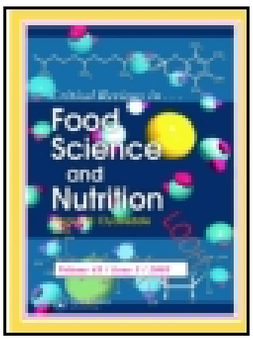

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REVIEW

Metabolic and functional interplay between gut microbiota and fat-soluble vitamins

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ABSTRACT

Gut microbiota is a complex ecosystem seen as an extension of human genome. It represents a major metabolic interface of interaction with food components and xenobiotics in the gastrointestinal (GI) environment. In this context, the advent of modern bacterial genome sequencing technology has enabled the identification of dietary nutrients as key determinants of gut microbial ecosystem able to modulate the host-microbiome symbiotic relationship and its effects on human health. This article provides a literature review on functional and molecular interactions between a specific group of lipids and essential nutrients, e.g., fat-soluble vitamins (FSVs), and the gut microbiota. A two-way relationship appears to emerge from the available literature with important effects on human metabolism, nutrition, GI physiology and immune function. First, FSV directly or indirectly modify the microbial composition involving for example immune system-mediated and/or metabolic mechanisms of bacterial growth or inhibition. Second, the gut microbiota influences at different levels the synthesis, metabolism and transport of FSV including their bioactive metabolites that are either introduced with the diet or released in the gut via entero-hepatic circulation. A better understanding of these interactions, and of their impact on intestinal and metabolic homeostasis, will be pivotal to design new and more efficient strategies of disease prevention and therapy, and personalized nutrition.

KEYWORDS

Fat-soluble vitamins; gut microbiota; gut-liver axis; omega-3 fatty acids; omega-6 fatty acids; vitamin A; vitamin D; vitamin E; vitamin K

Introduction

The symbiotic relationship of microbiota with the human intestine represents a master regulator of virtually all physiology processes of this organ including nutrients' metabolism, energy harvesting, detoxification, barrier function, immunity, and metabolic crosstalk with the liver tissue (reviewed in Eckburg et al. 2005; De Filippo et al. 2010).

The term "microbiome" was coined by the microbiologist Nobel laureate Joshua Lederberg to describe the microbial ecosystem (i.e., the "microbiota" that include bacteria, archaea, viruses, fungi) and its genome. At least 100 trillion bacteria compose the microbiome, with Firmicutes (gram-positive) and Bacteroidetes (gram-negative) that predominate bacterial phyla in healthy individuals (Eckburg et al. 2005). Minor populations include Actinobacteria, Proteobacteria and Verrucomicrobia. Microbiota is in intimate relationship with the host (thus identifying the holobiont or metaorganism[1]) as a complex symbiosis that is essential for human health (Inkpen 2019). Intestinal bacteria possess biosynthetic capabilities for multiple biologically relevant molecules such as vitamins (Das, Babaei, and Nielsen 2019), short chain fatty acids (Morrison and Preston 2016), amino acids (Ma et al. 2018; Ma and Ma 2019), and antimicrobial compounds (Heeney et al. 2019).

The gut contains the larger number of microorganisms in the human organism with a complex composition exhibiting important intra- and inter-individual variability (Liu, Shao, et al. 2017; Karl et al. 2018). Variability factors first include microbial exposure (Milani et al. 2017), diet (De Filippo et al. 2010), antibiotics (Buffie et al. 2012), and genetics (Goodrich et al. 2014). Although bacterial communities can show resistance and resilience to environmental changes (Sommer et al. 2017), several stress factors such as infection with particular pathogens or other pathological conditions, can lead to a disruption of the gut microbiota (GM) homeostasis named "dysbiosis."

The stability and microbial richness of the GM particularly vary during infancy, early childhood and elderly life stages (Spor, Koren, and Ley 2011). In these groups, environmental (modifiable) factors able to interfere with the gut ecosystem can add further microbial instability thus predisposing to conditions of dysbiosis. Identification and prevention of these factors are central to the therapeutic management of dysbiosis and prevention of its clinical correlates, including obesity and metabolic syndrome (Sonnenburg and Backhed 2016; Álvarez-Mercado et al. 2019; Duarte, Stefano, and Oliveira 2019), cardiovascular disease (Jin et al. 2019; Tang et al. 2019) and neurodegeneration (Giau et al. 2018; Kowalski and Mulak 2019).

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Table 1. Impact of western diet on intestinal microenvironment.

Effects of Western diet	References
Reduction of microbial diversity Increase Firmicutes (class of Clostridia) and Proteobacteria, and decrease Bacteroidetes Intestinal barrier dysfunction Decrease of mucus layer LPS translocation Inflammasome activation (e.g., metabolic endotoxemia) Alteration of intestinal immunity	Martinez-Medina et al. 2014; Agus et al. 2016; Zheng et al. 2017; Siracusa et al. 2018
Decrease butyrate production	Choi et al. 2019
Decrease the levels of intestinal epithelial cell-derived alkaline phosphatase (IAP)[a]	Ghosh et al. 2018
Promotion of chronic activation of NF-kB and other gut inflammatory pathways	Rocha et al. 2016

[a]Endogenous protein expressed by the intestinal epithelium which is involved in LPS detoxification

Dysbiosis was also associated to increase the risk of autoimmune diseases (Rizzetto et al. 2018) and depression (Luca et al. 2019).

Recently an increased number of studies have focused on mechanistic aspects linking dysbiosis with a broad-spectrum of pathogenic processes. It is becoming increasingly evident that GM and its dynamics throughout the lifecycle, significantly contribute to regulating the status, metabolism and function of essential micronutrients, such as the B-group vitamins (Yoshii et al. 2019). However, there is a knowledge gap about the relationship between GM and fat-soluble vitamins (FSVs), a group of natural lipids with important roles as antioxidants, cofactors and in gene regulation, which are at the core of important physiological regulatory processes. This review article summarizes the state of the art and discusses interactions between FSV and GM including physiological aspects, interfering factors and consequences on human health. This narrative review also addresses for the first time the role of FSV in potentially shaping the composition and function of GM with the aim to stimulate further mechanistic research on this important topic.

General concepts on GM modulators and their impact on FSV

The possibility that gut dysbiosis may interfere with the metabolism of fat-soluble micronutrients gathers evidence in literature. Environmental and constitutive factors with potential harmful effects on the GM and its symbiotic relationship with the host are many; for example, these include food-derived xenobiotics, such as pesticides, or synthetic fertilizers and food additives, as well as genetics, age and sex (all these and others have comprehensively been reviewed elsewhere; Liu, Shao, et al. 2017; Velmurugan et al. 2017; Karl et al. 2018). In this review article we will focus on environmental variables that have gained solid evidence to link by a causal relationship GM dysbiosis with changes in the metabolism and function of FSV, e.g., diet and drug therapy, with a particular regard to antibiotic therapy.

Dietary factors

Diet is reported to rapidly and reproducibly influence the gut microbial composition (David et al. 2014; Sonnenburg and Backhed 2016). In general, it is assumed that chronic exposure to a "western diet," which is relatively low in fibers and rich in saturated fats, sugar, animal proteins, additives and salt (Myles 2014), has negative effects on intestinal microenvironment and health status (summarized in Table 1). In this respect, dietary fats appear to play a main role in dysbiosis also linking this condition with changes in lipid metabolism. Recent evidence confirms that an excess of dietary fats may cause alterations of GM by increasing lipid absorption (Chang and Martinez-Guryn 2019), which may be the consequence of increased expression of cholecystokinin (Cckar) and Dgat2 receptors in the pancreas and the small intestine, respectively (Martinez-Guryn et al. 2018; Chang and Martinez-Guryn 2019).

The western diet is identified as one of the main causes of the today's obesity pandemic as well as of cardiometabolic complications observed in the general population; the latter include metabolic syndrome (MetS), nonalcoholic fatty liver disease (NAFDL), diabetes and cardio-cerebro-vascular disease (CVD) (Ghosh et al. 2018). Obesity and MetS are associated with lipid disorders and low serum levels of FSV (A, D, E, K) (Goncalves and Amiot 2017; Thomas-Valdes et al. 2017; Migliaccio et al. 2019), fostering the hypothesis that a suboptimal FSV status may play a role in increasing the prevalence and severity of metabolic and inflammatory complications of these diseases. A major mechanism for this alteration could be the increased sequestration of FSV in the adipose organ (Kardinaal et al. 1995; Migliaccio et al. 2019), and/or even in the fatty liver (Bartolini et al. 2017; Torquato et al. 2019), of subjects exposed to a Western diet and developing obesity and MetS phenotype. This could limit the bioavailability and function, also introducing potential toxicities, of these vitamins (Figure 1). Key aspects in these alterations may include: (1) a modified intestinal absorption and delivery of FSV to the liver through intestinal lipoproteins, (2) FSV accumulation in the liver and adipose organ, (3) altered hepatic metabolism of FSV for the delivery to peripheral tissues via VLDL lipoproteins as well as for biotransformation to active metabolites or excretion of the vitamin excess throughout detoxification and drug metabolism pathways (Galli 2007) (Figure 1). For example, NAFLD is reported to alter the intestinal metabolism of retinyl esters, retinol and retinoic acid (RA) formation in the liver that may lead to a modified retinoid X receptor (RXR) activity in

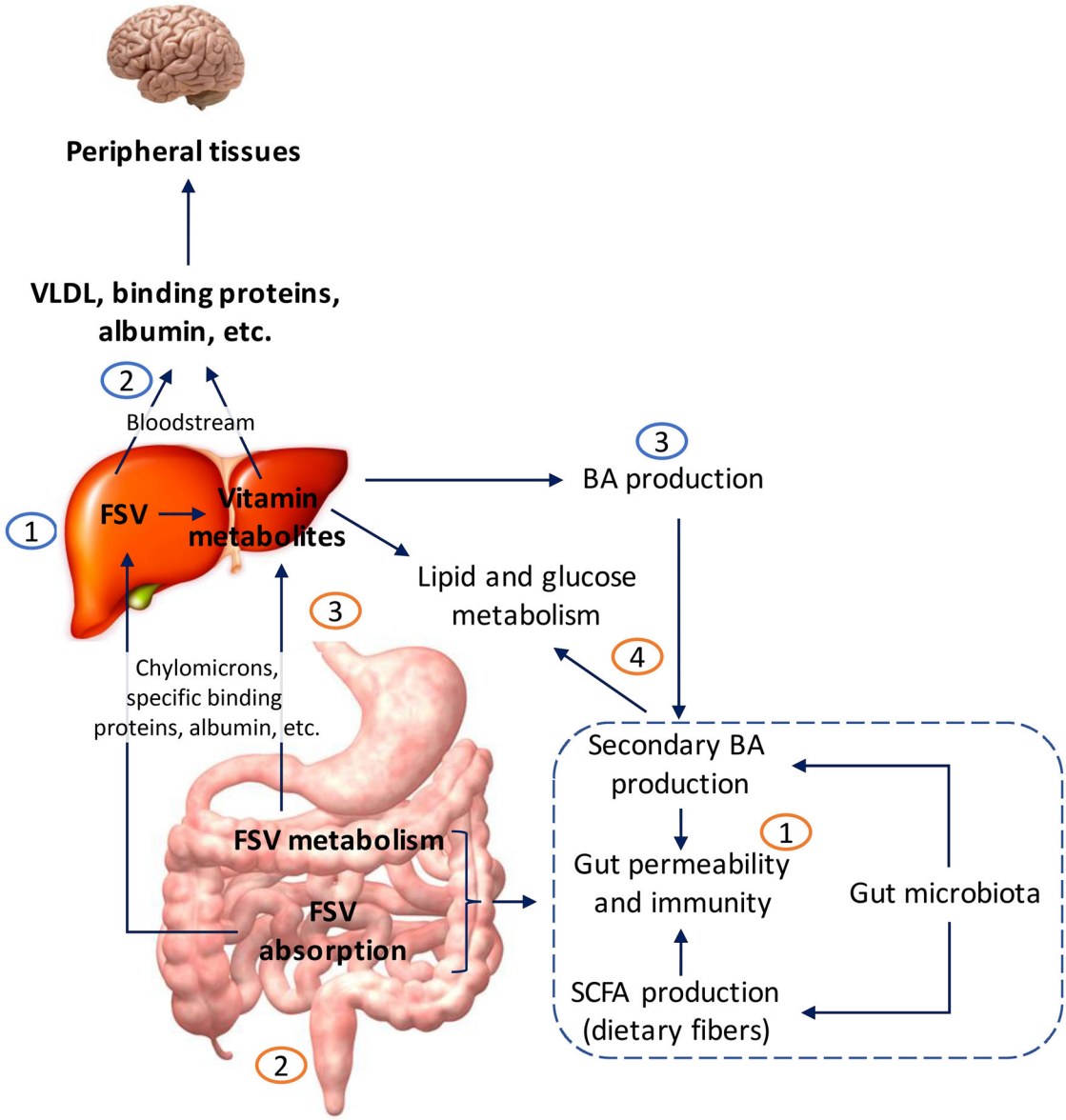

Figure 1. Hepatic and intestinal nodes of the interplay between gut microbiota and the metabolism of FSV. The proper functioning of the gut-liver axis ensures protection to physiological functions of intestine and liver. In detail, at intestinal level (orange), the gut microbiota can have effects on: (1) permeability of the intestinal membrane; (2) secretion of pancreatic cholecystokinin and consequent release of bile and pancreatic lipase into the duodenum; expression of genes involved in fatty acid oxidation and chylomicron synthesis; production of proteins involved in FSV transport in the enterocyte (as in the case of vitamin A); (3) vitamin metabolites production (as in vitamin A, E and K); vitamin bioactivation (as in vitamin D and E); (4) energy metabolism. At hepatic level (blue), relevant processes are: (1) the formation of the active metabolites of FSV, whose activity will also affect the energy metabolism; (2) production of proteins and lipoproteins involved in the transport of FSV and microbial metabolites to peripheral tissues; (3) production of primary bile acids (BA), which will be subsequently released into the intestine to become bacterial substrates.

the gastrointestinal (GI) tract and other tissues (Saeed et al. 2017). Fatty liver disease, that is associated with an altered gut-liver axis, inflammasome activation and hepatic lipotoxicity (Svegliati-Baroni et al. 2019), also promotes the sequestration of vitamin E into the lipid droplets of the liver cell (Bartolini et al. 2017). This altered cellular distribution curtails the formation of CYP450-derived long-chain metabolites of the vitamin, some of which function as pregnane X receptor (PXR) agonists (Podszun et al. 2017; Bartolini et al. 2020) and 5-lipoxygenase (Pein et al. 2018) and cyclooxygenase (COX) (Jiang et al. 2008) inhibitors. Furthermore, an increased auto-oxidation of this vitamin has recently been observed in fatty liver patients (Torquato et al. 2019), which may represent a major sign of lipid peroxidation and hepatic lipotoxicity, and a causal event of the inflammatory complications observed in this liver disease (Svegliati-Baroni et al. 2019).

Unlike Western diet, Mediterranean diet[2] associates with increased gut bacterial diversity as well as with a sustained intake of FSV (Table 2, the chart also includes average requirement and/or adequate intake for these vitamins). Dietary factors such as dietary fibers, the main prebiotics[3] of human nutrition, affect the gut-liver axis and have key regulatory roles on both the intestinal absorption and metabolism of FSV (Figure 1). The intake of dietary fibers in typical Mediterranean diet meets nutritional recommendations (25–30 g/day) and it is roughly twice relatively to US and UK diets (Tuohy et al. 2009). It can be increased up to 60 g/

Table 2. Examples of food items that are included in the Mediterranean diet and their average content of fat-soluble vitamins.[a]

Food item/ group (100 g)	Biological effect/nutritional characteristic	References	Vitamin A (RE)	Vitamin D (cholecalciferol)	Vitamin E (ATE)	Vitamin K (phylloquinone)	LA and ALA
Whole grain	Sources of: resistant starch, nonstarch polysaccharides (β-glucan and arabinoxylans), cellulose, lignin, hemicellulose, pectins and inulin that act as prebiotics, Polyphenols, fat soluble vitamins (vitamin A, E and K)	Simpson and Campbell 2015; Laitinen and Mokkala 2019; Choi et al. 2018; Ozdal et al. 2016	—	—	1.21 mg		LA: 1.10 g; ALA: 0.06 g
Tomatoes			42 μg	—	—	—	—
Leafy vegetables			241 μg	—	—	—	—
Pomegranate			15 μg	—	0.6 mg	16.40 μg	—
Pistachios			87 μg	—	4.57 mg	60 μg	LA: 6.20 g
Potatoes			3 μg	—	—	—	LA: 0.45 g; ALA: 0.15 g
Pumpkin			600 μg	—	—	—	
Beans			18 μg	—	—	—	LA: 0.15 g; ALA: 0.15 g
Chickpeas			30 μg	—	2.6 mg	—	LA: 2.59 g; ALA: 0.10 g
Lentils			10 μg	—	0.52 mg	—	LA: 0.91 g; ALA: 0.26 g
Walnuts	Rich in omega-3 fatty acids, polyphenols and fibers, influence the microbial composition, increasing Firmicutes, Bacilli taxa (lactobacilli), Clostridia (butyrate producing members) and reducing Bacteroidetes, reduce the secondary bile acids concentrations	Byerley et al. 2017; Holscher et al. 2018	6 μg	—	4 mg	2.70 μg	LA: 34 g; ALA: 6.64 g
Olive oil	Rich in oleic and linoleic acids and bioactive compounds such as polyphenols, phytosterols, vitamin E, β-carotene and others, olive oil polyphenols properties include: anti-inflammatory, antioxidant and chemo-preventive activity; Modulation of microbial composition, increasing bifidobacterial and IgA-coated bacteria; Inhibits the proliferation of bacterial groups (mainly Proteobacteria) associated with leptin resistance, increased levels of ghrelin, obesity and hippocampal behavioral deficits	Marcelino et al. 2019; Borzi et al. 2018; Prieto et al. 2018; Van Doorn et al. 2017	36 μg	—	21.42 mg	—	LA: 6.8 g; ALA: 0.73 g
Grape (*Vitis vinifera*)	Rich in polyphenols (e.g., proanthocyanidin, anthocyanins, stilbenes and gallic acid); modulates microbial population with increase numbers of beneficial bacteria (e.g., *Prevotella, Bifobacterium*); increases SCFAs; Improves lipid metabolism	Nash et al. 2018; Wu et al. 2019	4 μg	—	—	8.60 μg	LA: 0.02 g; ALA: 0.01 g
Milk and dairy products:							
Yoghurt	Source of probiotics and oligosaccharides with prebiotic function, cheese contains tryptophan, which is metabolized by the gut microbiota producing different aryl-hydrocarbon receptor agonists, including indole which modulates the immune response preserving the integrity of the intestinal barrier, caseins and serum proteins that can undergo lactic bacteria metabolism with sequent production of bioactive molecules with immunomodulatory, antihypertensive, antithrombotic and hypocholesterolemic activity, yoghurt stimulates the proliferation of bifidobacteria and lactobacilli, fermented dairy products may	Robinson 2019; Shimada et al. 2013; Pessione and Cirrincione 2016; Burton et al. 2017; Fernandez and Marette 2017; Astrup, Geiker, and Magkos 2019; Mozaffarian 2019	34 μg	0.04 μg	0.08 mg	—	LA: 0.08 g; ALA: 0.05 g
Soft cheese			248 μg	0.26 μg	0.46 mg	—	LA: 0.26 g; ALA: 0.31 g

(*continued*)

Table 2. Continued.

Food item/ group (100 g)	Biological effect/nutritional characteristic	References	Vitamin A (RE)	Vitamin D (cholecalciferol)	Vitamin E (ATE)	Vitamin K (phylloquinone)	LA and ALA
	protect from the risk of CVD and type 2 diabetes, sources of FSV, mainly vitamin A						
Tuna (*Thunnus thynnus*)	Source of long chain polyunsaturated fatty acids	—	450 μg	16.30 μg	0.55 mg	—	LA: 0.15 g; ALA: 0.09 g; EPA: 0.80 g; DHA: 2.15 g

Data from: bda-ieo.it (BDA project) and crea.gov.it.

RE, retinoic acid; ATE, alpha-tocopherol equivalents; LA, linoleic acid; ALA, alfa-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

[a]Examples of typical food items of Mediterranean diet and their health-promoting characteristics are reported in Willett et al. (1995); Medjakovic and Jungbauer (2013); Assaf-Balut et al. (2017); Becerra-Tomas et al. (2018); Cappello et al. (2018); Martini et al. (2020); Ramírez-Anaya et al. (2019).

AR[1] or AI[2] of fat-soluble vitamins (FSV): Vitamin A (AR) 490 μg RE/day for woman; 570 μg for men (EFSA Panel on Dietetic Products, Nutrition, and and Allergies 2015a); Vitamin D (AI) 15 μg/day (EFSA Panel on Dietetic Products, Nutrition, and and Allergies 2016); Vitamin E (AI) 11 mg/day for woman; 13 mg for man (EFSA Panel on Dietetic Products, Nutrition, and and Allergies 2015b); Vitamin K (AI) 70 μg/day (EFSA Panel on Dietetic Products, Nutrition, and and Allergies 2017); Omega 3 and Omega 6 (AI) Acid α-linolenic 0.5% (percentage of energy), linoleic acid 4%, DHA + EPA 250 mg/day (EFSA Panel on Dietetic Products, Nutrition, and and Allergies 2010).

[1]AR = daily intake level of a nutrient that meets the requirement of half of the subjects of a healthy population.

[2]AI = intake value that is established when there are not enough data to calculate the average need for a nutrient. It is calculated as the average intake level of a nutrient which is assumed to be adequate, based on specific observations or experiments.

day in specific vegetarian diets (den Besten et al. 2013). Dietary fibers such as cellulose, pectin, inulin, oligofructose and resistant starch stimulate bacterial production of short chain fatty acids (SCFAs, i.e., acetate, propionate and butyrate) (De Filippis et al. 2016) via saccharolytic fermentation (Morrison and Preston 2016). The average human diet is estimated to generate from 400 to 600 mmol SCFA per day by the fermentation of the fibers that reach the cecum, i.e., ≈10% of caloric requirements (den Besten et al. 2013). Besides their role as energy source for colonocytes and hepatocytes, SCFA modulate energy metabolism increasing fatty acid oxidation through signaling activation of AMP-activated kinase in the liver and adipose tissue (den Besten et al. 2015). SCFA also activate brown adipose tissue increasing of mitochondrial function and energy expenditure (Li et al. 2018), and improve insulin sensitivity (McNabney and Henagan 2017). They are also reported to regulate hunger, satiety (Tolhurst et al. 2012; Chambers et al. 2015) and intestinal pH (den Besten et al. 2013). Moreover, dietary fibers may have a role on intestinal immunity and barrier function. Acetic acid, the main SCFA produced by the colonic fermentation of dietary fibers in humans and other organisms (den Besten et al. 2013), regulates the intestinal immune response inducing the proliferation of regulatory T lymphocytes (Treg) (Engevik and Versalovic 2017) and the production of immunoglobulin A (IgA) through G-protein coupled receptor 43 (GPR43) activation. Those are important aspects of the host-microbiome interaction and gut homeostasis (Wu et al. 2017). In this regard, RA and its RXR-dependent activity play important roles in switching B-cells to IgA-producing cells. Propionic and butyric acids have also been reported to promote the intestinal barrier function improving expression of tight-junction proteins (Xia et al. 2017; Fang et al. 2019). However, recent studies postulate that large amounts of butyrate in a context of dysbiosis and inflammation, may aggravate inflammatory cues and promote liver tumorigenesis (Singh et al. 2018) suggesting the need for a more comprehensive understanding on risks and benefits that a sustained SCFA production may have on the gut-liver axis under specific conditions.

Another important point in which dietary factors influence the GM and consequently the gut-liver axis is the metabolism of bile acids (BAs). BA are ligands of farnesoid-X-receptor α (FXRα) as well as of other receptors including PXR, G protein-coupled and vitamin D receptors (VDR) (Zhou and Hylemon 2014). An increased production of BA, especially the secondary BA deoxycholic acid (DCA) and lithocholic (LCA) acid, is observed in the western diet and appears to influence the selection of specific bacterial strains (Table 1) at the expenses of others that are characteristic of vegetarian regimens (Riccio and Rossano 2018; Zeng et al. 2019). Intestinal bacteria have enzymes for the deconjugation, dehydrogenation, dihydroxylation and sulfation of primary BA, producing different secondary BAs. Dehydroxylation of chenodesoxycholic acid (CDCA) forms LCA, while epimerization of the same primary BA forms ursodeoxycholic acid (UDCA). Although from the same molecular origin, these two secondary BA have different hydrophobicity and consequently different degree of toxicity and activation of PXR and VDR that control their detoxification (Zhou and Hylemon 2014). LCA is toxic to mammalian cells and it has been related to colon carcinogenesis, while UDCA is reported to be chemoprotective (Liu, Hu, and Wan 2016) and hepatoprotective (Kim et al. 2018). Increased production of DCA is also associated with colorectal (David et al. 2014) and liver (Yoshimoto et al. 2013) cancers. Likewise, an increase of LCA is associated with vitamin D deficiency that is later discussed in more detail. Furthermore, probiotics introduced through fermented foods (Marco et al. 2017) may also contribute to a better intestinal health increasing microbial diversity, ultimately influencing FSV metabolism (Figure 1). If administered in adequate amounts, these live microorganisms can confer health benefits to the host, essentially interfering with potential pathogens and improving barrier function and immune system (Sánchez et al. 2017; Mohajeri et al. 2018). Several clinical trials, some of which are presented later in this review article, now report on a synergistic role that probiotics and dietary supplements, including FSV, may have in restoring

eubiosis thus preventing risk factors of disease associated with changes in the gut microbial ecosystem.

Antibiotics and other drug therapies

In the 1950s, it was found that introduction of antibiotics at low doses in food and water favored livestock growth in terms of body weight (Stokstad 1954; Zimmerman 1986). Therefore, it became obvious that antibiotics (such as macrolides) have important metabolic repercussions, which have also been observed in humans especially when administered in early age (Saari et al. 2015; Turta and Rautava 2016). These effects have raised concerns about the possibility that a chronic exposure to this type of drugs and possibly to other compounds with similar activity present in food, may lead to develop antibiotic-induced obesity, as well as ectopic fat deposition for instance in the liver tissue, increasing the risk of NAFLD and nonalcoholic steatohepatitis (NASH) (Aragones et al. 2019).

Mechanistically, antibiotic-induced dysbiosis can promote the proliferation of microorganisms that have greater ability in energy harvesting from the diet thus promoting its storage in the adipose tissue (Del Fiol et al. 2018). Other mechanisms proposed to explain the antibiotic-induced obesity include the alteration of mitochondrial matrix metalloproteinases in the adipocytes, leading to mitochondrial dysfunction and secondarily to obesity (Andrade et al. 2017).

Furthermore, antibiotic treatment has been shown to reduce lipid absorption and chylomicron synthesis (Sato et al. 2016) that in turn contributes to decreasing liver uptake and bioavailability of FSV. These antibiotic-induced changes of lipid metabolism are also associated with modified activity of mucosal mast cells and intestinal permeability (Sato et al. 2016).

In a recent study, antibiotic treatment (ampicillin, sulfamethoxazole and trimethoprim) and the consequent depletion of GM in rats, was demonstrated to interfere with the response to vitamin E supplementation modifying the vitamin status and the levels of CYP450-derived metabolites in the liver, feces and blood (Ran et al. 2019). Along with the demonstration of an active role of the GM on the catabolism and excretion of vitamin E, these findings highlight the interfering effect that antibiotics may have on another and emerging aspect of the biotransformation of this vitamin common to other FSV, that is its bioactivation to produce metabolites with biological activity different from the vitamin precursor (Galli et al. 2007; Schubert et al. 2018). In this respect, long-chain metabolites are the most potent bioactives formed by the activity of tocopherol ω-hydroxylases of human tissues (Schubert et al. 2018) and possibly of the GM (Ran et al. 2019). These have been demonstrated to act as anti-inflammatory (Pein et al. 2018) and detoxification agents (Podszun et al. 2017; Bartolini et al. 2020), and to prevent a key pathogenic process of Alzheimer disease (Marinelli et al. 2020).

The use of antibiotic therapy also contributed to reveal the role of the gut microbiome in the bioactivation or even in the *de novo* production of other vitamins. In 1967, Frick et al. reported that subjects treated with a broad-spectrum antibiotic and fed low vitamin K diets, showed significant reductions in plasma prothrombin levels (indicating vitamin K deficiency), when compared with nonantibiotic treated controls (Frick, Riedler, and Brogli 1967). It is now well documented that bacterial species resident in the gut lumen can produce menaquinones (MKs) with 7 or even higher number of isoprenyl units (Fusaro, Gallieni, et al. 2017), but despite such observations, there is still a knowledge gap about the actual quantitative contribution of gut microbiome to the vitamin K status and its multiple biological roles in the host. Conversely, it has been shown that for specific diseases marked by reduced absorption of vitamin D (e.g., inflammatory bowel disease) the intake of certain antibiotics (metronidazole and vancomycin) increased serum levels of vitamin 25(OH)D (Bora et al. 2018).

In addition to antibiotics also phosphate binders, commonly used in patients with chronic nephropathy, alter the vitamin status and induce changes in microbial populations possibly due to cross binding with FSV (vitamin K and D) and SCFA (Biruete et al. 2020). Other drug types such as proton pomp inhibitors and nonsteroidal anti-inflammatory compounds among others, have also been associated with alterations of the GM (Imhann et al. 2016, Vich Vila et al., 2020), which are worth investigating for possible interactions with metabolism, status and function of FSV.

Metabolic and molecular interaction between GM and FSV

Accumulating data in literature support the notion that GM influences intestinal absorption and post-adsorption metabolism of FSV (Figure 2, left chart). Moreover, FSV can modulate the gut microbial composition (Figure 2, right chart) either stimulating or inhibiting the proliferation of bacterial species. Supplementation studies with FSV in animal models and human studies carried out in different type of diseases have been a major source of information in this respect (Table 3). This type of interaction includes for instance the control gut microbial populations through the stimulation of bacterial production of antimicrobial molecules or immuno-mediated mechanisms (Cantorna, Snyder, and Arora 2019).

The following sections report a systematic analysis of known interactions between GM and FSV that are presented considering both the two directions of interaction (indicated in the subsections below as to GM $\Rightarrow$ FSV and FSV $\Rightarrow$ GM, and summarized in Figure 2).

Vitamin A

Vitamin A (retinol) naturally occurs as retinyl esters in animal products (offal, milk and derivatives) and carotenoids (mainly β-carotene) in fruits and vegetables. Digestion and absorption processes for vitamin A operate similarly than for food lipids (Reboul 2013; Jijon et al. 2018). Emulsion of vitamin A in lipid droplets with bile salt in the duodenum and subsequent enzymatic hydrolysis precedes retinyl ester

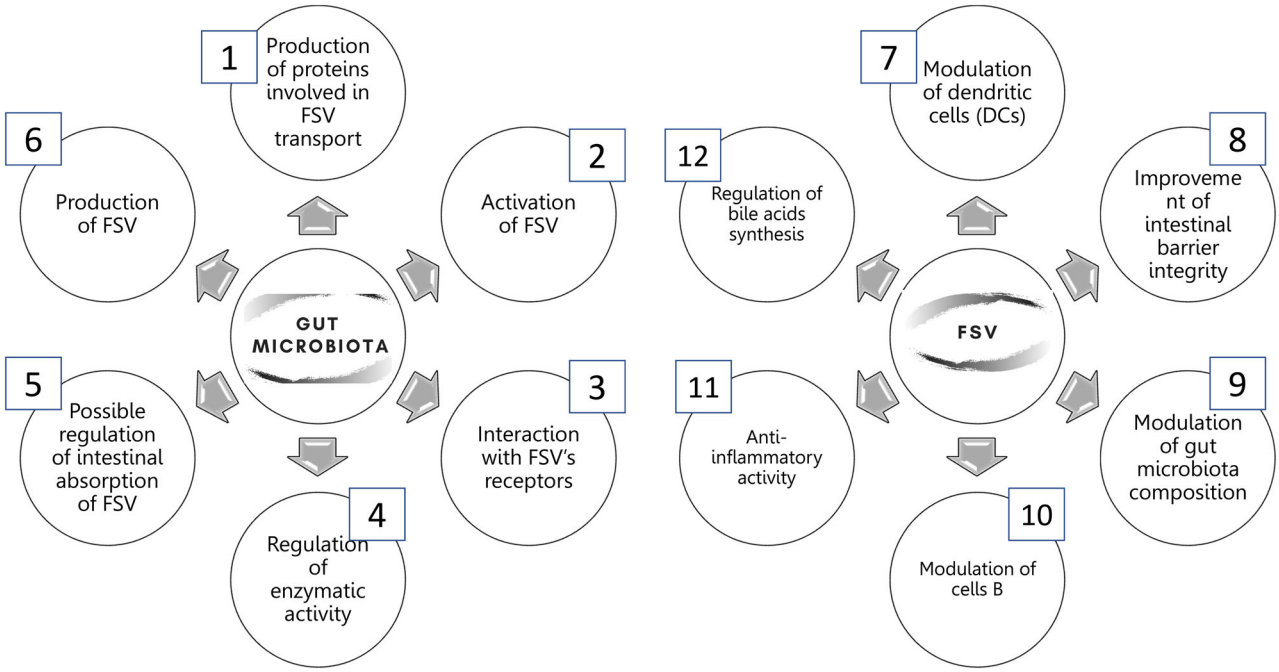

Figure 2. Components of the bidirectional interactions between the gut microbiota and FSV. This chart summarizes the main components of the interactions that link metabolic and functional aspects of gut microbiota and FSV. (Left panel) (1) The lipocalins produced by *E. coli* are involved in retinoid transport; (2) The enzyme retinaldehyde dehydrogenase (RALDH) of *E.coli* converts retinal to retinoic acid (RA); (3) the secondary bile acid lithocholic acid and MK-7, produced by the gut microbiota, interact with the vitamin D receptor (VDR); (4) gut microbiota inhibits CYP27B1 throughout the activity of FGF23; (5) microbial metabolites and components, such as SCFA and LPS, positively and negatively, influence the intestinal permeability to dietary lipids, respectively. Furthermore, an indirect role of the gut microbiota in the regulation of intestinal absorption of dietary lipids has been hypothesized to occur through mast cell activity and modulation of expression of the cholecystokinin receptor; (6) Gut microbiota is able to produce active metabolites of vitamin A, E and K. (Right panel) (7) Vitamin A and D modulate the activity of dendritic cells (DCs), stimulating tolerogenic DCs that reduce reactivity to the gut microbiota; (8) Vitamin A, D and omega-3/6 regulate the expression of genes encoding intestinal barrier proteins; (9) Vitamin A and D stimulate the growth of *Lactobacillus*, *Feacalibacterium* and omega-3/6 stimulate *Coprococcus* and Bifidobacteria; (10) RA stimulates the conversion of B-cells to IgA-producing cells; (11) Vitamin A and D induce the proliferation of Treg. Vitamin E with its metabolites, inhibits COX isoenzymes and 5-LOX; (12) Vitamin E induces Klotho which promotes FGF19-mediated inhibition of CYP7A1.

absorption in the intestinal epithelial cells (IECs) (Reboul 2013). The absorption of carotenoids in the intestine is partially controlled by the scavenger receptor class B type 1, which is regulated by the activity of beta-carotene oxygenase 1 (BCO1) via homeobox transcription factor intestine-specific homeobox (ISX) (Lyu et al. 2018). This transcription factor regulates the expression of the gene encoding for BCO1, which catalyzes the oxidative cleavage of β-carotene into two retinal molecules. ISX-deficient mice show increased intestinal expression of BCO1 and vitamin A levels in blood and tissues (Lobo et al. 2013).Vitamin A is mainly stored in liver stellate cells, but it is also present in adipocytes and other tissues under the inactive form of retinyl esters (Saeed et al. 2017). After hydrolysis to retinol and binding to the retinol binding protein, the vitamin is transported to target cells for uptake by means of RA 6 receptor (Oliveira, Teixeira, and Sato 2018). The enzymatic oxidation of retinol occurring at the cellular levels (including intestinal epithelial and immune cells, discussed later) forms the active metabolite RA, which interacts with the nuclear receptors RXRs (-α, -β and -γ) and retinoic acid receptor (RAR-α, -β and -γ). These bind specific DNA sequences, e.g., the RA response elements, thereby activating transcription of target genes (i.e., genes of immune response and reproduction) (Clagett-Dame and Knutson 2011; Erkelens and Mebius 2017).

Vitamin A has been described to exert multiple functions including anemia prevention (Michelazzo et al. 2013), regulation of spermatogenesis (Busada and Geyer 2016), promotion of conception and gestation in women (Clagett-Dame and Knutson 2011), and prevention of fetal malformations (Petrelli et al. 2019). It is also involved in the induction of thermogenesis (Guo et al. 2016), skin protection from bacterial infections (Harris et al. 2019), anti-inflammatory activity and immunomodulation (Bakdash et al. 2015; Abdelhamid and Luo 2018; Erkelens et al. 2020).

VA ⇒ GM interaction

RA is essential for the conversion of B cells to IgA-secreting cells (Abdelhamid and Luo 2018), which play important roles on intestinal immunity via interactions with the GM in different regions of the human gut (Tlaskalová-Hogenová et al. 2011; Tauschmann et al. 2013) (Figure 2, right panel). Studies in germ-free mice demonstrated that GM is essential for induction of B cell clone expansion and intestinal IgA production (Gommerman, Rojas, and Fritz 2014). Intestinal IgA are a heterogeneous population of immunoglobulins that bind to bacteria thus preventing their growth and paracellular passage through the intestinal barrier (Okai et al. 2017). For example, the mouse monoclonal IgA, clone W27, shows high affinity and inhibitory activity on bacterial growth for multiple commensal bacteria including *Escherichia coli*, but not for beneficial bacteria, such as *Lactobacillus casei*. Noteworthy, *in vivo* data also demonstrated that a reduced IgA production by a lower RA

Table 3. Effects of FSV supplements on gut microbiota composition in disease conditions.

Vitamin	Disease	Molecular process after vitamin's integration	References
A	Autism spectrum disorder (ASD) (study in humans)	↑ Bacteroidetes/Bacteroidales ↓ Bifidobacterium ↑ levels of CD38 and retinoic acid receptor-related orphan receptor alpha (RORA) mRNA (genes critical for society behavior in autism)	Liu, Liu, et al. 2017
	Norovirus infection (study *in vitro* and *in vivo* models)	RXRα critical in innate immunity Inhibition of viral replication ↑ *Lactobacillus* (with antiviral activity) ↑ expression level of IFN-β (key role in the antiviral response) through induction of retinoic acid-inducible gene 1 (RIG-1)	Lee and Ko 2016
	Persistent diarrhea (study in humans)	↑ microbiota diversity ↑ butyrate-producing bacteria (i.e., *Clostridium butyricum*) ↑ classes of *Bacilli, Gammaproteobacteria* and *Clostridia*	Lv et al. 2016
D	Cystic fibrosis (CF) (study in humans)	↑ genus *Lactococcus* ↓ taxa *Gammaproteobacteria* ↓ intestinal inflammation (inhibition of inflammation-induced epithelial cell apoptosis and reduction NF-κB nuclear translocation)	Kanhere et al. 2018
	Ulcerative colitis (UC) (study in humans)	↓ fecal calprotectin, albumin, platelet count ↑ Enterobacteriacae (in the fecal microbiota)	Garg et al. 2018
E	Liver dysfunction (study in humans)	↓ ALT, ASL, GGT Regulation of levels of tryptophan-derived metabolites, indoxyl sulfuric acid and 3-(3-indolyl)-2-oxopropanoic acid (with hepatoprotective effects) ↑ ascorbate sulfate content (antioxidant) ↓ tryptophan-originated uremic toxins ↓ inflammatory lipids such as 3-ketosphingosine and sphingosine ↓ *Bacteroides* abundance ↓ *Lactobacillaceae* abundance ↓ ratio of *Bacteriodetes/Firmicutes*	Kim et al. 2018
K	Colon cancer (study in mice)	↑ serum adiponectin levels ↓ inflammation and hyperplasia Regulation of expression of NF-κB, Caspase3 and GSK-3β[a] ↑ expression of VDR and p-AMP-activated kinase ↑ phyla of Proteobacteria and Deferribacteres ↓ phylum of Verrucomicrobia ↑ genus of *Lactobacillus* ↑ species *Clostridium leptum*, *Curvibacter lanceolatus*, *Odoribacter splanchnicus*, *Parasutterella excrementihominis*, *Psychrobacter phenylpyruvicus*, *Ruminococcus lactaris* ↑ production of SCFA	Zhang et al. 2017
Omega-3	Alzheimer (study in humans)	↑ abundance of butyrate-producing bacterial genera ↑ SCFA ↓ neuroinflammation	La Rosa et al. 2018
	Opioid-Seeking Behaviors (study in mice)	↑ *Bifidobacterium* and *Lactobacillus* (both possess anxiolytic properties) ↓ *Akkermansia* (can induce anxiety-like behavior)	Hakimian et al. 2019

[a]NF-kB, Caspase3 and GSK-3β are involved in chronic inflammation, cell proliferation and adiponectin regulation, respectively.

stimulation or severe dysbiosis can cause metabolic changes, such as intestinal malabsorption and reduction of body fat deposition (Gommerman, Rojas, and Fritz 2014).

In addition to IgA production, vitamin A stimulates the secretion of IL17 by Th17 cells that are important in immunomodulation and leukocyte recruitment during host defense against pathogens (Harris et al. 2019). In the GI, the expression of this cytokine requires both the microbial signal (in the intestine and liver) and the presence of vitamin A, thereby explaining the increased immunodeficiency and risk of infection associated with vitamin A deficiency. Furthermore, other studies demonstrated that the depletion of RARα in the IEC interferes with the intestinal mucosal homeostasis and immune response (Jijon et al. 2018). In particular, the signaling of RA downstream of its receptors is fundamental for the development of intestinal dendritic cells (DCs, clones CD103 and CD11b). The manipulation of RA receptor increases the number of caliciform and Paneth cells in the distal small intestine, with consequent increase in the secretion of antimicrobial peptides (in particular of Reg3γ) and reduction of commensal bacteria (Jijon et al. 2018).

Again, IEC are capable of producing RA and tumor growth factor β, both molecules stimulating the proliferation of tolerogenic CD103^{pos} DCs (Abdelhamid and Luo 2018). These DCs are involved in intestinal homeostasis since they promote Treg cell generation, and B and T cell migration to gut-associated lymphoid tissue, this process playing a major role in host defense in the gut. Thus, RA owns the potential to influence the whole intestinal immunity and its interaction with the microbiome at different levels of the GI tract. In this respect, it is worth mentioning that T-cell subsets of the GI mucosa vary significantly along the human

gut possibly following differential distribution of microbial components (Tauschmann et al. 2013). Treg that are enriched in the appendiceal orifice region (possible reservoir for commensal microbiota that facilitates re-inoculation of colonic bacteria after serious gut infections) and the ascending colon, while $CD8^{pos}$ T cells are enriched in the gastric mucosa (Tauschmann et al. 2013).

Recent studies suggest that this migration of lymphocyte subpopulations in the different segments of the human gut is possible thanks to the ability of $CD103^{pos}$ DCs to produce RA via activation of retinaldehyde dehydrogenase 1 and 2 (RALDH1 and RALDH2, respectively) (Oliveira, Teixeira, and Sato 2018). Other effects of RA on the intestinal immunity deriving from its activity on DCs, and consequently on intestinal lymphocytes such as T-cells and IgA producing-B-cells, include a reduced reactivity of the immune system toward GM (Figure 2, right panel), the monitoring of intestinal pathogens, and the modification of the intestinal bacterial composition (discussed earlier and in (Jijon et al. 2018).

The effects of RA on intestinal immune cells and microbial communities are also reported to modulate the intestinal barrier integrity (Figure 2, right panel). Mechanistically, this effect of RA appears to occur via the induction of expression of tight junction protein (Cantorna, Snyder, and Arora 2019; He et al. 2019) such as zonula occludens-2 (ZO-2). Expression of ZO-2 is induced by RA via toll-like receptor 4 (TLR-4) membrane receptor activation (Li et al. 2017). Interaction of vitamin A with TLR4 may involve the modulation of microbiota associated with colonic mucosa and particularly the relative abundance of *Bacteroidetes* and *Firmicutes* (Xiao et al. 2019). Important enough, the TLR4-mediated control of intestinal barrier is regulated through the activity of PXR that can be activated by bacterial metabolites, particularly indole 3-propionic acid (Venkatesh et al. 2014). This may suggest the existence of synergic effects between vitamin A and bacterial metabolism in the TLR-4 mediated regulation of genes important in the control of intestinal permeability.

Studies in murine models also identified the important role of RA (2-day treatment with 25 μg RA/g body weight) in sustaining liver regeneration by means of multiple mechanisms that, beside stem cell differentiation and proliferation, include a modification of the gut microflora (decreased Firmicutes/Bacteroides ratio and increased *Lactobacillus*) with consequent improvement in BA metabolism and function (Liu, Hu, and Wan 2016). In this study, the effect on BA included a reduced expression of CYP7A1 and sterol 12α-hydroxylase (CYP8B1), increased of fibroblast growth factor 15 (FGF15) and BA transporters (e.g., Asbt "apical sodium-dependent BA transporter"), as well as of BA hydrophilicity that stimulate lipid emulsification, micelle formation and intestinal absorption. Another effect was the increased expression of FGF21, a protein necessary for the oxidation and clearance of fatty acids that holds capacity to reverse insulin-resistance and liver injury (Liu, Hu, and Wan 2016).

GM ⇒ VA interaction

The symbiosis between gut tissue and microbiota affects also retinoid biosynthesis. GM produces proteins involved in vitamin A transport into the enterocyte (e.g., lipocalin Blc of *E. coli*), in the regulation of FXR and RXR expression through secondary and tertiary BAs, and in the activation of vitamin A through retinal conversion to RA (Srinivasan and Buys 2019) (Figure 2, left panel). Furthermore, GM enzymes can mimic the activity of the oxygenases BCO1 and BCO2 (β-carotene 9′,10′-oxygenase) allowing the production of retinoids from β-carotene. They can also perform *ex novo* synthesis of carotenoids via the mevalonate pathway (Srinivasan and Buys 2019). Experiments in germ-free mice demonstrated that commensal bacteria, in particular those belonging to the Clostridia class, can modulate RA concentrations and consequently the immune response suppressing retinol-dehydrogenase 7 activity in IECs (Grizotte-Lake et al. 2018).

Therefore, GM may play an important role in the regulation of intestinal absorption, metabolism and immunomodulation function of vitamin A. Considering, the role of vitamin A in modulating the GM described in the previous subsection, it is conceivable to conclude that the GM and the metabolism of vitamin A are linked by conditions of reciprocity and synergize to trigger a virtuous cycle of positive effects on the gut-liver axis, including improved immunity and integrity of the intestinal barrier, liver tissue regeneration and insulin function (Tlaskalová-Hogenová et al. 2011; Liu, Hu, and Wan 2016).

Vitamin D

Vitamin D can be synthesized in the skin starting from 7-dehydrocholesterol, following UV ray exposure, in particular UVB (280–315 nm light wavelength spectrum) (Göring and Koshuchowa 2015; Bosman et al. 2019). Skin synthesis produces cholecalciferol (vitamin D3) and ensures approx. 80% of the nutritional requirements for this vitamin. It has also been observed that UVB induce an increase in the alpha and beta diversity of the microbiota, bound to the modulation of innate and specific immune cells and related release of intestinal and immune mediators (Bosman et al. 2019). Dietary cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) also contribute to vitamin D status. Vitamins D2 and D3 require enzymatic activations by two isoforms of cytochrome P-450 expressed in the liver and kidney. Firstly, a hydroxylation step is achieved in the liver by 25-hydroxylase (CYP27R1) to produce and release 25-hydroxycholecalciferol in the circulation. A second activation step occurs in the kidney via 1-α-hydroxylase (CYP27B1) that generates 1,25-dihydroxycholecalciferol, or calcitriol, that is the metabolically active form of vitamin D. This latter hydroxylation reaction is stimulated by the parathormone (PTH) and is inhibited by the FGF-23, a protein mainly produced by osteoblasts and osteocytes (El-Fakhri et al. 2014). Specifically, PTH stimulates the expression of CYP27B1 upon decreased serum calcium concentrations. FGF-23 acts reducing the renal expression of sodium/phosphate transporters and CYP27B1 expression, and by the induction of

CYP27A1, a 24-hydroxylase enzyme responsible of vitamin D inactivation (Medrano et al. 2018). The biological effects of calcitriol are mediated by the VDR, a nuclear receptor broadly expressed in the body including intestine and immune cells (Sassi, Tamone, and D'Amelio 2018). This wide diffusion of VDR expression in human tissues indicates that vitamin D is not only involved in the control of calcium and phosphate metabolism and for this reason, it can find applications in the treatment of several diseases, some of which have recently been reviewed in (Amrein et al. 2020). In fact, beside the role in calcium metabolism, vitamin D participates in different regulatory processes. These include the reduction of pro-inflammatory cytokines stimulating hepcidin that is important to increase iron availability and prevent anemia (Syed et al. 2017; Medrano et al. 2018) and the regulation of molecular pathways relative to brain function (Cannell 2017; Ghaderi et al. 2019), nociception (Guida et al. 2020), cardiac contractility and blood pressure (Khammissa et al. 2018).

At the same time, the VDR may be critical for maintaining a healthy microbiome through the modulation of microbial metabolites with effects on the metabolism of carbohydrates, proteins/amino acids, lipids and xenobiotics (Chatterjee et al. 2020).

VD ⇒ GM interaction

Vitamin D is reported to influence intestinal immunity either by direct or indirect (GM-mediated) processes. Compelling evidence is available on the activity of vitamin D to enhance phagocytic activity, secretion of antimicrobial peptides (*β*-defensin, catelicidin) and expression of E-cadherin, claudin-1, ZO-1 and occludin proteins (Cantorna et al. 2014; Cantorna, Snyder, and Arora 2019) (Figure 2, right panel). Vitamin D also stimulates the proliferation of Th2 cells, thus sustaining the production of anti-inflammatory cytokines, and inhibits Th1 and Th17 clones that produce pro-inflammatory cytokines (Bivona, Agnello, and Ciaccio 2018). Moreover, vitamin D stimulates tolerogenic DCs (Sassi, Tamone, and D'Amelio 2018) (Figure 2, right panel) and regulates angiogenin-4 expression, which has bactericidal activity (Tabatabaeizadeh et al. 2018). Amongst the immune cell populations, $CD8^{pos}$ T cells exhibit the highest level of VDR expression. These cells are mostly found in the stomach where they represent the first line of defense against food antigens (Tauschmann et al. 2013). In a recent clinical trial testing for the effects of oral vitamin D3 supplementation (8-week treatment) in healthy volunteers, it was observed an increase in $CD8^{pos}$ T cells associated with changes in the microbial population particularly in the upper GI tract (stomach and duodenum) (Bashir et al. 2016). A 8-week Vitamin D3 treatment was found to reduce proteobacteria (i.e., the Gammaproteobacteria class in particular) at the gastric and duodenal levels, while Bacteroidetes increased. The reduction in Gammaproteobacteria was supposed to depend on the increase in $CD8^{pos}$ T cells in the upper GI tract. In this study, no significant effect in microbial composition, was found in the lower GI tract (ileum, colon) and feces (Bashir et al. 2016), suggesting that vitamin D may have different activity along the GI tract. In contrast, other studies showed that vitamin D induces changes in fecal microbiota (Luthold et al. 2017; Naderpoor et al. 2019). These conflicting results highlight the need for confirmatory vitamin D intervention studies with topographical analyses of the microbiome along the GI tract.

GM ⇒ VD interaction

Variations in the GM composition can interfere with vitamin D status and biological functions. This can occur directly through the activity of FGF-23 (produced mainly by osteocytes and osteoblasts), which inhibits CYP27B1 and induces CYP24A1, thereby interfering with the metabolic activation of the vitamin (Sassi, Tamone, and D'Amelio 2018) (Figure 2, left panel). In germ-free mice compared with conventional mice, higher levels of FGF-23 were reported along with hypocalcemia and lower levels of 1,25-dihydroxyvitamin D and 24,25-dihydroxyvitamin D (Bora et al. 2018). Moreover, the absence of the gut microflora can impair other physiological processes, such as the release of LPS that induces the activation of osteoclasts via tumor necrosis factor α (TNF-α) produced by bone marrow macrophages, which coincides with the reduction of FGF-23 (Sassi, Tamone, and D'Amelio 2018).

Indirectly, the GM can hinder the vitamin activity through secondary BAs, mainly LCA, which compete with vitamin D for VDR binding and activation (Ishizawa, Akagi, and Makishima 2018) (Figure 2, left panel). Not only, interacting with the VDR-LCA induces CYP24A1 mRNA expression in the ileum (but not in duodenum and jejunum) that leads to calcitriol inactivation (Ishizawa, Akagi, and Makishima 2018).

Other metabolic products of bacteria, such as SCFA and especially butyrate, increase the intestinal expression of VDR by suppressing inflammation (Sun 2016). Importantly, vitamin D deficiency in the intestine is associated with inflammation, shortened colon length, disordered mucosal structure, inflammatory cell infiltration. Vitamin D deficiency also links with reduction of the mucus layer by the alteration of the microbial composition that is characterized by increased *Akkermansia muciniphila*, an intestinal mucin-degrading bacterium (Zhu et al. 2019). Finally, some bacteria express enzymes involved in hydroxylation of steroids (i.e., *Streptomyces griseolus* with CYP105A1, *Sebekia benihana* with CYP-sb3a, *Pseudonocardia autotrophica* with Vdh) that are capable to hydroxylate and activate vitamin D (Szaleniec et al. 2018).

Vitamin E

The term vitamin E refers to eight lipophilic molecules, classified in the two subfamilies of tocopherols (TOHs) and tocotrienols (T3) that are mainly occurring in edible oils, nuts and seeds, such as corn oil, wheat germ, hemp, peanuts, sesame, almonds and walnuts (Torquato et al. 2020). α-tocopherol is the most relevant and biologically active

form retrieved in human tissues, mainly the adipose tissue that accounts for about 90% of total vitamin E of the body. Excess of vitamin E is metabolized in the liver to form a series of metabolites excreted in bile and urine (Schmolz et al. 2016; Galli et al. 2017). These catabolites include long-, intermediate- and short-chain metabolites that are generated through CYP450-mediated ω-hydroxylation and subsequent β-oxidation-like degradation of the side chain (Galli et al. 2007).

Vitamin E (e.g., α-tocopherol) is considered the most important fat-soluble antioxidant of cellular membranes and circulating lipoproteins, with important applications in prevention and adjuvant treatment of some chronic and degenerative diseases, such as atherosclerosis (Wallert et al. 2014), Alzheimer disease (Rizvi et al. 2014), neuroinflammation and neurotoxicity associated with epilepsy (Ambrogini et al. 2018). In addition to its antioxidant function, vitamin E and its related long-chain metabolites are PXR agonists (Landes et al. 2003; Podszun et al. 2017) with the demethyl configurations of the chroman ring as the most active ones (Bartolini et al. 2020; Marinelli et al. 2020). PXR is a nuclear receptor involved in the modulation of metabolic enzymes and transporters in the metabolism of xenobiotics and endobiotics such as steroids and β-amyloid peptides that are associated with the pathogenesis of Alzheimer disease (Marinelli et al. 2020). These metabolites exhibit also potent anti-inflammatory effects, inhibiting COXs (Jiang et al. 2008) and 5-LOX (Pein et al. 2018). 5-LOX is responsible for the production of leukotrienes which are potent pro-inflammatory mediators involved in DNA oxidative damage, allergic and autoimmune reactions, and several pathophysiological conditions such as cardiovascular and liver diseases, neurodegeneration and cancer (Pein et al. 2018; Schubert et al. 2018). Short chain carboxyethyl hydrochroman (CEHC) metabolites are water soluble molecules endowed of anti-proliferative, anti-inflammatory and antioxidant activity (Wallert et al. 2014).

VE ⇒ GM interaction

Both animal and human studies suggest that increasing the intake of vitamin E may improve immune and inflammatory responses and be associated with a reduced risk of infectious disease (Meydani, Lewis, and Wu 2018) (Figure 2, right panel). The immuno-modulatory activity of this vitamin appears to depend on different mechanisms (Galli et al. 2017; Azzi 2018). These include an increased expression of Klotho, an anti-aging and anti-inflammatory single-pass membrane protein predominantly produced in the kidney that acts as co-receptor of human fibroblast growth factor (FGF-19) (Lee and Han 2018; Kim et al. 2015). Klotho-FGF-19 binding is important in BA homeostasis by reducing expression of CYP7A1 (cholesterol-7-α hydroxylase).

In a recent study by Kim et al., α-tocopherol (400 IU, twice daily) has been reported to reduce *Bacteroides* and *Lactobacillaceae* abundance, and the ratio of *Bacteriodetes/Firmicutes* in human (Kim et al. 2018), and a recent but preliminary work by Choi et al. associated high and low doses of dietary α-tocopherol (9 mg vs. 3 mg per Kg BW) with different gut microbial compositions in mice (Choi et al. 2020). In particular, the *Firmicutes* to *Bacteroidetes* ratio marked by increased Proteobacteria and decreased Verrucomicrobias, was modified in the low-dose group relatively to both high-dose and standard diet groups. Important enough, the most abundant species in the Verrucomicrobias phylum is *Akkermansia muciniphila*, which is associated with pro-inflammatory and "leaky gut" phenotype due to increased degradation of the protective mucus layer (Zhu et al. 2019).

GM ⇒ VE interaction

The interaction between the GM and the metabolism and function of this vitamin is less characterized relatively to other FSV. Common symptomology of MetS and fatty liver disease is inflammation and oxidative stress in both the gut and liver (Svegliati-Baroni et al. 2019). These pathologies have shown to increase oxidation of polyunsaturated lipids and consequently of cellular vitamin E (Torquato et al. 2019). As a side note, bacterial endotoxemia can cause reduction of vitamin C levels with consequent decrease of co-antioxidant activity and bioavailability of α-tocopherol (Traber, Buettner, and Bruno 2019).

A direct effect of GM on vitamin E metabolism and status has recently been reported in rats treated with antibiotics and supplemented with vitamin E. The findings in this study support the notion that the GM can initiate the CYP450-dependent metabolism of vitamin E in the intestinal lumen (Ran et al. 2019) (Figure 2, left panel).

Vitamin K

Vitamin K consists of phylloquinone (PK) or vitamin K1 that is naturally occurring in vegetal sources such as fruits, nuts, whole grains, leafy green vegetables and soy (Walther et al. 2013), as well as vitamin K2 or MKs from bacterial origin (Fusaro, Gallieni, et al. 2017). Endogenous MK include MK-4 that is formed from PK in human tissues by conversion to menadione and its subsequent prenylation catalyzed by the enzyme UbiA prenyltransferase domain-containing protein 1 (UBIAD1) (Nakagawa et al. 2010). MK-4 is a ligand of the steroid and xenobiotic receptor (SXR) that is mainly expressed in the liver and intestine and is responsible for the expression regulation of genes involved in steroid metabolism and xenobiotic detoxification (Hirota and Suhara 2019). Also, MK-4 is likely a strong ligand of human PXR and also regulates the expression of CYP7A1 and CYP8B1, thus modulating the synthesis of BAs (Sultana et al. 2018).

Intestinal bacterial MK production significantly contributes to fulfill the vitamin K requirements (Haden 1957; Conly and Stein 1992; Conly and Stein 1994; Conly et al. 1994; Guss et al. 2019; Quinn et al. 2020). Vitamin K acts as a cofactor of gamma-glutamyl carboxylase (GGCX) that catalyzes the carboxylation of glutamic acid (Glu) residues into gamma-carboxyglutamic acid (Gla) residues in vitamin K-dependent proteins (Gla-proteins), a key step required for

protein activation. Vitamin K1 is mainly stored in the liver to support the carboxylation of coagulation factors, while vitamin K2 appears to be involved in the carboxylation of extra-hepatic proteins involved in homeostatic processes of the bone and vascular systems (Schurgers and Vermeer 2002; Fusaro et al. 2011).

Vitamin K deficiency appears to be linked to a complex phenotype known as the "calcium paradox." This paradox refers to a disruption of the normal distribution of calcium with reduced levels in the bone tissue and accumulation in the arterial wall (Flore et al. 2013; Fusaro et al. 2012). The "calcium paradox" associates thus with increased risk on one hand of osteoporosis and bone fractures and on the other hand of vascular calcifications and cardiovascular risk. The vitamin K-dependent matrix Gla-protein (MGP), prevents calcium storage in the arterial wall (Ponziani et al. 2017). Indeed, patients with small intestinal bacteria overgrowth, a condition of intestinal microbial dysbiosis, show a reduced production of MKs, increased levels of inactive MGP, vascular rigidity and a higher risk of atherosclerosis (Ponziani et al. 2017). Vitamin K is also required for the activity of the hormone osteocalcin involved in bone mineralization as well as proliferation and insulin production of pancreatic beta cells (Eden and Coviello 2019; Halder et al. 2019). Furthermore, MK-6, 12 and 13 and high levels of PK seem to be positively correlated with the cognitive function in the elderly and Alzheimer disease patients show reduced levels of PK (McCann et al. 2019). Vitamin K is indeed the cofactor for the γ-carboxylation of Gas6, a protein involved in chemotaxis, mitogenesis, cell growth and myelination of the brain (Denisova and Booth 2005). Vitamin K is also reported to have a role in sphingolipid metabolism alterations (Ferland 2012). Myelin-rich regions of the brain are relatively rich in MK-4, which has also been shown to inhibit oxidative damage, a hallmark of the age-dependent decline of brain functions. This effect appears to be independent from the γ-carboxylation of vitamin K-dependent proteins (Denisova and Booth 2005). The antioxidant effect of vitamin K could also occur through the activity of VKORC1-like 1 (VKORC1L1), a paralogue enzyme of Vitamin K epoxide Reductase Complex subunit 1 (VKORC1) that is broadly expressed in human tissues (Halder et al. 2019).

VK ⇒ GM interaction

MKs are reported to play a key role in intestinal homeostasis promoting the selective growth of symbionts (Fenn et al. 2017) (Figure 2, right panel). Moreover, MKs are involved in the respiratory electron transport chains of prokaryotes, also providing antioxidant activity and protection of cell membranes against lipid peroxidation (Walther et al. 2013).

MK-7 own immunomodulatory effects that may sustain the GM through the regulation of intestinal inflammation and immune function (Figure 2, right panel). MK-7 modulates the expression of cytokines such as TNF-α, interleukin-1α (IL-1α) and IL-1β, in human monocyte-derived macrophages (Pan et al. 2016). Furthermore, MK-7 are reported to prevent colon cancer in mice affecting gut microbial composition of the gut and providing efficient stimulation of bacterial metabolism (Zheng et al. 2017). Intriguingly enough, in this study both probiotics and MK-7 affected GM composition, together with adiponectin production, to promote anti-carcinogenic effects. The administration of *Lactobacillus casei* or MK-7 could reduce the risk of colorectal cancer decreasing pro-tumoral intestinal species, such as *Helicobacter apodemus*, *Helicobacter mesocricetorum*, *Allobaculum stercoricanis* and *Adlercreutzia equolifaciens* (Zheng et al. 2017).

GM ⇒ VK interaction

Bacteria involved in MKs production in food or colonic fermentation include *Bacillus subtilis* and Veillonella (MK-7), the Enterobacteria *Escherichia coli* and *Shigella* (MK-8), *Eubacterium lentum* (MK-6), and the Bacteroides *Prevotella* (MK-5, −11 and −13; Walther et al. 2013, Ponziani et al., 2017; Fusaro, 2017). Distal colon is reported to exhibit the highest concentration of MKs relatively to ileum (McCann et al. 2019). It is also worth mentioning that GM is able to stimulate VDR expression and thus it potentially can improve the vitamin D status trough MK-7 (Zhang et al. 2017) (Figure 2, left panel).

Bioavailability and plasma half-life values vary across MKs, with those of MK-7 being greater than MK-4 (Sato, Schurgers, and Uenishi 2012; Walther et al. 2013). Absorption of MKs can be mediated by biliary acids, but can also occur by passive diffusion (McCann et al. 2019). Besides vitamin K1, MKs are also present in the liver (Karl et al. 2015). Moreover, food matrix and nutrient composition can impact the delivery of MKs and their contribution to vitamin K status (Knapen et al. 2016).

Therefore, in this context, it is important to consider that intestinal dysbiosis may lead to a relative increase of MKs producers in the bacterial microflora, which may associate with increased risk of thrombotic events especially in patients affected by hypercoagulability or coagulopathies that require treatments with prothrombotic agents (Aydin 2017). Subjects taking supplements containing the FSV K and E have also been identified to be at higher risk of blood clotting (reviewed in (Galli et al. 2017)).

Omega-3 and omega-6 fatty acids

Linoleic (omega-6) and α-linolenic (omega-3) acid are essential fatty acids (EFAs) (Gammone et al. 2018). Improperly defined as vitamin F in some instances, these EFA are mainly found in vegetable oils (sunflower, peanut, corn, and soy), fruit oils (walnuts, almonds, etc.) as well as in fat-rich fishes (salmon, sardine, tuna, mackerel, herring).

Their "essentiality" depends on the fact that human cells do not have enough desaturase activity to introduce the omega-3 and omega-6 double bonds in fatty acid precursors from *de novo* lipogenesis or dietary sources (Di Pasquale 2009). Consequently, the long-chain omega-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are mainly formed from

Table 4. Essential fatty acids: metabolic and intestinal effects.

Essential fatty acid species	Biological activity	References
Omega 3	Reduction of fat excess and inflammation in the liver	Spooner and Jump 2019
	Anti-inflammatory effects through inhibition of TLR4-dependent signaling and NF-kB activation, or through PPAR-γ activation	Statovci et al. 2017
	Production of molecules that contribute to resolve inflammatory processes (resolvins, protectins, maresins)	Molfino et al. 2017
	Prevention of intestinal barrier dysfunction induced by chronic stress, increasing the expression of tight junction proteins	Liu et al. 2012; Cao et al. 2019
	Modulation of intestinal bacterial composition by increasing butyrate-producing species	Costantini et al. 2017; Watson et al. 2018
Omega 6	Induction of IAP expression which reduces intestinal permeability, LPS production, endotoxemia and inflammation	Kaliannan et al. 2015
	Pro-inflammatory pathway activation	Molfino et al. 2017;
	Alteration of microbial composition with increase of bacterial species associated with obesity and inflammation	Zhuang et al. 2017
	Hypothalamic leptin resistance	
	The release of lipoxins that promote anti-inflammatory processes	

alpha-linolenic acid through elongation and desaturation reactions, while arachidonic acid (AA) is formed from the linoleic acid precursor. DHA accounts for about 40% of the PUFA in the brain and 60% of the retina (Crawford, Bazinet, and Sinclair 2009), and AA is the most abundant PUFA in membrane lipids and an important precursor of eicosanoids (Martin, Brash, and Murphy 2016).

Several studies highlighted the important role of omega-3 in the prevention or adjuvant therapy of colorectal cancer (Volpato and Hull 2018). Proposed underlying mechanisms included: (1) modulation of COX metabolism and reduction of E2 prostaglandin production in cancer tissues; (2) increased production of lipid mediators involved in the resolution of inflammation; (3) alterations of the plasma membrane of tumor cells; (4) activation of pro-apoptotic pathways through G protein-coupled receptors.

Omega-3/6 ⇒ GM interaction

Together with the role in inflammatory pathways and endothelial function (Colussi et al. 2017), omega-3 fatty acids and their metabolites exhibit a number of effects on GI health and metabolism, including immune regulation, preservation of intestinal barrier and modulation of GM composition (Table 4).

A recent clinical trial suggested that the anti-carcinogenic effect of omega-3 could occur via changes in intestinal microbial composition (Watson et al. 2018). In this study, daily supplementation of 4 g mixed EPA/DHA for 8 weeks decreased the genera *Coprococcus* and *Faecalibacterium,* and increased the butyrate-producing genera *Bifidobacterium*, *Oscillospira*, *Roseburia* and *Lachnospira*, which are assumed to hold anti-carcinogenic potential.

Clinical trials

Recently, an increasing number of pre-clinical studies reported on interactions between GM and the metabolism of FSV. A few clinical trials have been carried out to investigate the effects of probiotics on outcomes related to vitamin D and omega 3 fatty acids.

In a double-blind, placebo-controlled, randomized, parallel-arm, multicenter study on 127 adults, Jones et al. demonstrated that treatment with *Lactobacillus reuteri* NCIMB 30242 (2.9×10^9 colony-forming units per capsule for 9 weeks), increased serum concentrations of 25-hydroxyvitamin D by 25.5% with respect to placebo (Jones, Martoni, and Prakash 2013).

A 12 week administration of vitamin D3 (50,000 IU every 2 weeks) and 8×10^9 CFU/day probiotics (containing *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Lactobacillus reuteri* and *Lactobacillus fermentum*, 2×10^9 CFU/g each), have shown synergistic effect on reducing testosterone production in women with polycystic ovary syndrome (Ostadmohammadi et al. 2019), and better indicators of inflammation and oxidative stress.

In another study carried out in schizophrenic patients, the same protocol of treatment with vitamin D3 and probiotics, lowered inflammatory parameters and the severity of associated metabolic syndrome (Ghaderi et al. 2019). Co-supplementation of vitamin D and probiotic also showed improvements in metabolic symptoms have also been observed in type 2 diabetes (Raygan et al. 2018) and gestational diabetes (Jamilian, Amirani, and Asemi 2019).

Furthermore, a weekly administration of 50,000 UI vitamin D in cystic fibrosis (CF) patients, decreased the relative abundance of Gammaproteobacteria and particularly *Escherichia/Shigella* and *P. aeruginosa* species that are associated with lung infection, oxidative stress lung tissue degeneration (Galli et al. 2012). Effects of vitamin D supplementation on GM composition of CF patients were also reported by Kanhere et al. (2018).

Kobyliak et al investigated the co-administration of omega-3 (5–25 mg omega-3/day), and a probiotic mixture (*Lactobacillus* and *Lactococcus*, 6×10^{10} CFU/g; *Bifidobacterium*, 1×10^{10}/g; *Propionibacterium*, 3×10^{10}/g; *Acetobacter*, 1×10^6/g) in NAFLD patients (Kobyliak et al. 2018). The study showed that 8 weeks of treatment with these factors improved liver fat, serum lipids, metabolic parameters and systemic inflammation. Clinical benefits of this probiotic and omega-3 fatty acids co-administration protocol were also reported in colorectal cancer patients

(Golkhalkhali et al. 2018), including improved quality of life, reduction of inflammatory biomarkers and chemotherapy side effects.

Conclusions and perspectives

There is increasing clinical and mechanistic evidence on the intertwined relationships between nutrients and GM functional ecology. Mediterranean diet has been associated to health-promoting effects on the GM unlike western diet. Often modulations of the microbial ecosystems have been assigned to effects of the dietary fiber and both macro- and micronutrients.

More recently, a number of molecular and functional interactions between FSV and GM have become evident. However, this relationship has appeared to be rather bidirectional. FSV influence the composition and function of the GM through the regulation of the immune response and inflammatory pathways, the preservation of intestinal barrier integrity, and the production of antimicrobial peptides and BAs. On the other way, GM and dysbiosis influence the status, metabolism and functions of FSV. This can occur for example via modulation of vitamin receptors (e.g., VDR for vitamin D, RAR for vitamin A or PXR for vitamin E), vitamin transport systems (e.g., by bacterial lipocalins and mucosal mast cell activity modulation that influences lipid absorption and therefore FSV absorption) and biotransformation pathways that can be responsible of both catabolism and bioactivation of vitamins, as well as of drug interactions or production of potentially harmful metabolites (see for example the case of vitamin K and the risk of blood clotting).

However, many aspects of this two-way relationship remain elusive. Further studies are needed to design both dietary and pharmacological strategies for the management of gut dysbiosis and its inflammatory, metabolic and nutritional correlates. Moreover, a better understanding of this interaction will help to shed light on disease-specific nutritional requirements and FSV status reference ranges. Additional efforts remain to be made also to build reliable integrated analytical platforms able to quantitatively and reproducibly capture the complex microbiome-nutrient interactome. Beside of metagenomics techniques these should include specific bioinformatics tools and metabolomic and lipidomic solutions with the same performance of platforms utilized in molecular nutrition studies (Rezzi et al. 2013).

Author contributions

The authors' responsibilities were as follows—V.S.: performed the literature review, conceived and composed the manuscript; F.G. and S.R.: conceived and edited the manuscript and provided formatting advice; M.E.: edited the final manuscript, and all authors: read and approved the final manuscript.

Disclosure statement

The other authors declare no conflicts of interest.

Notes

1. This term is used to define a host and its associated communities of microorganisms.
2. The Mediterranean diet is characterized by a high intake of whole grains, fruits, vegetables and legumes; moderate consumption of milk and derivatives, lipids (with preponderance of olive oil consumption), grape, dried fruit, fish and white meat, and low consumption of red meat and sweets.
3. A substrate that is selectively utilized by host microorganisms conferring a health benefit.

Abbreviations

BA	bile acid
BCO1	β-carotene 15,15'-oxygenase
COX	cyclooxygenase
CVD	cardio-cerebro-vascular disease
DCA	deoxycholic acid
DC	dendritic cell
DHA	docosahexaenoic acid
FGF	fibroblast growth factor
FSV	fat-soluble vitamin
GM	gut microbiota
IgA	immunoglobulin A
LCA	lithocholic acid
IEC	intestinal epithelial cell
LOX	lipoxygenase
MetS	metabolic syndrome
MK	menaquinone
PK	phylloquinone
PUFA	polyunsaturated fatty acid
PXR	pregnane X receptor
RA	retinoic acid
RXR	retinoid X receptor
SCFA	short-chain fatty acid
TLR	toll-like receptor
VDR	vitamin D receptor

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