Functional foods and dietary supplements for the management of dyslipidaemia

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Abstract | Dyslipidaemia is characterized by increased blood levels of total or LDL cholesterol and triglycerides, or decreased HDL cholesterol levels, and is a risk factor for cardiovascular disease. Dyslipidaemia has a high worldwide prevalence, and many patients are turning to alternatives to pharmacotherapy to manage their lipid levels. Lifestyle modification should be emphasized in all patients to reduce cardiovascular risk and can be initiated before pharmacotherapy in primary prevention of cardiovascular disease. Many functional foods and natural health products have been investigated for potential lipid-lowering properties. Those with good evidence for a biochemical effect on plasma lipid levels include soy protein, green tea, plant sterols, probiotic yogurt, marine-derived omega-3 fatty acids and red yeast rice. Other products such as seaweed, berberine, hawthorn and garlic might confer some limited benefit in certain patient groups. Although none of these products can reduce lipid levels to the same extent as statins, most are safe to use in addition to other lifestyle modifications and pharmacotherapy. Natural health products marketed at individuals with dyslipidaemia, such as policosanol, guggulsterone and resveratrol, have minimal definitive evidence of a biochemical benefit. Additional research is required in this field, which should include large, high-quality randomized controlled trials with long follow-up periods to investigate associations with cardiovascular end points.

All individuals at risk of cardiovascular disease (CVD) should consume a heart-healthy diet, which is low in saturated and trans fats, and high in fruits, vegetables and whole grains. Functional foods and supplements might be helpful in patients who are statin-intolerant or are reluctant to take a statin for other reasons, or in those patients who are not able to achieve LDL cholesterol targets at a maximally tolerated statin dose. Certain supplements and foods, such as soy protein, green tea, plant sterols, probiotic yogurt, marine-derived omega-3 fatty acids and red yeast rice, have been well studied in the past, and a significant literature exists on their use in this population. Other products are more novel and have only been recently examined in this context.

In this Review, we discuss the mechanism of action of well-studied and emerging functional foods and dietary supplements, as well as their safety and efficacy in managing dyslipidaemia.

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Dyslipidaemia

CVD remains a leading cause of death worldwide[1] despite being largely preventable with lifestyle management and medical treatment[2]. Risk factors for CVD include high plasma levels of total cholesterol, elevated LDL cholesterol levels, high plasma triglyceride levels, decreased plasma levels of HDL cholesterol, elevated BMI, high blood pressure, diabetes mellitus, sedentary lifestyle, an atherogenic diet and smoking[3]. Altered lipid levels are common in the adult North American population, in which the prevalence of dyslipidaemia is estimated to be ~53%[4]. The front-line therapy for the treatment of high cholesterol levels is statin medication; reduction in LDL cholesterol levels using statin therapy is associated with a significantly reduced risk of cardiovascular events and cardiovascular mortality[5]. Studies have shown that a 20% (~1 mmol/l) reduction in LDL cholesterol levels with statin therapy can reduce risk of CVD by 23–36%[6]. Unfortunately, statins can have undesirable adverse effects in some individuals, such as annoying myalgias, which can hinder medication compliance. As a result, many patients and health-care providers are looking for other ways to reduce LDL cholesterol levels such as functional foods and dietary supplements.

Cholesterol can be consumed in the diet, as it is found in foods of animal origin (meat, fish, seafood, poultry and dairy), but it can also be synthesized *de novo* in the

Key points

- Use of functional foods and dietary supplements is becoming increasingly prevalent among those individuals at risk of cardiovascular disease; however, limited clinical guidance is available for the use of safe and effective supplements
- Evidence supports the use of products such as soy protein, green tea, plant sterols, probiotic yogurt, marine-derived omega-3 fatty acids and lovastatin-containing red yeast rice in patients with dyslipidaemia
- Products such as seaweed, berberine, hawthorn and garlic might confer some limited lipid-lowering benefit in certain patient populations
- Policosanol, guggulsterone and resveratrol are unlikely to have lipid-lowering effects
- Functional foods and dietary supplements can be used in addition to pharmacotherapy to provide additional lipid lowering and could potentially reduce medication dose
- Very few long-term studies have been conducted, which has led to a paucity of information on clinical end points such as mortality and cardiac events

liver from acetyl-CoA by 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, which catalyses the rate-limiting step in this process. Dietary cholesterol is absorbed from the small intestine through Niemann–Pick C1-like protein 1 (NPC1L1) and is packaged into chylomicrons for transport to the liver, where it joins the hepatic cholesterol pool. Hepatic cholesterol is then packaged into VLDL particles and enters the circulation, where it is converted to LDL by lipoprotein lipase (LPL) and hepatic lipase. LDL particles can bind to LDL receptors (LDLR) for uptake in the liver, where they are recycled or metabolized to bile acids. High levels of circulating LDL cholesterol are a risk factor for atherosclerosis, as LDL cholesterol can deposit in the subendothelial space of arteries and become oxidized, thus triggering an inflammatory response. Accumulation of inflammatory cells and lipid deposits leads to the formation of atherosclerotic plaques that cause narrowing of arteries. This arterial constriction might become clinically apparent with a blockage that impedes blood flow; for example, if the arterial plaque ruptures and causes an obstructive clot to form. In parallel, HDL particles can transport cholesterol out of peripheral tissues (such as the vascular endothelium) and lipid-laden macrophages and back to the liver for recycling[7].

Serum triglycerides are also a biomarker of CVD risk; however, no direct mechanism by which triglycerides are atherogenic has been found; cholesterol that is carried within triglyceride-rich lipoprotein particles is the probable atherogenic entity. Triglycerides are carried in the bloodstream in chylomicrons and VLDL particles. High levels of triglycerides are often associated with low HDL cholesterol levels and are typically found in those individuals with diabetes mellitus or obesity, and those with a high dietary intake of added and/or refined sugars. Very high triglyceride levels (>10 mmol/l) are also a risk factor for pancreatitis[8].

The National Cholesterol Education Program has developed dietary and lifestyle recommendations for patients with elevated levels of cholesterol as part of their 'therapeutic lifestyle changes' (TLC) programme[9]. The TLC diet is focused on consuming a healthy overall diet and certain specific macronutrients (for example, fat). The guidelines also include recommendations to consume soluble fibre (at least 5–10 g per day), plant sterols or stanols (2 g per day) and omega-3 fatty acids from fish, but do not mention other functional foods and dietary supplements that might reduce cholesterol levels[9]. The 2014 American Heart Association/American College of Cardiology guidelines on lifestyle management to reduce cardiovascular risk focus on diets such as the Mediterranean diet but do not include recommendations on supplements, as they are not considered a 'lifestyle intervention' (REF. 10).

Functional foods and supplements

The US Department of Agriculture defines functional foods as "natural or processed foods that contain known or unknown biologically active compounds, which, in defined, effective nontoxic amounts, provide a clinically proven and documented health benefit for the prevention, management or treatment of chronic disease" (REF. 11). These functional foods can include items such as probiotic yogurt and fortified grain products. Dietary supplements are defined by the FDA as "a product intended for ingestion that contains a 'dietary ingredient' intended to add further nutritional value to (supplement) the diet" (REF. 12). Examples of dietary ingredients include vitamins, minerals, herbs, extracts, metabolites and amino acids. Use of dietary supplements is very prevalent in the USA, with an estimated 53% of adults reporting regular supplement use[13]. Of supplement users, 29% cited heart health and 19% reported maintaining healthy cholesterol levels as their reason for consuming dietary supplements[13]. Given this high prevalence of use, finding safe and effective functional foods and dietary supplements for use in this patient population is important.

Well-studied examples

Soluble fibre. Soluble fibre, found in psyllium, oats and barley, can absorb water in the gastrointestinal tract, which results in increased bulk of stools and a reduction in the intestinal transit time. Soluble fibre has the ability to bind to cholesterol and bile acids, thus inhibiting their intestinal absorption and increasing their excretion in faeces[14] (FIG. 1). Soluble fibre also undergoes some colonic fermentation to produce short-chain fatty acids, which have beneficial effects on cholesterol metabolism[15]. Studies in humans have consistently found that soluble fibre intake is associated with decreased levels of total cholesterol and LDL cholesterol. Several recent meta-analyses have shown statistically significant reductions in both total cholesterol and LDL cholesterol with soluble fibre intake[16–21]. Most studies have found no significant effects of soluble fibre consumption on triglyceride or HDL cholesterol levels[16,17,20,21]. To date, most trials conducted have been of relatively short duration (<12 weeks) and thus have not examined cardiovascular end points such as myocardial infarction or mortality[21]. To attain cholesterol-lowering effects, at least 3 g per day of soluble fibre should be consumed[16]; however, at least 10 g per day is recommended to achieve a clinically relevant reduction in levels of LDL cholesterol of 3–5%[22].

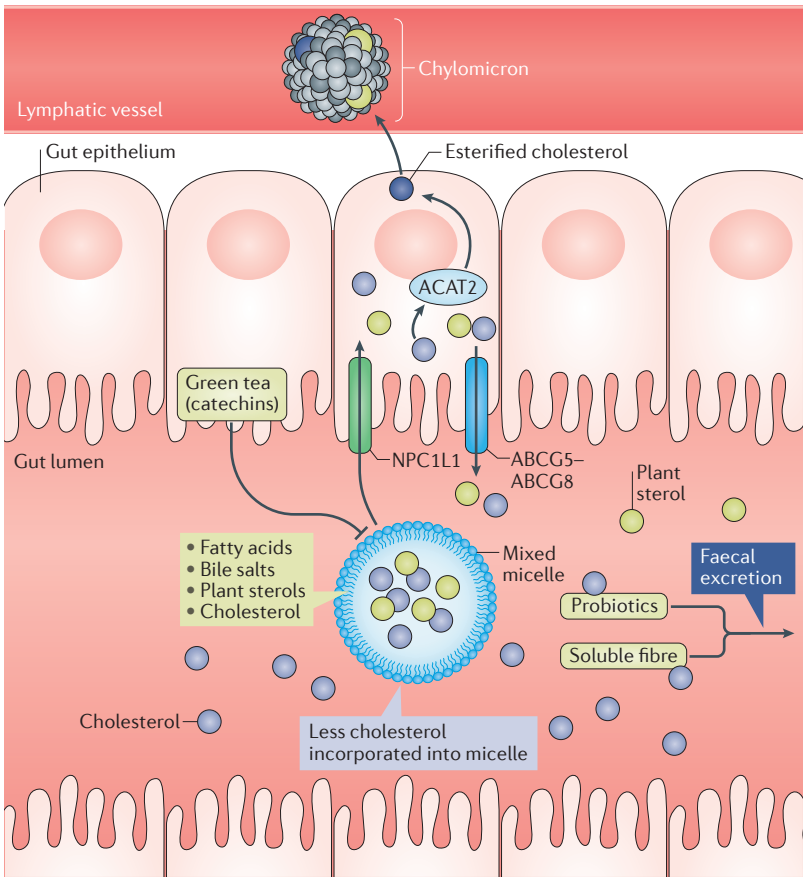

Figure 1 | **Intestinal action of functional foods and supplements.** Plant sterols inhibit dietary cholesterol absorption by competing with cholesterol for absorption in micelles in the gastrointestinal tract. Plant sterols displace animal cholesterol from micelles, which forces cholesterol to be excreted in the faeces. Plant sterols can also co-crystallize with cholesterol to form insoluble mixed crystals and interfere with lumenal hydrolysis of cholesterol by intestinal lipases and cholesterol esterases. Once inside the enterocyte, plant sterols are excreted back into the gut lumen by ATP-binding cassette subfamily G member 5 (ABCG5; also known as sterolin 1)–ABCG8 (also known as sterolin 2) heterodimeric transporter, whereas animal-derived cholesterol is esterified by acyl-CoA cholesterol acyltransferase 2 (ACAT2) and packaged into chylomicrons for transport in the lymphatic system. Green tea interferes with the formation of micelles and results in displacement of cholesterol from micelles. Soluble fibre, including that found in seaweed, binds to cholesterol and bile acids in the gastrointestinal tract, which makes them unavailable for absorption. Probiotic bacteria inhibit cholesterol absorption by absorbing cholesterol themselves and possess bile salt hydrolase activity, which can deconjugate bile acids and make their absorption less efficient. NPC1L1, Niemann–Pick C1-like protein 1.

Plant sterols. Plant sterols, or phytosterols, are steroid compounds that are found in plants and have a structure that is similar to cholesterol. Consumption of 2–3 g per day of plant sterols has been associated with a 5–15% reduction in LDL cholesterol levels, even in those individuals taking a statin[23]. Plant sterols compete with dietary animal-derived cholesterol for absorption into micelles in the gastrointestinal tract. Within the enterocyte, plant sterols are released from micelles and transported back to the intestine through the ATP-binding cassette subfamily G member 5 (ABCG5)–ABCG8 heterodimeric transporter[24] (FIG. 1). Most studies have not found a statistically significant effect of plant sterol supplementation on levels of HDL cholesterol[25,26]. One meta-analysis found a 6% reduction in triglyceride levels with no change in HDL cholesterol levels in patients with hypercholesterolaemia[27]. As most trials have been of short duration, no data are available on cardiovascular end points. Plant sterol supplements seem to be generally safe, although their use should be avoided in rare patients known to have sitosterolaemia, in whom a defect in the ABCG5–ABCG8 transporter prevents plant sterol excretion[28]. The recommended dose of plant sterols to achieve cholesterol lowering is 2–3 g per day; however, as plant sterols are present at only very low amounts in plants, the main dietary source of plant sterols is from functional food products fortified with plant sterols (such as margarine and orange juice). These products typically provide 1 g of plant sterols per standard serving. Further information on plant sterols can be found elsewhere[29].

Marine-derived omega-3 fatty acids. Fish oil is rich in the omega-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA; C20:5,n-3) and docosahexaenoic acid (DHA; C22:6,n-3). Meta-analyses have shown a consistent triglyceride-lowering effect of fish oil supplements, especially in patients with hypertriglyceridaemia[30–33]. These studies have also noted small, concurrent increases in levels of LDL cholesterol[30–33]; however, this effect has not been found with krill oil[34,35]. Krill oil has a greater ratio of EPA to DHA than fish oil, and most EPA and DHA in krill oil are in the form of phospholipids, which have higher bioavailability[34]. For this reason, lower doses of krill oil are able to produce triglyceride-lowering effects that are similar to the effects of higher doses of fish oil. Meta-analyses have also shown that, although DHA is more efficient at lowering triglyceride levels than EPA, DHA raises LDL cholesterol levels to a greater extent than EPA[31]. Several mechanisms by which EPA and DHA act to reduce triglycerides exist. Primary triglyceride-lowering actions include activation of peroxisome proliferator-activated receptors (PPARs) to increase expression of genes encoding proteins that are involved in fatty acid oxidation, inhibition of fatty acid incorporation into triglycerides and reduction of hepatic VLDL synthesis[36]. EPA and DHA also increase the activity of LPL, which secondarily reduces triglyceride levels[32,36]. Given that hypertriglyceridaemia is typically associated with low levels of HDL cholesterol, a concomitant increase in levels of HDL cholesterol with fish oil supplementation is expected; however, the available data are inconsistent. One meta-analysis found that monotherapy with DHA increased HDL cholesterol levels considerably more than placebo[32], whereas a randomized controlled trial (RCT) found that krill oil supplements, but not fish oil supplements, significantly increased levels of HDL cholesterol[35]. Fish oils have also been studied for their effects on other cardiovascular risk factors such as body weight and blood pressure; however, the data are not robust[33]. Many studies on fish oil supplementation have reported mortality and cardiac events as end points. A 2004 meta-analysis did not

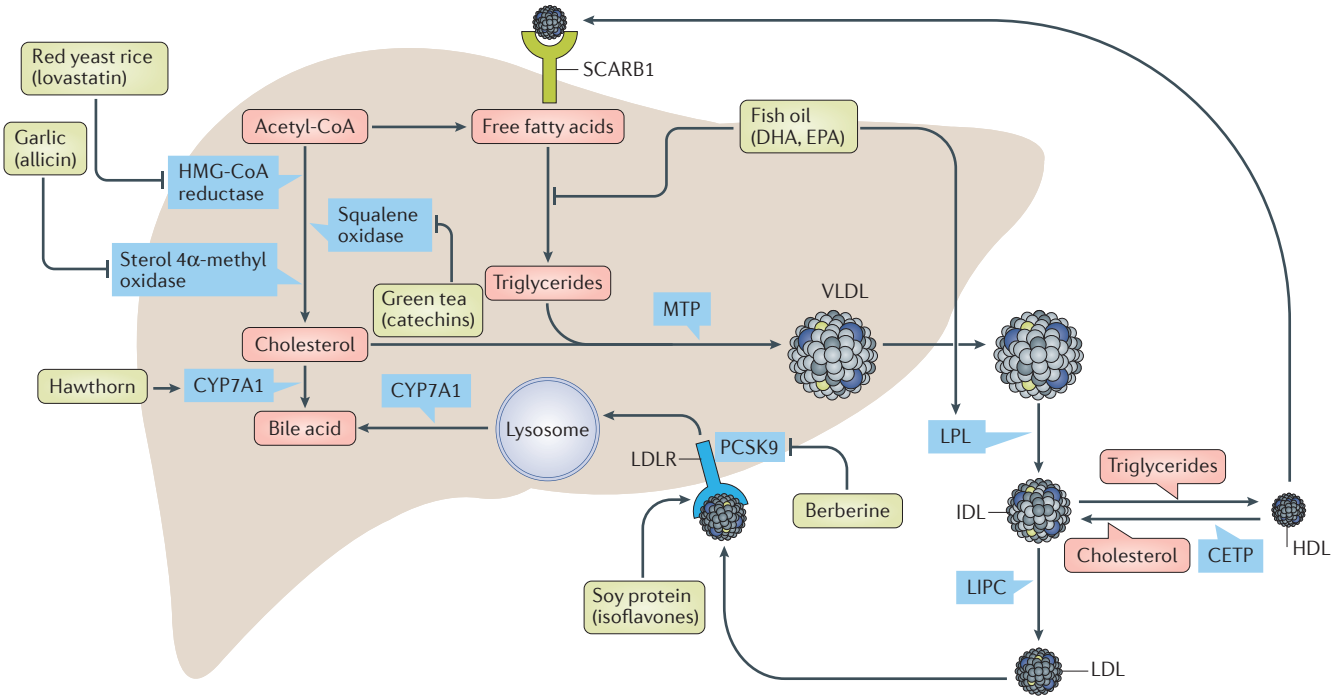

Figure 2 | **Hepatic action of functional foods and supplements.** Hepatic molecular targets are shown in blue boxes; lipid components are shown in red boxes; functional foods and supplements are shown in green boxes. Red yeast rice inhibits 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, a rate-limiting enzyme in the cholesterol synthesis pathway. Garlic inhibits cholesterol biosynthesis by inhibiting sterol 4α-methyl oxidase. Green tea reduces cholesterol biosynthesis by inhibiting squalene oxidase. Hawthorn is thought to upregulate cholesterol 7α-hydroxylase (CYP7A1), which increases bile acid production and reduces available hepatic cholesterol. Berberine inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme that is responsible for degradation of the LDL receptor (LDLR). When PCSK9 is inhibited, levels of LDL cholesterol decline owing to increased LDLR-mediated uptake of LDL cholesterol by the liver for recycling and excretion. The 7S globulin subunit of soy protein has been shown to upregulate LDLR. The isoflavone component of soy might also upregulate LDLR. Marine-derived omega-3 fatty acids increase the activity of lipoprotein lipase (LPL), an enzyme that catalyses the conversion of VLDL to intermediate-density lipoprotein (IDL) in the bloodstream; fish oils also have an inhibitory effect on fatty acid incorporation into triglycerides. Fish oils can also act as peroxisome proliferator-activated receptor agonists (not shown) to increase expression of genes encoding proteins involved in fatty acid oxidation, thereby reducing levels of fatty acids available for triglyceride synthesis. CETP, cholesteryl ester transfer protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LIPC, hepatic triacylglycerol lipase; MTP, microsomal triglyceride transfer protein; SCARB1, scavenger receptor class B member 1.

find a statistically significant reduction in total mortality, cardiac mortality or cardiac events in those individuals consuming fish oil supplements; however, a significant protective effect on heart failure was observed[33]. A later analysis in 2009 found a significantly reduced risk of cardiac death and all-cause mortality in high-risk groups consuming fish oil supplements[37]. Overall, robust evidence exists to suggest that fish oil supplements reduce triglyceride levels. However, fish oil supplements might also slightly increase levels of LDL cholesterol, although whether this translates to altered risk of cardiac events or mortality is uncertain. For patients with high levels of triglycerides and LDL cholesterol, a krill oil supplement should be considered, as the LDL cholesterol-raising effect has not been observed with krill oil. To achieve a reduction in triglyceride levels of 25–30%, a dose of 2–4 g per day of fish oil is recommended[38]. Further information on marine-derived omega-3 fatty acids is available elsewhere[38].

Red yeast rice. Red yeast rice is produced by fermentation of rice by *Monascus purpureus,* a species of mould. The active ingredient, monacolin K, was the first statin drug (lovastatin) to be isolated and approved for treatment of high cholesterol levels. Lovastatin reduces cholesterol levels by inhibiting HMG-CoA reductase, an enzyme that functions in hepatic cholesterol biosynthesis (FIG. 2). Given that the active ingredient is lovastatin, red yeast rice is regulated as a drug in the USA, and any over-the-counter supplements containing red yeast rice cannot contain lovastatin[39]. In other countries, red yeast rice is regulated as a supplement and can be purchased without prescription. Lovastatin-containing red yeast rice has been shown to be effective in lowering levels of LDL cholesterol and triglycerides[40–44]. Lovastatin-containing red yeast rice supplements can reduce levels of LDL cholesterol by 20–30% (comparable to low-dose statins) and triglyceride levels by 10–20%[45]. Lovastatin-containing red yeast rice might be helpful in patients

who decline traditional pharmacotherapy or perhaps in children[42]. Many patients who experience statin-induced myopathies might be interested in trying this dietary supplement as an alternative to statins; however, research has not shown that it improves muscle pain[45,46].

Policosanol. Policosanol is a long-chain sugar alcohol compound that is extracted from sugar cane, wheat germ, rice or maize[47]. Early promising studies of policosanol supplementation showed reductions in both total and LDL cholesterol levels[48,49]; however, over the past ten years, these studies have been called into question. These initial studies were performed by the same group in Cuba and were funded by Dalmer Laboratories. No other group outside of Cuba has yet been able to reproduce their results, even when using an identical policosanol preparation[50]. The data from these early Cuban studies skew meta-analytic data to suggest that an effect of policosanol exists[51]. No recent, high-quality trials have found policosanol to be effective at reducing cholesterol levels in humans[50,52–56]. Despite these findings, policosanol is still found in many combination supplements marketed as lowering lipid levels. Although policosanol is probably safe to consume, evidence suggests that the supplement is only minimally effective for use in treating dyslipidaemia. Further information on policosanol can be found elsewhere[57].

Newer examples

Berberine. Berberine, an isoquinoline alkaloid plant extract, has historically been used in traditional Chinese medicine to treat several conditions[58]. Berberine has gained interest in the past few years as a potential dietary supplement in patients with diabetes mellitus or dyslipidaemia. The mechanism by which berberine lowers levels of LDL cholesterol seems to partially involve proprotein convertase subtilisin/kexin type 9 (PCSK9) (FIG. 2). *In vitro*, berberine upregulates the levels of LDLR and downregulates those of PCSK9 in HepG2 cells[58,59]. In animal studies, both mice and hamsters treated with 200 mg/kg per day of berberine had lower serum levels of PCSK9 and LDL cholesterol, decreased expression of *Pcsk9* and decreased hepatic levels of hepatocyte nuclear factor 1α (HNF1α) compared with vehicle-treated animals[59]. PSCK9 binds to LDLR for degradation, which results in increased circulating levels of LDL cholesterol[60]. HNF1α is a transcription factor that is expressed in the liver and regulates the expression of multiple genes that are involved in bile acid synthesis and both lipid and carbohydrate metabolism. As the promoter region of the gene encoding PCSK9 contains an HNF1α binding site, berberine might act on HNF1α to reduce PCSK9 expression[61].

A 2013 meta-analysis found that, at doses of 0.6–1.5 g per day, berberine was associated with statistically significant reductions in levels of total cholesterol (−0.61 mmol/l), triglycerides (−0.50 mmol/l) and LDL cholesterol (−0.65 mmol/l), and significant increases in levels of HDL cholesterol (+0.05 mmol/l) in diverse adult populations[62]. Furthermore, when a berberine supplement was co-administered with simvastatin, the combined lipid-lowering effect was significantly greater than that of simvastatin alone, lowering levels of LDL cholesterol by 0.61 mmol/l[62]. As this analysis included all trials using berberine as an intervention and reporting lipid parameters as an outcome, some of the included patients probably did not have elevated levels of lipids. To address this gap in knowledge, a second meta-analysis that was performed in 2015 examined berberine intervention specifically in hyperlipidaemic populations[63]. This analysis found that berberine in combination with lipid-lowering therapy was associated with improvements in levels of total cholesterol, LDL cholesterol and HDL cholesterol compared with lipid-lowering therapy alone[63]. A limitation of both of these analyses was that most included studies were of low quality. Although current evidence suggests that berberine has a modest effect on improving lipid parameters, additional research is needed, particularly high-quality RCTs and studies looking at cardiovascular-risk end points. A dose of berberine of 0.5 g three times per day is recommended to achieve reductions in levels of LDL cholesterol and triglycerides of 10–20%[64]. Evidence exists suggesting that berberine also is a promising dietary supplement for use in patients with diabetes mellitus[63] or fatty liver disease[65].

Garlic. Garlic supplements are among the most commonly used supplements in patients with CVD[66]. Garlic supplements are available in several different forms, such as garlic powder, allicin, aged garlic extract and garlic oil. Despite a large body of research on efficacy, no consensus has been reached on the mechanism by which garlic lowers levels of cholesterol. On the basis of available research, garlic seems to decrease cholesterol synthesis via inhibition of HMG-CoA reductase[67] and sterol 4α-methyl oxidase[68] — an enzyme downstream of HMG-CoA reductase in the cholesterol synthesis pathway (FIG. 2). Studies on the effect of garlic on gene regulation have found downregulation of *MTP*[69], *ACAT*[67], *CETP*[70] and *NPC1L1* (REF. 71), and upregulation of *ABCG5* (REF. 71), *ABCG8* (REF. 71), *ABCA1* (REFS 71,72) and *AMPK*[73]. Garlic also has anti-inflammatory and antioxidant properties that might have a role in modulating cardiovascular risk. Aged garlic extract has been shown to slow development of atherosclerotic lesions in *Apoe*-knockout mice by suppressing inflammation and macrophage differentiation[74]. Aged garlic extract is also able to suppress LDL oxidation both *in vivo* and *in vitro*[75].

Several meta-analyses have been conducted, and all, with the exception of one[76], found that garlic supplement intake was associated with markedly decreased levels of total cholesterol[77–81]. Surprisingly, only two of these meta-analyses found a statistically significant decrease in LDL cholesterol levels with garlic supplementation[77,81]. Decreased triglyceride and increased HDL cholesterol levels were also noted, but only in some analyses[77,78]. Subgroup analysis on the type of garlic preparation that was used showed that aged garlic extract was the most effective preparation at lowering levels of total cholesterol[77,78]. Unsurprisingly, the effect was found to be more

robust in studies of longer duration and in patients with high lipid levels at baseline[77–79,81]. Other studies have also reported reduced carotid–intima media thickness[82] and reductions in both systolic and diastolic blood pressure with garlic supplementation[81,83]. A case–control study involving more than 1,400 Italian individuals found no relationship between garlic intake from food and risk of nonfatal myocardial infarction[84]. The main adverse effect that is associated with consumption of garlic supplements is halitosis; however, garlic also has antiplatelet effects and should be used with caution in patients who are already taking an anticoagulant or antiplatelet agent[77]. The totality of evidence suggests that consumption of garlic supplements (particularly aged garlic extract) is safe and might have a small cholesterol-lowering effect, as well as other possible benefits that reduce cardiovascular risk. To achieve cholesterol lowering of ~5%, a dose of allicin equal to 10 mg per day is recommended[80].

Guggulsterone. Guggulsterone (also known as guggul) is a plant steroid that is found in the resin of the Mukul myrrh tree (*Commiphora wightii*) and has a history of use in traditional Ayurvedic medicine[85]. Mechanistic studies have shown that guggul acts as an antagonist of the farnesoid X-activated receptor (FXR) both *in vitro* and *in vivo* in a mouse model[86,87]. FXR is a bile acid receptor that, when active, is able to suppress cholesterol 7α-hydroxylase (CYP7A1), which has a role in the transformation of cholesterol into bile acids. Thus, antagonism of FXR would be expected to increase cholesterol breakdown to bile acids. Despite these findings, guggul does not seem to be effective at lowering cholesterol levels in humans.

Research performed before 2003 showed promising results of guggul supplementation in improving lipid parameters, but many of these studies were not well designed[88]. More recent RCTs have not found an effect of guggul on lipid parameters[89]; one study actually found that LDL cholesterol levels were increased after guggul supplementation[90]. To date, no meta-analyses have been performed investigating the effects of guggul on lipid parameters. Common adverse effects that are associated with guggul use include gastrointestinal discomfort and skin rash[89,90]. Despite a lack of evidence on efficacy and the noted adverse effects, guggul is often still found in combination supplements marketed for cholesterol lowering. The dose that is found in these supplements and in the literature is typically 0.5–1 g 2–3 times per day.

Resveratrol. Resveratrol is a polyphenol compound that is found in the skin of red grapes. In the past decade, resveratrol has received a great deal of interest because of its presumed ability to prevent cancer, prolong lifespan, control diabetes mellitus and reduce the risk of CVD. As moderate alcohol consumption has been associated with a decreased risk of CVD[91], resveratrol in red wine was initially speculated to modulate this effect; however, this scenario is now thought to be implausible[92]. A consensus exists that resveratrol activates sirtuin 1 (SIRT1), which is an important regulator of energy homeostasis[93]. In a hamster model of diet-induced dyslipidaemia, resveratrol supplementation reduced HMG-CoA reductase activity and hepatic levels of *Hmgcr* (which encodes HMG-CoA reductase)[94]. As statins also target HMG-CoA reductase, the use of statin drugs in some studies could have masked the effects of resveratrol. Resveratrol has powerful antioxidant activity and has been shown to inhibit macrophage oxidation of LDL cholesterol *in vitro*[93], although this inhibition has yet to be demonstrated *in vivo* in humans[95].

Resveratrol supplementation trials in humans have produced conflicting results; however, pooled data do not show an LDL cholesterol-lowering or HDL cholesterol-raising effect[96]. Studies conducted in patients with type 2 diabetes mellitus (T2DM) have shown an LDL cholesterol-lowering effect of resveratrol[97,98]; however, another similar study actually found a marked increase in levels of LDL cholesterol following resveratrol supplementation[99]. Similarly, results in patients with T2DM have also been conflicting for HDL cholesterol[97,98]. Resveratrol is also a powerful antioxidant, which could potentially have a role in reducing CVD risk by inhibiting oxidation of LDL cholesterol[93]. Current research suggests that resveratrol supplementation is not effective in improving lipid levels, although, again, large prospective RCTs with CVD end points are desirable.

Probiotics. Probiotics are live bacteria that, when ingested, can colonize the human gastrointestinal tract and confer health benefits to the host. *Bifidobacterium animalis* (formerly known as *B. lactis*) and *Lactobacillus acidophilus* are the two most commonly studied probiotic strains. Many strains of probiotic bacteria possess bile salt hydrolase activity and are thus able to deconjugate bile acids. Cholesterol can co-precipitate with the deconjugated bile, and this complex is then excreted in the faeces (FIG. 1). Probiotic bacteria also have the ability to absorb cholesterol themselves, making it unavailable for absorption from the gastrointestinal tract. In addition, gut bacteria promote production of short-chain fatty acids from oligosaccharides, which can bind to PPARs and inhibit the activity of LPL. Finally, bacteria can convert cholesterol to coprostanol, which is not well absorbed[100].

To date, most studies on probiotics have been small in scale; however, the results are promising. Consumption of both conventional and probiotic yogurts has been shown to lower levels of total cholesterol and LDL cholesterol[101–103]. Probiotic yogurt, but not conventional yogurt, might also increase levels of HDL cholesterol[102,103]. Several meta-analyses have been conducted on the topic, and all have shown small but statistically significant reductions in levels of total cholesterol and LDL cholesterol (~3%) but no effect on levels of HDL cholesterol or triglycerides[104–106]. One meta-analysis also noted reductions in both BMI and waist circumference in the probiotic treatment group[106]. Most research has used yogurt as the method of delivering probiotics; trials using encapsulated probiotic supplements have not proven as efficacious[106]. Probiotic yogurt is widely available and can

easily be incorporated into a healthy diet. A minimum of 10^7 colony-forming units (CFU) per day is the recommended dose, which is equivalent to ~1–2 servings of yogurt (175–350 g) per day, depending on the brand.

Seaweed. Seaweed is a functional food that is gaining popularity owing to its high nutrient density. Seaweed and seaweed extracts are currently being studied for their antihyperlipidaemic effects. Seaweed is very high in fibre, which has the potential to reduce cholesterol levels, and, in addition, contains other bioactive compounds that could potentially affect cholesterol levels, such as fucoidan, taurine, phycobiliproteins and fucoxanthin[107]. No consensus has been reached on the mechanism by which these bioactive compounds might reduce levels of cholesterol. *In vivo* animal studies have noted decreased *Hmgcr* expression, decreased *Ldlr* and downregulation of *Npc1l1* expression, as well as decreased intestinal cholesterol absorption[108]. These hypolipidaemic effects have also been confirmed *in vitro*[109]. An extract from the seaweed *Sargassum fusiforme* acts as a selective agonist of liver X receptor-β (LXRβ), which is a transcriptional regulator of hepatic cholesterol homeostasis[110].

Given the relative novelty of this area of study, most studies on seaweed supplementation for lowering lipid levels have been done in animals. Results from animal studies have mostly shown marked improvements in dyslipidaemia, although the data are difficult to compare, as most studies used different species of seaweed (see Supplementary information S1 (table)). Preliminary studies in humans have shown promising results in both healthy individuals and those with T2DM, in whom seaweed supplementation was found to improve the levels of triglycerides and HDL cholesterol but not those of LDL cholesterol[111,112]. An observational study in Japan, where seaweed consumption is very common, did not find an association between dietary seaweed intake and serum levels of total cholesterol[113]. Certain types of seaweed and algae contain DHA, which can be extracted to produce a DHA-rich algal oil, similar to fish oil. Given the declining fish populations and the high costs that are associated with fish farming, finding new sources of EPA and DHA (such as algae) is important. One meta-analysis on the effects of algal oil on blood lipid parameters found that algal oil significantly reduced the levels of triglyceride while slightly increasing those of HDL cholesterol and LDL cholesterol[114].

Although data from animal studies have been promising, human data are inconclusive, and more RCTs are required to determine if seaweed is effective in patients with dyslipidaemia. Seaweed is also a good source of fibre and antioxidants, which makes it an excellent option to incorporate into a heart-healthy diet. Algal oil might also be a good vegetarian alternative to fish oil for those with hypertriglyceridaemia and normal levels of LDL cholesterol.

Hawthorn (Crataegus). Hawthorn fruit, which has historically been used in traditional Chinese medicine for cardioprotection and as a digestion aid, has gained interest in the past few years as a dietary supplement for use in patients with diabetes mellitus, dyslipidaemia or fatty liver disease. *Apoe*-knockout mice consuming chow supplemented with hawthorn had increased total antioxidant capacity and increased superoxide dismutase and glutathione peroxidase 1 activity[115]. mRNA levels of hepatic fatty acid synthase and sterol regulatory element-binding protein 1C were also reduced in hawthorn-fed animals[115]. Another possible mechanism by which hawthorn exerts hypocholesterolaemic effects is by increasing bile acid production[116] via upregulation of CYP7A1 (REF. 117) (FIG. 2). In addition, hawthorn-fed animals have been noted to have decreased cholesterol biosynthesis due to inhibition of acyl-CoA cholesterol acyltransferase (ACAT)[117,118].

As yet, very few high-quality RCTs have been conducted in humans on the effect of hawthorn on lipid parameters. Animal studies in mice and rats have shown promising results for decreasing LDL cholesterol levels[115,116]. In adult patients with T2DM and CVD, levels of total cholesterol and LDL cholesterol were reduced after 6 months of hawthorn treatment (1.2 g per day)[119]. Hawthorn intake also correlated with a reduction in plasma neutrophil elastase concentration, which is often elevated in CVD[119]. Initial findings suggest that hawthorn has some benefit in those individuals at risk of CVD; however, more high-quality RCTs need to be conducted before reaching a conclusion on the lipid-lowering efficacy of Hawthorn.

Green tea. Tea is made from the dried leaves of the *Camellia sinensis* plant. To produce black tea, the leaves are allowed to oxidize in a controlled environment, whereas green tea is produced from the unoxidized leaves. About 30% of adult individuals in the USA are tea drinkers, and consumption of green tea has been on the rise in North America, probably owing to its purported health benefits[120]. Catechins are a class of flavonol that are found in tea and have been postulated to be responsible for its cholesterol-lowering properties. The most abundant catechin compound in tea is epigallocatechin gallate[121]. Consumption of green tea catechins in supplement form (either capsule or powder) has been shown to have marked cholesterol-lowering effects in several meta-analyses[122–124]. Catechins are powerful antioxidants that prevent oxidation of LDL both *in vitro* and *in vivo* in humans[125]. Catechins also have a direct inhibitory effect on cholesterol synthesis *in vitro*, by inhibiting squalene oxidase, which catalyses a rate-limiting step in hepatic cholesterol biosynthesis[126]. Green tea might also inhibit intestinal lipid absorption by interfering with micelle formation[127].

Several meta-analyses have been conducted examining the effects of tea consumption on lipid parameters and have consistently shown a cholesterol-lowering effect of green tea or green tea extracts[122–124,128–130]. Meta-analyses have also found a small but significant LDL cholesterol-lowering effect of black tea; however, this reduction was not associated with a concurrent reduction in levels of total cholesterol[129,131,132]. Analyses comparing intake from beverages with that from supplements have produced conflicting results[123,124]. In observational

studies, consumption of both green and black tea was associated with a significantly decreased risk of all-cause mortality; however, only green tea consumption was associated with a significantly reduced risk of cardiovascular mortality[133]. Risk of cardiovascular mortality was reduced by 5% per additional cup of green tea per day[133]. Frequent green tea drinkers possibly lead overall healthier lifestyles than non-tea drinkers, which might have contributed to the observed effect.

Soy protein. Soy protein can be consumed directly by eating soybeans and soy products or as a supplement in the form of soy protein isolate. The cholesterol-lowering effect of soy protein is probably due to both reduced consumption of saturated fats in the diet and the effects of bioactive compounds in soy itself. The 'intrinsic' effects of soy have been estimated to contribute to a 4.3% reduction in levels of LDL cholesterol, whereas the displacement of dietary animal protein by soy contributes to a further 3.6–6.0% reduction in LDL cholesterol levels[134]. The intrinsic effect might be mediated by isoflavones in soy, which are phyto-oestrogens and can thus exert oestrogenic effects in the body. Oestrogen is able to increase levels of HDL cholesterol and decrease levels of LDL cholesterol[135]. Given the drop in oestrogen levels at menopause, isoflavones might be expected to be most effective in menopausal women; however, this prospect does not seem to be the case. Other potential mechanisms of soy protein action include alteration of expression of genes that are regulated by sterol regulatory element-binding proteins[136,137] and upregulation of LDLR by the soybean 7S globulin subunit[138] (FIG. 2).

Observational studies have found a decreased risk of CVD associated with high intake of soy protein in both men and women[139,140]. This reduction in risk might be due to a reduced intake of saturated fats as a consequence of consuming less animal protein and/or to the hypolipidaemic effects of the soy protein itself. Several meta-analyses have been conducted examining the effect of soy protein or soy isoflavone intake on lipid levels, and all have found a slight hypolipidaemic effect[141–147]. Most studies noted a reduction in levels of total cholesterol following soy intake[143–147]. Four analyses found significantly increased levels of HDL cholesterol[141,143,145,146], and six found a significant reduction in triglyceride levels[141–143,145–147]. Subgroup analyses comparing premenopausal and perimenopausal women with postmenopausal women found attenuation of the hypolipidaemic effects in postmenopausal women[143,147]. Furthermore, the only meta-analysis that did not report a hypocholesterolaemic effect of soy only included studies of postmenopausal women[142]. Interestingly, two analyses noted that the reduction in cholesterol levels was greatest in those individuals with the lowest baseline lipid levels[143,144]. Two analyses examined the effect of soy protein with low or no isoflavones and found no effect[142,147]; however, isoflavone isolate alone was also found to have no effect[147]. In conclusion, soy protein is a good choice for replacing animal protein in the diet owing to its favourable nutritional profile, marginal lipid-lowering effect and association with reduced cardiovascular risk. Although some evidence exists that compounds found in soy might have hypocholesterolaemic effects, replacement of saturated fat in the diet with soy protein could be the primary reason for the observed hypocholesterolaemic effects. These effects might be attenuated in postmenopausal women and are less evident with isoflavone isolates. The amount of soy protein that is recommended for lipid lowering is 25–50 g per day.

Conclusions

Use of health-promoting functional foods and dietary supplements has been increasing over the past few decades. Lifestyle modification is emphasized as a foundation for longevity; in particular, a diet high in fruits, vegetables and whole grains and low in saturated and trans fats can reduce the risk of CVD. Functional foods such as soy protein, green tea, plant sterol-fortified products and probiotic yogurt can be incorporated into a heart-healthy diet and might promote further reductions in cholesterol levels if consumed often. Good evidence exists to support the use of fish oil supplements (2–4 g per day) to lower triglyceride levels and of lovastatin-containing red yeast rice to produce cholesterol-lowering effects that are similar to those of low-dose statins. Other products such as seaweed, berberine, hawthorn and garlic might offer some limited lipid-lowering benefit; however, additional research is needed to determine the mechanism and magnitude of their effects. Other supplements marketed at people with dyslipidaemia, such as policosanol, guggulsterone and resveratrol, are unlikely to have any benefit. Although this Review focused on lipids, several functional foods and supplements have been shown to improve other cardiovascular risk factors such as blood pressure and glycaemic control. Overall, most functional foods and supplements being studied for the treatment of dyslipidaemia have only a small effect on lipid parameters, and non-pharmacological treatment of dyslipidaemia should focus on the whole diet. Given that many of these functional foods and supplements exert their effects through different mechanisms (FIG. 1,2), the potential for additive effects when taken in combination should be taken into account. The Portfolio diet, developed by David Jenkins, emphasizes consumption of functional foods to lower cholesterol levels and can result in reductions in LDL cholesterol levels of up to 30%[148]. A summary of the recommended doses and expected effects of functional foods and supplements for the management of dyslipidaemia is presented in TABLE 1.

The supplement industry is not well regulated, and many products available might be ineffective. Furthermore, a lack of standardization exists, which means that some products might contain contaminants (including pharmaceuticals) or doses of the bioactive compound in excess of that reported on the label[149]. For these reasons, health-care professionals need to be able to identify products that might be beneficial for their patients, especially those who refuse pharmacological therapy. Additional research is required in this field, as most studies of supplements conducted so far have been of short duration. Another gap in knowledge is the

Table 1 | **Recommended dose and expected outcome of functional foods and supplements**

Functional food or supplement	Expected outcome	Recommended dose	Refs
Soluble fibre	Reduction in LDL cholesterol levels by 3–5%	10 g per day	22
Plant sterols	Reduction in LDL cholesterol levels by 5–15%	2–3 g per day	29
Fish oil	Reduction in triglyceride levels by 25–30%; might slightly increase LDL cholesterol levels (not Krill oil)	2–4 g per day	38
Red yeast rice	Reduction in LDL cholesterol levels by 20–30%, reduction in triglyceride levels by 10–20%; might increase HDL cholesterol levels	1.2–4.8 g per day	45
Soy protein	Reduction in LDL cholesterol levels by 3–5%	25–50 g per day	148
Berberine	Reduction in total cholesterol, LDL cholesterol and triglyceride levels by 10–20%; might increase HDL cholesterol levels	0.5 g three times daily	64
Garlic	Reduction in total cholesterol levels by ~5%	~10 mg allicin per day	80
Green tea	Slight reduction in total cholesterol and LDL cholesterol levels; 5% reduction in CVD risk per additional cup per day	≥200 mg green tea catechins per day or ~2.5 cups of tea per day	123
Probiotics	Reduction in total cholesterol and LDL cholesterol levels by ~3%; might increase HDL cholesterol levels	10^7 CFU per day or 175–350 g per day of probiotic yogurt	105
Seaweed	Might improve triglyceride and HDL cholesterol levels	48 g per day	111
Hawthorn	Might reduce total cholesterol and LDL cholesterol levels	1.2 g per day	119

CFU, colony-forming units; CVD, cardiovascular disease.

lack of studies with cardiovascular outcome data, and, although desirable, these types of trials are unlikely to be conducted. Only soy protein consumption and green tea intake have been associated with significant reductions in cardiovascular risk in observational studies. Use of functional foods and dietary supplements can be part of a global approach to lipid lowering as they can reduce LDL cholesterol levels to help people to achieve lipid targets and spare medication dose. These products are safe to consume at recommended doses and are unlikely to interact with conventional lipid-lowering therapies, thus potentially motivating patients to adhere to their evidence-based drug treatment by producing a healthy compromise.

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The authors declare no competing interests.

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