Cardiology Research and Cardiovascular Medicine
Chico L, et al. Cardiolog Res Cardiovasc Med 10: 290.
www.doi.org/10.29011/2575-7083.100290
www.gavinpublishers.com

OPEN ACCESS

GAVIN PUBLISHERS

Review Article

Management of Dyslipidemia and Cardiometabolic Disorders: Pharmacological Therapies, Nutraceuticals, or Both?

Lucia Chico[1*], Giulia Della Scala[1], Linda Balestrini[1], Lucia Filippucci[2]

[1]Laboratori Aliveda srl, Crespina Lorenzana, Pisa, Italy.

[2]Unità Operativa Cardiologia Riabilitativa e Prevenzione Patologie Cardiovascolari, USL Umbria1, Perugia, Italy.

***Corresponding author:** Lucia Chico, Laboratori Aliveda, Crespina Lorenzana Pisa, Italy.

Citation: Chico L, Della Scala G, Balestrini L, Filippucci L (2025) Management of Dyslipidemia and Cardiometabolic Disorders: Pharmacological Therapies, Nutraceuticals, or Both?. Cardiol Res Cardio vasc Med 10:290. DOI:https://doi.org/10.29011/2575-7083.100290

Received Date: 05 December, 2025; **Accepted Date:** 11 December, 2025; **Published Date:** 12 December, 2025

Abstract

Dyslipidemia, characterized by abnormal lipid profiles, represents a central contributor to cardiometabolic disorders, including metabolic syndrome and type 2 diabetes, and remains a major public health challenge. While pharmacological therapies demonstrate established efficacy in lowering low-density lipoprotein cholesterol (LDL-C) levels, a considerable proportion of patients fail to achieve guideline-recommended targets. Moreover, conventional therapeutic approaches predominantly target isolated aspects of dyslipidemia, leaving significant residual cardiovascular risk factors – including hypertriglyceridemia, insulin resistance, and chronic low-grade inflammation – inadequately addressed. Treatment-related adverse effects further compromise long-term therapeutic adherence, underscoring the critical need for complementary therapeutic strategies.

Nutraceuticals, with their broad spectrum of actions and generally favorable safety profile, can offer a supportive perspective: rather than acting on a single pathway, they may influence lipid metabolism, glucose regulation, and inflammatory processes simultaneously. By complementing pharmacological therapy, nutraceuticals align with the multifactorial nature of cardiometabolic disorders and may help address residual risk.

This review explores the combined potential of pharmacological and nutraceutical approaches, reflecting on their strengths, limitations, and possible integration within a holistic strategy for the management of dyslipidemia and related cardiometabolic conditions.

Key words: Dyslipidemia, cardiometabolic diseases, pharmacological treatments, nutraceuticals, synergistic approaches

Introduction

Dyslipidemia is one of the primary causal risk factors for the development of atherosclerotic cardiovascular disease (ASCVD). It is characterized by elevated plasma concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-C) and/or triglycerides (TGs), as well as decreased levels of high-density lipoprotein cholesterol (HDL-C) [1]. The accumulation of lipids within the arterial intima is the first step that triggers a cascade of local inflammatory responses, which promotes the development of atherosclerotic plaques [2]. Dyslipidemia is frequently associated with a cluster of cardiometabolic abnormalities – including central obesity, hyperglycemia, insulin resistance, and hypertension – that collectively define the metabolic syndrome (MetS). MetS is associated with a high risk of both cerebrovascular and cardiovascular diseases. Indeed, each feature of MetS represents an independent risk factor for CVD, and their coexistence exerts synergistic and deleterious effects on vascular health. Moreover, MetS often precedes and contributes to development of type 2 diabetes (T2D). When the two conditions coexist, they act in concert to further amplify the overall cardiovascular risk [2,3].

Among these interconnected metabolic alterations, dyslipidemia seems to play a particularly central role, as demonstrated by

its frequent clustering with other metabolic abnormalities in defined syndromic patterns. Moreover, the management of one alteration (e.g., dyslipidemia) can affect the course of others, (e.g., hyperglycemia) [4]. This interconnection highlights the need for therapeutic strategies capable of addressing multiple components of MetS simultaneously.

Pharmacological treatment of dyslipidemia primarily relies on statins, which are effective in reducing LDL-C levels and cardiovascular risk [5]. Other lipid-lowering drugs – including ezetimibe, proprotein convertase subtilisin-kexin 9 (PCSK-9) inhibitors, bempedoic acid – can be used alone or in combination to address specific lipid abnormalities [6]. However, despite their efficacy, conventional therapies often target individual metabolic parameters and may be limited by residual cardiovascular risk, patients' intolerance, or adverse effect. These limitations have prompted growing interest in complementary or alternative approaches that act through broader metabolic pathways.

In recent years, increasing attention has been directed toward natural compounds with multi-target metabolic activity, which may offer a more holistic approach to cardiometabolic risk reduction.

Bioactive molecules of marine and terrestrial origin – including those derived from animal, plant, and fungi sources – have demonstrated the capacity to modulate several pathophysiological axes relevant to atherosclerosis and MetS. These include not only lipid metabolism, but also glycemic control, low-grade systemic inflammation, and endothelial dysfunction, which collectively contribute to the development and progression of cardiometabolic disorders [7,8].

This review explores the evolving scenario of dyslipidemia management, questioning whether pharmacological therapies are sufficient to meet the complexity of cardiovascular risk. Might this be the space where carefully selected nutraceuticals, not as substitutes but as allies, can offer an added dimension? By exploring mechanisms of action and clinical evidence, we reflect on whether a more integrated approach might better align with the multifaceted nature of lipid disorders.

Pharmacological treatments

Statins

Statins represent the first-line pharmacological intervention for hypercholesterolemia, with well-established efficacy in reducing total cholesterol and LDL-C [6, 9]. These agents act as selective and competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the mevalonate pathway of cholesterol synthesis. The inhibition of hepatic cholesterol synthesis triggers a compensatory upregulation of LDL receptors (LDLR) on hepatocyte membranes, thereby enhancing the clearance of circulating LDL-C [10].

Since the late 1980s, starting with lovastatin, a range of statins – including simvastatin, pravastatin, atorvastatin, rosuvastatin and pitavastatin – have been approved, expanding therapeutic options in clinical practice. Statin type and dosage are tailored according to cardiovascular risk, which remains a pivotal determinant in reaching LDL-C goals in dyslipidemia management (Table 1) [10,11].

Current treatment guidelines focus on lowering LDL-C as the primary strategy to reduce CVD risk, positioning statins as the cornerstone of dyslipidemia therapy. However, many patients – particularly those with T2D – remain at high residual CVD risk despite reaching LDL-C targets, due to persistent lipid abnormalities. This residual risk is often attributed to mixed dyslipidemia, characterized by elevated TG and low HDL-C levels [12, 13].

Statins exert modest effects on HDL-C and can reduce in TG levels at higher doses, but these changes are often insufficient to fully mitigate the residual cardiovascular risk [14, 15].

Moreover, statin intolerance remains a relevant clinical challenge, affecting approximately 10% - 25% of treated patients. The most frequently reported adverse events are statin-associated muscle symptoms (SAMS), which include mild to moderate myalgia, weakness, fatigue and muscle pain, while severe manifestations such as rhabdomyolysis are rare [16, 17]. In some cases, non-muscle-related adverse effects and laboratory abnormalities may also occur, either independently or in association with SAMS [16].

Additionally, statin therapy has been associated with modest, dose-dependent alterations in glucose metabolism, including increased fasting glucose, glycosylated hemoglobin A1C (HbA1C), and a higher incidence of T2D, especially in subjects with predisposing risk factors. Genetic studies have further supported this association, with variants of the HMGCR gene linked to a 2% - 6% increased risk of T2D. Although the underlying mechanisms are not yet fully elucidated, it has been hypothesized that statin-induced inhibition of the mevalonate pathway may impair insulin secretion, potentially due to cholesterol accumulation and lipotoxicity in pancreatic β-cells, contributing to abnormal glycemia [18, 19].

Therapy	*Statin type (dose)*	*Expected LDL-C reduction*
Low intensity statin	Simvastatin (10 mg) Pravastatin (10 – 20 mg) Lovastatin (20 mg)	< 30%
Moderate intensity statin	Atorvastatin (10 – 20 mg) Rosuvastatin (5 – 10 mg) Simvastatin (20 – 40 mg) Pravastatin – Lovastatin (40 – 80 mg) Pitavastatin (1 – 4 mg)	< 50%
High intensity statin	Atorvastatin (40 – 80 mg) Rosuvastatin (20 – 40 mg)	≥ 50%

Table 1: Effect of the main statins on LDL-C reduction.

Nonstatin therapies

When statin therapy fails to achieve lipid targets or is not tolerated, additional or alternative lipid-lowering agents are recommended as part of comprehensive approach to dyslipidemia management. Bile acid sequestrants, Ezetimibe, PCSK9 inhibitors, and bempedoic acid act on lowering LDL-C in this context. On the other hand, fibrates, niacin, and omega-3 fatty acids may offer additional benefits in patients with mixed dyslipidemia, particularly in presence of low HDL-C and elevated TG levels [13].

Ezetimibe

Among the available nonstatin options, ezetimibe is often the first-line adjunct therapy, especially in cases of statin intolerance, non-adherence, or when LDL-C targets are not met despite maximally tolerated statin therapy [20]. Initially approved as a monotherapy and later in fixed combination with simvastatin, ezetimibe is widely used in clinical practice.

Ezetimibe is a Nieman-Pick C1-Like 1 (NPC1L1) inhibitor that reduces intestinal absorption of both dietary and biliary cholesterol, thereby reducing LDL-C levels [21]. Clinical trials have shown its efficacy. An 18% LDL-C reduction has been observed with ezetimibe 10 mg/day, and its combination with statins provides an additional 15-24% decrease – exceeding the modest 6-8% gain obtained by simply increasing statin doses [22]. More recently, rosuvastatin/ezetimibe (10 mg + 10 mg) achieved greater LDL-C reductions and fewer side effects than rosuvastatin (20 mg) alone [23].

Similarly, ezetimibe/simvastatin (10/20 mg) was more effective than atorvastatin (20 mg) to reduce LDL-C levels (78% versus 52%) and to achieve the LDL-C target in patients with coronary heart disease [24]. This combination also lowered total cholesterol and TGs, thought effects on HDL-C were minimal [25].

Importantly, the IMPROVE-IT trial confirmed that patients at very high risk – particularly those with T2D – derive the most benefit from ezetimibe/statins therapy, with significant reduction myocardial infarction and strokes, potentially due to effects beyond cholesterol lowering, such as on inflammation and platelet activity [26].

Bile acid sequestrants

Bile acid sequestrants (BASs), including cholestyramine, colestipol, and colesevelam, are non-absorbable resins that lower cholesterol by binding bile acids in the intestine. This binding prevents their reabsorption and disrupts the enterohepatic circulation, which in turn stimulates hepatic conversation of cholesterol into bile acids [27]. As a compensatory mechanism, hepatocytes upregulate LDLRs, thereby enhancing the clearance of circulating LDL-C and ultimately reducing plasma LDL-C levels. Initially developed for the treatment of hypercholesterolemia, BASs were subsequently found to improve glycemic control in patients with T2D, likely via modulation of bile acid composition, hepatic glucose metabolism, and incretin release [28].

Long-term studies with cholestyramine demonstrated a 20% reduction in LDL-C, associated with a 19% relative risk reduction in myocardial infarction and coronary heart disease-related death.

Modest improvement in glycemic parameters, including reduction in fasting plasma glucose (FPG) and HbA1C, were also observed [29].

Colesevelam, the most recently developed BAS, has been extensively studied both as monotherapy and in combination with other lipid-lowering or glucose-lowering agents. As monotherapy, it reduces LDL-C by 15–20% and produce an additive reduction of ~10% when combined with statins, ezetimibe, fibrate, or niacin [30].

In patients with T2D, colesevelam added to therapy with metformin, sulfonylureas, or insulin consistently reduces HbA1c by ~0.5% and FGP by 13-15 mg/dL. LDL-C reductions ranged from 6.7% to 15.9%, while TG levels increased by 4.7 to 21.5% [29].

Similar increases in TGs (10%-12%, dose-dependent) have been observed in patients with primary hypercholesterolemia treated with colesevelam monotherapy, along with a modest HDL-C increase of approximately 10%. Due to their lack of intestinal absorption, BASs do not exhibit systemic toxicity. However, their use is commonly associated with gastrointestinal adverse effects, primarily constipation [31].

Proprotein convertase subtilisin-kexin 9 (PCSK-9) inhibitors

When statins and ezetimibe are insufficient to achieve LDL-C goals, particularly in patients at very high risk or with statin intolerance, PCSK9 inhibitors represent an effective alternative to further reduce LDL-C and cardiovascular events [32].

PCSK9 is a key regulator of LDL receptor (LDLR) availability on hepatocytes. By binding to LDLRs and promoting their degradation, PCSK9 reduces hepatic clearance of LDL-C, leading to elevated circulating LDL-C levels [33]. Monoclonal antibodies such as evolocumab, elirocumab, and tafolecimab inhibit circulating PCSK9, preventing its interaction with LDLRs and thereby enhancing receptor recycling and LDL-C clearance [34,35].

Large-scale trials including FOURIER, ODYSSEY, and CREDIT-2 have demonstrated that subcutaneous administration every 2-4 weeks reduces LDL-C levels up to 60% [36-38].

Notably, evolocumab significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke by 16% in the first year and 25% in subsequent years in high-risk patients [38].

In terms of safety, PCSK9 inhibitors are generally well tolerated, with most adverse event being mild to moderate. However, long-term trials such as OSLER-1 have reported a high incidence of adverse events (94%), with 23% classified as severe and 27% leading to treatment discontinuation [39]. Common side effects of alirocumab and tafolecimab include injection-site reactions, myalgia, and upper respiratory infection [38,40]. These findings underline the importance of long-term safety monitoring to maintain adherence and therapeutic efficacy.

An alternative strategy is inclisiran, a small interfering RNA (siRNA) that inhibits hepatic PCSK9 synthesis. Approved for use in ASCVD and familial hypercholesteremia, it offers the practical advantage of twice-yearly dosing, potentially improving adherence [41]. Innovative approaches, such as PCSK9-targeted vaccines, are also under investigation and may offer new therapeutic avenues in the future [34, 42].

Bempedoic acid

Bempedoic acid is an oral prodrug that lowers LDL-C by inhibiting ATP-citrate lyase (ACLY) in hepatocytes [43]. Once activated to bempedoic acid-CoA by very long-chain acyl-CoA synthetase 1 (ACSVL1) – expressed in liver but not in skeletal muscle – it reduces hepatic cholesterol and TG synthesis, upregulates LDLR expression, and lowers high-sensitivity C-reactive protein (hs-CRP) by ~ 20%, contributing to anti-inflammatory effects and ASCVD risk reduction [9].

It is available as 180 mg tablets, alone or in fixed combination with 10 mg of ezetimibe and is indicated for adults with primary (heterozygous familial or non-familial) or mixed dyslipidemia who are statin-intolerant or unable to achieve LDL-C targets despite maximal tolerated therapy [44,45]. The combination with ezetimibe offers a synergistic effect on LDL-C reduction, with results comparable to moderate-intensity statins. However, concomitant use with simvastatin at doses >20 mg/day is contraindicated [43, 46].

The absence of ACSVL1 in skeletal muscle minimized the risk of myotoxicity, making bempedoic acid suitable for patients with SAMS. Nevertheless, treatment may lead to increases in serum uric acid and creatinine levels, likely via inhibition of the organic anion transporter 2 (OAT2), potentially triggering gout flares in predisposed subjects. These effects are generally reversible upon discontinuation, highlighting the importance of renal function monitoring during therapy [47].

In addition, bempedoic acid appears to have a favorable profile on glucose metabolism. Compared to placebo, a lower incidence of new-onset diabetes has been reported in both normoglycemic and prediabetes patients, along with modest but significant reduction in HbA1c levels in patients with prediabetes and T2D [46].

Although the aforementioned therapies have demonstrated significant efficacy in lowering LDL-C and reducing cardiovascular events, their effects on other lipid fractions remain limited.

Specifically, these agents exert only modest effects on TG levels and negligible impact on HDL-C concentrations, which play a critical role in residual cardiovascular risk, particularly in patients with mixed dyslipidemia [35, 48].

This limitation is especially relevant in patients with MetS, T2D, or visceral obesity, where dyslipidemia – characterized by elevated TGs, LDL-C, and low HDL-C remains prevalent despite optimal LDL-C lowering. Clinical guidelines, including those from ESC/EAS (2023) and AHA/ACC (2019), recognize LDL-C as the primary therapeutic target bur also emphasize the importance of managing other lipid abnormalities in high-risk population.

These considerations highlight the need for complementary treatment strategies aimed at a broader modulation of the lipid profile.

Fibrates and others conventional treatments

Fibrates

Fibrates represent the main therapeutic class used to manage elevated TG levels. This group include gemfibrozil, bezafibrate, ciprofibrate and fenofibrate, all of which act as agonists of peroxisome proliferator-activated receptors (PPARs). These agents are administrated as prodrugs and undergo hepatic conversation to their active form. Among them, fenofibrates – selective for PPARα – are the most widely used in clinical practice due to its favorable efficacy [49, 50]. By activating PPARα, fibrates lower serum TG levels by approximately 20–40% and increase HDL-C by 5–20%, thereby contributing to a reduction in cardiovascular and cerebrovascular risk in subjects with hypertriglyceridemia. In patients with mixed hyperlipidemia, fibrates can be used either as monotherapy or associated with statins. However, such combination therapy requires careful monitoring due to the potential risk of adverse effects, particularly SAMS. This risk is partly related to the ability of fibrates to alter gene and protein expression in skeletal muscle, potentially leading to muscle damage and dysfunction [50].

Niacin

Niacin (vitamin B3) exerts broad lipid-modifying effects by reducing concentrations of all atherogenic ApoB-containing lipoproteins, inhibiting hepatic VLDL and TG synthesis, and suppressing the release of free fatty acids from adipose tissue. Moreover, niacin exhibits vascular protective properties, including antioxidant, anti-inflammatory, and anti-thrombotic effects. At pharmacological doses (2-3 g/day), it reduces LDL-C by over 20%, TGs by 30-40%, and increases HDL-C by approximately 25%, making it the most effective available agent for raising HDL-C levels [46, 51]. Despite these favorable effects on the lipid profile, randomized trials have failed to demonstrate additional cardiovascular benefit when niacin is added to background statin therapy [52]. This lack of incremental efficacy, combined with a high incidence of adverse effects – including cutaneous flushing, impaired glucose tolerance, and hepatotoxicity – has substantially limited the clinical role of niacin. As a result, its use has progressively declined, and it is no larger recommended in the current lipid management guidelines [46, 53].

Omega-3 fatty acids

Omega-3 fatty acids (O3FAs), particularly eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), represent an additional therapeutic option for the management of hypertriglyceridemia.

Although naturally present in marine sources and certain plant-based food, they are considered part of conventional lipid-lowering therapy only when administrated at pharmacological doses. EPA and DHA exert their primary lipid-modifying effect by reducing hepatic VLDL synthesis and enhancing triglycerides clearance, resulting in a dose-dependent TG reduction of approximately 10-50% depending on baseline values [54]. Notably, EPA-only formulations exhibit a more favorable lipid profile compared to mixed preparation. A critical distinction emerges between formulation types: while mixed EPA+DHA preparation may increase LDL-C levels, particularly in patients with severe hypertriglyceridemia (≥500 mg/dL), purified EPA formulations do not induce such increases. The effects on other lipid parameters remain modest, with minimal impact observed on HDL-C, total cholesterol, or lipoprotein(a) [Lp(a)] concentrations. O3FAs are generally well tolerated with few contraindications or significant drug interactions [32, 55].

Despite early observational data linking O3FAs-rich diets to reduced cardiovascular risk, results from randomized trials have yielded inconsistent findings. This apparent paradox has been explained through recent large-scale interventional studies that emphasize the critical importance of both for formulation specificity and dosing strategies. Low-dose EPA+DHA supplements have failed to demonstrate consistent clinical benefit in both primary and secondary cardiovascular prevention. In contrast, high-dose EPA-only interventions have shown significant cardiovascular risk reduction across multiple trials, including JELIS, REDUCE-IT, and RESPECT-EPA. Conversely, comparable doses of mixed EPA+DHA formulations failed to produce cardiovascular benefit in trials such as STRENGTH or OMEMI [32, 46, 56].

These differential clinical outcomes suggest that EPA may exert unique pleiotropic effects that extend beyond triglyceride reduction. Proposed mechanisms include anti-inflammatory, antioxidative, and plaque-stabilizing effects, potentially mediated by bioactive metabolites such as resolvin E1and 18-HEPE. The presence of DHA in mixed formulations may attenuate these

beneficial effects or exert competing physiological actions that diminish cardiovascular benefit [56].

Nutraceutical intervention

In recent years, there has been growing interest in the use of natural bioactive compounds in lipid management (Table 2). Derived from different sources, these agents exert metabolic, anti-inflammatory, and antioxidant effects, with some demonstrating specific lipid-modifying properties.

Among them, phytosterols, monacolin K, and berberine appear to be the most effective lipid-lowering nutraceuticals.

Unlike conventional pharmacological therapies, nutraceuticals can act on multiple targets simultaneously and are generally associated with fewer side effects. This multimodal action may offer broader benefits in the context of residual cardiovascular risk, particularly in patients with dyslipidemia, MetS, or statin [57].

Given some limitations of current lipid-lowering therapies to treat different aspects of dyslipidemia and the persistence of residual cardiovascular risk despite optimal pharmacological treatments, an important question arises: can selected nutraceuticals, alone or in combination with standard therapies, provide clinical support in this setting? To explore this hypothesis, several nutraceutical agents with lipid-lowering potential have been studied in both experimental and clinical context. In the following section, we review the most promising of these compounds – focusing on their mechanisms of action, available clinical evidence, and their potential role in integrative strategies aimed at improving lipid profiles and reducing cardiometabolic risk.

Natural compounds	**Mechanisms of action**	**LDL-C effect**	**TG effect**	**HDL-C effect**	**Total-C effect**	**Notes**
O3FAs (EPA/DHA)	↓ VLDL and TG	Neutral or ↑ 5–10%	↓ 20–50% (dose-dependent)	↑ 5–10%	↓ 5–10%	Variable on LDL Strong for TG at pharmacological levels
Phytosterols	↓ absorption of cholesterol at intestinal level	↓ 10–15%	Neutral	Neutral	↓ 10–15%	EFSA approved
Monacolin K – RYR	HMG-CoA reductase inhibition (like statins)	↓ 15–25%	↓ 5–10%	↑ 1–2%	↓ 15–25%	EFSA regulated
Berberine	AMPK phosphorylation LDLR upregulation PCSK9 inhibition Anti-inflammatory	↓ 15–25%	↓ 10–20%	↑ 2–5%	↓ 15–25%	Supported by RCTs Safe at high doses
Fenugreek	LDLR upregulation	↓ ~10%	↓ 15–20%	↑ 2–5%	↓ ~10%	Good, especially in T2D
Reishi	LXRs upregulation ABCG5/8 modulation Anti-inflammatory – antioxidant	↓ 5–10%	↓ up to 20%	↑ ~ 5%	↓ 5–10%	Moderate

↓: decrease; ↑: increase; RCTs: randomized clinical trials; T2D: type 2 diabetes; RYR: red yeast rice; AMPK: AMP-activated protein kinase

O3FAs: omega-3 fatty acids; EPA: eicosapentanoic acid; DHA: docosahexanoic acid; LDLR: low-density lipoprotein cholesterol receptor; LXRs: liver X receptors; PCSK9: Proprotein convertase subtilisin/kexin type 9

Table 2: The most promising natural compounds for dyslipidemia management

Phytosterols

Phytosterols, which include plant sterols and stanols, are naturally occurring steroidal compounds. To date, over 250 distinct phytosterols and structurally related derivatives have been identified across a wide range of plant and marine sources [58, 59].

Phytosterols reduce intestinal cholesterol absorption by competing with cholesterol for incorporation into micelles, leading to lower plasma LDL-C levels. Despite their structural similarity to cholesterol, their bioavailability is very low – less than 5% compared to 50-60% for cholesterol – primarily due to poor water solubility and active efflux by ABCG5/8 transporters. After partial absorption via NPC1LC, a small fraction enters the circulation, mainly within LDL particles, or is incorporated into HDL via ABACA1 transporters; the remainder is excreted back into the intestinal lumen or bile. Genetic factors also influence phytosterol absorption. Variants in NPC1L1 and apolipoprotein E (ApoE3/4 or ApoE4/4 alleles) have been associated with higher uptake, although mechanisms are not fully understood [58, 60].

Initially hindered for therapeutic application due to poor bioavailability, phytosterols regained interest following chemical modification such as esterification, which increase lipophilicity and facilitate their incorporation into fat-rich food products. Notably, when adequately formulated into foods, free phytosterols can achieve LDL-lowering effects comparable to those of esterified forms, which improved their incorporation into food products and enhanced functional efficacy. These findings underscore the importance of the delivery system over the specific chemical form of phytosterols. As a result, current formulation strategies are increasingly focused on optimizing both chemical modifications (such as esterification) and physical techniques (such as microencapsulation) to improve their bioavailability [59-61].

Meta-analyses and regulatory assessments indicated that an intake of 1.5 – 3.0 g/day of plant sterols or stanols can reduce serum LDL-cholesterol concentrations by up to 12%, with maximal effect achieved within 2 – 3 weeks [61,62].

In addition to their lipid-lowering effect, phytosterols have been shown to improve insulin resistance, modulate lipid metabolism, and potentially reduce the risk atherosclerosis related CVD [61]. Some evidence suggests that daily consumption of 1.5 – 2.0 g/day of plant sterol/stanols may reduce TGs by 6% – 20% and increase HDL-cholesterol by 5 – 11%, particularly in subjects with atherogenic dyslipidemia [61]. However, a network meta-analysis of 131 trials found no significant effect of plant sterols/stanols supplementation on TG or HDL-C levels [63]. At higher intakes, some studies suggest difference in the efficacy between plant sterols and stanols; however, the available evidence is insufficient, and well-designed trials are needed to draw definitive conclusions regarding their relative efficacy as such levels [61].

Data also support the mild hypoglycemic effect of phytosterols. A meta-analysis of 20 randomized controlled trials involving 1306 participants showed that phytosterol supplementation modestly decreased insulin levels, fasting plasma glucose, and HbA1c, although these changes were not clinically significant [64].

Red Yeast Rice - Monacolin K

Red Yeast Rice (RYR) is produced by fermentation of white rice and Monascus purpureus fungus. The specific fermentation conditions influence the composition of the final product, including the presence of red pigments, characteristic flavor compounds, and bioactive substances such as monacolins. Among these, monacolin K represents the principal bioactive compound and is structurally identical to lovastatin, exerting its cholesterol-lowering effects by competitively inhibiting HMG-CoA reductase [65].

The lipid-lowering efficacy of RYR has been assessed in different intervention studies, showing that monacolin K (from 4 to 10 mg) can significantly reduce elevated LDL-C levels, without appreciable effects on TG or HLD-C concentrations [66, 67].

These findings were corroborated by meta-analysis demonstrating that RYR lowers LDL-C with an efficacy comparable to low-intensity or low-doses statin therapy. A modest increase in HDL-C and a negligible reduction in TG levels was also reported following daily RYR intakes ranging from 1200 to 4800 mg/day, corresponding to 4 mg to 24 mg of monacolin K [68].

The EFSA has assessed the claim that a daily intake of 10 mg monacolin K from red yeast rice (RYR) contributes to maintaining normal LDL-C plasma levels in adults from the general population. However, due to the structural similarity and shared biosynthetic pathway between monacolin K and lovastatin, the EFSA/ANS Panel raised safety concerns in 2018 [69]. Reported adverse effects were comparable to those observed with lovastatin, predominantly involving musculoskeletal and connective tissues, with rhabdomyolysis representing the most severe outcome. Additional adverse events were reported in decreasing order of frequency in the hepatic, nervous, gastrointestinal, and cutaneous/subcutaneous systems [70, 71].

The quality and composition of RYR products can vary substantially, and their regulatory classification differs across jurisdictions. In the United States, products containing monacolin K are classified as prescription drugs, whereas in Europe they are marketed as food supplements and are available without prescription [71].

Monacolin K from RYR has a demonstrated LDL-C–lowering effect, recognized by the EFSA for intakes of 10 mg/day in adults. However, safety concerns at doses ≥10 mg/day and

reports of severe adverse reactions even at 3 mg/day have led to regulatory restrictions. Commission Regulation (EU) 2022/860 set a maximum daily dose of 3 mg, and RYR supplementation is contraindicated in individuals younger than 70 years and in those already receiving statin therapy due to the risk of additive toxicity. This regulation was subsequently amended by Commission Regulation (EU) 2024/2041, clarifying that the EFSA-approved claim for LDL-C reduction no longer applies at intakes below 3 mg/day [70,72].

Berberine

Among natural compounds with lipid-lowering potential, berberine – a natural isoquinoline alkaloid extracted from plants such as *Berberis vulgaris* L. and *Berberis aristata* DC – has attracted increasing interest due to its pleiotropic actions on metabolic health [73, 74].

Clinical trials have confirmed the efficacy and safety of berberine, with high adherence rates and no discontinuation due to adverse events. Even at high doses (up to 2000 mg/day for 20 days), berberine was well tolerated in hypercholesterolemic patients, even in cases of mild to moderate gastrointestinal side effects such as diarrhea and nausea, which have occasionally been reported at higher doses [75,76].

Regarding its lipid-lowering efficacy, berberine monotherapy (500 mg twice daily for 3 months) has demonstrated significant reductions in LDL-C, total cholesterol, and TG levels in patients with T2D and dyslipidemia [75.77].

These findings are supported by a systematic review and meta-analysis of randomized controlled trials evaluating berberine in combination with simvastatin, which confirmed a greater reduction in total cholesterol and TG levels compared to statin monotherapy. Importantly, the incidence of adverse effects – including elevated transaminases and statin-associated myalgia – was significantly lower in patients receiving berberine either alone or in combination with simvastatin, compared to those treated with statins alone [78].

These observations suggest a potential role for berberine in patients with statin intolerance or in those requiring combination strategies to achieve lipid targets with improved safety profile.

Beyond lipid-lowering effects, berberine has also been associated with broader metabolic benefits.

In patients with T2D, clinically reduction in HbA1c and waist circumference have been reported, while in patients with obesity, modest weight loss (~2.2 Kg) has been observed [75, 79, 80], suggesting potential utility in the management of cardiometabolic risk beyond dyslipidemia.

These multiple effects are likely related to berberine ability to modulate metabolic homeostasis through several mechanisms, in contrast to conventional single-target pharmacological treatments. These include activation of AMP-activated protein kinase (AMPK), upregulation of hepatic LDLRs, downregulation of PCSK9 and inhibition of Nod-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome.

Activation of AMPK

AMPK is a central regulator of energy homeostasis, promoting ATP-generating pathways such as glycolysis and fatty acid oxidation, while simultaneously inhibiting ATP-consuming pathways, including fatty acid and cholesterol synthesis. Genetics models support its role in metabolic regulation: mice lacking AMPKα, the catalytic subunit of AMPK, develop insulin resistance, glucose intolerance, and increased adiposity under a high-fat diet. Similarly, systemic and liver-specific AMPKα2 deficiency induces hypertriglyceridemia in vivo. Notably, antidiabetic drugs like metformin act partly via hepatic AMPK activation to improve lipid metabolism and alleviate hepatic steatosis [81].

Berberine exerts many of its metabolic effects trough AMPK activation. In obese animal models, chronic berberine administration reduces body weight and improves insulin sensitivity via AMPK activation in adipose tissue. In skeletal muscle, it enhances glucose uptake by stimulating both AMPK and p38 MAPK pathways. In hepatocytes, berberine activates AMPK and promotes fatty acid oxidation leading to improved lipid profiles and reduced hepatic fat accumulation in high-fat-fed animals [82].

Furthermore, in a rat model of hyperhomocysteinemia – a condition associated with increased cardiovascular risk and dysregulation of cholesterol biosynthesis – berberine reduced both serum and hepatic cholesterol levels by inhibited HMG-CoA reductase activity. This occurred independently of changes in HMG-CoA reductase gene or protein expression, suggesting a post-translational regulatory mechanism. Moreover, berberine restored hepatic levels of phosphorylated AMPK, which were suppressed in hyperhomocysteinemic rats. Since AMPK activation promotes HMG-CoA reductase inactivation through phosphorylation, these findings support AMPK as a key upstream mediator in the inhibition of cholesterol biosynthesis by berberine [83].

Inhibition of NLRP3 inflammasome

Emerging evidence indicates that berberine exerts anti-inflammatory effects partly by modulating the NLRP3 inflammasome, a multiprotein complex involved in the release of pro-inflammatory cytokines such as IL-1β and IL-18. Activation of NLRP3 is a key contributor to pyroptosis, a pro-inflammatory form of programmed cell death that plays a role in cardiac inflammation

and glucotoxicity, particularly in the pathophysiology of atherosclerosis, myocardial ischemia-reperfusion injury, diabetic cardiomyopathy, and insulin resistance [84].

In a study using both db/db diabetic mice and high glucose-treated H9C2 cells, berberine treatment significantly reduced NLRP3-dependent inflammation. This effect was associated with decreased mitochondrial reactive oxygen species (mtROS) generation and suppressed mTOR phosphorylation, two up-stream events known to promote inflammasome activation [85].

Moreover, previous evidence supports the possibility that AMPK activation may contribute to the observed effects, as seen with other agents such as metformin which inhibits NLRP3 via the AMPK/mTOR axis. Thuse, berberine anti-inflammatory actions may involve both AMPK-dependent and -independent mechanisms, including modulation of ROS/NF-kB and mTOR signaling [86]. Overall, these findings suggest that berberine may attenuate NLRP3-mediated inflammation through multi-target mechanisms, highlighting its potential as an adjunct strategy for cardiometabolic protection.

Modulation of PCSK9 and LDLR expression

In addition to its effects on inflammation and cholesterol synthesis, berberine also modulates pathways involved in LDL-C clearance. It is known that LDLR and PCSK9 are both transcriptionally regulated by sterol-responsive element binding protein 2 (SREBP-2), which is activated in response to intracellular cholesterol depletion. Moreover, PCSK9 expression is regulated by hepatocytes nuclear factor 1α (HNF1α), a transcription factor involved in its basal expression [87].

In HepG2 liver cells, berberine has been shown to reduce PCSK9 expression by downregulation of HNF1α, a process mediated by activation of the ubiquitine-proteasome system [88]. This mechanism differs from that of statins, which increase both LDLR and PCSK9 via SERBP-2 activation, partially offsetting their effect. Unlike statins, berberine does not activate HNF1α, allowing for enhanced LDLR expression without a concomitant rise in PCSK9 levels [73].

In vivo studies in dyslipidemic mice fed a high-cholesterol diet demonstrated that berberine treatment (200 mg/Kg/day for 16 days) resulted in a time-dependent decrease in total cholesterol and LDL-C. These effects were accompanied by a ~50% reduction in circulating PCSK9, a 42% reduction in hepatic HNF1α, and a ~67% increase in hepatic LDLR protein expression, confirming that berberine enhances LDL-C clearance via modulation of HNF1α–PCSK9–LDLR axis [89].

Synergistic combinations with berberine

Given the multifaceted metabolic effects of berberine, its combined use with other nutraceuticals has been investigated. In this context, the PROMOTE study demonstrated that co-administration of berberine (600 mg twice daily) with probiotics (~50 billion CFU once daily at bedtime) significantly improved fasting HbA1c levels in drug-naive T2D patients, with enhanced reductions in total cholesterol, TGs, and LDL-C compared to berberine alone [90, 91].

Another recent study assessed the effects of berberine (1200 mg) combined with cinnamon (600 mg) over 3 months in patients with T2D. This combination significantly reduced HbA1c, fasting blood glucose and LDL-C levels compared to placebo. However, no significant improvements were observed in total cholesterol, TGs, and HDL-C levels, compared to placebo [92], suggesting selective effects on specific metabolic parameters.

More complex formulations have been developed to address statin intolerance or insufficient lipid control.

A 6-month trial compared the lipid-lowering efficacy of a formulation containing berberine (500 mg), policosanols (10 mg), and RYR (200 mg) – termed BBR/P/RR – against ezetimibe in 228 patients with primary hypercholesterolemia and statin intolerance or refusal. Both treatments significantly reduced LDL-C, total cholesterol and TGs, with no effects on HDL-C levels. Notably, BBR/P/RR was better tolerated and more effective than ezetimibe in lowering LDL-C (~32% vs. 25%) and total cholesterol (24% vs. 19%). Furthermore, combined therapy with BBR/P/RR plus ezetimibe in a subgroup of patients resulted in superior lipid improvement compared to monotherapy with reduction of 28% vs. 18% for total cholesterol, 37% vs. 23.5% for LDL-C, and 23% vs. 18% for TGs [93]. Similar benefits were reported in patients with heterozygous familial hypercholesterolemia (HeFH), where adding BBR/P/RR to a stable lipid-lowering regimen (statins alone or combined with ezetimibe) further decreased total cholesterol (44% vs. 35.5%), LDL-C levels (53% vs. 43%), alongside reduction in TGs levels (23% vs 18%.) not seen with ezetimibe alone [93].

In patients with coronary disease post-percutaneous coronary intervention (PCI) and high-dose statin intolerance, a nutraceutical formulation containing berberine (500 mg), RYR (200 mg, providing 3 mg of monacolin K), policosanol (10 mg), folic acid (0.2 mg), coenzyme Q10 (2 mg), and astaxanthin (0.5 mg) was compared to ezetimibe. After 3 months, 28% of patients in the nutraceutical group achieved LDL-C target with good tolerability. Those not achieving the goal continued combined therapy (nutraceutical + ezetimibe), resulting in 72.5% of patients reaching the LDL-C targets at 12 months [94].

These findings were further supported by the ADHERENCE trial, where 100 statin-intolerant patients post-PCI were randomized to low-dose statin (LDS) alone or LDS plus the same nutraceutical combination. After 3 months, the combination group showed a significant reduction in LDL-C (−26.8%) and total cholesterol (−17.5%), with 70% achieving LDL-C <70 mg/dL [95].

In addition to the clinical evidence presented, preliminary unpublished observational data also support the efficacy of a nutraceutical formulation combining berberine (500 mg) with other two unconventional but emerging compounds: fenugreek (150 mg) and reishi (200 mg). As reported in (Table 3), subjects with mild hypercholesterolemia treated with this formulation – termed BBR-FG-R – showed favorable outcomes in terms of metabolic profile, both when administrated independently and in combination with statins. Patients with mild hypercholesterolemia showed a significant, time-dependent improvement. Following a period of 3 months, BBR-FG-R demonstrated a significant improvement in lipid parameters, which further improved after a period of 6 months. A decline of 30.5% in LDL-C, 21.1% in total cholesterol, 16.6% in TGs, and an 8.8% increase in HDL-C was observed, with the normalization of each lipid values. In addition, a decline of 28.1%, in CRP levels, 5.3% in fasting glucose, and 3.4 % in HbA1C was observed.

Moreover, in patients with moderate hypercholesterolemia that remained not adequately controlled by statins (atorvastatin 10-20 mg/day or rosuvastatin 5-10 mg/day), the addition of the nutraceutical resulted in additional significant improvements. A reduction in LDL-C and total cholesterol of 39.6% and 28.6%, respectively, was observed, along with a decrease in TGs of 25.8% and LDL-C of 7.9%. This was accompanied by a decline in inflammatory and glycemic markers also improved, with CRP decreasing by 55%, fasting glucose by 8.6%, and HbA1C by 5.1%.

Biomarker (mg/dl)	**Baseline[(a)]**	**3 months[(b)]**	**6 months[(c)]**	**Δ^{a-c} absolute (relative %)**	***p value***
Monotherapy with BBR-FG-R (N=26)					
Total Cholesterol	215.1 ± 23.9	185.7 ± 22.6	169.7 ± 22.2	-45.4 (-21.1%)	p<0.001 a *vs.* b *vs.* c
LDL-C	141.1 ±21.0	112.2 ± 20.8	98.1 ± 20.8	-43.0 (-30.5%)	p<0.001 a *vs.* b *vs.* c
HDL-C	43.9 ±4.2	46.8 ± 3.2	47.8 ± 4.9	+3.9 (+8.8%)	p<0.01 a *vs.* b p<0.001 c *vs.* a
TGs	153.1 ± 22.4	130.8 ± 16.8	127.7 ± 17.4	-25.4 (-16.6%)	p<0.001 b and c *vs.* a
CRP	0.32 ± 0.2	0.27 ± 0.16	0.23 ±0.13	-0.09 (-28.1%)	p<0.01 c *vs.* a
Glycemia[§]	106.3 ± 7.9	104.3 ± 6.2	100.6 ± 6.1	-5.7 (-5.3%)	p<0.001 c *vs.* a
Hb1Ac (%)[§§]	5.9 ± 0.2	5.8 ± 0.2	5.7 ± 0.3	-0.2 (-3.4%)	p<0.001 c *vs.* a p<0.05 c *vs.* b
Combination therapy with statins and BBR-FG-R (N=8)					
Total Cholesterol	275.4 ± 23.6	193.1 ± 69.6	196.5 ± 10.0	-78.9 (-28.6%)	p<0.001 c *vs.* b *vs.* a
LDL-C	196.1 ± 15.9	137.9 ± 13.8	118. 5 ± 8.7	-77.6 (-39.6%)	p<0.05 b *vs.* a p<0.01 c *vs.* a
HDL-C	48.1 ±8.2	52.5 ± 7.3	51.9 ± 8.3	+3.8 (+7.9%)	p<0.05 c *vs.* a

TGs	172.3 ± 16.7	138.8 ± 17.4	127. 9 ± 6.5	-44.4 (-25.8%)	p<0.01 a *vs.* b p<0.001 c *vs.* a
CRP	0.6 ± 0.2	0.45 ± 0.1	0.27 ± 0.1	-0.33 (55%)	p<0.01 c *vs.* a
Glycemia	109.4 ± 6.0	102.8 ± 4.2	100.0 ± 2.4	-9.4 (-8.6%)	p<0.01 a *vs.* b p<0.001 c *vs.* a
Hb1Ac (%)	5.9 ± 0.2	5.7 ± 0.2	5.6 ± 0.2	-0.3 (-5.1%)	p<0.05 b *vs.* a p<0.01 c *vs.* a

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TGs: triglycerides; CRP: C-reactive protein; Hb1Ac: glycated hemoglobin.

BBR-FG-R contains: berberis extract (DE titrated to 85%): 590 mg, providing berberine 500 mg; G. lucidum extract (DE titrated to 10%): 200 mg, providing polysaccharides 20 mg; Fenugreek extract (DE titrated to 50%):150 mg, providing saponins 75 mg.

Δ: difference between values at 6 months and baseline. Data expressed as mean ± standard deviation. Repeated Measures ANOVA with Bonferroni post-hoc test for parametric data and Friedman test with Dunn's post-hoc test for non-parametric data. § and §§: 14 and 10 patients, respectively (baseline values outside the normal range).

Table 3: Preliminary unpublished observational data

Collectively, findings highlight the potential of berberine-based combinations to optimize lipid management while providing additional metabolic and anti-inflammatory benefits, particularly in statin-intolerant patients or those not achieving their therapeutic target. This evidence also supports the investigation of other promising nutraceuticals with synergistic mechanisms of action, including fenugreek and reishi, which are examined in the following sections.

Fenugreek

Fenugreek (*Trigonella foenum-graecum*), a member of the Fabaceae family, has emerged as a promising nutraceutical for dyslipidemia management, with its beneficial effects primarily attributed to bioactive steroidal saponins [96]. At the molecular level, fenugreek enhances lipid metabolism through multiple pathways, reducing lipid accumulation and upregulating LDLR expression by downregulating key adipogenic transcription factors such as SREBP-1, peroxisome proliferators activated-receptor-γ (PPAR-γ), and CAAT element-binding proteins-α (c/EBP-α).

In vitro studies demonstrate that fenugreek treatment (50 µg/ml for 18 h) significantly reduces intracellular TG and cholesterol levels while increasing LDL uptake via LDLR upregulation [97].

Preclinical investigations in animal models have yielded heterogeneous but generally supportive results for fenugreek hypolipidemic and hepatoprotective properties. Studies in C57BL6/J mice supplemented with 2% fenugreek for 16 weeks showed improvements in HDL-C and LDL-C concentrations, along with reduced hepatic expression of fatty acid binding protein 4 (FABP4), a regulator of lipid metabolism linked to inflammation, though no significant changes were observed in total cholesterol or TGs [98]. More robust effects were observed with specific bioactive compounds, such as 4-hydroxyisoleucine (50 mg/kg/day for 4 weeks), which normalized plasma glucose and lipid profiles to near-control values in type 1 diabetic models [99].

Additionally, daily administration of fenugreek at 15 mg/kg in C57BL6/J mice induced dose- and time-dependent reductions in circulating LDL-C, TGs, and body weight [97], while supplementation with 8 g per 100g of normal diet demonstrated protective effects against cholesterol- induced steatosis in hamsters [100].

Clinical evidence consistently supports fenugreek efficacy, particularly in T2D patients. In controlled trials, 10 g/day of fenugreek seed powder for 8-12 weeks produced substantial reduction in fasting blood glucose (−25%), TGs (−30%), and VLDL cholesterol (−30.6%), while simultaneously increasing adiponectin levels. These improvements were accompanied by reductions in total cholesterol and HbA1c levels, with enhanced effects observed when seeds were consumed after soaking in hot water rather than mixed with yogurt [101,102]. Beyond diabetes, fenugreek has demonstrated lipid-lowering efficacy in patients with mild-to-moderate hypercholesterolemia, with 40 mg daily supplementation for 8 weeks significantly reducing total cholesterol, LDL-C, and non-HDL-C levels [103]. Comparable lipid ratio improvements (total cholesterol/HDL, VLDL/HDL, TG/

HDL) were observed with fenugreek-enriched chapatis containing fenugreek seed (0.75 g) and *Nigella sativa* (4.7 g) over 12 weeks, though LDL/HDL remained unchanged (Rao et al., 2020). Polyherbal formulations show enhanced efficacy in treatment-resistant patients. A combination containing *Allium sativum* (300 mg), *Aloe vera* (300 mg), *Nigella sativa* (1.8 g), *Plantago psyllium* (1 g), *Silybum marianum* (500 mg), and *Trigonella foenum-graecum* (2.5 g) improved fasting glucose, HbA1c, LDL-C, and triglycerides in advanced T2D patients unresponsive to conventional therapy after 40 days [104]. When added to standard therapy for 14 weeks, this formulation significantly reduced total cholesterol, LDL-C, triglycerides, and HbA1c versus placebo, though fasting glucose remained unaffected [105].

Ganoderma lucidum

Ganoderma lucidum (reishi), a medicinal mushroom extensively utilized in traditional Chinese medicine, has emerged as a promising therapeutic agent for cardiometabolic risk management [106, 107]. This fungal species contains over 200 polysaccharides and 432 secondary metabolites, including terpenoids and steroidal compounds, which contribute to its broad spectrum of biological activities relevant to dyslipidemia and glucose homeostasis [107, 108].

Preclinical investigations demonstrate exciting lipid-lowering effects comparable to conventional statin therapy. In hyperlipidemic animal models, G. lucidum ethanol extract (EEG) administered at increasing doses (6, 24, and 96 mg/kg/day) produced dose-dependent reductions in total cholesterol and LDL-C levels, comparable to atorvastatin (2.5 mg/kg/day). Additionally, EEG significantly increased HDL-C levels and attenuated hepatic steatosis and aortic plaque formation compared to hyperlipidemic controls, without increasing serum creatin kinase (CK) levels [109]. The underlying mechanisms involve upregulation of liver X receptors (LXRs) and their downstream targets within the ABC transporter superfamily (ABCA1, ABCG1, ABCG5/8), enhanced hepatic CYP7A1 expression and activity, and increased fecal bile acid excretion [110, 111]. Similarly, G. lucidum polysaccharides (GLP) demonstrate comparable efficacy through LXRα-mediated pathways, enhanced bile acid biosynthesis, and suppression of FXR–FGF15 signaling, while exhibiting anti-inflammatory and antioxidant properties via NF-κB and Nrf2–Keap1 pathway modulation [106]. Collectively, these findings suggest that G. lucidum improves lipid metabolism through activation of bile acid synthesis, promotion of reverse cholesterol transport, and reduction of cholesterol absorption, while maintaining a potentially superior safety profile compared to statin therapy [109].

Although preclinical data are promising, clinical evidence remains inconsistent and requires further validation [112]. While early studies reported modest improvements in lipid profiles and antioxidant capacity [113], a randomized, placebo-controlled trial in patients with mild hypertension and/or hyperlipidemia demonstrated reductions in triglycerides and insulin levels with increased HDL-C following 12-week supplementation (1.44 g/day), though atherogenic lipid ratios remained unchanged [114]. Conversely, other investigations failed to demonstrate significant effects on glycemic parameters in patients with metabolic syndrome [115]. These inconsistent findings likely reflect variations in study design, extract composition, mushroom components used (fruiting body vs. mycelium, with the latter typically containing higher bioactive compound concentrations dosage, and patient populations, emphasizing the need for well-designed, large-scale trials to definitively establish clinical efficacy [116].

Conclusions

Several pharmacological strategies are available for lipid lowering, ranging from statins to newer agents such as bempedoic acid. Despite their proven efficacy, a considerable proportion of patients still fail to reach therapeutic targets, often due to adverse effects or nocebo responses that compromise adherence. This has prompted growing interest in complementary strategies, including nutraceuticals, which may offer pleiotropic benefits on lipid metabolisms, glycemic control, and systemic inflammation. The regulatory framework remains a crucial aspect, particularly in the case of monacolin k from RYR, whose use has been progressively restricted due to safety and variability in content. In contrast, berberine has shown consistent efficacy in improving both lipid and glucose parameters, although its clinical application is still limited by poor bioavailability, which innovative delivery systems can help overcome. Beyond these better-known compounds, less explored nutraceuticals – such as reishi and fenugreek – are emerging as promising candidates, with the potential to modulate metabolic pathways.

Importantly, the integration of nutraceutical with pharmacological agents may represent a rational alternative to intensifying pharmacological multi-therapy. By combining agents with complementary mechanisms, it may be possible to enhance efficacy, improve tolerability, and sustain long-term adherence, while reducing the burden of side effects often associated with multiple-drug regimens. A similar rationale applies to nutraceutical combinations: while some natural compounds may provide modest benefits when used alone, their synergistic use – by targeting different aspect of lipid and glucose metabolism or inflammation – may amplify clinical outcomes and open new opportunities for personalized interventions.

Beyond the dichotomy between drugs and nutraceuticals, the future may lie in their thoughtful integration, offering clinicians

and patients new tools to balance efficacy with tolerability and to finally reduce the burden of residual cardiometabolic risk.

Conflicts of interest

L.C., L.B, and G.D.S are employed by Laboratori Aliveda. The remaining authors declare no potential conflict of interest.

Author contributions

L.C.: original draft preparation; L.B. and G.D.S.: critical review; L.F. observational data and critical review. All authors have read and approved the final version of the manuscript.

References

1. Yamamoto T, Wada F, Harada-Shiba M (2016) Development of Antisense Drugs for Dyslipidemia. Journal of Atherosclerosis and Thrombosis 23: 1011–1025.
2. Porez G, Prawitt J, Gross B, Staels B (2012) Bile acid receptors as targets for the treatment of dyslipidemia and cardiovascular disease. Journal of Lipid Research 53: 1723–1737.
3. Grundy SM (2016) Metabolic syndrome update. Trends in Cardiovascular Medicine, 26: 364–373.
4. Berberich AJ, Hegele RA (2022) A Modern Approach to Dyslipidemia. Endocrine Reviews, 43:611–653.
5. Dybiec J, Baran W, Dąbek B, Fularski P, Młynarska E, Radzioch E, et al. (2023) Advances in Treatment of Dyslipidemia. International Journal of Molecular Sciences, 24:13288.
6. Chait A, Eckel RH, Vrablik M, Zambon A (2024) Lipid-lowering in diabetes: An update. Atherosclerosis, 394: 117313.
7. Guarino G, Strollo F, Carbone L, Della Corte T, Letizia M, et al. (2017) Bioimpedance analysis, metabolic effects and safety of the association Berberis aristata/Bilybum marianum: A 52-week double-blind, placebo-controlled study in obese patients with type 2 diabetes. Journal of Biological Regulators and Homeostatic Agents, 31: 495–502.
8. Mannarino MR, Ministrini S, Pirro M (2014) Nutraceuticals for the treatment of hypercholesterolemia. European Journal of Internal Medicine 25: 592–599.
9. Wichaiyo S, Supharattanasitthi W (2021) Bempedoic Acid: A New Non-statin Drug for the Treatment of Dyslipidemia. Clinical Drug Investigation 41: 843–851.
10. Sizar O, Khare S, Patel P, Talati R (2025) Statin Medications. In StatPearls. StatPearls Publishing.
11. Olsson AG, Istad H, Luurila O, Ose L, Stender S, et al. (2002) Effects of rosuvastatin and atorvastatin compared over 52 weeks of treatment in patients with hypercholesterolemia. American Heart Journal 144: 1044–1051.
12. Agouridis AP, Rizos CV, Elisaf MS, Filippatos TD (2013) Does combination therapy with statins and fibrates prevent cardiovascular disease in diabetic patients with atherogenic mixed dyslipidemia? The Review of Diabetic Studies: RDS, 10: 171–190.
13. Reiner Z (2013) Managing the residual cardiovascular disease risk associated with HDL-cholesterol and triglycerides in statin-treated patients: A clinical update. Nutrition, Metabolism, and Cardiovascular Diseases: NMCD 23: 799–807.
14. Gaw A (2003) HDL-C and triglyceride levels: Relationship to coronary heart disease and treatment with statins. Cardiovascular Drugs and Therapy, 17:53–62.
15. Sawhney JPs, Ramakrishnan S, Madan K, Ray S, Jayagopal PB, et al. (2024) CSI clinical practice guidelines for dyslipidemia management: Executive summary. Indian Heart Journal 76: S6–S19.
16. Laufs U, Lincoff AM, Nicholls SJ, Li N, Bloedon L, et al. (2025) Characteristics and outcomes of patients with and without statin-associated muscle symptoms treated with bempedoic acid in the CLEAR Outcomes trial. Journal of Clinical Lipidology 19: 337–347.
17. Vinci P, Panizon E, Tosoni LM, Cerrato C, Pellicori F, et al. (2021) Statin-Associated Myopathy: Emphasis on Mechanisms and Targeted Therapy. International Journal of Molecular Sciences 22: 11687.
18. Laakso M, Fernandes Silva L (2023) Statins and risk of type 2 diabetes: Mechanism and clinical implications. Frontiers in Endocrinology, 14:1239335.
19. Sattar N (2023) Statins and diabetes: What are the connections? Best Practice & Research. Clinical Endocrinology & Metabolism 37: 101749.
20. Chilbert MR, VanDuyn D, Salah S, Clark CM, Ma Q (2022) Combination Therapy of Ezetimibe and Rosuvastatin for Dyslipidemia: Current Insights. Drug Design, Development and Therapy, 16: 2177–2186.
21. Olmastroni E, Scotti S, Galimberti F, Xie S, Casula M (2024) Ezetimibe: Integrating Established Use with New Evidence - A Comprehensive Review. Current Atherosclerosis Reports 27: 10.
22. Knopp RH, Gitter H, Truitt T, Bays H, Manion CV, et al. (2003) Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. European Heart Journal, 24:729–741.
23. Tran AV, Tran BLT, Bui NM, Le ATT, Nguyen DT, et al. (2024) Efficacy of Dyslipidemia Control by Combination Therapy with Rosuvastatin 10 Mg and Ezetimibe 10 Mg Compared with Rosuvastatin 20 Mg Monotherapy in Patients with Chronic Coronary Syndromes: A Randomized, Single-blind Controlled Trial. Cardiovascular & Hematological Agents in Medicinal Chemistry 22: 390–398.
24. Daskalopoulou SS, Mikhailidis DP (2006) Ezetimibe/simvastatin single tablet versus rosuvastatin in patients with hypercholesterolemia. Current Medical Research and Opinion, 22:2037–2039.
25. Boutari C, Karagiannis A, Athyros VG (2021) Rosuvastatin and ezetimibe for the treatment of dyslipidemia and hypercholesterolemia. Expert Review of Cardiovascular Therapy, 19:575–580.
26. Giugliano RP, Pedersen TR, Park JG, De Ferrari GM, Gaciong ZA, et al. (2017a) Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: A prespecified secondary analysis of the FOURIER trial. Lancet, 390: 1962–1971.
27. Padda IS, Fabian D, Johal GS (2025) Familial Combined Hyperlipidemia. In StatPearls. StatPearls Publishing.
28. Feng Y, Li Q, Ou G, Yang M, Du L (2021) Bile acid sequestrants: A review of mechanism and design. The Journal of Pharmacy and Pharmacology, 73:855–861.
29. Hansen M, Sonne DP, Mikkelsen KH, Gluud LL, Vilsbøll T, et al. (2012) Effect of bile acid sequestrants on glycaemic control: Protocol for a systematic review with meta-analysis of randomised controlled trials. BMJ Open, 2: e001803.
30. Karr S (2017) Epidemiology and management of hyperlipidemia. The American Journal of Managed Care, 23: S139–S148.

31. Davidson MH, Donovan JM, Misir S, Jones MR (2010) A 50-week extension study on the safety and efficacy of colesevelam in adults with primary hypercholesterolemia. American Journal of Cardiovascular Drugs: Drugs, Devices, and Other Interventions, 10:305–314.

32. Feingold KR, Feingold KR, Faisal Ahmed S, Anawalt B, Blackman MR, Boyce A, et al. (2000). Cholesterol Lowering Drugs.

33. Grześk G, Dorota B, Wołowiec Ł, Wołowiec A, Osiak J, et al. (2022) Safety of PCSK9 inhibitors. Biomed Pharmacother, 156:113957.

34. Bao X, Liang Y, Chang H, Cai T, Feng B, et al. (2024) Targeting proprotein convertase subtilisin/kexin type 9 (PCSK9): From bench to bedside. Signal Transduction and Targeted Therapy, 9:13.

35. Rosenson RS, Hegele RA, Fazio S, Cannon CP (2018) The Evolving Future of PCSK9 Inhibitors. Journal of the American College of Cardiology 72: 314–329.

36. Chai M, He Y, Zhao W, Han X, Zhao G, et al. (2023) Efficacy and safety of tafolecimab in Chinese patients with heterozygous familial hypercholesterolemia: A randomized, double-blind, placebo-controlled phase 3 trial (CREDIT-2). BMC Medicine, 21:77.

37. Giugliano RP, Pedersen TR, Park JG, De Ferrari GM, Gaciong ZA, et al. (2017b) Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: A prespecified secondary analysis of the FOURIER trial. Lancet, 390:1962–1971.

38. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, et al. (2015) Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. The New England Journal of Medicine 372: 1489–1499.

39. Koren MJ, Sabatine MS, Giugliano RP, Langslet G, Wiviott SD, et al. (2019) Long-Term Efficacy and Safety of Evolocumab in Patients With Hypercholesterolemia. Journal of the American College of Cardiology, 74: 2132–2146.

40. Liu HH, Li S, Li JJ (2025) Tafolecimab, a Third Monoclonal Antibody for PCSK9 as the Novel Lipid-Lowering Drug Around the World: A Narrative Review. Drugs 85: 627–642.

41. Singh A, Cho LS (2024) Nonstatin therapy to reduce low-density lipoprotein cholesterol and improve cardiovascular outcomes. Cleveland Clinic Journal of Medicine 91: 53–63.

42. Chackerian B, Remaley AT (2024) PCSK9 vaccines: A promising new strategy for the treatment of hypercholesterolemia? Journal of Lipid Research, 65:100524.

43. Albosta M, Grant JK, Michos ED (2023) Bempedoic Acid: Lipid Lowering for Cardiovascular Disease Prevention. Heart International, 17:27–34.

44. Markham A (2020) Bempedoic Acid: First Approval. Drugs 80: 747–753.

45. Ruscica M, Sirtori CR, Carugo S, Banach M, Corsini A (2022) Bempedoic Acid: For Whom and When. Current Atherosclerosis Reports 24: 791–801.

46. Jain P (2024) Traditional and novel non-statin lipid-lowering drugs. Indian Heart Journal, 76:S38–S43.

47. Bays HE, Banach M, Catapano AL, Duell PB, Gotto AM, et al. (2020) Bempedoic acid safety analysis: Pooled data from four phase 3 clinical trials. Journal of Clinical Lipidology, 14: 649-659.e6.

48. Toth PP, Fazio S, Wong ND, Hull M, Nichols GA (2020) Risk of cardiovascular events in patients with hypertriglyceridaemia: A review of real-world evidence. Diabetes, Obesity & Metabolism 22: 279–289.

49. Barter PJ, Rye KA (2006) Cardioprotective Properties of Fibrates: Which Fibrate, Which Patients, What Mechanism? Circulation, 113:1553–1555.

50. Canfora I, Pierno S (2024) Hypertriglyceridemia Therapy: Past, Present and Future Perspectives. International Journal of Molecular Sciences, 25:9727.

51. Pieper JA (2002) Understanding niacin formulations. The American Journal of Managed Care 8: S308-314.

52. Kolber MR, Ivers N, Allan GM (2012) Niacin added to statins for cardiovascular disease. Canadian Family Physician, 58:842.

53. Alhomoud IS, Talasaz A, Mehta A, Kelly MS, Sisson EM, et al. (2023) Role of lipoprotein (a) in atherosclerotic cardiovascular disease: A review of current and emerging therapies. Pharmacotherapy, 43:1051–1063.

54. Rodriguez D, Lavie CJ, Elagizi A, Milani RV (2022) Update on Omega-3 Polyunsaturated Fatty Acids on Cardiovascular Health. Nutrients 14: 5146.

55. Innes JK, Calder PC (2020) Marine Omega-3 (N-3) Fatty Acids for Cardiovascular Health: An Update for 2020. International Journal of Molecular Sciences, 21:1362.

56. Sherratt SCR, Libby P, Budoff MJ, Bhatt DL, Mason RP (2023) Role of Omega-3 Fatty Acids in Cardiovascular Disease: The Debate Continues. Current Atherosclerosis Reports 25: 1–17.

57. Zhao J, Cao Q, Xing M, Xiao H, Cheng Z, et al. (2020) Advances in the Study of Marine Products with Lipid-Lowering Properties. Marine Drugs 18: 390.

58. Baumgartner S, Bruckert E, Gallo A, Plat J (2020) The position of functional foods and supplements with a serum LDL-C lowering effect in the spectrum ranging from universal to care-related CVD risk management. Atherosclerosis, 311:116–123.

59. Brufau G, Canela MA, Rafecas M (2008) Phytosterols: Physiologic and metabolic aspects related to cholesterol-lowering properties. Nutrition Research, 28:217–225.

60. Barkas F, Bathrellou E, Nomikos T, Panagiotakos D, Liberopoulos E, et al. (2023) Plant Sterols and Plant Stanols in Cholesterol Management and Cardiovascular Prevention. Nutrients, 15:2845.

61. Li X, Xin Y, Mo Y, Marozik P, He T, et al. (2022) The Bioavailability and Biological Activities of Phytosterols as Modulators of Cholesterol Metabolism. Molecules 27: 523.

62. EFSA Panel, (2012 n.d.). Scientific Opinion on the substantiation of a health claim related to 3 g/day plant sterols/stanols and lowering blood LDL-cholesterol and reduced risk of (coronary) heart disease pursuant to Article 19 of Regulation (EC) No 1924/2006. EFSA Journal, 10:2693.

63. Osadnik T, Goławski M, Lewandowski P, Morze J, Osadnik K, et al. (2022) A network meta-analysis on the comparative effect of nutraceuticals on lipid profile in adults. Pharmacological Research 183: 106402.

64. Salehi-Sahlabadi A, Varkaneh HK, Shahdadian F, Ghaedi E, Nouri M, et al. (2020) Effects of Phytosterols supplementation on blood glucose, glycosylated hemoglobin (HbA1c) and insulin levels in humans: A systematic review and meta-analysis of randomized controlled trials. Journal of Diabetes and Metabolic Disorders 19: 625–632.

65. Angelopoulos N, Paparodis RD, Androulakis I, Boniakos A, Argyrakopoulou G, et al. (2023) Low Dose Monacolin K Combined with Coenzyme Q10, Grape Seed, and Olive Leaf Extracts Lowers LDL Cholesterol in Patients with Mild Dyslipidemia: A Multicenter,

Randomized Controlled Trial. Nutrients, 15:2682.

66. Benjian C, Xiaodan H, Huiting P, Yishi LI, Yongtao C, et al. (2022) Effectiveness and safety of red yeast rice predominated by monacolin K β-hydroxy acid form for hyperlipidemia treatment and management. Journal of Traditional Chinese Medicine, 42:264–271.

67. Cicero AFG, Derosa G, Parini A, Maffioli P, D'Addato S, et al. (2013) Red yeast rice improves lipid pattern, high-sensitivity C-reactive protein, and vascular remodeling parameters in moderately hypercholesterolemic Italian subjects. Nutrition Research, 33:622–628.

68. Gerards MC, Terlou RJ, Yu H, Koks CHW, Gerdes VE (2015) Traditional Chinese lipid-lowering agent red yeast rice results in significant LDL reduction but safety is uncertain—A systematic review and meta-analysis. Atherosclerosis, 240: 415–423.

69. EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), Younes M, Aggett P, Aguilar F, Crebelli R, Dusemund B, et al. (2018) Scientific opinion on the safety of monacolins in red yeast rice. EFSA Journal. European Food Safety Authority, 16: e05368.

70. EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Turck D, Bohn T, Cámara M, Castenmiller J, De Henauw S, et al. (2025) Scientific Opinion on additional scientific data related to the safety of monacolins from red yeast rice submitted pursuant to Article 8(4) of Regulation (EC) No 1925/2006. EFSA Journal. European Food Safety Authority, 23: e9276.

71. Trogkanis E, Karalexi MA, Sergentanis TN, Kornarou E, Vassilakou T (2024) Safety and Efficacy of the Consumption of the Nutraceutical "Red Yeast Rice Extract" for the Reduction of Hypercholesterolemia in Humans: A Systematic Review and Meta-Analysis. Nutrients 16: 1453.

72. Norata GD, Banach M (2024) The Impact of Red Yeast Rice Extract Use on the Occurrence of Muscle Symptoms and Liver Dysfunction: An Update from the Adverse Event Reporting Systems and Available Meta-Analyses. Nutrients 16: 444.

73. Paryani M, Gupta N, Jain SK, Butani S (2025) Lowering LDL cholesterol by PCSK9 inhibition: A new era of gene silencing, RNA, and alternative therapies. Naunyn-Schmiedeberg's Archives of Pharmacology 398: 6597-6615.

74. Xu X, Yi H, Wu J, Kuang T, Zhang J, et al. (2021).Therapeutic effect of berberine on metabolic diseases: Both pharmacological data and clinical evidence. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie 133: 110984.

75. Ji L, Ma J, Ma Y, Cheng Z, Gan S, et al. (2025) Berberine Ursodeoxycholate for the Treatment of Type 2 Diabetes: A Randomized Clinical Trial. JAMA Network Open, 8: e2462185.

76. Di Bisceglie AM, Watts GF, Lavin P, Yu M, Bai R, et al. (2020) Pharmacokinetics and pharmacodynamics of HTD1801 (berberine ursodeoxycholate, BUDCA) in patients with hyperlipidemia. Lipids in Health and Disease, 19:239.

77. Zhang Y, Li X, Zou D, Liu W, Yang J, et al. (2008) Treatment of Type 2 Diabetes and Dyslipidemia with the Natural Plant Alkaloid Berberine. The Journal of Clinical Endocrinology & Metabolism 93: 2559–2565.

78. Zhang L-S, Zhang J-H, Feng R, Jin X-Y, Yang F-W, et al. (2019) Efficacy and Safety of Berberine Alone or Combined with Statins for the Treatment of Hyperlipidemia: A Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials. The American Journal of Chinese Medicine 47: 751–767.

79. Ilyas Z, Perna S, Al-thawadi S, Alalwan TA, Riva A, et al. (2020) The effect of Berberine on weight loss in order to prevent obesity: A systematic review. Biomed Pharmacother, 127:110137.

80. Solà R, Valls R-M, Puzo J, Calabuig J-R, Brea A, et al. (2014) Effects of poly-bioactive compounds on lipid profile and body weight in a moderately hypercholesterolemic population with low cardiovascular disease risk: A multicenter randomized trial. PloS One 9: e101978.

81. Kim WS, Lee YS, Cha SH, Jeong HW, Choe SS, et al. (2009) Berberine improves lipid dysregulation in obesity by controlling central and peripheral AMPK activity. American Journal of Physiology-Endocrinology and Metabolism, 296: E812–E819.

82. Yin J, Ye J, Jia W (2012) Effects and mechanisms of berberine in diabetes treatment. Acta Pharmaceutica Sinica B 2: 327–334.

83. Wu N, Sarna LK, Siow YL, O K (2011) Regulation of hepatic cholesterol biosynthesis by berberine during hyperhomocysteinemia. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 300: R635–R643.

84. Dai L, Zhu L, Ma S, Liu J, Zhang M, Li J, et al. (2022) Berberine alleviates NLRP3 inflammasome induced endothelial junction dysfunction through Ca2+ signalling in inflammatory vascular injury. Phytomedicine, 10:154131.

85. Zhong C, Xie Y, Wang H, Chen W, Yang Z, et al. (2024). Berberine inhibits NLRP3 inflammasome activation by regulating mTOR/mtROS axis to alleviate diabetic cardiomyopathy. European Journal of Pharmacology 964: 176253.

86. Zhou H, Feng L, Xu F, Sun Y, Ma Y, et al. (2017) Berberine inhibits palmitate-induced NLRP3 inflammasome activation by triggering autophagy in macrophages: A new mechanism linking berberine to insulin resistance improvement. Biomedicine & Pharmacotherapy 89: 864–874.

87. Momtazi AA, Banach M, Pirro M, Katsiki N, Sahebkar A (2017) Regulation of PCSK9 by nutraceuticals. Pharmacological Research 120: 157–169.

88. Li X, Xin Y, Mo Y, Marozik P, He T, et al. (2022) The Bioavailability and Biological Activities of Phytosterols as Modulators of Cholesterol Metabolism. Molecules 27: 523.

89. Dong B, Li H, Singh AB, Cao A, Liu J (2015) Inhibition of PCSK9 transcription by berberine involves down-regulation of hepatic HNF1α protein expression through the ubiquitin-proteasome degradation pathway. The Journal of Biological Chemistry, 290: 4047–4058.

90. Wang S, Ren H, Zhong H, Zhao X, Li C, et al. (2022) Combined berberine and probiotic treatment as an effective regimen for improving postprandial hyperlipidemia in type 2 diabetes patients: A double blinded placebo controlled randomized study. Gut Microbes 14:b2003176.

91. Zhang Y, Gu Y, Ren H, Wang S, Zhong H, et al. (2020) Gut microbiome-related effects of berberine and probiotics on type 2 diabetes (the PREMOTE study). Nature Communications 11: 5015.

92. Mansour A, Sajjadi-Jazi SM, Gerami H, Khorasanian AS, Moalemzadeh B, et al. (2025) The efficacy and safety of berberine in combination with cinnamon supplementation in patients with type 2 diabetes: A randomized clinical trial. European Journal of Nutrition 64: 102.

93. Pisciotta L, Bellocchio A, Bertolini S (2012) Nutraceutical pill containing berberine versus ezetimibe on plasma lipid pattern in hypercholesterolemic subjects and its additive effect in patients with familial hypercholesterolemia on stable cholesterol-lowering treatment. Lipids in Health and Disease 11: 123.

94. Marazzi G, Pelliccia F, Campolongo G, Quattrino S, Cacciotti L, et al. (2015) Usefulness of Nutraceuticals (Armolipid Plus) Versus Ezetimibe and Combination in Statin-Intolerant Patients With Dyslipidemia With

Coronary Heart Disease. The American Journal of Cardiology 116: 1798–1801.

95. Marazzi G, Campolongo G, Pelliccia F, Quattrino S, Vitale C, et al. (2017) Comparison of Low-Dose Statin Versus Low-Dose Statin + Armolipid Plus in High-Intensity Statin-Intolerant Patients With a Previous Coronary Event and Percutaneous Coronary Intervention (ADHERENCE Trial). The American Journal of Cardiology 120: 893–897.

96. No authors listed (2012) Fenugreek. In LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. National Institute of Diabetes and Digestive and Kidney Diseases.

97. Vijayakumar MV, Pandey V, Mishra GC, Bhat MK (2010) Hypolipidemic Effect of Fenugreek Seeds Is Mediated Through Inhibition of Fat Accumulation and Upregulation of LDL Receptor. Obesity 18: 667–674.

98. Knott EJ, Richard AJ, Mynatt RL, Ribnicky D, Stephens JM, et al. (2017) Fenugreek supplementation during high-fat feeding improves specific markers of metabolic health. Scientific Reports, 7:12770.

99. Haeri MR, Limaki HK, White CJB, White KN (2012. Non-insulin dependent anti-diabetic activity of (2S, 3R, 4S) 4-hydroxyisoleucine of fenugreek (Trigonella foenum graecum) in streptozotocin-induced type I diabetic rats. Phytomedicine, 19:571–574.

100. Kassaee SM, Goodarzi MT, Kassaee SN (2021) Ameliorative Effect of Trigonella Foenum Graecum L. on Lipid Profile, Liver Histology and LDL-Receptor Gene Expression in High Cholesterol-Fed Hamsters. Acta Endocrinologica (Buchar), 17:7–13.

101. Rafraf M, Malekiyan M, Asghari-Jafarabadi M, Aliasgarzadeh A (2014) Effect of Fenugreek Seeds on Serum Metabolic Factors and Adiponectin Levels in Type 2 Diabetic Patients. International Journal for Vitamin and Nutrition Research 84: 0196–0205.

102. Kassaian N, Azadbakht L, Forghani B, Amini M (2009) Effect of Fenugreek Seeds on Blood Glucose and Lipid Profiles in Type 2 Diabetic Patients. International Journal for Vitamin and Nutrition Research, 79:34–39.

103. Badiee Gavarti M, Askari A, Roohafza H, Askari M, Teimouri Jervekani Z, et al. (2025) The effect of the fenugreek hydrolyzed protein on lipid profile in patients with mild-to-moderate hypercholesterolemia: A confirmatory triple-blind randomized-controlled clinical trial. Phytomedicine Plus, 5:100691.

104. Zarvandi M, Rakhshandeh H, Abazari M, Shafiee-Nick R, Ghorbani A (2017) Safety and efficacy of a polyherbal formulation for the management of dyslipidemia and hyperglycemia in patients with advanced-stage of type-2 diabetes. Biomedicine & Pharmacotherapy 89: 69–75.

105. Ghorbani A, Zarvandi M, Rakhshandeh H (2019) A Randomized Controlled Trial of a Herbal Compound for Improving Metabolic Parameters in Diabetic Patients with Uncontrolled Dyslipidemia. Endocrine, Metabolic & Immune Disorders Drug Targets, 19:1075–1082.

106. Wang W, Zhang Y, Wang Z, Zhang J, Jia L (2023) Ganoderma lucidum polysaccharides improve lipid metabolism against high-fat diet-induced dyslipidemia. Journal of Ethnopharmacology, 309: 116321.

107. Chen B, Tian J, Zhang J, Wang K, Liu L, et al. (2017) Triterpenes and meroterpenes from Ganoderma lucidum with inhibitory activity against HMGs reductase, aldose reductase and α-glucosidase. Fitoterapia, 120:6–16.

108. Thakur P, Khanal S, Tapwal A, Kumar D, Verma R, Chauhan P, Sharma N (2024) Exploring Ganoderma lucidum: Morphology, cultivation and market potential. World Journal of Microbiology & Biotechnology 40: 369.

109. Lai P, Cao X, Xu Q, Liu Y, Li R, et al. (2020) Ganoderma lucidum spore ethanol extract attenuates atherosclerosis by regulating lipid metabolism via upregulation of liver X receptor alpha. Pharmaceutical Biology 58: 760–770.

110. Parikh M, Patel K, Soni S, Gandhi T (2014) Liver X receptor: A cardinal target for atherosclerosis and beyond. Journal of Atherosclerosis and Thrombosis 21: 519–531.

111. Fiévet C, Staels B (2009) Liver X receptor modulators: Effects on lipid metabolism and potential use in the treatment of atherosclerosis. Biochemical Pharmacology, 77:1316–1327.

112. Li H, Dong B, Park SW, Lee H-S, Chen W, et al. (2009) Hepatocyte nuclear factor 1alpha plays a critical role in PCSK9 gene transcription and regulation by the natural hypocholesterolemic compound berberine. The Journal of Biological Chemistry 284: 28885–28895.

113. Wachtel-Galor S, Tomlinson B, Benzie IFF (2004) Ganoderma lucidum ("Lingzhi"), a Chinese medicinal mushroom: Biomarker responses in a controlled human supplementation study. The British Journal of Nutrition 91: 263–269.

114. Chu TTW, Benzie IFF, Lam CWK, Fok BSP, Lee KKC, et al. (2012) Study of potential cardioprotective effects of Ganoderma lucidum (Lingzhi): Results of a controlled human intervention trial. The British Journal of Nutrition, 107:1017–1027.

115. Klupp NL, Kiat H, Bensoussan A, Steiner GZ, Chang DH (2016) A double-blind, randomised, placebo-controlled trial of Ganoderma lucidum for the treatment of cardiovascular risk factors of metabolic syndrome. Scientific Reports, 6:29540.

116. Aref M, Khoshhali M, Ghasemi P, Adeli S, Heidari-Beni M, et al. (2023) Effect of Ganoderma lucidum on serum lipid profiles: A systematic review and meta-analysis on animal studies. Journal of Research in Medical Sciences, 28:70.