrin-coated vesicles loaded with NPs, lose the protein layer, and degrade by fusion with lysosomes, releasing the NPs into different compartments of the cell. In caveolin-mediated endocytosis, NPs are captured by the pockets (caveolae) formed on the surface of the cell membrane under the action of caveolin proteins that are linked to cholesterol membrane. Dynamin and actin, close the caveolae and form caveolin-coated vesicles, loaded with NPs.

Cellular uptake of NPs by *macropinocytosis* is done without the participation of the aforementioned membrane proteins (clathrins, caveolins, dynamin). In macropinocytosis, the microparticles are captured in large membrane protrusions ( $> 1 \mu\text{m}$ ) formed by actin polymerization under the action of tyrosine kinases. These macropinocytic extensions fuse with the cell membrane to form macrosome vesicles ( $\approx 10 \mu\text{m}$ ) that detach and travel through the cell, where they interact with lysosomal enzymes and release the NPs (Murugan et al. 2015). Some lipophilic biomolecules or lipid-based nanocarriers such as SLNs and nanoliposomes, cross the epithelial cells through *transcytosis*. In this case, the lipophilic NPs recognized by certain receptors interact with the lipid bilayer causing the cell membrane to curve with the formation of deep holes. After closing these pits,

the vesicles loaded with NPs are detached. The transcytotic vesicles traffic the cell without interacting with the cellular organelles and exits from cells by exocytosis pathway, reaching to the systemic circulation.

*Phagocytosis* is another pathway for endocytic delivery of NPs. Before being absorbed through the cell membrane surface, the NPs undergo the opsonization process, which consists of coating them with various proteins called opsonins, such as: immunoglobulins and complement proteins. The opsonized NPs are then recognized by some membrane receptors (Fc receptors, complement receptors, mannose/fructose receptors and scavenger receptors) that induce actin activation and the formation of large protrusions on the surface of the cell membrane, capable of including and internalizing the NPs. By actin contraction, the cell membrane extension closes and the phagosome is formed which, during cell trafficking, like pinosomes, undergoes lysosomal degradation (Behzadi et al. 2017; Salatin and Khosrourshahi 2017).

### Paracellular transport of NPs

In the epithelial layer, cells are joined by tight junctions consisting of transmembrane integral proteins such as claudins and occludins. These proteins form negatively charged channels that allow the selective passage of molecules, ions or NPs depending on their size, shape and surface charge (Lingaraju et al. 2015). To improve the efficiency of paracellular transport, some researchers have modified the surface charge of NPs by coating them with polycation biopolymers, such as chitosan or using different compounds such as: salicylates, surfactants, middle-chain fatty acids, and bile acids, which contribute to the opening of tight junctions (Maiti 2017).

### Influence of the physicochemical properties of NPs on their cellular uptake

The cellular transport mechanism, efficiency of cellular uptake and toxicity risks are influenced by the physicochemical properties of the NPs (Foroozandeh and Aziz 2018; Liu, Workalemahu, et al. 2017; Reinholtz, Landfester, and Mailänder 2018) such as: size, shape (morphology), and surface characteristics (charge, hydrophobicity or hydrophilicity, functionality, etc.), which will be discussed briefly as below.

**Size and shape.** The size and shape of NPs have a major influence on their cellular uptake. Transcellular transport and distribution of NPs in organs and tissues are limited by the size of human cells, which is between 1 and 100  $\mu\text{m}$  and the diameter of blood vessels of about 4  $\mu\text{m}$  (Murugan et al. 2015). Many studies have suggested that the optimum size of NPs for cellular uptake is between 50 and 100 nm. Larger particles (200–1500 nm) can enter cells through pinocytosis or phagocytosis (Behzadi et al. 2017; Chithrani, Ghazani, and Chan 2006).

Some researchers investigated the “corona effect” on the size and shape of NPs and consequently on their cellular uptake (Ding et al. 2018; Mirshafiee et al. 2016). The “corona effect” is the result of the adsorption of proteins

from biological fluids on the surface of NPs. Francia et al. (2019) investigated the formation of different corona proteins on the surface of two NPs (silica NPs with a size of 50 nm and 200 nm and nanoliposomes with a size of 100 nm) dispersed in serum with various protein concentrations (12 and 62 mg/mL, respectively). For the study of cellular uptake, and cytotoxicity of protein-coated NPs, the authors used *in vitro* cell models, such as: HeLa cells, A549 cells, and primary HUVEC (human umbilical vein endothelial) cells. The results showed that uptake of NPs decreased in serum protein concentration due to both higher protein content at the start which cover the particles and competition between proteins relative to the same receptor.

Different mechanisms for intracellular transport have been highlighted, depending on the composition of the corona NPs and the type of cells; the role of the LDL receptor in the recognition of the NPs under different conditions has also been described. The relationship between NP shape and cellular uptake has been extensively studied lately. Although the reported results are sometimes contradictory, a common conclusion is drawn, however, so that the shape of the NPs strongly influences their interaction with mammalian cells (Behzadi et al. 2017; Murugan et al. 2015). Thus, some authors showed that gold spherical NPs had a much higher cellular uptake than rod-shaped NPs of the same size (Chithrani, Ghazani, and Chan 2006), while other authors reported that silica long-rod NPs had a higher cellular uptake and retention than spheres and short rods (Hao et al. 2012).

**Surface characteristics.** In designing nanocarriers used in food fortification, a special attention is paid to modulation of surface characteristics, such as: charge, chemical composition, hydrophobicity, and functional groups. These characteristics crucially influence the stability of NPs, their interaction with the cell membrane, the transport mechanisms and the distribution in the systemic circulation (Liu, Workalemahu, et al. 2017; Behzadi et al. 2017). Most published studies claimed that cationic and neutral NPs penetrated much more easily through the cell membrane than anionic NPs due to the attractive interactions exhibited by negative lipid bilayer groups toward positive NP charges (Lin et al. 2018). Some researchers demonstrated that anionic NPs were mainly internalized by caveolae-mediated endocytosis while cationic NPs were absorbed by clathrin-mediated endocytosis (Fröhlich 2012; Lamson et al. 2020). Inside the cell, the fate of NPs is different, depending on the surface charge. Thus, positively charged NPs do not interact with lysosomes, whereas negatively charged NPs accumulate in lysosomes and are subject to enzymatic degradation (Reinholtz, Landfester, and Mailänder 2018). Functionalization of NPs contributes on the one hand to higher stability of NPs due to steric repulsions and on the other hand, influences their interaction with membrane receptors, or inhibits opsonization of NPs involved in phagocytosis (Barreto et al. 2011; Karakoti et al. 2015).

The hydrophobicity of NPs plays an important role in various cellular processes including, receptor recognition, protein adsorption, cell membrane transport, etc. (Desmet

et al. 2017). The influence of the surface hydrophobicity of the NPs on their penetration through the lipid bilayer of the cell membrane has been investigated by both theoretical methods and experimental analysis. Some authors modeled the interaction of different NPs with lipid molecules in the membrane bilayer and suggested that hydrophobic NPs are capable of penetrating through the bilayer, and forming thermodynamically stable structures with the phospholipid tails; while hydrophilic NPs are distributed only on the membrane surface, being repelled by the polar heads of the phospholipids molecules. These hydrophilic NPs can alter the surface of the cell membrane, allowing their transport by endocytosis (Curtis et al. 2015). Other authors published a computational study in which the process of passing hydrophobic and hydrophilic NPs with different elasticities through the lipid bilayer was modeled. They showed that hydrophilic rigid NPs have a higher cellular uptake rate than hydrophobic rigid NPs (Wang et al. 2019).

### Bioaccessibility and bioavailability of different nanoencapsulated bioactives

In this section, the recent studies on improving the  $B_{AC}/B_{AV}$  of various bioactive compounds will be discussed in a classified format; for each group, first a brief overview of their structure and properties will be presented and then, the role of different nanocarriers on improving their bioefficiency will be explained.

### Polyphenols

Polyphenols are found in many vegetables and fruits as secondary metabolites which contribute to the growth, color, flavor and defense of plants against insects and pathogens (Assadpour, Jafari, and Esfanjani 2017). They have antioxidant activity and play an important role in the prevention of cardiovascular and neurodegenerative diseases, and even some forms of cancer (Vittorio et al. 2017). All polyphenols have two or more hydroxyl groups linked to benzene rings in their structure, as shown in Table 1.

In plants, polyphenols can be in several forms: free polyphenols (aglycones); glycosides (aglycone + glycone), esters or polymers. In glycosides, the sugar substituent can be linked to both the oxygen atom of a hydroxyl group (O-glycosides) and a carbon atom of the aglycon (C-glycosides). The most common sugars linked to aglycones are: glucose, galactose, rhamnose, xylose, arabinopyranose, and arabinofuranose (Manach et al. 2004). Also, there may be flavonoid-diglycosides in which the aglycone binds to a disaccharide, such as neohesperidose (glucose and rhamnose 1-6 linked) and rutinose (glucose and rhamnose 1-2 linked). Most phenolic acids are found linked to plant components (glucose, quinic acid or smaller polyphenols) through ester, etheric or acetal bonds. The lignans are found mainly in free forms.

### Oral bioavailability of polyphenols

The  $B_{AV}$  of polyphenols has been extensively studied lately (Chen, Cao, and Xia 2018; Scheepens, Tan, and Paxton 2010; Teng and Chen 2019; Faridi Esfanjani and Jafari 2016). The results have shown that polyphenols are generally natural compounds with a low  $B_{AV}$ . The main factors that limit their  $B_{AV}$  are: low solubility (< 100 µg/mL), low chemical stability in GI fluids; high molecular mass (500–4000 Da), chemical structure of the polyphenols (aglycon, glycosides and polymer forms), low absorption rate, high metabolism and rapid elimination. Also, the  $B_{AV}$  of polyphenols is affected by food matrix effect, food processing and high affinity for proteins (D'Archivio et al. 2010). The  $B_{AV}$  of polyphenols is the result of physical and chemical processes both in the small intestine and especially in the large intestine.

It has been shown that only 5%–10% of the total intake of polyphenols is absorbed into the small intestine; the rest are metabolized in the colon or are excreted through urine or feces (Cardona et al. 2013; Chen, Cao, and Xia 2018). After ingestion, most of free polyphenols are absorbed from the small intestine. Conjugated polyphenols (glycosides, esters, polymers), except unchanged anthocyanin glycosides, are absorbed into the small intestine only after separation of aglycones from the sugar, organic acid or other polyphenols.

The transport mechanisms of polyphenols through epithelial membranes have been extensively studied lately (Del Rio et al. 2013; Karas, Ulrichová, and Valentová 2017; Teng and Chen 2019). Studies have shown that some glycosides are hydrolyzed by an enzyme anchored to the microvilli of enterocyte cells, called lactase phlorizin hydrolase (LPH). The aglycones thus formed, pass through the intestinal membrane through passive diffusion (paracellular and transcellular transport). Although some studies have found that there are no specific receptors on the surface of small intestinal epithelial cells to provide active transport of polyphenols (Li, Cui, et al. 2015; Kottra and Daniel 2007); however, it has been reported that some polar glycosides (isoflavone glycosides) can be hydrolyzed by cytosolic β-glucosidase (CBG) found in epithelial cells, and aglycon passes through the epithelial membrane via active transport, provided by the sodium-dependent glucose transporter (SGLT1) (Wolffram, Block, and Ader 2002). The glycosylated flavonoids inhibit the action of this transporter (Vladimir-Knežević et al. 2012).

The mechanism of polyphenols uptake differs depending on the type of sugar linked to the aglycone, the lipophilicity of the aglycones, and the molecular weight. Thus, some researchers have shown that quercetin-4'-glucoside is hydrolyzed by LPH and absorbed in the small intestine, while quercetin-3-rutinoside can be hydrolyzed by both enzymes (LPH and CBG), but over 80% of the cases, it passes into the colon where it undergoes transformations under the action of the microbiota (Crozier, Del Rio, and Clifford 2010; Day et al. 2003; Graefe et al. 2001; Sesink et al. 2003). Other researchers confirmed that the permeability rate of methylated flavones through the monolayer of Caco-2 cells line was 5–8 times larger than non-methylated ones (Wen and Walle 2006).

**Table 1.** Polyphenols: structures, sources, and health benefits.

Class	Structure	Polyphenolic compound	Food-plant source	Content (mg/kg fresh wt or mg/L) <sup>a</sup>	Health benefits	
Flavones		Apigenin (4',5,7-OH) Luteolin (3',4',5,7-OH)	Celery Capsicum pepper	20–140 50–10	UV-VIS photo-protector, antioxidant, anti-inflammatory, anti-microbial, anti-cancer activities	
Flavonols		Quercetin (3',4',3,5,7-OH) Kaempferol (4',3,5,7-OH)	Yellow onion Curly kale Leek	350–1200 300–600 30–225	Antioxidant, anti-cancer, anti-inflammation, anti-diabetes properties	
Flavanones		Naringenin (4',5,7-OH) Hesperetin (3',5,7-OH;4'-OCH <sub>3</sub> )	Lemon juice Grape fruit juice	50–300 <sup>a</sup> 100–650 <sup>a</sup>	Antioxidant activity, coronary heart disease prevention, anticancer activity, anti-human immunodeficiency virus functions	
Flavanols		Catechin (4',5',3,5,7-OH) Gallocatechin (3',4',5',3,5,7 OH)	Apricot Blackberry Grape Apple Green tea	200–250 100–130 30–175 20–120 100–800 <sup>a</sup>	Protective effects on endothelial function and diabet; antioxidant and anti-inflammation properties; decrease the risk of cardiovascular disease	
Anthocyanidins		Cyanidin (3',4',3,5,7-OH) Pelargonidin (4',3,5,7-OH)	Blackberry Black currant	1000–4000 1300–4000	Antioxidant activity; preventing neuronal diseases, cardiovascular illnesses, cancer, diabetes, inflammation etc	
Isoflavonoids		Daidzein (4',7-OH) Genistein (4',5,7-OH) Glycitein (4',7-OH; 6-OCH <sub>3</sub> )	Soybeans Miso Tempeh	200–900 250–900 430–530	Estrogenic activities, preventing breast cancer risk, cardiovascular and skin diseases, osteoporosis and obesity; antioxidant activity	
Phenolic acids	Hydroxy-benzoic acid (HBA)		p-HBA (4-OH) Gallic acid (3,4,5-OH)	Blackberry Black currant	80–270 40–130	Ameliorate cardiovascular diseases such as hypertension, atherosclerosis and dyslipidemia, antioxidant activity
	Hydroxy-cinnamic acid		Ferulic acid (4-OH, 3-OCH <sub>3</sub> ) Caffeic acid (3,4-OH) Chlorogenic acid (5-O-caffeoyle quinic acid)	Aubergine Cereals Kiwi Cherry	600–660 12–100 600–1000 180–1150	Reducing obesity, diabetes, dyslipidemia, inflammation, etc.
Stilbenes		Resveratrol (3,5,4'-OH)	Red wine	0.6–7	Antioxidant, cardioprotective, anti-inflammatory and anticancer properties	
Lignans		Secoisolariciresinol (4,9,4',9'-OH; 3,3'-OCH <sub>3</sub> )	Linseed	3700	Antioxidant activity; estrogen antagonists; preventing breast cancer, prostate cancer, colon and skin cancer, diabetes, etc.	

<sup>a</sup>mg/L.

In summary, studies in the last decade have shown that aglycone molecules absorbed into intestinal epithelial cells may undergo the following biotransformations, which limit the  $B_{AV}$  of polyphenols:

**phase I metabolism**, including oxidation, reduction or hydrolysis reactions that ensure a higher hydrophilicity of the polyphenol molecules or the formation of functional groups (hydroxyl groups) capable of participating in phase II conjugation reactions (Scheepens, Tan, and Paxton 2010);

**phase II metabolism** (conjugation reactions phase), in which the aglycons are transformed by sulfotransferases (SULTs), uridine-5'-diphosphate glucuronosyltransferases (UGT), catechol-O'Methyltransferase (COMTs), and glutathione-S-transferases into the appropriate conjugate products such as sulfates, glucuronides, methylated derivatives, and glutathione conjugates respectively, with a higher hydrophilicity than parent polyphenols. Phase II conjugation reactions are mainly found in polyphenols containing a large number of hydroxyl groups, such as epi-gallocatechin-3-gallate (EGCG);

**phase III metabolism** (efflux process), happens during the return in the intestinal lumen of the aglycones unmetabolized or conjugated products. Efflux process is performed with the participation of ATP-binding cassette efflux transporters (ABC) such as p-glycoprotein (P-gp), multidrug resistance associated proteins (MRP-2, MRP-3), and breast cancer resistance proteins (BCRPs) (Murakami and Takano 2008; Li, Jiang, et al. 2015). P-gp, MRP-2 and BCRP are localized in the brush border of apical membrane, which transport the polyphenol molecules from inside the cells to the intestinal lumen, thus opposing the passage of polyphenols molecules into the systemic circulation; while MRP-3 is localized on the basolateral membranes and favors the transport of molecules from inside the cells to the blood stream. MRP-3 is found also in hematocytes where it ensures the return of metabolites to the intestinal lumen but MRP-2 is in the both apical and basolateral membranes of intestinal epithelia.

**hepatic metabolism**, contributes to the transformation of polyphenols reached into the liver by portal circulation, in

specific metabolites phase I metabolism and phase II metabolism. From the hepatocytes, the metabolites are transported by the MRP-3 transporter into the bile and then into the intestinal lumen (enterohepatic recirculation), where they pass into the colon. Some metabolites are released by the kidneys or are distributed by the blood stream to tissues (Ho et al. 2013). Gradolatto et al. (2004) studied the hepatic metabolism of apigenin using in vitro liver model and ex vivo experiments. They found that in phase I metabolism, the apigenin was oxidized by cytochrome P450 monooxygenases (P450s) and three metabolites were obtained: luteolin, scutellarein and iso-scutellarein. In phase II metabolism, apigenin and luteolin were transformed into glucuronoconjugates, sulfoconjugates and methylconjugates (Figure 2).

### Bioaccessibility and bioavailability of nanoencapsulated polyphenols

Numerous studies have investigated the factors that affect the  $B_{AV}$  of polyphenols, such as: chemical structure, natural source, extraction techniques, food matrix, food processing, host-related factors (GIT conditions, microbiota and digestive enzymes) (Bohn 2014; Jakobek 2015; Li, Jiang, et al. 2015; Zou et al. 2016). Most polyphenols are insoluble in water and have a very low permeability coefficient, which can be grouped in Classes II and IV in BCS or  $B^*(-A^*(-)T^*(-))$  in NuBaC. Therefore, researchers have developed new methods to improve the  $B_{AV}$  of polyphenols, such as encapsulation in different kinds of nanocarriers: lipid-based nanocarriers (nano/microemulsions, SLNs, NLCs), surfactant-based nanocarriers (nanoliposomes, niosomes, cubosomes, hexosomes), polymeric nanocarriers (protein-based, polysaccharide-based, their complexes/conjugates), and inclusion complexes (cyclodextrins, amylose) (Esfanjani, Assadpour, and Jafari 2018; Li, Jiang, et al. 2015; Vittorio et al. 2017). These kinds of nanocarriers ensure a higher solubility and chemical stability of polyphenols in GI fluids, avoid interaction with other components, controlled release in certain GIT compartments, increased digestibility, and improved absorption processes through the intestinal wall (Katouzian and Jafari 2016; Rafiee et al. 2019b; Rezaei, Fathi, and Jafari 2019).

### Bioconversion of polyphenols in the large intestine (colon)

Most of the free or conjugated polyphenols pass into the colon. Research in recent decades has shown that biotransformations of polyphenols in the colon are key steps in achieving the  $B_{AV}$  and therapeutic effects of polyphenols. The colon is similar to a bioreactor in which there are over 500 bacteria at a concentration of  $10^{11}$ – $10^{12}$  CFU/mL (van Duynhoven et al. 2011).

From the community of colonic bacteria, the most sensitive anaerobic bacteria to the presence of polyphenols (flavonols and flavones) are *Clostridium orbiscindens* and *Eubacterium ramulus*. They are commonly used in dynamic in vitro gut models such as the Reading model, the Simulator of the Human Intestinal Microbial Ecosystem (SHIME), and the TNO Intestinal Model 2 (TIM2) (Schoefer et al. 2003; van Duynhoven et al. 2011, Pearce et al. 2018). These models mimic the physico-chemical and microbiological conditions of the colon as realistic as possible and offer the possibility of periodic analysis of metabolites from polyphenol bioconversion. Non-absorbed polyphenols in the stomach or small intestine, together with the polyphenols undergoing the efflux process and the metabolites in the liver returned to the intestinal lumen pass into the colon. Some of these compounds are excreted by feces, and the remaining is absorbed by enterocyte cells where they undergo specific biotransformations phase II metabolism (glucuronidation, sulfonation, methylation) and efflux process. Metabolites that have passed through the epithelial layer of large intestine reach the liver where they are also subjected to phase II reactions; then metabolites undergo enterohepatic recirculation. Some of these metabolites may even have a certain therapeutic effect, such as equol which has shown higher phytoestrogenic activity than parent polyphenol (daidzein) from which it originates (Setchell, Brown, and Lydeking-Olsen 2002). Most polyphenols are excreted through the kidneys. In vivo studies on the  $B_{AV}$  of polyphenols have revealed different amounts of polyphenols in the urine (e.g., 30%–40% for gallic acid and 0%–1.5% for anthocyanins), depending on the type of polyphenol, the food matrix, and the digestion time (Manach et al. 2005).

The bioefficiency of encapsulated polyphenols has been studied by some authors in terms of  $B_{AC}$ , when they evaluated the solubility, release rate and digestibility of polyphenols using in vitro, static and dynamic models that mimic GIT conditions; others completed these studies with the investigation of the absorption of free or encapsulated polyphenols using different human cell lines (e.g., Caco-2 cells) or in vivo experiments (volunteers or animals) (Costa and Ahluwalia 2019; Li, Jiang, et al. 2015; Pearce et al. 2018). Table 2 shows an overview of the main types of polyphenol-loaded nanocarriers that may contribute to higher  $B_{AV}$  of polyphenols.

Studies in recent decades have shown that lipid-based nanocarriers are excellent colloidal delivery systems which can contribute to improving the  $B_{AV}$  of polyphenols (Esfanjani, Assadpour, and Jafari 2018; Akhavan et al. 2018). Nanoemulsions are by far the most effective colloidal systems used to fortify foods with polyphenols because most of them have a solubility < 100 µg/mL (Kaur and Kaur 2014). For example, curcumin, a natural polyphenol from turmeric (*Curcuma longa*), has a water solubility of 11 ng/mL at room temperature. In vegetable oils, the solubility of curcumin differs depending on the nature of the oil and the solubilization conditions (Rafiee et al. 2019a). It has been shown that at room temperature after 48 h stirring, the solubility of curcumin was 7.58 mg/mL in corn oil, 7.38 mg/mL in soybean oil, and 1.39 mg/mL in oleic acid (Araiza-Calahorra, Akhtar, and Sarkar 2018). Many works have been published in the literature, investigating the physico-chemical characteristics of curcumin-loaded nanoemulsions, their fate in GI fluids (Zheng et al. 2017, 2019; Zou et al. 2015), as well as antioxidant, anticancer, anti-inflammatory, antimicrobial and

**Table 2.** Recent studies on the bioaccessibility and cellular uptake of encapsulated polyphenols and phytosterols.

Bioactive compound	Nanocarriers	Characteristics of nanocarriers	Bioaccessibility ( $B_{AC}$ )	Cellular uptake in vitro models	References
Curcumin (Cur)	Inclusions complexes/ -4- $\alpha$ -glucanotransferase-modified rice (GS) - $\beta$ -cyclodextrin (CD) - maltodextrin (MD)	Curcumin solubility in complex nanocarriers increased by approximately 2,241- 2,846-fold, compared to pure curcumin	Simulated digestion model (stomach, intestine); GS-Cur : 2.73%; MD-Cur: 1.75%; CD-Cur: 1.55% Cur pure: 0.24%	Not been studied	Park, Rho, and Kim (2019)
Curcumin	Nanomicelles/polycaprolactone-grafted oligocarrageenan	Size 184 nm Encapsulation efficiency 10%	Not been studied	Endothelial EA-hy926 cells line model Cur-loaded nanomicelles facilitated the uptake of Cur into the endothelial cells by clathrin- or caveolae-mediated endocytosis.	Youssef et al. (2019)
Curcumin	WPI-nanoemulsions (NEs); WPI/chitosan multilayer NEs	WPI-NEs: Size ≈ 186 nm $Z_p$ ≈ -52 mV WPI/chitosan multilayer NEs: Size ≈ 5700 nm $Z_p$ ≈ +40 mV	Dynamic gastrointestinal model (stomach, duodenum, jejunum and ileum); WPI-NEs $B_{AC} = 29.8\%$ , WPI/chitosan multilayer NEs $B_{AC} = 37.2\%$	Caco-2 cells line Cellular antioxidant activity ( $\mu\text{Mol Quercetin L}^{-1}$ ) mgQuercetin): WPI-NEs 1.79, WPI/chitosan multilayer NEs 2.08, Cur free 0.21	Silva et al. (2019)
Curcumin	Hyaluronic acid/chitosan nanoparticles	Size: 166–1626 nm Encapsulation efficiency 75%–90%	Release into isotonic glucose solution 51.6% (4 h)	C6 glioma cells model; uptake amount 72.5% clathrin- and caveolae-mediated endocytosis	Yang et al. (2015)
Epigallocatechin-3-gallate (EGCG)	Nanoliposomes	Size: 180 nm Encapsulation efficiency 85.8%	Static gastrointestinal model Release rate: SGF with pepsin; $B_{AC} = 21\%/4\text{ h}$ SIF with trypsin; $B_{AC} = 37\%/4\text{ h}$	mechanism transport Caco-2 cells line Viability of Caco-2 cells; EGCG free: 80% (conc 0.5 mg/L); 45% (conc 10 mg/L) EGCG-loaded nanoliposomes: 65% (conc 0.5 mg/L); 20% (conc 10 mg/L)	Luo et al. (2014)
EGCG	Nanostructured lipid carriers (NLCs) functionalized	Size: ≈300 nm Encapsulation efficiency: ≈90%	Not been studied	Caco-2 apparent permeability (Papp)/24 h: Free EGCG: $1.35 \times 10^{-6}$ cm $\cdot$ s $^{-1}$ EGCG-loaded NLCs: $1.28 \times 10^{-6}$ cm $\cdot$ s $^{-1}$	Yang et al. (2015)
Resveratrol	PLGA nanoparticles	Size: 190 nm (PLGA-NPs); 176.1 nm (RSV-PLGA-NPs)	In vitro release: SGF (pH = 1.2, BPS solution): 10.56% (8 h) SIF (pH = 6.8, BPS solution): 12.49% (8 h)	Folic acid-functionalized NLCs: $2.38 \times 10^{-6}$ cm $\cdot$ s $^{-1}$ HeLa cells line, Cells viability: 90%–100%	Wan et al. (2018)

(continued)

Table 2. Continued.

Bioactive compound	Nanocarriers	Characteristics of nanocarriers	Bioaccessibility ( $B_{AC}$ )	Cellular uptake in vitro models	References
Phytosterols	Nanoporous corn and wheat starch bioerogels	Encapsulation efficiency: 97.25% Impregnation capacity: 100–180 mg phytosterol/g gel	Simulated intravenous fluid (pH = 7.4, BPS solution); 29.21 (8 h). $B_{AC}$ of phytosterols in monolith gels = 14.3%–27.7%. $B_{AC}$ of phytosterols in powdered gels = 7%–10% Not been studied	Dynamic gastrointestinal model (oral, gastric and intestinal digestion) $B_{AC}$ of phytosterols free = 1.2%–1.4% HT29-MTX intestine cell model Apparent permeability coefficient ( $P_{app}$ ): $P_{app(CH)} = 0.33 \times 10^{-6} \text{ cm} \cdot \text{s}^{-1}$ $P_{app(CH+Sit)} = 0.00 \text{ cm} \cdot \text{s}^{-1}$ $P_{app(CH+Supp)} = 0.006 \times 10^{-6} \text{ cm} \cdot \text{s}^{-1}$	Ubeyitogullari et al. (2019) Yi et al. (2016)
Phytosterols + Cholesterols	Cholesterol-micelles Cholesterol + $\beta$ -sitosterol micelles (CH + Sit) Cholesterol + Supplement micelles (CH + Supp)	Size: 2.3–3 nm Z-potential: –13 to –50 mV	Not been studied	HT29-MTX intestine cell model Apparent permeability coefficient ( $P_{app}$ ): $P_{app(CH)} = 0.33 \times 10^{-6} \text{ cm} \cdot \text{s}^{-1}$ $P_{app(CH+Supp)} = 0.006 \times 10^{-6} \text{ cm} \cdot \text{s}^{-1}$	Yi et al. (2016)

Cur, curcumin; RSV, resveratrol; CH, cholesterol; Sit, sitosterol; GS 4,  $\alpha$ -glucanotransferase; CD, cyclodextrin; MD, maltodextrin; WPI, whey protein isolate; NE, nanoemulsion; NLC, nanostructured lipid carrier; PLGA, poly(D,L-lactide-co-glycolide);  $B_{AC}$ , bioaccessibility; SGF, simulated gastric fluid; SIF, simulated intestinal fluid; EGCG, epigallocatechin-3-gallate;  $P_{app}$ , apparent permeability coefficient.

antiviral properties of curcumin (Gera et al. 2017; Mahmood et al. 2015; Yoon et al. 2018).

The very small size of the oil droplets in oil-in-water (O/W) nanoemulsions (<100 nm) ensures a large interfacial surface that favors the interaction of lipids with digestive enzymes (Zheng et al. 2019). Also, multilayer-nanoemulsions, obtained by successively depositing of several polymerlayers with different charges on the surface of droplets, allow the manipulation of the surface properties emulsion droplets in order to increase the stability of the nanoemulsions and their absorption rate through intestinal epithelial membrane (Li et al. 2010). For instance, Pinheiro, Coimbra, and Vicente (2016) prepared lactoferrin (LF) and LF/alginate multilayer nanoemulsions loaded with curcumin and studied their behavior in GIT using a dynamic GI model, simulating stomach, duodenum, jejunum and ileum conditions. The results showed that the behavior of curcumin-loaded multilayer nanoemulsions was different, depending on the type of biopolymer that stabilized the nanoemulsions. In the stomach, the size of LF-stabilized nanoemulsions remained unchanged due to the positive charges of LF that induced droplet repulsion; while LF and alginate-stabilized nanoemulsions were unstable, and droplets formed large aggregates. In contrast, in the intestinal fluids, both nanoemulsions and multilayer nanoemulsions were destroyed by flocculation and coalescence, due to the presence of bile salts that removed the LF layer and allowed lipase access to the surface of the oil droplets, hydrolyzing lipids into FFAs, DAGs and MAGs. The  $B_{AC}$  of curcumin was expressed in terms of curcumin concentration in mixed micellar phase collected from jejunal and ileal compartments. The results showed that the  $B_{AC}$  of curcumin ranged from 2 to 4%. Curcumin from LF nanoemulsions had a higher  $B_{AC}$  in the jejunal compartment, and the  $B_{AC}$  of curcumin in multilayer nanoemulsions was higher in the ileal compartment, consistent with the amount of FFAs released in these GIT compartments. Also, it was revealed that alginate acts as a factor controlling the rate of lipid digestion and FFA adsorption within the GIT.

Other researchers have studied the effect of chitosan on the  $B_{AC}$  and cellular uptake of curcumin-loaded nanoemulsions (Silva Santos et al. 2019; Li, Cui, et al. 2015). As an example, Silva et al. (2019) found that the  $B_{AC}$  of curcumin from chitosan multilayer nanoemulsions was higher (37.2%) than curcumin from nanoemulsions stabilized with whey protein isolate (29.8%). The cellular uptake studies performed on a Caco-2 cells line showed that the permeation rate for curcumin nanoemulsions was 1.55 times lower than for curcumin multilayer nanoemulsions ( $1.93 \times 10^{-6} \text{ cm} \cdot \text{s}^{-1}$ ) since chitosan facilitates the enlargement space between enterocyte cells enhancing the paracellular transport of curcumin, across the Caco-2 cells monolayer.

In order to increase the biological activity of polyphenols, some scientists have studied the possibility of co-encapsulating them in colloidal systems. Aditya et al. (2015) prepared water-in-oil-in-water ( $W_1/O/W_2$ ) double emulsions co-loaded with curcumin and catechin by the two-step method. Catechin, being a hydrophilic compound, was entrapped in

the internal water phase ( $W_1$ ), while curcumin was solubilized in the oil phase. The authors obtained relatively stable double emulsions, with an average diameter of  $d_{23} \approx 500$  nm, and a negative electrokinetic potential ( $Z_p \approx -18$  mV). Encapsulation efficiency was higher for emulsions in which a single compound was encapsulated (88%, for curcumin and 97%, for catechin) compared to co-loaded double emulsions. The  $B_{AC}$  of the two polyphenols in double emulsions (curcumin/catechin or co-loaded curcumin and catechin) was also studied using a static digestion model. The results showed that the  $B_{AC}$  of curcumin was higher than that of catechin. Individually encapsulated curcumin had a  $B_{AC}$  of  $\approx 72\%$ , while the  $B_{AC}$  of curcumin co-loaded with catechin was  $\approx 68\%$ , compared with a low  $B_{AC}$  of pure curcumin in ethanol solution ( $\approx 16\%$ ). Other authors have highlighted the increase of antioxidant effect by co-encapsulating polyphenols, such as: curcumin + resveratrol in SLNs (Coradini et al. 2014), gallic acid + curcumin, and ascorbic acid + quercetin in niosomes (Tavano et al. 2014).

There are numerous works published in the last 10 years which have investigated the biological properties of other polyphenols encapsulated in different types of nanocarriers, such as: EGCG in nanoliposomes (Luo et al. 2014), EGCG in SLNs (Granja et al. 2019; Shtay et al. 2019), EGCG in polymeric NPs (Tyagi et al. 2017), resveratrol in

nanoemulsions (Davidov-Pardo and McClements 2015), resveratrol in SLNs and NLCs (Neves et al. 2016; Pandita et al. 2014), resveratrol in microemulsions (Yang et al. 2018), and resveratrol in polymeric NPs (Wan et al. 2018). A brief overview of the relevant studies can be seen in Table 2.

### Phytosterols

Phytosterols are known as plant sterols. As shown in Figure 3, their chemical structure is similar to that of the most important sterol produced in the body of mammals, i.e., cholesterol. The chemical structure of phytosterols differs from cholesterol by the alkyl substituents at C-24 position and a double bond at C-5 position of sterol ring or at C-22 position of the extra alkyl group (Figure 3). There are over 250 phytosterols identified in plants which can be grouped into two main classes: “sterols” or  $\Delta^5$ -sterols with a double bond in the sterol ring (C-5 position), and “stanols” or  $\Delta^5$ -stanols, with a saturated sterol ring ( $5\alpha$ -sterols).

Phytosterol molecules, like cholesterol, are amphiphilic molecules which coexist with phosphoglycerides in the biological membrane. Therefore, cholesterol and phytosterols crucially influence the functional properties of the biological membrane, such as: fluidity, permeability, activity of membrane enzymes, and membrane transport. The highest

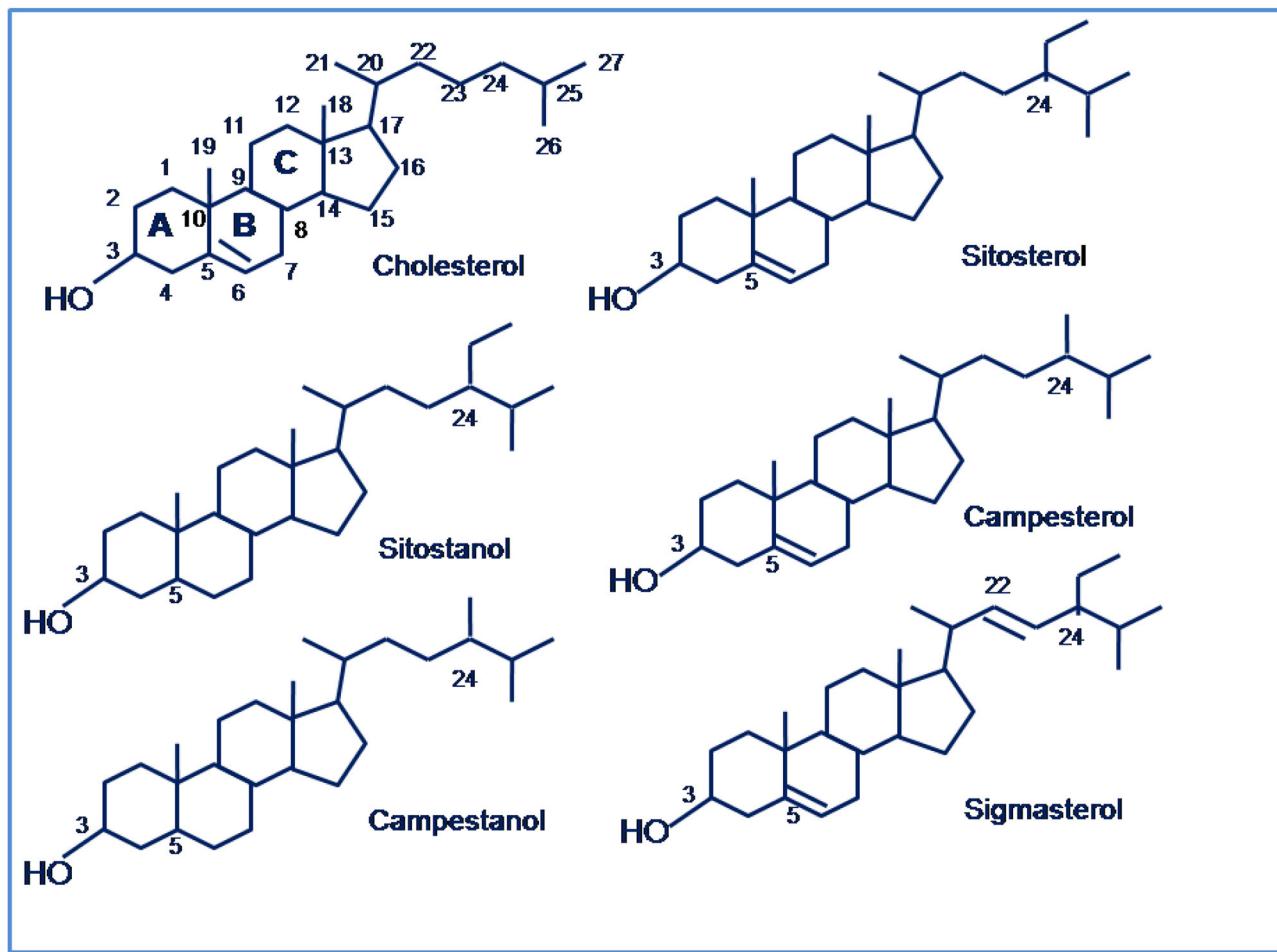


Figure 3. Structures of cholesterol and common phytosterols.

content of plant sterols and stanols is found in vegetable oils, such as: corn oil (809–1557 mg/100 g), sunflower oil (374–725 mg/100 g), soybean oil (229–459 mg/100 g), fresh fruits and vegetables and cereals (Brufau, Canela, and Rafecas 2008). In a typical diet, the mean daily intake of phytosterols is about 300–400 mg and that of phytstanols is about 30 mg (Gylling and Simonen 2015). Attention of researchers to phytosterols has increased greatly since the 1950s, when Peterson published a paper revealing that phytosterols from soybeans lower the serum cholesterol level (Peterson 1958).

In recent decades, the research on the bioactivity of phytosterols has been extended focusing on the following objectives:

1. optimization of the ratio of daily consumption of plant sterols/stanols and reducing the low density lipoprotein (LDL)-cholesterol concentrations in plasma;
2. establishing the mechanisms involved in the lower cholesterol level and the  $B_{AV}$  of phytosterols;
3. development of strategies for improving the  $B_{AV}$  of phytosterols.

The consumption of foods rich in phytosterols, which assure a daily intake of 1.5–3.0 g/d, contributes to a 10%–15% decrease in LDL-cholesterol level (Kopeć and Failla 2018). This intake is very difficult to meet, due to the low content of sterols/stanols in fresh fruits, vegetables, cereals or oils. For example, in order to ensure a daily intake of 1.0 g sterols/stanols, a person should consume about 2 kg fruits, or 1 kg grains or 100 g vegetable oils daily. To eliminate this obstacle, fortification of some staple foods with plant sterols/stanols has been carried out (Jones et al. 2018). Thus, since 2000, the European Community (EC) has authorized the food manufacturers to produce food products fortified with phytosterols, such as margarine, milk and yogurt, with the recommendation that these foods should be intended only for adults with a high LDL-cholesterol levels ( $\geq 5$  mmol/L) (EFSA 2012). The EC also recommended that the daily dose of phytosterols should not exceed 3 g because it has been found that over this dose, the cholesterol is not decreased and high consumption of phytosterols/phystanols may cause diseases such as sitosterolemia or may affect the  $B_{AV}$  of other hydrophobic biocomponents in foods, such as  $\alpha$ - and  $\beta$ -carotene and lycopene (Baumgartner et al. 2017; EFSA 2012; Ras and Trautwein 2017).

### **Hypocholesterolemic effect and bioavailability of plant sterols and stanols**

The mechanisms by which phytosterols lower the LDL cholesterol in the blood have been studied by many research teams worldwide. Most of the published results explain the decrease of LDL-cholesterol level by the following mechanisms (Dumolt and Rideout 2017; Jones et al. 2018; Rozner and Garti 2006):

1. competition between cholesterol molecules and phytosterol molecules in the formation of mixed micelles

involved in cholesterol solubilization and its transport through membrane;

2. co-crystallization of phytosterols and cholesterol at the oil/water interface of the emulsion droplets during food digestion;
3. the different action of the transporters involved in the molecular absorption of cholesterol and free or esterified phytosterols.

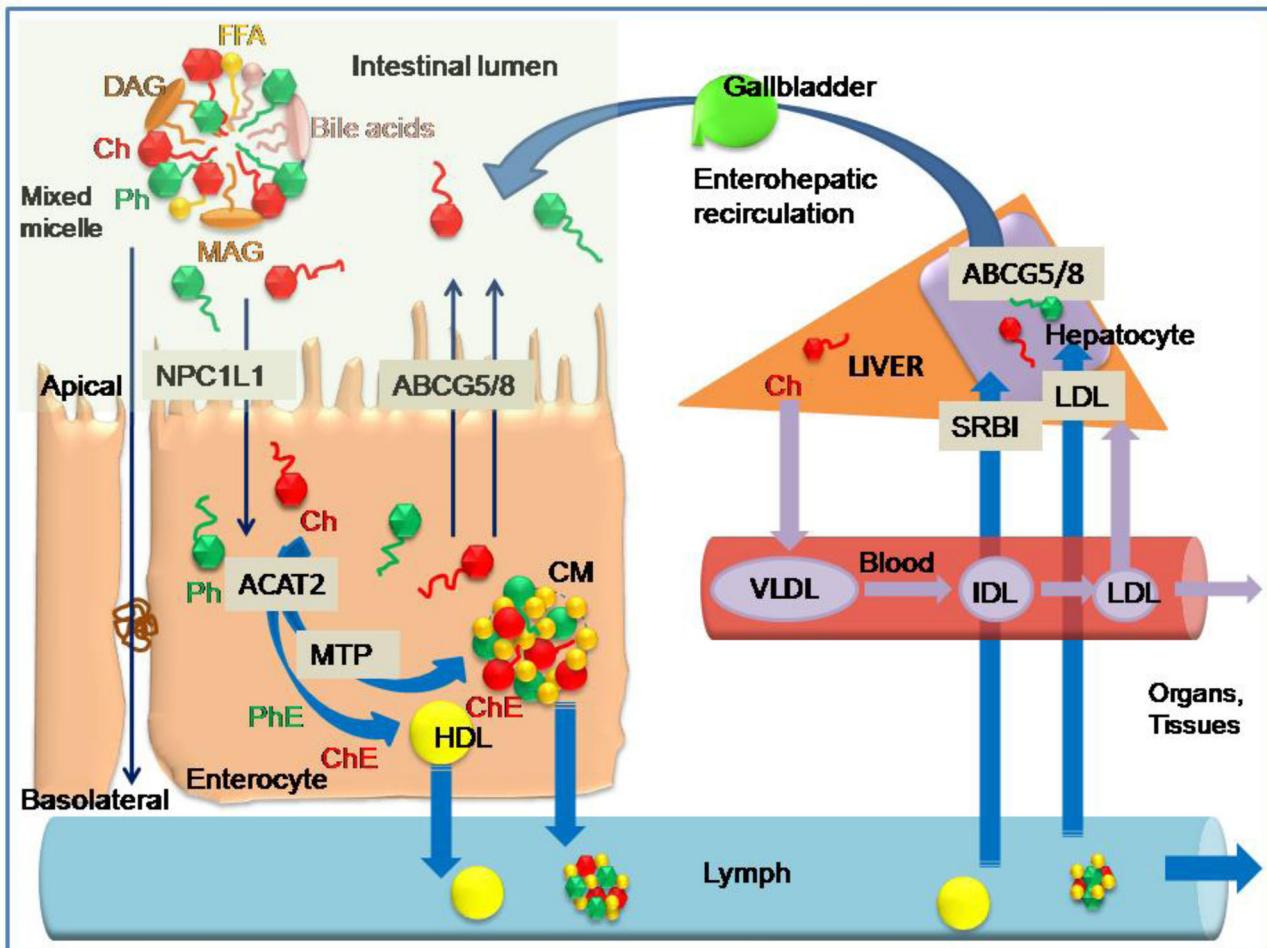
The first two processes are based on lowering the solubility of cholesterol in the presence of phytosterols. Thus, in order to be absorbed through the epithelial layer of the intestine, free or esterified cholesterol must be solubilized in the mixed micelles consisting of bile acid salts, MAGs, DAGs, FFAs, phospholipids and cholesterol. Phytosterols have a higher affinity for mixed micelles than cholesterol and, therefore, their presence in foods causes the elimination of cholesterol from the micelles and reduces its absorption. Studies have shown that the intestinal absorption of cholesterol is mainly due to the energetic active transport supported by ATP with the involvement of the transporters located in the intestinal brush-border membranes. As depicted in Figure 4, the following processes occur in the cellular uptake of cholesterol:

1. influx transport, mediated by Niemann-Pick C1-like 1 transporters (NPC1L1), which ensures the passage of the cholesterol and phytosterol molecules from intestinal lumen into enterocyte cells;
2. efflux transport, mediated by ATP-binding cassette transporters (ABCG5 and ABCG8) that ensure the return of cholesterol and phytosterol molecules from enterocytes into the lumen;
3. re-esterification of cholesterol and phytosterols into enterocyte cells in the presence of fatty acids and acyl-coenzyme A/cholesterol acyltransferase (ACAT 2);
4. inclusion of esterified and non-esterified cholesterol in chylomicrons together with triglycerides, phospholipids and apolipoproteins;
5. passage of chylomicrons into the lymph and liver.

### **Bioaccessibility and bioavailability of nanoencapsulated phytosterols**

Phytosterols and phytstanols are natural compounds which are solid, crystalline, insoluble in water and poorly soluble in fats and vegetable oils. Therefore, their  $B_{AV}$  is very low (0.5%–2%). In recent years, some strategies have been developed for increasing the  $B_{AV}$  of phytosterols based on particle size reduction, decreasing crystallinity (Cao et al. 2016) or encapsulation in different types of nanocarriers, such as: nanoemulsions (Chen et al. 2016; Liu and Tang 2014), SLNs and NLCs (Varshosaz et al. 2014; Silva Santos et al. 2019), cyclodextrin inclusion complexes (Meng, Pan, and Liu 2012; Rossi et al. 2019), and nanoliposomes (Poudel et al. 2019; Wang, Acevedo, and Marangoni 2017), as shown in Table 2.

Most of the mentioned studies investigated the physicochemical characteristics of the nanocarriers loaded with phytosterols, such as: morphology, size, electrical charge,



**Figure 4.** Absorption and metabolism of cholesterol and phytosterols via nanodelivery systems. Ch, cholesterol; Ph, phytosterol; PhE, phytosterol ester; DAG, diacylglyceride; MAG, monoacylglyceride; FFA, free fatty acid; MTP, microsomal triglyceride transfer protein; SR-BI, scavenger receptor class B type I (reverse cholesterol transporter); IDL, intermediate-density lipoprotein; LDL, low-density lipoproteins; VLDL, very low-density lipoproteins; ACAT2, acetyl-CoA acetyltransferase; ABCG5/8, ATP-binding cassette (ABC) transporters; NPC1L1, Niemann-Pick C1-like; CM, chylomicron.

physical and chemical stability, encapsulation efficiency, and  $B_{AV}$  of phytosterols. As an example, Ubeyitogullari et al. (2019) published some interesting results on the encapsulation of phytosterols in nanoporous starch aerogels. They studied the  $B_{AV}$  of phytosterols both by introducing phytosterol-loaded aerogels into simulated GI fluids and by including them firstly in real foods with different fat contents, then digested using *in vitro* GIT model. Phytosterol-loaded aerogels were prepared using wheat starch aerogels (WSAs) and corn starch aerogels (CSAs). The mixtures of starch and phytosterols were expanded using supercritical carbon dioxide. The authors evaluated the effect of the morphology of starch aerogels (surface area, pore size) on the impregnation capacity and  $B_{AC}$  of phytosterols, since phytosterols were impregnated in monolithic and powdered aerogels. The highest impregnation capacity of phytosterols was in CSAs both in monolithic state (195 mg FS/g gel) and in powdered state (173 mg FS/g gel). *In vitro*  $B_{AC}$  studies were performed using a multiple stage GIT model. In the simulated GI fluids, enzymes were used, such as:  $\alpha$ -amylase, porcine pepsin, and fungal lipase, and  $B_{AC}$  was expressed as a percentage of the phytosterols in the bioaccessible fraction relative to the total amount of phytosterols included in the aerogel.

Physical mixtures of phytosterols and starch, for which  $B_{AC}$  was 1.4%, for wheat starch and 1.2% for corn starch, were used as control samples. The highest  $B_{AC}$  was for the phytosterols impregnated in starch aerogels in monolithic state: 27.7% for wheat starch gel and 14.3% for corn starch gel. The  $B_{AC}$  of phytosterols impregnated in starch aerogels in powdered state was <10% (Ubeyitogullari et al. 2019).

In another study, Ubeyitogullari and Ciftci (2019) used low-crystallinity phytosterols impregnated in WSAs to fortify foods with a different fat content, such as granola bars and puddings. The results showed that the  $B_{AV}$  of the encapsulated phytosterols was higher than that of the free phytosterols, and the fat content did not significantly influence the  $B_{AV}$  of the phytosterols. Thus, the  $B_{AC}$  of non-encapsulated phytosterols ranged between 28.0%–29.8% and 31.3%–31.5% for low-fat granola bars, and regular-fat granola bars, respectively.  $B_{AC}$  of phytosterols impregnated in WSAs was 88.2% and 91.8% for low-fat granola bars, and regular-fat granola bars, respectively.

Yi et al. (2016) published an interesting study on the cellular uptake of cholesterol in the presence of phytosterols. The authors prepared four types of mixed micelles as well micelles without cholesterol, micelles with cholesterol, co-

micelles with cholesterol and pure analytical  $\beta$ -sitosterol, and co-micelles with cholesterol and commercial pine derived phytosterol supplements (77.6%  $\beta$ -sitosterol, 11.3%  $\beta$ -sitostanol, 6.6% campesterol, 1.2% campestanol, 0.7% stigmasterol, and about 3% of other sterols). For preparation of mixed micelles, components that appear during digestion were used: oleic acid, monoglycerides, sodium taurocholates, and buffered saline solutions corresponding to the simulated intestinal fluid. Mixed micelles with an average diameter of 2.3–3.0 nm and a negative electrokinetic potential (−13 to −50 mV) were obtained. The competitive cellular uptake between cholesterol and phytosterols was studied using an HT29-MTX intestine cell model. In contrast to Caco-2 cells line, the HT29-MTX cells line forms a mucus layer on the apical surface of the cells. The growth conditions of the cells were studied and a tissue consisting of several layers of cells was obtained, revealed by AFM analysis. To evaluate the influence of phytosterols on the inhibition rate of cholesterol transport through epithelial cell layers, the apparent permeability coefficient ( $P_{app}$ ) was calculated. The results revealed that  $P_{app}$  of cholesterol micelles was  $0.33 \cdot 10^{-6}$  cm/s, the  $P_{app}$  of the  $\beta$ -sitosterol + cholesterol co-micelles was 0.00, and the  $P_{app}$  of commercial pine derived phytosterol

supplements + cholesterol was  $0.006 \cdot 10^{-6}$  cm/s. These results confirmed that  $\beta$ -sitosterol is a cholesterol transport inhibitor and the pine derived phytosterol supplements blocked the transport of cholesterol through the epithelial layer of the intestine.

### Carotenoids

Carotenoids are hydrophobic pigments found in plants, vegetables, marine animals and some species of algae and fungi (Mutsokoti et al. 2017). Depending on the chemical structure, the plant carotenoids can be grouped into three main classes (Kopec and Failla 2018), as shown in Figure 5:

1. carotenes, as nonpolar carotenoids that contain a large number of conjugated double bonds (> 9), including lycopene,  $\alpha$ - and  $\beta$ -carotene;
2. xanthophylls, as polar carotenoids, containing one or two hydroxyl groups, including lutein, zeaxanthin, and  $\beta$ -cryptoxanthin;
3. apo-carotenoids, as carotenes or xanthophylls with a lower molecular weight, obtained from carotenoid

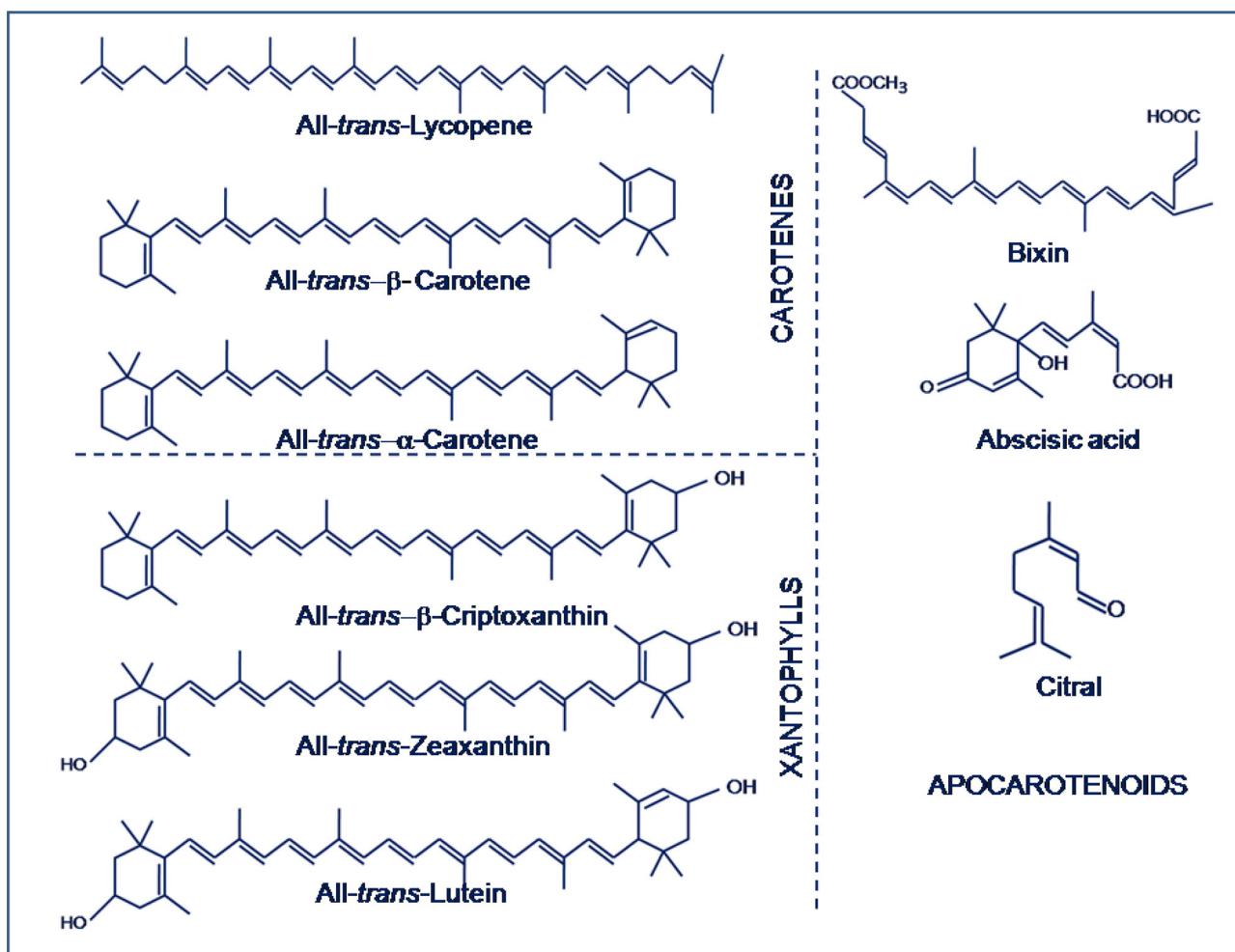


Figure 5. Structures of common carotenoids.

metabolism or food processing, including citral, bixin, and abscisic acid.

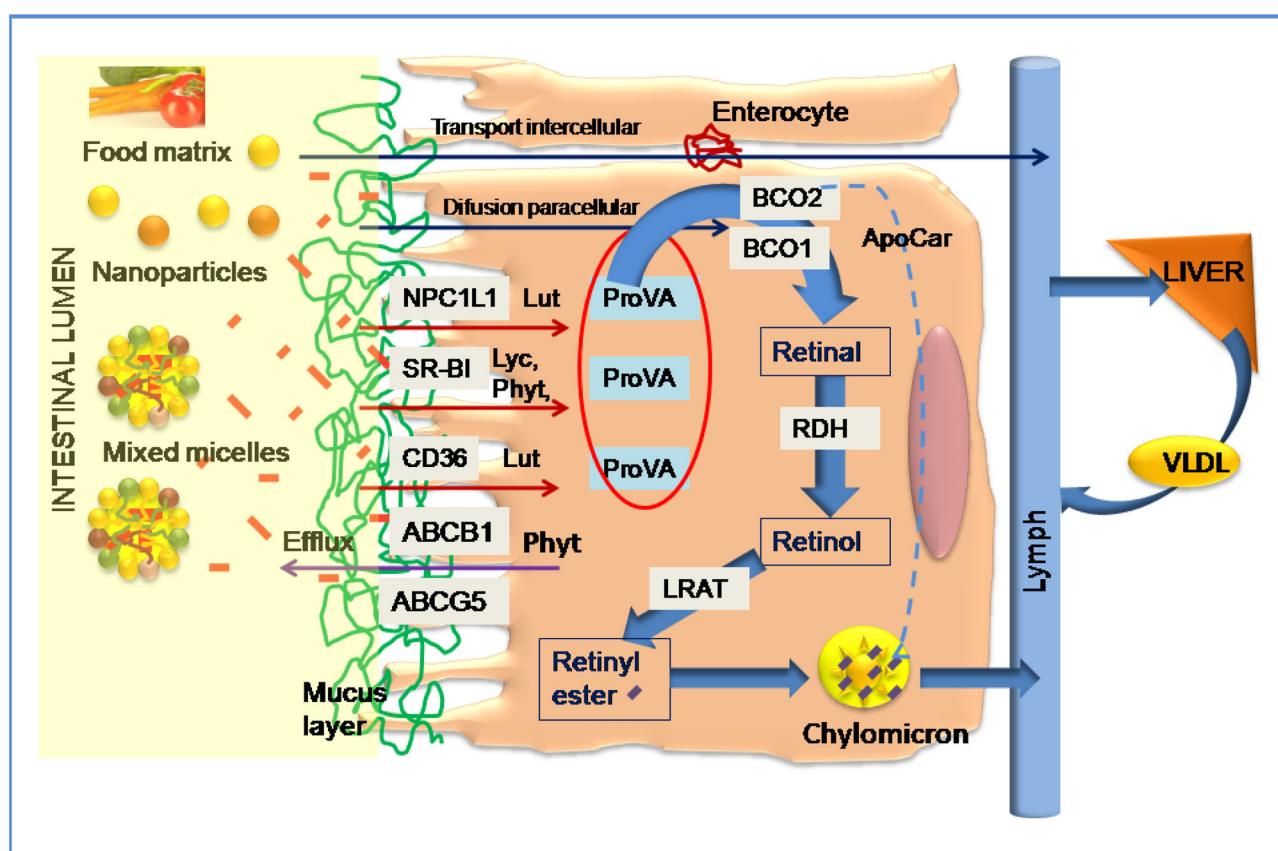
In plants, some carotenoids are found in the free form; e.g., lycopene and  $\beta$ -carotene, while others, such as  $\beta$ -cryptoxanthin and lutein are found in both free and esterified forms with various fatty acids. Due to the presence of double bonds in their main chain, carotenoids can exist as *trans*- and *cis*-isomers. Most carotenoids in plants are in the form of all-*trans* isomers, which are more energy stable than *cis* isomers. During food thermal processing, a *trans* isomer can be transformed into *cis* isomer. Polarity, free or esterified form and type of *cis-trans* isomers are important factors which influence the  $B_{AV}$  of carotenoids (Desmarchelier and Borel 2017).

Lately, the bioactivity of carotenoids has been studied intensively, highlighting their main biological functions; e.g., antioxidant activity, immunomodulatory activity, improvement of vision function and inhibiting the development of degenerative diseases, such as cataracts and glaucoma, skin protection again UV radiation, and so on (Kopec and Failla 2018; Rostamabadi, Falsafi, and Jafari 2019). Some carotenoids, such as  $\alpha$ -/ $\beta$ -carotene, and  $\beta$ -cryptoxanthin are considered to be provitamin A, because their molecules are metabolized in the liver leading to the formation of vitamin A (Rehman et al. 2020).

### Bioaccessibility and uptake of carotenoids

$B_{AC}$ , or carotenoid digestion, like other lipophilic biocomponents, represents a set of physico-chemical and enzymatic processes whereby a fraction of the carotenoid molecules found in ingested foods reaches to the epithelial wall of the membrane, where absorption occurs. After ingestion of food, the carotenoid molecules must be released from the delivery systems (plant and fruit cells, food matrix, nanocarriers, etc.) and then solubilized in GI fluids. The main way to solubilize carotenoids is to emulsify them in small droplets, followed by their inclusion in the mixed micelles consisting of bile salts, free or esterified cholesterol, phospholipids, mono- and di-glycerides and FFAs obtained from triacylglyceride digestion. Numerous studies have investigated both the dietary factors, such as the physico-chemical characteristics of carotenoids, the biostructure of plant tissues, food matrix, the structure of nanocarriers, an processing techniques, as well as the host-related factors, such as: peristaltic movement of GIT walls, pH and salinity of GI fluids, enzyme activity, interaction with other components, all affecting the carotenoid  $B_{AC}$  (Desmarchelier and Borel 2017; Lin et al. 2018).

A key step in oral  $B_{AV}$  of carotenoid molecules is their uptake into epithelial cells and passage into the systemic circulation. In the last decade, several teams of researchers have studied the mechanisms involved in the absorption, metabolism and distribution of carotenoids within the body, highlighting the two transport ways: passive transport



**Figure 6.** Absorption and metabolism of carotenoids. Lut, lutein; Lyc, lycopene; Phyt, phytoene; NPC1L1, Niemann-Pick C1-like 1; SR-BI, scavenger receptor class B type I; CD36, cluster determinant 36; ABCB1 and ABCG5, ATP-binding cassette (ABC) transporter; ProVA, provitamin A; ApoCar, apocarotenoids; BCO1,  $\beta$ -carotene oxygenase 1; BCO2,  $\beta$ -carotene oxygenase 2; RDH, retinol dehydrogenase; LRAT, lecithin-retinol acyltransferase; VLDL, very low lipoproteins.

(diffusion), generated by an excess of carotenoids in the lumen, and the active transport generated by a series of proteins with the role of transporters. As shown in Figure 6, the following steps are involved in the absorption of carotenoids by enterocytes, although some results are not conclusive and others are still pending:

1. passage of mixed micelles loaded with free or esterified carotenoids through the mucus layer;
2. destruction of mixed micelles and release of carotenoids on the apical surface of enterocyte cells;
3. diffusion of carotenoid molecules from the lumen into enterocyte cells;
4. active transport of carotenoids inside enterocyte cells (influx transport), involving the lipid transporters;
5. efflux transport;
6. intracellular metabolism of carotenoids;
7. the passage of carotenoids and their metabolites from cells into the systemic circulation.

Studies have shown that the efficiency of carotenoid absorption varies between 10% and 30%, depending on the structure of the molecules. Thus, polar carotenoids (xanthophylls) and flexible carotenoids (phytoene, phytofluene) have a higher affinity for membrane-specific lipid transporters and consequently have a higher  $B_{AV}$  (Reboul 2019).

### ***Bioaccessibility and bioavailability of encapsulated carotenoids***

The low  $B_{AV}$  of carotenoids from natural sources has led to the development of new strategies for extraction and isolation of carotenoids and their encapsulation in different nanodelivery systems (Maqsoudlou et al. 2020; Rehman et al. 2020; Rostamabadi, Falsafi, and Jafari 2019). Carotenoids are solid, lipophilic, and sensitive to light, temperature and oxygen. Therefore, their encapsulation into different nanocarriers is a widely used method for protecting them against aggressive environmental factors and improving their  $B_{AV}$  (Assadpour and Jafari 2019). The most studied types of nanotransporters that contribute to the improvement of carotenoid  $B_{AV}$  are nanoemulsions (Meng et al. 2019; Rostamabadi, Falsafi, and Jafari 2019; Yuan et al. 2019), solid lipid nanoparticle (SLNs) and nanostructured lipid carriers (NLCs) (Salvia-Trujillo et al. 2013), nanoliposomes (Tan et al. 2014), and polymeric NPs (Jain et al. 2018; Kamil et al. 2016; Wei et al. 2018), as described briefly in Table 3.

In the last decades, several reviews have been published presenting the latest information regarding either the types of nanocarriers used in carotenoid delivery (Rostamabadi, Falsafi, and Jafari 2019; Soukoulis and Bohn 2018; Rehman et al. 2020), or the factors that influences the  $B_{AV}$  of carotenoids (Lin et al. 2018; Kopec and Failla 2018; Moran et al. 2018; Xavier and Mercadante 2019; Liang et al. 2019; Desmarchelier and Borel 2017). For instance, West and Castenmiller (1998) summarized the factors that affect the  $B_{AV}$  and bioconversion of carotenoids using a mnemonic acronym term “SLAMENGHI.” Each letter in this term refers to a factor involved in the carotenoid  $B_{AV}$ . “S” refers

to the physico-chemical characteristics of “Species” of carotenoids; “L” derives from “Linkage” of functional groups to carotenoids molecules (esters, aldehydes, etc.); “A” expresses “Amount” of carotenoids consumed in a meal; “M” represents the influence of food “matrix” on carotenoid  $B_{AC}$  and  $B_{AV}$ ; “E” refers to the role of “Effectors” of absorption (nutrients and drugs) on carotenoid uptake; “N” expresses “Nutrient status of the host” (e.g., effect of vitamin A status on  $\beta$ -carotene  $B_{AV}$  and bioconversion); “G” shows the influence of “genetic” factors on interindividual variability of the  $B_{AV}$  of fat-soluble biocomponents (vitamins, phytosterols, etc.); “H” refers to “host-related factors” (sex, age, and disease); and “I” expresses the interactions of the factors mentioned above.

Some authors reported that carotenoid  $B_{AC}$  increases when plant carotenoid sources are co-ingested with lipids (González-Casado et al. 2018; Mutsokoti et al. 2017). This is because the lipids used as excipients favor the extraction of carotenoids from the crushed plant tissues in the oral cavity. Carotenoids and lipid excipients are emulsified by biosurfactants from GI fluids. Lipolytic enzymes convert triglycerides into mono and di-glycerides, and free fatty acids which, together with phospholipids, cholesterol, and bile salts contribute to the micellar solubilization of carotenoids. In most papers, carotenoid  $B_{AC}$  has been expressed as the carotenoid fraction in the mixed micellar phase.

Digestion of carotenoid-loaded emulsions is influenced by several factors, such as: type and amount of oil, type of surfactant, and size of droplets (Zhang et al. 2016; Salvia-Trujillo and McClements 2016). Some authors studied the influence of lipid content and type, used as excipients or as delivery systems, on carotenoid  $B_{AC}$  (Zhang, Zhang, Zhang, Decker, & McClements 2015). The results showed that the  $B_{AC}$  of  $\alpha$ - and  $\beta$ -carotene increased from about 7% to about 45% when corn oil level increased from 0% to 8%. It was also shown that the carotenoid  $B_{AC}$  was higher when long-chain triacylglycerides (LCTs, such as corn oil) used than medium-chain triglycerides (MCTs, such as canola oil and soybean oil) due to the ability of LCTs to form mixed micelles with large non-polar cores in which a higher amount of carotenoids is solubilized. Other studies have shown that non-edible oils (mineral oils, essential oils) do not contribute to the improvement of carotenoid  $B_{AC}$  due to the lack of lipolysis compounds (Salvia-Trujillo et al. 2013).

The unsaturation degree of fatty acids from oils used as excipients or delivery systems also influences the  $B_{AC}$  of carotenoids. Yi et al. (2015) demonstrated that the  $B_{AV}$  of  $\beta$ -carotene was higher when co-ingested with saturated fatty acids-rich oils than with polyunsaturated fatty acids (PUFAs)-rich oils. Verkempinck et al. (2018) investigated carotenoid  $B_{AC}$  in emulsions with different unsaturated oils. The authors studied the kinetics of the TAG lipolysis processes and the micellization of digestion products and carotenoids, using a static GIT model. For preparation of the emulsions, oils rich in fatty acids with different degrees of unsaturation were used, such as: oleic acid-rich olive oil, linoleic acid-rich soybean oil, and linolenic acid-rich linseed oil. These oils were enriched with  $\beta$ -carotene and lycopene

**Table 3.** Recent studies on the bioaccessibility and cellular uptake of encapsulated carotenoids.

Bioactive compound	Nanoemulsions/ food matrix	Characteristics of nanocarriers	Bioaccessibility ( $\beta_{AC}$ )	Cellular uptake	References
$\beta$ -carotene (BC)	Nanoemulsions (NES)	BC in oil phase or tea polyphenols (TP) in aqueous phase; The TP-BC NESs showed a significantly higher Z-potential value compared to the BC NESs	"In vitro" multiple stages GIT model with enzymes $\beta_{AC}$ of BC from BC-NESs: SSF: 75%–80% SGF: 20%–23% SIF: 10%–20%	"In vivo" absorption study. Twenty-one male Sprague-Dawley rats were used. The contents of the gastric tract (small intestine, large intestine) and feces as well as the liver were analyzed at 1, 6 and 12 h after oral-administration. The BC was detected at 450 nm and vitamin A was detected at 294 nm. Total content BC from BC-NESs: BC-NESs; TP-BC-NESs: ~48 µg/g at 1 h ; ~55 µg/g at 1 h ~53 µg/g at 6 h ; ~50 µg/g at 6 h ~40 µg/g at 12 h; ~50 µg/g at 2 h TP-BC NESs had a higher conversion efficiency of BC to vitamin A compared to the BC NESs	Meng et al. (2019)
$\beta$ -carotene	Zein-propylene glycol-alginate composite nanoparticles	The properties of BC-composite nanoparticles varied with different mass ratios of zein to propylene-glyco: -size: ~400–750 nm -Z-potential: +24 to –25 mV -encapsulation efficiency: 37%–69%	"In vitro" two-stage gastrointestinal model, with pancreatin in SIF. At lower zein content, the BC release rate increased in SGF (60 min) (7.78 to 12.81%) and decreased in SIF(180 min) (33.38% to 20.32%)	"In vitro" static multiple stages GIT model, with enzymes $\beta_{AC}$ of BC from spinach: -SC NESs: ~29% -Tween NESs: ~14% -OSA-starch NESs: ~7% The degradation ( $D^*$ ) of $\beta$ -carotene in TGI stages was determined. -SC NESs: 41.8% -Tween NESs: 35.8% -OSA-starch NESs: 32.3% The potential absorption of $\beta$ -carotene was calculated ( $\beta_{AC} \cdot D^*$ ): -SC NESs: 12.0% -Tween NESs: 5.0% -OSA-starch NESs: 2.6%	Wei et al. (2018)
$\beta$ -carotene	Excipient nanoemulsions stabilized by sodium caseinate (SC), Tween20 and octenyl succinic anhydride (OSA)-modified starch	Mean droplet diameter: -SC NESs: 205 nm -Tween NESs: 195 nm -OSA-starch NESs: 180 nm PDI: -SC NESs: 0.099 -Tween NESs: 0.145 -OSA-starch NESs: 0.125 Z-potential: -SC NESs: –29.9 mV -Tween NESs: –7.4 mV -OSA-starch NESs: –21.6 mV	"In vitro" static GIT model, with enzymes Cocoa butter lipid nanoparticles -Particle size and Z-potential varied with lipid, surfactant amount and digestion conditions; - $\beta$ -carotene was more stable LNP	Not been studied	Yuan et al. (2019)
$\beta$ -carotene	Lipid nanoparticles	Corn oil lipid nanoparticles Cocoa butter lipid nanoparticles	"In vitro" static GIT model, with enzymes -corn oil LNPs showed a higher rate constant for FFAs and MAGs release compared to cocoa butter LNPs	Not been studied	Salvia-Trujillo et al. (2013)

(continued)



Table 3. Continued.

Bioactive compound	Nanocarriers/ food matrix	Characteristics of nanocarriers	Bioaccessibility ( $B_{AC}$ )	Cellular uptake	References
$\beta$ -carotene	Nanoemulsions	inside corn oil LNP s that inside cocoa butter LNP s  $\beta$ -carotene-O/W NEs stabilized with chlorogenic acid-lactoferrin-polydextrose (CA-LF- PD) conjugatesurfactant Droplet size, charge, andmicrostructure of $\beta$ -carotene NEs were analyzed at the passage through a simulated GIT model (mouth, stomach, small intestine) The CA-LF-PD conjugate-stabilized NEs were more stable and had high $\beta$ -carotene accessibility  High internal phase emulsion gels (HIPEs) were prepared using preheated whey protein isolate (WPI) and cold-set gelation was induced by glucono- $\delta$ -lactone (GDL)	-the micellarization of FFA from corn oil LNP s showed a higher rate constant and a higher final value when compared to cocoa butter LNP s -the average FFA micellarization ratio was 88.8%, in corn oil LNP s and 38.8% in cocoa butter LNP s; both emulsified systems presented a similarly high MAG micellarization rate, which averaged between 90 and 100%. -the MAG micellarization rate, was high for both LNP s (90%-100%) "In vitro" static GIT model, with enzymes: A) Full GIT model B) Simple GIT model $\beta$ -carotene $B_{AC}$ : LF-stabilized NEs: ~2.5% (A); ~3% (B) CA-LF-stabilized NEs: ~4% (A); ~2% (B) CA-LF-PD coni-stabilized NEs: ~5.5% (A); ~6.3% (B)	"In vitro" static GIT model, with enzymes: A) Full GIT model B) Simple GIT model $\beta$ -carotene $B_{AC}$ : LF-stabilized NEs: ~2.5% (A); ~3% (B) CA-LF-stabilized NEs: ~4% (A); ~2% (B) CA-LF-PD coni-stabilized NEs: ~5.5% (A); ~6.3% (B)	Liu, Ma, et al. (2017)
$\beta$ -carotene	Emulsion gels (emulgels)		"In vitro" static multiple stages GIT model, with enzymes: $\beta$ -carotene retention: Without LDL: 44.2% for 2.5% WPI-HIPEs 82.5% for 10% WPI-HIPEs For 7.5% WP: 59.4% without LDL 71.2% with LDL $\beta$ -carotene $B_{AC}$ : Without LDL: 41.14% for 2.5% WPI-HIPEs 72.3% for 10% WPI-HIPEs For 10% WP: 72.3% without LDL 88.34% with LDL	Not been studied	Liu et al. (2019)
Lutein	Polymer nanoparticles Lutein- loaded micelles		Poly(lactic-co-glycolic) acid nanoparticles (PLGA-NP) Lutein-loaded micelles were prepared by rehydrated freeze- dried/ultraconication method	A. Bioavailability of lutein in animal model Male Fischer 344 rats were used Lutein was quantified in plasma, liver, and mesenteric fat depot Area under curve (AUC) (h ng/mL): Plasma: free lutein 2.5; PLGA-NP 193 <sup>9</sup> Liver: free lutein 846.9; PLGA-	Kamil et al. (2016)

NP 493.8			
	Mesenteric fat: free lutein 117.9; PLGA-NP 519.9		
	B. Intestinal absorption of lutein in Caco-2 cell monolayers The uptake and secretion of lutein was tested in three delivery vehicles: (i) micelle, (ii) PLGA-NP, and (iii) PLGA-NP plus additional micelle components.		
	Total absorption (cell uptake + secretion) at 1.18 µg/mL oral dose lutein: Micelles: ~28% PLGA-NP: ~7%		
Astaxanthin	"In vitro" static GIT model, with enzymes: Astaxanthin $B_{\text{AC}}$ : Uncooked salmon: ~42% Cooked salmon: 20%–36% Commercial supplements: 30%–65% Krill oil supplements: ~70% Astaxanthin isomers $B_{\text{AC}}$ : Uncooked salmon: $Cis$ -Astaxanthin 39.6% $Trans$ -Astaxanthin 49.6%	"In vitro" Caco-2 human intestinal cells model Cellular uptake of astaxanthin: Uncooked salmon: ~12% Cooked salmon: ~12%–15% Supplements krill oil: ~17%	Chitchumroon and Failla (2017)
Salmon; Supplements; Krill oil	Uncooked and cooked salmon Commercial supplements Phospholipid-rich krill oil supplement		
Lycopene	Lycopene-whey protein nanoparticles (LYCWPI-NPs) Particle size : 218.9–348.2 nm PDI: 0.168–0.383 Encapsulation efficiency: 53.7%–64.7% Loading capacity: 8.2–12.3	"In vitro" cellular uptake: The MCF-7 cells model was used After 3 h incubation: LYC free: 24.18% LYC-WPI-NPs: 46.7 After 5 h incubation: LYC free: 33.07% LYC-WPI-NPs: 64.2% Cytotoxicity of lycopene: Cell survival (LYC 50 µM/mL, after 48 h incubation: LYC free: ~78% LYC-WPI-NPs: ~70%	Jain et al. (2018)

BC,  $\beta$ -carotene; TP, tea polyphenol; NE, nanoemulsion;  $B_{\text{AC}}$ , bioaccessibility;  $D^*$ , degradation rate; SGF, simulated gastric fluid; SIF, simulated intestinal fluid; SSF, simulated salivary fluid; GIT, gastrointestinal transit; SC, sodium caseinate; OSA, octenyl succinic anhydride; LNP, lipid nanoparticle; FFA, free fatty acid; MAG, monoacylglycerol; CA, chlorogenic acid; LF, lactoferrin; PD, polydextrose; HIPE, high internal phase emulsion; PLGA-NP, poly(lactic-co-glycolic) acid nanoparticle; WPI, whey protein isolate; GDL, glucono- $\delta$ -lactone; LYC, lycopene; LYCWPI, lycopene-whey protein; PDI, polydispersity index.

using carrot or tomato purees. The results showed that both the rate of TAG hydrolysis reaction and the amount of hydrolyzed TAGs varied with the degree of unsaturation of the fatty acids present in the oils. Thus, it was found that TAG digestion was faster for olive oil emulsions than for soybean oil and linseed oil emulsions; which means that oils containing monounsaturated free fatty acids (MUFAs) are digested more readily than oils rich in free PUFAs. The authors suggested that these results are due on the one hand to the folded structure of PUFA chains whose steric hindrance opposes the action of lipolytic enzyme, and on the other hand to the higher surface activity of PUFAs, which determines the preferential distribution of PUFA molecules on the surface of oil droplets, preventing the access of the enzyme to the ester groups of TAGs (Verkempinck et al. 2018).

By studying the kinetics of the self-association process of digestion products (MAGs and FFAs) in the mixed micelles, the authors reported that only a part (45%–75%) of the MAGs and FFAs contributed to the formation of the micelles. Also, the similar values of the rate constants of the micelle process suggest that, during TAG hydrolysis, the MAG and FFA molecules are incorporated simultaneously into the mixed micelles. The kinetics of carotenoid  $B_{AC}$  revealed a difference, depending on the degree of unsaturation of the oils. Thus, the values of the rate constants showed that carotenoids penetrated faster in the mixed micelles formed at the digestion of olive oil emulsions compared to soybean oil and linseed oil emulsions. Finally, different values of carotenoid  $B_{AC}$  were obtained;  $B_{AC}$  of  $\beta$ -carotene in carrot-enriched olive oil emulsions was 13%, whereas in carrot-enriched soybean oil emulsions it was 8%–10% (Verkempinck et al. 2018).

Similar differences were also obtained for the  $B_{AC}$  of *trans*-lycopene, which was 19% for tomato-enriched olive oil emulsions compared to tomato-enriched soybean oil and linseed oil emulsions for which the  $B_{AC}$  of *trans*-lycopene was approximately 9.5%. The authors also reported differences between the values of bioactivities depending on the type of carotenoids. Thus, in all carrot-based emulsions, the  $B_{AC}$  of  $\beta$ -carotene was higher than that of  $\alpha$ -carotene, because  $\alpha$ -carotene is more hydrophilic than  $\beta$ -carotene and is less accessible to mixed micelles. Also, in tomato-based emulsions, the  $B_{AC}$  of *trans*-lycopene was lower (19%) than that of  $\beta$ -carotene (24%). The authors suggested that these results are due to the rigid linear structure of *trans*-lycopene which makes it remain significantly in undigested oil droplets, as compared to the more flexible  $\beta$ -carotene molecules that are released more easily from the oil droplets and are incorporated faster in mixed micelles (Verkempinck et al. 2018).

Other studies investigated the influence of carotenoid content in nanocarriers on their  $B_{AV}$ . In this respect, some authors found that the  $B_{AV}$  of  $\beta$ -carotene in nanoemulsions or nanoliposomes decreased significantly at higher  $\beta$ -carotene levels (Tan et al. 2014; Wang et al. 2012). Compared to the number of studies that investigated the  $B_{AC}$  of carotenoids from different delivery systems, the cellular uptake of carotenoids from nanocarriers has not been studied that much. Most studies showed that carotenoid uptake is

essentially influenced by their molecular structure. Thus, *cis* and all-*trans*-isomers have been shown to be absorbed differently by cell membranes.

Although in many studies, which used both "in vitro" models (Caco-2 cells), and animal and human experiments, it has been reported that all-*trans* carotenoids are absorbed faster than *cis*-isomers (Failla, Chitchumroonchokchai, and Ishida 2008; Moran et al. 2018); however, some authors have reported either a similarity in the absorption of the two isomers of BC (Svelander et al. 2011), or a higher absorption of the *cis*-BC isomer than all-*trans*-BC, due to the higher incorporation rate of the *cis*-isomer into mixed micelles (Mutsokoti et al. 2017). The structure of carotenoids influences the release in GIT segments, their incorporation rate into the mixed micelles, and the interaction with the phospholipids in the bilayer of cellular membrane. For instance, Tan et al. (2014) using the in vitro multi-stage GIT model, studied the fate of liposomes loaded with  $\beta$ -carotene or lycopene in GIT segments and reported that most of the  $\beta$ -carotene was released slowly into simulated intestinal fluid; while lycopene released was faster into simulated intestinal fluid. The authors explained this behavior by the interaction of  $\beta$ -carotene and lycopene molecules with phospholipids from the liposomal bilayer. Thus, the  $\beta$ -carotene molecules, which contain two  $\beta$ -ionone cycles, orient perpendicularly to the hydrocarbon chains of the phospholipids in the liposomal bilayer, making it difficult to release them; on the other hand, the linear structure of the lycopene allows a parallel orientation with the hydrocarbon chains of the phospholipids and consequently favors its rapid release.

In a recent study, de Oliveira et al. (2020) investigated the influence of heat treatment on the  $B_{AC}$  and  $B_{AV}$  of carotenoids from different salad varieties. The authors found that in the fresh lettuce, the  $\beta$ -carotene level was around 10 mg/100 g, while lutein was approximately 3 mg/100 g. By lettuce boiling, over 70% of the carotenoids were lost, and  $B_{AC}$  decreased 2–7 times due to their degradation. In vitro digestion of raw lettuce showed that the  $B_{AC}$  of  $\beta$ -carotene was lower (~10%) than lutein (15%). However, if the content of carotenoids in mixed micelles was related to the amount of carotenoids remaining after boiling, the lutein  $B_{AC}$  was 35.8%, and that of  $\beta$ -carotene was 19.6%, suggesting that the release of carotenoids and their incorporation into the mixed micelles is more effective in processed samples. Carotenoid uptake results revealed that raw lettuce had a very low absorption through the Caco-2 epithelial cell layer (lutein 0.08% and  $\beta$ -carotene 0.06%), while carotenoid absorption from cooked lettuce increased approximately seven-fold (lutein 0.62% and  $\beta$ -carotene (0.44%). Some authors suggest that the higher value of lutein  $B_{AV}$  compared to that of  $\beta$ -carotene is due to the presence of hydroxyl groups which increases the lutein polarity, favoring the permeation of the molecules through the epithelial cells layer (Nagao 2014). It has been concluded that the  $B_{AV}$  of carotenoids is independent of the amount of carotenoids from the initial source.

Other authors showed that isomerization is an important factor affecting the  $B_{AV}$  of carotenoids as a result of thermal

food processing. In this regard, Aherne et al. (2010) investigated the  $B_{AV}$  of  $\beta$ -carotene isomers. They used an *in vitro* digestion model coupled with a human intestinal Caco-2 cells line and determined the  $B_{AC}$  and absorption of  $\beta$ -carotene isomers (all-*trans*, 9-*cis*, 13-*cis*, and 15-*cis*) from raw, boiled, and pureed carrot. In all samples, the content of all-*trans*- $\beta$ -carotene was higher than the *cis*- $\beta$ -carotene, and by thermal processing, both all-*trans* and *cis*-isomers increased, which suggests isomerization of carotenoids during sample processing. After “*in vitro*” digestion, they observed an increase in the content of all-*trans*- $\beta$ -carotene in the micellar fraction from cooked carrots, compared to the micellar fraction from raw carrot. The highest all-*trans*- $\beta$ -carotene level was found in pureed carrot due to the high level of processing (mechanical, thermal) that allowed the release of BC from the food matrix. Also, the *cis*- $\beta$ -carotene level in the micellar phase obtained in the cooked carrot digestion was higher than raw carrot digestion. These results confirmed the role of processing in the release of carotenoids from plant tissues and degradation of caroteno-protein complexes. The content of  $\beta$ -carotene isomers in the micellar fractions obtained at the digestion of cooked carrots, varied in the order: all-*trans*  $\sim$  13-*cis*  $>$  9-*cis*  $>$  15-*cis*. Results on cellular uptake of  $\beta$ -carotene isomers showed that the amount of all-*trans*-, 13-*cis*-, and 15-*cis*- $\beta$ -carotene isomers passing through the Caco-2 cell layer was higher for cooked carrot than for raw carrot, and the absorption of all *trans*- and 13-*cis*- $\beta$ -carotene isomers from pureed carrot was higher than from boiled carrot.

Table 3 shows an overview of the most recent studies regarding the  $B_{AV}$  of some carotenoids encapsulated in different types of nanocarriers.

### Vitamins and minerals

Vitamins (vit) are important micronutrients for normal growth and functioning of the human body. Since they are not synthesized, or are synthesized in a very small amount by the mammalian body, the vitamins intake is ensured through the consumption of fruits, vegetables, meat and meat products, milk and dairy products (Borel and Desmarchelier 2018; Said 2011). Vitamins have a beneficial effect on human health, preventing the development of diseases such as: decreased bone resistance (vit D), decreased visual activity (vit A), neural tube defects (folate), and reduced oxidative processes in the cell membrane (vit E). Depending on the solubility, vitamins are grouped into two classes:

1. water-soluble (hydrosoluble) vitamins: B<sub>1</sub> (thiamin), B<sub>2</sub> (riboflavin), B<sub>3</sub> (niacin), B<sub>5</sub> (pantothenic acid), B<sub>6</sub> (pyridoxal), B<sub>7</sub> (biotin), B<sub>9</sub> (folic acid), B<sub>12</sub> (cyanocobalamin), and C (ascorbic acid).
2. fat-soluble (liposoluble) vitamins: A (retinol, retinal, and retinyl esters), D<sub>2</sub> (ergocalciferol), D<sub>3</sub> (cholecalciferol), E (tocopherol), K<sub>1</sub> (phylloquinone), and K<sub>2</sub> (menaquinone).

Research in recent years has highlighted the specific functionalities of each vitamin, and their estimated average requirements (Borel and Desmarchelier 2018; Glowka, Stasiak, and Lulek 2019) along with the synergistic effects of vitamins and different minerals, which contribute to improving their  $B_{AV}$ , such as: calcium and vit D, iron and vit C (Nair and Augustine 2018). Some minerals, like vitamins, are not synthesized in the human body, but are necessary for the growth and development of bones and teeth or are involved in the enzymatic systems specific to biological functions, which are labeled as essential minerals (Gharibzahedi and Jafari 2017). The mineral intake is ensured by the consumption of cereals, vegetables, fruits, milk and dairy products, meat and meat products, fish, etc. (EFSA 2017).

### Intestinal absorption of vitamins and minerals

In recent years, many scientists have studied the intestinal absorption of vitamins and minerals showing that they can pass through the epithelial layer of the GI membrane both through the diffusion of molecules or NPs (passive transport) and by active transport mediated by transporters (Said and Nexo 2018). The results of these researches explained the transporters, transport mechanisms and intracellular metabolism of water-soluble and fat-soluble vitamins. Hydrosoluble vitamins, which are in esterified forms in foods, are first hydrolyzed in the stomach (e.g., phosphorylated thiamin is converted into free thiamin by phosphatases). Then, the free, non-ionized or ionized hydrosoluble vitamin molecules are surrounded by water molecules and absorbed in the small intestine (vitamins from foods), or in the colon (vitamins generated by the microflora of the large intestine).

Some specific transporters are involved in the absorption of hydrosoluble vitamins such as thiamin transporters (THTR 1 and THTR2) for the apical membrane absorption of thiamin (vit B<sub>1</sub>) and riboflavin transporters (RFT1 and RFT2) for the absorption of riboflavin (vit B<sub>2</sub>). *In vitro* studies using the Caco-2 cells model have shown that Biotin (vit B<sub>7</sub> or vit H) and pantothenic acid (vit B<sub>5</sub>) are absorbed in the intestine and colon by the involvement of Na<sup>+</sup>-dependent multivitamin transporter (SMVT) in the apical brush-border membranes; while folic acid (vit B<sub>9</sub>) is absorbed as folate monoglutamates by specific pH-dependent, Na<sup>+</sup>-independent carrier-mediated mechanism, with the participation of proton-coupled folate transporter (PCFT) and reduced folate carrier (RFC) (Said 2011).

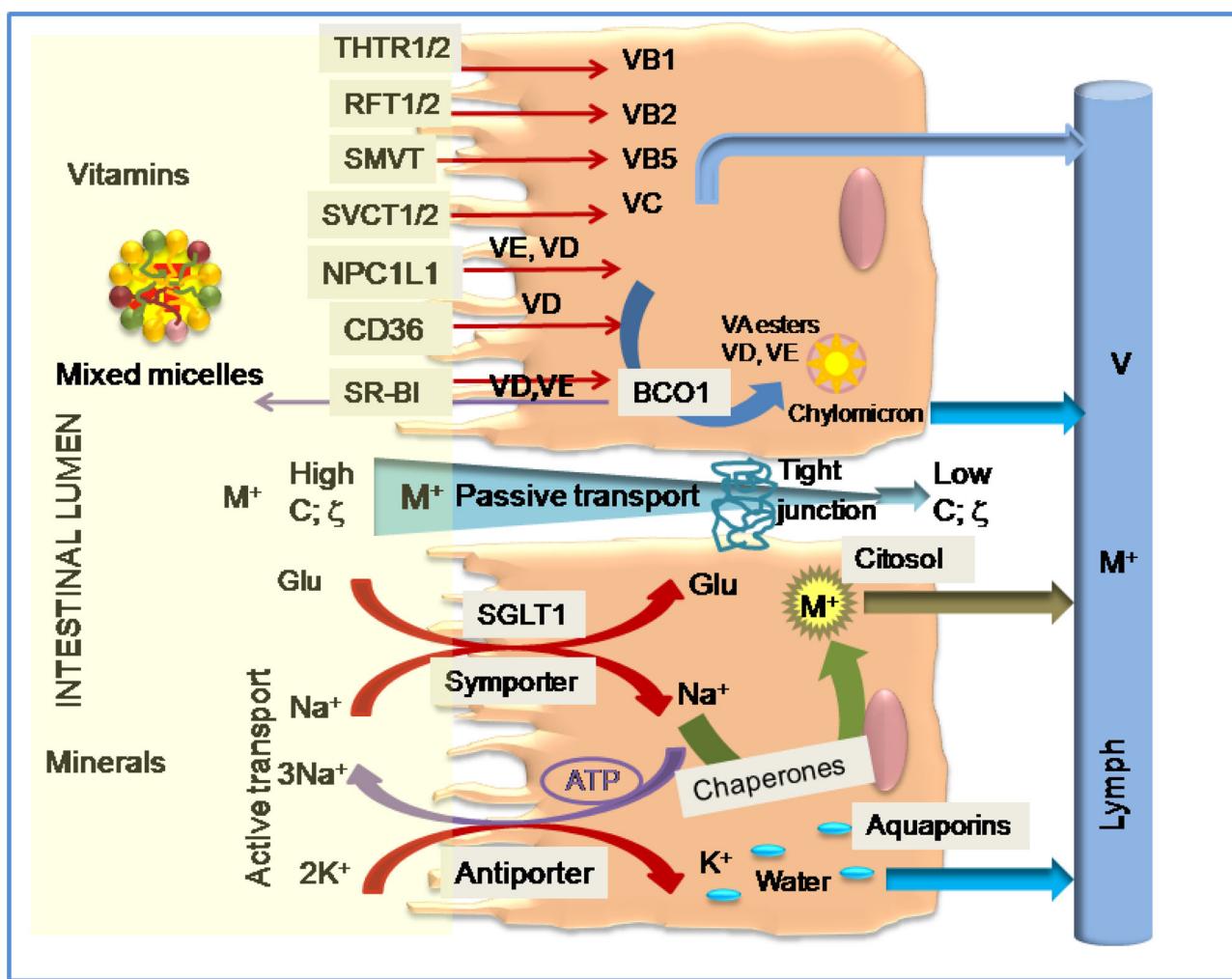
Vit C (ascorbate) is one of the most studied vitamins due to its involvement in multiple metabolic processes such as: oxidative damage of membrane cells, oxidative modification of LDLs, cytotoxicity to tumor cells, lowering the vascular smooth-muscle-cell apoptosis, and decreased cataract risks (Li and Schellhorn 2007). The ascorbate is found in two forms: a reduced form: ascorbic acid (AA), and an oxidized form known as dehydro-L-ascorbic acid (DHAA). In enterocyte cells, DHAA is converted to AA by DHAA reductase. Intestinal absorption of AA is done using sodium-dependent cotransporters: (e.g., sodium vit C transporters: SVCT1 and SVCT2), which prefer L-ascorbic acid more than D-isoascorbic acid, and never DHAA. DHAA is absorbed with the involvement

of glucose transporters (GLUT1 and GLUT3). After absorption through the apical surface epithelial membrane, the internalized hydrosoluble vitamins pass directly into the blood.

Liposoluble vitamins are absorbed into GIT segments like other lipophilic components, such as phytosterols and carotenoids. The passage liposoluble vitamin molecules through the apical surface of the epithelial membrane is made, using the specialized carrier-mediated mechanisms (Figure 7). Some transporters are involved in the internalization of vitamins by influx transport, such as: SR-B1 (vit E and D), NPC1L1 (vit E and D), and CD36 (vit D); while other transporters participate in the return of vitamins to the intestinal lumen by efflux transport, such as: SR-B1 (vit E and D) and other potential efflux transporters for vit A, D, and E (Reboul 2013). Fraction of liposoluble vitamins that did not back to the lumen, traffics the cell with the help of intracellular transporters (e.g., Cellular Retinol-Binding Protein II (CRBPII, for retinol transport), and then it is incorporated into chylomicrons that pass into the lymph. Some of the liposoluble vitamins (A, D and possibly E) are transported through the basolateral side of enterocytes by ATP Binding Cassette transporters (ABCA1 and possibly ABCG1) (Reboul 2013).

Minerals are absorbed in all GIT sectors, but most of them are absorbed in the small intestine. The  $B_{AV}$  of minerals is influenced by a variety of factors, such as: the chemical form of the minerals (free or bound to other compounds), their interaction with other substances present in food or the health status of the people. For example, iron absorption from plants is more difficult than from meat because, in plants, iron is found in iron non-heme form, while in meat it is found in heme form. Also, some inhibitors, such as phytic acid (6-phosphoinositol) from whole grain, lentils, nuts, or oxalic, tannic and chlorogenic acids from cereals, vegetables, spices, reduce the  $B_{AV}$  of iron, calcium and zinc (Gharibzahedi and Jafari 2017). An excess mineral can inhibit the absorption of another mineral involved in the same absorption mechanism (e.g., excess iron reduces the absorption of zinc).

Studies on cellular uptake of minerals have shown that minerals can pass through the bilayer of epithelial cells by both paracellular and intracellular transports (Goff 2018). The minerals uptake by one of the two mechanisms is influenced by different factors, such as: the concentration of mineral ions in the lumen, the size of the mineral atom, the electrical charge of the ions, the ionized state (free, or bound



**Figure 7.** Absorption and metabolism of vitamins and minerals. VB1/2/5, vitamins B1/2/5; VE, vitamin E; SGLT1, sodium-dependent glucose transporter; THTR1/2, thiamin transporters; RFT1/2, riboflavin transporters; SMVT, sodium-dependent multivitamin transporter; NPC1L1, Niemann-Pick C1-like 1; CD36, cluster determinant 36; SR-B1, scavenger receptor class B type I; BCO1,  $\beta$ -carotene oxygenase 1; Glu, glucose.

to proteins), the source of minerals, and interaction with other components (Corte-Real and Bohn 2018). The paracellular transport of ions is also influenced by the structure of claudin proteins that are in tight junctions. Thus, some of the claudin proteins are negatively charged and form pores with a negative charge, which repel the anions and favor the passage of cations, while other claudin proteins are positively charged and form anion-selective pores, as depicted in Figure 7.

Due to the hydrostatic pressure or the osmotic pressure created between the two spaces, the water molecules that pass through the tight junctions, are linked to the mineral ions by ion-dipole bonds favoring an additional mechanism of paracellular transport, called solvent drag transport (Goff 2018). At low levels of mineral ions in the lumen, the concentration and electrical potential gradients are insignificant and cannot ensure their passive transport. Under these conditions, the ions can penetrate into the lipophilic bilayer of the epithelial membrane only under the action of transporter proteins, called symporters. The symporters select the ions very strictly, depending on the degree of ionization, the electrical charge, the valence, and the atomic mass, and transport them from the intestinal space to the cellular space. Some ions, such as  $\text{Na}^+$  ions, are co-transported by especially glucose transporter proteins (SGLT) located on the apical brush border membrane.

An important role in the membrane transport of ions is played by antiporters or ion exchangers. These are membrane proteins involved in the secondary active transport that provide transport of different ions in various directions. For example, the sodium-calcium exchanger is an antiporter that ensures the removal of one  $\text{Ca}^{2+}$  ion from the cell when three  $\text{Na}^+$  ions pass into the cell. This ensures the electrolytic (osmotic) balance of the cells. After passing through the lipid bilayer, inside the cell, most ions are taken up by vesicles or specialized transporter proteins called chaperones and passed into the cytosols. They transport them to the basolateral membranes, where they pass into the interstitial fluid, consequently into the systemic circulation. Capture of the internalized ions in the cytosol determines the formation of concentration gradient, favoring the intracellular transport of the ions by diffusion. Also, the intracellular transported ions can be accompanied by water molecules, which, after cell trafficking, are released into the interstitial fluid through specialized pores called aquaporins located in basolateral membranes (Goff 2018).

### **Bioaccessibility and bioavailability of vitamins and minerals in nanocarriers**

Due to their special structure, vitamins are sensitive molecules, which require protection against aggressive physico-chemical agents such as temperature, light and oxidants. One of the strategies for vitamin protection is their encapsulation within different nanocarriers (Katouzian and Jafari 2016). In recent years, many studies have focused on investigating the fate of nanocarriers loaded with vitamins in GIT and the influence of nanocarriers on the  $B_{AC}$  and  $B_{AV}$  of vitamins, as summarized in Table 4. Some authors

investigated the factors affecting the main processes involved in the  $B_{AC}$  of vitamins, such as the release from nanocarriers and food matrix, solubility, physical-chemical stability and the digestion of vitamins, using “*in vitro*” models to simulate GIT conditions; others studied the cellular uptake of vitamins using “*in vitro*” or “*in vivo*” methods (Table 4).

Vit D is an important nutrient for human health. It contributes to the development of bones and teeth and prevents diseases such as osteoporosis, obesity, hypoparathyroidism, cancer, diabetes, cardio-vascular diseases, and multiple sclerosis (Ramalho, Coelho, and Pereira 2017). Vit D is found in two different chemical forms: vit D<sub>2</sub> (ergocalciferol) and vit D<sub>3</sub> (cholecalciferol); only vit D<sub>3</sub> is synthesized in the human body, by the skin after exposure to sunlight. Consumption of dietary supplements and foods fortified with vit D are the most accessible ways to combat vit D deficiency. In general, food fortification is done with vit D<sub>3</sub> in the form of cholecalciferol, alfalcacidiol, and calcitriol or in combination with some minerals such as calcium or other vitamins (Maurya, Bashir, and Aggarwal 2020).

Because vit D<sub>3</sub> is a hydrophobic compound, most delivery systems are lipid-based nanocarriers. Some studies have investigated the influence of lipid type on the  $B_{AC}$  of vit D<sub>3</sub> (Maurya and Aggarwal 2017). For instance, Tan et al. (2019) studied the influence of oil type on the  $B_{AC}$  of vit D<sub>3</sub> in nanoemulsions stabilized with whey protein isolate. They prepared four types of nanoemulsions with different oil phases: digestible oil: corn oil (DO); indigestible oil: mineral oil (IO); oil phase mixture (OM): DO + IO in equal masses; and emulsions mixture (EM): DO emulsions + IO emulsions in equal masses. The  $B_{AC}$  of vit D<sub>3</sub> was analyzed using a static *in vitro* digestion model standardized in accordance with INFOGEST consortium protocol (Minekus et al. 2014). The authors first studied the kinetics of lipid digestion by measuring the content of FFAs obtained by digestion at different time intervals. Kinetic curves showed that for nanoemulsions containing only DO, about 75% of FFAs were rapidly released in the first 10 min, after which the release rate increased slowly to about 90% (after 20 h digestion). For the emulsions prepared with mixtures of oils (OM and EM), the release rate in the first minutes was similar to DO emulsions, with the difference that after 10 min digestion, only 40% of FFAs were released, then followed a slow release up to about 56% FFAs (after 20 h digestion). The release rate of FFAs from IO emulsions was about 1% at the end of digestion. These results suggested that only the edible oil participates in the digestion process and the presence of mineral oil in the mixture did not influence the digestion of the corn oil in the first minutes of digestion. The  $B_{AV}$  of vit D<sub>3</sub> from the four prepared emulsions was evaluated by measuring the vit D<sub>3</sub> content in the micellar phase from the small intestine, obtained after 1 day of digestion. The highest  $B_{AV}$  was for DO nanoemulsions (75.2%), compared to IO nanoemulsions (20.7%). Vit D<sub>3</sub>-loaded nanoemulsions containing the two oils (OM and EM) had approximately the same  $B_{AV}$  (35.6%), which revealed that the composition of nanoemulsions is more important than the initial location of the two oils. Similar results were obtained by Ozturk et al.

**Table 4.** Selected studies on the bioaccessibility and bioavailability of encapsulated vitamins and minerals.

Vitamins/minerals	Nanocarriers/food matrix	Characteristics of nanocarriers	Bioaccessibility ( $B_{AC}$ )	Absorption/bioavailability	References
Vitamin A	Milk protein complexes: Sodium caseinate-VA complex (NaCas-VA), Succinylated sodium caseinate-VA complex (SNaCas-VA) Reassembled sodium caseinate-VA complex (RNaCas-VA) Reassembled succinylated sodium caseinate-VA complex (RSNaCas-VA) Milk fortified with different sodium caseinate-VA complexes	not been studied	<i>In vitro</i> static digestion model $B_{AC}$ in SIF (180 min); NaCas-VA: 85.17% SNaCas-VA: 90.62% RNaCas-VA: 87.67% RSNaCas-VA: 90.91% Free-OilyVA: 68.05% Peptide content during <i>in vitro</i> digestion: NaCas-VA: ~420 µg/mg protein SNaCas-VA: ~430 µg/mg protein RNaCas-VA: ~400 µg/mg protein RSNaCas-VA: ~410 µg/mg protein	<i>In vitro</i> Caco-2 cell model: Cytotoxicity of milk protein-VA complexes: 80%-90% Caco-2 cell viability Vitamin A uptake: Protein-VA complexes: NaCas-VA: 33.34% (2 h); 33.89% (4 h) SNaCas-VA: 37.04% (2 h); 44.96% (4 h) RNaCas-VA: 39.60% (2 h); 45.71% (4 h) RSNaCas-VA: 45.14% (2 h); 56.39% (4 h) Free-OilyVA: 30.29% (2 h); 32.37% (4 h) Protein-VA complexes fortified milks (4 h): NaCas-VA: ~48% SNaCas-VA: ~55% RNaCas-VA: ~60% RSNaCas-VA: ~64% Free-OilyVA: 32.37% <i>In vitro</i> VA fortified milk: ~58%	Rana et al. (2019)
Vitamin D <sub>3</sub>	Whey protein isolate and lotus root amylopectin composite gels (WPI-LRA)	Molecular weight of LRA: 1.86 × 10 <sup>5</sup> Da. The amylose content of LRA: 1.88%. Gel strength (kPa): ~16 (pH = 5); ~53 (pH = 7); ~30 (pH = 8) Water holding capacity (%): ~60% (pH = 5); ~97% (pH = 7); ~78% (pH = 8).	$B_{AC}$ of VD3 in SIF: ~82% (4 h incubation) Stability of VD3 (Retention of VD3%): Room temperature: ~2% (after 5 days storage of free VD3) ~80% (after 5 days storage of VD3-composite gel) UV-light irradiation: ~2% (after 2 h irradiation) ~95% (after 2 h irradiation)	<i>In vivo</i> animal experiments: Eight-week-old male C57BL/6 mice were used. The concentration of 2,5-Dihydroxy vitamin D3 in the serum after 30 days feeding: Free VD3: ~15 ng/ml, WPI-LRA-VD3: ~35 ng/ml.	Liu et al. (2020)
Vitamin D <sub>3</sub>	VD3-loaded β-lactoglobuline (βlg)-based coagulum	βlg-VD3 complex + glucono-d-lactone → VD3-loaded βlg-based coagulum Encapsulation efficiency of VD3 in the βlg-based coagulum: 94.5%	Release of VD3 in SIF: ~82.6% (after 6 h incubation, with pancreatin) ~96.3% (after 6 h incubation without pancreatin).	<i>In vivo</i> animal experiments: Adult male Wistar rats were used. The serum level of 25(OH)D3 of the rats fed (3 weeks): VD3-entrapped coagulum : 58-10 <sup>3</sup> nM, βlg-VD3 complex: 20.9 · 10 <sup>3</sup> nM, free VD3: 15-1 · 10 <sup>3</sup> nM.	Djarrassouba et al. (2015)
Vitamin D <sub>3</sub>	Whey protein-stabilized nanoemulsions	Oil phase of VD3-loaded NEs: -digestible oil (DO); -indigestible oil (IO); -“oil mixture” (OM) in equal masses of DO and IO -emulsion mixture (EM) formed by mixing equal masses of an IO-NE with a DO-NE;	Free fatty acids released in SF: DO - NEs: 101% IO - NEs: 1% OM- and EM-NEs: ~56% $B_{AC}$ : DO - NEs: 75.2% IO - NEs: 20.7% OM- and EM - NEs: ~35.6%	Not been studied	Tan et al. (2019)

Vitamin D <sub>3</sub>	O/W Pickering emulsions	O/W Pickering emulsions stabilized by nanofibrillated cellulose (NFC) The mean particle diameter ( $d_{32}$ ): Initial: ~0.22 µm Mouth: ~0.24 µm Stomach: ~0.24 µm Small intestine: ~0.18 µm Z-potential: to -24.5 mV	Simulated GIT model: mouth, stomach, small intestine. B <sub>AC</sub> : VD3-loaded NEs stabilized by NFC (0.1%, 0.3%); ~85% VD3-loaded NEs stabilized by NFC (0.5%); ~84% VD3-loaded NEs stabilized by NFC (0.7%); ~76% VD3-loaded NEs stabilized by whey protein isolate	Not been studied	Winuprasith et al. (2018)
Vitamin D <sub>3</sub>	O/W nanoemulsions	Oil phase of VD3-loaded NEs: -medium chain triglycerides (MCT) -corn oil (CO) -fish oil (FO) -orange oil (OO) -mineral oil (MO) The mean particle diameter ( $d_{32}$ ): Initial: 0.14–0.19 µm (CO-, FO-, MO-NEs; 0.29 µm (OO-NEs), Mouth: 0.16–0.2 µm (CO-, FO-, MO-NEs; 0.5 µm (OO-NEs), Stomach: 0.16–0.2 µm (CO-, FO-, MO-NEs; 1.0 µm (OO-NEs), Small intestine: 1.25 µm (MCT-NEs); 3.0 µm (PO-NEs); 0.5 µm (OO-NEs), Z-potential: Initial: -65 to -70 mV Mouth: -18 to -35 mV Stomach: - 5 to -28 mV	Simulated GIT model: mouth, stomach, small intestine. (2 h incubation): MCT-NEs: ~110% FO-NEs: ~65% CO-NEs: ~58% MO-NEs: ~5% OO-NEs: ~0.0% Free fatty acids released in SIF A. In micelle phase: MCT-NEs: ~20% FO-NEs: ~88% CO-NEs: ~85% MO-NEs: ~38% OO-NEs: ~70% B. In filtered micelle MCT-NEs: ~22% FO-NEs: ~40% CO-NEs: ~30% MO-NEs: ~18% OO-NEs: ~40%	Not been studied	Ozturk et al. (2015)
Vitamin E	Whey protein isolate nanoparticles	Vitamin E microcapsules were prepared using three techniques: spraydrying (SD), freeze-drying (FD) and spray freeze-drying (SFD). The mean particle diameter ( $d_{43}$ ): SD: 195.8 µm FD: 279.0 µm SFD: 145.3 µm	<i>In vivo</i> animal experiments, Adult male Wistar rats were used, The pharmacokinetics parameters: -maximum plasma concentration (C <sub>max</sub> ): SD: 7.348 µg/mL (time max 4 h) FD: 7.693 µg/mL (time max 4 h) SFD: 9.449 µg/mL (time max	Parthasarathi and Anandharanakrishnan (2016)	(continued)

Table 4. Continued.

Vitamins/minerals	Nanocarriers/food matrix	Characteristics of nanocarriers	Bioaccessibility ( $B_{AC}$ )	Absorption/bioavailability	References
$\text{Fe}^{2+}$	Liposomes	The ferrous glycinate liposomes were prepared by reverse phase evaporation method Particles size: 70 – 500 nm	Not been studied	3 h) -area under the curve (AUC): SD: 109.84 $\mu\text{g}/\text{mL}\cdot\text{h}$ FD: 104.38 $\mu\text{g}/\text{mL}\cdot\text{h}$ SFD: 124.46 $\mu\text{g}/\text{mL}\cdot\text{h}$ <i>In vitro</i> Caco-2 cell model. The effects of liposomal carriers, phytic acid, zinc and particle size on iron transport through the Caco-2 cells were investigated. The iron transport from ferrous glycinate liposomes was higher than that from ferrous glycinate. Zinc ions and phytic acid inhibited the iron transport from ferrous glycinate liposomes and ferrous glycinate.	Baomiao et al. (2017)

VA, vitamin A; VD3, vitamin D<sub>3</sub>; NaCaS, sodium caseinate; RnaCaS, reassembled sodium caseinate;  $B_{AC}$ , bioaccessibility; SGF, simulated gastric fluid; SIF, simulated intestinal fluid; WPI, whey protein isolate; LRA, lotus root amylopectin; blg,  $\beta$ -lactoglobuline; DO, digestible oil; IO, indigestible oil; MCT, medium chain triglycerides; NE, nanoemulsion; NFC, nanofibrillated cellulose; CO, corn oil; FO, fish oil; MO, mineral oil; OO, orange oil; SD, spray drying; FD, freeze drying; SFD, spray freeze-drying.

(2015) who investigated the digestion kinetics and the  $B_{AV}$  of vit D<sub>3</sub> from nanoemulsions prepared with digestible oils (corn oil, fish oil and MCTs) and indigestible oils (mineral oil and orange oil).

In another study, Yang and McClements (2013) investigated the influence of carrier oil type on the digestion and  $B_{AC}$  of emulsified vit E. The authors prepared O/W nanoemulsions containing  $\alpha$ -tocopherol acetate, using the LCTs and MCTs as carrier oils and quillaja saponin as a natural surfactant. For the digestion study and the  $B_{AV}$  assessment of the vit E, the prepared emulsions were passed through a three-step simulated GIT model (mouth, stomach and small intestine). The results regarding the kinetics of lipid digestion showed that in the first minutes of digestion, the release rate of FFAs was similar for all the nanoemulsions because the lipase access to the surface of the oil droplets was the same. After about 10 min digestion, the release rate of FFAs was dependent on the composition of the emulsions. Thus, the content of FFAs released at the digestion of MCT-nanoemulsions was higher than LCT-nanoemulsions, and the presence of vit E in the nanoemulsion caused an increase in the level of FFAs released at digestion. The authors suggested that these results are due to the higher ability of MCT-FFAs to disperse into the aqueous phase, leaving the surface of the oil droplets and consequently, increasing lipase access to MCTs, as compared to LCT-FFAs whose affinity for water is low and so, the molecules of MCT-FFAs remain on the surface of the oil droplets inhibiting the lipase activity.

To determine the  $B_{AC}$  of vit E, the authors measured the concentration of  $\alpha$ -tocopherol and  $\alpha$ -tocopherol acetate, after filtering the micellar phase using a 450 nm pore size filter that selected NPs capable of passing through the pores of the mucin layer on the surface of the epithelial membrane (Yang and McClements 2013). The results showed that the  $B_{AC}$  of vit E from LCT-nanoemulsions was higher (~39%) than from MCT-nanoemulsions due to the higher volume of the micelles formed by LC-FFAs which allows solubilization of a higher amount of vit E. The authors also reported that during digestion,  $\alpha$ -tocopherol acetate is converted into  $\alpha$ -tocopherol. Other researchers studied the factors that influence the  $B_{AV}$  of vitamins, such as: molecular forms (e.g., vit D: vit D<sub>2</sub>, vit D<sub>3</sub> and 25 (OH) D, vit E:  $\alpha$ -,  $\gamma$ -tocopherols, vit A: retinol, retinyl ester, provitamin carotenoids), food matrix, carriers type, interactions with dietary lipids and fibers, interactions with micronutrients, host-related factors (age, GIT, genetic variations), etc. (Borel, Caillaud, and Cano 2015; Borel, Preveraud, and Desmarchelier 2013; Maurya and Aggarwal 2017).

Walia and Chen (2020) studied the variation of vit D  $B_{AV}$  depending on the composition and size of the droplets of nanoemulsion delivery systems. They prepared vit D-loaded nanoemulsions using canola oil as a carrier and pea protein and lecithin as surfactants. For the study of cellular uptake, a Caco-2 cells model was used. The results showed that cellular uptake of nanoemulsions were size, time, composition, and concentration dependent. The cellular uptake efficiency of pea-protein nanoemulsions with particle sizes

of 230 nm was 2.3 fold higher than nanoemulsions with particles sizes of 350 nm; but the cellular uptake efficiency of lecithin nanoemulsions with particle sizes of 150 nm was lower than pea-protein nanoemulsions with particle sizes of 230 nm.

An interesting study was published by Rana et al. (2019) who investigated the  $B_{AC}$  and  $B_{AV}$  of vit A (VA) encapsulated in sodium caseinate (SC) complexes in different forms: native SC-VA complexes (NaCas-VA), and modified SC-VA complexes (succinylated SC-VA complex (SNaCaS-VA), reassembled SC-VA complexes (RNaCaS-VA) and reassembled succinylated SC-VA complexes (RSNaCaS-VA)).  $B_{AC}$  of VA from protein complexes was determined using a simulated *in-vitro* digestion model, and for the cellular uptake study, they used a Caco-2 cell line. The authors also studied the  $B_{AC}$  and  $B_{AV}$  of VA from a milk fortified with SC-VA complexes and free VA (oily form) and the results were compared with control sample (unfortified milk). The results showed that during the gastric phase digestion (30 min), ~ 25% of free VA was degraded due to the pH drop from 5.0 to 1.8, while in the simulated intestinal fluid, the loss of VA was only 7%. The  $B_{AC}$  of VA in protein complexes was significantly higher (85%) than free VA. The  $B_{AC}$  of vit A in the protein complexes decreased in the order: RSNaCas-VA > SnaCas-VA > RnaCas-VA > NaCas-VA.

After gastric digestion (30 min), approximately 89% of the free VA remained undergraded, while in the simulated duodenal fluid (pH = 6.5, 90 min), approximately 75% of the free VA was found. For milk protein-complexes, the retention degree of VA after gastric digestion (30 min) was between 27.51% (RSNaCas-VA) and 54.98% (SNaCas-VA), and at the end of intestinal digestion (180 min), the retention degree of VA was over 85%. Total absorption of VA was calculated as the sum of vitamin transported through the Caco-2 cells layer and the amount of vitamin remaining in the enterocyte cell layer. For VA-protein complexes, both the transport of VA (20.11%) and retention (25%) were higher than free VA (transport 14.39% and retention 13.9%). The  $B_{AV}$  of VA in milk fortified with milk protein-vitamin complexes was higher than in fortified milk with free VA. The total uptake of VA from fortified milk was significantly higher (~ 38% for free VA and ~ 62% for RSNaCas-VA) than from free VA (30%) and protein complexes (55% for RSNaCas-VA).

The presence of minerals in GI fluids affects both the  $B_{AC}$  and  $B_{AV}$  of liposoluble food micronutrients such as: carotenoids, vitamins, phytosterols, and lipophilic polyphenols (Corte-Real and Bohn 2018; Schuchardt and Hahn 2017). The interaction between calcium and vit D is one of the most studied interactions of minerals with vitamins. Some studies have shown that divalent minerals affect the  $B_{AC}$  and  $B_{AV}$  of vit D due to their interaction with bile acids, which are removed from mixed micelles by precipitation; while other studies have shown that minerals alter the zeta potential of particles and micelles causing their aggregation (Corte-Real et al. 2017). To study the interaction of calcium with vit D<sub>3</sub> during digestion, Dima and Dima (2018) co-encapsulated calcium and vit D<sub>3</sub> in W/O/W double

emulsions, using different sources of calcium: calcium carbonate (CaC), tricalcium phosphate (CaP), and calcium gluconate (CaG). The prepared emulsions were immobilized in alginate- and chitosan-microparticles. The authors analyzed the variation of particle size, electrokinetic potential and fate modification of the double emulsions and the polymeric microparticles in the simulated GI fluids, using the single- and the multiple-stage static GIT models. Also, the release rate of calcium ions during digestion and the  $B_{AV}$  of vit D<sub>3</sub> encapsulated in free double emulsions, and polymeric microparticles loaded with double emulsions were measured. The results showed that the release rate of calcium ions from both the free double emulsions and those entrapped in the polymer microparticles was higher when calcium gluconate was used in the internal aqueous phase, due to the high solubility of CaG. For all emulsions, FFAs release rate and vit D<sub>3</sub> $B_{AC}$  were lower than the control sample containing NaCl in the aqueous phase, due to the precipitation of calcium salts of FFAs, and the influence of calcium on the micellization.

Iron is another mineral of major importance in the human body due to its involvement in the formation of erythrocyte. Therefore, to avoid iron deficiency it is recommended to use fortified foods or dietary supplements. The  $B_{AV}$  of iron, as well as other minerals, is very low. Lately, there has been an increased interest in fortifying foods using different types of iron-loaded nanocarriers that can contribute to improving iron  $B_{AV}$  (Abbasi and Azari 2011; Churio et al. 2018). Bryszewska (2019) evaluated the  $B_{AC}$  of iron from dietary supplements and thermo-resistant modified starch-microparticles prepared by spray drying and loaded with ferrous sulfate or ferrous lactate; it was confirmed that iron from food fortified with microparticles had a higher  $B_{AC}$  than from dietary supplements. Other authors reported an increased efficacy of dietary supplements containing different iron salts (ferric pyrophosphate, ferric ammonium citrate) encapsulated in liposomes (Hussain et al. 2019; Yu, Chang, and Yu 2015). Baomiao et al. (2017) investigated the iron transport from ferrous glycinate liposomes through the layer of enterocyte cells using Caco-2 cell model. They studied the effects of liposome size, phytic acid and zinc on the cellular uptake of iron and found that the amount of iron transported by Caco-2 cells from ferrous glycinate-loaded liposomes was significantly higher (146.1%; 120 min incubation) than free ferrous glycinate. Also the iron transport rate increased at higher iron concentrations and decreased with higher particle sizes and higher phytic acid levels.

An important aspect that some researchers have focused is the pro-oxidant activity of mineral ions. For instance, Cui et al. (2016) investigated the effects of sodium and potassium chloride on lipid oxidation in O/W emulsions stabilized with Tween-20. The results showed that sodium and potassium chloride did not influence the physical stability of the emulsions, but promoted lipid oxidation. The authors observed that the prooxidative effect of sodium and potassium ions increased at higher salt concentrations and diminished by the presence of chelators, such as deferoxamine and ethylenediaminetetraacetic acid. In another work,

Prichapan, McClements, and Klinkesorn (2018) examined the effects of ferrous sulfate and rice bran stearin on the physical and oxidative stability of W/O emulsions stabilized with polyglycerol polyricinoleate (PGPR). They reported that rice bran stearin crystals contributed to the increased physical stability of the emulsions and the encapsulation efficiency, and decreased the release rate of ferrous ions from the water droplets of the emulsion. Higher ferrous sulfate concentrations in water droplets led to a lower oxidative stability of W/O emulsions. Similar results were obtained by Dridi et al. (2016) who studied the effect of  $\text{Fe}^{2+}$  ions from different sources (ferrous chloride, ferrous sulfate, ferrous lactate and ferrous gluconate) on the oxidative stability of W/O emulsions prepared with different edible oils. It was revealed that the oxidation rate of the oils increased at higher encapsulated iron concentrations and decreased in the order of: ferrous chloride > ferrous sulfate > ferrous lactate > ferrous gluconate. This hierarchy was explained by the ability of lactate and gluconate anions to promote iron chelation. Other authors have encapsulated iron in W/O/W double emulsions and investigated the influence of biopolymers on the pro-oxidant activity of iron (Dima and Dima 2020; Duque-Estrada et al. 2019).

### **Future trends and conclusions**

In recent years, research in the field of food nanobiosystems has diversified greatly, highlighting the following main trends: the investigation of new materials that contribute to improving the quality of nutraceutical-loaded nanocarriers; development of strategies for the preparation of innovative nanobiosystems, able to ensure the increase of nutraceutical bioefficiency; expanding *in vitro*, *ex vivo* and *in vivo* studies of the mechanisms involved in the bioaccessibility, bioavailability and bioactivity of free and encapsulated nutraceuticals.

Encapsulating systems play a decisive role in modulating the physico-chemical characteristics of nutraceutical-loaded NPs. Thus, numerous food grade and biocompatible materials with, bioadhesive, bioactive properties and with a minimal impact on the environment were tested, such as: collagen, gelatin, silk fibroins, chitosan, cellulose and derivatives, alginates, carrageenans, pectin, polyvinyl alcohol, acid polylactic and its derivatives etc. Particular attention has been paid to polyelectrolytes (anionic and cationic) that allow the preparation of composite materials, such as proteins/polysaccharides conjugates and the modification of the surface charge that influences the absorption of NPs. Chitosan is one of the most studied materials lately due to its chemical structure and special biological properties (DuttaGupta, Jadhav, and Kadam 2015). The positive charge of chitosan facilitates the paracellular transport of NPs, but reduces the time of circulation through the blood and increases the rate of hepatic absorption. The functionalization of chitosan is a way of modulating the physico-chemical properties. Thus, by carboxylation, chitosan is transformed into a pH-sensitive polyanion, which can be complexed with polycations or coupled with other ligands, such as polyethylene glycol or folic acid, improving the cellular absorption of

NPs by binding to receptors on the cell surface (Wang et al. 2013).

In fact, researchers' interest in developing new methods for functionalizing the surface of NPs using a wide range of ligands, such as small molecules (amines, amino acids, peptides), biomolecules (oligonucleotides, nucleic acids), surfactants (sodium dodecyl sulfate, cetyl trimethylammonium bromide, lipid-derived compounds, alkane thiols), polymers (dextran, starch, polyethylene glycol [PEG]), dendrimers, etc. has recently increased (Heinz et al. 2017). Through functionalization, it modulates the surface electrical charge of NPs, improves cell absorption and targeted release of bioactive compounds, increases the blood circulation time of NPs and avoids the destruction of NPs by the immune system. Degradation of NPs under the action of enzymes in saliva, stomach or small intestine causes a sudden release of nutraceuticals in these GIT sectors and a possible degradation of them. To improve the bioavailability of pH-sensitive nutraceuticals in the upper GIT, colon-targeted nutraceutical delivery systems were prepared using synthetic polymers/ copolymers, such as: cellulose acetate phthalates, hydroxypropyl methyl-cellulose phthalate, copolymers of methacrylic acid and methyl methacrylate, called Eudragit®, and natural polymers, such as: pectin, guar gum, inulin, chitosan/alginate, pectin/chitosan etc (Lee et al. 2020; Sabra, Roberts, and Billa 2019). In this regard, it is required to intensify studies on the effect of the microbiota on the behavior of NPs in GIT segments and in particular in the colon.

According to literature from the last decade, an important goal of food scientists is to harness natural resources for the design and development of NPs with applications in the agri-food sector, such as: fertilization and plant protection, functional food preparation, biosensors used in food analysis and control, intelligent and eco-friendly packaging manufacturing, etc. Accordingly, the researchers' attention is focused on the development of new strategies for obtaining bio-NPs, which are based on the use of microorganisms or plant extracts. Thus, some researchers have encapsulated bioactive compounds in yeast cells (Dadkhodazade et al. 2018) and others have prepared metal/metal oxide NPs using biological materials such as: bacteria, fungi, algae, and plant extracts (Khalilzadeh and Borzoo 2016; Singh et al. 2018).

Assessment of the nutraceuticals bioefficiency in different food matrices or pharmaceutical formulas is an important step in food and drug design. Numerous studies published recently have revealed the interest of researchers for the unitary definition of concepts that express the bioefficiency of bioactive compounds, such as: bioaccessibility, bioavailability and bioactivity. Also, the increased concerns for the improvement of the *in vitro*, *ex vivo* and *in vivo* methods used in the study of the physico-chemical and metabolic processes of the orally administered nutraceuticals are highlighted.

To this end, many research networks have designed and developed various dynamic *in vitro* models that use computational intelligence methods to better simulate the *in vivo* conditions of GIT corresponding to specific human population: infants, children, the elderly (Shani-Levi et al. 2017). The development of functional foods in accordance with

consumer requirements requires intensified studies on factors influencing the bioavailability of nutraceuticals (food matrix, food processing and storage, food packaging) and on changes in food and bioactive components during digestion, absorption and metabolism. Various strategies to improve the bioavailability of nutraceuticals are currently being researched, such as the use of food excipients and the incorporation of nutraceuticals into various nanobiosystems. The physico-chemical processes that define bioaccessibility, such as: release, chemical interactions and solubilization of free or encapsulated nutraceuticals have been extensively studied while cell absorption and metabolism of nutraceuticals require in-depth studies to properly understand the biochemical mechanisms that influence their therapeutic effect. In this sense, scientists understood the need to improve the lines of human or animal cells to model as accurately as possible the mechanisms involved in cellular uptake (cell diversity from model, the presence of mucus layer, the presence and action of transporters, intracellular transformations, etc.).

There are also few studies investigating the behavior of free or encapsulated nutraceuticals in colon-specific conditions, although it has been shown to play an important role in the bioavailability of nutraceuticals, such as polyphenols and in the biological effects of dietary fiber. Although some cytotoxicity studies of NPs have been performed, the mechanisms by which NPs in food can cause various chronic diseases have not yet been fully elucidated. This review presents the essential aspects about the bioaccessibility and bioavailability of nutraceuticals incorporated in different delivery systems. The work gives also an overview of the mechanisms involved in the absorption and metabolism of free bioactive compounds because: in GIT the largest amount of biocomponent is released from the food matrix, respectively from NPs and participates freely in the absorption and metabolism processes; it was considered necessary to highlight the specificities of the absorption and metabolism mechanisms of the main classes of biocomponents studied: polyphenols, phytosterols, carotenoids, vitamins and minerals. Although in the last 50 years a very large number of studies have been carried out on the basis of which numerous types of bio-NPs have been designed, developed and characterized, however, currently, consumers cautiously accept the presence of NPs in food and European Food Safety Authority (EFSA) approved the use in the agri-food sector only 55 types of nanoparticles (<https://www.efsa.europa.eu/en/supporting/pub/en-621>, June 6, 2020).

More toxicity studies and accurate information are needed to increase the consumer confidence in the benefits of functional foods prepared with encapsulated nutraceuticals.

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