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Medicinal plants and their bioactive compounds in the control of hyperlipidemia: A comprehensive review

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Abstract

Hyperlipidemia is one of the chronic diseases that is caused by various metabolic disorders. Although lipid-lowering drugs are available, it is still an important factor in exacerbating cardiovascular disease in patients with diabetes, hypertension and obesity. Factors such as patients' dissatisfaction with the use of common lipid-lowering drugs, the occurrence of side effects due to excessive and long-term use of these drugs, diseases caused by hyperlipidemia and the costs imposed on patients have led to an increase in the desire for alternative and traditional therapies. Epidemiological observations show that adherence to diet, use of alternative therapies, consumption of medicinal plants and fruits, in addition to reducing treatment costs, have had satisfactory results in the side effects of hyperlipidemia in many communities. It should be noted that the tendency to use medicinal plants to lower blood lipids in most societies, even in developed countries has become widespread. Consumption of these plants is especially significant when conventional therapies are not able to control the disease. Although arbitrary use of medicinal plants by patients with hyperlipidemia may improve the disease, because they are taken irregularly and at an unknown dose, they may interfere with conventional drugs and disease control. In this review, the role of common medicinal plants in the control and reduction of hyperlipidemia and the possibility of their toxicity and drug interactions are investigated.

Abbreviations: LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; VLDL: Very Low-Density Lipoprotein; ROS: Reactive Oxygen Species; NO: Nitric Oxide; iNOS: inducible Nitric Oxide Synthase; HMG-CoA: Hydroxy Methylglutaryl Coenzyme A; NF-κB: Nuclear Factor Kappa B; IL: Interleukin; TNF: Tumor Necrosis Factor; DV: Daily Value; PKA: Protein Kinase A; PKB: Protein Kinase B; ERK: Extracellular Signal-Regulated Kinase; CREB: cAMP-Response Element Binding Protein; AST: Aspartate Transaminase; ALT: Alanine Transaminase;

Introduction

Hyperlipidemia is a well-known metabolic derangement that predisposes to atherosclerosis and cardiovascular, cerebrovascular, and peripheral vascular diseases [1]. Hypercholesterolemia is an important factor in exacerbating these diseases. Globally, the prevalence of hyperlipidemia is reported 39%. Recent estimates have shown that around 28.5 million people from the adult population have high levels of total serum lipids, with the reported prevalence being 11.9% [2]. Serum lipid levels are reported to be influenced by anthropometric, demographic, environmental and genetic factors [3-5]. In the Middle East, the dyslipidemia level is as high as 70% [6]. In Iran, the prevalence for hypercholesterolemia, hypertriglyceridemia, high levels of low-density lipoprotein cholesterol (LDL), and low levels of high-density lipoprotein cholesterol (HDL) are estimated as 41.6%, 46.0%, 35.5% and 43.9%, respectively among both sexes and in both rural and urban areas. Hypercholesterolemia, high LDL and low HDL are more prevalent in women, whereas hypertriglyceridemia is more prevalent in men. All types of lipid component abnormalities are more prevalent in urban residents [7].

Atherosclerosis is a lipoprotein-driven, multifocal, smoldering, immunoinflammatory disease that leads to plaque formation at specific sites of the arterial tree through intimal inflammation, necrosis, fibrosis, and calcification. Atherogenesis can be divided into five key steps, which are i) LDL oxidation caused by free radicals, ii) remodeling of extracellular matrix, iii) upregulation of adhesion molecules, iv) collection and formation of fibrous plaques, and v) endothelial dysfunction [8,9]. Reactive oxygen species (ROS) and nitric oxide (NO) can increase the LDL oxidation and may hasten the atherosclerotic process and plaque rupture [10].

Atherosclerotic plaques are typically described as containing a large lipid-rich necrotic core representing more than half of the plaque volume, a thin fibrous cap and a heavy infiltrate of macrophages and

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lymphocytes, which then turn into foamy cells that exude more fat and cause more inflammation. The coronary arteries, the large branches of the aortic arch, and the abdominal aorta and its visceral and major lower extremity branches are locations specifically susceptible to the atherosclerotic process. Plaque localization in these sites accounts for most of the clinical manifestations of the disease [8,9].

If the plaque shatters open, they'll initiate the clotting process. Blood clot commonly improves on the irregular surfaces of arteries, which then may become separated, thus blocking the downstream blood flow. Most heart attacks and strokes happen when a plaque in heart or brain suddenly bursts. When a coronary artery is at least 60–70% blocked and stable, most usually angina is caused by physical activity or stress or emotional stress which conducts to myocardial ischemia. The best therapy for atherosclerosis/arteriosclerosis is prevention [11,12]. Hence, routine medical accesses mostly pay attention to lifestyle alterations, such as lessening in the intake of saturated fatty acids, ceasing smoking, and rhythmic exercise. Drugs are also used to diminish lipid levels or hypertension; however, most of them possess substantial side effects [13,14]. In recent years, the use of alternative therapies, especially herbal medicine and their supplements has increased in most countries to treat a variety of diseases, including hyperlipidemia, hypertension, diabetes, and cardiovascular diseases [15-17]. One of the major problems facing physicians as well as consumers of medicinal plants is the lack of sufficient data about the safety of the drug and its effect on the disease [18,19].

Fortunately, comprehensive research have been conducted on the impressiveness of medicinal herbs used in traditional medicine over the recent years to prove their efficiencies and/or deficiencies. In this review, we aimed to acquaint some encouraging medicinal plants effective in the control and/or treatment of hyperlipidemia, in addition to presenting the probability of their poisoning and drug interaction.

Medicinal plants that reduce blood lipids

In traditional medicine, there are various medications used to treat hyperlipidemia in which the role of medicinal plants is consequential. Recent studies executed on medicinal herbs and dietary supplements used in traditional medicine signify that the compounds demonstrate in them, including food fibers, vitamins, flavonoids, sterols, and other antioxidant compounds can decrease lipids, inhibit LDL oxidation, and eliminate oxygen free radicals. Therefore, they are effective in recovery of this disease by affecting the immune system and improving the body's metabolic disorders [20-22].

Cynara cardunculus var. *scolymus* (Artichoke)

The globe artichoke (*Cynara cardunculus* var. *scolymus*), also known by the name's French artichoke and green artichoke in the U.S., is a variety of flowering plants characterized by leaves with sharp prickles on the margins, mostly in the family Asteraceae that cultivated as a food. Another variety of the same species is the wild cardoon, a perpetual plant native to the Mediterranean region [23,24]. This vegetable grows to 1.4–2 m tall, with intensely lobed, silvery, glaucous-green leaves. The flowers mature in a large head from an edible bud about 8–15 cm diameter with multiple triangular scales; the individual florets are purple [23,24].

The leaf extracts of *C. cardunculus* are greatly used alone or in connection with other herbs for embittering alcoholic and soft drinks; they are also used to prepare herbal teas or herbal medicinal products [23,24]. In Persian medicine, the plant parts are usually used for managing cardiovascular system disorders, functional anxiety and agitation [16,25].

Artichoke contains the bioactive agents apigenin, luteolin, anthocyanidins (peonidin, delphinidin and cyanidin), in conjunction with the soluble fibers inulin and pectin, and cynarin (1,3-O-dicaffeoylquinic acid) [26,27]. Apigenin and luteolin are flavones, a type of flavonoids, with a yellow crystalline appearance. Apigenin-7-rutinoside and narirutin has antioxidant and antimicrobial activities [27]. Peonidin has shown potent inhibitory and apoptotic effects on cancer cells *in vitro*, notably metastatic human breast cancer cells [28,29]. Cynarin, luteolin, and chlorogenic acid (5-O-caffeoylquinic acid) possesses potential effects on choleretic and cholesterol lowering, anti-LDL oxidation, anti-atherosclerotic, hepatoprotective, nephroprotective, antiviral, antioxidant, antibacterial, anti-diabetic, anti-carcinogenic, and immunomodulatory activities [28-30]. Luteolin and chlorogenic acid are significant players in reducing the synthesis of cholesterol as well as its total level [31]. In addition, cynarin and cyanidin downregulate the expression of inducible nitric oxide synthase (iNOS) in human coronary smooth muscle cells [32]. Luteolin interfere with the biosynthesis of cholesterol and facilitate biliary secretion from the liver [28,29]. These compounds diminish cholesterol by inhibiting HMG-CoA reductase and having a hypolipidemic influence [33-36].

Furthermore, this plant is a rich source of polyphenolic compounds, mainly caffeoylquinic acids and its derivatives (caffeic acid, dihydrocaffeic acid, ferulic acid, and dihydroferulic acid), flavonoids (apigenin and luteolin), cooperatively with the polysaccharide inulin. Caffeoylquinic acids and flavonoids present in artichoke leaf extract causes a significant decrease in the levels of total cholesterol, triglyceride, LDL and VLDL [37]. Meanwhile, artichoke leaf extract is rich in antioxidants and has a cholesterol-lowering effect; therefore, interferes with atherosclerosis [21,36]. Additionally, it is composed of fatty acids, triterpenes, and sesquiterpenes, as major metabolites [38]. Lipid-lowering sesquiterpenes, such as cynaropicrin, aguerine, and grosheimin suppress serum triglyceride level in 2 h after artichoke administration [39]. Moreover, cynaropicrin has therapeutic potential on hepatitis C virus and overpowers photo-aging of the skin by inhibiting the transcription activity of NF-κB signaling [40,41]. The main phenolic compounds encompass scavenging activity against free radicals and act as a shield against oxidative damage to proteins, lipids, and DNA [20].

Other compounds discovered in artichoke that could contribute to its lipid-lowering properties comprise the family of phytosterols. Phytosterols have been reported to lower cholesterol and LDL plasma levels and may have clinical application for the prevention of non-alcoholic fatty liver disease and cardiovascular diseases [42,43]. The physiological functions of phytosterols can be contemplated as an antioxidant, anti-inflammatory and antipyretic effects. Phytosterols will compete with cholesterol in the intestine and impede the absorption of cholesterol, thereby reducing the level of LDL in the plasma [43]. β-sitosterol and stigmasterol are the major phytosterols discovered in artichoke, which are believed to reduce cholesterol absorption from the intestine [33]. At least 1–2 g/day of isolated phytosterols are necessary to decrease LDL and cholesterol concentrations.

In a 100-gram reference serving, cooked artichoke supplies 74 calories, is a rich source of folate, and is a moderate source of vitamin K, vitamin C, magnesium, sodium, potassium and phosphorus. Six g of the dried herb is the optimal dose to reduce dyspepsia [44]. However, the best dose for hyperlipidemia supposed to be effective ranges from 2 to 3 g/day [37]. No side effect has been perceived in utilizing leaves of artichoke. However, pregnant or nursing women, young children, individuals with severe liver or kidney disease and gallstones should use the leaves with caution [45].

Medicago sativa (Alfalfa)

Medicago sativa (alfalfa, the father of all foods), also called lucerne, is a leguminous flowering plant with high contents of phytoestrogens (including spinasterol, coumestrol, and coumestan) and saponin. It has bundles of tiny purple flowers followed by fruits twisted in 2 to 3 turns containing 10–20 seeds. Dehydrated alfalfa leaf is commercially available as a dietary complement in various forms, such as tablets, powders and tea.

This plant has long been used as traditional herbal medicine and possesses cerebroprotective, cardioprotective, hepatoprotective, hypolipidemic, antioxidant, anticancer, antimicrobial, anthelminthic, estrogenic, anti-inflammatory, antiviral, and antidiabetic effects [46,47]. It is used in the treatment of heart disease, stroke, cancer, diabetes, indigestion, halitosis, constipation, and menopausal disorders in women [46,47]. Many studies proved that saponins are the main active compounds in alfalfa [48–52].

The whole plant material contains many important substances, including saponins (soyasapogenols, hederagenins, bayogenins, medicagenic acids, zahnic acids); sterols (β-sitosterol, α-spinasterol, stigmasterol, cycloartenol, and campesterol); coumarins (myrsellinol, scopoletin, esculetin, and 4-coumaric acid); flavones and isoflavones (quercetin, myricetin, luteolin, apigenin, chrysoeriol, tricin, medicarpin, sativan, vestitol, formononetin); phytoestrogens (coumestrol, genistein, daidzein, and biochanin A); L-canaverine; alkaloids (trigoneline, stachydrine, and homostachydrine); plant acids (malic, oxalic, malonic, maleic, and quinic); enzymes (isoflavone reductase, vestitone reductase, iminopeptidase, and two aminopeptidases); vitamins and growth factors (vitamins A, B_1, B_6, B_{12}, C, E, and K_1; niacin; pantothenic acid; biotin; folic acid); amino acids (valine, lysine, arginine, leucine, isoleucine, tryptophan, phenylalanine, methionine, asparagine and threonine); sugars (sucrose, fructose, arabinose, xylose, galactose, ribose, mannoheptulose); polyamines (norspermidine, and norspermine); proteins; minerals; trace elements; and other nutrients [46,47,49,50]. The alfalfa saponins of the aerial parts and roots have been identified as mono-, bis-, or tridesmosides of medicagenic acid, hederagenin, zahnic acid and soysapogenol B. Among them, medicagenic acid and hederagenin glycosides have been recognized as the biologically active saponins [46,49,50]. Saponins are responsible for the lessening of cholesterol absorption and prevention of atherosclerotic plaque formation in experimental animals. Alfalfa meals prevented hypercholestrolemia, triglyceridemia and atherogenesis [51,52].

Alfalfa top saponins have been shown to decrease cholesterolemia without changing the levels of HDL-cholesterol; hence, they reduced the total cholesterol/HDL-cholesterol ratio. Furthermore, they decreased intestinal absorption of cholesterol, increased fecal excretion of endogenous and exogenous neutral steroids and bile acids, and decreased the percentage distribution of fecal deoxycholic and lithocholic acids [49–51]. Heat-treated *M. sativa* seeds decrease significantly total serum cholesterol concentrations, LDL and apolipoprotein B in type-II hyperlipoproteinemic patients. Cholestaid™, a product available in the USA containing 900 mg of alfalfa extract with 100 mg citric acid, is said to neutralize the cholesterol in the stomach before it reaches the liver, thus facilitating the excretion of cholesterol from the body with no side effects or toxicity [46,49].

Health beverage manufactured from alfalfa buds was found beneficial in maintaining normal digestive function and nutrition balance in the human body, reducing cholesterol, and preventing osteoporosis, arteriosclerosis and aging. Extracts prepared from alfalfa roots may be used to prepare medical preparations like powder, pill, or decoction for lowering the levels of cholesterol and lipid in blood, improving the liver function and the control and transmission of nerve tissue, and treating calculus [46,49].

L-Canaverine isolated from the plant has been shown to have antineoplastic activity against particular types of leukemia cells in mice and specific toxicity in dog cancer cells grown *in vitro*. In addition, alfalfa has been reported to be beneficial in the treatment of peptic ulcers, polycystic ovaries, prolactin excess, hemorrhage, dysuria, bowel disturbances, scurvy, secondary hypothyroidism, herpes simplex virus (HSV) infections, and arthritis [46,49,50].

Raw alfalfa seeds and sprouts are a source of the amino acid L-canavanine. Canavanine competes with arginine, resulting in the synthesis of dysfunctional proteins [53]. Raw unsprouted alfalfa has toxic effects in primates, including humans, which can result in lupus-like syndrome or lupus flares. The lupus-like effects may include muscle pain, skin sores with inflammation and scarring, fatigue, abnormal blood test results, changes in how the immune system functions, and kidney problems [53,54]. Coumestrol, apigenin and quercetin exhibit strong estrogenic activity and have potential for use in treatment of hormone-related cancers [55]. Coumestrol lead to pathological side effects and is suspected of causing infertility in livestock [56]. Taking off coumestrol and canavanine from alfalfa leaf provided an extremely potent form of saponins, which reduce serum cholesterol levels without serious adverse effects.

Raw alfalfa seed sprouts are comprised of 93% water, 2% carbohydrates, 4% protein, and contain negligible fat. In a 100-gram reference amount, raw alfalfa sprouts supply 23 kilocalories of food energy and 29% of the daily value of vitamin K. They are a moderate source of vitamin C, some B vitamins, phosphorus, and zinc [57].

For curing high cholesterol, a dose of 40 g of heated seeds taken by mouth 3 times daily has been suggested. A dose of two tablets (1 g each) of Cholestaid™ taken by mouth 3 times daily for up to two months, then one tablet 3 times daily, has been recommended. Pregnant and/or lactating women, and people with a history of lupus-like disease should avoid alfalfa supplements. Meanwhile, this plant is a rich source of vitamin K. Therefore, it is contraindicated in people consuming warfarin [58].

Trigonella foenum-graecum L (Fenugreek)

Fenugreek (*Trigonella foenum-graecum*) is a medicinal clover-like plant in the family Fabaceae. This plant has a single stem that is smooth, or with dispersed tomentum. Leaves are oval, serrated, comprising of 3 small obovate to oblong leaflets. Flowers are pale yellow or whitey purple. Seeds are curved pods and have bitter and aromatic taste. This plant primarily was indigenous to Iran and then was transferred to other regions of the world [59,60].

In recent years, some health beneficial physiological attributes of fenugreek seeds have been seen in animal studies as well as human trials. These include cardioprotective, DNA-protective, gastroprotective, haemato-protective, hepatoprotective, immunomodulatory, hypocholesterolemic, antidiabetic, antihypertensive, antioxidant, antineoplastic, anti-breast cancer, anti-arthritis, anti-allergic, anti-cataract, antibacterial, endothelial dysfunction correction, thyroid dysfunction repair, antinociceptive and anti-inflammatory effects [60–62].

Constituents of fenugreek seeds include flavonoids (orientin, isoorientin, vitexin, epigenin, and quercetin), alkaloids (trigonelline, gentanin and carpaine choline), polyphenols, coumarins (cinnamic acid and scopoletin), vitamins (C, A, D, and B_1), niacin, iron, phosphate,

calcium, potassium, amino acids (4-hydroxyisoleucine, lysine, arginine, and L-tryptophan), soluble dietary fiber, gum and saponins (diosgenin, yamogenin, tigogenin, gitogenin, sarsapogenin, yuccagenin, and smilagenin) [60-62]. Trigonelline is the major alkaloid of fenugreek and has hypoglycemic, hypolipidemic, neuroprotective, antimigraine, sedative, memory-improving, antibacterial, antiviral, and anti-tumor activities, and it has been shown to reduce diabetic auditory neuropathy and platelet aggregation [63]. It acts by affecting β-cell regeneration, insulin secretion, activities of enzymes related to glucose metabolism, reactive oxygen species, axonal extension, and neuron excitability [63,64]. Trigonelline is transformed into niacin when the seed is grilled. Sotolon is a powerful aromatic component responsible for the distinctive maple syrup smell of fenugreek [63]. Polyphenols and germacrene-D are the most abundant components in fenugreek that could improve hyperlipidemia and the cardiovascular system [65-67].

4-Hydroxyisoleucine has been shown to cause an increase in pancreatic insulin secretion, and inhibit α-amylase activity, and diminish the elevated plasma triglyceride and total cholesterol levels [68-70]. Furthermore, 4-hydroxyisoleucine administered orally (50 mg/kg/day) for 4 weeks not only lowered the blood glucose level but also significantly lowered the elevated lipids (total cholesterol, triglycerides, and LDL) level in rats [71-73]. In experimentally hyperlipidemic rabbits, the aqueous emulsified fenugreek seeds powder reduced significantly the serum total cholesterol, LDL, and the atheriogenic index, with significant increase in the HDL [74].

Diosgenin, the main sapogenin, is an estrogen precursor and may help in managing menopause and hypolipidemia [75]. Diosgenin plays an anti-atherosclerosis role by improving endothelial dysfunction, improving the lipid profile through lowering the level of total cholesterol, triglyceride, and LDL and increasing the HDL level, inhibiting macrophage proliferation, migration and differentiation, and inhibiting vascular smooth muscle cell proliferation, migration and mineralization [76]. Moreover, diosgenin can inhibit the accumulation of triglyceride and the expression of lipogenic genes in HepG2 cells. Furthermore, diosgenin inhibited the transactivation of Liver-X-receptor-α [77,78]. Diosgenin can be used to manufacture many pharmaceuticals such as progesterone [69,76].

One more principal ingredient of fenugreek which has been stated to have modulating effect on dyslipidemia is saponin [79]. Saponins can impressively hasten cholesterol metabolism and process of reverse cholesterol transport, meanwhile interdict cholesterol synthesis and therefore effectively lessen total cholesterol level [79]. Additionally, saponins induces release of testosterone in males, increases secretory functions and induces uterine contractions in females [80,81]. Therefore, fenugreek extract and leaf must be contraindicated in women during early pregnancy to avoid risk of abortion, and during menstruation to reduce risk of excessive bleeding [81]. Furthermore, fenugreek contain a gel-like liquefiable fiber which react with bile acids and produces too big micelles which cannot be absorbed absolutely by alimentary canal and brings down the triglyceride, cholesterol and LDL levels [82]. Plus, fenugreek seed may reduce the amount of primary substrate for triglyceride synthesis [82].

The galactomannan of fenugreek gum and the crude saponins exhibited the lipid-lowering effect [62]. Atherogenic lipids, such as triglyceride, cholesterol and LDL, were found to decrease significantly in soluble dietary fiber fraction of fenugreek-fed rats [72,73,82]. The consumption of fiber-rich fenugreek seed powder resulting in reduction of cholesterol content of liver cells coupled with upregulation of hepatic apo-B, apo-E receptors and increased clearance of circulating LDL and VLDL [83,84]. Fenugreek seeds resulted in an increase in HDL and a decrease in LDL levels in type 2 diabetic patients [85,86].

Fenugreek was disclosed to bring about the hypocholesterolemic effect through heightened excretion of fecal bile acids and neutral sterols; depletion of cholesterol supplies in the liver was also included. Dietary fenugreek also has the property of stimulating bile formation in the liver and of converting cholesterol to bile salts [66]. Moreover, fenugreek considerably diminish fasting blood sugar, postprandial glucose and HbA_1c in clinical trial studies [87,88].

In a double-blind clinical trial study that was performed on borderline hyperlipidemic people, total cholesterol, triglyceride, and LDL decreased significantly after 2 months of fenugreek use [89]. Moreover, hypolipidemic activity of fenugreek on type 2 diabetic patients revealed significant total cholesterol and triglyceride reduction in a meta-analysis [88]. In addition, significant effect for fenugreek was reported on total cholesterol, triglyceride, LDL reduction and HDL elevation in type 2 diabetic patients [65,67,86].

Fenugreek reduces the levels of lipid peroxidation and concomitantly increase the levels of superoxide dismutase and glutathion in the cartilage. Fenugreek also cause a decrease in the levels of pro-inflammatory cytokines such as IL-1α, IL-1β, IL-2, IL-6, and TNF-α in blood [90].

In a 100-gram reference amount, fenugreek seeds provide 323 kcal of food energy and contain 9% water, 58% carbohydrates, 23% protein, and 6% fat, with calcium at 40% of the Daily Value (DV). Fenugreek seeds (per 100 grams) are a rich source of protein (46% DV), dietary fiber, B vitamins, and dietary minerals, particularly manganese (59% DV) and iron (262% DV) [59,60].

The normal consumption of fenugreek seeds by the population in Iran is reported to be 40 g/day/adult. Some individuals who received 25 g of powdered fenugreek leaf showed digestive problems like diarrhea and cramp that were eliminated after 3 to 4 days. No important change happened in blood variables and no renal or liver side effects were observed. No special side effects have been reported for fenugreek [59].

Allium sativum L (Garlic)

Garlic (*Allium sativum*) is a species of bulbous flowering plant in the family Alliaceae. It is local to Iran and Central Asia. Garlic has a tall, erect flowering stem that grows up to 1 m. The leaf blade is flat, linear, and solid with an acute apex. The bulb is aromatic and includes outer layers of thin sheathing leaves encircling an inner sheath that encloses the clove. It produces hermaphrodite flowers [91].

Some studies have demonstrated the beneficial effects of garlic consumption, such as immunomodulatory, antioxidant, cardioprotective, hepatoprotective, renoprotective, neuroprotective, DNA-protective, anti-inflammatory, antibacterial, antiviral, antifungal, anti-parasitic, anticancer, anti-hypertensive, anti-atherosclerotic, anti-hyperlipidemic, anti-obesity, antidiabetic, anti-platelet aggregation, and endothelial-dysfunction repair [92-94].

Garlic contains 65% water, 28% carbohydrates, 2.3% organosulfur compounds, 2% proteins, 1.2% free amino-acids, and 1.5% fiber. It also contains fat-soluble vitamins (K, E, D, A), water-soluble vitamins (C, B_1, B_2, B_3, B_6, and B_8), and minerals (Fe, Mg, Ca, P, K, Na, and Zn). Moreover, garlic is rich in several sulfur-containing compounds such as alliin, allicin, ajoenes, vinyldithiins, diallyl polysulfides, and S-allyl cysteine; as well as enzymes, saponins, flavonoids (quercetin), and Millard reaction products, which are not sulfur-containing compounds [93,94].

A great number of sulfur compounds participate in the smell and taste of garlic. Allicin has been discovered to be the compound most liable for the hot feeling of raw garlic. Allicin opens heat-temporary receptor potential channels that are responsible for the scorching feel of heat in foods. Cooking garlic eliminates allicin, therefore softening its piquancy. In addition, sulfur compounds in garlic are responsible for changing garlic green or blue during pickling and cooking. Under acidifying and heating conditions, the sulfoxide alliin reacts with common amino acids to make pyrroles. Alliin is a by-product of the amino acid cysteine. When fresh garlic is chopped or crushed, the enzyme alliinase converts alliin into allicin, which is responsible for the aroma of fresh garlic [93,94]. Allicin and other thiosulfinates in garlic are unsteady and create some other compounds, such as diallyl sulfide (DAS), diallyl disulfide (DADS) and diallyl trisulfide (DAT), dithiins and ajoene. Allicin, along with its decomposition products DADS and DAT, are major contributors to the characteristic odor of garlic, with other allicin-derived compounds, such as vinyldithiins and ajoene [95,96]. Aged garlic lacks allicin but may have some activity because of the presence of S-allyl cysteine. S-allyl mercaptocysteine from aged garlic has anti-proliferative, anti-metastatic and pro-apoptotic effects in various cancer models [97]. DADS is a major bioactive component of garlic and has several beneficial biological functions including anti-inflammatory, antioxidant, antimicrobial, cardioprotective, neuroprotective, and anti-carcinogenic activities [96,98,99]. The great mechanisms of action of DADS in disease prevention and/or treatment comprise inhibition of inflammation, oxidative stress, and cellular apoptosis. Mechanisms, including the activation of protein kinase B (PKB), extracellular signal-regulated kinase 1/2 (ERK1/2), protein kinase A (PKA), and cAMP-response element binding protein (CREB) and the inhibition of histone deacetylases (HDACs), can also mediate the cellular protective effects of DADS in different tissues and organs [96,98].

Garlic oil administration in streptozotocin- and alloxan-diabetic animals for 3 weeks at a dose of 100 mg/kg body weight diminishes the glucose, total cholesterol, triglycerides, urea, uric acid, creatinine, AST, and ALT levels and also increased serum concentration of insulin [100,101]. Moreover, a purified NO-generating protein from garlic reduces pro-inflammatory cytokine TNF-α and the stress responsive NF-κB-expression in human blood and liver cell of diabetic mice [101,102]. Fresh garlic homogenate administration reduces the serum level of glucose, total triglyceride, and total cholesterol and prevents streptozotocin-induced diabetic nephropathy possibly through the inhibition of kidney oxidative damage and increase of NO bioavailability [103]. The metabolic effects of time-released garlic powder tablets in patients with type 2 diabetes indicated that garlic reduces cardiovascular disease risks [104].

Additionally, hypolipidemic and hypoglycemic activity of garlic on type 2 diabetic and non-alcoholic fatty liver patients revealed significant total cholesterol, triglyceride and LDL reduction and HDL elevation [105,106]. In women with polycystic ovary syndrome, garlic supplementation significantly reduced serum total cholesterol, triglyceride, and LDL levels and systolic blood pressure [107]. In patients with metabolic syndrome, treatment with 100 mg/kg body weight raw crushed garlic 2 times a day with standard diet for 4 weeks significantly reduced components of metabolic syndrome including waist circumference, systolic and diastolic blood pressure, triglycerides, fasting blood glucose and significantly increased serum HDL [108]. Oral treatment of aqueous garlic extract on heavy metal-induced changes in serum lipid profile showed a significant decrease in serum LDL, VLDL and triglyceride level as well as increase in serum HDL level [109]. Garlic tablet administration in patients with type 2 diabetes for 12 weeks at a dose of 300 mg/kg body weight significantly reduced total cholesterol, LDL, while significantly increased HDL level [106,110]. In various studies, the hyperlipidemic patients received garlic tablets at doses of 300, 600, 900, 1200, and 1500 mg per day, respectively, for 24 weeks. The results showed a significant reduction in fasting blood glucose, HbA1c, serum cholesterol, triglyceride, and LDL levels while increased the HDL level [111-113]. Moreover, garlic significantly improved superoxide dismutase, catalase and glutathione peroxidase in erythrocytes of diabetic patients [114]. Therapy of hyperlipidemic patients with garlic at a dose of 20 mg/kg body weight daily with 1 tablespoon lemon juice significantly decreased the total cholesterol, LDL, and fibrinogen levels [111].

Aged black garlic is a form of raw garlic obtained *via* Millard reaction under high temperature and humidity for a period of time. Comprehensive *in vitro* and *in vivo* studies have demonstrated that aged black garlic has a variety of biological activities such as antioxidant, anti-inflammatory, anti-cancer, anti-obesity, anti-diabetic, anti-allergic, hypolipidemia, nephroprotective, cardioprotective, and hepatoprotective effects [115-117]. Several studies reported higher contents of water-soluble antioxidants compounds (S-allyl cysteine, S-allyl mercaptocysteine), organosulfur compounds, 5-hydroxymethylfurfural, polyphenol, volatile compounds, and other products compared to fresh garlic after the thermal processing [115,117]. It has been reported that S-allyl cysteine sulphoxide has significant antidiabetic and hypolipidemic effects in type 2 diabetic and atherogenic rats [118-120]. Administration of black garlic at a dose of 200 mg/kg body weight decreased the concentration of blood glucose and ameliorated diabetic condition and increased liver and intestinal HMG-CoA reductase activity and liver hexokinase activity [116]. Intake of aged garlic extract also reduced hydroperoxide as an indicator of oxidative stress [116].

The side effects of long period garlic consumption are greatly unknown. Possible side effects include gastrointestinal discomfort, sweating, dizziness, allergic reactions, bleeding, and menstrual irregularities [94].

If greater-than-suggested doses of garlic are taken with anticoagulant medications, this can conduct to a higher risk of bleeding. Garlic may interact with warfarin, saquinavir, antihypertensives, calcium channel blockers, the quinolone family of antibiotics such as ciprofloxacin, and hypoglycemic drugs, as well as other medications [94].

Glycine max L. (Soybean)

Glycine max, commonly called soybean, is an annual legume that belongs to Fabaceae family. It characterizes white to purple-pink flowers and trifoliate leaves. Flowers are small and ornamentally insignificant, somewhat resembling those of peas. Fruit may be a hairy pod that grows in clusters of 3-5. Each pod contains 2-4 seeds.

Particular studies have demonstrated the advantageous effects of soybean consumption, such as cardioprotective, neuroprotective, anti-atherosclerotic, antidiabetic, antihypertensive, anti-hyperlipidemic, anti-geriatric dementia, anti-osteoporotic, antimutagenic, anticancer, and antibacterial [121-124].

Soybean consists of proteins (40%), carbohydrates (30%), lipids (18%), vitamins and minerals and moisture (12%). Moreover, it contains phytic acid, glyceollins, triterpenes, phenolics, isoflavones, lignans, carotenoids, coumarins, protease inhibitors, oligosaccharides, and dietary fibers [125]. Soybean oligosaccharides have the capability to advance the rapid growth of probiotic bacteria [126]. Phenolics have exhibited antioxidant properties to inhibit DNA damage caused by reactive oxygen species [127]. Glyceollins have biological activities in-

cluding cholesterol-lowering, antibacterial, antifungal, antiestrogenic, insulinotropic and lessening of vascular contraction [123].

The major isoflavones found in soybeans are aglycons including daidzein, genistein, and glycitein; and glycosides including daidzin, genistin, and glycitin. Isoflavones have the power to activate estrogen receptors in the vagina, oocytes, and mammary glands. Moreover, isoflavones with an impact on the menstrual cycle, reduces the risk of breast cancer [128,129]. Besides, isoflavones diminishes the severity of symptoms in women with menopausal syndrome [130,131]. Isoflavones have been highlighted as phytoestrogens that lessens the risk of osteoporosis by promoting vitamin D activity and increasing calcium absorption [132]. Isoflavones have potential effects on the prevention of metabolic syndrome [133]. Amongst the soybean isoflavones, genistein inhibits the growth and development of cells that cause breast, colon, lung, prostate, and skin cancers *in vitro*. Furthermore, genistein restrains the formation of blisters by hindering vasculogenesis [134]. Besides, isoflavones reduce blood cholesterol by as much as 35% [134].

Soybean seeds contain 2.6% phytic acid. Phytic acid is considered a non-nutritional compound as it influences the use of bivalent ions and minerals in the body by binding to them and reducing their absorption. However, it has beneficial effects such as hypoglycemic, antioxidant, anticancer, lipid-lowering and antibacterial [135]. Phytic acid has many functions, including storage of phosphorus and cations, preventing the oxidation of cells, and lowering incidence of colorectal cancer. Plus, phytic acid displays antitumor activity [135]. Protease inhibitors of soybeans function as antioxidant and anticancer agents that restrain the production of superoxide radicals or H_2O_2 by tumor promotor factors. In addition, protease inhibitors in soybeans promote insulin secretion [128,129].

Lignans have characteristics similar to estrogen. Lignans suppress the biosynthesis and metabolism of estrogen, and the formation of bile acids from cholesterol. Therefore, reducing the risk of cancers. Lignans have synergistic effects with flavonoids and can intensify anticancer properties. Lignin downregulates the proliferative potential of breast cancer cells [136]. Saponin is a bipolar, heat-stable sugar complex. It possesses functions such as lowering cholesterol, stimulating immune responses, and anticancer effects. Saponins have essential roles in the inhibition of DNA synthesis in tumor cells, and in the reduction of cervical and epidermal cancer cell growth [128,129]. Soybean dietary fibers can be categorized as water–soluble (pectin and gum) and –insoluble (cellulose). Specifically, one of the most important effects of soybean dietary fiber is the lessening of cholesterol levels [129]. Soybean-derived peptides diminish hyperlipidemia by regulating trans-intestinal cholesterol excretion and bile acid synthesis [137].

Several investigations have stated that soy protein consumption can reduce cholesterol, triglyceride, and LDL levels in hyperlipidemic and peritoneal dialysis individuals [138-143]. Furthermore, several meta-analysis studies have reported that soy protein intake can decrease blood cholesterol and LDL level and improve the LDL/HDL ratio in hyperlipidemic patients. Intake of soy protein was allied with mean changes in serum lipid profile as a decrease of 9.3% in cholesterol, 12.9% in LDL, 10.5% in triglyceride, and an increase of 2.4% in HDL [144-152].

Principal studies recommend 40 g of soybean protein daily. In individuals with iodine deficiency, soybean can restrain the performance of the thyroid gland. Besides, soy can decrease absorption of calcium, iron, and zinc. Clinical studies suggest that neither soy nor isoflavone intake affects male reproductive hormones [153].

Silybum marianum (Milk thistle)

Silybum marianum is a member of Asteraceae family, which encompasses daisies and thistles. It has large purple flowering heads and grows as a stout thistle in rocky soils. The leaves are characterized by milky veins. It is one of the most thoroughly researched plants in the treatment of the liver diseases [154].

S. marianum has been found to exhibit antioxidant, anti-inflammatory, immunomodulatory, lipid-lowering, anti-obesity, antihypertensive, antidiabetic, anti-cancer, anti-Parkinson's, skin-protective, cardioprotective, renoprotective, neuroprotective, and hepatoprotective effects [155-158].

Silymarin, derived from fruits and seeds of *S. marianum*, is a mixture of flavonolignans containing silibinin (silybin); isosilybin; silychristin; and silydianin. There are also small fragments of other flavonols such as dehydrosilybin, quercetin, taxifolin, and kaempferol, and phospholipids, which contains linoleic, oleic, and palmitic acids, and tocopherol [155-158].

Silybin is the more important active ingredient of silymarin. Silybin can lessen *de novo* synthesis of cholesterol by inhibition of HMG-CoA reductase, which is a rate-limiting enzyme in cholesterol biosynthesis. Moreover, silymarin can hinder resorption of cholesterol from the intestine. Besides, it decreases the synthesis of triglyceride and activates β-oxidation of fatty acids in liver [157,158]. Also, silymarin is an ally against insulin resistance [159].

Several animal studies have stated that silymarin consumption can reduce cholesterol, triglyceride, and LDL levels in hyperlipidemic and hyperglycemic rats [160-164]. Several meta-analysis studies have indicated that silymarin supplementation in combination with other supportive therapies can reduce total cholesterol, LDL, and triglyceride and improve HDL concentration [165-169]. Combination of silymarin with other treatments boosted its efficacy [170-174].

Milk thistle is believed safe in dosages of 420 mg/day orally in separated doses for up to 40 months. Silymarin would possibly exert abdominal discomfort and somehow laxative effects in some patients.

Red Yeast Rice

Red yeast rice is the result of rice fermented with a type of yeast called *Monascus purpureus*. It contains different chemicals including monacolins (polyketides), azaphilone pigments (monascin, monascinol, ankaflavin and rubropunctamine), protein, fiber, sterols, fatty acids, flavonoids, lignans, coumarins, terpenoids, and polysaccharides [175,176]. These chemicals affect cholesterol levels. Monacolin K, which is identical to the drug lovastatin, is the most plentiful in red yeast rice. Monacolin K, inhibits production of cholesterol *via* blocking the activity of the HMG-CoA reductase [177,178]. Moreover, recent studies show that monacolin L, monascinol, and monascodilone also have HMG-CoA reductase activity [178]. Red yeast rice is most commonly used for hyperlipidemia, heart attack, heart disease, hypertension, diabetes, and cancer [175,176]. Red yeast rice is known to have antibacterial, anti-cancer, antioxidant, anti-inflammatory, anti-hypertensive, and hypolipidemic effects [179,180].

Red yeast rice could reduce the risk of vascular diseases associated with hyperlipidemia, through repression of atheroma formation and enhance blood fluidity, by lowering levels of chylomicrons and VLDL [180,181]. Monacolin K suppresses atheroma formation in atherosclerosis by reducing phospholipase A_2 activity, improving effects on

blood circulation, and pleiotropic effects on nitric oxide production. Moreover, monascin and ankaflavin inhibit oxidation of LDL, and this improves the vascular endothelial function in dyslipidemic subjects [180,181].

Studies have shown that certain red yeast rice products that contain statin can significantly decrease levels of total cholesterol, triglyceride, and specifically LDL [182-188]. Long-term intake of a processed food product containing red yeast rice at 2.4 g/day significantly reduced LDL levels by 22% and total cholesterol by 16% in 12 weeks [189].

Red yeast rice might cause the same side effects as lovastatin, including liver damage, severe muscle pain, and muscle damage. People with liver problems and pregnant and/or breast-feeding women should not use red yeast rice. Cyclosporine, gemfibrozil, hepatotoxic drugs, antifungal azole drugs, cytochrome P450 3A4 (CYP3A4) inhibitors, protease inhibitors (used to treat HIV), statins, and niacin interacts with red yeast rice [189,190].

Commiphora mukul (Guggul, Guggulipid)

Guggul is made from the gum resin of the *Commiphora mukul*, a small thorny tree that is known as the tree of myrrh. *Commiphora mukul* is a seed plant within the Burseraceae. The plant is natural to southern Pakistan and western India. This tree has been employed in Ayurvedic medicine for centuries, and ancient Hindu texts dating back to 600 BC recommend it for treating atherosclerosis [191].

Guggul has antioxidant, antimicrobial, anti-inflammatory, anti-platelet aggregation, anti-infertility, antihyperglycemic, antiarthritic, antiatherosclerotic, anti-cancer, hypolipidemic, fibrinolytic, cytotoxic, thyroid stimulatory, and cardioprotective properties [192,193]. Today guggul gum resin is used for arthritis, acne, eczema, psoriasis, hyperlipidemia, and weight loss [194].

Guggul contains terpenoidal constituents (monoterpenoids, diterpenoids, triterpenoids, and sesquiterpenoids), steroids (*E*-guggulsterone, *Z*-guggulsterone, and guggulsterols), flavonoids (muscanone, quercetin, naringenin), cembranoids, guggultetrols, lignans (sesamin and diayangambin), sugars (arabinose, galactose, fructose), and amino acids [195].

The extract of gum guggul, called guggulipid. The stereoisomers *E*- and *Z*-guggulsterone have been identified as the active agents in this extract [196]. These compounds are antagonist ligands for the bile acid receptor farnesoid X receptor (FXR), which is an important regulator of cholesterol homeostasis in the liver [197-199]. The cembranoids did not display a considerable effect on FXR, but lowered the cholate-activated rate of human pancreatic IB phospholipase A_2, which controls intestinal absorption of cholesterol [200].

Several clinical studies have demonstrated that administration of guggulipid, the ethyl acetate extract of gum guggul, significantly lowers cholesterol, LDL, and triglyceride levels in patients with hyperlipidemia. These studies have generally reported a 10 to 20% decrease in triglyceride levels and a 20 to 30% decrease in cholesterol levels [201-204].

Taking 3 to 6 g of guggul daily seem to lower total cholesterol, LDL, triglycerides, and raise HDL in people with hyperlipidemia who eat a normal diet. Taking guggul 3 g/daily for 4 months can improve symptoms of rheumatoid arthritis [204].

Guggul can cause side effects like dyspepsia, headaches, nausea, vomiting, loose stools, diarrhea, belching, and hiccups. Guggul can even cause hypersensitivity reactions like skin rash and itching. These adverse reactions are more common with higher doses, such as 6 g/day [204].

Guggul might act like estrogen in the body. Guggul is likely unsafe during pregnancy and breast-feeding. It appears to support menstrual flow and stimulates the uterus. Guggul can slow blood clotting and might cause bleeding or bruising in people with bleeding disorders [193,194]. Table 1 summarized the bioactive components, effects, and mechanisms of guggul and other medicinal plants on hyperlipidemia treatment.

Table 1: Effects and mechanisms of medicinal plants in the control of hyperlipidemia.

No	Medicinal Plants	Active ingredients	Lipid metabolism	Mechanism of action	References
1	*Cynara cardunculus* var. *scolymus*	Polyphenols, cynarin, chlorogenic acid	↓TC, TG, LDL, VLDL; ↑HDL	1) Inhibit cholesterol and triglyceride synthesis; 2) Inhibit cholesterol esterification and absorption; 3) Promote fatty acid oxidation; 4) Improve lipid transport protein system	[27–29,33,37]
		Flavonoids, luteolin, apigenin	↓TC, TG, LDL, Apo B; ↑Apo A_1	1) Inhibit lipid synthesis; 2) Promote bile acids biosynthesis; 3) Promote fatty acid oxidation and lipolysis	[37]
		Sesquiterpenes, cynaropicrin, aguerine	↓TG	Suppress serum triglyceride level	[38,39]
		Phytosterols	↓TC, TG, LDL; ↑HDL	1) Inhibit intestinal lipid absorption; 2) Promote lipids transport and decomposition	[42,43]
		Soluble fibers, pectin, inulin	↓TC, TG, LDL	1) Promote bile acids biosynthesis; 2) Inhibit intestinal bile acid reabsorption	[27–29]
2	*Medicago sativa*	Saponin	↓TC, TG, LDL; ↑HDL	1) Inhibit intestinal cholesterol absorption; 2) Promote fecal bile acids excretion; 3) Regulate gut microbiota	[46,47,49–52]
		Sterols	↓TC, TG, LDL; ↑HDL	Promote lipids transport and decomposition	[46,47]
		Flavonoids, quercetin	↓TC, TG, LDL; ↑HDL	1) Promote mitochondrial fatty acid oxidation; 2) Improve insulin resistance; 3) Inhibit cholesterol biosynthesis; 4) Promote cholesterol change to bile acid	[46,47]
3	*Trigonella foenum-graecum*	Flavonoids, Vitexin	↓TC, TG	Inhibit *de novo* lipogenesis	[60–62]
		Alkaloids, Trigonelline	↓TC, TG, LDL	1) Inhibit cholesterol esterification and absorption; 2) Promote fatty acid oxidation; 3) Increase insulin sensitivity	[63,64]

		Polyphenols	↓TC, TG, LDL, VLDL; ↑HDL	1) Inhibit cholesterol and triglyceride synthesis; 2) Promote fatty acid oxidation; 3) Improve lipid transport protein system	[60–62]
		4–Hydroxyisoleucine	↓TC, TG, LDL, FFA; ↑HDL	1) Inhibit cholesterol and triglyceride synthesis; 2) Promote fatty acid oxidation and lipolysis; 3) Improve insulin resistance	[68–70]
		Soluble fibers	↓TC, TG, LDL, VLDL; ↑HDL	1) Reduce cholesterol synthesis; 2) Decrease lipids and bile acids reabsorption; 3) Increase fecal cholesterol and bile acids excretion	[69]
		Diosgenin	↓TC, TG, LDL; ↑HDL	1) Inhibit cholesterol absorption; 2) Decrease liver cholesterol concentration; 3) Facilitate cholesterol excretion	[69,75–77]
		Saponin	↓TC, TG, LDL; ↑HDL	1) Inhibit cholesterol synthesis; 2) Increase reverse cholesterol transport; 3) Regulate gut microbiota	[79]
4	*Allium sativum*	Alliin; Allicin	↓TC, TG, LDL; ↑HDL	1) Modulate cholesterol and triglyceride metabolism; 2) Reduce hepatic lipid level	[93–95,106,107]
		S-allyl cysteine	↓TC, TG, LDL; ↑HDL	1) Inhibit lipid deposition; 2) Decrease myeloperoxidase activity and lipid hydroperoxide in serum 3) Decrease plasma concentration of F2-isoprostanes	[93,94]
		Polyphenols	↓TC, TG, LDL; ↑HDL	1) Inhibit triglyceride and cholesterol synthesis; 2) Promote fatty acid oxidation; 3) Inhibit cholesterol esterification and absorption; 4) Improve lipid transport protein system	[93,94,106,107]
		Saponin	↓TC, TG, LDL; ↑HDL	Modulate the composition, abundance and diversity of gut microbiota	[93,94,106,107]
		Flavonoids, quercetin	↓TC, TG, LDL; ↑HDL	1) Inhibit lipid synthesis; 2) Promote fatty acid oxidation; 3) Promote bile acids synthesis and excretion; 4) Promote cholesterol convert to bile acid; 5) Improve insulin resistance	[93,94,106,107]
		DAS; DADS; DATS	↓TC, TG, LDL	1) Increase superoxide dismutase activity; 2) Inhibit Lipid peroxidation	[95,96,98]
5	*Glycine max*	Phytoalexins, glyceollins	↓TC, TG, LDL, VLDL	1) Inhibit cholesterol esterification and absorption; 2) Inhibit lipid peroxidation in liver; 3) Modulate triglyceride and cholesterol metabolism; 4) Decrease triglyceride storage; 5) Alter expression of the genes related to cholesterol in liver	[121–123]
		Phytic acid	↓TC, TG, LDL	1) Decrease triglyceride and cholesterol synthesis; 2) Increase fecal cholesterol and bile acids excretion	[121,123,135]
		Isoflavones, genistein, daidzein	↓TC, TG, LDL	1) Reduce hepatic lipid synthesis; 2) Decrease bile acids biosynthesis; 3) Decrease cholesterol reabsorption	[124,132–134]
		Soy lipids; Lecithins and phospholipids	↓TC, TG, LDL	1) Inhibit intestinal cholesterol absorption; 2) Promote biliary cholesterol excretion	[121,123]
		Pectin	↓TC, TG, LDL	1) Promote bile acids biosynthesis; 2) Inhibit intestinal bile acid reabsorption	[121,123,128]
		Peptides	↓TC, TG, LDL	1) Promote cholesterol efflux; 2) Decrease triglyceride fatty acid fractional synthesis; 3) Motivate bile acid biosynthesis and excretion	[125,129,137,138]
		Saponin	↓TC, TG, LDL; ↑HDL	Regulate gut microbiota	[121,123,128]
		Soy fibers	↓TC, TG, LDL	1) Improve intestinal flora diversity; 2) Regulate gut microbiota	[121,123,128]
		Lignans	↓TC, TG, LDL	Inhibit bile acids biosynthesis	[136]
6	*Silybum marianum*	Silybin (Silibinin)	↓TC, TG	1) Decrease *de novo* cholesterol biosynthesis; 2) Inhibit HMG-CoA reductase activity	[155,157]
		Silymarin	↓TC, TG, LDL	1) Inhibit lipids biosynthesis; 2) Inhibit intestinal cholesterol absorption; 3) Increase cholesterol efflux; 4) Promote fatty acid oxidation; 5) Improve insulin resistance	[155–159]
		Kaempferol	↓TG	Inhibit fatty acid synthesis and adipogenesis	[155,157,158]
		Quercetin	↓TC, TG, LDL; ↑HDL	1) Inhibit cholesterol biosynthesis; 2) Promote cholesterol convert to bile acid; 3) Promote fatty acid oxidation; 4) Improve insulin resistance	[155–159]
7	*Red Yeast Rice*	Monacolin K, Monacolin L	↓TC, TG, LDL, VLDL	1) Inhibit lipids biosynthesis; 2) Inhibit HMG-CoA reductase activity; 3) Decrease phospholipase A_2 activity	[175–177,180]

		Polysaccharides	↓TC, TG, LDL; ↑HDL	1) Inhibit lipid synthesis; 2) Inhibit lipids absorption; 3) Promote fatty acid oxidation and lipolysis; 4) Promote bile acids synthesis and excretion; 5) Regulate gut microbiota	[175–177,180]
8	*Commiphora mukul*	Guggulsterone (*E*- and *Z*)	↓TC, TG, LDL; ↑HDL	1) Decrease hepatic steroid production; 2) Increase plasma LDL catabolism; 3) Increase hepatic LDL clearance; 4) Increase cholesterol catabolism and excretion; 5) Regulate cholesterol metabolism; 6) Increase bile salts excretion	[192,194–196]
		Cembranoids	↓TC, TG, LDL,	1) Decrease phospholipase A_2 activity; 2) Inhibit cholesterol and triglyceride absorption	[200]
		Quercetin; Naringenin	↓TC, TG, LDL; ↑HDL	1) Inhibit lipids biosynthesis; 2) Promote cholesterol metabolism; 3) Promote fatty acid oxidation	[193,195]

Discussion

Hyperlipidemia has been proved to influence the antioxidant situation of various organs and their lipoprotein levels, as well [22]. Lipid-decreasing medicinal herbs may lessen hyperlipidemia, avoiding atherosclerosis and cardiovascular endothelium destruction [21]. Herbal medicine is based on the theory that plants contain natural substances that can advance health and relieve disease. Beneficial effects of medicinal herbs have been ascribed partially to their antioxidant properties [22]. The present review emphasizes the phytochemical, pharmacological, clinical and toxicological reports on medicinal plants effective on hyperlipidemia.

Hyperlipidemia enhances the yield of free radicals, which in line raises oxidative stress and LDL oxidation [20,205]. While this course, LDL converts to oxidized-LDL, causes the expression of adhesion molecules, motivates activation of T-lymphocytes and macrophages, intensifies the production of foam cells, and pulls macrophages toward the sarcoplasmic network. Oxidation of LDL has a critical role in the establishment of atherosclerotic plaques [9,10]. Free radicals are involved in a broad diversity of diseases, including diabetes, atherosclerosis, cardiovascular diseases, neurological disorders, and mental disabilities [20].

Inflammation is also related to cardiovascular disease. For instance, C-reactive protein is increased in atherosclerosis. It has been shown that patients with high C-reactive protein levels are also more tending to hypertension and type 2 diabetes, and both of these diseases are related to atherosclerosis [179]. Reduction of free radicals by plant's antioxidants, apart from diminishing hyperlipidemia, can decrease the feasibility of atherosclerosis [20]. Several experimental and clinical studies have shown that plants that have antioxidant activity can battle pathologic conditions particularly for the treatment and prevention of life-intimidating diseases such as brain injury, diabetes, hypertension and cardiovascular diseases [118,127,206].

Antioxidants such as selenium, and vitamins C and E were believed as being able to hinder cell membrane oxidation. Recently their common use has been limited because of their incompetent effects. Therefore, natural compounds with antioxidant and bioactive components appear to have beneficial effects. Essentially, medicinal herbs have bioactive constituents [43,93,129,207]. Hence, they can be very impressive in modulating oxidative stress, so sheltering various organs such as heart, kidney, and liver from oxidative damages. Furthermore, they have been shown to negate cardiovascular disease risk factors and are capable of providing drug supply in complementary and alternative medicine [208,209].

Saponins, flavonoids, phenolics, phytoestrogens, coumarins, alkaloids, amino acids, phytosterols, vitamins and terpenes constitute major classes of phyto-ingredients of medicinal plants [27,46]. Recent accomplished studies indicate their uses such as neuroprotective, renoprotective, hepatoprotective, cardioprotective, hypolipidemic, antidiabetic, antioxidant, anti-atherosclerotic, anti-ulcer, anticancer, antimicrobial, immunomodulatory, estrogenic, and nutritive for human health [43,49,94,156,158]. Despite the fact that different ingredients of medicinal plants can have antioxidant properties, the leading part of such effects is ascribed to polyphenolic compounds [38,124,161]. A lot of medicinal herbs such as artichoke, alfalfa, fenugreek, garlic, soybean, and so forth possesses antioxidant activities because of their polyphenolic compounds [38,124,125,207].

Conclusion

Nowadays, hyperlipidemia and its side effects are recognized as one of the health problems in most communities. In addition to intensifying the metabolic disorders, hyperlipidemia exacerbates cardiovascular disease, especially in patients with diabetes and hypertension. Ingredients in dietary supplements and medicinal herbs, including saponins, glycosides, polyphenols, flavonoids, triterpenoids, sterols, fibers and other antioxidant compounds, can affect the metabolism of lipids by influencing the metabolic reactions of various tissues. In most cases, the lipid-lowering effects of medicinal plants are due to their antioxidant properties.

Author contributions

D.M., E.K.A., M.E.A. and F.B.G. conceived, designed, and collected the data and literature for the manuscript and assisted in the data analysis. I.M. supervised the study and wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

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Data availability

The datasets supporting the conclusions of this article are included within the article.

Ethical approval

Not applicable.

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