



Food-derived nutraceuticals for hypercholesterolemia management, mode of action and active ingredients

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ARTICLE INFO

Keywords:

Hypercholesterolemia
Food supplement
Diet intervention
Natural product

ABSTRACT

Nutraceuticals and functional foods are considered useful tools in the management of moderate plasmatic cholesterol levels. Natural compounds derived from plant, animal, or bacterial foods sources can influence cholesterol levels acting with different mechanisms and literature revealed their mode of action, and their potential usefulness in hypercholesterolemia. This review summarizes the upgrade in the field of nutraceuticals and functional foods claimed with hypocholesterolemic properties considering relevant literature published in the years 2009 to present. Ingredients with these properties will be described considering their molecular targets, their occurrence, and effects. Food derived compounds will be discussed for their potentiality to become active ingredients of food or food supplements with hypo-cholesterolemic properties, with a specific action on a biological target. The information's obtained underline the new challenges for the nutraceuticals in hypercholesterolemia management indicating the most promising ingredients to be developed as new useful tools for the implementation of the human health.

1. Introduction

A new health paradigm has emerged in the recent years raising attention on the relation of health with diet and nutrition. Consumers purchase and use dietary supplement, functional foods and nutraceuticals with the aim to maintain health (Chhabra, Bakshi, & Kaur, 2021; Chopra et al., 2022; K. Liu et al., 2020; Sachdeva, Roy, & Bharadvaja, 2020; Scicchitano et al., 2014; Sut, Baldan, Faggian, Peron, & Dall'Acqua, 2016). These products due to their natural origin are considered safe by consumer and industrial companies due to high market request are developing new and innovative products (Chhabra et al., 2021). The dietary intervention and the use of supplements, can be useful for the cholesterol reduction at least for some group of the patients, but it is important that all health professionals make appropriate use of all the different intervention strategies as dietary improvement, positive lifestyle changes, nutraceuticals, food supplements, and drugs (Hunter & Hegele, 2017; Poli et al., 2018). The dietary intervention can be the first step reducing saturated fatty acids, while increasing polyunsaturated lipids. These latter have a limited impact on LDL cholesterol levels (Rees et al., 2013), but omega-3 unsaturated fats have positive impact of cardiovascular health and on triglyceride levels (Johnston, Korolenko, Pirro, & Sahebkar, 2017; Poli et al., 2008).

The most important constituents can be summarized as dietary fiber, prebiotics, probiotics, polyunsaturated fatty acids, antioxidants and large different type of herbal products containing phytochemicals (Chhabra et al., 2021; Chopra et al., 2022; Sachdeva et al., 2020). All these natural or food derived product are in general processed to obtain concentrated products that can be formulated in pharmaceutical forms as tablets, capsules, syrups, or oral powders or can be included in foods as soups, yogurt, or beverages. Several areas of application are present for the nutraceuticals and food supplement and the cardiovascular prevention is one of the most important. Cardiovascular diseases (CVD) are diffused in many countries of the world and are related to inhabits as physical activity and diet, so influence in their prevention can be related to dietary inhabits and physical activity (Ghada A. Soliman, 2019; Gunness & Gidley, 2010; Jesch & Carr, 2017; Korcz, Kerényi, & Varga, 2018; Mach et al., 2020; Poli et al., 2008; Rees et al., 2013). Blood pressure and cholesterol are the major modifiable cardiovascular disease (CVD) risk factors and large literature data indicated some food and food derived products with potential usefulness. Fibers, complex polysaccharides of vegetal or fungal origin, prebiotics (Anderson et al., 2009; Bazzano, 2008; Ghada A. Soliman, 2019; Jesch & Carr, 2017; Kaczmarczyk, Miller, & Freund, 2012; Korcz et al., 2018; Tang et al., 2017; N. Wang et al., 2021), but also peptides (V. Kumar, Kurup, & Tiku, 2021;

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<https://doi.org/10.1016/j.fbio.2023.102866>

Received 5 February 2023; Received in revised form 15 May 2023; Accepted 15 June 2023

Available online 28 June 2023

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Lammi, Aiello, Boschin, & Arnoldi, 2019; Maestri, Marmiroli, & Marmiroli, 2016; Nagaoka, 2019; Sosalagere, Adesegun Kehinde, & Sharma, 2022; Yamauchi, Ohinata, & Yoshikawa, 2003) and notably different classes of phytochemicals (Poli et al., 2008, 2018; Sosalagere et al., 2022; Tang et al., 2017) have been considered in this regard showing that different compounds can have a role in the management of hypercholesterolemia.

Different classes of food derived natural products have been studied for their specific hypocholesterolemic properties (Chen, Ma, Liang, Peng, & Zuo, 2011; Gunness & Gidley, 2010; Jesch & Carr, 2017; Jia et al., 2019; Johnston et al., 2017; Kobayashi, 2019; V. Kumar et al., 2021; Li et al., 2020; Liu & Yeh, 2002; Mäkinen, Chit-chumroonchokchai, Adisakwattana, Failla, & Ariyapitipun, 2012; Poli et al., 2018; Sivamaruthi, Kesika, & Chaiyasut, 2019; Sobenin, Myasoedova, Il'tchuk, ZHANG, & Orekhov, 2019). The overall literature on this topic is emphasizing the need for new reliable evidence for other food derived ingredients acting as hypocholesterolemic agent (Poli et al., 2018).

This review summarizes the upgrade in the field of dietary supplements and nutraceuticals in the management and prevention of hypocholesterolemia. Composition, occurrence of bioactive compounds, specific targets on the cholesterol metabolic pathways will be discussed. Specific classes of food derived compounds with notable activity on the selected pathways will be considered for their potentiality to become new hypocholesterolemic agents, with a specific action on a biological target.

2. Methodology

Three databases, namely PubMed, Scopus, ISI web of sciences have been used to search for relevant articles on the selected topic. Multiple searches were performed in the period July 2021–August 2022, and a period of time from 2009 to present was covered. Keywords used for the search were hypercholesterolemia, food supplements, phytochemicals

and hypercholesterolemia, phenolic, phytosterols, triterpene, terpenoids, cholesterol. The search covered the period searching for specific review published in the last 3 years. Articles were selected on the basis of their relevance to the topic (food supplements for hypercholesterolemia management) and preferring the most recently published.

3. The main targets for modulation of cholesterol homeostasis

Cholesterol levels in human body are determined by the interplay between *de novo* biosynthesis, uptake, export and storage (J. Luo, Yang, & Song, 2020) leading a resulting plasmatic concentration. Dietary cholesterol and bile acids are mainly absorbed in intestine (Fig. 1). The liver is the main site of cholesterol biosynthesis and delivers both endogenously synthesized and exogenously acquired cholesterol to the bloodstream (Fig. 1). After processing in the bloodstream, the Very-low-density-lipoproteins (VLDLs) generate circulating LDLs, which can be taken up by peripheral cells via receptor-mediated endocytosis (Goldstein & Brown, 2009; J. Luo et al., 2020). The reduction of blood cholesterol levels can be obtained acting on the absorption or inhibiting the synthesis. Different class of food constituents have demonstrated their crucial role in this field (Hunter & Hegele, 2017). Schematic representation of cholesterol homeostasis is represented in Fig. 1 that is adapted from the image of a recent review of Kobayashi et coll (Kobayashi, 2019).

The main proteins that are relevant for each step of the cholesterol absorption pathway are pancreatic triglyceride lipase, carboxyl ester lipase, and BA transporter in determining the rate of cholesterol absorption, the Niemann-Pick C-1 like-1 (NPC1L1) protein as intestinal membrane gatekeepers for cholesterol efflux and influx, ATP binding cassette (ABC) transporters (ABCG5, ABCG8 and ABCA1) and scavenger receptor class B type 1 (SR-B1) (Hui & Howles, 2005). Then, ABCG5 and ABCG8, involved in the transport of cholesterol back to the intestinal lumen, limit intestinal absorption and facilitates biliary secretion of cholesterol (Yu et al., 2014). Different natural products can modulate

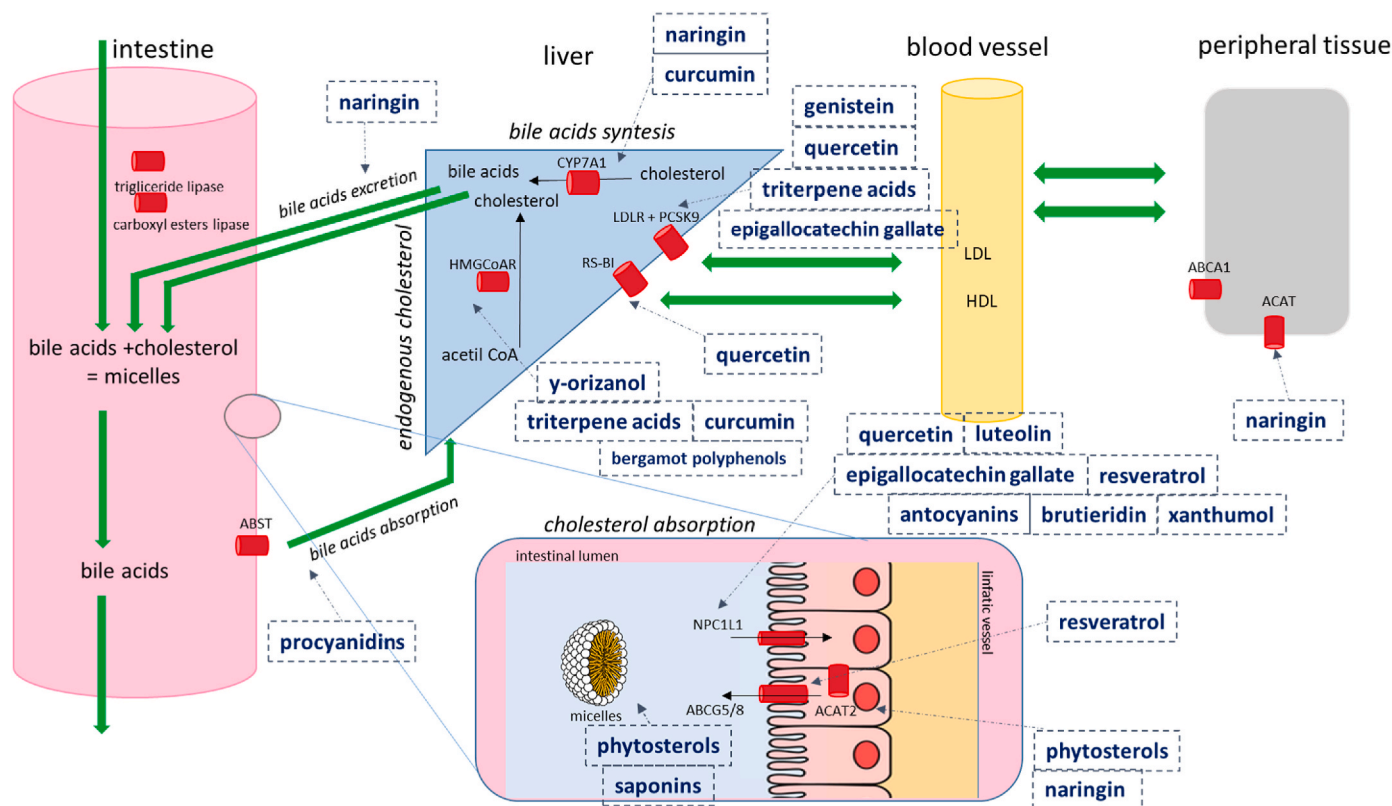


Fig. 1. Schematic representation of cholesterol homeostasis.

this key transporter crucial for cholesterol absorption thus far identified as phytosterols, soluble fibers, phospholipids (Elliot D. Jesch & Carr, 2017).

Thus, nutraceutical influencing cholesterol blood levels can either reduce the absorption or increase excretion or reduce the endogenous synthesis. In many cases nutraceutical with some efficacy on the cholesterol homeostasis can act with multiple mechanisms also because the interaction with one of the different metabolic pathways of cholesterol induce modification to other. As example the increased excretion of cholesterol and reduced absorption that is induced by dietary fiber induce increase in the LDLR synthesis in the liver.

3.1. Nutraceuticals targeting the biosynthesis of endogenous cholesterol

The endogenous cholesterol synthesis starts from acetyl-CoA and involves actions of more than twenty enzymes, mostly occurring in liver cells. The crucial players of the cholesterol biosynthetic pathway are the sterol regulatory element-binding protein 2 (SREBP2), a transcriptional regulator of cholesterol biosynthesis, and the two rate-limiting enzymes of the biosynthetic pathway, the 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMGCoAR) and the squalene monooxygenase (J. Luo et al., 2020).

Very limited nutraceutical can claim reduction of the biosynthesis of cholesterol, monacolin K (also known as lovastatin) and related compounds from red yeast rice (RYR) can act efficiently on HMGCoAR. EFSA have given scientific report on this supplement in 2018 indicating efficacy and possible side effects (Maged Younes, Peter Aggett, Fernando Aguilar, Riccardo Crebelli et al., 2018), and recently the European commission approved the REGULATION (EU) 2022/860, in which the maximum allowed amount of monacolin in food supplement is fixed at 3 mg/dose to reduce possibility of side effects (Commission Regulation (EU) 2022/860 of June 1, 2022 amending Annex III to Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards monacolins from red yeast rice). This modification to the regulation will induce changes in nutraceutical composition and will stimulate companies to find other ingredients with similar efficacy but increased safety. Recently some *in vitro* data shown that hepatic cells treated with the vitamin K1 form menaquinone-7 (MK-7) significantly reduced cholesterol biosynthesis (−38%) and induced HMGCoAR and low-density lipoprotein receptor (LDLR) at both mRNA and protein levels indicating possible new candidate in MK-7 as new ingredient for this target (Lupo et al., 2020). In a recent review authors summarized the literature related to medicinal plant and natural product with ability to inhibit HMGCoAR (Mahdavi et al., 2020). In their paper different plant materials (as green tea, flaxseed, garlic, aloe, cranberry, cinnamon) as well as purified natural products (berberine, resveratrol, curcumin) were listed as potential active agents able to diminish the expression or the activity of HMGCoAR (Mahdavi et al., 2020). Reviewed literature compared results obtained with different *in vitro* and animal models, different preparations and doses thus is very difficult to conclude the real effects of these products on human and their potential efficacy in management of hypercholesterolemia.

3.2. Nutraceutical targeting low density lipoprotein receptor (LDLR) and PCSK9 in liver

LDL is a major cholesterol transport carrier in human blood. LDL is taken up by the cells through endocytosis via its receptor LDLR, a glycoprotein located on the surface of the cells, that undergoes lysosomal degradation. Although LDLR is expressed in all cells, plasma LDL cholesterol levels are mainly regulated by LDLR in the liver, where 80% of total LDLR are present. PCSK9 has been known to play a major role in LDL cholesterol metabolism by binding to LDLR and promoting its degradation. The LDLR and PCSK9 genes have a sterol responsive element (SRE) in the promoter region, and transcription of these genes are regulated through SREBP2. Therefore, SREBP2 activation induces

not only LDLR but also PCSK9 (Hui-xian Yang et al., 2020; Zanka, Kawaguchi, Okada, & Nagaoka, 2020). Up to now limited clinically evidenced natural compounds have been demonstrated to be targeted on LDLR and many less also on PCSK9 (Adorni, Zimetti, Lupo, Ruscica, & Ferri, 2020). The alkaloid berberine, used in nutraceuticals and in herbal medicine, is an inducer of hepatic LDLR and 500 mg dose proved its effects on small trial in humans (Kong et al., 2004). Furthermore, berberine inhibits PCSK9 protein expression and counteracts the inducing effect of various statins that led an increased expression of both LDLR and PCSK9 (Adorni et al., 2020). Nevertheless efficacy of berberine still need studies due to the lack of high-quality randomized clinical trial (Mach et al., 2020).

Specifically considering PCSK9 a recent review summarized the data about natural product with the ability to interfere with this metabolic pathway and several polyphenols demonstrated at least *in vitro* and *in vivo* inhibiting properties as quercetin, resveratrol and curcumin among other (Adorni et al., 2020), nevertheless studies are needed to assess their potential usefulness and efficacy in human when administered as nutraceutical products. In minor extent some polyphenol fractions have been studied for their ability to induce LDL-R and for example cocoa, apple grapeseed, and procyanidins have been claimed for this effect nevertheless their role and efficiency need to be extensively studied (Hunter & Hegele, 2017; Kobayashi, 2019; Poli et al., 2018). Many other nutraceutical constituents indirectly increase the LDLR expression as phytosterols, dietary fibers and also the statins as the RYR (Vekic et al., 2022).

3.3. Nutraceuticals affecting bile acids (BAs) function and their reabsorption

BAs play an important role in the absorption and digestion of dietary lipids. The transport of BA between liver and intestine is referred to as the enterohepatic circulation of bile, which plays important roles in liver function, liver physiology, and metabolic regulation. BA act as detergents allowing the lipids to “dissolve” in an aqueous environment, facilitating their delivery to the brush border (Jesch & Carr, 2017; Slijepcevic & Van De Graaf, 2017). Dietary cholesterol accounts for approximately 300 mg/d, whereas biliary cholesterol is estimated to contribute 800–1400 mg/d. The liver and not the diet is therefore the primary source of cholesterol available for intestinal absorption, a point that is often underappreciated (Jesch & Carr, 2017).

Liver maintains cholesterol homeostasis and hepatocyte cholesterol is catabolized into BA and steroid hormones, secreted as is in bile, used in cell membranes or stored as cholesteryl esters. The major route by which hepatic cholesterol is eliminated is via BA synthesis through a cascade of fourteen enzymatic reactions with cholesterol 7 α -hydroxylase being the rate limiting enzyme CYP7A1 (Gunnness & Gidley, 2010). Over expression of CYP7A1 can be a strategy to increase the BA production. Beta glucan from barley are able to upregulate CYP7A1 transcription, without affecting cholesterol absorption or synthesis (Y. Wang et al., 2017). Guggulsterone, a phytosterol present in guggul gum can modulate CYP7A1. This compound strongly inhibits the human CYP7A1 gene by activation of pregnane X receptor (PXR) (Owsley & Chiang, 2003), but its effects as hypocholesterolemic agent in human are limited (Hunter & Hegele, 2017). Numerous reports have described that polyphenols increases BA excretion causing the corresponding reductions in total and LDL cholesterol in animal and *in vitro* studies (Chambers, Day, Aboufarrag, & Kroon, 2019). There are three main mechanisms by which BA excretion can be augmented by polyphenols, increased expression of CYP7A1, reduced expression of intestinal BA transporters, and changes in the gut microbiota (Chambers et al., 2019). After micelles formed by BAs have facilitated the solubilization, digestion, and absorption of lipids in the proximal small intestine, BA are reabsorbed in the distal small intestine (ileum) by the apical sodium-dependent bile acid transporter specific bile acid transporter, (ASBT) and sodium taurocholate co-transporting polypeptide (NTCP) (van de Peppel et al.,

2020). Some probiotics strain can have influence on BA metabolism influencing the deconjugation and conversion of primary to secondary BS, with an impact on cholesterol homeostasis (M. Kumar et al., 2012; T. D. T. Nguyen, Kang, & Lee, 2007; Palaniyandi, Damodharan, Suh, & Yang, 2020; Sivamaruthi et al., 2019; L. Wang et al., 2018), their potential usefulness in this area is of great interest mainly due to their limited side effects and high acceptability by consumers.

3.4. Nutraceuticals implicated in the reverse cholesterol transport (RCT)

RCT is the process responsible for cholesterol delivery from peripheral cells and tissues to the liver for secretion, representing a key mechanism by which high density lipoprotein (HDL) exerts anti-atherogenic properties. Acyl-coenzyme A: cholesterol acyltransferase (ACAT) catalyzes intracellular esterification of cholesterol and formation of cholesterol ester. Cholesterol esterification limits its solubility in the cell membrane lipids and promotes accumulation in the fat droplets within cytoplasm. Thus, normal ACAT activity prevents potentially toxic accumulation of free cholesterol in various cell membranes, like in macrophages leading foam cell formation (Chang et al., 2006). ACAT-mediated cholesterol esterification plays a part in production and release of VLDL by the liver, modulate hepatic cholesterol biosynthesis and catabolism and plasma cholesterol concentration (Vaziri & Liang, 2002).

RCT is initialized by ATP-binding cassette transporter A1 (ABCA1), that transport the excess of cholesterol from peripheral cells to lipid-free Apo A-I, resulting in nascent pre β -HDL formation (Ouimet, Barrett, & Fisher, 2019), and finally to the liver for BA synthesis and excretion. The receptor SR-BI is a physiological high-affinity receptor for HDL. It mediates the uptake of cholesteryl esters from HDL-C to hepatocytes, a process termed selective lipid uptake, thus playing a crucial role in the later stage of RCT (Ren, Jiang, & Zhao, 2018).

Several lipids and lipophilic vitamins as well as lipid soluble phytochemicals have been evaluated as potentially active compounds on RTC and a recent review summarized the most relevant findings in animal studies (Papotti, Escollà-Gil, Julve, Potì, & Zanotti, 2021). It is accepted that supplementation of Short chain Fatty Acids (SFA) increase the levels of HDL-C in humans (Astrup et al., 2020; Papotti et al., 2021) but the different fat sources used in humans suggest the need for further studies to confirm this finding. Considering mono unsaturated fatty acids (MUFA) a general increase in RTC is reported and promotion of macrophage-to-feces RCT *in vivo* (Papotti et al., 2021). Considering the poly unsaturated fatty acids (PUFA) review indicated that they strongly influences HDL metabolism in mice, rats, and hamsters with a general effect of reducing circulating levels (Papotti et al., 2021), but the most important role of such nutrients on cardiovascular health is related to the anti-inflammatory activity of omega-3 series and to the balance of intake of omega-3 omega-6 (Simopoulos, 2008). Hempseed extract (HS) with specific ratios of omega 6 PUFA and omega-3 PUFA was studied for its anti-hypercholesterolemic effects in rats and authors concluded that HS effects on cholesterol and cardiovascular diseases are mediated through redox-sensitive modulation of inflammatory pathways (Kauschal, Dhadwal, & Kaur, 2020).

Furthermore, recent studies also include the influence of microbiota in the effectiveness of omega-3 PUFA lipids as hypocholesterolemic agents. In hamster the administration of *Cucumis melo* seed oil with 71.3% polyunsaturated fatty acids increased the production of fecal short-chain fatty acids and changed microbiota composition. Thus this oil can reduce plasma cholesterol via promoting the excretion of fecal acidic sterols and modulating gut microbiota (Hao, Zhu, et al., 2020a).

One study considered intervention with 30 g of oils, rich in omega-3 alpha-linolenic acid and phytonutrients, in 126 volunteers with borderline hypercholesterolemia and revealed the association between beneficial effects on the blood lipid profile with abundance of Clostridia class in the microbiota (R. R. X. Lim et al., 2022).

4. Nutraceutical with potential usefulness in hypercholesterolemia management

Different vegetable foods have been claimed with hypocholesterolemic properties. Their main classes of secondary metabolites are summarized in Fig. 2 and can be grouped in four classes namely triterpene scaffold compounds, sulfur containing compounds, small molecular weight phenolics and high molecular weight phenolics. Different classes of polyphenols have been studied for their hypocholesterolemic properties, both non-polymeric polyphenols as well as complex tannins or procyanidins characterized by high complexity and high number of monomers will be considered. Due to the complex nature of plant foods this schematization is based on the chemical structures of the most characteristic constituents. Nevertheless, is necessary to remember that multiple compounds are always present in the plant constituents and in most of the cases act as a Phyto complex. Thus, for example the presence of phenolics in garlic or triterpene in berries cannot be forgotten, as well as the presence of fibers, fatty acids, peptides participating to the activity of the phytocomplex should be taken into account.

4.1. Phytosterols and triterpene

Phytosterols are vegetable sterols naturally occurring in vegetable oils and in smaller amounts in vegetables, fresh fruits, nuts, grains, and legumes. The most diffused are sitosterol, campesterol, and stigmasterol and they present structural similarities with cholesterol. Recently a complete review considered the phytosterols from their activity a possible clinical relevance (Salehi et al., 2021).

It was already shown in 1950 that phytosterols could lower serum LDL-C concentrations. Meta-analysis has reported that a daily intake of 2.5 g plant sterols/stanols reduced serum LDL-C concentrations up to 10% but with little or no effect on HDL-C and TG levels (Smet et al., 2012). More recent literature indicate a certain degree of heterogeneity among individuals in cholesterol lowering (Fumeron, Bard, & Lecerf, 2017; Mach et al., 2020).

Phytosterols can modulate cholesterol absorption by inhibition of cholesterol ester hydrolysis, competition with cholesterol for solubilization into mixed micelles, competition for transport across the apical membrane of enterocytes, and impaired intracellular re-esterification of cholesterol by ACAT-2 for incorporation into chylomicrons and secretion into the lymphatic system (Jesch & Carr, 2017). Absorption of dietary cholesterol esters is dependent upon hydrolysis by pancreatic cholesterol esterase (PCE) that is responsible for the hydrolysis of both cholesterol and phytosterol esters. The rate of hydrolysis of PCE is influenced by sterol structure, with cholesterol esters having the highest rate of hydrolysis, followed by sitosterol, stigmasterol, and stigmasterol esters. PCE may play a discriminatory role in the hydrolysis of sterol esters, specifically phytosterols that can compete with cholesterol for incorporation into mixed micelles (Brown et al., 2010). Furthermore, for the absorption process, cholesterol should be included in micelles, but papers reported higher affinity of phytosterols versus cholesterol for the micelles. In the presence of sufficient amount phytosterols, the cholesterol will form a separate oil phase within the intestinal lumen, making it generally unavailable for the absorption (Brown et al., 2010; Elliot D Jesch and Carr, 2017; Smet et al., 2012).

The literature up to now have evidenced that phytosterols may have some effect in cholesterol management with the mode of action related to absorption or excretion but not to *de novo* synthesis. Based on documented LDL-C lowering effect and the absence of adverse signals, and considering the doses (>2 g/day with the main meal), plant sterols/stanols may be considered as useful ingredients in functional foods as potential tools for cholesterol management (Mach et al., 2020).

Specific class of modified phytosterols are compounds indicated as γ -Oryzanol (OZ), a mixture of different ferulic acid esters with phytosterols such as campesterol, stigmasterol, or β -stigmasterol, mainly present in rice bran. The ester bond of OZ is broken down during digestion

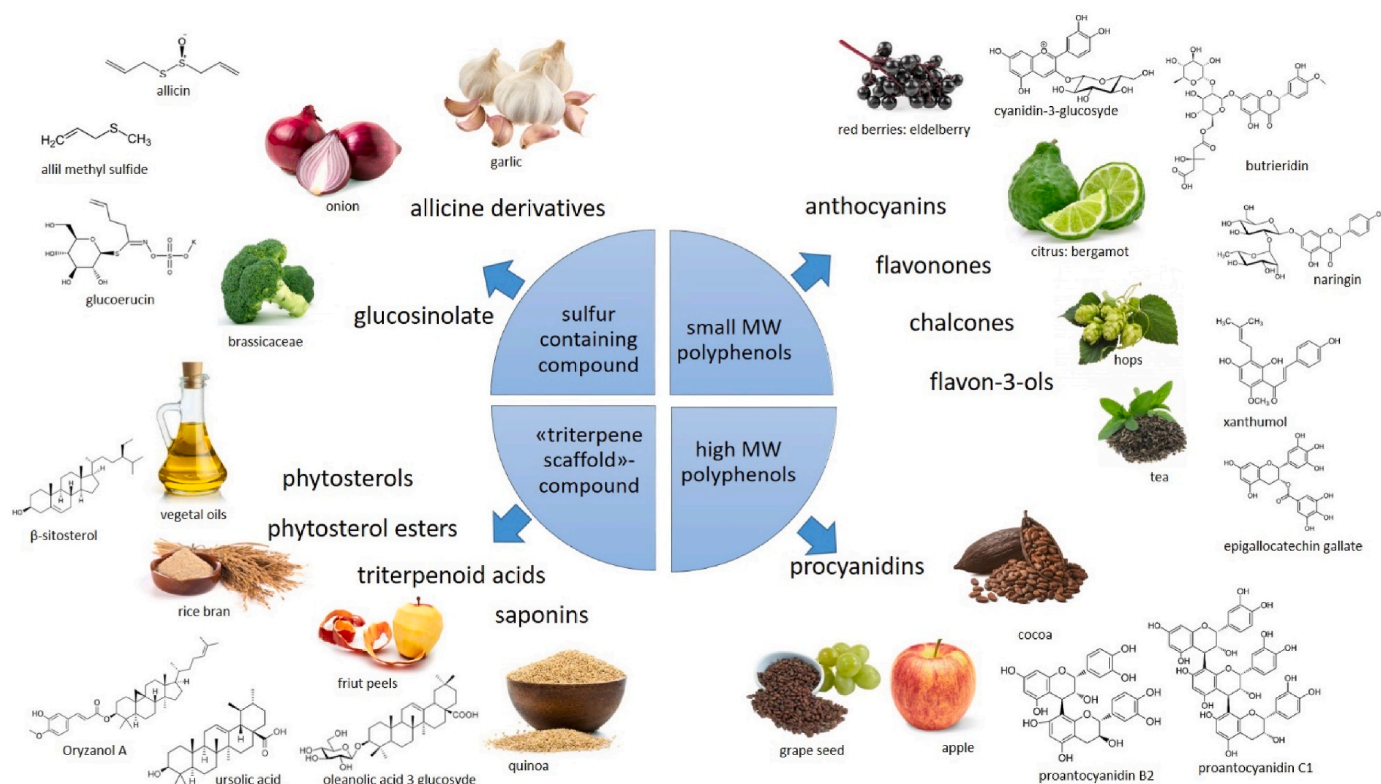


Fig. 2. Schematization of the most studied classes of plant secondary metabolites used for the management of hypercholesterolemia.

followed by phytosterols release, with subsequent beneficial effects on metabolic dysregulation. Daily intake of campesterol, stigmasterol, or β -stigmasterol could interfere with cholesterol absorption (Jesch & Carr, 2017), lower pro-inflammatory cytokine production and increase serum adiponectin level (O. Wang et al., 2015). A part of OZ is hydrolyzed in ferulic acid and plant sterols inside the body, and some OZ is absorbed as its intact form (Sawada et al., 2019). OZ significantly decreased apical uptake of cholesterol into Caco-2 intestinal cells. In rat liver, OZ inhibited HMGCoAR activity (Mäkynen et al., 2012). From a dietary point of view, present rice-based diet contains nutritional gaps mainly due to the milling process which removes healthy promoting compounds present on rice bran. Therefore, less milling, or brown rice composition is highly recommended to achieve nutritional sustainability. Brown rice contain relatively high amount of dietary fiber, moderate amount of protein, unsaturated lipid, micronutrients and several bioactive compounds like OZ useful in hypercholesterolemia control (J.-S. Lee, Sreenivasulu, Hamilton, & Kohli, 2019). Despite large research on mode of action of OZ, limited clinical trial have been published (Berger et al., 2005) thus further research are needed to assess potential usefulness in cholesterol management.

Triterpenoid and triterpenoid acids are constituents of the human diet, since they have been found in a great variety of fruits, vegetable oils and cereals. In the Western world, the individual average human consumption of triterpenes is estimated to be approximately 250 mg per day, and in the Mediterranean countries, the average intake could reach 400 mg per day (Furtado et al., 2017). One product that is rich in triterpene is *Protium heptaphyllum* resin. The neutral terpenoids α , β -amyrin have been considered as main constituents. When administered at 100 mg/kg a mixture of α , β -amyrin induced significant decreases in VLDL and LDL cholesterol and an elevation of HDL cholesterol in mice fed on a high-fat diet (HFD) (Santos et al., 2012). In a recent work, Mannino and co-workers studied the triterpenes of *Protium heptaphyllum* gum resin extract for their cholesterol-lowering potential. Results highlighted the effect of this extract on the modulation of HMGCoAR, PCSK9, LDLR,

FXR, IDOL, and PPAR on human hepatocytes demonstrating cholesterol reduction and the regulation of the expression of proteins involved in its metabolism (Mannino, Iovino, et al., 2021b). The *Protium* gum resin extract was composed by volatile monoterpenoids, non-acid and acid triterpenoids. Authors considered as most promising compounds the oleanolic, ursolic, elemenolic acids but their activities were studied only as *Protium* gum resin extract (Mannino, Iovino, et al., 2021b).

Other research paper, on the other hand, described the evaluation of hypocholesterolemic activity for some pure triterpenoids. Promising activity was reported for ursolic acid (UA), its supplementation in hamsters reduced by 15% plasma cholesterol and inhibited by 2.6–9.2% the intestinal cholesterol absorption. Authors revealed by *in vitro* experiment efficient displacement of cholesterol from micelles caused by UA. Authors also reported that UA modified the microbiota, causing a decrement in the ratio of *Firmicutes* to *Bacteroidetes*, and enhancing the growth of short chain fatty acid (SCFA)-producing bacteria in the intestine. Thus UA exert its cholesterol-lowering activity with different mechanisms and due to the ability to modulate the gut microbiota (Hao, Kwek, et al., 2020a).

The poor toxicity of UA makes this compound very attractive for the use as hypocholesterolemic agent. Metabolomic analysis revealed that in mice treated with 45 mg/kg of UA there was a modification of lipid metabolism of the liver. Authors revealed that UA alleviated the diet-induced hypercholesterolemia via the irreversible inhibition of HMGCS1, the enzyme producing the HMG-CoA. The discovery of this specific mechanism of action demonstrated the potential of UA as a novel hypocholesterolemic agent (Ma et al., 2022).

Saponins are triterpenoid compounds present in many vegetables and legumes, that present a sugar moiety linked to a hydrophobic aglycone called sapogenin. This class of compounds were studied for their potential health benefits in the treatment of obesity and in particular in cholesterol absorption (Marrelli, Conforti, Araniti, & Statti, 2016).

Saponins and sapogenins have been studied for their effects on

hyperlipidemia since many years, and the mechanisms proposed to explain their effect, imply the formation of large, non-absorbable aggregates in the gastro-intestinal tract formed by saponin and cholesterol or saponin and BS, leading to direct or indirect lowering effect on the serum cholesterol (Milgate & Roberts, 1995; Santos et al., 2012; Vinarova et al., 2015). The influence of saponin and sapogenin on cholesterol bio accessibility have been recently studied in saponin-rich extracts from fenugreek and quinoa and their hydrolysates. Both saponin-rich extracts and pure compounds shown positive effects on lipid metabolism (Navarro Del Hierro, Casado-Hidalgo, Reglero, & Martin, 2021). The hydrolysis of saponin-rich extracts increased the activity, showing comparable or superior effect to plant sterols in cholesterol bioaccessibility. Oleanolic acid and diosgenin, tested as pure compound, did not shown strong cholesterol-reducing bioaccessibility (Navarro Del Hierro et al., 2021) suggesting that other constituents contribute to the overall activity. The effect of saponins of the non-hydrolyzed extracts, especially in the case of fenugreek, may be due to interactions with other compounds contained in extract (Navarro Del Hierro et al., 2021).

4.2. Low molecular weight polyphenols

Many different polyphenols have been studied for cholesterol modulation effect. Luteolin, curcumin, cyanidin-3-glucoside, chlorogenic acid, and catechin have been evidenced as able to inhibit the expression of NPC1L1, furthermore, luteolin, quercetin, and epigallocatechin gallate (EGCG) inhibit the transport of NPC1L1 (Kobayashi, 2019). Natural products with high concentrations of polyphenols stimulated the trans intestinal cholesterol excretion (TICE) pathway by altering the genes involved in cholesterol flux from the basolateral to the apical membrane of enterocytes (J. Hong, Kim, & Kim, 2021; S. Jeon, Kim, & Kim, 2021).

Several studies have documented the hypocholesterolemic effect of anthocyanin-rich plants *in vitro* and *in vivo* (Chamnansilpa et al., 2020; De Souza et al., 2012; S. Jeon et al., 2021; S. Liu, You, Zhao, & Chang, 2018).

Berries as whole fruits, juices, and purified extracts have been shown to lower total and LDL-C, and increase HDL-C in clinical studies in participants with elevated blood lipids, type 2 diabetes or metabolic syndrome (Basu, 2019). A recent systematic review and meta-analysis revealed that habitual intake of anthocyanins and anthocyanin-rich berries could protect against CVDs improving blood lipid profiles and decreasing circulating proinflammatory cytokines (L. Xu, Tian, Chen, Zhao, & Yang, 2021). Anthocyanin rich extract of açai berry was administrated in HFD rats and in liver the expression of the LDL-R, ABCG5, and ABCG8 genes was significantly increased by the presence of açai pulp (De Souza et al., 2012). The anthocyanin-rich fraction of *Prunus domestica* and other plants, demonstrate to inhibited pancreatic lipase and cholesterol esterase, reduce the solubility of cholesterol in artificial micelles, and significantly reduce the cholesterol uptake into Caco-2 cells (Chamnansilpa et al., 2020).

Black elderberry extract rich in antocyanins significantly decreased the mRNA and protein levels of genes for cholesterol absorption, such as NPC1L1 and ABCA1, and induces genes alteration in the direction of flux cholesterol from the basolateral to apical side of enterocytes in Caco-2 model (S. Jeon et al., 2021).

Bilberry extract altered the genes for cholesterol flux from basolateral to the apical membrane of enterocytes, namely NPC1L1 and ABCA1, potentially stimulating TICE. These mechanisms support the potential usefulness of bilberry extracts in the prevention of hypercholesterolemia (J. Hong et al., 2021).

Green tea is a popular beverage worldwide rich in polyphenol, mainly catechins constituting 25–30% of total polyphenols. The most abundant compounds in green tea are epicatechin (EC), epigallocatechin (EGC), epicatechingallate (ECG) and epigallocatechin gallate (EGCG) (Khan & Mukhtar, 2007). Tea polyphenols can delay the onset or

progression of numerous diseases such as cardiovascular disorders and metabolic diseases (Imai & Nakachi, 1995; Maron et al., 2003). Recently catechins of white tea extract were studied in *in vitro* model to demonstrated their ability to improve lipid homeostasis (K. Luo et al., 2020a). White tea extract stimulated LDL-C uptake through targeting LDLR, as a consequence of the activation of sterol regulatory element-binding protein 2 (SREBP2) and peroxisome proliferator-activated receptor δ (PPAR δ) (K. Luo et al., 2020b). EGCG, one of the predominant constituents found in green tea, suppresses PCSK9 production by promoting nuclear FoxO3a, and reducing nuclear HNF1 α , resulting in up-regulated LDLR expression and LDL uptake in hepatocytes. Thereby inhibiting liver and circulating PCSK9 levels, and ultimately lowering LDL-C levels (Cui et al., 2020). In another paper, authors reported that EGCG activates LDLR expression via 67LR-independent pathway in HepG2 cells (Zanka et al., 2020). A systematic review and meta-analysis of randomized controlled trials highlighted that green tea consumption lowers LDL cholesterol and TC (R. Xu, Bai, Yang, & Chen, 2020) indicating the role of this beverage in lipid control.

The non-Camellia tea, hawk tea, made from buds or leaves of *Litsea coreana* Levl. Var. lanuginosa is very popular in southwestern China and was studied for its hypocholesterolemic properties. Hawk tea extract was active targeting two key axes in cholesterol metabolism. It inhibited NPC1L1-mediated free cholesterol uptake, thereby inducing the transcription of LDLR downstream of SREBP2 pathway (J. Feng et al., 2019). On the other hand, HTE inhibits MTP- and APOB-mediated very-low-density lipoprotein (VLDL) production by suppressing hepatocyte nuclear factor 4 α (HNF4 α) (J. Feng et al., 2019). EGCG, kaempferol and quercetin were identified as the bioactive components responsible for the effects on the NPC1L1-SREBP2-LDLR axis and HNF4 α /APOB axis, respectively. Hawk tea works as a previously unrecognized cholesterol-lowering agent in a multi-target and multi-component manner (J. Feng et al., 2019).

Another phenolic compound, quercetin, a flavonoid mostly found in onions, grapes, berries, cherries, broccoli, and citrus fruits (Anand David, Arulmoli, & Parasuraman, 2016), have multiple action on cholesterol-related metabolism. Recent meta-analysis reported that quercetin supplementation reduced total-cholesterol, LDL-cholesterol, among patients with metabolic syndrome or related disorders (Tabrizi et al., 2020). Quercetin is able to inhibit cholesterol absorption by Caco-2 cells and human embryonic kidney 293 T cells expressing NPC1L1 (Nekohashi et al., 2014) and at the same time induce of RCT (Ren et al., 2018). Authors investigated the effect of quercetin in HepG2 cell model and in C57BL/6 mice, and this flavonoid enhances SR-BI expression by stimulating the PPAR γ /LXR α pathway (Ren et al., 2018). Another work investigated the role of quercetin against atherosclerosis (AS) in apoE $^{-/-}$ mice by regulating the expression of PCSK9, cluster of differentiation 36 (CD36), peroxisome proliferator-activated receptor γ (PPAR γ), liver X receptor α (LXR α) and ABCA1. Mice in the model group had higher serum TC, LDL-C, oxLDL, TNF- α and IL-6 levels, and lower IL-10 levels. The protein expression levels of PCSK9 and CD36 were increased, while those of PPAR γ , LXR α and ABCA1 were decreased in the aortas and livers of the model group mice. Treatment with quercetin attenuated all these effects, demonstrating that quercetin prevents the development of atherosclerosis in apoE $^{-/-}$ mice by regulating the expression of PCSK9, CD36, PPAR γ , LXR α and ABCA1 (Jia et al., 2019). Due to its large diffusion in the diet, the daily intakes of quercetin can be significant to exert its action on lipid metabolism. Many studies considered the purified quercetin, but investigations are also needed considering the compound present in different food matrix and the possible interaction or synergies with other phytoconstituents, as we reported for the example of tea. In many vegetables the presence of quercetin is more abundant in glycosidic form. A common glycosylated quercetin derivative, quercetin-3-glucoside (Q3G) inhibits PCSK9 secretion, stimulated LDLR expression, and enhanced LDL-C uptake (Mbikay, Sirois, Simoes, Mayne, & Chrétien, 2014). Same researchers evaluated the effect of Q3G in HCD-fed mice, and results highlights that

Q3G attenuates the increase in plasma cholesterol and insulin, accentuates the decrease in plasma PCSK9, and increases hepatic and pancreatic LDLR and PCSK9 (Mbikay et al., 2018).

A series of thirty-four polyphenols were studied for their ability to inhibit cholesterol uptake by Caco-2 cell monolayer cultures (Nekohashi et al., 2014). Authors selected as most promising compounds luteolin and quercetin due to their significant inhibitory activity and due to their ubiquitous presence in herbs and edible plants. Structures of the two flavonoids are very similar differing only for the absence of hydroxy group in position 3 in luteolin. Luteolin and quercetin inhibited cholesterol absorption in the *in vitro* model of Caco-2 cells and human embryonic kidney 293 T cells directly affecting cholesterol uptake mediated by NPC1L1 (Nekohashi et al., 2014). Authors demonstrated that cholesterol levels decreased in rats fed with luteolin or quercetin, than control group concluding that luteolin and quercetin reduce blood cholesterol levels by inhibiting intestinal cholesterol absorption (Nekohashi et al., 2014). Details on the mode of action of luteolin in this regard were investigated using *ex vivo* approach and result revealed that luteolin inhibited the expression of NPC1L1 by decreasing the expression of SREBP2 and HNF4a and by inhibiting SREBP2 access to the binding elements in the promoter region. Authors concluded that daily intake of polyphenol, such as luteolin, may prevent the increase in blood cholesterol (Ogawa, Yamanashi, Takada, Abe, & Kobayashi, 2017).

Further research demonstrated that luteolin upregulated the expression of liver X receptor (LXR) α , ABCG1, and SRB1, in HepG2 hepatocytes. Luteolin-stimulated expression of ABCG1 and SRB1 was reversed by inhibitory compound of LXR α . Luteolin administration also upregulated the expression of ABCG1, and SRB1 as well as cholesterol 7 α -hydroxylase (Cyp7a1) in the liver of diet-induced obese mice. Thus, luteolin was able to decrease the level of blood cholesterol and non-high-density lipoprotein cholesterol in obese mice (Park et al., 2020).

Bergamot flavonoids are claimed to modulate lipid profile, and their activity could be related to the regulation of several metabolic enzymes, expressed in the liver, blood and endothelial cells (Janda et al., 2016; Lamiquiz-Moneo et al., 2020). Neohesperidin, neohesperidin, naringin, melitidin and brutieridin represent more than 95% of Bergamot Polyphenol Fraction (BPF), while the remaining 5% is mainly due to rhoifolin, diosmin, poncirin and other. Many suggested that BPF flavonoid are responsible for the pharmacological effects, and brutieridin and related compounds were claimed to act as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, thereby mimicking statins action (Janda et al., 2016).

It is possible that HMGCoAR inhibition *in vivo* is a complex effect of cooperation of AMPK inhibitory properties of naringin with other properties of flavonoids, including cAMP phosphodiesterases inhibition, ROS scavenging and other molecular and physiological effects (Janda et al., 2016). Up to now, BFE constituents' action is exert not directly in the cholesterol synthesis but by different pathways. Naringin is glycosidic flavonoid common in citrus species and largely present in grapefruit (*Citrus paradisi*) and also in Bergamot. The hypocholesterolemic effect of naringin was assessed in male rabbits were fed 0.5% high-cholesterol diet or high-cholesterol diet supplemented with either 0.05% naringin or 0.03% lovastatin for 8 weeks (S.-M. Jeon, Park, & Choi, 2004). Naringin and lovastatin contributed to hypocholesterolemic action via down-regulated ACAT activity and higher excretion of fecal sterols in response to high-cholesterol feeding. Also, naringin supplement preserved tissue morphology from high cholesterol diet tissue damages (S.-M. Jeon et al., 2004).

Nevertheless, the mechanism of action of the BPF was not still fully understood, and to fill this gap a study recently investigated bergamot fruit extract (BFE) and its principal constituents, neohesperidin, naringin, neohesperidin, melitidin, and brutieridin for their ability to regulate cholesterol levels in HepG2 and Caco-2 cells. Results shown that BFE and its constituents did not directly inhibit HMGCR activity but may downregulate HMGCR expression (Huang, Tocmo, Nauman, Haughan, & Johnson, 2021). Authors concluded that BFE can exert its

hypocholesterolemic activity through several mechanisms, including cholesterol biosynthesis in HepG2 cells and cholesterol cellular transport in Caco-2 (Huang et al., 2021). In 2020 the first systematic review aiming to explore the effect of bergamot in lipid profile in humans was published showing that clinical studies suffer of heterogeneous experimental design and scientific quality. Further issue was related to the form of administered bergamot preparation varying from purified compound to dried extracts, thus evidencing significant difference in doses and type of administered constituents. Thus further studies are needed to assess its potential usefulness (Lamiquiz-Moneo et al., 2020).

One of the most common constituents in citrus is naringin and this compound is able to decrease the serum and liver cholesterol levels by 24.04 and 28.37% in ApoE $^{-/-}$ mice fed with a high-fat diet (F. Wang, Xu, Li, & Zhang, 2020a). Nontargeted metabolomics showed that naringin modulated the hepatic levels of cholesterol derivatives, increasing the excretion of BA and neutral sterols (F. Wang, Xu, et al., 2020a). Naringin is considered to be largely resistant to enzymatic breakdown in the stomach and small intestine and, thereby, mainly reach the colon intact (X. Guo, Li, Guo, & Li, 2020). Naringin may influence the composition and function of the gut microbiota after oral intake, influencing the gut microbiota–liver–cholesterol axis (F. Wang, Xu, et al., 2020a). Bacteria in our gut display a range of enzymatic activities capable of acting on bile acids (Molinero, Ruiz, Sánchez, Margolles, & Delgado, 2019). BAs can suffer several microbial-mediated transformations including deconjugation, carried out by bile salt hydrolases that hydrolyze the amide bond, and transformation of primary deconjugated BAs into secondary BAs mainly by a 7 α -dehydroxylation (Molinero et al., 2019). Naringin modulated the abundances of bile salt hydrolase- and 7 α -dehydroxylase-producing bacteria, promoting BA synthesis from cholesterol by upregulating CYP7A1 via suppression of the FXR/FGF15 pathway. In addition, naringin facilitated RCT by downregulating PCSK9/IDOL (F. Wang, Xu, et al., 2020a).

There is overwhelming evidence that different flavonoids can activate AMPK, both *in vitro* and *in vivo* as a result of dietary supplementation with flavonoids in animal and human studies (Janda et al., 2016). The molecular basis of phytochemicals with emphasis on their ability to control intracellular signaling cascades of AMP-activated kinase (AMPK) responsible for the inhibition of adipogenesis was investigated in several works (Hwang et al., 2005; C. G. Lee, Koo, & Kim, 2015).

Other classes of flavonoids such as the soy isoflavone genistein have been reported to possess therapeutic effects for obesity, diabetes, and cardiovascular diseases (Yamagata & Yamori, 2021). In HepG2 cell line, genistein at dosage of more than 1.00 μ M was able to increase the intracellular cholesterol levels by up regulating SREBP-2/LDLR/HMGCoAR pathway and suppressing PPAR γ /LXR α /ABCA1 pathway (Lu, Zheng, Yin, & Jiang, 2019). The non-protein constituents of soy have been evaluated for CVD risk factors such as hypertension, hyperglycemia, inflammation, and obesity beyond cholesterol lowering (Dan Ramdath, Padhi, Sarfaraz, Renwick, & Duncan, 2017). The available evidence suggests that non-protein soy constituents can improve markers of cardiovascular health however, additional studies are required to independently elucidate these effects (Dan Ramdath et al., 2017). Genistein, daidzein and glycitein have been claimed to act as HMGCoAR inhibitors while peptides have been considered as LDLR activators (Chen et al., 2011). A recent meta-analysis on ten randomized placebo-controlled trials evaluated the impact of soy isoflavone on plasma levels in clinical trials but did not demonstrate any significant effect (Simental-Mendía et al., 2018). Several other reviews discuss the effects of soy supplementation dealing with isoflavone, peptides and proteins suggesting lipid lowering activities (Dan Ramdath et al., 2017; Simental-Mendía et al., 2018; Taku et al., 2007; Wilson, Meservey, & Nicolosi, 1998; Yamagata & Yamori, 2021). Thus, the literature data related to soy compounds and hypocholesterolemic effects is not univocal suggesting the need for further research.

Spices not only make our food palatable, but also give health

beneficial effects when used in judicious quantities. Curcumin and curcuminoids are contained in *C. longa* are used as spice, food supplement, in different food preparation and are contained in many foods as food additive or natural colorant. Efficacy of oral curcuminoid fraction were tested in high-cholesterol fed rats and a significant decrease in total plasma cholesterol and LDL-C but an increase in HDL-C was observed when compared with rats that were fed a high-cholesterol diet alone. The results a significant increase in the expression of CYP7A1, hemoxygenase 1, and LDLR but a significant decrease in HMGCoAR level when compared with rats fed a normal or high-cholesterol diet, showing that turmeric prevents hypercholesterolemia and the formation of fatty liver by the modulation of expressions of enzymes that are important to cholesterol metabolism (Yiu et al., 2011). *In vitro* study on Caco2 cells revealed that Curcumin inhibits cholesterol uptake through suppression of NPC1L1 expression in the intestinal cells (D. Feng, Ohlsson, & Duan, 2010). The same authors validate the results in a *in vivo* model in hamsters demonstrating that curcumin act by suppressing SREBP-2 and down-regulating NPC1L1 expression, explaining the hypocholesterolemic effects of curcumin (D. Feng, Zou, Zhang, Li, & Lu, 2017).

The potential mechanistic role of curcumin related to intestinal microbiota and cholesterol absorption was studied in high-fat diet (HFD) hamsters with or without supplemented curcumin for 12 weeks. Curcumin significantly decreased cholesterol levels in the serum and reduced the bile cholesterol saturation index. Gut microbiota analysis via 16 S rRNA sequencing revealed that curcumin was able to increase microbiota associated with bile acid metabolism and short-chain fatty acid production. This led to up-regulate the expression of hepatic cholesterol 7- α hydroxylase and increased the synthesis of bile acids. Same authors demonstrated also that curcumin significantly down-regulated the expression of intestinal Niemann-Pick C1-like protein 1 (NPC1L1) in hamsters and reduced cholesterol absorption in Caco-2 cells. These findings demonstrated that dietary curcumin has the potential to prevent bile cholesterol supersaturation through modulating the gut microbiota and inhibiting intestinal cholesterol absorption (T. Hong et al., 2022). The efficacy and safety of hypolipidemic effects of turmeric and curcumin in patients with cardiovascular risk factors was evaluated in a meta-analysis. Authors stated that curcumin may be used as a well-tolerated dietary adjunct to conventional drugs, but research is required to resolve uncertainties related to dosage form and dose (S. Qin et al., 2017).

Resveratrol (3,5,4'-trihydroxy-trans-stilbene, RSV) is a polyphenolic compound, which is present in the skin of grapes. RSV in mice fed with HFD or HCD reduced blood cholesterol levels (Pang et al., 2021). RSV undergoes rapid and extensive metabolism in enterocytes before it enters the systemic circulation, leading to a low bioavailability of <1%, and elicits its cholesterol lowering effect mainly via its interaction with the small intestine (Bird, Raederstorff, Weber, & Steinert, 2017). RSV and Glucuronide resveratrol (GRSV) its main metabolite can reduce hepatic cholesterol increasing the synthesis and efflux of bile acids and decreasing the synthesis and increasing cholesterol efflux. Authors indicate the importance to study the effects of the RSV metabolites in the future studies (Shao et al., 2016). RSV promoted *trans*-intestinal cholesterol excretion (TICE) in the intestinal perfusion test and up-regulated the expressions of ABCG5/8 and ABCB1a/b by up to 8 times in the duodenum mucosa but not in the liver. RSV also significantly downregulated the expression of intestinal NPC1L1. RSV administration increased the BA pool size but did not affect cholesterol consumption or *de novo* cholesterol synthesis. In conclusion, RSV could decrease circulating cholesterol levels through enhancing TICE and limiting cholesterol absorption via selective activation of intestinal LXR α (Pang et al., 2021).

Recent paper demonstrated the ability of xanthohumol (XN), a prenylated chalcone present in hops, to suppress NPC1L1 gene expression through downregulation of hepatocyte nuclear factor 4 α (HNF-4 α) and to inhibit cholesterol uptake in Caco-2 cells (Thang et al., 2019). XN markedly abolished lovastatin-induced NPC1L1 overexpression in

Caco-2 cells being a potential cholesterol-lowering agent and supplement for statin therapy (Thang et al., 2019). XN inhibits cholesteryl ester transfer protein (CETP) resulting in an increase in HDL levels. The inhibition CETP which catalyzed cholesterol transfer between lipoproteins, leads to an increase in HDL-cholesterol is considered to be one important anti-atherogenic target (Hirata et al., 2012). XM was compared to naringenin chalcone and this latter showed weak CETP inhibition. In addition, isoxanthohumol and naringenin drastically decreased the inhibitory activity. These inhibitory effect can be attributed to XN's prenyl group and chalcone structure (Hirata et al., 2012). Gallo et al., demonstrated the involvement of AMPK in the anti-angiogenic effects of XN on endothelial cell line. The anti-angiogenic activity of XN was more potent than epigallocatechin-3-gallate (EGCG) (Gallo et al., 2016). Other research investigated the effect of XN in preadipocytes and results showed a partially modulation of AMPK signaling pathway suggesting that XN may have potential therapeutic implications for obesity (Samuels, Shashidharamurthy, & Rayalam, 2018).

Fruits, cereals, beans, and nuts are food sources of procyanidins. Specifically PAs sources in the American diet are apples (32.0%), followed by chocolate (17.9%) and grapes (17.8%) (Gu et al., 2004; Haixia Yang, Xie, et al., 2021a). Procyanidins can be classified as monomeric, oligomeric, or polymeric variants depending on the polymerization degree (Haixia Yang, Xie, et al., 2021b) and their chemical characteristics, and analytical methods aimed at their identification and quantification in plant matrices were recently reviewed by Mannino et al. (Mannino, Chinigò, et al., 2021a). Oligomeric proanthocyanidins are currently marketed as medicinal products that target vascular disorders and are characterized by their effects on energy homeostasis (Sommella et al., 2019). Proanthocyanidins may inhibit cholesterol and BA absorption, modulate lipid-digesting cascade, with the inhibition of pancreatic α -amylase, pancreatic lipase, phospholipase A2, and decrease hepatic lipogenesis (Nie & Stürzenbaum, 2019). Under high intake of fats, proanthocyanidins induce catabolic activities by regulating enzyme activity, mainly enhancing cholesterol degradation and excretion (T. K. Wang, Xu, et al., 2020b).

Studies focusing on functional activities, dietary effects, interaction with proteins, changes occurring under gastrointestinal conditions, metabolic fate, and cytotoxic actions of individual oligomeric procyanidins are poorly developed (Toro-Urbe, Herrero, Decker, López-Giraldo, & Ibáñez, 2020). The complexity of the food matrix and the number of isomers of procyanidins in apple, cacao, grapes and other foods allow partial separation of oligomers (Toro-Urbe et al., 2020). Usually, the activity of procyanidin were evaluated testing procyanidin-rich fractions with a specific degree of polymerization which imply a mixture of very similar chemical structures closely eluting in chromatographic systems (Bombai et al., 2017; Sugiyama et al., 2007).

Cocoa catechins and oligomeric procyanidins have been studied for their hypocholesterolemic effect. Cocoa powder supplementation significantly lowered plasma cholesterol concentrations, and significantly increased fecal cholesterol and total BA excretion in rats compared to control group (Osakabe & Yamagishi, 2009; Yasuda et al., 2008). Micellar solubility of cholesterol *in vitro* was significantly lower in the presence of procyanidin B2 (dimer), B5 (dimer), C1 (trimer) and A2 (tetramer), which are the main components of polyphenol extract from cocoa powder (Yasuda et al., 2008). Beneficial effects of dark chocolate/cocoa product consumption on LDL were reported in clinical trials (Tokede, Gaziano, & Djoussé, 2011). Thus, cocoa derived PAC can play a role in the cholesterol levels control but correct information should be clarified to population avoiding misinformation, considering that chocolate is a hyper caloric food and its consumption should be moderate.

Easy to prepare, convenient to consume, and inexpensive, apple is a fruit compatible with modern lifestyles. Even if apple constituents are well described and characterized from a chemical point of view

(Kalinowska, Bielawska, Lewandowska-Siwkiewicz, Priebe, & Lewandowski, 2014; Oszmiański, Lachowicz, Gławdel, Cebulak, & Ochmian, 2018; Sut, Zengin, Maggi, Malagoli, & Dall'Acqua, 2019; Waldbauer, McKinnon, & Kopp, 2017), the role of highly polymeric procyanidins, which are major non-absorbable flavonoids, in the biological effects of apple is not completely understood. Cholesterol modulation effect by apple procyanidins were exert in liver cell homeostasis. Polyphenolic extract apple, with abundant PACs, limits cholesterol production by diverting necessary materials citrate and acetyl-CoA to Krebs's cycle (Sommella et al., 2019). The whole process is based on the reprogramming of hepatic cell metabolism and promoting mitochondrial respiration instead (Sommella et al., 2019). From a dietary point of view, current evidence proved that daily assumption of two apple is able to lower serum cholesterol and improve cardiometabolic biomarkers in mildly hypercholesterolemic patient in a clinical trial (Koutsos et al., 2020; Tenore et al., 2016). The effect of daily apple consumption on plasma cholesterol levels is dependent on the kind of apple cultivar and its polyphenolic compositions (Tenore et al., 2016), that was mainly related to the proanthocyanin content. Recently a complete review on the proanthocyanidin's effect summarized their action for lipid disorders suggesting several mechanism, as decreased intestinal chylomicron secretion and lipid absorption, repressed hepatic lipogenesis, and LDL secretion and adjust triglyceride, lipoprotein, and cholesterol concentrations *in vitro* and *in vivo* (Nie & Stürzenbaum, 2019). PACs with a degree of polymerization >4 reach the colon almost intact where they are degraded into phenolic acids by gut bacteria and absorbed into the circulation, where they may contribute to systemic health-promoting properties (Kawabata, Yoshioka, & Terao, 2019).

Grape seeds extract (GSPE) is a rich source of polyphenols, as monomeric catechin and epicatechin, gallic acid and polymeric and oligomeric PACs. GSPE is not strictly considered a food, and usually are administrated as food supplement. GSPE effect on oxidative stress, inflammation and metabolic syndrome (MeS)-related disorders such as obesity, diabetes and cardiovascular risk disease *in vivo*, was studied rising attention for its health promoting properties (Rodríguez-Pérez, García-Villanova, Guerra-Hernández, & Verardo, 2019). GSPE supplementation was investigated for the effects on cholesterol-regulating enzymes gene expression, *in vivo* model (Jiao, Zhang, Yu, Huang, & Chen, 2010). Results affirmed that supplementation of 0.5% or 1.0% GSPE could decrease plasma total cholesterol and triacylglycerol level. Analyses demonstrated that GSPE did not affect SREBP2 and LDLR however, increased mRNA of HMGCoAR. Most importantly authors concluded that the hypocholesterolemic activity of GSP was most likely mediated by enhancement of BA excretion and up-regulation of CYP7A1 (Jiao et al., 2010). Furthermore, other *in vitro* and *in vivo* experiments demonstrated that GSPE PACs modulates Fxr-dependent intestinal BA transporter expression, leading to increased fecal BA excretion and increased hepatic biosynthesis increasing hepatic Cyp7a1 (Heidker, Caiozzi, & Ricketts, 2016). GSPE was efficient in the increase of RCT and *Trans*-intestinal Cholesterol Excretion (TICE), via intestine specific LXR α activation, suggesting the simultaneous interaction with multiple cholesterol-regulating enzymes (Ricketts & Ferguson, 2018). Literature related to the supplementation of GSPE in humans was recently reviewed. Meta-analysis demonstrated that GSPE intake significantly reduced TC, LDL cholesterol, triglycerides, and C-reactive protein levels, but did not affect HDL cholesterol levels, and anthropometric measurements (Asbaghi et al., 2020). Meta-analysis reported that GSE supplementation favorably affect serum levels of LDL and TAG concentrations, but it did not affected total- and HDL-cholesterol concentrations (Anjom-Shoae, Milajerdi, Larijani, & Esmailzadeh, 2020). Another meta-analysis concluded that GSPE does not exerted a favorable effect on lipid profile in humans but a significant reduction of plasma levels of LDL-C and oxLDL-C was observed with a daily grape polyphenol supplementation >400 mg/day provided by whole grape products (i.e., pomace) (Lupoli et al., 2020).

The final consideration about polyphenols is that despite the large

amount of study and clinical trials results are still inconclusive due to different extract/product composition, different doses, length of the treatment and in general design of the trial. On the other hand, large diffusion of this class of compound points out the safety and lack of side effect in different cluster of population.

Garlic is used in numerous forms as extracted oil, powdered, or raw garlic. Dietary sulfur intake mostly originated from methionine and cysteine from protein, but alliaceous and cruciferous vegetables contributed up to 42% of total sulfur intake (Doleman et al., 2017). Allium vegetables, such as onions, leeks and garlic, contains alk(en)yl cysteine sulfoxides, S-allyl cysteine, allicin derivatives (Ramirez, Locatelli, González, Cavagnaro, & Camargo, 2017), while cruciferous vegetables, such as cabbages, kales and broccoli contains glucosinolates. A meta-analysis suggested the significant role of different garlic preparations in hypercholesterolemia (Sun, Wang, & Qin, 2018). In rat hepatocytes S-Alk(en)yl cysteines derivatives water-soluble organosulfur compounds inhibited cholesterol synthesis by deactivating HMGCoAR via enhanced phosphorylation, but not changing levels of mRNA or the amount of the enzyme (Liu & Yeh, 2002). Current research suggests that glucosinolates exert several health promoting effects but their action for control cholesterol is not well established (Connolly et al., 2021; Du, Fan, & Li, 2021). Glucosinolates are inactive biologically in the organism but are hydrolyzed by the enzyme myrosinase released as a result of chewing, leading to the formation of active derivatives such as isothiocyanates and indoles (Esteve, 2020). Literature related to sulforaphane, one of the most studied isothiocyanate, reported new insights concerning preclinical strategies for treating diseases including obesity as well as cardiovascular disease (Du et al., 2021). Sulforaphane induced AMPK phosphorylation in adipose tissue and decreased the activities of acetyl-CoA carboxylase and HMGCoAR when administered in high-fat diet (HFD)-induced obesity C57BL/6 N mice (Choi et al., 2014). Supplementation in high fat diet C57BL/6 J mice of benzyl isothiocyanate and phenethyl isothiocyanate suppressed the expression of LXR α , SREBP1c, stearoyl-CoA desaturase 1, fatty acid synthase, and acetyl-CoA carboxylase in both epididymal adipose and liver tissues (Chuang et al., 2019). Findings indicate that glucosinolate derived compound ameliorate HFD-induced obesity but there are limited data related to cholesterol control. A summary of the most significant secondary metabolites useful for cholesterol management is reported in Table 1.

4.3. Fibers

Food sources of soluble fiber include vegetables such as carrots, broccoli, onion, and artichokes, and fruits including bananas, berries, apples, and pears, as well as legumes, oats, and barley. Soluble fibers include viscous fibers such as β -glucans, fructans (inulin, fructooligosaccharides), gum, pectin, mucilage, and non-viscous fibers such as hemicellulose. Soluble fibers absorb water, leading to gel formation, which increases food transit time, delays gastric emptying, decreases nutrient absorption, and slows digestion. Soluble fibers have been shown to lower blood cholesterol by several mechanisms (Ghada A. Soliman, 2019). Dietary intervention can be performed using dietary fiber as a substitute for saturated fat to maximize the effects of low-fat diet on LDL-C levels, and to minimize the untoward effects of a high-carbohydrate diet on other lipoproteins. A fat modified diet that provides 25–40 g per day of total dietary fiber, including 7–13 g of soluble fiber, is well tolerated, effective, and recommended for plasma lipid control (Mach et al., 2020; Poli et al., 2008).

Several studies have shown a positive relationship between diets rich in soluble dietary fibers (SDF) such as β -glucan, pectin, guar gum and psyllium, and reduced serum cholesterol. Three major biological mechanisms have been proposed to explain the cholesterol-reducing effects of SDF, prevention of bile salt (BS) re-absorption from the small intestine leading to an excess fecal BS excretion; reduced glycemic response leading to lower insulin stimulation of hepatic cholesterol synthesis; and physiological effects of fermentation products of soluble

Table 1
Plant derived compounds with potential usefulness on hypercholesterolemia.

Food and nutraceutical	Active ingredient	Targets	doses	references
Vegetable oils	Phytosterols	Inhibition of cholesterol ester hydrolysis Competition with micelles formation and transport ACAT-2 down regulation (<i>in vivo</i> model, Hamster; <i>in vitro</i>)	2–5 g/day (Mach et al., 2020)	Jesch and Carr (2017) (Field, Born, & Mathur, 2004) (Jesch, Seo, Carr, & Lee, 2009) (Dumolt & Rideout, 2017; Salehi et al., 2021)
Oryza sativa Rice bran	γ -Oryzanol	No alteration of micelles formation <i>in vitro</i> induction HMG-CoA R in rat model	50 and 800 mg/die (Berger et al., 2005)	Mäkynen et al. (2012)
Vegetable peels, <i>Protium heptaphyllum</i> gum resin, fruits	Triterpene acids, Ursolic acid	modulation of HMGCR, PCSK9, LDLR, FXR, IDOL, and PPAR on human hepatocytes	300/500 mg/die (Geerlofs, He, Xiao, & Xiao, 2020)	(Hao, Kwek, et al., 2020b; Mannino, Iovino, et al., 2021b)
Fenugreek and quinoa	Saponins	inhibited pancreatic lipase on isolated enzyme reduction cholesterol absorption (simulated <i>in vitro</i> digestion)	50 g of quinoa (Atefi, Mirzamohammadi, Darand, & Tarrahi, 2022)	Navarro Del Hierro et al. (2021)
Different Red berries	cyanidin-3-glucoside, extracts rich in anthocyanin	inhibit the expression of NPC1L1, downregulation of the gene and protein expression of NPC1L1, ACAT2, and MTP, and the upregulation of gene and protein expression of ABCG5 and ABCG8 in rat intestines inhibited pancreatic lipase and cholesterol esterase, reduce the solubility of cholesterol in artificial micelles, reduce the cholesterol uptake into Caco-2 cells	100–600mg/die (Wallace, Slavin, & Frankenfeld, 2016)	Kobayashi (2019) (S. Liu et al., 2018) Chamnansilpa et al. (2020)
Tea, and other sources	epigallocatechin gallate	inhibit the transport of NPC1L1 modulation NPC1L1- SREBP2- LDLR axis suppresses PCSK9 production by promoting nuclear FoxO3a, and reducing nuclear HNF1 α , resulting in up-regulated LDLR expression and LDL uptake in hepatocytes activates LDLR expression via 67LR-independent pathway	107 and 856 mg/die (Momose, Maeda-Yamamoto, & Nabetani, 2016)	Kobayashi (2019) (J. Feng et al., 2019) Cui et al. (2020) Zanka et al. (2020)
Tea, onions, grapes, berries, cherries, broccoli, and citrus fruits	quercetin	inhibit the transport of NPC1L1 downregulation HNF4 α -MTP/APOB axis, decreasing the production of very-low-density lipoprotein increased the expression level of SR-BI in HepG2 cells, reverse cholesterol transport induction protein expression levels of PCSK9 and CD36 were increased, while PPAR γ , LXR α and ABCA1 were decreased in the aortas and livers in mice	≥ 250 mg/day (W. Guo, Gong, & Li, 2019)	Nekohashi et al. (2014) (J. Feng et al., 2019) Ren et al. (2018) Jia et al. (2019)
Different fruits, vegetables, infusion plants	quercetin-3-O-glucoside	inhibits PCSK9 secretion, stimulated LDLR expression, and enhanced LDL-C uptake <i>in vitro</i> (hepatocytes)	Not reported	(Mbikay et al., 2014, 2018)
Different fruits, vegetables, infusion plants	Luteolin	Inhibit the expression and the transport of NPC1L1 decreasing the expression of SREBP2 and HNF4a (<i>in vitro</i> caco2 cells, <i>in vivo</i> rats)	Not reported	(Nekohashi et al., 2014; Ogawa et al., 2017)
<i>Curcuma longa</i>	Curcumin and curcuminoids	Inhibit the expression of NPC1L1 (Caco2 cells) increase in the expression of CYP7A1, hemeoxygenase 1, LDL, decrease in HMG CoA R level (<i>in vivo</i> in rats)	0.5–2 g/die (L. Qin, Kang, & Wang, 2016)	Kobayashi (2019) Yiu et al. (2011)
Citrus bergamia fruit	polyphenol bergamot fraction	decreased HMGCR levels and increased AMP-kinase phosphorylation (HepG2 and Caco-2 Cells)	0.5–2 g/die of bergamot extracts (C. Nauman & J. Johnson, 2019)	Huang et al. (2021)
Citrus bergamia fruit	brutieridin	reduction in cholesterol uptake and decreased the level of NPC1L1 (HepG2 and Caco-2 Cells)	0.5–2 g/die of bergamot extracts (C. Nauman & J. Johnson, 2019)	Huang et al. (2021)
Citrus species fruit	naringin	down-regulated ACAT activity and higher excretion of fecal sterols in response to high-cholesterol feeding modulated the hepatic levels of cholesterol derivatives, increasing the excretion of bile acids and neutral sterols. promoted bile acid synthesis from cholesterol by upregulating CYP7A1 via suppression of the FXR/FGF15 pathway. Facilitated reverse cholesterol transport by downregulating PCSK9/IDOL (<i>in vivo</i> rabbits)	1 g/die (Alam, Kauter, & Brown, 2013)	(S.-M. Jeon et al., 2004) (F. Wang, Xu, et al., 2020)
Glycine max seeds, soy	Genistein	up regulating SREBP-2/LDLR/HMGCR pathway and suppressing PPAR γ /LXR α /ABCA1 pathway (<i>in vitro</i> Hep G2 cells)	100 mg die (Amerizadeh, Asgary, Vaseghi, & Farajzadegan, 2022)	Lu et al. (2019)
<i>Vitis vinifera</i> berry	Resveratrol	decrease circulating cholesterol levels through enhancing intestinal excretion and limiting cholesterol absorption via selective activation of intestinal LXR α : upregulated the expressions of Abcg5/8 and Abcb1a/b in the duodenum mucosa but not in the	50–3000 mg/die resveratrol (Cao, Liao, Xia, Wang, & Sun, 2022)	Pang et al. (2021)

(continued on next page)

Table 1 (continued)

Food and nutraceutical	Active ingredient	Targets	doses	references
Humulus lupulus, Hops cones	xanthohumol	liver. downregulated the expression of intestinal NPC1L1 (<i>in vitro</i> caco2 cells, <i>in vivo</i> mice) to suppress NPC1L1 gene expression through downregulation of hepatocyte nuclear factor 4 α (HNF-4 α) and inhibits cholesterol uptake in Caco 2 cells. Inhibition of cholesteryl ester transfer protein (CETP)	12 mg/die (Neumann, Frank, Venturelli, & Egert, 2022)	(Hirata et al., 2012; Thang et al., 2019)
Apples, chocolate and grapes	procyanidins	inhibit absorption of cholesterol and bile acids, modulate lipid-digesting cascade, with the inhibition of pancreatic α -amylase, pancreatic lipase, phospholipase A2, and decrease hepatic lipogenesis (decreased mRNA expression of fatty acid synthase and (SREBP)-1c) (<i>in vitro</i> and <i>in vivo</i>)	0.5–2.5 g/die grape or apple extract (Koutsos et al., 2020; Lupoli et al., 2020)	Nie and Stürzenbaum (2019)
Garlic	Allicin, sulfur compound	HMGCoAR deactivation (rat hepatocytes)	300 mg- 5 g of garlic or garlic powders (Sun et al., 2018)	(Liu & Yeh, 2002)

dietary fibers, mainly propionate (Gunness & Gidley, 2010). *In vivo* studies have shown that ingestion or administration of some viscous SDF results in a 35–65% excess excretion of BA/BS in the feces leading to a substantial reduction in total plasma cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) by diversion to synthesis of BA/BS (Gunness & Gidley, 2010). Soluble fibers form a viscous layer in the small intestine and by increasing gut viscosity it reduced the reabsorption of bile acids, in turn increasing the synthesis of bile acids from cholesterol (Fuller, Beck, Salman, & Tapsell, 2016).

A high level of fiber intake has health-protective effects and disease-reversal benefits (Anderson et al., 2009; Bazzano, 2008), thus considering the amount (10–30 g/die) needed for efficacy also indicated in the recent guidelines (Mach et al., 2020) the intake can be obtained with increasing serving of fiber rich foods as integral bran, not refined cereals, seeds and their derivatives. In this context the use of concentrated sources of SDF as for example beta-glucane, psyllium powder, fructans and other mucilages in food supplements of functional food can be of benefit to ensure sufficient doses (Anderson et al., 2009; Bazzano, 2008). Recent review considered in this area oat (Grundty, Fardet, Tosh, Rich, & Wilde, 2018), guar gum (N. Wang et al., 2021) as example, and authors also indicate the importance not only of the administered doses but also the way of processing and converting starting materials in food products (Henrion, Francey, L  , & Lamothe, 2019). Consumption of specific dietary ingredients, such as dietary fibers and prebiotics, is an avenue by which the microbiota can be positively modulated (Korcz et al., 2018). Polysaccharide bio-transformations by microbiota may affect the production and ratio of different short-chain fatty acids (SCFA), as well as the deconjugation and conversion of primary to secondary BS, with an impact on cholesterol homeostasis (Silva et al., 2021).

Supplementation with dietary fibers can beneficially alter the microbiota. Dietary fiber carbohydrates can be degraded in the colon by bacteria, producing SCFAs, i.e. acetate, propionate, butyrate, gases (carbon dioxide, hydrogen, methane) and water. SCFAs are an important indicator of bacterial fermentation in the colon, and serve as fuels in different tissues and may play a role in the regulation of cellular processes (Markowiak-Kope   & Sli  ewska, 2020). Dietary fibers acting as prebiotics due to their interaction with BA in the small intestine, induces the fecal loss of free BA. This stimulates the liver to synthesize new bile salts from the available cholesterol, which obviously reduces hepatic free cholesterol levels. Increased SCFA production in the caecum and colon, due to microbial fermentation of soluble fibers, can alter hepatic lipogenesis and significantly promote fecal excretion of BA. All four common SCFAs can decrease plasma cholesterol levels, but propionate has been suggested to directly inhibit hepatic cholesterol synthesis, whereas acetate stimulates lipogenesis. Moreover, propionate is an inhibitory molecule that might use acetate as a precursor for the transport into hepatocytes (Korcz et al., 2018). There is a well-established interaction and mutual role of fibers and microbiota, in fact agrarian diets high in fruit/legume fiber are associated with greater microbial

diversity (Simpson & Campbell, 2015) thus considering the complex structures of fibers and the great chemical diversity of prebiotics, as well as the impressive number of bacteria living in the gut further studies focusing on fiber-microbiota interaction will be new challenge in the next years.

4.4. Probiotics

Supplementation of diet with fermented products or lactic acid bacteria containing dairy products has shown the potential to reduce serum cholesterol levels. Several possible mechanisms for cholesterol reduction induced by probiotics have been proposed as assimilation of cholesterol by growing cells, binding of cholesterol to cellular surface, incorporation of cholesterol into the cellular membrane, deconjugation of bile via bile salt hydrolase, coprecipitation of cholesterol with deconjugated bile salts, binding action of bile by fiber, and production of short-chain fatty acids by oligosaccharides (M. Kumar et al., 2012). Probiotic consumption significantly improved the health status of hypercholesteremic patients by reducing the LDL-C, total cholesterol, triglyceride levels, and increased the HDL-C. Considering recent meta-analysis, results are controversial and depend on several factors such as probiotic strain, dose, duration of the treatment, lifestyle changes, etc. (Sivamaruthi et al., 2019; L. Wang et al., 2018). A recent review specifically considered the hypocholesterolemic effect of probiotics and authors stated that the most important mechanisms are the suppression of the reabsorption of BA and inhibition of the intestinal cholesterol absorption. Many other mechanisms are under investigation but still poorly understood (Hassan et al., 2019).

Different probiotic strains have been considered for their potential hypocholesterolemic activities. Literature supported the effects for some of the strain but obtained data are in many cases limited to *in vivo* animal studies or to limited number of patients (Jones, Martoni, Parent, & Prakash, 2012; T. D. T. Nguyen et al., 2007). Some recent examples of such probiotics are *Lactobacillus reuteri* NCIMB 30242 (Jones et al., 2012), *Lactobacillus plantarum* TAR4(P. S. Lim, Loke, Ho, & Tan, 2020), *Enterococcus faecium* Strain 132 and *Lactobacillus paracasei* Strain 201 (L. Yang, Xie, et al., 2021b), *Lactobacillus plantarum* LP3 (Ding et al., 2020), *Lactobacillus fermentum* MJM60397 (Palaniyandi et al., 2020), some of these strains have been proposed as new ingredients for food supplements targeted on hypocholesterolemia.

4.5. Protein and peptides

Hypocholesterolemic activity of peptides obtained from plant sources has gained importance in recent years. These peptides lower blood cholesterol and lipid levels. The mechanism by which they exert their effect could be the stimulation of gall bladder to secrete BA, modifying liver's lipid metabolism or regulating the receptors for hormones and cholesterol (Maestri et al., 2016; Nagaoka, 2019; Sosalagere et al.,

2022).

The most frequently occurring amino acid residues in these peptides are the hydrophobic amino acids such as leucine, tryptophan, and tyrosine. This is because hydrophobic amino acids can interact with lipids and bile compounds, and the hydrophilic residues present in the sequence contribute to cholesterol and lipid reduction by inhibiting certain enzymes (Maestri et al., 2016; Sosalagere et al., 2022).

Dietary protein have been considered in the past as potential regulator of serum cholesterol concentration and the main food sources considered have been milk, buckwheat and soy (Nagaoka, 2019). Concerning the relationship between dietary protein and lipid metabolism, it is often mentioned that dietary animal proteins produce a higher serum cholesterol concentration in rats than do vegetable proteins. Vegetable derived proteins or peptides have been considered for their hypocholesterolemic properties and in particular buckwheat proteins are considered able to act by inhibiting BA reabsorption (Chen et al., 2011; Zhang et al., 2017). Effects of tartary buckwheat protein (TBP) were investigated in hamsters. TBP were able to lower plasma TC, enhancing the BA excretion via up-regulation of hepatic CYP7A1 and inhibiting the dietary cholesterol absorption via down-regulation of intestinal NPC1L1, ACAT2 and ABCG5/8 (Zhang et al., 2017).

Soy peptides, as soystatin, are able to reduce cholesterol by different mechanisms acting by indirect mode on micelle formation as well as by directly influencing cholesterol metabolic pathways (Nagaoka, 2019). Soy derived peptides and proteins have been considered in this regard but the study have evaluated the administration of the whole soy constituents including isoflavones (Chen et al., 2011). Considering results from clinical trials, authors raised questions about the clinical significance of the hypocholesterolemic effects of soy (Dewell, Hollenbeck, & Hollenbeck, 2006). Soy lecithin was studied mainly in the '90 in human clinical trial (Oosthuizen et al., 1998) and animal model (Wilson et al., 1998). Effects of phospholipids could be attributed to their ability in reducing intestinal cholesterol absorption, enhancing biliary cholesterol excretion and modulating the expression and activity of transcriptional factors and enzymes that are involved in lipoprotein metabolism (Sahebkar, 2013). Soy lecithin was traditionally used to control lipids levels but up to now there is no convincing evidence regarding the hypocholesterolemic effect (Sahebkar, 2013).

Another legume studied for its hypocholesterolemic action is lupin. Protein fraction shown hypocholesterolemic activity similar to that of other leguminous proteins in rats (Sirtori et al., 2004). Clinical study showed that incorporation of 25 g/d of lupin protein into a variety of complex food products lowers total and LDL cholesterol, triacylglycerols in hypercholesterolemic subjects, with stronger effects in subjects with severe hypercholesterolemia (Bähr, Fechner, Kiehnopf, & Jahreis, 2015). The mechanism of action was demonstrated in detail in HepG2 cell model. Lupin peptides are able to interfere with the HMGCoAR activity, up-regulating the LDL receptor and SREBP2 proteins via the activation of PI3K/Akt/GSK3 β pathways (Lammi, Zanoni, Scigliuolo, D'Amato, & Arnoldi, 2014).

A recent paper evaluated the impact of rice bran protein hydrolysate (RBPH) on cholesterol homeostasis. The result of SDS-PAGE suggests RBPH may be resistant to digestion in the gastrointestinal tract. The RBPH modulates cholesterol homeostasis in two way, first by restricting the recycle of bile salt to the liver by inhibition of cholesterol micelles and second by inhibition of regulatory enzyme HMGCoAR in the cholesterol synthesis pathway (V. Kumar et al., 2021).

An *in vivo* study investigated the changes in cholesterol metabolism in response to whole pinto beans (wPB) and their hulls (hPB) supplemented in hamsters. The expressions of HMGCoAR and ACAT2 were significantly decreased in animals receiving wPB (by 89.1% and 63.8%, respectively) and hPB (by 72.9% and 47.7%, respectively) compared with their saturated fat diet-fed counterparts (A. T. Nguyen et al., 2019). Pinto beans remediated high cholesterol induced by high saturated fat diet by decreasing hepatic cholesterol synthesis and intestinal cholesterol absorption, effects which were partially exerted by the hulls (A. T.

Nguyen et al., 2019).

Related to the ingredients from animal origin, milk derived peptides were identified as hypocholesterolemic agents (Nagaoka et al., 2001). Lactostatin peptide from β -lactoglobulin, formed by Ile-Ile-Ala-Glu-Lys, showed to strongly influence the serum cholesterol level and exhibited greater hypocholesterolemic activity than β -sitosterol, in rats (Nagaoka et al., 2001). Authors indicated that the peptide is able to modulate extracellular signal-regulated kinase (ERK) pathway and calcium channel in CYP7A1 transactivation pathway, showing interference with BA synthesis (Chen et al., 2011). Glutamic acid and lysine amino acids appear to be crucial for the activation of CYP7A1 gene expression (Chen et al., 2011). Another peptide, β -Lactotensin (His-Ile-Arg-Leu) derived from milk β -lactoglobulin reduces serum cholesterol level via NT2 receptor, similar to neurotensin in mice (Yamauchi et al., 2003).

Cattle heart protein hydrolysate and cattle heart protein hydrolysate ultra-filtrate have shown strong hypocholesterolemic activity in rats and a novel cholesterol-lowering dipeptide (Phe-Pro, FP) have been identified and characterized from these products. FP increased fecal cholesterol, decreased ABCA1 expression in the rat jejunum and reduced cholesterol absorption in Caco-2 cells (Banno et al., 2019).

Several research papers have considered the potential role of peptides both of vegetable and animal origin as hypocholesterolemic agents. Up to date some structure activity relationships and some mechanisms of action have been identified for several peptides, nevertheless issues have limited the effective application in humans. Product suffers of poor stability being as example substrate of circulating peptidase, poor absorption and critical oral bioavailability (Lammi et al., 2019). Furthermore difficulties in production and high costs (Sosalagere et al., 2022) can be also limiting step. Finally formulation in final products can be a challenge for overcoming stability, solubility and permeability (Banno et al., 2019). The peptides due to their food derived origin, both of animal and vegetable sources, and their proteic nature appear to be highly safe and present also multiple actions being candidates as multi-functional agents that is highly attractive in cholesterol management and cardiovascular health (Lammi et al., 2019).

5. Application of food, functional foods and food supplements as complementary treatment for hypercholesterolemia management

Many studies have shown the potential activity of different classes of food constituents as useful ingredients for the preparation of foods, functional foods or food supplements (Chen et al., 2011; Chhabra et al., 2021; Chopra et al., 2022; Johnston et al., 2017; Mach et al., 2020; Nagaoka, 2019; Poli et al., 2018; Salehi et al., 2021; Scicchitano et al., 2014; Sivamaruthi et al., 2019). Due to the different nature of the constituents these active substances can be present in very different amounts in the food sources, and their efficacy for hypercholesterolemia control can be related to different amount of intake. For example, fibers should be consumed in high quantity to exert some efficacy (10–30 g/day), as well as phytosterols (2–5 g/day). On the other hands compounds belonging to the classes of polyphenols as the flavonoids of citrus or the anthocyanins have been studied for these effects considering daily intake of about 50–200 mg. This suggest that some of the ingredients are more suitable for the preparation of functional foods, as example the yogurt or milk products with phytosterols while other are more efficiently included in tablets or capsules as dried extracts of citrus or green tea. A summary of the most diffused ingredients in this area and the estimated doses available in the more common food source are presented in Table 1. The role of the food supplement can be complementary to classical therapy and to dietary intervention, currently available supplements and functional foods can effectively reduce plasma LDL cholesterol levels by about 5–25%, either alone or in combination (Poli et al., 2018).

Due to their food source many compounds present low to negligible toxicity as for example the anthocyanin that may decrease LDL

cholesterol among individuals with elevated markers, with little to no safety concerns (Wallace et al., 2016). Up to now more research in this field is also needed in fact also for very well-known compounds and diffused in several vegetable foods, as quercetin, data are non-consistent. Despite significant data on the effects of quercetin on the biological pathways of cholesterol biochemistry, evidence from clinical trials does not suggest any clinically relevant effect on cholesterol plasma levels, apart from a significant reduction of triglycerides at doses above 50 mg/day (Sahebkar, 2017). Green tea was able to lowers LDL cholesterol and TC, but not HDL cholesterol or triglycerides in both normal weight subjects and those who were overweight/obese (R. Xu et al., 2020). Soy isoflavones significantly reduced serum total and LDL cholesterol but did not change HDL cholesterol and triacylglycerol. Soy protein that contained enriched or depleted isoflavones also significantly improved lipid profiles. Reductions in LDL cholesterol were larger in hypercholesterolemic than in normocholesterolemic subject (Dewell et al., 2006).

6. Perspective and future directions

ESC/EAS guidelines suggest significant role of selected food and food supplements as a potential intervention for mildly hypocholesterolemic patients. The challenges of food industry in this area are mainly two. The first is that these products must ensure the maximum level of safety because they are used in self-administration modes. For this reason, they must present limited to negligible toxic effects and ingredients that have shown safety are in general the preferred up to now. The second is the development of products that can have significant effect on the cholesterol levels offering a tool that can be used in all the cases that cannot be eligible for conventional therapies with statins or other drugs. Fibers and prebiotics, phytosterols, probiotics can play a role in this area offering new opportunities for consumers as well as for physicians, nutritionists and dietitians. Consumers may find on the market both functional foods enriched with some of the abovementioned ingredients, as fortified yogurt with phytosterols or cereals with fibers of beta-glucane, as well as food supplements presenting a more “pharmaceutical” appearance being formulated in tablets, capsules or oral powders. The efficacy of the products is strictly related to correct administered amount of active ingredient. For example, phytosterols that need to be introduced in the diet in gram amounts are mostly presented in functional foods. On the other hand, several secondary metabolites that are present in many vegetable foods are in general consumed in low amount and the study revealed potential activity at low doses. Such compounds as for example phenols, terpenoids, sulfur containing compounds. One example on all other is the RYR, that present as active ingredient a pharmaceutical substance, lovastatin.

Considering the published literature large number of papers are available mostly for the demonstration of activity of specific compounds on molecular targets related to cholesterol level control. Also *in vivo* studies are present mostly confirming the claimed activities. Nevertheless, the clinical studies suffer of poor design or limited number of subjects or suffer of bias related to the different sources of active ingredients leading to a frequent inconsistency of data that only in few cases support an efficient control of cholesterol.

Some food can be good source of such compounds, many vegetables can be valuable source of prebiotics and fibers and correct dietary intake of such compounds can play a positive role in hypocholesterolemia control. Phytosterols are present in vegetables in so low amount that fortified sources are needed to reach correct doses. Polyphenols are largely present in the fruit and vegetables, but their bioavailability is poor and the serving number of fruits and vegetable in many cases is not sufficient to reach the doses that have been considered in the study published up to now in the field of lipid management. Recent research has pointed out the potential effects on hypocholesterolemia of several classes of phytoconstituents pointing out the potential usefulness of plant species and plant foods that up to now have not been considered in

this regard. Thus, in the next years it can be presumed that novel active ingredients will be presented on the market offering new opportunities to consumer. Thus, there is a strong rational support for the use of dietary supplements in the moderate hypercholesterolemia underlying the importance of dietary intervention. These results are in line with the data obtained in more of thirty years of research comprising both *in vitro*, *in vivo* and clinical trials. The role of companies involved in the design, production and commercialization of the cholesterol targeted food supplements is very important especially related to the improvement of functional foods and food supplements, quality, standardization and in the evaluation of the efficacy of the products evaluating the efficacy of the ingredients and the proposed combinations as well as the safety profiles in order to increase in parallel safety and effects. What can be expected for the future is an evolution of the consumer demand for foods, functional foods and food supplements with clear claim in the area of cholesterol level control with consistent data about their efficacy and safety.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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