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Review Article

Comprehensive Review of Contemporary Therapeutic Strategies in the Management of Hyperlipidemia

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Abstract

Background: Antihyperlipidemic agents play a crucial role in managing lipid disorders, particularly in reducing low-density lipoprotein cholesterol (LDL) and triglyceride levels. These agents help prevent cardiovascular diseases (CVD) by targeting various mechanisms that regulate lipid metabolism.

Objective: This review examines the current landscape of antihyperlipidemic agents, focusing on their mechanisms of action, therapeutic efficacy, and adverse effects.

Methods: A full literature screen was conducted across multiple databases, such as PubMed, Scopus, and Web of Science, to identify relevant studies published between 2000 and 2025. Studies were selected based on inclusion criteria such as relevance to lipid-lowering therapies, human clinical data, and a focus on agents like statins, fibrates, PCSK9 inhibitors, and new siRNA-based therapies.

Results: The review highlights the diverse pharmacological classes of antihyperlipidemic agents, including statins, fibrates, and novel therapies such as PCSK9 inhibitors and antisense oligonucleotides. Efficacy data indicate that these agents significantly reduce LDL-C levels, while adverse effects, such as gastrointestinal disturbances and hepatic toxicity, are common but manageable. Emerging treatments like inclisiran show promising results in enhancing long-term lipid control.

Conclusion: Antihyperlipidemic agents remain essential in managing hyperlipidemia and preventing CVD. Future research should focus on optimizing the use of these therapies and exploring novel agents with better efficacy and safety profiles.

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1. Introduction:

Hyperlipidemia is characterized by increased levels of lipids or lipoproteins in plasma, which is one of the major risk factors for

cardiovascular disease (CVD) and consequently atherosclerosis. It is characterized by several lipid disorders, including elevated levels of cholesterol (TC) and triglycerides (TG) and low levels of high-density lipoprotein (HDL), resulting in an increased risk of CVD and stroke (1, 2).

These lipid disorders are caused by different aetiologies like genetic susceptibility, unhealthy diet, sedentary lifestyle, and comorbid disease states like Diabetes, Hypothyroidism, etc. Hyperlipidemia is becoming increasingly common worldwide, making it essential to diagnose and manage these patients earlier. Recent data emphasize the worldwide research focus on hypercholesterolemia and its contribution to cardiovascular death and disability (3).

Lipids are building blocks and essential for cell function and energy storage. These are transported in the blood through lipoproteins, which are complex particles containing lipids and proteins. Lipoproteins consist of several classes, such as low-density lipoprotein (LDL), high-density lipoprotein (HDL), and very low-density lipoprotein (VLDL). An imbalance in these lipoproteins, such as excessive levels of LDL and VLDL or a deficit of HDL, is an important step in the pathogenesis of hyperlipidemia and consequent CVD. Comprehending the molecular mechanisms is critical for developing targeted therapies to address lipid profiles(4).

The management and control of hyperlipidemia usually combines modification of lifestyle through diet and physical activity changes with medicinal therapy. Common pharmacological agents to lower lipid levels are statins, fibrates, and bile acid sequestrants. Statins are still first-line treatment for dyslipidemia as they reduce LDL cholesterol effectively; however, other agents such as PCSK9 inhibitors and new therapies are becoming more important parts of lipid management (5). The changing spectrum of lipid-lowering treatment indicates a continued need for research and innovation to improve provided care, especially in patients with familial hypercholesterolemia or resistant lipid disorders. Apart from pharmacological treatment, a variety of complementary therapies are being investigated for their role in the management of hyperlipidemia, including herbal medicine. Herbs like Ferulago abbreviata have been shown in other studies to help control cholesterol and triglyceride levels; these may be considered by patients who prefer natural treatment (6). Considering that the prevalence of hyperlipidemia is still increasing worldwide, it becomes essential to incorporate different strategies, including both standard and alternative treatments together, for further enhancement of patients' outcomes and lowering the occurrence of cardiovascular diseases.

Objective: This review evaluates the effectiveness and mechanisms of action of existing antihyperlipidemic medications, including statins, fibrates, and PCSK9 inhibitors, for lipid metabolism disorders. It covers common side effects and pharmacokinetic properties. And highlights emerging treatments like inclisiran and recommends developing newer, more effective, and safer therapeutic agents for hyperlipidemia.

2. Methodology:

2.1 Databases Searched

We conducted a wide-ranging search of electronic databases (PubMed, Scopus, Web

of Science, Google Scholar, and Embase) for studies that would be included in the current review

2.2 Data Range

Data were extracted from publications from January 2000 to September 2025. This period was chosen to include seminal works and more recent advances in the field, aiming for a comprehensive overview of the topic.

Keywords

The following keywords were employed during the database search: LDL cholesterol reduction, Familial hypercholesterolemia, Atherosclerotic cardiovascular disease, RNA interference therapy, Antihyperlipidemic agents, Lipid-lowering drugs, Cholesterol-lowering agents, Statins, Fibrates, PCSK9 inhibitors, Niacin, Bile acid sequestrants, Ezetimibe, Omega-3 fatty acids, Apolipoprotein B inhibitors, and siRNA.

2.3 Inclusion Criteria

Studies were included if they were experimental, clinical trials, observational studies, meta-analyses, or review articles published in peer-reviewed journals. And were published in English.

2.4 Exclusion Criteria

Studies were excluded if they were unrelated to lipid-lowering therapies or siRNA interventions. Had insufficient data on therapeutic outcomes or adverse effects, were not published in peer-reviewed journals or in languages other than English, or were conference abstracts, grey literature, or non-peer-reviewed sources.

2.6 Data Extraction

Two reviewers independently extracted data on: Mechanism of action, clinical outcomes, adverse effects, and study methodologies. Key findings, including LDL cholesterol reduction and adverse events

3. Lipid and lipoproteins

Lipids are organic compounds that are critical for the organism's functioning, supporting cellular processes such as forming cell membranes, serving as energy reserves, and acting as hormones and intracellular messengers. These molecules are hydrophobic, meaning they are insoluble in water, which makes their transport in the bloodstream complex. Lipoproteins, which are complexes of lipids and proteins, facilitate this transport, ensuring lipids are carried to and from tissues (7, 8).

Cholesterol, fatty acids, triglycerides, phospholipids, and steroid hormones are considered the major types of biological lipids. Lipids are transported through the bloodstream by lipoproteins because of their lipophilic nature. TG synthesized in the liver is transported to peripheral tissues as VLDL. Triglycerides from dietary sources are transported as chylomicrons, and cholesterol, which can be newly synthesized in the liver or absorbed in part from the gut, is carried by LDL particles. HDL transports cholesterol to the liver and removes excess cholesterol from tissues for elimination (9).

Plasma lipid levels are influenced by dietary intake, biosynthesis, and excretion, which are mediated by bile acids. Lipid overload is characterized by the deficiency of either LDL receptors or apolipoprotein E (apoE), which impairs lipoprotein capture in peripheral cells and the liver, leading to excessive blood levels of lipoproteins and an elevated risk of atherosclerosis in these individuals (3). Lipoproteins found in plasma represent about 700 mg/dL mixture of lipid/ protein with the

following composition: 200 mg/dL protein, 160 mg/dL phospholipids,180mg/ dL cholesterol, and 160 mg/dL triglyceride (10, 11).

Lipoproteins are the transporters of lipophilic compounds in the bloodstream. They are spherical with a lipid core containing triglycerides and cholesteryl esters surrounded by a phospholipid monolayer and apolipoproteins. Such a structure enables lipoproteins to exist as lipid-soluble structures in the aqueous environment of the bloodstream (12, 13). Different classes of lipoproteins exist, and each performs unique functions in lipid transport. Apolipoprotein B-100 is present in VLDL, LDL, and lipoprotein (a), whereas apolipoprotein B-48 is only present in chylomicrons [21]. HDL has more than 20 different apolipoproteins; apolipoprotein A-I (apo A-I) is present in all HDL subtypes, whereas other proteins are found at low frequency throughout the HDL volume (11). Lipoproteins can be categorized into five classes based on size, density, and composition: chylomicrons (CM), LDL, VLDL, intermediate-density lipoproteins (IDL), and HDL (13, 14). CM: These lipoproteins transport lipids absorbed from the intestines, including triglycerides, cholesterol, and phospholipids, to the bloodstream. They are broken down by lipoprotein lipase, which releases fatty acids for storage (15). Cholesterol: Cholesterol is critical for cell membranes and serves as a precursor for steroid hormones and bile acids. It is obtained from both endogenous synthesis and dietary intake. Elevated LDL levels often result from diseases like hypothyroidism, diabetes, and polycystic ovary syndrome (16, 17). Triglycerides: It is also known as triacylglycerol (TAG), and it is synthesized from alcohol and sugar. Triglycerides are stored in fat cells and transported via VLDL(18). HDL: HDL helps transport excess cholesterol from tissues back to the liver for elimination, a process mentioned as reverse cholesterol transport, which is why it is known as the "good" cholesterol (19, 20). LDL and Lipoprotein (a): LDL carries cholesterol and triglycerides, while lipoprotein (a) resembles LDL but includes an additional apolipoprotein that inhibits thrombolysis, contributing to coronary artery disease and atherosclerosis (11, 12). VLDL**:** VLDL transports triglycerides synthesized in the liver to peripheral tissues. In conditions like hypertriglyceridemia, VLDL's role in transporting lipids is crucial (21).Figure 1.

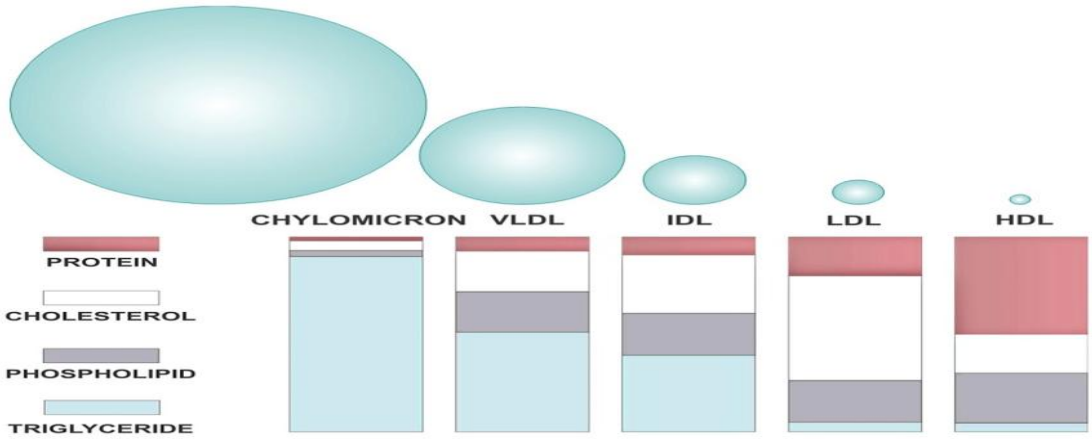

Figure 1: The diagram of lipoproteins(22)

4. Hyperlipidemia:

Hyperlipidemia causes lipid or lipoprotein levels to be elevated in the blood, which is a considerable risk factor for atherosclerosis. This condition may involve high levels of TC, TG, or low levels of HDL(23). Lipoproteins are central to the classification of hyperlipidemia, as they are the carriers of lipids through the bloodstream. Managing lipid levels is crucial for preventing cardiovascular diseases (24).

4.1 Classification of hyperlipidemia: Based on lipid type: A) Hypercholesterolemia: characterized by an increase in plasma cholesterol; b) Hypertriglyceridemia refers to elevated triglycerides in the bloodstream(25). Based on the cause factor: Hyperlipidemia may be A) Primary hyperlipidemia: arises from genetic defects, either monogenic or polygenic, which lead to increased production of TG and LDL, or reduced clearance of HDL(26). B) Secondary dyslipidemia: It is represented in up to 40% of all dyslipidemias, and it is acquired due to other diseases, including diabetes, hypothyroidism, obesity, alcohol use, and renal failure. This condition accounts for up to 40% of dyslipidemias and can often be reversed if the underlying cause is treated(27, 28).

4.2 Diagnosis of Hyperlipidemia:

Hyperlipidemia diagnosis requires laboratory tests to measure total cholesterol (TC), TG, LDL, and HDL. Elevated TC, TG, LDL, and very-low-density lipoprotein (VLDL) and reduced HDL levels indicate abnormal lipid profiles. Testing must be done after fasting for at least 12 hours (29). For deciding dyslipidemia in the patient the following steps should be considered: A)Two tests, 1-8 weeks apart, to confirm elevated lipid levels if TC exceeds 200mg/dL; B) Detailed patient evaluation, including history, gender, menstrual status, and comorbidities; C) Investigating secondary causes, such as pancreatitis, liver disease, and stroke history; D) Agarose-gel lipoprotein electrophoresis may be used to identify the affected lipoprotein class (30).

5. Management of hyperlipidemia:

Hyperlipidemia, as part of metabolic syndrome, involves both genetic and environmental factors. Pharmacological treatment is important for reducing lipid levels and preventing atherosclerotic cardiovascular disease (ASCVD). Guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) and NICE suggest medications are effective in managing both primary and secondary hyperlipidemia. These treatments aim to normalize lipid profiles (31, 32).

5. 1 Non-pharmacological intervention:

Before pharmacological therapy, lifestyle improvements, such as dietary changes, exercise, and weight management, are recommended. Non-pharmacological strategies can help control hyperlipidemia, especially when secondary causes like diabetes and obesity are involved. These methods may provide results similar to drug therapy in improving lipid levels (33). Non-pharmacological interventions such as:

5.1.1 Nutrition: Nutritional modifications are crucial in managing hyperlipidemia. Saturated and trans high-fat diets increase TG, LDL, and total cholesterol, while unsaturated fats (e.g., olive oil) can raise HDL and lower LDL. Reducing saturated fats and trans fats can lower the risk of hyperlipidemia. Studies show

that switching from saturated fats to unsaturated fats reduces LDL by 9-12% (34, 35). Reducing cholesterol and saturated fat intake and increasing polyunsaturated fat intake can significantly improve lipid profiles, reducing the risk of CVD (24, 36). A Mediterranean diet, which focuses on healthy fats, omega-3 fatty acids, and plant-based foods, helps lower cholesterol and triglycerides(37).

5.1.2 Exercise: Regular daily exercise is considered a step in managing hyperlipidemia. It helps maintain healthy body weight, reduces insulin resistance, and improves lipid profiles. Studies show that exercise reduces TG (by 7.1mg/dL) and LDL (by 3.9mg/dL), while increasing HDL (by 1.9 to 2.5mg/dL). In patients with cardiovascular disease (CVD), regular exercise provides even greater benefits, reducing TG by 19mg/dL and increasing HDL by 3.7mg/dL (38). Both the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) recommend at least half an hour of moderate exercise or 20 minutes of vigorous exercise five days a week to improve lipid profiles and prevent hyperlipidemia in individuals aged 18–64 years (24, 37).

5.2 Pharmacological therapy

5.2 Classification of hypolipidemic drugs:

5.2.1 Statins (HMG-CoA reductase inhibitors: Statins (e.g., atorvastatin, simvastatin, rosuvastatin) are first-line therapy for hyperlipidemia, reducing cholesterol synthesis by inhibiting HMG-CoA reductase, leading to increased LDL receptor activity on cell surfaces and a reduction in LDL levels. Statins also reduce oxidative stress and vascular inflammation, particularly beneficial post-acute coronary syndrome(39).

Statin inhibits enzyme of HMG-Co A reductase, by inhibiting de nova synthesis of cholesterol so it cause a reduction the biosynthesis of the cholesterol and increase total LDL-receptor on the cell surface, as a result of reducing cholesterol synthesis and raising LDL metabolism, the potency of the agents for decreasing the LDL is different for example atorvastatin, Rosuvastatin and Pitavastatin are more potent than simvastatin, pravastatin, and then lovastatin and fluvastatin(40, 41). All statins have lower bioavailability in the systemic circulation because they undergo first-pass metabolism. Absorption of each one is between 30% and 85%. All statins undergo hepatic metabolism and are predominantly excreted via bile(40, 42). Common side effects include gastrointestinal disturbance, myalgia, liver enzyme elevation, rash, and severe effects like rhabdomyolysis (43). Table 1

5.2.2 Niacin (nicotinic acid): Niacin belongs to the group of vitamins called water-soluble B vitamins and lowers TG, LDL, and VLDL while raising HDL levels. It reduces free fatty acids in adipose tissue by preventing lipolysis and additionally decreasing TG synthesis (44). It decreases the concentrations of TG, LDL, and VLDL while elevating the level of HDL in the bloodstream (45). Likewise, in adipose tissue, it Also, reduces TG biosynthesis through lipolysis prevention, which leads to the prevention of free fatty acid transfer to hepatocytes(44). Recently, some studies found another mechanism of action, such as: 1) It inhibits diacylglycerol acyltransferase 2 in the liver, which causes decreased Apo B-

containing lipoproteins and inhibits triglyceride synthesis. 2) It reduces HDL metabolism and elevates HDL concentration as a result of reducing the surface expression of hepatic ATP synthase β-chain. 3) Inhibition of redox-sensitive genes because of the elevation in the redox potential in arterial endothelial cells(46).

After oral administration of niacin, it is converted to nicotinamide in the body, which, after metabolism, is eliminated in the urine(40). Common effects include flushing and gastrointestinal discomfort. Rare side effects include hyperglycemia, elevated uric acid, and hepatotoxicity(47, 48), Table 1.

5.2.3 Fibrates: Agents such as bezafibrate, gemfibrozil, and fenofibrate belong to fibrates, which activate peroxisome proliferator-activated receptor alpha (PPAR-α), mainly reducing TG-rich lipoproteins (VLDL and IDL)(49). This group is the first choice for hypertriglyceridemia to reduce TG-rich lipoproteins (VLDL and IDL)(50). It is more effective in the treatment of type III dysbetalipoproteinemia, which reduces triglycerides by (50%-70%) and total cholesterol by (40%-50%)(51).

The activation of the PPAR-α isoform through binding to the ligands, which leads to a change in the target genes' function(51), which leads to Lipolysis, decreased production of TG, and elevated uptake of fatty acid by the liver, production of a high amount of LDL-receptor, which causes Elevate the HDL formation and promote Adenosine triphosphate (ATP)-binding cassette protein-A1-mediated reverse cholesterol transport, as a result of it, the concentration of HDL is raised (52, 53).

Fenofibrate is a prodrug metabolized to fenofibric acid (active form) eliminated by the kidneys in the urine(40). Both fenofibrate and ciprofibrate are prodrugs and differ from other fibrates; the bioavailability of fenofibrate is approximately 60%(54). Side effects include gastrointestinal discomfort, myopathy, liver enzyme elevation, and gallstones. Caution is recommended for patients with a history of hepatic or renal dysfunction(11, 55). Table 1.

5.2.4 Bile acid–binding resins: The liver synthesizes bile acids from the endogenous cholesterol in the liver. Bile acid sequestration directly binds to bile acids in the intestinal duct, and it leads to an alteration in the homeostasis of bile acids, and as a result of this interruption, the concentration of LDL decreases in hypercholesterolemia(56, 57). Bile acids can be classified as (colestipol, cholestyramine, colestimide, and colesevelam), which reduce the concentration of hepatic bile acids by approximately 40% (58).

Cholesterol is converted to bile acid via 7α-hydroxylation and excreted into the intestinal tract, but is reabsorbed in the jejunum and ileum, a process controlled by negative feedback. When bile acid sequestrants are administered to a patient, the rate of bile acid elimination increases tenfold, leading to upregulation of the LDL receptor in the liver and increased LDL uptake (11). These drugs are not absorbed into the bloodstream and remain in the intestines, where they are excreted in feces(40). Gastrointestinal discomfort and constipation are considered common side effects. Prolonged use may impair fat-soluble vitamins (A, D, E, K), leading to vitamin deficiencies(59), Table 1.

5.2.5 Cholesterol absorption inhibitor: Ezetimibe, approved in 2002, is used primarily to reduce total cholesterol, LDL, and Apo-B in patients with familial and non-familial hypercholesterolemia. It inhibits intestinal cholesterol absorption by 50%, making it effective when combined with other therapies, as it alone does not reach target lipid levels (60, 61). Ezetimibe inhibits the gastrointestinal absorption of cholesterol and phytosterols, even after a high-fat diet (11).

Ezetimibe reaches maximum plasma concentration in 2–3 hours and is metabolized in the liver with a half-life of 13–22 hours. It is primarily excreted in feces(61). Side effects include headache, musculoskeletal pain, and upper respiratory infections. Rare effects include voice changes and gastric discomfort(62-64). Table 1.

5.2.6 Proprotein convertase subtilisin/Kexin type 9 (PCSK9) inhibition: in this class, alirocumab and evolocumab inhibit the binding of PCSK9 to LDL receptors in the liver, which leads to increased recycling of LDL receptors and thereby reduces LDL receptor degradation. As a result of this procedure, LDL uptake by the liver reduces plasma LDL concentration (65)(66).

Alirocumab reaches its maximum plasma concentration within 3–7 days, with a half-life of 17–20 days. Evolocumab has a half-life of 11–17 days. Common adverse effects of bronchitis include upper respiratory infections and injection site reactions(67), Table 1.

5.2.7 Inhibition of microsomal triglyceride transfer protein (IMTP): MTP inhibitors (e.g., lomitapide) reduce LDL in patients with homozygous familial hypercholesterolemia. MTP is involved in lipoprotein assembly in the liver and intestines (68). IMTP is considered one of the important substances in the liver and intestinal duct for excretion and assembly of lipoproteins, which lomitapide inhibits the formation of VLDL in the liver and TG in the intestinal ducts, causing a decrease in the concentration of cholesterol in the bloodstream, which, at a dose of 24mg/kg/day, can reduce LDL by 50.9%(69).

After oral administration of lomitapide, the bioavailability is 7% because it undergoes first-pass metabolism(70). Adverse effects include gastrointestinal disturbances, steatosis, and elevated liver enzymes (71). Table 1.

5.2.8 Omega-3 fatty acids: It are recommended by the American Heart Association for reducing cardiovascular disease (CVD) risk in hyperlipidemic patients. These fatty acids effectively lower triglyceride levels(72, 73).

The exact mechanism of action of omega-3 fatty acids (OM3FAs) is unclear, although some studies have suggested that they suppress the formation of sterol regulatory element-binding protein-1c, thereby reducing lipogenesis (74). Also, it decreases the amount of substrate that is required for the synthesis of TG and VLDL. Another idea is that it increases the concentration of LPL, which causes the removal of TG from (74). The pharmacokinetic information data is not sufficient, especially in pregnancy(75).

The common side effects include: altered platelet function, gastrointestinal discomfort, epigastric or abdominal pain, flatulence, constipation or watery stool, and altered immune function (76). Table 1.

5.2.9 Adenosine Triphosphate-Citrate Lyase Inhibitors (ACL Inhibitors)

ACL is a cytosolic enzyme that catalyzes the cleavage of citrate (transported from mitochondria) into acetyl-CoA and oxaloacetate. Acetyl-CoA is a pivotal building block, a precursor for both de novo fatty acid synthesis and cholesterol biosynthesis(77). By preventing ACL in hepatocytes, bempedoic acid reduces the supply of acetyl-CoA for cholesterol and fatty acid synthesis. This decreases intracellular cholesterol synthesis, which triggers compensatory upregulation of the LDL receptor through excitation of sterol regulatory element-binding protein pathways, thereby enhancing hepatic uptake of LDL and reducing plasma LDL levels(78).

Bempedoic acid is a first-in-class small-molecule ACL inhibitor. Importantly, it is administered as a prodrug: once ingested, it is transformed in the liver by the enzyme Very-long-chain acyl-CoA synthetase 1 (ACSVL1) into its active CoA-thioester form, which then selectively inhibits ACL(79). Clinical and preclinical research has shown that bempedoic acid can effectively reduce LDL and other atherogenic lipoproteins: reductions of 20–25% in LDL-C, approximately 15% in apoB, about 19% in non–HDL–C, and about 16% in total cholesterol have been reported in patients with hypercholesterolemia or mixed dyslipidemia(79).

Beyond lipid-lowering effects, ACL inhibition may modulate inflammatory pathways. Some preclinical evidence suggests that bempedoic acid can suppress pro-inflammatory signaling (e.g., reducing cytokine and adhesion molecule expression), potentially contributing to atherosclerosis prevention(80).

Given the substantial proportion of patients who either fail to reach LDL-C targets on statins or are statin-intolerant, ACL inhibitors like bempedoic acid expand the therapeutic armamentarium. As they act upstream of HMG-CoA reductase, ACL inhibitors offer a complementary (and sometimes additive) mechanism, particularly when used in combination with statins or other lipid-lowering agents such as ezetimibe(81).

5.2.10 Microsomal Triglyceride Transfer Protein Inhibitors (MTP Inhibitors)

The microsomal triglyceride transfer protein (MTP) is a heterodimeric protein complex located in the lumen of the endoplasmic reticulum (ER) in hepatocytes and enterocytes. It is essential for the lipidation (addition of triglycerides, cholesterol esters, and phospholipids) of nascent ApoB, an important step in the production and release of apoB-containing lipoproteins, namely VLDL in the liver and chylomicrons in the intestine. Lomitapide selectively binds to and inhibits MTP, thereby inhibiting the conversion of TG (and other lipids) to apoB. As a result, the assembly of VLDL and chylomicrons is impaired. This reduces the secretion of these lipoproteins into the circulation, resulting in lower plasma levels of VLDL, LDL (after VLDL is metabolized), and triglycerides (82).

Because this mechanism does not depend on LDL receptor-mediated clearance, MTP inhibition offers a receptor-independent strategy for lowering atherogenic lipoproteins, a key advantage in receptor-deficient individuals (e.g., HoFH)(83). Clinical trials and real-world studies have consistently shown that lomitapide significantly reduces LDL and other atherogenic lipoproteins in patients with

HoFH. In a recent systematic review and meta-analysis, including data from 209 HoFH patients, lomitapide therapy was associated with a mean LDL-C reduction of about 49.3%, total cholesterol reduction of ~46.1%, and apolipoprotein B reduction of ~51.0%. Reductions were also observed in triglycerides, VLDL-C, and non–HDL–C. High-density lipoprotein C (HDL-C) levels remained relatively unchanged(84).

In clinical practice, it is typically reserved for individuals with severe hypercholesterolemia refractory to conventional LDL-lowering therapy (statins, ezetimibe, PCSK9 inhibitors), particularly when LDL receptor function is minimal or absent, or when LDL-target goals remain unmet despite maximal tolerated therapies(83).

Gastrointestinal (GI) side effects, (85)such as nausea, diarrhea, and abdominal discomfort, are among the most frequently reported adverse events, particularly early in therapy. Furthermore, because MTP inhibitors reduce the assembly of all apoB-containing lipoproteins (including chylomicrons), care must be taken to manage potential nutritional consequences (e.g., fat-soluble vitamin absorption), especially with long-term use(86).

5.2.11 Apo B Antisense Oligonucleotides

Apolipoprotein C-III is shown to manage a range of circulating triglyceride-rich lipoproteins (TRLs) and is becoming the most abundant type of Apo C-III for humans. In plasma, Apo C-III is found mostly in VLDL and chylomicrons, while it is less abundant in HDL and LDL. Apo C-III was activated as an LPL inhibitor and a major regulator of plasma TRL concentrations (87). Apo B antisense oligonucleotides are short synthetic nucleotide sequences that bind specifically to messenger RNA (mRNA) for apoB, the structural protein of VLDL, IDL, and LDL particles. By binding to apoB mRNA, they inhibit its translation, leading to decreased apoB biosynthesis in the liver and reduced production of atherogenic lipoproteins (88). Consequently, serum levels of LDL cholesterol and total cholesterol decrease significantly(11). Examples include mipomersen and volanesorsen (Waylivra), used primarily for familial hypercholesterolemia and other severe lipid disorders resistant to standard therapy(86, 88). Notable adverse effects include redness, pain (injection site), flu-like symptoms, and elevated hepatic transaminases(11). Long-term therapy may lead to hepatic steatosis (fatty liver).

5.2.12 siRNA Agents (Small Interfering RNA)

Inclisiran has been demonstrated to reduce LDL-C levels by ~ 50% from baseline in clinical trials. Importantly, the drug is administered via a subcutaneous injection only twice per year (after an initial double dosing sequence) due to its unique mechanism making it remarkably convenient and significantly improving adherence compared to daily or even bi-weekly injectable therapies(89).

siRNA agents act through RNA interference, selectively silencing target genes by degrading complementary mRNA. The siRNA drug inclisiran (Leqvio) targets the mRNA encoding PCSK9, a protein that promotes LDL receptor degradation on hepatocytes(90). By inhibiting PCSK9, inclisiran enhances LDL receptor recycling and increases LDL clearance from the circulation(90). Inclisiran reduces LDL cholesterol by 50–60% and is indicated for heterozygous familial hypercholesterolemia

and atherosclerotic cardiovascular disease requiring additional LDL reduction beyond statins(91). Side effects are generally mild, including injection site reactions and transient flu-like symptoms; Arthralgia, elevated liver enzymes, and worsening diabetes mellitus, making the drug generally well tolerated(92)

Table 1: Classification of Antihyperlipidemic agents and their mechanism of action

Drug Class	Mechanism of Action	Therapeutic Efficacy	Serious Adverse Effects
Statins	Inhibit HMG-CoA reductase to reduce cholesterol synthesis in the liver, increasing LDL receptor activity and enhancing LDL clearance.	Highly effective in reducing LDL cholesterol, lowering cardiovascular disease (CVD) risk, and preventing heart attacks and strokes.	Rhabdomyolysis (muscle breakdown), liver toxicity, gastrointestinal issues, and myalgia.
Fibrates	Activate PPAR-α to increase lipolysis, decrease triglyceride production, and raise HDL cholesterol levels.	Effective in lowering triglycerides and increasing HDL cholesterol, reducing the risk of cardiovascular events associated with high triglyceride levels.	Liver dysfunction, pancreatitis, myopathy (muscle pain), and gallstones.
PCSK9 Inhibitors	Block the action of PCSK9, allowing more LDL receptors to remain on the liver cells, increasing LDL clearance from the bloodstream.	Significant reduction in LDL cholesterol, particularly in patients with familial hypercholesterolemia or those resistant to statins, lowering cardiovascular risk.	Severe allergic reactions (rare), injection site reactions, and upper respiratory infections.
Niacin (Nicotinic Acid)	Inhibit lipolysis in adipose tissue, reducing the availability of free fatty acids to the liver, which reduces triglyceride and LDL cholesterol production, and increases HDL cholesterol by reducing its metabolism.	Effective in increasing HDL cholesterol and reducing triglycerides and LDL cholesterol, improving lipid profiles and reducing cardiovascular risk.	Flushing, gastrointestinal discomfort, hyperglycemia, hepatotoxicity, and gout.
Ezetimibe	Inhibit cholesterol absorption in the intestines, reducing total cholesterol and LDL levels.	Effective when used in combination with other therapies to achieve target lipid levels, particularly in familial hypercholesterolemia.	Headache, musculoskeletal pain, upper respiratory infections, and rare liver dysfunction.
Bile Acid Sequestrants	Bind bile acids in the intestines, preventing their reabsorption, increasing LDL receptor activity in the liver and lowering LDL cholesterol.	Effective in lowering LDL cholesterol and improving lipid profiles, especially in patients with high cholesterol levels.	Gastrointestinal discomfort, constipation, and impaired fat digestion; prolonged use may cause deficiencies in fat-soluble vitamins (A, D, E, K).
Cholesterol Absorption Inhibitors	Inhibit the absorption of cholesterol and phytosterols from the gastrointestinal tract.	Effective in reducing LDL cholesterol and total cholesterol, particularly useful in combination with statins to achieve target lipid levels.	Headache, abdominal pain, and gastrointestinal discomfort; rare liver dysfunction.
Omega-3 Fatty Acids	Reduce triglyceride levels by promoting the breakdown of fats in the liver and improving lipid metabolism, beneficial in hypertriglyceridemia.	Effective in reducing triglyceride levels, beneficial in hypertriglyceridemia and associated CVD risk.	Altered platelet function, gastrointestinal discomfort, epigastric or abdominal pain, flatulence, constipation, and altered immune function.
MTP Inhibitors	Inhibit the transfer of triglycerides to lipoproteins, impairing the formation of VLDL and chylomicrons in the liver and intestine, thus reducing LDL and triglycerides.	Significantly reduce LDL and triglycerides, particularly for patients with familial hypercholesterolemia or other severe lipid disorders.	Gastrointestinal disturbances, liver enzyme elevation, and steatosis (fatty liver).
Apolipoprotein B Antisense Oligonucleotides	Bind to mRNA for apolipoprotein B, inhibiting its translation, leading to decreased production of atherogenic lipoproteins (VLDL, IDL, LDL).	Significant reduction in LDL cholesterol and total cholesterol, especially in patients with familial hypercholesterolemia and atherosclerotic cardiovascular disease.	Injection site reactions, flu-like symptoms, and elevated hepatic transaminases; long-term therapy may cause hepatic steatosis (fatty liver).

Note: HMG-CoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A. It is an enzyme involved in cholesterol synthesis in the liver. LDL: Low-Density Lipoprotein. Often referred to as "bad cholesterol," it carries cholesterol from the liver to cells and can lead to plaque buildup in arteries if elevated. PPAR-α: Peroxisome Proliferator-Activated Receptor Alpha. A receptor that, when activated, helps regulate fat metabolism and lipid levels. PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9. A protein that regulates LDL receptor levels on liver cells, influencing LDL cholesterol clearance. HDL: High-Density Lipoprotein. Often referred to as "good cholesterol," it helps remove excess cholesterol from the bloodstream. Niacin: Also known as nicotinic acid, a B vitamin that affects lipid metabolism. VLDL: Very Low-Density Lipoprotein. A type of lipoprotein that carries triglycerides in the bloodstream and can contribute to atherosclerosis if elevated. Apolipoprotein B (ApoB): A protein that is essential for the formation of atherogenic lipoproteins (VLDL, IDL, LDL), which are implicated in the development of atherosclerosis. MTP: Microsomal Triglyceride Transfer Protein. A protein that helps transport triglycerides to lipoproteins, influencing their formation. IDL: Intermediate-Density Lipoprotein. A type of lipoprotein

that is formed as VLDL particles lose triglycerides. Cholesterol Absorption Inhibitors: A class of drugs that block the absorption of cholesterol in the intestines. Apolipoprotein B Antisense Oligonucleotides: A type of drug that binds to the mRNA of apolipoprotein B to reduce the production of atherogenic lipoproteins.

6. Combination therapies: Different classes of anti-hyperlipidemic agents are used in combination for several reasons, as follows(93, 94): The ability to reduce the concentration of lipids in combination therapy is synergistic and more profound than single therapy.

A single drug cannot decrease the levels of some forms of lipids, such as TG, LDL, VLDL, or cholesterol, but the combination therapy of different classes can reduce the target lipid or all types of lipids. In combination therapy, a small dose of different classes can produce the desired effect compared to a large dose of a single drug. Combination therapy of various groups has fewer side effects, is more potent, well-tolerated, and safe compared to single therapy(95, 96).

Some examples of combination therapy used for reducing hyperlipidemia worldwide may be mentioned as follows: 1)HMG-CoA reductase inhibitors and bile acid-binding resins. 2)Statin plus Niacin. 3) HMG-CoA reductase inhibitors and Ezetimibe. 4)Statin and Fenofibrate. 5) Combination of Resins, Ezetimibe, Niacin, and Statin. 6) Combination of PCSK9 inhibitor with Statin and Ezetimibe

7. Herbal therapy:

In developing countries, herbal and traditional medicine play a significant role in healthcare due to their efficacy, safety, and popularity within communities. There is a growing trend toward self-medication with herbal remedies(97).

Herbal medicine, with roots in ancient civilizations like Sumeria, China, and India, uses various plant parts (seeds, flowers, leaves, etc.) for treating diseases (98). Sometimes, in the state of herbal medicine, botanical medicine, or phytomedicine, the terms are used as synonyms; a different part of plants is used, such as seeds, flowers, berries, leaves, bark, stems, and roots, for the treatment of various medical conditions (99).

Herbal medicine remains important in treating various diseases, with studies showing that nearly 80% of the global population trusts botanical medicine for healthcare. Despite advances in pharmaceutical drugs, plant-based treatments still offer substantial benefits in clinical settings. Pharmacological studies in the 19th century revealed plant-derived active ingredients, and their clinical use remains important to this day. According to the WHO, about 80% of humans globally have faith in botanical medicine for various types of diseases (99).

Herbal medicines can be administered in various forms, such as teas, syrups, capsules, and essential oils. The efficacy of these medicines can vary depending on extraction methods, solvents, and the plant part used. Active ingredients can differ between batches, depending on factors like the plant's growing conditions and the extraction process(100).

Herbal plants contain bioactive compounds that work synergistically to treat diseases. These compounds are classified into primary constituents (amino acids, proteins, sugars, etc.) and secondary constituents (flavonoids, terpenoids, alkaloids, and steroids(101), One of the common problems which frequency noted by the doctors and people who use the botanical medicine as a treatment are low or lake of enough information about the efficacy, safety, and mechanism of action of the plant on the health fortunately, in the last 30 years there

was a large number of studies recorded about the plants which include: safety, efficacy, toxicity, activity eta (102). The summary of some natural products and their mechanism of action is shown in Table 2.

Table 2: List of numerous natural products and their mechanism in the treatment of dyslipidemia

No.	**Natural Product**	**Source**	**Mechanism of Action**	**Effects on Lipid Levels**	**References**
1	Garlic (Allium sativum)	Garlic bulb	Inhibits HMG-CoA reductase, improves lipid metabolism	↓ Total Cholesterol, ↓ LDL, ↑ HDL	Liang, et al, 2025 (103)
2	Ginseng (Panax ginseng)	Root of Panax ginseng	Modulates lipid metabolism and reduces cholesterol synthesis	↓ LDL, ↓ Triglycerides	Cecarini, et al.2023(104)
3	Fenugreek (Trigonella foenum-graecum)	Seeds	Inhibits cholesterol synthesis, reduces lipogenesis	↓ LDL, ↓ Triglycerides, ↑ HDL	Chen, et al, 2017 (105)
4	Turmeric (Curcuma longa)	Rhizome	Reduces lipid peroxidation and enhances antioxidant activity	↓ LDL, ↓ Total Cholesterol, ↓ Triglycerides	Cheng, et al. 2025 (106)
5	Ginger (Zingiber officinale)	Root of ginger	Increases bile secretion, enhances lipolysis	↓ LDL, ↑ HDL	Asghari-Jafarabadi,et al 2022 (107)
6	Green Tea (Camellia sinensis)	Leaves	Inhibits lipid absorption, boosts fat metabolism	↓ Total Cholesterol, ↓ LDL, ↑ HDL	Xu, et al, 2020(108)
7	Cinnamon (Cinnamomum verum)	Bark	Improves insulin sensitivity, reduces cholesterol absorption	↓ LDL, ↑ HDL	Silva, et al, 2022(109)
8	Psyllium (Plantago ovata)	Seeds of Plantago species	Forms gel-like substances that reduce cholesterol absorption	↓ LDL, ↓ Total Cholesterol	Mohammadi, et al. 2024 (110)
9	Olive Oil (Olea europaea)	Fruit of the olive tree	Rich in monounsaturated fats that improve lipid profiles	↑ HDL, ↓ LDL, ↓ Triglycerides	Kourek, et al.2025(111)
10	Milk Thistle (Silybum marianum)	Seeds	Acts as an antioxidant, protects liver cells from oxidative stress	↓ Total Cholesterol, ↑ HDL	Taleb, et al.2018(112)
11	Coconut Oil (Cocos nucifera)	Coconut fruit	Increases HDL by modulating fat metabolism	↑ HDL, ↓ LDL	Neelakantan et al, 2020 (113)
12	Bitter Melon (Momordica charantia)	Fruit	Reduces liver cholesterol synthesis and increases insulin sensitivity	↓ LDL, ↓ Triglycerides	Alam, et al.2015(114)
14	Cucumber (Cucumis sativus)	Fruit	Acts as a diuretic, promotes fat metabolism	↓ Total Cholesterol, ↓ LDL	Soltani, et al. 2017(115)
15	Flaxseed (Linum usitatissimum)	Seeds	Rich in omega-3 fatty acids, reduces triglyceride levels	↓ LDL, ↓ Triglycerides	Mohammadi, et al. 2025 (116)
16	Black Seed (Nigella sativa)	Seeds	Increases HDL, reduces cholesterol absorption	↓ LDL, ↓ Total Cholesterol, ↑ HDL	Rounagh, et al. 2024(117)
17	Ginkgo Biloba (Ginkgo biloba)	Leaves	Improves blood circulation, antioxidant effects	↑ HDL, ↓ LDL	Xie, et al. 2009 (118)
18	Chia Seeds (Salvia hispanica)	Seeds	Rich in omega-3 fatty acids and fiber, lowers fat production	↓ LDL, ↓ Triglycerides, ↑ HDL	Fateh, et al. 2024 (119)
19	Apple Cider Vinegar	Fermented apple juice	Enhances bile secretion, reduces cholesterol synthesis	↓ LDL, ↓ Total Cholesterol	Hadi, et al.2021(120)

Note: HMG-CoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A, an enzyme involved in cholesterol synthesis in the liver. LDL: Low-Density Lipoprotein, often referred to as "bad cholesterol," which carries cholesterol to the cells and can contribute to plaque buildup in arteries if elevated. HDL: High-Density Lipoprotein, often referred to as "good cholesterol," which helps remove excess cholesterol from the bloodstream and carries it to the liver for excretion. TG: Triglycerides, VLDL (very-low-density lipoprotein). ↑: Increase, ↓: Decrease.

Conclusion

Antihyperlipidemic agents are still the mainstay for treating hyperlipidemia and subsequently play an important role in CVD prevention. Such a review emphasizes the therapeutic benefit from diverse pharmacological classes, including first-line agents like statins, to newer, more effective

therapies like PCSK9 inhibitors and inclisiran, a new-generation siRNA agent for LDL suppression. These conventional agents, in conjunction with supportive lifestyle changes, offer an effective way of managing the lipid profile. In addition, the development of new drugs and additional research efforts to integrate other treatment options, such as herbal medicine, highlight the innovative range of lipid-lowering treatments available for management. Further studies should be directed toward existing treatment optimization and new drug discovery with enhanced efficacy and safety profiles, leading to improved patient outcomes worldwide

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