



Review

Recent Molecular Mechanisms and Beneficial Effects of Phytochemicals and Plant-Based Whole Foods in Reducing LDL-C and Preventing Cardiovascular Disease

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Abstract: Abnormal lipid metabolism leads to the development of hyperlipidemia, a common cause of multiple chronic disorders, including cardiovascular disease (CVD), obesity, diabetes, and cerebrovascular disease. Low-density lipoprotein cholesterol (LDL-C) currently remains the primary target for treatment of hyperlipidemia. Despite the advancement of treatment and prevention of hyperlipidemia, medications used to manage hyperlipidemia are limited to allopathic drugs, which present certain limitations and adverse effects. Increasing evidence indicates that utilization of phytochemicals and plant-based whole foods is an alternative and promising strategy to prevent hyperlipidemia and CVD. The current review focuses on phytochemicals and their pharmacological mode of actions for the regulation of LDL-C and prevention of CVD. The important molecular mechanisms illustrated in detail in this review include elevation of reverse cholesterol transport, inhibition of intestinal cholesterol absorption, acceleration of cholesterol excretion in the liver, and reduction of cholesterol synthesis. Moreover, the beneficial effects of plant-based whole foods, such as fresh fruits, vegetables, dried nuts, flax seeds, whole grains, peas, beans, vegan diets, and dietary fibers in LDL-C reduction and cardiovascular health are summarized. This review concludes that phytochemicals and plant-based whole foods can reduce LDL-C levels and lower the risk for CVD.

Keywords: plant-based foods; LDL; CVD; lipid oxidation; dietary fiber; cholesterol; hyperlipidemia

1. Introduction

Cholesterol is circulated in the human body by five major types of lipoproteins: high-density lipoprotein (HDL), low-density lipoprotein (LDL), intermediate-density lipoprotein (IDL), very low-density lipoprotein (VLDL), and chylomicrons [1]. The metabolism and plasma levels of cholesterol are mostly regulated by the liver. During the first step of LDL formation, intrahepatic cholesterol, either via gut absorption or de novo synthesis, is repackaged by the liver along with phospholipids, triglycerides (TGs), and proteins into VLDL particles, which then enter the general blood circulation and are converted into more cholesterol-enriched species, first IDL and then LDL, by lipoprotein lipase and cholesteryl ester transfer protein (Figure 1A). The concentrations of these circulating lipoprotein species are then regulated by the liver primarily by clearance through LDL receptors on the hepatocyte surface [2,3].

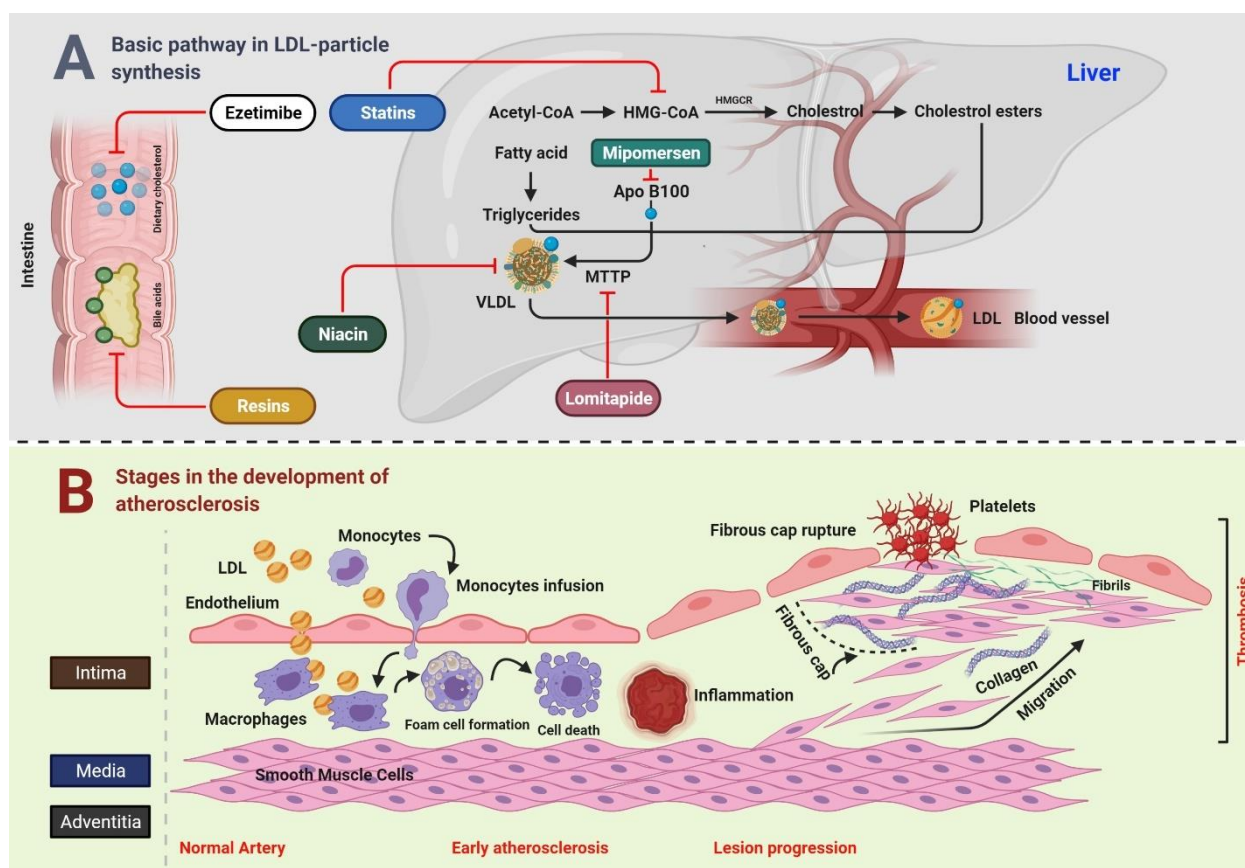


Figure 1. Connection between LDL and CVD.

Figure 1A Bile acids and dietary cholesterol are absorbed from the lower and upper small intestine, respectively. Cholesterol absorption inhibitor, for example, ezetimibe, and bile acid sequestrants (resins) disrupt these pathways, subsequently reducing the intrahepatic cholesterol pool. The synthesis of cholesterol occurs in the liver through a multistep process that starts with acetyl-CoA. HMGCR is the rate-limiting enzyme, whose action is blocked by statins. TG are produced by esterification of fatty acids on a 3-carbon glycerol backbone. TG and esterified cholesterol are assembled by microsomal triglyceride transfer protein MTTP into nascent VLDL particles with ApoB100 on their surface, whereas MTTP and ApoB100 remain the targets for lomitapide and mipomersen, respectively. In the blood, endovascular lipases process VLDL particles to LDL particles, which are catabolized by the LDLR mainly on liver cells. Niacin inhibits the transport of VLDL. Figure 1B Key steps in the development of atherosclerosis include early atherosclerosis, lesion progression, and thrombosis. LDL play a crucial role in the development of atherosclerosis. During early atherosclerosis, monocytes are captured by the endothelial cells of the inner layer of arterial wall. The endothelial permeability assists the LDL particles in migrating into the arterial wall. Monocytes become mature, and are transformed to macrophages, which uptake the LDL particles yielding to fat-laden foam cells. Early atherosclerosis is followed by lesion progression where the smooth muscle cells move from the middle layer of the arterial wall into the tunica intima. The last step is the thrombosis which is characterized by the rupturing of the fibrous cap of a plaque and establishment of contact of blood coagulation components with the thrombogenic plaque.

2. Correlation of LDL Cholesterol with CVD

Several investigations provide strong evidence that LDL cholesterol (LDL-C) is a potent cardiovascular risk factor [4]. Early studies such the “Multiple Risk Factor Intervention Trial” measured total cholesterol instead of LDL-C, indicating a strong correlation

between cholesterol and cardiovascular mortality [5]. However, this relationship can be assigned to LDL-C because LDL contains a major part of total cholesterol. Multiple investigations have confirmed LDL-C to be the most atherogenic lipoprotein. Studies have shown that circulating LDL particles penetrate the endothelium of arterial walls and are oxidized. Then, these oxidized LDL particles induce inflammation of the overlying endothelium and surrounding smooth muscle cells [6] (Figure 1B). Persistent elevations in circulating LDL-C levels have been directly linked to the progression from early-stage fatty streaks to advanced-stage, lipid-rich plaques. For instance, LDL receptor-deficient mice, which fail to clear LDL from the blood, have excessive LDL-C, which promoted the development of severe atherosclerosis [7], whereas mice with virtually no LDL-C did not develop atherosclerosis irrespective of diet and other risk factors for coronary heart disease (CHD) [8].

An epidemiological study demonstrated LDL-C as an independent predictor of CVD risk, as LDL-C levels > 160 mg/dL are associated with > 1.5 -fold greater risk of CHD than levels < 130 mg/dL [9]. However, besides the role of LDL-C as a risk marker, researchers have also established it as a true risk factor based on investigations where inhibition of LDL-C via β -hydroxy- β -methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors decreased cardiovascular events [10]. These findings have been verified by multiple large randomized controlled trials of LDL lowering like the MRC/BHF Heart Protection Study in 20,536 UK adults [11]. Most of the time, these trials focused to investigate the actions of statins, and were further supported by large meta-analyses. For instance, the Prospective Pravastatin Pooling Project (PPP) pooled the data from the West of Scotland Coronary Prevention Study (WOSCOPS), the Cholesterol and Recurrent Events trial (CARE), and the Long-term Intervention with Pravastatin in Ischemic Disease study (LIPID), providing over 100,000 person-years of follow-up [12]. Likewise, the prospective meta-analysis of the Cholesterol Treatment Trialists' (CTT) Collaboration pooled the data from 14 randomized statin trials, containing over 90,000 individuals [13]. These trials offer exceptional statistical power for proving the potency and safety of statin therapy for a multitude of patient subgroups and endpoints.

It has been reported that statin treatment reduced the five-year incidence of major coronary events, stroke, and coronary revascularization by about one-fifth per mmol/L reduction in LDL-C [14]. Another meta-analysis from the CTT Collaboration analyzed the efficacy and safety of more intensive versus standard LDL-C lowering by statin therapy. The data were collected from 170,000 participants in a total of 26 randomized trials, which demonstrated that further decrease in LDL-C (0.51 mmol/L at one year vs. standard therapy) reduced the incidence of major coronary events by 15% [15]. Based on this information, guidelines have been established suggesting different target levels of LDL-C for different subgroups of patients. Almost all cardiovascular guidelines point to the evidence for LDL-C being both a prime cause of CHD, and a primary target of therapy [16]. Moreover, although many single-nucleotide polymorphisms (SNPs) of genes associated with increased LDL-C levels, including LDL receptor (LDLR), apolipoprotein E (ApoE), proprotein convertase subtilisin/kexin type 9 (PCSK9), and apolipoprotein B (ApoB), have been correlated with an increased risk of CVD, specific SNPs of these same genes have been associated with decreased LDL-C levels and lower risks of CVD [17–20].

At present, hyperlipidemia is primarily treated with allopathic antihyperlipidemic drugs. However, due to intolerance and adverse effects associated with these medicines, plant-based foods are important alternatives [21,22]. Plant-based foods contain various bioactive phytochemicals that can decrease LDL levels through multiple hyperlipidemia-related biological pathways. Consumption of plant-based foods has emerged as a promising and potentially cost-effective approach to decrease LDL levels while also adhering to the concept of “green” healthcare [23,24]. The following sections describe the underlying mechanisms of phytochemicals to reduce the cholesterol levels and prevent CVD.

3. Major Cholesterol Regulatory Mechanisms of Phytochemicals

3.1. Acceleration of Reverse Cholesterol Transport

Reverse cholesterol transport (RCT) is a crucial pathway that removes excess cholesterol from peripheral tissues and delivers them to the liver [25,26]. The RCT comprises of three main processes: cholesterol efflux, where excess cholesterol is removed from cells; modulation of lipoprotein, where HDL gains structural and functional changes; hepatic lipid uptake, where HDL delivers cholesterol to the liver, which is finally excreted into bile and feces [27]. In vivo investigations have demonstrated that promotion of RCT might decrease CVD and atherosclerotic plaque burden [28].

3.1.1. Cholesterol Efflux

Cholesterol efflux is referred to the removal of excess cholesterol from macrophages. Studies have demonstrated the ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1) to be the most important transporters contributing to regulate cholesterol efflux from cells. ABCA1 is responsible for the efflux to lipid-free apolipoprotein A-I (ApoA-I), whereas ABCG1 regulates efflux to mature HDL [29–31]. It has been reported that promotion of cholesterol efflux effectively inhibited the formation of foam cells and subsequent atherosclerosis caused by dyslipidemia [32,33].

Multiple investigations have suggested that phytochemicals such resveratrol [34], puerarin [35], leonurine [36], luteolin [37], andrographolide [38], leoligin [39], chrysin [40], and allicin [41] could enhance cholesterol efflux to HDL through ABCA1 or ABCG1. A Chawla et al. [42] reported that the PPAR γ -LXR-ABCA1 pathway contributed to cholesterol efflux in macrophages. It was demonstrated that most of the above-mentioned phytochemicals increased the expressions of ABCA1 or ABCG1 through PPAR γ or LXR. Moreover, previous studies have reported that quercetin-induced ABCA1 levels and cholesterol efflux were mediated by activation of TAK1-MKK3/6-p38 signaling cascade [43–45].

3.1.2. Modulation of Lipoprotein

Besides cholesterol efflux, inhibiting lipid uptake in macrophages is another mechanism to inhibit foam cell formation, which eventually leads to suppress atherosclerotic plaque formation. CD36 (cluster of differentiation 36) and scavenger receptor class A (SR-A) are mainly responsible for uptake of lipoprotein-derived cholesterol by macrophages [46]. Several mechanisms have been described for phytochemicals through which they induce intracellular cholesterol efflux. For instance, a study reported that icariin, an active flavonol diglycoside, downregulated the CD36 expressions level through p38MAPK signaling pathway [47]. Additionally, paeonol was shown to repress the CD36 at both mRNA and protein levels by inhibiting the nuclear translocation of C–Jun [48]. Puerarin blocked the TLR4/NF κ B signaling and decreased the expressions of CD36 [49]. Likewise, rographolide [38], and salvianolic acid B [50] were reported to inhibit CD36. An investigation reported that ginsenoside-Rd blocked the activity of SR-A, which caused reduction of oxidized LDL uptake and cholesterol aggregation in macrophages [51].

After removal from cells, free cholesterol is converted to cholesteryl esters by lecithin: cholesterol acyltransferase (LCAT) to form mature HDL [52]. Relevant investigations have been conducted on phytochemical in this area. Researchers have demonstrated that curcumin [53] and naringin [54] increased the RCT via LCAT and exerted anti-atherosclerosis effects.

It has been reported that cholesterol ester transporter (CETP) transfers cholesterol esters (CEs) from HDL towards ApoB-containing lipoproteins, resulting in reduced concentration of HDL and ApoA-I, while elevating the concentration of CE in VLDL and remnants [55]. As CETP elevates the concentration of VLDL and LDL-C, its specific knock-down can reduce atherosclerotic CVD [56]. It has been reported that anthocyanins could effectively inhibit the activity of CETP in humans [57].

3.1.3. Hepatic Lipid Uptake

As already mentioned, that cholesterol metabolism is mostly regulated by the liver, where it takes up LDL and HDL-CE particles by LDLR and scavenger receptor class B type I (SR-BI), respectively. The LDLR binds to LDL on the cell surface. PCSK9 has been shown to post-transcriptionally downregulate the LDLR by binding to the receptor's epidermal growth factor repeat A (EGF-A) on the cell surface and shuttling it to the lysosomes for degradation [58].

Multiple phytochemicals have been shown to alleviate atherogenesis by modulating the activity of LDLR and PCSK9. For instance, berberine was shown to upregulate the hepatic expression of LDLR and sterol regulatory element-binding protein 2 (SREBP-2), whereas it downregulated the expression of hepatocyte nuclear factor 1 [59,60]. Another investigation reported that berberine exerted anti-lipid effects by regulating hepatic LDLR and PCSK9 via the ERK signaling pathway [61]. Piseth Nhoek et al. [62] reported that flavonoid compounds, 3,7,2'-trihydroxy-5-methoxy-flavanone and skullcapflavone II, isolated from the roots of *Scutellaria baicalensis*, downregulated the PCSK9 at mRNA level via sterol regulatory element-binding protein-1 (SREBP-1). Furthermore, other phytochemicals such as curcumin [63], and tanshinone IIA [64], also modulated the activity of LDLR via downregulation of PCSK9.

Lipoprotein lipase (LPL) is the rate-limiting enzyme in the circulation of cholesterol metabolism, hydrolyzing the TG core of circulating TG-rich lipoproteins, VLDL, and chylomicrons [65]. In addition, hepatic lipase is required for the hydrolysis of triglyceride-rich lipoproteins [66]. A study reported that paeoniflorin regulated the GALNT2-ANGPTL3-LPL signaling pathway to diminish dyslipidemia in mice [67]. Yan Zhang and coworkers reported that osthole (an active constituent obtained from the fruit of *Cnidium monnieri* (L) Cusson) decreased the TC and TG in rat serum, and this effect was related with the elevated activities of LPL and hepatic lipase [68] (Figure 2).

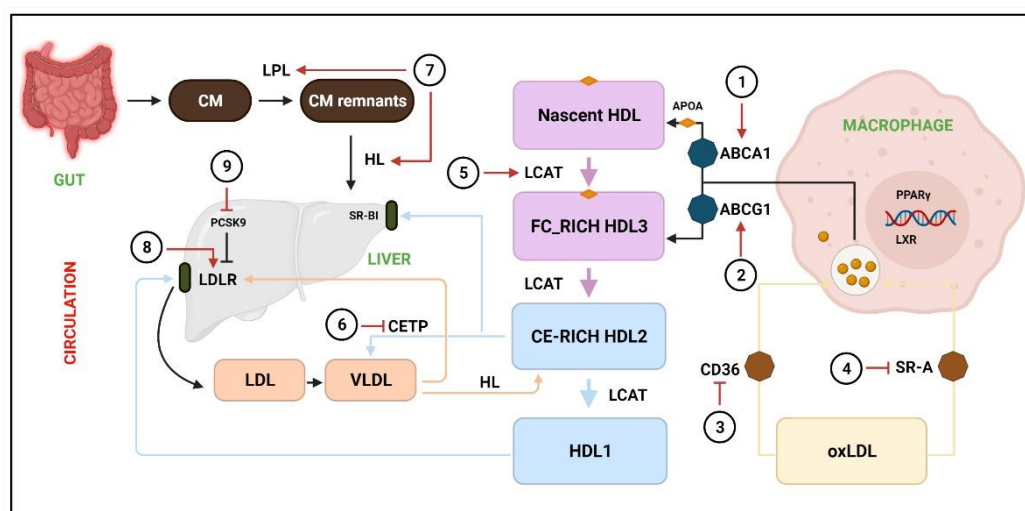


Figure 2. Acceleration of RCT by various phytochemicals.

RCT is responsible to facilitate the transport of excess cholesterol from peripheral tissues to the liver, where it is redistributed to other tissues or eliminated from the body through the gallbladder. The transport of cholesterol into macrophages occurs through CD36 and SR-A, whereas extra cholesterol is effluxed through ABCA1 and ABCG1 to the nascent HDL and free FC-rich HDL3, respectively. LCAT converts nascent HDL, FC-rich HDL3, and CE-rich HDL2 to HDL1, whereas CETP catalyzes HDL2 to VLDL. Next, HDL2 and VLDL are taken up by SR-BI and LDLR, respectively. (1, 2) The activity of ABCA1 and ABCG1 is promoted by resveratrol [34], puerarin [35], leonurine [36], luteolin [37],

andrographolide [38], leoligin [39], and chrysin [40]. (3) Downregulation of CD36 by icariin [47], paeonol [48], and puerarin [49], salvianolic acid B [50], and rographolide [38]. (4) Inhibition of SR-A by ginsenoside-Rd [51]. (5) LCAT levels are elevated by naringin [54] and curcumin [53]. (6) CETP is downregulated by crocin anthocyanins [57]. (7) LPL and HL are stimulated by paeoniflorin [67] and osthole [68]. (8) LDLR expression is increased by berberine [59,60]. (9) PCSK9 expression are downregulated by 3,7,2'-trihydroxy-5-methoxy-flavanone, skullcapflavone II [62], curcumin [63], and tanshinone IIA [64]. CM = chylomicron; CM remnants = chylomicron remnants; HL = hepatic lipase; FC = free cholesterol; CE = cholesterol ester; oxLDL = Oxidized low-density lipoprotein; LXR = Liver X receptor.

3.2. Inhibition of Intestinal Cholesterol Absorption

Absorption of cholesterol refers to the transfer of intraluminal cholesterol into enterocytes or thoracic duct lymph [69]. The food substances and bile enter from the intestinal lumen into enterocytes via the transmembrane protein Niemann-Pick C1 like1 (NPC1L1) [70]. Inside the enterocytes, free cholesterol is esterified to CEs by an enzyme called acyl CoA: cholesterol acyltransferase-2 (ACAT)-2 in the endoplasmic reticulum [71]. Afterward, CEs and TG, under the action of MTTP, form chylomicrons, which are then secreted into the lymphatic system [72]. Studies have reported that inhibition of intestinal cholesterol absorption effectively lowered the plasma LDL-C level [73] and reduced the risk of CVD [74]. Thus, it is necessary to block excessive absorption of cholesterol from the diet and bile [75].

3.2.1. Cholesterol Uptake Inhibition

Phytochemicals show blood lipid-lowering effects and inhibit cholesterol uptake mainly by targeting NPC1L1. It has been shown that downregulation of NPC1L1 considerably reduces intestinal cholesterol absorption [70], which is modulated by SREBP-2 [76] and LXR [77]. Curcumin has been shown to block cholesterol uptake by binding to the NPC1L1-related transporter [78,79]. A study reported the curcumin response elements to be present in the region between −291 and +56 of NPC1L1 promoter [80]. Additionally, curcumin was shown to inhibit NPC1L1 pathways by activating the SREBP2 transcription factor [80]. Jun Zou and Dan Feng reported that lycopene, the predominant carotenoid in tomatoes, blocked intestinal cholesterol absorption by blockade of the LXR α pathway [81]. Another study reported that ankaflavin and monascin suppressed the protein levels of NPC1L1 associated with small intestine tissue lipid absorption [82].

3.2.2. Enhancement of Cholesterol Esterification

Studies have reported that ACAT2 exhibits a strong connection with the plasma cholesterol levels and catalyzes the formation of cholesteryl ester in enterocytes [71,83]. Phytochemicals such as oleanolic acid and ursolic acid have been reported to reduce cholesterol levels by inhibiting the activity of ACAT [84,85]. Additionally, downregulation of MTTP is associated with decreased ApoB secretion and chylomicron assemblage. Flavonoids, such as hesperetin [86], quercetin [87], taxifolin [88], tangeretin [89], and naringenin [86] have shown MTTP inhibitory activities. Ioanna Vallianou and Margarita Hadzopoulou-Cladaras reported that camphene, in response to a decrease in the intracellular cholesterol exerts, upregulated the expression of SREBP-1 and blocked the activity of MTTP [90]. It was shown that Tanshinone IIA repressed the MTTP's transcripts and stimulated cellular ApoB proteasomal degradation [91]. Likewise, nobiletin [92], tangeretin [92], and lignin [93] have been shown to reduce the secretion of ApoB. Collectively, phytochemicals inhibit excessive cholesterol absorption and reduce blood lipid levels by downregulating NPC1L1, MTTP, ACAT2, ApoB, LXR, and SREBP (Figure 3).

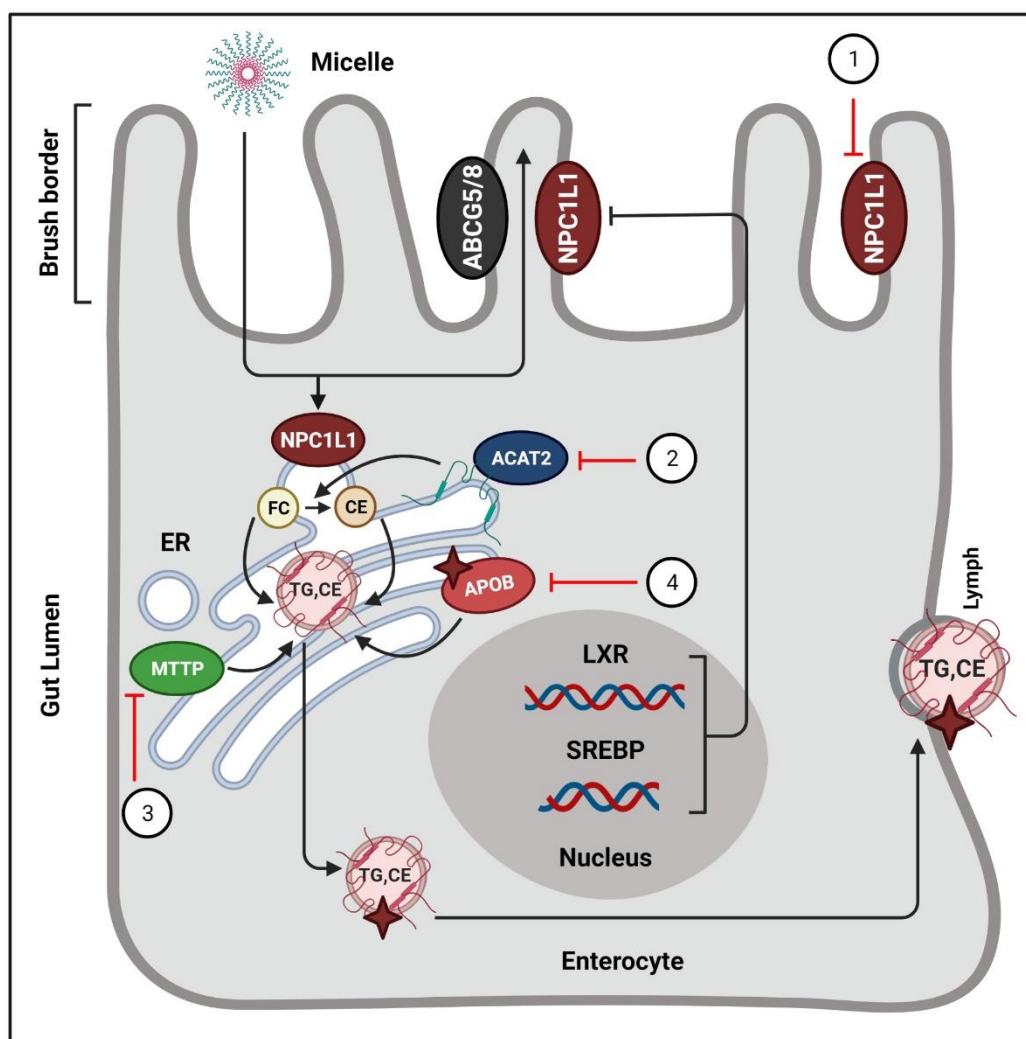


Figure 3. Phytochemicals block the absorption of intestinal cholesterol.

In intestinal lumen, cholesterol incorporates into bile salt micelles and diffuses to the brush border membrane of enterocytes via NPC1L1. Inside the intestinal cells, free cholesterol is esterified by ACAT-2, and afterwards they enter the lymphatic system in the form of chylomicrons. Phytochemicals exert their actions to regulate these processes. (1) NPC1L1 is suppressed by curcumin [78,79], lycopene [81], monascin, and ankaflavin [82]. (2) ACAT2 is targeted by oleanolic acid, and ursolic acid [84,85]. (3) The activity of MTP is blocked by hesperetin [86], quercetin [87], taxifolin [88], tangeretin [89], and naringenin [86]. (4) Tanshinone IIA stimulates the proteasomal degradation of cellular ApoB [91]. ER = endoplasmic reticulum; FC = free cholesterol; CE = cholesterol ester; ABCG5/8 = ATP-binding cassette sub-family G member 5/8; TG = triglycerides

3.3. Promotion of Cholesterol Excretion in the Liver

Hepatic cholesterol, after conversion to bile acids, is removed from the body through biliary secretion [94]. Cholesterol 7 α -hydroxylase (CYP7A1) is the first and rate-limiting enzyme in the bile acid synthesis pathway, which performs a crucial role in maintaining cholesterol homeostasis [95,96]. The activity of CYP7A1 has been shown to be promoted by phytochemicals such as catechins and gypenosides [97,98]. Furthermore, utilization and excretion of cholesterol was improved by palmitine (main alkaloids in *Coptis chinensis*) and jatrorrhizine (extracted from *Rhizoma coptidis*) through upregulation of

CYP7A1 mRNA [99,100]. Another phytochemical called columbamine, obtained from *Rhizoma coptidis*, indirectly transactivated CYP7A1 by the stimulation of hepatocyte nuclear factor 4- α and fetoprotein transcription factor, resulting in enhanced cholesterol catabolism and bile acids secretion [101]. A study demonstrated that punicalagin and ellagic acid extracted from pomegranate enhanced cholesterol metabolism in human hepatocytes by activating the PPAR γ -CYP7A1 signaling [102] (Figure 2).

3.4. Inhibition of Cholesterol Synthesis

The synthesis of cholesterol is regulated through an elegant system of feedback inhibition that senses intracellular cholesterol and eventually regulates several proteins participating in cholesterol homeostasis [103,104]. Squalene synthase (SQS) and HMGCR remain the crucial enzymes involved in cholesterol homeostasis, and the genes of these enzymes are regulated by SREBP-2 [105]. Likewise, AMP-activated protein kinase (AMPK) remains a key sensor in the regulation of lipid metabolism [106]. It was reported that alteration of AMPK restricted the rate of HMG-CoA expression, which, in turn, regulated the synthesis of cholesterol [107].

Studies have described several phytochemicals such as curcumin [108], leoligin [109], ODP-Ia [110], puerarin [111], and geraniol [112], which could suppress the synthesis of cholesterol through inhibition of HMGCR. Moreover, certain phytochemicals have been shown to inhibit synthesis of cholesterol by activating the AMPK [62–70]. SREBPs contribute to the intake of cholesterol and exert regulatory effect on genes encoding HMGCR [113]. Emodin has been reported to inhibit the transcription of SREBP-2 and subsequently suppress the biosynthesis of cholesterol [114]. T Grand-Perret et al. [115] reported that activation of SCAP/SREBP signaling pathway remarkably inhibited cholesterol biosynthesis. Another study reported that (-)-epicatechin and tetramethylpyrazine blocked the SCAP/SREBP-1c pathway, which resulted in the amelioration of atherosclerosis and lipid metabolism disorders [116,117]. Hassan Hajjaj and coworkers [118] reported that 26-oxygenosterol, obtained from *Ganoderma lucidum*, downregulated lanosterol 14 α -demethylase, which is responsible for the conversion of 24, 25-dihydrolanosterol into cholesterol. A study demonstrated SQS to be an attractive target for antihyperlipidemic drugs due to its contribution in cholesterol synthesis [119]. Yankun Chen et al. [120] reported that cynarin inhibited SQS and led to decrease the TG levels (Figure 4).

(1) HMGCR is blocked by curcumin [108], leoligin [109], ODP-Ia [110], puerarin [111], and geraniol [112]. (2) Activation of AMPK by phytochemicals such as curcumin, tanshinone IIA, and paeoniflorin leads to inhibition of cholesterol synthesis [62–70]. (3,4) Emodin inhibits the transcription of SREBP-2 [114], whereas (-)-epicatechin and tetramethylpyrazine block the SCAP/SREBP-1c pathway [116,117]. (5) 26-oxygenosterol promotes the activity of SQS and subsequently block cholesterol synthesis [118]. (6) Cynarin exerts inhibitory action in the process where 24,25-dihydrolanosterol forms cholesterol [120]. SCAP = sterol regulatory element binding protein (SREBP) cleavage-activating protein.

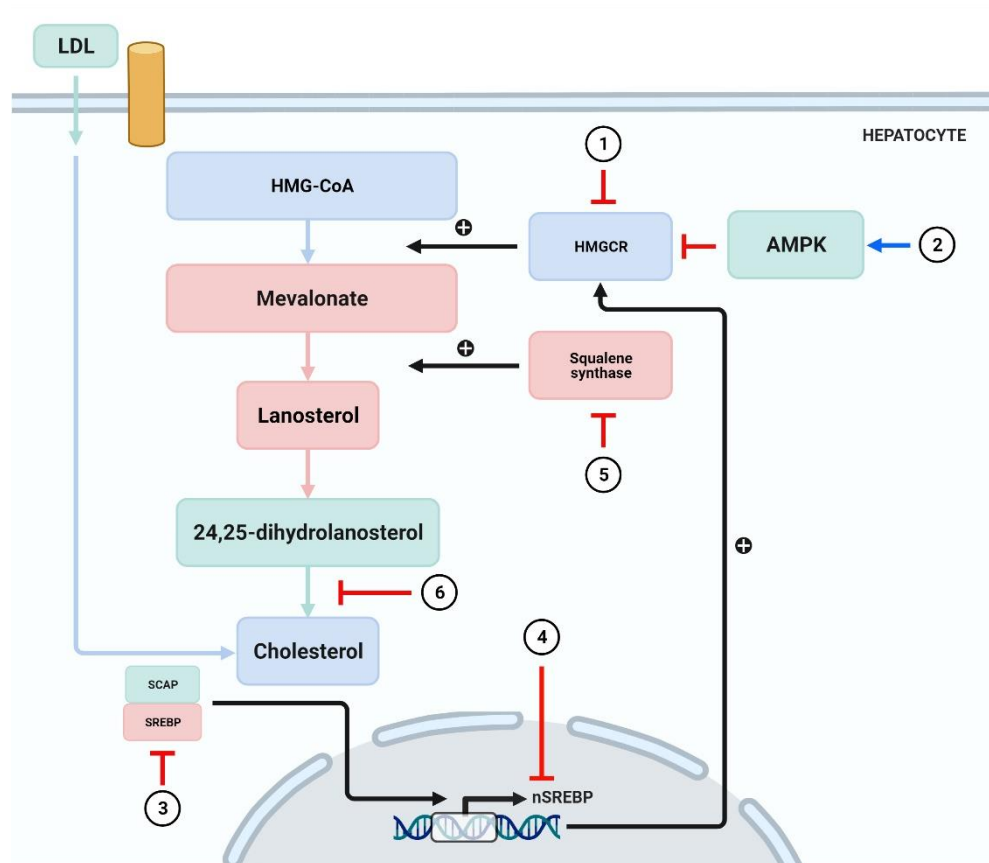


Figure 4. Phytochemicals inhibit the synthesis of cholesterol.

4. Plant-Based Whole Foods Reducing LDL-C and Contributing to Prevent CVD

Low intake of fruits and vegetables was reportedly responsible for ~25.5 million premature deaths globally in 2013 [121]. Vegetables and fruits are good sources of various beneficial substances, such as dietary fiber, minerals, vitamins, and antioxidant entities, which can collectively reduce the risk of chronic disorders and total mortality and exert beneficial effects on the gut microbiota [122–124]. The intake of vegetables, fruits, and dietary fiber has been reported to have positive effects on serum cholesterol levels and platelet aggregation [125]. The results of a meta-analysis found that a daily increase of 200 g of fruits and vegetables reduced the relative risks of CHD, stroke, and CVD by 8–16%, 13–18%, and 8–13%, respectively [126]. Moreover, daily consumption of ~500 g of fruits and vegetables has been correlated with a 22% lower risk of CVD than with a dietary intake of 0–40 g/day [126].

4.1. Grapes (*Vitis Vinifera*)

Grapes are rich sources of phenolic compounds, with an appreciable anthocyanin content of ~46% [127]. Although anthocyanins convey antioxidant, anti-inflammatory, antihypertensive, and antiplatelet activities [128], some studies have reported conflicting results regarding the effects on lipid profiles [129,130].

The effects of grape juice on dyslipidemia were studied using a mouse model homozygous for the absence of the LDLR gene (*LDLR^{-/-}*) and fed a hyperlipidemic diet. During this study, 30 male mice (12 weeks old) were assigned to one of three groups (10 mice/group): the HL group, which received a high-fat diet; the HLU group, fed a high-fat diet and grape juice (2 g/kg/day), and the HLS group, which received a high-fat diet along with simvastatin (20 mg/kg/day). Blood pressure, lipid levels, glycemic and insulinemic profiles, and C-reactive protein levels were determined. It was noted that the 60-day outcomes of the HLU and HLS group were similar, as the addition of grape juice diminished

dyslipidemia and effectively elevated HDL-C levels. Moreover, left ventricular hypertrophy and arterial hypertension was prevented in the HLU group. These results suggest that dietary grape juice can potentially prevent CVD [131].

Various clinical trials have found that grape polyphenols are effective against cholesterolemia. For instance, van Mierlo et al. [132] reported that, compared with a placebo, the intake of grape polyphenols (800 mg/day) for 2 weeks led to decreased TC and TG levels. Similar outcomes were obtained by another investigation on 60 healthy volunteers who received 700 mg/day of a polyphenol-rich grape extract supplement for one month [133]. A study of 44 pre- or postmenopausal women found that dietary supplementation of lyophilized grape powder (39 g/day for 4 weeks) effectively reduced serum levels of LDL-C, ApoE, ApoB, and TGs [134]. Furthermore, administration of grape polyphenols for three weeks and consumption of red wine for one month was reported to reduce LDL-C levels and the risk of CVD [135,136].

4.2. Cranberries (*Vaccinium Macrocarpon*)

Cranberries are a rich source of flavonoids (flavanols, flavan3-ols, and anthocyanins) and phenolic acids (ellagic, benzoic, and hydroxycinnamic acids), which contribute to reducing the risk of CVD through antioxidant, anti-inflammatory, and antithrombotic mechanisms [137]. Wilson et al. first reported the LDL-protective properties of cranberry juice (pressed berries), as 0.10% cranberry juice suppressed the formation of thiobarbituric acid reactive substances via Cu²⁺-induced oxidation of LDL [138]. Another study reported that dietary intake of 2.8 mg/g of cold-pressed cranberry seed oil inhibited LDL oxidation [139]. Besides improving the resistance of LDL to oxidation, cranberry extract has also been shown to increase cholesterol uptake by HepG2 cells and to enhance the synthesis of LDL receptors, which resulted in accelerated cholesterol excretion in vivo [140]. In another study of the effects of cranberry juice powder on blood cholesterol levels, pigs with familial hypercholesterolemic (FH) were fed a diet supplemented with 47 g/day of citric acid and 57 g/day of fructose for two weeks. On day 15, 150 g/day of cranberry juice powder was added and continued for four weeks. Total blood cholesterol, HDL, and LDL levels were observed weekly. At baseline, LDL levels in the FH pigs were 11-fold greater than in normal pigs (428 vs. 37 mg/dL, respectively), whereas total blood cholesterol was sevenfold greater (458 vs. 67 mg/dL, respectively). At the end of the investigation, the LDL levels decreased to 94 mg/dL and total blood cholesterol to 92 mg/dL in the FH pigs. These findings indicate that cranberry juice powder can decrease cholesterol levels in hypercholesterolemic individuals [141].

4.3. Pomegranate (*Punica Granatum*)

Pomegranates contain several potent antioxidants (anthocyanins and tannins), which act as effective anti-atherogenic agents [142]. Daily consumption of pomegranate juice has been shown to reduce serum LDL-C and TG levels and to increase HDL-C levels [143]. The considerable amounts of steroidal compounds in pomegranate seed oil were reported to decrease cholesterol levels [144]. A study of the effect of concentrated pomegranate juice on cholesterol profiles of type-2 diabetes patients with hyperlipidemia reported that daily intake of 40 g of pomegranate for 8 weeks effectively reduced TC and LDL-C levels, as well as the TC/HDL-C and LDL-C/HDL-C ratios [145]. Moreover, pomegranate juice was found to reduce LDL accumulation and increase HDL levels by 20% in humans, whereas a 90% decrease in LDL levels was noted in mice [146]. Al-Moraie et al. [147] reported that consumption of 1–5 mL/kg of pomegranate juice for 28 days effectively decreased LDL-C, VLDL-C, TC, and TG levels while elevating the expression of antioxidant enzymes and HDL-C levels. A study investigating the correlation of punicalagin (the main polyphenol in pomegranate) with ApoB100 that surrounds LDL particles showed that punicalagin bound to ApoB100 at low concentrations (0.25–4 µM) and stimulated LDL influx to macrophages (up to 2.5-fold) in a dose-dependent manner. The study further demonstrated that LDL influx to macrophages occurred specifically via the LDL receptor.

The most important fact demonstrated by this investigation was that the interaction of punicalagin with LDL led specifically to LDL influx to the macrophages without their conversion into foam cells. The study concluded that upon binding to ApoB100, punicalagin induced LDL influx to macrophages, thereby decreasing circulating cholesterol levels [148].

4.4. Apple (*Malus Domestica*)

The effect of apple polyphenols on blood lipid profile has been the focus of numerous studies. A study, while investigating the cholesterol-lowering effect of five different apple species (annurca apple, red delicious, Granny Smith, fuji, and golden delicious) in mildly hypercholesterolaemic healthy subjects, showed that annurca apples exerted the most significant effects; allowing a reduction in TC and LDL-C levels by 8.3% and 14.5%, respectively, while increased HDL-C level by 15.2% [149]. Another study observed the effects of eating two apples/day for four months on blood cholesterol levels. The results showed that blood cholesterol was lowered by 14.5% as compared with the untreated group, whereas HDL-C levels were increased by 15% [150]. However, other than a change in oxidized LDL levels, there was no reduction in blood cholesterol [151]. Another study of lyophilized apples found that administration of 0.21–1.43 g of polyphenols daily for one month did not improve the cardiovascular health of obese patients [152]. Similar results were obtained from another investigation where 300 g golden delicious apple per day for eight weeks increased the serum levels of VLDL and TG, but had no effect on TC, LDL-C, HDL-C, LDL/HDL ratio, and ApoB [153]. Hence, dietary supplementation of apple as whole fruit led to inconsistent results. Although the polyphenolic content of apples was found to lower blood cholesterol levels and LDL oxidation, these data are insufficient to conclude that apples, as a dietary nutraceutical, can lower plasma cholesterol [154,155].

4.5. Dried Nuts

Nuts are rich in polyunsaturated fatty acids, phytosterols, polyphenolics, and fiber [156]. Many studies have reported that daily consumption of nuts can improve cardiovascular health [2–159]. Almonds, pistachios, and walnuts are the most highly consumed nuts worldwide [160]. In a previous meta-analysis, of all edible nuts, pistachios were found to improve blood lipid profiles and effectively reduce serum TG, TC, and lipoprotein levels. Walnuts were second to pistachios in lowering TGs and cholesterol. Controlled levels of LDL, TGs, and TC are important serum markers of cardiovascular health [128,60,161]. Almonds were found to reduce LDL levels more effectively compared with other markers. Mechanisms responsible for the lipid-lowering abilities of nuts include reduced absorption of dietary cholesterol and increased bile production. Nuts are also reported to have an inhibitory effect against HMG-CoA, which is required for biosynthesis of cholesterol via acetyl CoA. Multiple bioactive constituents (phytosterols and fiber) may also individually convey cardiovascular benefits [162–164]. Ellagitannins and lutein in nuts have also been shown to reduce blood lipid levels [165,166]. At the cellular level, nuts have been reported to influence the expression levels of several miRNAs associated with lipid metabolism and uptake [167,168].

Several meta-analyses of the cardiovascular benefits of nuts have reported similar results. However, there have been conflicting reports, as one study claimed that walnuts and pistachios do not lower serum TG levels [169]. As a possible explanation for these conflicting findings, some studies evaluated nut-enriched foods containing other ingredients, such as skimmed milk and components of Mediterranean diets, which could influence the effects of nuts [169–172]. Nonetheless, the superiority of pistachios in lowering blood cholesterol is reportedly due to the greater content of β -carotene, γ -tocopherol and lutein [156].

The reported effects of nut-enriched diets on body weight varies among studies, as some reported a slight reduction in adipose tissue content in response to daily intake of nut-enriched foods [173], whereas others found that the high fat and calories of nuts can

cause weight gain [160]. In a meta-analysis of 34 studies, only one reported significant weight loss, whereas the others found no significant correlation between a nut-enriched diet and body weight [174,175].

When compared with lipid-lowering drugs, such as statins, the effect of nuts on cholesterol seems to be quite modest. Moreover, the duration of most of the studies were relatively short (<six months), whereas dyslipidemia disorders are chronic. Hence, well-designed studies of larger populations for greater durations are required to accurately evaluate the effects of nut-enriched diets on cardiovascular health. Another concern is the reliance on self-reporting the frequency and quantity of nut-enriched diets, which may be misleading. Furthermore, many studies failed to report daily intake of nuts on regular basis. In addition, nuts, such as pecans, peanuts, and Brazil nuts, were often not included in the studies. Most meta-analyses did not conduct sensitivity analysis due to limited data. Hence, based on the available published studies with sensitivity analysis, diets enriched with pistachios and walnuts have more favorable lipid-lowering effects than other nut-enriched diets. However, the quality of evidence is debatable due to the several shortcomings addressed earlier [176].

4.6. Fruits of *Opuntia* Spp.

Many studies have reported that consumption of various fruits of *Opuntia* spp. can significantly lower TC [177,178]. A recent study also reported the lipid-lowering effects of juice consumption at 150 mL/day for two weeks consecutively in both healthy and hyperlipidemic populations [179]. The processes thought to be involved in this effect was a reduction in fat absorption in the intestine, increased bile synthesis and secretion, and increased density of LDL receptors at cholesterol uptake sites. The high fiber content of fruits has been suggested to be the primary lipid-lowering ingredient. Reduced enterohepatic recirculation of bile is another factor responsible for indirect reduction in blood cholesterol levels [180]. Other studies have suggested that pectin derived from fruit also promotes the production of bile by increasing the biosynthesis of chenodeoxycholic acid and increased uptake of LDL from the blood. Other studies have reported such effects without reporting the quantity of daily fiber intake. Hence, due to the phytochemical constituents and fiber content, *Opuntia* spp. are good candidates for managing CVD [177].

4.7. Flax Seeds

Flax seeds are rich in dietary fiber, which consists of pentose- and hexose-based hydrophilic polymers, such as arabinoxylans, galactose, ketose (fructose), pectin, and omega-3 fatty acids, which form high consistency solutions in the gut [181]. Beverages containing flax fibers have been reported to reduce fasting levels of TC and LDL by 12% and 15%, respectively [182]. Another study reported that consumption of roasted flax seed powder for three months significantly reduced serum levels of TG, TC, VLDL, and LDL [183].

Lignans isolated from the flax seeds are being extensively studied for their hypocholesterolemic effects. A study was conducted for two months, in patients with high blood cholesterol, to observe the effects of administering the dietary secoisolariciresinol diglucoside (SDG) from flax seeds on lipid profile. The results exhibited that dose of 600 mg SDG was sufficient to reduce TC and LDL up to 24%. Authors concluded that flax seed lignans had significant anti hypercholesterolemic effects [184]. Another study was conducted which involved ingestion of whole flax and sunflower seeds by a special population of hypercholesterolemic postmenopausal women. Patients were given 38 g of one diet for six weeks followed by switching of diet for another six weeks. The washout period between two dietary regimens was a two-week interval. Flax seed diet was able to reduce TC and LDL up to 6.9% and 14.7% respectively. Marked reduction in the concentrations of lipoprotein A (7.4%) was also observed. Reduction in TC and LDL due to sunflower seeds was lower than flax seeds. The authors were of the view that the above effects of whole seeds of both plants were due to the presence of linoleic acids, and fibers present

in adequate amounts [185]. Another study investigated the effects of ground flax seeds on the lipid profile of patients taking statins to control blood cholesterol. The randomised double blind study conducted for 12 months involved the administration of 30g ground seeds to 58 patients. A significant reduction in LDL (15%) was observed after one month of diet therapy. 11% reduction in TC was observed after 6 months of flax seeds intake. The authors also reported fading of flax seeds effects on cholesterol lowering after 6 months of treatment. Combining flax seeds diet with statins caused a consistent reduction in LDL by 8.5% after 12 months [186].

4.8. Whole Grains

Whole grains, such as rice, corn, barley, and rye, are rich sources of fiber. An analysis of 64 studies [183] concluded that regular intake of oat reduced serum TG and LDL levels by up to 19% and 23%, respectively. Among these 64 studies, some also described the favorable HDL-elevating effects of oat. Another review of 24 studies reported that intake of whole grain foods also lowered serum TC and LDL levels, with the most dominant effect on TC [183].

Yet another study conducted on 12754 individuals to observe their dietary habits with respect to adequate intake of whole grains (more than 3 oz per day) and their daily dose of statins. The researchers reported that one fourth of total individuals were regular in consuming whole grains and statins for the total duration of study (12 months). They also reported that concomitant use of dietary and pharmacological means of cholesterol control was better than either of the two regimens used alone. Therefore, inclusion of whole grains in adequate amounts lessens the odds of patients in developing more severe forms of cardiovascular emergencies [187]. Just as two or more servings of refined sugars and carbohydrates have been associated with greater risk of developing CVDs, daily servings of whole grains (two or more) have been associated with 10–20% lower risk of developing CVDs [188]. Another study assessed the effect of whole grains by analysing the data from 24 studies. Whole grain intake caused reduction in triglycerides and cholesterol levels without affecting HDL [189]. A study assessed the effects of a diet containing whole grains, fruits and vegetables on CVD risk and weight gain. A total of 75 overweight women were randomized and given one of the above-mentioned diets for 10 weeks. The results, when examined after 10 weeks, showed that women who took whole grains for 10 weeks displayed better lipid control profile (lowered LDL), lower hypertension, and greater weight reduction than those who were given fruits and vegetables [190]. Another study tried to analyse the effect of specific grains against whole grains in reducing CVD risk. A prospective study conducted on 2329 old age (late 50s) individuals with previous history of myocardial infarction (MI). Examination of eating habits of these individuals followed by risk estimation using Cox proportional hazard model revealed that whole grains are effective in lowering the risk of future CVDs. Among individual grains, rye and oats were found to be specifically more effective than other individual grains in lowering risk of MI and other CVDs [191].

4.9. Soy Components

Soy proteins are one of the plant based food components approved by FDA for their health claim regarding their cholesterol reducing effects. Researchers studied 46 trials after the approval to judge if the health claim still holds value. Of 46, 41 had data on LDL-C while 43 had data on TC. Analysis showed that 25 mg daily dose of soy proteins for 6 weeks caused reduction in LDL-C and TC by 4.76 and 6.41 mg/dL respectively. This reduction amounted to 3–4% reduced LDL-C by consumption of soy proteins, in adults [192]. Combining phospholipids, soy fibers and proteins revealed a synergistic effect on lowering blood cholesterol than soy proteins alone [193]. Another study conducted in population of postmenopausal women, reported that soy phytosterols (4g) taken in combination with fibers and soy proteins induce greater antihyperlipidemic effects than soy proteins alone [194].

Soy isoflavones have been reported to regulate lipogenesis, beta oxidation of fatty acids, and lipolysis by inhibiting the Akt/mTORC1 pathway [99]. In addition, isoflavones were reported to reduce serum TC and LDL levels by 1.7% and 3.6%, respectively, in hypercholesterolemic patients with a lesser effect in normal individuals [195]. Another study found greater lipid-lowering effects in earlier periods of treatment with overall reductions in serum TC, LDL, and TG levels of 3.7%, 5.25%, and 7.27%, respectively. Moreover, soy isoflavones were reported to increase the amount of beneficial HDL by 3.03% [196]. A meta-analysis confirmed that whole soya from four weeks to one year reduced more serum LDL compared with processed soya-extracts [197].

Consumption of 2 g/day of soybean leaf extract for 12 weeks was reported to reduce serum TG levels in overweight subjects with mildly high blood glucose levels [110], whereas another study showed that 70 mg/day for three months decreased serum TG levels in postmenopausal women [198].

Soy isoflavones include daidzein, genistein, and glycitein, which occur as glycosides. The linkage is broken by digestive enzymes to liberate the active aglycone portion of glycosides. A study of the lipid-lowering effects of daidzein (soy isoflavone) at 40 and 80 mg/day for six months found that the effects on TG levels were dose-dependent [199]. In the colon, daidzein is converted to S-equol. In a previous study, 10 mg/day of S-equol was found to reduce blood LDL levels and the cardio-ankle vascular index [200]. Although daidzein is metabolized in the colon, 30–50% of the Caucasian population had dissimilar results among the different groups. Likewise, genistein at 54 mg/day for 12 months increased HDL levels from 46.4 mg/dl to 56.8 mg/dl (22.4% increase) and decreased LDL levels from 108.8 mg/dl to 78.7 mg/dl (27.66% decrease) in postmenopausal women [201].

4.10. Vegetarian Diet

Vegetarian diets excludes meat, poultry and fish. Vegan diet, in addition to the exclusions of vegetarian diet, also excludes eggs and dairy products. Health benefits of vegetarian diets are due to the presence of adequate quantities of *n*-6 fatty acids, fiber, carotenoids, folate, ascorbic acid, vitamin E and magnesium. On the other hand, these diets lack sufficient protein, vitamin A, B12 and zinc. Vegan foods are low in calcium too due to absence of dairy products [202]. A scientific opinion suggested that a person does not need to become vegan or vegetarian to improve their cardiovascular health but slight changes in dietary components and habits might do the needful [203].

Reducing consumption of meat is thought to be correlated with improved cardiovascular health [204]. Vegetarian and Mediterranean-type diets have been recommended as health imparting diets by the American College of Cardiology/American Heart Association. The diets of Africans are largely plant-based, which have been associated with a lower prevalence of CVD [205]. A study conducted in the US reported a clear correlation between meat consumption and CVD [206]. Another significant study showed that a vegetarian diet reduces the risk of CVD by 32%, as vegetables have anti-inflammatory and antioxidant effects due to the prevalence of carotenoids, flavonoids, and other polyphenols [207]. A main drawback of such diets is the lower availability of proteins and certain minerals, especially zinc and calcium. Some researchers have argued that the presence of trypsin inhibitors (pulses, tomato), lyso-alanine (in processed vegetables), and glucosinolates in plant-based foods can also cause harm to the body due to the addition of non-vegetarian diets; thus, a slight reduction in consumption of vegetarian diets is recommended [208–210].

A meta-analytic study of 11 trials was conducted to observe the effects of vegetarian diets on lipid profile. Random effect model was used for determination of net changes in lipid profile. Vegetarian diets caused significant reduction in TC and LDL-C without having significant effect on lowering triglycerides [211]. A meta analytic and prospective study reported that vegetarian diets continued for 5 years or more reduced the risk of mortality from CHD by 24% [212]. A study conducted in Taiwanese patients to compare the effects of vegetarian diet against an omnivorous diet on CVDs reported that vegetarian

diet was more effective in lowering TC and LDL-C. No effect was observed on HDL-C and TGs. However, homocysteine levels (indicative of folate and B12 deficiency) were higher in the vegetarian population [213].

5. Dietary Fiber

Fibers are carbohydrate polysaccharides that are not hydrolyzed by digestive enzymes in gastrointestinal tract. Low fiber intake has been associated with a higher risk of CVD. In contrast, fiber-rich foods, such as fruits and vegetables, have been associated with a low risk for CVD [214]. This correlation is attributed to the increased bile secretion induced by fibers, lower fatty acid biosynthesis, increased insulin sensitivity at target tissues, feeling satiated due to increased indigestible bulk in the intestine, lower cravings, and improved bowel habits [215,216]. Beta glucan has been shown to increase the consistency of stomach and intestinal contents and reduce enterohepatic recirculation of bile via adsorption of bile acids by viscose fiber dispersion and inhibition of micelle formation for lipid emulsification, which leads to indirect reduction in blood cholesterol levels (Figure 5). Moreover, pectin and guar gum have been reported to possess such effects [217]. A previous meta-analysis of 15 studies with a large combined cohort of ~1 million reported a correlation between mortality and fiber consumption and found that daily intake of ~30 g/day of dietary fiber reduced the risk of mortality due to CVDs by 23% [218]. The source of fiber also affects its physiological function [219], as soluble fibers have cholesterol-lowering effects, whereas insoluble fibers can prevent sudden increases in blood glucose levels [220]. Beta glucan is a soluble fiber found in oat and barley. Many studies have associated the intake of 3 g beta glucan per day with lower serum TG, cholesterol, and LDL levels (5–10%) [186]. In a murine model of hypertension, dietary fiber was found to play a role in the downregulation of early growth response 1, which is a transcription factor that regulates many genes and pathways involved in the progression of CVD [219,221]. Another meta-analysis reported that intake of 3 g/day of beta glucan contained in fibrous foods decreased LDL levels with no effect on HDL and TGs [222]. Another study of 2295 individuals over a period of ~5 years found that fibrous foods, such as pulses, fruits, and vegetables, reduced the risk of CVD [223].

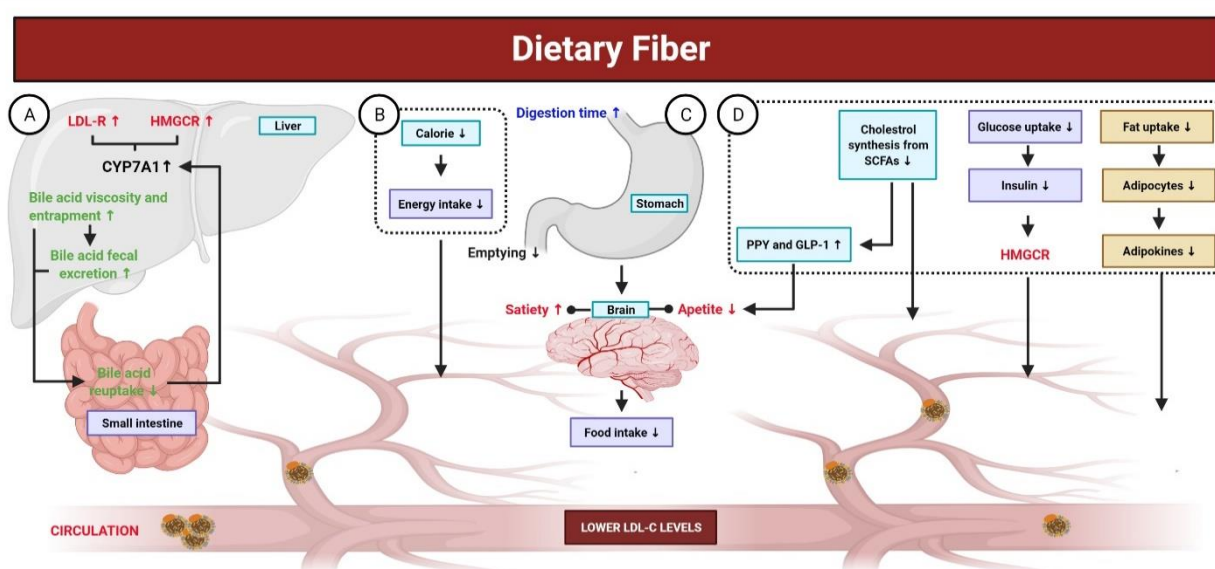


Figure 5. Mechanisms of dietary fiber in the gut.

Figure 5A Dietary fibers elevate the fecal excretion of bile acid, decrease its re-uptake in the small intestine, and inhibit bile acid permeation. A reduced enterohepatic pool of bile acid stimulates the CYP7A (the rate-limiting enzyme involved in the production of

bile acid), which, in turn, enhances liver uptake of LDL-C from blood through the upregulation of LDL-R and HMGCR. Figure 5B, C Dietary fibers exhibit fewer calories and their consumption results in a prolonged digestion time with delayed gastric emptying. Additionally, it leads to an increase in bulk-forming and satiety, as well as viscosity-induced reduced absorption of cholesterol, which eventually lower the concentration of LDL-C. Figure 5D Reduced cholesterol synthesis from SCFAs, produced by dietary fibers fermentation in the intestine, contributes to decrease the concentration of LDL-C. Certain SCFAs (propionate) enhances the release of PYY and GLP-1, both of which contribute to reduce LDL-C concentration. Additionally, dietary fibers intake leads to reduced fat uptake, altering the production of adipokines (TNF- α , resistin, and leptin), which play key roles in lipid metabolism and improving cholesterol concentration. The viscosity of dietary fibers reduces the intestinal absorption of glucose, leading to decreased secretion of insulin. Insulin is responsible for stimulating HMGCR; thus, lower insulin could decrease the concentration of LDL-C.

5.1. Epidemiological Evidence on Dietary Fiber and Health

Risk factors for CVD include obesity, diabetes, and hypertension. A prospective cohort study reported that consumption of 7 g/day of total fiber reduced the risk of CVD by 9% [224]. The same amount has been reported to decrease the risk of type-2 diabetes up to 6%, especially with whole grain foods [225]. Additionally, the study also revealed that three servings of whole grain bread reduced the risk of diabetes by 32% [225]. The ability of fibers (beta glucan) to reduce hypertension has also been observed in healthy individuals, although the reduction has been modest, as systolic pressure was reduced by 2.9 mmol Hg and diastolic pressure by 1.5 mm Hg [226]. Another systematic review deduced from various trials that the fibers content in a cereal bowl of porridge with an oat snack reduced blood cholesterol; 0.15 mmol in unclassified participants and 0.20 mmol in participants with hypercholesterolaemia [227].

Butyrate is used as an energy source by various bacteria for survival. Other SCFAs also affect fatty acid biosynthesis and oxidation. Once absorbed into the portal circulation, propionate and acetate can reduce hepatic synthesis of cholesterol and lipids [228]. Moreover, the receptor-mediated activation of SCFAs causes change in the activity of protein kinase A, which affects lipid metabolism. Propionate has also been reported to cause the release of peptide YY and glucagon-like peptide 1, which affects the metabolism and muscle uptake of free fatty acids and reduces the severity of hepatic steatosis. Adipokines are chemical messengers responsible for the metabolism of body fat and adipocytes. Fiber consumption has been reported to reduce the production of adipokines, which may result in lower production of fatty tissue. These chemical messengers are also involved in glyce-mic metabolic control [229,230].

5.2. Fiber Supplements

It has been estimated that risk of CHD in a population reduces by 2% for every 1% decrease in cholesterol [231]. Estimates indicate that in the two decades (1980–2000), health conscious behavior led to significant reductions in cholesterol intake that caused 33% reduction in mortality due to CHD in US [3,232]. Intake of dietary fibers in adequate amount is found in 5% adults. Therefore, supplements are required to provide concentrated form of fiber. Among many marketed products, psyllium, β -glucan and inulin are famous as natural supplements. Semisynthetic processed fibers include wheat dextrin, cyclodextrin and methylcellulose [233]. β -glucan containing foods can reduce the cholesterol levels of consumers. Viscous fibers such as those containing β -glucan have greater tendency to reduce cholesterol absorption. A study was conducted on 345 individuals to assess the effect of processed β -glucan supplement on LDL-C. Results depicted that administration of 3 g high viscosity β -glucan (achieved via low heat and pressurized processing) caused 5.5% reduction in LDL-C against placebo (wheat fiber) [234]. Cyclodextrin, which is produced from corn, is reported to reduce TC by 5%, LDL by 6.7%, and ApoB by 5.6%.

This reduction in lipids occurs due to the presence of cyclodextrin in the diet without changing any other dietary component, although this effect was more pronounced in patients with high serum TG and cholesterol levels [235]. A study of the effect of 2 g/day of cyclodextrin on post prandial TG levels found that the dose was sufficient to reduce blood TG levels after a fatty meal [236].

6. Concluding Remarks and Future Directions

Scientists believe that CVD can be prevented through adoption of healthy lifestyle habits and optimal improvements in risk factors including high levels of LDL-C. Phytochemicals and plant-based whole foods can achieve better LDL-C control, and their addition is highly recommended to preventive strategies either for all subjects or more focused to patients with CVD. Our review focused the beneficial effects of phytochemicals and plant-based whole foods in the management of hyperlipidemia and CVD prevention.

Phytochemicals regulate the process of lipid metabolism and multi-target intervention, which occur in cholesterol biosynthesis, absorption, transport, and elimination. NPC1L1, HMGCR, PCSK9, and CYP7A1 remain the key molecules involved in these processes. In addition, during these processes, transcription factors such as LXR, SREBP, PPAR α , and PPAR γ actively participate and mediate the lipid-lowering actions of phytochemicals. The outcomes regarding the utilization of phytochemicals are promising and emphasize the potential indication of these phytochemicals in different categories of patients. The phytochemicals described in this review are diverse, including polyphenols (pomegranate), alkaloids (berberine), flavonoids (taxifolin, quercetin), and saponins (ginsenoside). These phytochemicals are mostly safe and well tolerated. Collectively, the phytochemicals can reduce the levels of LDL-C and prevent CVD by regulating different metabolic pathways.

Plant-based whole foods are known for their LDL-C lowering potential and cardiovascular health benefits [237,238]. These foods include vegetables, fruits, legumes, nuts, whole grains, dietary fibers, and seeds [157,237]. Plant-based whole foods are abundant in dietary fibers, unsaturated fatty acids, plant proteins, multiple micronutrients like vitamins, and phytochemicals like polyphenols and phytosterols [237]. These foods influence the development of CVD either directly or indirectly by different underlying mechanisms. For example, replacing saturated fats with unsaturated fatty acids in the diet is known to reduce LDL-C [239,240]. It has been reported in multiple observational studies and randomized controlled trials, that replacing saturated fatty acids with vegetable oil polyunsaturated fatty acids decreases the risk of CVD [239].

Dietary fibers, especially viscous soluble fibers like beta-glucan, inhibit the intestinal absorption of cholesterol and re-absorption of bile acids, producing SCFAs in the colon, which may influence hepatic cholesterol synthesis, and eventually result in LDL-C-lowering effect [241]. A significant correlation has been established between dietary fibers intake and lower risk of all-cause mortality [218] and mortality from CVD as well as CHD [218,241]. Phytosterols have also been shown to block the intestinal cholesterol absorption and reduce the concentrations of circulating LDL-C [242]. Siying S Li et al. [98] showed that replacing animal protein with plant protein resulted in lower LDL-C.

Of note, all plant-based whole foods are not necessarily effective in lowering CVD risk because not all plant-based whole foods exhibit beneficial CV effects [237,243]. As we mentioned earlier that golden delicious apple per day for eight weeks elevated the serum levels of VLDL and TG, and did not show considerable effect on TC, LDL-C, HDL-C, LDL/HDL ratio, and ApoB [153]. Similarly, foods pattern with more refined grains have been linked with a higher CVD risk [244]. Therefore, the quality of plant-based whole foods and food components are of prime importance.

Although plant-based foods are generally perceived positively because of their health benefits, there are also multiple barriers that hinder the switch to, and maintenance of a plant-based diet. Common hurdles encompass health concerns that plant-based foods

may lack specific nutrients, enjoyment of eating meat and animal-based foods, and reluctance to change dietary behavior [245,246]. Similarly, there are certain other limitations and unresolved issues. For example, several bioactive components of plant-based foods have not yet been characterized; thus, further intensive investigations are needed. Moreover, the dosage of plant-based foods greatly varies, which subsequently leads to inconsistent outcomes. It is worth mentioning that plant-based foods can reduce LDL-C when utilized in defined effective nontoxic quantities. Hence, further studies are needed to optimize the doses of processed products, extracts, and compounds obtained from plant-based foods to enhance efficacy and minimize toxicity and adverse effects. Moreover, to obtain the maximum advantages of plant-based foods for the management of LDL-C and CVD, current knowledge about bioavailability and toxicity in human must be improved. The antihyperlipidemic effects of plant-based foods need to be investigated at the cellular and molecular levels in high-quality studies with systemic and in-depth analyses. Furthermore, large-scale clinical trials are also required to assure the hypolipidemic effects. Despite these shortcomings, gaps, and limitations that have to be addressed, plant-based foods are an effective strategy to manage LDL-C and CVD.

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Abbreviations

Acetyl CoA	Acetyl coenzyme A
Akt	Protein kinase B
ApoB	Apolipoprotein B
ApoB100	Apolipoprotein B100
ApoE	Apolipoprotein E
CHD	Coronary heart disease
CVD	Cardiovascular disease
CYP7A1	Cytochrome P450 Family 7 Subfamily A Member 1
ERK	Extracellular Signal-Regulated Kinase
GLP-1	Glucagon-like peptide-1
HDL	High-density lipoprotein
HDL-C	HDL cholesterol
HMG-CoA	β -hydroxy- β -methylglutaryl coenzyme A
HMGCR	β -hydroxy- β -methylglutaryl coenzyme A reductase
IDL	Intermediate-density lipoprotein
LDL	Low-density lipoprotein
LDL-C	LDL Cholesterol
LDLR	Low-density lipoprotein receptor
LDLR ^{-/-}	Deleted low-density lipoprotein receptor
LXR	Liver X receptor
MKK3	Mitogen-activated protein kinase kinase 3
mTORC1	Mammalian target of rapamycin complex 1 or mechanistic target of rapamycin complex 1
MTTP	Microsomal triglyceride transfer protein large subunit
PPAR α	Peroxisome proliferator-activated receptor alpha
PPAR β	Peroxisome proliferator-activated receptor beta
PPAR γ	Peroxisome proliferator-activated receptor gamma
PPY	Peptide YY
ROS	Reactive oxygen species
SCFAs	Short-chain fatty acids

S-equal	7-Hydroxy-3-(4'-hydroxyphenyl)-chroman
SNP	Single-nucleotide polymorphism
SOD	Superoxide dismutase
SREBP-1c	Sterol regulatory element-binding protein-1c
TAK1	Mitogen-activated protein kinase kinase kinase 7
TC	Total cholesterol
TGTC	TriglyceridesTotal cholesterol
VLDL	Very low-density lipoprotein
TG	Triglycerides
VLDL	Very low-density lipoprotein

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