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Herbal Products for Cholesterol Lowering: A Narrative Overview

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Abstract

Introduction: Hypercholesterolemia is a leading cardiovascular risk factor with a global prevalence of approximately 24%, contributing substantially to atherosclerotic disease. Despite the well-established efficacy of statins and other pharmacological agents, adherence remains a challenge due to adverse effects and patient reluctance toward conventional therapy.

Purpose: This narrative review synthesizes current evidence on the lipid-modulating properties of seven herbal products and nutraceuticals: garlic, green tea, guggul, red yeast rice, fenugreek, artichoke, and berberine. It focuses on their mechanisms of action, clinical efficacy, and safety profiles.

Current knowledge: The reviewed compounds exhibit diverse lipid-lowering mechanisms, including HMG-CoA reductase inhibition, LDL receptor upregulation, reduced intestinal cholesterol absorption, and enhanced bile acid excretion. Red yeast rice, owing to its lovastatin content, holds the strongest clinical evidence, achieving LDL-C reductions of 15-34%. Berberine and artichoke leaf extract also show consistent lipid-lowering effects. Evidence for garlic, green tea, and fenugreek is promising but heterogeneous. Guggul data remain conflicting, with some trials reporting adverse lipid outcomes.

Conclusions: These nutraceuticals may serve as adjunctive interventions alongside lifestyle modification in selected patients but cannot replace established pharmacotherapy. Large-scale, standardized randomized controlled trials are needed to confirm their efficacy and long-term safety.

Key words: Hypercholesterolemia, Hypolipidemic Agents, Phytotherapy, Dietary Supplements, Dyslipidemias, Cardiovascular Diseases

1. Introduction

Hypercholesterolemia remains a major global public health concern and represents a key component of the broader spectrum of dyslipidemias. Epidemiological data indicate that the overall prevalence of hypercholesterolemia is approximately 24.1%, while other lipid abnormalities are also highly common, including hypertriglyceridemia (28.8%), low high-

density lipoprotein cholesterol (HDL-C) (38.4%), and elevated low-density lipoprotein cholesterol (LDL-C) (18.93%). Furthermore, sex-specific analyses reveal important differences in dyslipidemia distribution, with hypertriglyceridemia more commonly observed in men, while women tend to present a higher prevalence of low HDL-C levels [1]. Dyslipidemia is one of the most common cardiovascular risk factors worldwide, occurring alongside traditional contributors such as tobacco use, unhealthy lifestyle behaviors, and elevated blood pressure. Importantly, elevated total cholesterol is strongly associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD), with evidence suggesting that each 10 mg/dL increase corresponds to an approximate 5–10% rise in risk [2].

Cholesterol originates from both in situ biosynthesis and systemic circulation. De novo synthesis begins with acetyl-CoA, which is converted into mevalonate in a rate-limiting step catalyzed by HMG-CoA reductase, allowing tight regulation of cellular cholesterol levels. Mevalonate is subsequently converted into squalene and then into lanosterol. From this point, cholesterol biosynthesis proceeds via two pathways: the Bloch pathway, in which lanosterol is converted to desmosterol, and the Kandutsch–Russell pathway, leading to the formation of 7-dehydrodesmosterol [3].

Due to their hydrophobic nature, cholesterol and triglycerides are insoluble in aqueous environments and therefore must be transported in the bloodstream as lipoproteins. These are spherical macromolecular complexes composed of a core containing triglycerides and cholesteryl esters, surrounded by a surface monolayer of phospholipids, free cholesterol, and apolipoproteins [2]. Lipoproteins are classified into five main types based on their density: chylomicrons (CM), very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL), which can interconvert during lipid transport and metabolism. Their protein components, including apolipoproteins such as ApoA, ApoB, ApoC, ApoD, and ApoE, play essential roles in maintaining structural integrity and regulating lipid transport and cellular uptake [3].

Different lipoproteins perform distinct functions in cholesterol transport. Low-density lipoprotein (LDL), which contains apolipoprotein B-100, is primarily responsible for transporting cholesterol from the liver to peripheral tissues by mediating binding to specific cell-surface receptors. Under normal physiological conditions, this cholesterol is utilized for essential processes such as cell membrane synthesis and hormone production. However, when LDL levels are excessive, the particles can undergo oxidative modification, which triggers the initiation and progression of atherosclerosis [4]. High-density lipoprotein (HDL), on the other hand, is involved in reverse cholesterol transport or efflux, which helps remove excess cholesterol from tissues. HDL facilitates the circulation of this surplus cholesterol and delivers it to the liver for recycling or disposal. This process protects against the formation of atherosclerotic plaques and inflammation, which is why HDL is commonly referred to as “good cholesterol” [5].

Reduction of low-density lipoprotein cholesterol (LDL-C) is one of the most effective modifiable strategies to lower cardiovascular disease (CVD) risk. Management is typically combined with lifestyle interventions such as diet and exercise of hypercholesterolemia and it relies on drugs that lower LDL-C through different mechanisms. Statins, the first-line therapy, inhibit HMG-CoA reductase, reducing hepatic cholesterol synthesis and increasing LDL receptor–mediated clearance. Ezetimibe decreases intestinal cholesterol absorption by blocking the NPC1L1 transporter, thereby enhancing LDL removal. PCSK9 inhibitors (e.g., alirocumab, evolocumab) prevent degradation of LDL receptors, increasing their recycling and LDL-C clearance. Bempedoic acid inhibits ATP citrate lyase upstream of HMG-CoA reductase, reducing cholesterol

synthesis and upregulating LDL receptors. Inclisiran, an siRNA therapy, decreases hepatic PCSK9 production, leading to increased LDL receptor availability and reduced circulating LDL-C [6].

Current guidelines for the management of dyslipidemia do not recommend dietary supplements or vitamins as part of standard therapy [7,8]. However, despite the well-established efficacy of statins, adherence remains a significant issue, as some patients discontinue treatment due to statin-associated muscle symptoms or concerns about adverse effects [6]. Consequently, there is ongoing interest in herbal medicines and natural products as potential alternatives or adjuncts in the management of hypercholesterolemia and other dyslipidemias. These approaches may be particularly appealing to individuals who are reluctant to use conventional pharmacotherapy, highlighting the need for further research into their efficacy and safety. The aim of this narrative review is to summarize and evaluate the current evidence on the use of herbal medicines and natural products in the management of hypercholesterolemia. Particular attention is given to their mechanisms of action, efficacy, and safety.

2. Methods

This article constitutes a narrative review of the literature aimed at analyzing current scientific evidence regarding the use of herbal medicines for lowering cholesterol levels and improving lipid profiles. Studies investigating these agents both as adjunctive therapies and as primary treatment options in dyslipidemia were taken into account.

A literature search was conducted for publications from 2016 to 2026 using electronic databases, including PubMed, Scopus, Web of Science, and the Cochrane Library. Clinical trial registries such as ClinicalTrials.gov were also searched. Additionally, supplementary tools, including Google Scholar and ResearchGate, were utilized to identify further relevant studies. The search strategy also incorporated snowballing techniques, whereby references of selected articles were manually reviewed to identify further eligible studies.

The research query was constructed using a combination of keywords related to herbal medicines and lipid disorders, expanded to ensure comprehensive coverage of the topic. Keywords referring to herbal interventions included general terms such as “herbal medicine”, “phytotherapy”, “medicinal plants”, “herbs” and “phytochemicals” as well as specific agents with documented or potential lipid-lowering effects, including “garlic”, “Allium sativum”, “green tea”, “artichoke”, “guggul”, “red yeast rice”, “monacolin K”, “red rice koji”, “fenugreek”, and “berberine”. These were combined with keywords related to lipid disorders, including “hypercholesterolemia”, “hyperlipidemia”, “cholesterol”, “LDL”, “HDL”. The search strategy employed Boolean operators to combine terms: synonyms within each category were linked using OR, while terms from the herbal medicine group were combined with lipid disorder terms using AND.

The literature search was performed in April and May 2026. The inclusion criteria encompassed experimental studies, including randomized controlled trials (RCTs) and quasi-experimental studies, as well as review articles, including systematic reviews and meta-analyses. Only studies conducted in human populations were considered. Publications in languages other than English and Polish were excluded.

The aim of this review was to provide a comprehensive and synthesized overview of current evidence that may support clinical decision-making in the management of patients with dyslipidemia, particularly in cases where conventional pharmacotherapy is poorly tolerated or declined by patients. The limitations of this review include the potential subjectivity in the

selection of literature and the restriction to selected databases, which may have influenced the completeness of the evidence base.

3. Overview

3.1. Garlic

Garlic (*Allium sativum* L.) has long been used as both a dietary ingredient and a traditional medicinal remedy, particularly in Asian countries, for the prevention and treatment of various diseases. [9,10]. It contains multiple organosulfur compounds, such as allicin, alliin, S-allyl cysteine (SAC), ajoene, diallyl sulfides, diallyl disulfide and diallyl trisulfide, that are thought to be responsible for many of its biological effects. Commercially available garlic preparations include fresh or raw garlic, garlic powder, garlic oil, aged garlic extract (AGE), aged black garlic, dried garlic homogenate and tablet formulations. It is important to note that these preparations differ substantially in terms of their composition of active compounds, bioavailability, and potential clinical efficacy. AGE has attracted particular interest as it contains stable sulfur compounds, especially S-allylcysteine, and may exert antioxidant and endothelial-protective effects [9].

Garlic may exert lipid-lowering effects through multiple mechanisms associated mainly with its organosulfur compounds [9]. Garlic and its constituents may decrease cholesterol absorption, as well as the synthesis of cholesterol and fatty acids, by inhibiting enzymes involved in cholesterol biosynthesis. These include HMG-CoA reductase, squalene monooxygenase, lanosterol 14α-demethylase and sterol 4α-methyl oxidase [9,11,12]. Other proposed mechanisms include enhancing bile acid excretion and inhibiting hepatic fatty acid synthesis [11,12]. Furthermore, garlic and aged garlic extract (AGE) have been reported to suppress LDL oxidation and reduce oxidative stress, potentially contributing to anti-atherosclerotic effects [9,11,12]. Garlic and its active compounds may also modulate inflammatory pathways involving IL-1, TNF-α and nitric oxide signaling. Furthermore, garlic has been shown to influence the expression of proteins and genes associated with lipid transport and metabolism, including microsomal triglyceride transfer protein, acyl-CoA cholesterol acyltransferase, cholesteryl ester transfer protein, Niemann–Pick C1-like 1, ABC transporters and AMPK signaling pathways [9].

Available evidence suggests that garlic supplementation may have lipid-lowering effects, particularly with regard to total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). In a network meta-analysis of 26 garlic trials involving 1,620 participants, Osadnik et al. demonstrated that garlic supplementation reduced LDL-C levels, with a mean difference (MD) of −0.21 mmol/L compared with placebo or no intervention [13]. Similarly, Sun et al. reported significant reductions in both TC and LDL-C levels following garlic supplementation in a meta-analysis of 14 randomized controlled trials involving 1093 participants with hyperlipidemia [11]. Du et al. reported comparable findings in a meta-analysis of 21 randomized controlled trials involving 1,603 participants with dyslipidemia or hyperlipidemia who were not receiving lipid-lowering drugs. They observed reductions in TC (WMD −0.64 mmol/L) and LDL-C (WMD −0.44 mmol/L) [12]. In a systematic review and meta-analysis evaluating multiple garlic preparations, Li et al. demonstrated a significant reduction in TC levels following garlic supplementation. Although reductions in LDL-C were also observed, the findings were affected by publication bias and heterogeneity, and were no longer statistically significant after sensitivity analyses [10].

The effects of garlic supplementation on HDL-C appear to be less consistent. Although Sun et al. reported a moderate increase in HDL-C levels, the findings were not consistent across sensitivity analyses [11]. Similarly, Du et al. observed only a small increase in HDL-C levels, whereas Li et al. reported no statistically significant overall effect [10,12]. Evidence regarding the effects of garlic on triglyceride levels is also inconsistent. Sun et al. found no significant effect on TG concentrations, whereas Du et al. demonstrated a modest reduction [11,12]. Li et al. similarly reported no significant overall effect on triglycerides [10].

In a randomized clinical trial, Ashraf et al. investigated standardized garlic tablets (KWAI®; 300 mg tablets containing 1.3% alliin and 0.6% allicin) and observed significant improvements in lipid profile parameters, including reductions in TC, LDL-C and TG together with increased HDL-C levels. Importantly, the study suggested that higher doses (1.2–1.5 g/day) and longer treatment duration (24 weeks) were associated with greater lipid-lowering effects. However, these findings should be interpreted cautiously due to the relatively small sample size and methodological limitations of the study [14].

Importantly, substantial heterogeneity was observed across studies, which may be partly explained by differences in garlic formulations, dosage, intervention duration and study populations. Overall, current evidence suggests that garlic supplementation may improve selected lipid profile parameters, particularly TC and LDL-C levels; however, further high-quality long-term studies are needed [11,12].

3.2. Green tea

Tea derived from the plant *Camellia sinensis* is one of the most widely consumed beverages worldwide, second only to water [15,16]. Green tea represents nearly 20% of total tea intake worldwide. Its leaves exhibit hypolipidemic and anti-obesity properties due to their high content of biologically active compounds, including polyphenols, alkaloids, essential oils, vitamins and amino acids [17].

In particular, green tea is rich in antioxidant compounds known as catechins, including epigallocatechin gallate (EGCG), epicatechin (EC), and epigallocatechin (EGC). Among these compounds, EGCG is present in the highest concentration and has additionally been shown to possess anti-inflammatory and antioxidant properties [16–18].

According to the study conducted by Xu and colleagues, the beneficial effects of green tea on lipid regulation are moderated by catechins. The authors described several potential mechanisms underlying these effects.

- First, EGCG may attenuate endothelial dysfunction induced by oxidized LDL via the Jagged-1/Notch signaling pathway in human umbilical vein endothelial cells, thereby reducing the formation of atherosclerotic plaques.
- Second, catechins exhibit potent antioxidant activity, which may inhibit LDL oxidation.
- Third, EGCG has been shown to increase LDL receptor-binding activity in HepG2 cells in a dose-dependent manner through regulation of the sterol regulatory element-binding protein-1 (SREBP-1) pathway.
- Fourth, catechins may reduce intestinal lipid absorption by interfering with micelle formation [16,18].

A study conducted by Wang and colleagues investigated the effects of green tea on metabolic parameters in mice. The animals were divided into three groups, each receiving a high-fat diet supplemented with different concentrations of green tea powder for a period of 12 weeks. Following the intervention, cecal microbiota composition and fecal short-chain fatty acids were analyzed. Although administration of green tea extract did not significantly affect overall body weight, it greatly reduced the mass of internal organs. Additionally, green tea supplementation significantly lowered serum leptin concentrations while improving leptin sensitivity and reducing leptin resistance. An increase in serum adiponectin levels was also observed. Since adiponectin is associated with lipoprotein metabolism, its elevation may contribute to increased HDL-C levels and reduced triglyceride concentrations. In contrast, mice maintained singly a high-fat diet developed leptin resistance, which subsequently contributed to insulin resistance and hepatic steatosis [19].

In another in vivo study conducted in 2022, researchers evaluated the effects of probiotics combined with potential prebiotics, including green tea, using rats. Forty-eight adult male rats were divided into seven groups, each consisting of eight animals. The first group received a high-fat diet, the second served as the negative control group, while the remaining groups received probiotics supplemented with potential prebiotics. Similarly to previous findings, individual prebiotic supplementation reduced liver and kidney mass as well as relative subcutaneous fat mass, while exerting only a minor effect on total body weight. Similar observations were previously reported by Chen and colleagues. General, present evidence suggests that green tea extract may effectively improve plasma lipid profiles, alleviate oxidative stress, and reduce liver enzyme levels in rats fed a high-fat diet [17,20].

A systematic review and meta-analysis conducted by Xu and colleagues demonstrated that green tea supplementation can reduce plasma triglyceride levels, total cholesterol, and low-density lipoprotein cholesterol in both in vitro and animal studies. Despite that, the results of human clinical trials remain inconsistent. The authors observed that previous meta-analyses were consistent with their findings [16].

A 2023 systematic review and meta-analysis conducted by Mani and colleagues evaluated the impact of green tea supplementation on cardiovascular risk factors. The results indicate that green tea consumption is associated with moderate improvements in lipid profile parameters. These improvements were statistically significant. It particularly reduced triglyceride and LDL cholesterol levels. Additionally, the meta-analysis showed an increase in HDL cholesterol levels. A beneficial effect on glycemic control was also observed. Similar findings were previously reported in a 2014 meta-analysis by Onakpoyaa and colleagues [18,21]. These findings further support the hypothesis that green tea exerts a positive effect on lipid metabolism, particularly by increasing HDL cholesterol levels [18].

Despite promising findings, Xu with colleagues emphasize that determining the optimal dose of green tea supplementation to achieve the desired effect remains a challenge for researchers [16].

Unfortunately, research also reveals adverse effects of green tea supplementation. For patients with calcium oxalate kidney stones, green tea may be the primary source of oxalates in their diet [16].

3.3. Guggul

Guggul is an oleo-gum resin gathered from plants within the Burseraceae family, mainly *Commifora mukul* and *Commiphora wightii*, and has been well known in Ayurvedic medicine for at least 600 years [22,23]. Guggulipid extracted from this resin and its content of plant sterols, mainly guggulsterones E and Z, is responsible for its biochemical properties. Eastern medicine

has been exploring the properties of this substance since 1994 [22,24]. Before that, most of the studies on guggul's therapeutic properties have been carried out in Asia, mostly in India. They suggested that guggulipid causes significant reductions in serum total cholesterol, low-density lipoprotein, and triglycerides, as well as elevations in high-density lipoprotein, however, the majority of available literature is limited due to the small sample sizes and flawed methodology [22].

Andrea Leiva et al. [25] conducted a study on the effects of gugulipid on cholesterol metabolism and cardiovascular health in male mice. They used C57BL/6 mice, apolipoprotein E knockout (ApoE KO) mice, and SR-BI KO/ApoER61h/h mice placed under similar conditions. One group received a standard low-fat/low-cholesterol diet, and the other an atherogenic diet with or without gugulipid. They observed: liver abnormalities, elevated liver enzyme levels, impaired endothelial function, increased cholesterol levels, more extensive atherosclerotic plaque formation, and a higher risk of premature death from ischemic heart disease in the group treated with guggulipid. Their findings are consistent with one of the first high-quality randomized clinical trials carried out in human population, which indicated increases in serum LDL levels associated with the use of guggul compared to placebo [22,26].

Fogacci et al. [27] in their randomized clinical trial assessed the effects of a supplement containing berberine, red yeast rice, milk thistle, and guggul dry extract (50 mg, standardizing to 1.3 mg of active guggulsterones) on cholesterol metabolism and the cardiovascular system in humans. Their study group consisted of 49 men and 31 women with low-density lipoprotein-cholesterol (LDL-C) between 130 and 190 mg/dl with a low estimated cardiovascular disease risk. Before randomization, all patients were on a Mediterranean diet for 4 weeks. After 8-weeks period they reported reduction in low-density lipoprotein cholesterol (-18.1% ± 1.9%), total cholesterol (-15.2% ± 1.4%), and high-sensitivity C-reactive protein (-3.7% ± 0.7%) in group receiving treatment in comparison to the baseline and placebo group. Additionally, endothelial reactivity significantly improved post-treatment within the active group, although the between-group difference versus placebo was not statistically significant. The limitation of their study on the guggul therapeutic potential is that it has been utilized in combination with other substances, which are described as potentially lowering cholesterol.

3.4. Red yeast rice

Red yeast rice (RYR; also known as red koji, Beni-Koji or Hongqu) is produced by culturing filamentous fungi of the genus *Monascus* on steamed rice, yielding a product with a characteristic deep-red color from the pigments secreted during fungal growth. Its origins lie in East and Southeast Asia, where the humid and warm climate favors use of fungi as opposed to malt or fruit-based fermentation typical of Western food cultures [28].

Monacolins are a class of metabolites produced during the fermentation of RYR by *Monascus* species. At least fourteen have been identified, including monacolins J, L, and X. The structural diversity within this compound family suggests that mixtures of monacolins, as found in RYR preparations, may exert synergistic or additive pharmacological effects. The most extensively studied and pharmacologically significant member of this class is monacolin K (MK), also known as lovastatin. The primary mechanism by which MK lowers cholesterol is competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, rate-limiting hepatic cholesterol biosynthesis. Beyond direct enzyme inhibition, MK modulates a broader network of lipid-metabolic regulators, including enzymes and transcription factors governing HDL-C, LDL-C, and apolipoprotein B [29].

Because the primary active compound in red yeast rice is lovastatin, it may cause side effects similar to those associated with statins, such as muscle pain or weakness, liver dysfunction, and gastrointestinal symptoms including nausea or abdominal discomfort [30].

Trogkanis et al., in a systematic review and meta-analysis restricted to 14 double-blind clinical trials, found that RYR extract produces statistically significant reductions in total cholesterol and LDL-cholesterol of approximately 37 and 36 mg/dL, respectively, compared to placebo. Effects on HDL-cholesterol, triglycerides, and apolipoproteins were inconsistent across studies and not significant in pooled analyses. Reported adverse events were rare and non-life-threatening, with no life-threatening complications observed [31].

Cicero, Fogacci, and Banach characterized RYR as the most effective cholesterol-lowering nutraceutical currently available, noting that daily consumption of monacolin K reduces LDL-cholesterol plasma levels by 15–25% within six to eight weeks. This reduction is accompanied by proportional decreases in total cholesterol, non-HDL-cholesterol, apolipoprotein B, matrix metalloproteinases 2 and 9, and high-sensitivity C-reactive protein. Additional benefits on pulse wave velocity and endothelial function were documented, and a long-term Chinese trial in post-myocardial infarction patients supported a role in secondary cardiovascular prevention. The authors concluded that the risk associated with 3–10 mg of monacolin K per day is minimal, with mild myalgia reported only in previously statin-intolerant subjects [32].

English confirmed these figures in a narrative review, reporting LDL-cholesterol reductions of up to 34% compared to placebo at the same daily dose range, alongside reductions in blood pressure and inflammatory markers [33].

Jamialahmadi et al., in a meta-analysis specifically focused on monacolin K-containing supplements across a range of doses and durations, reinforced the finding that such products are effective in lowering lipid levels, with LDL-cholesterol emerging as the most consistently affected [34].

3.5. Fenugreek

Fenugreek (*Trigonella foenum-graecum* L.) is a leguminous plant traditionally used both as a culinary ingredient and as a medicinal herb. In the context of cardiovascular and metabolic health, most interest has focused on fenugreek seeds, which contain soluble fiber, particularly galactomannan, steroidal saponins, alkaloids such as trigonelline, flavonoids, free amino acids including 4-hydroxyisoleucine, and other bioactive compounds [35–37]. These constituents may be relevant to lipid metabolism, although the clinical significance of each individual component remains difficult to isolate because most human studies have evaluated whole seed powder or complex seed extracts rather than purified compounds [38,39].

The lipid-lowering potential of fenugreek is usually explained by several complementary mechanisms. First, its soluble fiber fraction, especially galactomannan, may reduce intestinal absorption of nutrients and lipids by increasing luminal viscosity and modifying nutrient diffusion and absorption [37]. Second, steroidal saponins and fiber-containing fractions have been proposed to influence cholesterol and bile acid handling in the intestine, which may increase fecal elimination of bile acids and cholesterol-derived compounds [35–37]. Because bile acids are synthesized from cholesterol, increased bile acid loss may theoretically enhance hepatic cholesterol utilization and contribute to reductions in circulating total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) [36,37]. Third, fenugreek may exert indirect lipid-modulating effects through improved glycemic control and insulin sensitivity, which is particularly relevant because many clinical trials have been conducted in patients with type 2 diabetes mellitus or prediabetes rather than in patients with isolated dyslipidemia [40,41].

Clinical evidence suggests that fenugreek supplementation may have beneficial effects on serum lipids, but the magnitude and consistency of these effects vary between studies. In a systematic review and meta-analysis focused specifically on lipid profile, Heshmat-Ghahdarijani et al. evaluated randomized clinical trials in which fenugreek intake was associated with changes in at least one lipid parameter, including triglycerides (TG), TC, LDL-C, or high-density lipoprotein cholesterol (HDL-C) [39]. This analysis supports the view that fenugreek may improve selected lipid parameters, although heterogeneity between trials limits the certainty of a uniform effect across populations and preparations [39].

A second systematic review and meta-analysis of randomized controlled trials by Askarpour et al. also reported favorable effects of fenugreek supplementation on blood lipids. In that analysis, fenugreek was associated with reductions in TC, TG, and LDL-C, as well as an increase in HDL-C, while no significant effect was observed on body weight or body mass index [38]. This distinction is clinically relevant because it suggests that the lipid effects observed in the included trials were not necessarily explained by weight loss alone. However, the included studies differed in participant characteristics, baseline metabolic status, fenugreek formulation, dose, and duration of supplementation, which restricts the ability to define a single optimal regimen [38,39].

The relationship between fenugreek, glucose metabolism, and lipid profile is particularly important in patients with diabetes or prediabetes. Gong et al. conducted a meta-analysis in these populations and found that fenugreek improved hyperglycemia and showed lipid-related benefits, particularly for TC, although effects on other lipid fractions were less consistent and required further confirmation [40]. This supports a cautious interpretation: fenugreek may be most relevant as part of a broader metabolic intervention rather than as a specific cholesterol-lowering agent comparable to established pharmacotherapy [40,41].

More recent evidence has expanded this metabolic perspective. A dose-response meta-analysis of randomized clinical trials assessing components of metabolic syndrome found that fenugreek supplementation significantly improved TG and HDL-C, together with fasting plasma glucose, waist circumference, and systolic blood pressure, while effects on body mass index and diastolic blood pressure were not significant [41]. These findings suggest that fenugreek may influence several interconnected cardiometabolic risk factors. Nevertheless, they also reinforce that fenugreek should be discussed as a complementary nutritional or herbal intervention rather than as a replacement for standard lipid-lowering treatment [38,41].

Individual randomized trials show why the evidence should not be overstated. In an exploratory double-blind randomized placebo-controlled trial in participants with early glucose dysregulation, Pickering et al. assessed a specialized *Trigonella foenum-graecum* seed extract over 12 weeks. The study reported improvements in some glycemic outcomes and TG, but did not demonstrate significant changes in TC, LDL-C, or HDL-C compared with placebo [42]. This finding is important because it shows that not all fenugreek preparations or study populations produce broad lipid improvements.

In contrast, Geberemeskel et al. reported favorable changes in lipid profile among newly diagnosed patients with type 2 diabetes receiving fenugreek seed powder solution, including reductions in TC, TG, and LDL-C and an increase in HDL-C [43]. However, the dose used in this study was high, which may limit direct extrapolation to commercially available dietary supplements or to routine dietary use [43]. A more recent double-blind randomized clinical trial in patients with type 2 diabetes evaluated fenugreek seed dry extract and found limited between-group lipid effects, with HDL-C being the main lipid parameter showing improvement

[44]. Together, these trials indicate that the clinical response may depend on dose, formulation, baseline metabolic status, and duration of intervention [42–44].

From a safety perspective, fenugreek is generally considered well tolerated in clinical studies, but adverse effects should be considered, especially when medicinal doses are used. Gastrointestinal symptoms, such as bloating, diarrhea, flatulence, nausea, dyspepsia, or abdominal discomfort, may occur, particularly at higher doses [42,45]. Because fenugreek has been associated with glucose-lowering effects, caution is warranted in patients receiving glucose-lowering medication, particularly when fenugreek is used in concentrated extracts or high-dose seed powder preparations [40,45]. Use during pregnancy should be approached conservatively at medicinal doses because toxicological data have raised concerns about reproductive and developmental safety, even though culinary exposure is a different context from high-dose supplementation [45].

Overall, fenugreek appears to be a promising adjunctive herbal product for lipid profile modulation, especially in individuals with coexisting metabolic disturbances such as type 2 diabetes, prediabetes, or metabolic syndrome. The most consistent findings concern reductions in TG and TC, with less uniform effects on LDL-C and HDL-C across individual trials [38–41]. Current evidence does not support fenugreek as a substitute for established lipid-lowering therapies, but it may have a role as part of a broader lifestyle-based approach. Future trials should use standardized preparations, clearly defined doses, longer follow-up, and lipid endpoints as primary outcomes in populations with well-characterized dyslipidemia [38,39,41].

3.6. Artichoke

Artichoke (*Cynara cardunculus* L. var. *scolymus*), a plant native to the Mediterranean basin, has a long history of use for digestive and hepatic complaints. Its therapeutic potential is attributed to a rich profile of bioactive compounds, including phenolic acids (chlorogenic acid, cynarin, caffeic and ferulic acids), flavones (apigenin and luteolin and their glycosides), anthocyanins, and the prebiotic carbohydrate inulin. Luteolin inhibits insulin-dependent HMG-CoA reductase activity, thereby suppressing hepatic cholesterol biosynthesis, while artichoke extracts further reduce cholesterol through inhibition of intestinal absorption via acetyl-coenzyme A acetyltransferase (ACAT) and increased biliary excretion [46].

A 2017 systematic review and meta-analysis by Sahebkar et al. pooled data from 9 RCTs including 702 subjects and found that artichoke leaf extract (ALE) supplementation was associated with significant reductions in total cholesterol, LDL-C, and triglycerides, with no significant change in HDL-C. Importantly, meta-regression revealed that the magnitude of LDL-lowering correlated directly with baseline LDL-C concentrations, suggesting that patients with more pronounced dyslipidemia stand to benefit most. Neither dose nor duration of supplementation independently predicted the LDL response [47].

A more recent comprehensive meta-analysis by Jafari et al., encompassing 15 trials and 985 participants, confirmed these lipid-lowering effects, reporting reductions in total cholesterol, LDL-C, and triglycerides, again without a significant effect on HDL-C. Subgroup analyses indicated that effects were more pronounced in older adults and in those with healthy or overweight BMI, and that shorter intervention durations of eight weeks or less produced greater reductions in total cholesterol and LDL-C [48].

A narrative review by Santos et al. synthesized the clinical evidence on mechanisms and noted that effective ALE doses in published trials ranged from 2 to 3 g/day, with reported LDL reductions of 8-49 mg/dL, total cholesterol reductions of 12-55 mg/dL, and triglyceride reductions of 11-51 mg/dL across studies [49].

HDL-C has been largely unaffected in most trials; however, a prospective study by Rondanelli et al. in adults with low HDL-C and mild hypercholesterolemia found a significant increase in HDL-C following 60 days of ALE supplementation (500 mg/day), alongside reductions in the ApoB/ApoA ratio and total-C/HDL-C ratio [50]. Notably, ALE also showed meaningful lipid-lowering effects in a double-blind RCT of chronic kidney disease patients, a population with distinct dyslipidemia characterized by small dense LDL particles and elevated cardiovascular risk, where 640 mg/day for 6 weeks significantly reduced total cholesterol and LDL-C without adverse events [51].

ALE is generally well tolerated at recommended doses. Across recent RCTs, adverse event rates are low: with dyspepsia reported in 1 of 45 patients (~2%) in one active-treatment arm [52]. Gastrointestinal complaints (bloating, flatulence, nausea), associated primarily with high soluble fiber intake rather than the extract itself; more relevant when consuming whole artichoke hearts than standardized ALE [49]. Some trials reported no adverse effects [50,51].

3.7. Berberine

Berberine is an isoqinoline plant-based alkaloid- the active component of *Coptidis rhizoma, Coptis chinensis* and *Berberis vulgaris* - traditional Chinese herb often used also in Ayuverdic medicine [53–55]. Through years of research berberine was sought to have antidiabetic, cholesterol-lowering and even anti-cancer activity [56], as well as positive effect in treating endocrine dysfunctions like PCOS [57]. It is a well-known and highly distributed nutraceutical gaining increasing popularity not just as a supplement, but also as a form of treatment.

The mechanism of berberine on modulating cholesterol has been partially ascertained as being not confined to a single receptor or gene. Rather it involves simultaneous modulation of multiple intersecting cellular pathways.

The primary mechanism of action includes increasing expression of LDL receptors by elongating the biological half-life of mRNa responsible for LDLR, which leads to increased uptake of LDL in blood [55,58,59]. Berberine also suppresses transcription of PCSK9- the enzyme that binds to LDL receptors on the surface of hepatocytes, targeting LDL for lysosomal degradation. That prevents degradation of internalized receptors, allowing them to recycle back to the cell surface to capture additional LDL particles [55,58,60]. Berberine also activates AMPK pathway, which coordinates energy balance and lipid synthesis. AMPK is a central regulator of cellular energy homeostasis. Activation of the kinase leads to suppression of anabolic processes, including hepatic lipogenesis, downgrading synthesis of new fatty acids and cholesterol. That directly reduces subsequent secretion of lipids [58,61]. Other metabolic pathways activated by berberine include activation of acetylo-CoA carboxylase and increase of peroxisome proliferator-activated receptors (PPARs). In addition to inhibiting synthesis and enhancing hepatic uptake, berberine actively promotes the physical elimination of cholesterol from the body. Experimental studies (e.g., in high-fat diet-induced hyperlipidemic hamsters) have demonstrated that berberine administration directly promotes and accelerates the fecal excretion of cholesterol, thereby preventing its intestinal reabsorption and subsequent tissue accumulation [53].

Many studies also found connections between berberine supplementation Gut microbiota [62]. Berberine exhibits a complex effect on Gut microbiome- it inhibits the proliferation of pathogenic and pro-inflammatory bacteria, while simultaneously promoting the selective growth of beneficial bacteria strains [62]. Berberine improves intestinal barrier function by increasing the proportion of mucin-degrading bacteria produced. Increasing the number of short-chain fatty acid producing bacteria leads to a more regulated inflammatory response. Berberine supplementation also decreases the amount of Gram-negative bacterial strains that

often produce LPS (Endotoxin plasma lipopolysaccharide), which leads to lower levels of inflammatory cytokines. It was also shown to regulate TL4/TnF-a activation induced by LPS [62]. Increase of bile-acid decomposing bacteria directly leads to cholesterol regulation. Decomposing of bile acids directly enhances bile-acid receptors such as FXR and TGR5. Berberine is an agonist of those receptors and regulates bile acid signal and function.

The pharmacokinetics of metabolism of natural berberine, show that it has very low bioavailability after oral administration [58,63]. It is an effect of low absorption in the intestines and fast metabolism in the body, but rather than it being a limitation, this pharmacokinetics profile facilitates a direct intensive interaction with the Gut microbiota, because the bacteria are responsible for transforming berberine into absorbable form. From a clinical point of view, the state of a patient's microbiota directly reflects the possible anti-hypercholesterolemic effect of berberine. Profiling an individual's microbiota prior to the initiation of therapy can facilitate the prediction of cholesterol-decreasing efficacy of Berberine supplementation for that specific patient. This represents a promising advancement toward the personalization of dyslipidemia management using nutraceuticals [64].

Low bioavailability was also addressed by production of derivatives such as HTD1801 which is a compound of berberine and ursodeoxycholic acid which also has cholesterol-lowering effect. Administration was connected with decrease in LDL serum levels and had minor adverse effects [65]. Another derivative has been made with structural changes of berberine by creating an analog with Carbon-9 position. Such optimization may lead to improved target receptor engagement and enhanced systemic absorption [63,66].

In a randomized controlled study conducted in 2021, a group of male patients, who had been taking berberine for 12 weeks reported larger reduction in cholesterol than a group taking placebo [55]. Those results are compatible with other studies testing berberine effect on both humans and animals. Regular berberine supplementation was often connected to improved cholesterol-levels, lower risk of cardiovascular diseases and was a well-documented tool in treatment of metabolic-syndrome [55,60,67]. Experimentation studies also showed synergistic effects of therapy with berberine and resveratrol. Combination of the two lead to higher hypolipemic effectiveness through increased activation of metabolic pathways [54]. Mice given berberine and resveratrol showed decreased plasma level of total cholesterol, triglycerides and LDL-c, in comparison to control groups.

Even though berberine is often well tolerated with low incidence of experienced adverse effects such as: gastrointestinal discomfort, diarrhea, nausea, fullness, and increase in plasma bilirubin levels [58,67–69]. Berberine can interact with many drugs- such as macrolides or statins, and should be avoided in pregnant women and infants [58]. Although it is a safe supplement, it should be advised carefully, after individual consideration of each patient.

While there is enough scientific evidence to prove efficiency of berberine supplementation, the economical aspect of the treatment is often forgotten. Study conducted by White et al. 2024, showed that the cost effectiveness of nutraceuticals, including berberine, is worse in comparison to commonly used statins [70]. The market availability of supplementation is very high, with a wide variety of forms and doses, without the prescription. Unfortunately, available products are often of variable quality, without pharmaceutical standardization [65].

In conclusion, berberine is an efficient, natural hypolipidemic substance. Its unique mechanism of action, different from commonly used statins, makes it a very promising treatment option for patients with metabolic syndrome or not tolerating usual types of medication. Although there are still issues with bioavailability, development of new derivatives, such as HTD1801 shows

that berberine has an increasing role in treatment of cardiovascular diseases, including management of blood cholesterol levels.

All in all, berberine can be successfully used as a supplement to additionally support low cholesterol as well as in management of blood glucose levels, but its usage should be careful, while considering all the benefits and possible risks for the patients.

4. Conclusions

The nutraceuticals discussed in this review, including green tea, artichoke, guggul, garlic, red yeast rice, fenugreek, and berberine, demonstrate varying degrees of beneficial effects on lipid profile improvement, as well as potential antioxidant and anti-inflammatory properties that may contribute to cardiovascular protection. However, despite these promising findings, the current body of evidence remains limited.

A substantial proportion of the available data concerning mechanisms of action and therapeutic effects originates from animal models. Human clinical studies are still relatively scarce, often characterized by small sample sizes, heterogeneous methodologies, and inconsistent outcomes. Consequently, further large-scale, well-designed randomized controlled trials are necessary to establish the efficacy, optimal dosing, long-term safety, and clinical relevance of these compounds in the management of hypercholesterolemia. Among the nutraceuticals reviewed, red yeast rice, particularly due to its content of lovastatin, appears to have the strongest evidence supporting its lipid-lowering efficacy.

Although most of the described nutraceuticals are generally considered relatively safe and are not associated with severe adverse effects in the majority of users, potential side effects should not be overlooked. Most of the discussed nutraceuticals may be linked primarily with mild gastrointestinal symptoms. However, certain compounds may also produce more specific side effects; for example, red yeast rice may cause myalgia and hepatotoxicity due to its lovastatin content. In addition, these products may interact with conventional pharmacotherapy, especially when used improperly or without medical supervision. Additionally, the variability in composition and quality of commercially available herbal preparations remains an important concern.

Overall, these nutraceuticals may be considered as adjunctive therapy supporting lifestyle modification and dietary interventions in selected patients with dyslipidemia. Nevertheless, they should not serve as the foundation for hypercholesterolemia treatment. This is primarily due to the insufficient level of high-quality clinical evidence, the superior efficacy and standardization of established conventional therapies, and the relatively high cost of long-term use of many herbal and nutraceutical products.

Disclosure

Supplementary Materials

Not applicable.

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