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The role of pharmacological interventions in managing hyperlipidemia: A closer look at different drugs

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Abstract

Hyperlipidemia is a medical condition characterized by an increase in plasma lipids, including triglycerides, cholesterol, cholesterol esters, phospholipids, and plasma lipoproteins, which is a leading risk factor for cardiovascular diseases. The pathophysiology of hyperlipidemia is influenced by endothelial damage to blood vessels, leading to a loss of nitric oxide, increased inflammation, and lipid accumulation in the deepest layer of the endothelial wall. Lipid-lowering drugs like statins can reduce LDL levels by 25-60%, but they have negative impacts on clinical outcomes. Lipoprotein metabolism involves various enzymes, and atherosclerosis accumulates fat, cholesterol, and calcium in artery linings, creating fibrous plaques that reduce blood flow and oxygen supply, leading to heart damage and death. Lipoprotein metabolism involves various enzymes, including lipoprotein lipase (LPL), hepatic lipase (HL), lecithin cholesterol acyl transferase (LCAT), cholesterol ester transfer protein (CETP), microsomal triglyceride protein (MTP), and acyl Co-A transferase (ACAT).

Atherosclerosis accumulates fat, cholesterol, and calcium in artery linings, creating fibrous plaques. This leads to reduced blood flow and oxygen supply, causing heart damage and death. Reducing LDL and total cholesterol can significantly lower the incidence of strokes.

Reducing LDL and total cholesterol can significantly lower the incidence of strokes. Traditional antihyperlipidemic medicines have negative effects, and herbal treatments like onion, garlic, guggul, and Asparagus racemosus have been shown to have anti-diabetic and antihyperlipidemic properties.

Keywords: Hyperlipidemia; Lipoprotein; Fibrates; Statins; HMG-CoA; MTP; Guggul

1. Introduction

Hyperlipidemia is a metabolic disorder that affects the serum lipid and lipoprotein profile by increasing the net level of low-density lipoprotein cholesterol (LDL-C), very low-density lipoproteins (VLDL-C), total cholesterol (TC), and triglycerides (TAG), while decreasing the concentrations of high-density lipoproteins in the blood circulation. One important protective component that aids in completely eliminating cholesterol from the artery wall is high-density lipoprotein. One commonly used method to evaluate the atherogenicity index is the ratio of total cholesterol to high-density lipoprotein; a ratio of greater than 4.5 is considered atherogenic [1].

Hypercholesterolemia and hypertriglyceridemia are the leading causes of atherosclerosis, which has a significant link to ischemic heart disease. There is a strong link between IHD and high death rates. More increased plasma cholesterol levels result in more than four million deaths every year. Atherosclerosis is the process by which arteries harden as a result of cholesterol buildup in the arterial wall, causing the narrowing of the arteries. Hyperlipidemia increases

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atherosclerosis and atherosclerosis-related conditions, such as coronary, cerebrovascular, and peripheral vascular diseases [2].

2. Pathophysiology

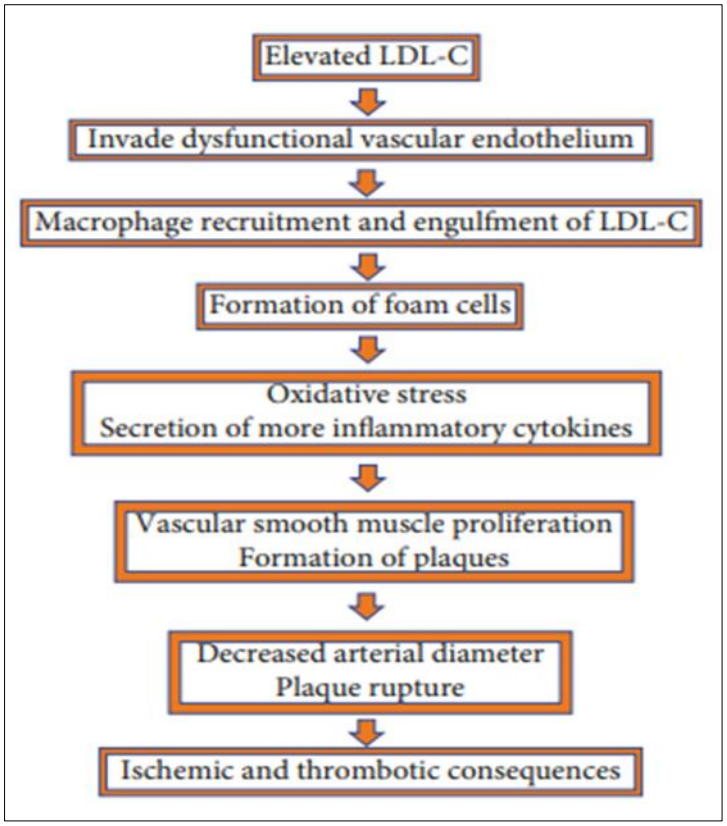

Figure 1 Pathophysiology of hypercholesterolemia leading to damage to the heart

Dyslipidemias involve clinically increased levels of cholesterol and triglycerides that may be accompanied with decreased HDL levels [3].

Because of the substantial problems and higher rates of mortality and morbidity associated with hyperlipidemia, a large number of studies and scientists have attempted to elucidate the actual pathophysiology of the condition in greater depth. This is done to accomplish early disease detection and aggressive treatment, which helps to reduce complications and enhance patient health. According to current research and reviews, hyperlipidemia is caused by endothelial damage to blood vessels, which results in a loss of nitric oxide in the damaged site, an increase in the inflammatory response around the affected area, and the accumulation of lipids in the deepest layer of the endothelial wall, where macrophage cells engulf the lipids, forming what is known as a foam cell with cholesterol [4].

The production of foam cells will result in necrosis, apoptosis, and mitochondrial malfunction. Simultaneously, smooth muscle cells wrap the foam cell, causing fibrotic plague, and prevent the foam cells from being destroyed. On the other hand, activation of platelet activity by tissue factors causes plague rupture and thrombosis. Plague can develop quickly, resulting in blood vessel occlusion, or slowly, causing blood vessel stenosis. In both routes, lipid plague remains the primary cause of CVD development and decline in patient health.

In addition to CVD, patients with hyperlipidemia may experience tendon dysfunction, particularly the patellar tendon. This is because hyperlipidemia produces a greater number of macrophages over time.

This is because with time, hyperlipidemia will develop a bigger number of macrophages in the tendon tissues, collagen fiber degradation, and replacement by lipid instead of collagen, resulting in less effective tendons that are readily damaged [5].

3. Lipoproteins

Molecular complexes of lipids and proteins are called lipoproteins. Lipoproteins are large molecular assemblages made up of phospholipids, triglycerides, and free and esterified cholesterol. The liver is the organ where lipoproteins are made. Lipoprotein particle structure: The hydrophobic core of each lipoprotein particle is surrounded by a monolayer of polar, amphipathic lipids. The hydrophobic center is protected by a covering made of these polar lipids [6].

3.1. Classification of Lipoproteins

There are six main classes of lipoproteins

- Chylomicron
- Chylomicron Remnants
- Very low-density lipoprotein cholesterol (VLDL-C)
- Intermediate density lipoprotein cholesterol (IDL-C)
- Low-density lipoprotein cholesterol (LDL-C)
- High-density lipoprotein cholesterol (HDL-C)

3.2. Enzyme Breakdown: Understanding Lipoprotein Metabolism

3.2.1. Lipoprotein lipase (LPL)

LPL is a multifunctional enzyme found on endothelial cells of the heart, muscle, adipose tissue, macrophages, and lactating mammary glands. LPL is involved in the hydrolysis of triglyceride (TG) into two free fatty acids and monoacylglycerol. Besides, LPL aids in the receptor-mediated lipoprotein uptake of chylomicron remnants, cholesterol-rich lipoproteins, and free fatty acids [7,8].

3.2.2. Hepatic lipase (HL)

The multifunctional protein HL controls the metabolism of lipoproteins. It is produced by hepatocytes and is present in the ovary and adrenal glands. Triglycerides and phospholipids found in plasma lipoproteins are hydrolyzed by HL. Furthermore, HL influences the transport of lipids within cells by promoting the absorption of lipoproteins by proteoglycans and cell surface receptors [9].

3.2.3. Lecithin cholesterol acyl transferase (LCAT)

An essential enzyme in the metabolism of HDL is lecithin cholesterol acyltransferase. It changes free cholesterol into cholesteryl esters, which are subsequently trapped in the lipoprotein's core and produce mature HDL [10].

3.2.4. Cholesteryl ester transfer protein (CETP)

Esterified cholesterol esters (CE) are transferred from HDLs to chylomicrons, VLDL and LDL, more quickly by Cholesteryl Ester Transfer Protein (CETP), also known as plasma lipid transfer protein. This process occurs in exchange for triglycerides and is catalyzed by this hydrophobic plasma glycoprotein. Reduced LDL and elevated HDL levels are associated with ACETP deficiency [11].

3.2.5. Microsomal triglyceride protein (MTP)

Microsomal triglyceride protein (MTP) is a lipid transfer protein that facilitates the transfer of neutral lipids, triglycerides, and cholesterol esters across the membrane of the lumen of microsomes isolated from the liver and intestinal mucosa. The formation of apo B-containing lipoproteins requires the presence of microsomal triglyceride protein. MTP is now known to play a critical role in the manufacture of glycolipid-presenting molecules and the regulation of cholesterol ester biosynthesis [12].

3.2.6. Acyl Co-A transferase (ACAT)

Acyl Co-A transferase (ACAT) is a membrane-bound protein that converts long-chain fatty acyl-CoA and cholesterol into cholesteryl esters. ACAT is important in cellular cholesterol homeostasis in numerous tissues and prevents the harmful accumulation of excess cholesterol in a cell. Furthermore, the significance of ACAT stems from its important function in the assembly and secretion of apolipoprotein-B-containing lipoproteins in the liver and intestines [13].

3.3. Exploring the Benefits of Lipid-lowering Drugs

Statins, such as atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin, can reduce LDL levels by 25-60% by inhibiting HMG-CoA reductase. Vitamin B3 decreases VLDL formation, while fibrates stimulate lipoprotein lipase, reducing LDL levels by 15% and triglycerides by 35%. 2-Azetidiones inhibit sterol transporter at the brush boundary, while bile acid sequestrants reduce cholesterol and LDL through bile duct sequestration. ACL inhibitors reduce LDL-C by blocking cholesterol production in the liver.

- **Statins:** They are the first line of lipid-lowering medications, while others, which will be addressed later, are added to improve statin efficacy, statin intolerance, or severe hypertriglyceridemia. Statins can reduce LDL and triglyceride levels (at higher doses) while raising HDL levels [14].
- **Ezetimibe:** Ezetimibe is known to hinder cholesterol absorption and reduce levels of LDL-C, apolipoprotein B (apo B), and non-HDL in individuals with primary hyperlipidemia, mixed hyperlipidemia, and familial hypercholesterolemia (FH) [15].
- **Fibrates:** Fibrates are reported to lower triglycerides by up to 50% while increasing HDL by 5 to 20%. Despite its lipid-lowering effects, fibrates have a negative impact on clinical outcomes. They are primarily used to decrease triglycerides and reduce the incidence of pancreatitis [16].
- **Nicotinic Acid:** Although niacin dramatically increases high-density lipoprotein cholesterol (HDL-C), it has not been found to enhance patient outcomes in statin-treated patients. Niacin can help lower LDL when used with statins and ezetimibe in people with extremely high cardiovascular risk, such as homozygous or heterozygous familial hypercholesterolemia, but not in secondary prevention [17].
- **PCSK9 Inhibitors:** Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a new class of medications licensed to lower LDL. They have been found to reduce LDL by up to 60% in statin-treated individuals. The FDA has approved alirocumab and evolocumab for adult patients with heterozygous familial hypercholesterolemia or clinical ASCVD who require further LDL-cholesterol reduction in addition to diet modification and maximally tolerated statin therapy. The FDA has also approved evolocumab for adult patients with homozygous familial hypercholesterolemia who need further lowering of LDL-C in addition to conventional LDL-reducing medications like statins or ezetimibe [18].
- **Bile Acid Sequestrants (BAS):** Bile acid sequestrants comprise cholestyramine, colestipol, and colesevelam. Bile acid sequestrants are used to treat primary hypercholesterolemia, commonly in combination with statins or nicotinic acid. Cholestyramine has been demonstrated to reduce cardiovascular mortality and morbidity in patients by 19% when compared to placebo, and it also benefits Type 2 diabetics by lowering blood sugar levels. Bile acid sequestrants can also rapidly lower plasma thyroid hormone levels, making them useful for refractory thyrotoxicosis. They can also increase HDL-C. They can be used to treat pruritus in patients suffering from cholestatic illness and partial biliary blockage [19].

3.4. New Potential Targets and Treatments: Unlocking New Possibilities

3.4.1. Acyl-CoA cholesterol acyltransferase inhibitors (ACAT)

ACAT has two isoforms: ACAT-1 and ACAT-2. This class of enzymes catalyzes the conversion of cholesterol into cholesteryl esters. This inhibits the harmful accumulation of excess cholesterol in a cell. ACAT-1 contributes to the development of atherosclerosis by attracting monocytes that are transformed into foam cells in the arterial wall, implying that ACAT-1 inhibitors may have an antiatherogenic effect, while ACAT-2 inhibitors may play an important role in reducing cholesterol absorption in the gut. Furthermore, the relevance of ACAT stems from its important role in the congregation, as well as the release of apolipoprotein B-containing lipoproteins in the liver and intestines. Some of the powerful ACAT inhibitors that are currently in Clinical development belongs to the class of naphthoquinone derivatives. Avasimibe and Eflucimibe lower plasma cholesterol levels while slowing the growth and development of atherosclerosis by inhibiting (ACAT) Acyl-CoA cholesterol acyltransferase [20].

3.4.2. Microsomal Triglyceride Transfer Protein (MTP) Inhibitors

The formation of apo B-containing lipoproteins requires the presence of microsomal triglyceride protein. Microsomal triglyceride protein (MTP) catalyzes the transfer of neutral lipids, triglycerides, and cholesterol esters between the intestinal mucosa membrane and the lumen of liver-isolated microsomes, also known as lipid transfer protein. MTP is now known to have an important function in the manufacture of glycolipid-presenting molecules as well as in the regulation of cholesterol ester biosynthesis. This technique to suppressing MTP may be useful for lowering atherogenic lipoprotein levels, resulting in considerable reductions in blood lipoproteins such as plasma triglycerides, LDL, and VLDL cholesterol. In vitro and in vivo models were used to assess the effects of a series of newly synthesized phosphonate esters on MTP activity, and they were found to inhibit MTP activity potently in both models. Data also

reveal that lomitapide (AEGR-733, originally BMS-201038), a new hypercholesterolemia medication, is effective as an MTP inhibitor [21].

3.4.3. Acyl Coenzyme A: Diacylglycerol Acyltransferase (DGAT)

Diacyl glycerol acyltransferase (DGAT) is a microsomal enzyme that catalyzes the addition of Acyl CoA to 1,2-diacylglycerol, the final step in triglyceride production. These two isoforms of DGAT were discovered to be DGAT-1 and DGAT-2. Several studies have indicated that inhibiting DGAT1 is an effective target for the treatment of hyperlipidemia. In vitro experiments shown that a two-week therapy with compound T863 reduced serum and liver triglycerides, as well as serum cholesterol in mice. T863 is a strong inhibitor of DGAT [22].

3.4.4. Squalene Synthase Inhibitors

Squalene synthase (SqS) is the first committed step in sterol synthesis; the enzyme catalyzes farnesyl pyrophosphate to produce squalene, which includes cholesterol. Squalene synthase inhibitors show promise in drug discovery as a lead chemical for the development of possible hyperlipoproteinemia treatments. It has been reported that the oral treatment of BMS-188,494, a putative SqS inhibitor, reduced plasma cholesterol levels in experimental rats [23].

3.4.5. Cholesteryl Ester Transfer Protein (CETP) Inhibitors

CETP promotes atherosclerosis by initiating reverse cholesterol transport. In the liver, it facilitates the transfer of cholesteryl ester from anti-atherogenic HDLs to proatherogenic apolipoprotein B-containing lipoproteins such VLDL and LDL. Furthermore, most studies found evidence that suppression of CETP slows the evolution of atherosclerosis. Dalcetrapib and anacetrapib were discovered to represent a new class of drugs in Phase III clinical studies. Dalcetrapib increased HDL cholesterol levels by 31% without affecting LDL levels, while it decreased CETP activity by 50% [24].

4. Complications of hyperlipidaemia

- Atherosclerosis: It is a prevalent condition in which fat, cholesterol, and calcium accumulate in the artery linings. This deposition leads to the creation of fibrous plaques.

A plaque typically consists of three components:

  - Atheroma, which is a fatty, soft, yellowish nodular mass found in the core of a bigger plaque that comprises of macrophages, which are immune cells.
  - A coating of cholesterol crystals
  - Calcified outer layer. Atherosclerosis is a leading cause of cardiovascular diseases [25].
- Coronary Artery Disease (CAD): Atherosclerosis is the leading cause of CAD. It is distinguished by the narrowing of the arteries that provide blood to the myocardium, resulting in reduced blood flow and insufficient oxygen to meet the needs of the heart. The constriction may proceed to the point where the heart muscle suffers damage due to a lack of blood supply. An elevated lipid profile is linked to the development of coronary atherosclerosis [26].
- Myocardial Infarction (MI): MI is a condition that happens when the blood and oxygen supply to the cardiac arteries become partially or fully restricted, causing heart cell damage or death. The occlusion is usually caused by a clot in an artery. This ailment is usually referred to as a heart attack. According to the studies, one-fourth of myocardial infarction survivors had hyperlipidemia [27].
- Angina Pectoris: Angina is not a medical condition, but rather a sign of a larger cardiac problem. It is defined by chest pain, discomfort, or a squeezing sensation. Angina is caused by a loss or lack of blood supply to a portion or all of the heart muscle. Poor blood circulation is frequently caused by CHD when the coronary arteries are partially or completely blocked [28].
- Ischemic stroke or Cerebrovascular Accident (CVA): It occurs when the circulation of blood in a portion of the brain is stopped or reduced. When the blood supply for oxygen, glucose, and other nutrients is disturbed, brain cells die and become dysfunctional. Strokes are usually caused by an artery being blocked by a blood clot or a fragment of atherosclerotic plaque breaking away in a tiny channel within the brain. Clinical studies demonstrated that reducing LDL and total cholesterol by 15% considerably lowered the incidence of the first stroke [29].

4.1. Uncovering the Surprising Health Benefits of Lipid Reduction with Ayurvedic Herbs

Hyperlipidemia is the largest risk factor for coronary heart disease. Currently, allopathic antihyperlipidemic medicines are associated with a considerable number of negative effects. Herbal treatment for hyperlipidemia has minimal

negative effects, is inexpensive, and may be obtained locally. Medicinal plants are the "backbone" of traditional medicine, and they are regarded as a healthy source of life for all people due to their numerous medicinal capabilities and the fact that they are completely natural. Medicinal plants are widely utilized to cure a variety of diseases and have a significant impact on the global economy. Traditional medicinal approaches based on plants, herbs, and shrubs have traditionally played an important part in the worldwide health system.

Natural medications are generally less harmful, have less side effects, and are readily available, hence the demand for herbal drugs is increasing [30].

- *Allium cepa* Linn. (onion) : S-methyl cysteine sulphoxide (SMCS), a sulfur-containing amino acid derived from onion, has anti-diabetic and antihyperlipidemic properties. Oral administration of SMCS at a dose of 200 mg/kg body weight daily for 45 days to alloxan diabetic rats significantly controlled their blood glucose and lipid levels in Serum and tissues were affected, and the activities of liver hexokinase, glucose 6-phosphatase, and HMG Co-A reductase were normalized. The effects of SMCS were comparable to those of insulin and glibenclamide [31].
- *Allium sativum* Linn. (Garlic) : Several animal and human studies have proven the efficacy of garlic as a herbal remedy to reduce a multitude of risk factors that play a decisive role in the genesis and progression of arteriosclerosis, including decreases in total cholesterol, LDL-C, HDL-C, serum triglyceride, and fibrinogen concentrations [32].
- *Commiphora Mukul* (Guggul): Guggulipid, an oleoresin and a combination of various steroid lipids, at 1.2 g/day for 6 weeks lowered cholesterol by 15% and triglycerides by 20%. When 1.5 g of guggulipid was supplied daily for 12 weeks, cholesterol levels decreased by 16.9% and triglycerides decreased by 27%. In a 12-week study of 135 patients with ischemic heart disease, guggul powder (8 g/day) reduced blood cholesterol (27%), serum triglycerides (36%), phospholipids (20%), and free fatty acids (37%) [33].
- *Asparagus racemosus* (Shatavari): Feeding A. racemosus at a rate of 5% to hypercholesterolemic animals reduced total lipids (29%), total cholesterol (29%), triglycerides (39%), LDL-C (33%), VLDL-C (39%), atherogenic index (37%), and increased HDL-C content (11%). A. racemosus treatment resulted in a further drop in total lipids (64%), total cholesterol (38%), triglycerides (52%), LDL-C (44%), VLDL-C (52%), and atherogenic index (49%). The reduction in total lipids, total cholesterol, triglycerides, LDL-C, VLDL-C, and atherogenic index was dose-dependent and statistically significant. A 21% rise in HDL-C levels was also observed at the 10% dose when compared to the animal treated with the 5% dose.
  A. racemosus also reduced total lipids (26% and 36%, respectively), total cholesterol (46% and 57%, respectively), and triglycerides (38% and 57%, respectively) in the liver of treated groups when compared to the control [34].
- *Withania somnifera.* Dunal (Solanaceae): Commonly known as Ashwagandha, Indian ginseng, or winter cherry, is a stiff gray-whitish tiny shrub that grows 30-90 cm tall and has lanceolate oblong leaves with very short stalks. It is found in the drier regions of Punjab, Gujarat, Simla, and Kumaon in India. They are heavily covered in tiny gray stellated tomentum (filamentous hairlike growth). The flowers (7-12 mm across) are yellow, dioecious, and polygamous. The seeds are dark brown, ear-shaped, and glabrous, with a pungent fruity odor. The berries and fleshy fruit have carminative and depurative properties and are also used to treat dyspepsia and flatulence [35].

5. Conclusion

In conclusion, this review sheds light on the pathophysiology of hyperlipidemia and the diverse array of lipid-lowering drugs available, emphasizing their potential benefits and limitations. Additionally, it explores the promising potential of herbal treatments like onion, garlic, guggul, and Asparagus racemosus in managing hyperlipidemia. This insightful review not only deepens our understanding of the condition but also underscores the need to explore alternative treatment options for better management of hyperlipidemia. Moving forward, further research and clinical trials in this area could significantly benefit society by providing more holistic and effective approaches to combating this prevalent health concern.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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