ADVANCES IN DYSLIPIDEMIA THERAPY: FROM PHYTOCHEMICALS TO NANOCARRIERS

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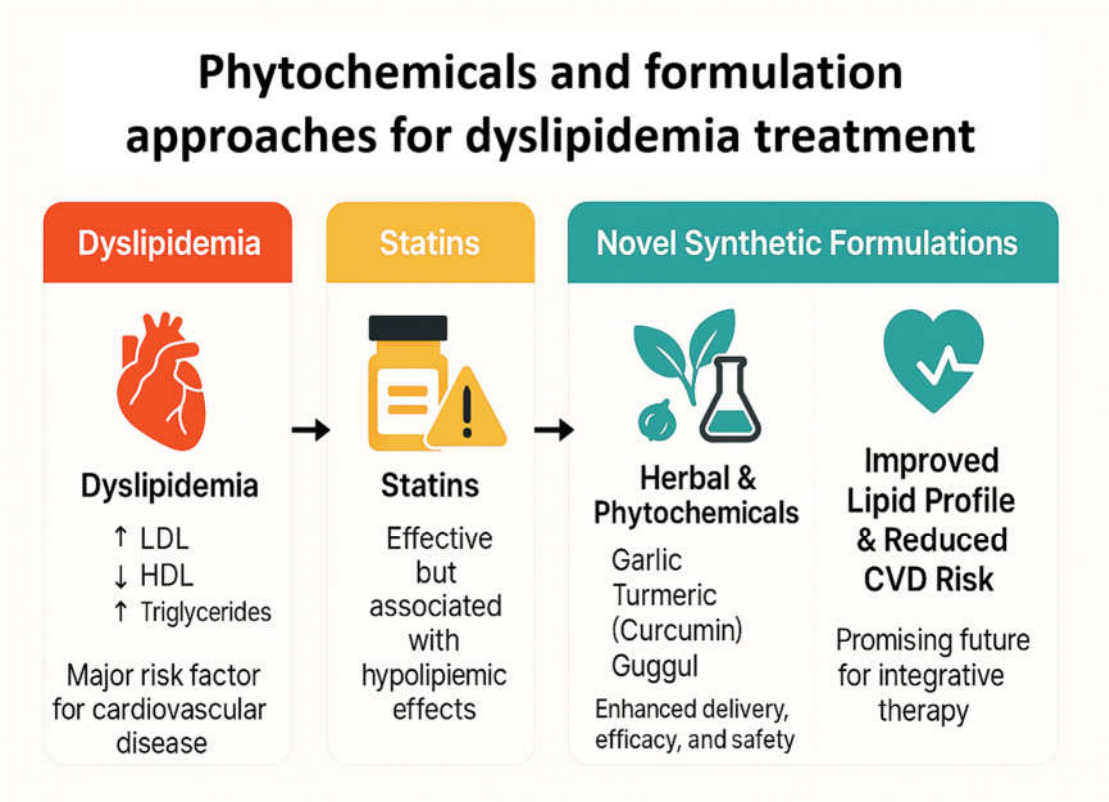
GRAPHICAL ABSTRACT



ABSTRACT

Dyslipidaemia, a metabolic condition marked by abnormal lipid levels, is a leading contributor to cardiovascular diseases, the world's leading cause of mortality. Statins are first-line drugs to manage dyslipidaemia. However, their use is often limited due to adverse effects. This review aims to evaluate the therapeutic potential of plant extracts and phytochemicals as safer alternatives to statins in dyslipidemia management, with a focus on their mechanisms of action and advances in formulation strategies to enhance their clinical utility. A comprehensive search of databases including Scopus, PubMed, and ScienceDirect was conducted up to 2025. Studies reporting the lipid-lowering effects of plant extracts and phytoconstituents, particularly those targeting HMG-CoA reductase and proprotein convertase subtilisin/kexin type 9 (PCSK9), were included. Literature on novel formulation approaches to improve the bioavailability and efficacy of these compounds was also reviewed. Phytochemicals such as curcumin, berberine, monacolin K, epigallocatechin-3-gallate, policosanol, beta-glucan, and phytosterols exhibit HMG-CoA reductase inhibitory activity comparable to statins. Berberine, quercetin, and policosanol also inhibit PCSK9, enhancing LDL receptor expression and reducing serum LDL cholesterol. Recent advancements in nanoformulations especially nanoparticles have shown potential to improve the solubility, stability, and targeted delivery of these bioactives. Plant-derived compounds offer a safer and promising alternative for the treatment of dyslipidemia, especially in populations vulnerable to the side effects of conventional drugs. Incorporating novel formulations may further enhance their therapeutic efficacy and pave the way for their integration into clinical practice for cardiovascular risk reduction.

KEYWORDS: Dyslipidemia, HMG CoA reductase, nanoformulations, natural compounds, phytoconstituents, plant extracts

1. INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the United States and around the world. Dyslipidaemia is a key risk factor for CVD and it is a common public health issue [1]. Dyslipidaemia refers to an alteration of plasma lipid levels, particularly, a rise in total cholesterol (TC), triglycerides (TG), and, low density lipoprotein (LDL). Hypercholesterolemia and decreased high density lipoproteins (HDL) levels are the two changes that contribute the most to an increased risk of CVD and can also occur in combination [2]. Hyperlipidaemia is a metabolic condition characterized by elevated levels of TC, LDL, and very-low-density lipoprotein cholesterol (VLDL-C). This condition often affects lipid metabolism. As per the World Health Organization (WHO), 40 percent of the population has high plasma cholesterol levels, which is a serious warning as high plasma cholesterol is the leading cause of death globally [3].

The treatment for dyslipidemia is reliant on the hyperlipidemia type. Hypolipidemic or lipid-lowering drugs are prescribed for Primary hyperlipidaemia while the treatment for Secondary hyperlipidaemia is prescribed on the basis of disease factors including hypothyroidism, renal lipid nephrosis, and diabetes **(Fig. 1)** [4]. Synthetic drugs comprising statins, fibrates, and bile acid sequestrants are commonly used to treat dyslipidemia. Conversely, they cause recurring adverse effects such as myopathy, rhabdomyolysis, gallstone growth [5], [6]. Although, statins, fibrates, ezetimibe, orlistat, naltrexone, buproprion, liraglutide, topiramate, and lorcaserine have been approved to treat dyslpidemia, they are accompanied by adverse effects such as abdominal discomfort, vomiting, nausea, constipation, insomnia, and headache [7]. As a consequence, there is a need to discover alternative, safe, and effective therapeutic approaches for the treatment of dyslipidemia.

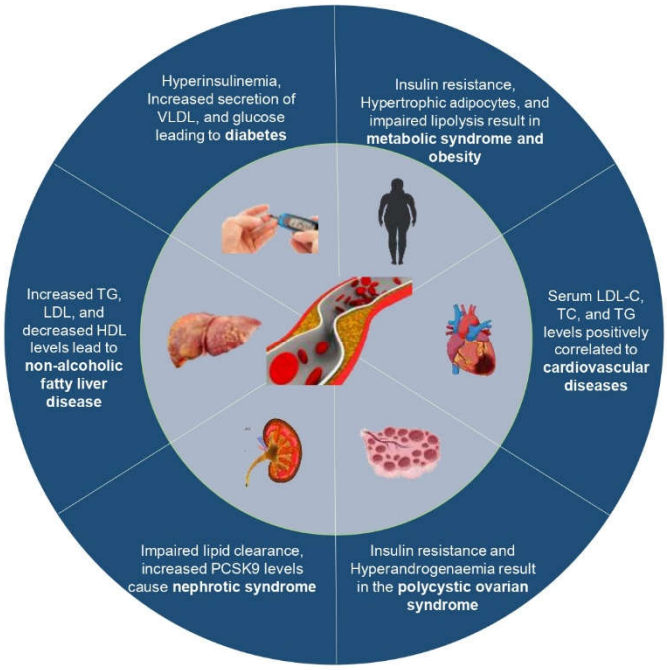


Fig. 1 Dyslipidaemia and its associated complications

Alternative treatment strategies include dietary change and the use of natural compounds. Herbal medicine is being used worldwide to prevent or treat a variety of ailments for decades. They are used for their hypoglycaemic, hypolipidemic, or antioxidant activities. Several clinical trials have demonstrated that the bioactive compounds from herbal sources improve the lipid profile safely and effectively [8]. The natural compounds and plant extracts are economic, effective, safe, and easily obtainable [9]. Lately dietary management, exercise, and pharmacological therapy have all been used to treat hyperlipidaemia. Since synthetic lipid-lowering medications, such as statins and fibrates, often have side effects and contraindications when used in long term, the use of natural hypolipidemic therapies to prevent and treat hyperlipidaemia and associated consequences appears to be critical **(Fig. 2)** [10].

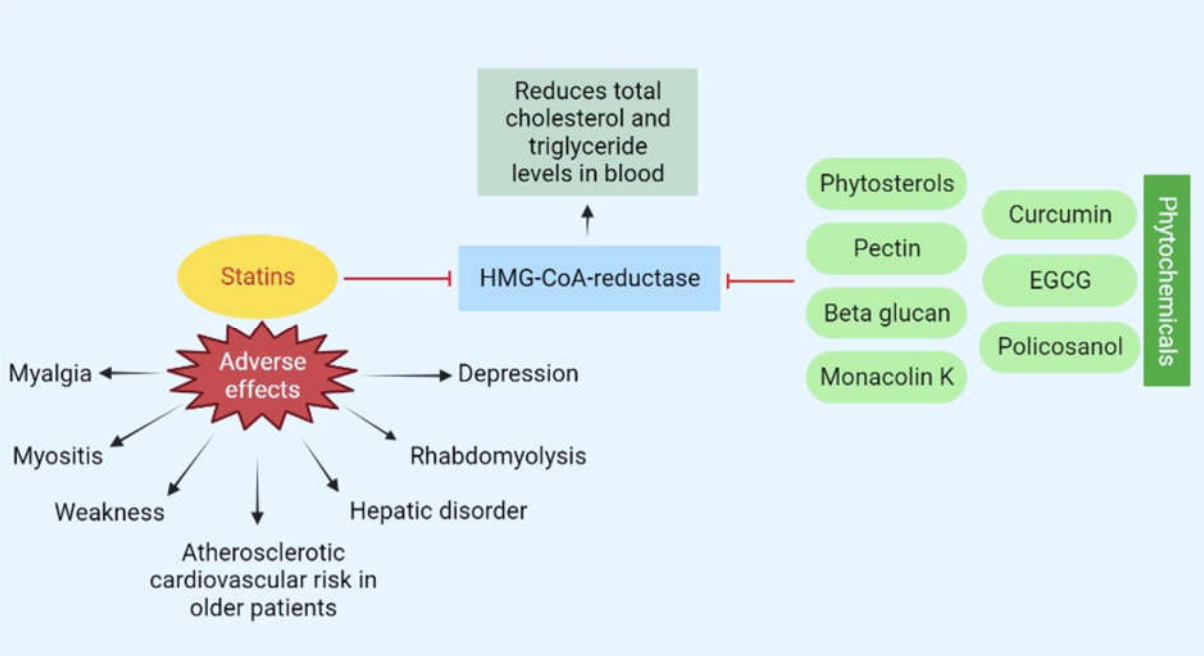


Fig. 2 Phytochemicals with mechanism of action similar to statins

In 2019, guidelines to be considered for dyslipidaemia treatment were given by the European Society of Atherosclerosis and the European Society of Cardiology which include various functional foods and dietary supplements. Nutraceuticals may be used alone or in combination as a supplement or an alternative treatment to statins. In 2021, the European Society of Cardiology released guidelines for the prevention of CVD in clinical practise for the usage of nutraceuticals with lipid lowering activity that could advance the quality of treatment in clinical settings [11]. The current review focuses on plant extracts and isolated phytochemicals explored for their role in the treatment and management of dyslipidaemia.

2. METHODS

This review was compiled focusing on literature past decade. A range of articles from databases such as SCOPUS, Springer, Google Scholar, PubMed, Science Direct, and Web of Science were explored for literature review. The keywords included ‘dyslipidemia, ‘phytochemicals’, ‘plant extracts’, ‘phytoconstituents’, ‘HMG CoA reductase’, and ‘natural compounds’. Further, papers were probed using these words to broaden the literature search.

3. PLANT EXTRACTS FOR DYSLIPIDAEMIA

Few clinical investigations have been carried out to evaluate the anti-lipid potential of herbs in patients with dyslipidaemia. Lipid oxidation was altered by dill and basil, whereas lipid peroxidation was reduced by ginger and evening primrose oil. Celery and blueberry inhibited lipid production and lipid catabolism induced lipid accumulation respectively. Green tea, grape, and Dandelion suppressed adipocyte differentiation and lipogenesis, while fenugreek stimulated lipase enzymes, nigella reduced the enzymatic activity of hepatic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, and ginseng upregulated adiponectin expression in adipocytes **(Fig. 3)**[12].

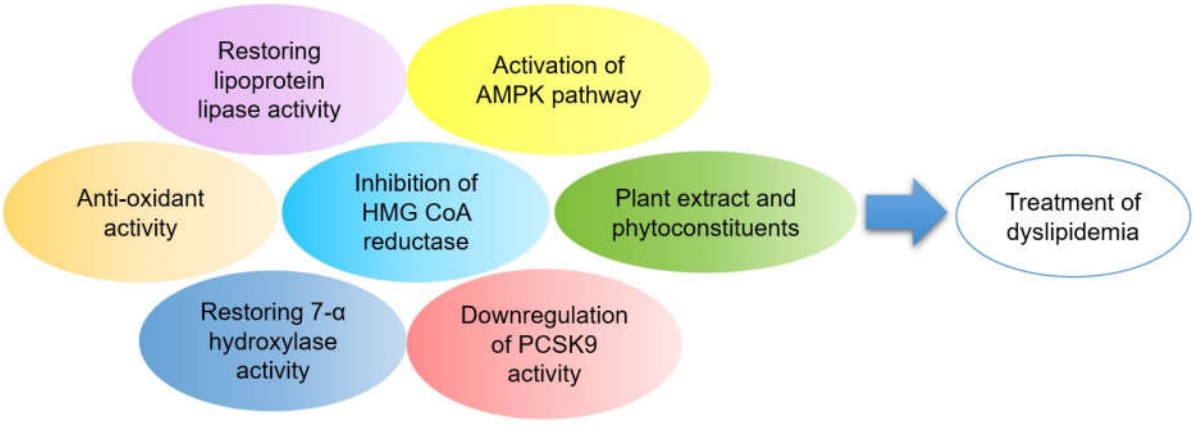


Fig. 3 Mechanism of action of plant extracts in the treatment of dyslipidemia

3.1. Lagenaria siceraria

L.siceraria of the family, Cucurbitaceae has a role in the treatment of CVD. The β-glycosidase–elastase enzyme in the fruit extract *and* metabolites such as phenolic compounds, flavonoids, and saponins contained in the leaf and fruit extracts of *L. siceraria* are stated to have antihyperlipidemic potential [4], [11]. Charu Katare *et al*. reported the effect of *Lagenaria Siceraria* in triton induced hyperlipidaemic animals. Saponins affect the cholesterol absorption in the intestinal lumen by binding to it and also increasing the activity of lipoprotein lipase.

Flavonoids regulate the lipid levels in the blood, while soluble dietary fibres lower cholesterol levels in the blood. The study concluded that levels of TC, VLDL, TG, and LDL in the serum were reduced significantly and the HDL level was improved upon treatment with the extract following 90 days of therapy [13]. Suraj Kumar et al., (2019) elucidated the effect of L. siceraraia extract in high cholesterol diet fed rats and reported significant reduction in the serum levels of TG, TC, VLDL, and LDL followed by an increase in HDL. The effect was better than control but less than lovastatin treated groups [14]. Shendge and Belemkar (2018) reported reduction in the serum TC and TG levels upon treatment with L. siceraraia methanolic extract for 28 days in female and male Wistar rats [9].

3.2. Glycyrrhiza glabra

Glycyrrhiza glabra and its active compounds such as Glabridin (an isoflavan) and isoliquiritigenin (a flavonoid) have potential antioxidant properties for the oxidation of LDL. In an investigation done in rats with hyperlipidaemia induced by a high fat diet (HFD), it was found that ethanolic fractions of *G. glabra* roots (400 mg/kg) displayed a substantial rise in the plasma level of HDL and free radical scavenging leading to lipid lowering activity [15]. Several animal studies reported anti hyperlipidaemic potential of G. glabra in HFD induced obese rats [16], HFD fed rats[17], alloxan induced diabetic mice [18], and high fructose diet fed rats [19].

3.3.Nigella sativa

Nigella sativa is a traditional medicinal plant reported to control hyperlipidaemia in humans and animals. Kirn-e-Muneera et al. compared the efficacy of *N. sativa* (1000 mg/kg) with Simvastatin (20 mg/kg) in libidium diet fed rats and reported the potential of N. sativa in improving the lipid profile in a comparable way to Simvastatin. The study concluded that polyunsaturated fatty acids in seed was responsible for the lipid-lowering action [20]. A clinical study revealed improvement in waist-to-hip ratio, BMI, reduction in TC, CRP, LDL, and TG

blood levels while increasing HDL by *N. Sativa* following four weeks of therapy[21]. *N. sativa* demonstrated anti-dyslipidaemia activity in letrozole induced PCOS rats[22] and HFD induced hyperlipidaemic rats[23]. In a clinical trial involving dyslipidaemia patients, *N. sativa* extract reduced the serum levels of TC, TG, and LDL and increased serum HDL following 6 weeks of treatment and was considered to be effective in the dyslipidaemia management [24].

3.4.Curcuma longa

Curcuma longa, commonly called turmeric of the family Zingiberaceae is a common condiment used worldwide. An investigational study by Jogdand and Padhy, (2019) reported reduction in serum TG, TC levels and increased HDL in diabetic hyperlipidaemic rats when treated with *C. longa* (300 and 500 mg/kg) and its effect was comparable to Atorvastatin. Turmeric increases the activity of cholesterol 7α hydroxylase in the liver, indicating a higher rate of cholesterol catabolism [25].

3.5. Cassia plants

C. occidentalis Linn. Belongs to Caesalpiniaceae family. Fidele N *et al*. studied the activity of *C. occidentalis* (240, 320, and 400 mg/kg) aqueous extract in hypercholesterolemia rats. There was a reduction in the levels of LDL-C, TC, VLDL-C, TG and TC, and lipid peroxidation index in the rats, whereas accelerated excretion of faecal cholesterol. The hypolipidemic effect of the *C. occidentalis* extract was hypothesised to be facilitated by lowering or inhibiting cholesterol absorption in the intestine, increasing the activity of an enzyme called 7- α-hydroxylase, which converts cholesterol into biliary acids, and increasing reverse cholesterol transport [8].

3.6. Medicago sativa

Medicago sativa or alfalfa from the family Fabaceae is been used in the treatment of hyperlipidaemia. The effectiveness of *M. sativa* in the treatment of hyperlipidaemia was evaluated in diabetic hyperlipidaemia rats induced with streptozotocin (STZ). The organic

solvent extracts of *M. sativa* sprouts displayed a reduction in the levels of TC, VLDL, TG and LDL similar to rosuvastatin, an HMG-CoA reductase inhibitor. The study reported that *M. sativa* methanolic extract demonstrated better antihyperglycemic and antihyperlipidemic activity in STZ-induced diabetic hyperlipidaemia rats. The anti-hyperlipidaemic activity of the extract was attributed to the presence of omega-3 fatty acids and phytosterols in high content which decreases plasma levels of cholesterol and inhibits the synthesis and absorption of cholesterol in the liver and intestine of the rats respectively [4].

3.7. Curatella americana

Curatella americana L. of the family Dilleniaceae demonstrated superior hypolipidemic activity. Saponin is one of the chief chemical constituents in *Curatella americana* with the potential to reduce serum levels of cholesterol. The leaves of the *Curatella americana* offer protection against lipid peroxidation and decrease oxidative stress through free radical scavenging. The findings from the study indicated a reduction in the serum levels of TG and cholesterol by extract, thereby exhibiting significant anti-hyperlipidaemic activity [26].

3.8. Mango peel

Mango peel is high in antioxidants, flavonoids, carotenoids, and polyphenols. Arshad et al., (2021) reported reduction in LDL, TC, TG, levels and improvement in HDL level after ingesting mango peel powder, whereas thiobarbituric acid reactive substances (TBARS) displayed elevation in antioxidant activity, indicative of the effectiveness of mango peel in the management of dyslipidaemia in obese patients. As a result, it appeared to protect against LDL oxidation induced vascular damage [27].

3.9. Pitaya

Pitaya or dragon fruit contains phytocompounds and betalains which is been used as a dietary supplement. Holanda et al., (2021) compared the efficacy of Pitaya with Simvastatin in the

treatment of dyslipidaemia in hypercholesterolemic diet induced adult female mice. The treatment with Pitaya decreased TC, LDL-C, TG, glycemia, and liver enzymes such as aspartate aminotransferase and alanine aminotransferase while HDL-C levels were increased. Red Pitaya was found to possess hypoglycaemic and dyslipidaemia effects, thus reducing CVD risk. It can be concluded that the Pitaya can be used as a potent nutraceutical in the treatment of hypercholesterolemia due to the presence of flavonoids, betacyanin, and oligosaccharides [5].

3.10. Myrsine Africana

The methanolic extract of *Myrsine Africana* leaves contains flavonoids, saponins, tannins, phenolic, and steroidal compounds. In a study, diabetes was induced in mice by injection of alloxan. The methanolic extract of the leaves reduced elevated TC, and TG increased HDL-C levels following 14 days of treatment. In general, the antihyperlipidemic and antihyperglycemic properties of these phytocompounds are due to the restoration of pancreatic tissue function by increasing insulin production or inhibiting the glucose absorption in the intestine, or facilitating metabolites in the process dependent on insulin. *M. africana* either indirectly controls hyperglycaemia or directly induces the metabolism of lipids and controls dyslipidaemia [28].

3.11. Coccinia grandis

Plant-derived phenolic chemicals have a lipid-lowering effect. In STZ-induced diabetic rats, methanolic extract of *C. grandis* decreases phospholipids, free fatty acids, cholesterol, and TG levels. In rats fed with HFD, peritoneal, mesenteric, and epididymal fat deposition was considerably reduced when they were given a *C. grandis* ethanolic extract. The mechanism behind the reduction in lipid levels may be the prevention of differentiation of adipocytes and down-regulation of gene expression that encodes adiponectin, Glucose transporter type 4

(GLUT4), and Peroxisome proliferator-activated receptor (PPARγ). The *C. grandis* ethanolic extract reduced cholesterol levels in a similar way to Metformin [29].

3.12. Nipa Palm Vinegar (NPV)

Vinegar is used as alternative medicine in the treatment of hyperlipidaemia. Moragot and Wiyada (2020) looked at the antilipidemic properties of the Nipa palm due to the presence of phenolic compounds. Nipa Palm Vinegar (NPV) inhibited cholesterol esterase, pancreatic lipase, and suppressed the micellization of cholesterol in a dose-dependent way [6]. This finding suggests that NPV could be explored as a natural antilipidemic agent, however, it should be thoroughly evaluated in preclinical and clinical studies.

4. ISOLATED COMPOUNDS

The International Lipid Expert Panel (ILEP) stated that therapy with phytocompounds appears to be highly safe and tolerable and recommended them to be an alternative lipid-lowering agent for Statins in patients who are intolerant to it. Natural AMP-activated protein kinase (AMPK) activators such as resveratrol, salvianolic acid, curcumin, ginsenosides, berberine, quercetin, and naringenin are used to treat CVD [30]. Lipid-lowering activity has also been investigated using combination formulations. Berberis aristata, Silybum morianum, and monacolin K were used as one combination. The combination of red yeast rice (Monacolin K), astaxanthin, Policosanol, folic acid, Berberine, and coenzyme Q10 lowered LDL-C, TC, and TG levels in plasma while increasing HDL. Berberine, Monacolin K, and *Morus alba B* leaf extract was used to lower LDL-C and TC. As a result of their lipid-lowering characteristics, nutraceuticals may be useful in the treatment of dyslipidaemia [31]. Some of the isolated compounds with lipid-lowering effects have been discussed **(Figure 4)**.

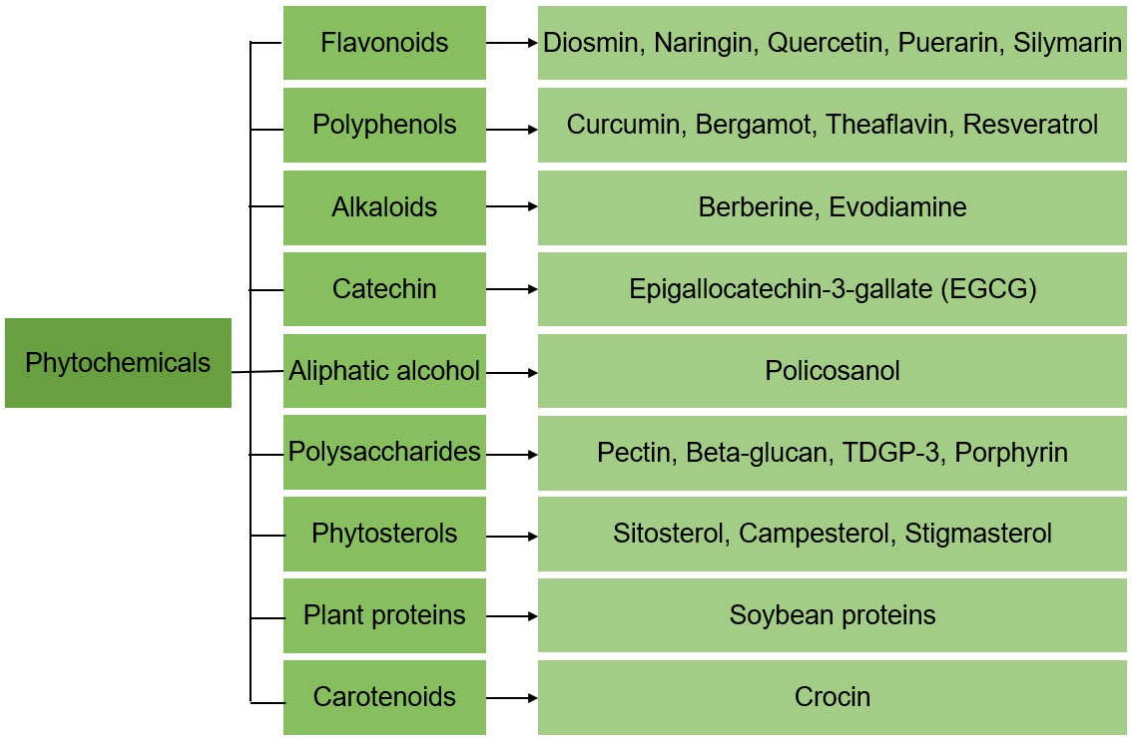


Fig. 4 Phytochemicals and active constituents with examples used in the treatment of dyslipidaemia

4.1. Diosmin

Diosmin (DS) is a flavone glycoside present in citrus fruits. In a study evaluating the role of DS (100 and 200 mg) administered orally in hyperlipidaemic mice, treatment with 200 mg DS decreased TC, VLDL-C, TG, LDL-C, TC, and increased HDL-C substantially. The therapeutic effects of DS as an antihyperlipidemic and for hepatoprotection have been observed to be equivalent to those of a typical cholesterol-lowering medication that inhibits cholesterol synthesis such as atorvastatin [3].

4.2. Curcumin

Curcumin, a polyphenol is just as effective as statins at lowering TC and TG in the blood as it increases HMG-CoA reductase expression. In comparison to the control group, long-term administration of curcumin daily for 30 days considerably reduced blood TC, LDL, TG, and

marginally increased HDL [32]. Saeed et al (2020) in their meta-analysis reported decrease in the serum levels of TG, TC, LDL, and increase in serum HDL levels by curcumin indicating its potential role as hypolipidemic agent [33].

4.3.Berberine

Berberine, an isoquinolone alkaloid is found to be prolific in patients intolerant to statin treatment. Berberine's antihyperlipidemic activity is mediated by upregulating hepatic LDL receptor (LDLR) expression through LDLR mRNA regulation and downregulating the enzyme expression of proprotein convertase subtilisin or Kexin type 9 (PCSK9) [34]. Berberine reduces cholesterol by inhibiting its absorption and promoting its excretion. Co-administration of berberine with silymarin was found to be effective in maintaining normal lipid levels in diabetic subjects with altered lipid profile [35].

4.4.Epigallocatechin-3-galate (EGCG)

Catechins in green tea prevents obesity and its complications, such as hypercholesterolemia and hyperglycaemia. EGCG is believed to function by inhibiting the HMG Co-A reductase enzyme and lowering fat absorption from the gut [36]. Diabetic mice administered with different doses of EGCG such as 50, 100, and 200 mg/kg per day reduced blood levels of TG, TC, and LDL [37]. In mice fed with HFD, EGCG (30 mg/kg/day) reduced TC, TG, LDL, and glucose levels within 6 weeks of treatment [38]. In HFD induced hyperlipidaemic rats, EGCG considerably lowered blood TC, TG, FFA, and LDL-C levels whereas boosted serum HDL [39].

4.5.Monacolin K

Monacolin K acts by similar mechanism as statins that is inhibition of HMG CoA reductase. Xuezhikang, a purified extract of red yeast rice (RYR), and 600 mg of monacolin (2.5–3.2 mg/capsule) lowers cholesterol when administered twice a day. In reality, the main active

component of RYR, monacolin K is now sold under the name lovastatin [34]. Armolipid Plus is a complex nutraceutical that has 200 mg of RYR, Monacolin K (3 mg), berberine (500 mg), coenzyme Q10 (2 mg), Policosanol (10 mg), Astaxanthin (0.5 mg), and folic acid (0.2 mg) in a single tablet. This is the most well-studied hypolipidemic nutraceutical in terms of lipid reduction and safety of usage [40].

4.6.Bergamot

Bergamot polyphenolic fraction (BPF) has been shown to have a hypolipemic impact. Adenosine monophosphate-activated protein kinase (AMPK) pathway involved in metabolism of lipid and glycogen in the liver, and its dysfunction has been linked to fat storage and liver damage in hyperlipidaemia patients. BPF modulates AMPK and improves lipid profile. In diet-induced hypercholesterolemic rats, administration of BPF at a 20 mg/kg dose for 90 days substantially reduced TC, LDL-C, TG, and glucose, along with HDL [41].

4.7.Policosanol

Policosanol, isolated from sugar cane has a lipid-lowering effect. Ishaka et al. (2020) studied the effects of rice bran wax policosanol and its nano emulsion in hyperlipidaemic Sprague Dawley rats and reported significant reduction in TC, TG, and LDL values [42]. On contrary, a meta-analysis by Hui Dong and Fuer Lu et al. (2017) reported 5mg of policosanol did not significantly influence body weight, TG and was less efficient at enhancing HDL-C compared to statins [43]. Policosanol's hypolipidemic property is related to its ability to inhibit HMG-CoA reductase and PCSK9 [44].

4.8.Pectin

Pectin is a natural heteropolysaccharide present in plant cell and the underlying mechanism by which pectin reverses obesity is by altering gut microbiota and short chain fatty acid contents [45]. In hypercholesterolemia mice, ethanol extracts of Lemon orange peel and Bali orange

peel lowered TC, TG, HDL-LDL levels, and Malondialdehyde (MDA) levels, suggesting that it can be an antidyslipidemic and antioxidant [46]. Hawthorn's pectin reduces blood TC, LDL, and hepatic TC in high-fat-fed rats by inhibiting HMG-CoA [47].

4.9.Evodiamine

Evodiamine is an indoloquinazoline alkaloid been used as a dietary supplement aiding in weight loss and improving lipid metabolism. In hyperlipidaemic mice, evodiamine decreased TG, LDL, and TC while elevating HDL, suggesting that it may protect against CVD [48].

4.10. Theaflavin

Theaflavin and other tea polyphenols have been shown to decrease the expression of pancreatic lipase, involved in fat metabolism. Furthermore, it increases lipolysis in 3 T3-L1 adipocytes through inducing mitochondrial uncoupling proteins and the AMPK pathway, which is beneficial in obesity control. Interference with cholesterol micellar solubilization is another probable mechanism by which theaflavin lowered lipid levels [49].

4.11. Beta glucan

Chemically, β-glucans are polysaccharides and form structural components in the cell walls of microorganisms, mushrooms and grains. In rats, β-glucans reduced TC, TG, and MDA levels. In hamsters, β-glucans lowered LDL plasma levels by facilitating faecal excretion of lipids and regulating HMG-CoA reductase activity. β-glucan obtained from yeast distinctly decreased TC in hypercholesterolemic mice [50]. β-glucans can reduce LDL and moderate cholesterol levels in animals and humans [51].

4.12. Phytosterols

Phytosterols include campesterol, stigmasterol, and β-sitosterol. The hypocholesterolaemia effect of phytosterols is through inhibition of HMG-CoA reductase, acetyl CoA carboxylase and malic enzyme [52]. Phytosterols are structurally and functionally similar to cholesterol. Primary phytosterols are stigmasterol, sitosterol, sitostanol, campestanol, and campesterol. They are present in naturally obtained food and the daily intake ranges from 200 to 400 mg [53]. Mycosterols obtained from mushroom or fungi contains ergosterol as a principal component that reduces hepatic TG, TC, LDL and also intestinal cholesterol absorption [54].

4.13. Soybean proteins

Soy is a good example of functional food, and its hydrolysate has been shown to influence lipolysis in adipocytes. In cellular and mouse models, peptides from soy hydrolysates alter blood cholesterol levels by influencing transintestinal cholesterol excretion and bile acid metabolism. Soy hydrolysate treatment reduced blood cholesterol in high cholesterol diet fed rats [55].

4.14. Quercetin

In humans, quercetin inhibits fat accumulation and initiates apoptosis in fat cells, inhibits fat cell production and increases its necrosis [56]. Cristina et al., (2022) reported notable reduction in the elevated total protein (TP), serum levels of TC, TG, albumin, and LDL while an increase in HDL was found when HFD fed BALB/c mice were treated with quercetin. The mechanism behind lipid lowering activity of Quercetin was through inhibition of activity of LDLR and PCSK9 in the liver [57]. The lipid lowering potential of Quercetin is also by attenuation of PPAR-α [58]. *Malva neglecta* plant extract contains quercetin which has hypolipidemic potential. In alloxan-induced diabetic rats, the plant extract significantly reduced weight, levels of blood glucose, TG and TC, while HDL levels were increased compared to the control [59].

4.15. Puerarin

Puerarin, an isoflavonoid present in *Pueraria lobata Ohwi* is known to reduce body weight and improves the metabolism of lipids and glucose *in vivo* and *in vitro* in diabetic animals. Puerarin suppresses TNF-α, modulates PARP-1/PI3K/AKT pathway, and reduces levels of adipokines such as resistin, and leptin, which are the underlying mechanism of metabolic effects. Puerarin significantly reduced TC, non-esterified fatty acid, TG levels, and augmented phospholipid and HDL levels. But, a significant reduction in LDL levels was not observed compared to control [60]. Thus, Puerarin is claimed to have a possible role in the treatment of obesity and underlying complication.

4.16. Silymarin

Milk thistle or Silybum marianum contains Silymarin, a flavonolignan. Silybin is a major flavonolignan present in Silymarin. Clinical studies have reported lipid and cholesterol-lowering effects of Silymarin in hypercholesteraemic patients. The mechanism behind lowering blood and bile cholesterol levels is by reducing the synthesis of cholesterol in the hepatocytes and by increasing the cholesterol conversion rate. It also reduces cholesterol, LDL, and TG levels, whereas increases HDL levels in the blood [61].

4.17. Crocin

Crocin is one of the main pigments in saffron. Crocin decreased TC, LDL, and TG in plasma while increasing HDL in HFD fed rats. In STZ induced diabetic rats, crocin reduced LDL, TC levels and increased HDL levels. Hydroalcoholic extracts of saffron possess hypercholesteraemic and hypolipidemic properties. The antihyperlipidemic property of saffron or crocin is due to PPARα receptor activation [62]. In a clinical trial, crocin significantly increased Cholesteryl ester transfer protein levels in serum, a protein involved in the modulation of lipoproteins and plasma lipids. Although the data revealed an increase in TG

and HDL and a decrease in TC, LDL, and fasting blood sugar, the differences were not significant when compared to the control group [63].

4.18. Resveratrol

Resveratrol is an antioxidant phytoestrogen. Resveratrol (200 mg/day) considerably reduced LDL-C and HDL-C by modulating genes involved in the metabolism of lipids. Resveratrol decreased lipid accumulation and enhanced glycogen storage in hepatocytes and muscle by stimulating lipolysis in adipocytes [64]. In a clinical trial involving dyslipidaemia patients, TC level was significantly lowered following supplementation of resveratrol (250 mg/day). The cholesterol lowering property of resveratrol is due to the presence of phenolic hydroxy groups in its structure resulting in the reduction of blood cholesterol levels and unsaturated fatty acid oxidation [65]. A. Raškovic´ et al (2019) reported enhanced glycaemic control in diabetic rats and reduced elevated TG and LDL, concomitantly increasing the HDL in HFD fed hyperlipidaemic rats. Modulation in the lipid parameters following resveratrol supplementation is believed to be mediated through HMG-CoA down-regulation, increased hepatic cholesterol 7a-hydroxylase (CIP7A1) expression resulting in augmented bile acid synthesis and secretion. Additionally, resveratrol upregulates the LDLR expression in hepatic cells thereby, enhancing hepatic uptake of LDL through AMPK pathway [66].

4.19. Naringin

Naringin, a flavonoid is an inhibitor of HMG-CoA reductase and acetyl-coenzyme A acetyltransferase (ACAT). Studies have shown a reduction in the Naringin reduces levels of TC, LDL, body weight, BMI, and waist-to-hip ratio by Naringin. It increases adiponectin, thereby reducing body weight and increasing HDL. Naringenin, a metabolite of Naringin increases fatty acid oxidation in hepatic cells by augmenting peroxisomal β-oxidation and

activity of ACAT [67], [68]. Naringin (200 mg/kg) decreases plasma levels of cholesterol and TG [69].

4.20. Porphyran

Porphyran is a sulphated polysaccharide obtained from red algae, *Porphyra haitanensis*. It has a potential antioxidant and antihyperlipidemic properties. Zhan et al. (2017) reported amelioration of lipid profile through reduction of elevated TG, TC, LDL and increased HDL [70]. The intraperitoneal injection of Porphyran in mice reduced the peroxidation of lipids, and increased superoxide dismutase (SOD) and GSH-Px activities, thereby enhancing the total antioxidant capacity [71].

4.21. TDGP-3

TDGP-3 is a polysaccharide isolated from *Tetrastigma hemsleyanum Diels et Gilg.* In a study evaluating its antihyperlipidemic effect in HFD induced mice, TDGP-3 suppressed weight gain induced by HFD. It decreased elevated TG, LDL, and TC and reduced HDL. The mechanism of action of TDGP-3 against hyperlipidaemia was thoroughly associated with antioxidant property and regulation of lipid metabolism. Xin Peng et al. (2020) stated restoration in the elevated blood levels of LDL, TG, and TC and increase in HDL by TDGP-3 in HFD induced hyperlipidaemia mouse when administered at a dose of 300 mg/kg for five days. It can be concluded that TDGP-3 might be a potential antihyperlipidemic agent [72].

5. NOVEL DRUG DELIVERY STRATEGIES FOR DYSLIPIDEMIA USING SYNTHETIC AGENTS

Although phytochemicals show lipid-lowering potential, limitations like poor bioavailability hinder their efficacy. Advances in novel formulations for synthetic drugs offer valuable strategies that can also enhance phytochemical delivery in dyslipidemia therapy. Despite the

widespread use of conventional lipid-lowering agents such as statins, fibrates, and cholesterol absorption inhibitors, issues such as low bioavailability, poor solubility, systemic toxicity, and off-target effects limit their therapeutic potential [73]. To overcome these drawbacks, novel formulation strategies using nanotechnology and targeted delivery systems have been explored to improve efficacy, safety, and patient compliance in dyslipidemia management.

5.1. Polymeric Nanoparticles

Polymeric nanoparticles (NPs), including PLGA and PLGA-b-PEG, offer promising platforms for enhancing drug loading, targeted delivery, and controlled release. These biodegradable nanocarriers can encapsulate lipophilic drugs used in lipid disorders, enabling site-specific delivery while minimizing systemic side effects. For instance, PLGA nanoparticles were developed to improve hepatic targeting of rimonabant, restoring its metabolic benefits without triggering the neuropsychiatric side effects typically associated with CB1R inhibition [74]. Moreover, polymeric NPs loaded with statins have shown enhanced therapeutic outcomes, including the potential to stimulate cardiac stem cell growth, with PLGA demonstrating high drug encapsulation and sustained release [75].

5.2. Lipid-Based Nanoparticles

Lipid nanoparticles, including **s**olid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), have gained significant attention for delivering lipid-lowering drugs due to their biocompatibility and ability to improve oral bioavailability. Statin-loaded SLNs have exhibited superior absorption and sustained release compared to free drugs [76], [77]. A formulation combining atorvastatin-SLNs with coenzyme Q10 and vitamin E showed enhanced lipid-lowering effects in hyperlipidemic rats, with significant reductions in triglycerides and LDL-C compared to atorvastatin-SLNs alone [78]. Similarly, lovastatin-loaded NLCs prepared with Myverol exhibited improved gastric stability and higher plasma

drug levels than conventional formulations [79]. Transdermal delivery of atorvastatin through nanotransfersomal gels has also shown promising results. This approach significantly lowered total cholesterol, triglycerides, and LDL-C in hyperlipidemic rats, with reduced liver toxicity compared to oral atorvastatin, which failed to show notable lipid-lowering effects. These findings suggest that nanotransfersomes may offer a safer and more effective route of administration [80]. Another study demonstrated the potential of simvastatin-loaded SLNs, showing high entrapment efficiency (89.81%) and enhanced biochemical, histological, and immunohistochemical outcomes in high-fat diet-induced hyperlipidemic animals, outperforming the free drug [81].

5.3.Metallic Nanoparticles

Metallic nanoparticles (NPs), such as those based on selenium or gold, have been evaluated for their lipid-lowering and antioxidant potential. Selenium nanoparticles (SeNPs) reduced hyperlipidemia and vascular injury in ApoE-deficient mice by modulating cholesterol metabolism and oxidative stress. SeNPs significantly lowered triglyceride and LDL-C levels while raising HDL-C, demonstrating comparable efficacy to atorvastatin [82]. Gold nanoparticles (AuNPs) have also shown potential in modulating lipid metabolism and reducing atherogenic indices, improving total antioxidant capacity and lipid parameters in diabetic models [83].

5.4.PCSK9-Targeted Approaches

PCSK9 inhibitors represent a cutting-edge approach in dyslipidemia therapy. While monoclonal antibodies are already in clinical use, newer delivery strategies include small interfering RNA (siRNA) and vaccination approaches [84], [85]. Inclisiran, an siRNA-based drug, targets PCSK9 mRNA, leading to reduced PCSK9 protein levels and a sustained LDL-C

reduction for up to six months. Phase I and II trials demonstrated significant efficacy, and ongoing Phase III studies suggest that biannual dosing may maintain lipid-lowering effects with good safety and tolerability [86], [87]. PCSK9 vaccines offer another emerging alternative, potentially more cost-effective and long-acting than antibodies [88]. Animal studies have shown that peptide-based PCSK9 vaccines can maintain improved lipid profiles for up to 40 weeks and reduce atherosclerotic lesions. Early-phase human trials are underway to evaluate their safety and immunogenicity [89], [90].

6. CONCLUSION AND FUTURE PERSPECTIVES

Dyslipidemia remains one of the most prevalent risk factors for cardiovascular diseases worldwide, contributing significantly to global morbidity and mortality. To date, statins have been used as first-line treatment for dyslipidaemia, but they are often associated with adverse effects. Therefore, the quest for novel anti-hyperlipidaemic drugs with less adverse effects usually derived from plant origin is of significant interest. Plant-derived phytochemicals have shown encouraging results in improving lipid profiles by modulating metabolic pathways and restoring lipid balance.These natural compounds, whether used alone or alongside conventional therapies, offer potential benefits in managing hyperlipidemia. However, challenges such as poor bioavailability and limited clinical data hinder their broader application. The development of novel drug delivery systems, including nanoformulations, can address these limitations and enhance therapeutic outcomes. Future efforts should focus on rigorous clinical trials and formulation development to establish phytochemicals as effective agents in dyslipidemia treatment.

Author contribution

The authors have made substantial contribution to conceptualization, investigation, methodology, writing- original draft, review, and submission

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Conflict of interest

The author has no conflict of interest to declare.

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