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A COMPREHENSIVE ASSESSMENT ON CONVENTIONAL MEDICATIONS ANDNUTRITIONAL SUPPLEMENTS AVAILABLE FOR HYPERLIPIDEMIA

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ABSTRACT:

There are many chronic disorders that have troubled the humankind, hypercholesterolemia probably stands first in the queue of being the root cause of most diseases effecting the heart, kidney, brain and blood vessels. Developing because of unhealthy eating habits, sedentary lifestyle and affecting mostly financially privileged class of society, it has contributed enormously to the global health burden. Scientists have come up with considerable numbers ofboth synthetically derived and naturally derived therapeutic agents to halt the detrimental effects of this disorder that only gets worse over time. Some of these drugs, such as Rosuvastatin and Atorvastatin have been used quite efficiently and they provide multi- dimensional protection to the human body. While others such as PCSK9 inhibitors and ANGPTL 3 inhibitors provide even better alternative to already existing therapies. Despite these excellent agents, the efficacy and potency of herbal derived products cannot be neglectedand prove to be extremely popular among general populace to counter this disorder. In this review, we lay down epidemiology, pathophysiology and lipid lowering drugs, both syntheticand herbal.

Keywords: Hyperlipidemia, Hdl, Vldl, Rosuvastatin, Atorvastatin, Curcumin.

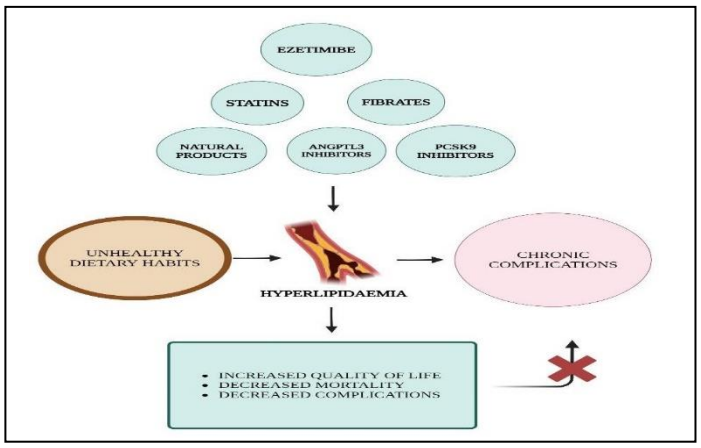


Fig 1: Graphical abstract.

1. INTRODUCTION

Increased levels of serum total cholesterol (TC), LDL (low-density lipoprotein), VLDL (very low-density lipoprotein), and reduced levels of HDL (high-density lipoprotein) are characteristics of hyperlipidaemia and caused by diets heavy in lipids and carbs (Jing YS et al.,2022;9 Zhu F et al.,2024;10 Rauf A et al.,2022). Elevated LDL cholesterol has also been frequently associated with a higher chance of developing plaque buildup and ultimately developing vascular disease, according to a variety of trials and studies which are major complications of hyperlipidaemia. As an alternative, (HDL) cholesterol helps to maintain normal cholesterol levels, which reduces the risk of atherosclerotic vascular disease. (Hill MF et al.,). One of the foremost risk factors for the onset of coronary artery disease and the advancement of vascular sclerosis plaques is hyperlipidaemia (Farnier M et al.,1998). The most advantageous alterations in lipid levels are probably those that result from Reduced intake of trans and saturated fats, increased consumption of poly- and monounsaturated fats, moderation in alcohol use, addition of plant sterols or stanols, and isocalorically increasing tree nut consumption (Kelly RB et al.,2010). Genetics, nutrition, medicine, and other variables have all contributed to the substantial increase in the occurrence of hyperlipidaemia, which is now one of the most prevalent clinical conditions in humans (Nana He et al.,2020). Primary and secondary hyperlipidaemia are the two broad categories into which it falls. There are three types of primary hyperlipidaemia: isolated high TG, isolated elevated cholesterol, and elevated levels of both. Primary hyperlipidaemia is mostly caused by environmental causes and geneticmakeup. Drugs, food, or pre-existing conditions are some of the additional factors that might contribute to secondary hyperlipidaemia (Ezeh KJ et al., 2021). Elevations of TG, LDL-C, and TC are intimately linked to hypothyroidism. Because THs regulate the synthesis, conversion, and clearance of cholesterol, the thyroid gland is important to this step (Su X et al.,2022). Atherosclerosis is the arterial stiffening brought on by cholesterol buildup in the arterial wall, which narrows the arteries. Hyperlipidemia accelerates atherosclerosis and disorders linked to it, including peripheral vascular disease, heart disease, and stroke (El-Ezzy AI et al.,). Atherosclerotic plaques develop in the blood vessel's intima and are primarily found on the walls of big and medium-sized blood vessels. Atherosclerosis is a multifactorial disease. It is believed that hyperlipidaemia poses a serious risk for developing atherosclerosis and other cardiovascular and cerebrovascular illnesses (Miao J et al.,2020;15 Navar-Boggan Am et al.,2015). Serum cholesterol levels of 240 mg/dL, TG levels of 200 mg/dL, and LDL levels of160 mg/dL were considered indicators of hyperlipidaemia (Feng X et al.,2022). Increased oxidative stress results in a notable formation

of total peroxide in hyperlipidaemia, which maycause oxidative changes in LDL (Hameed MS et al.,). Angina symptoms typically start to show up gradually when the coronary artery blockage increases to a percentage greater than 75%. Typically, blood clots form on the uneven surfaces of arteries, and they have the potential to separate and obstruct blood flow downstream. These blood coagulations are typically the reason for strokes and heart attacks. Additionally, the blood arteries with atherosclerosis are typically fragile and prone to rupture (Bahmani M et al.,2015). Pharmacological therapy, exercise, and diet restriction have all been used to treat hyperlipidaemia. It appears that the useof natural hypolipidemic medications is need to turn aside and cure high cholesterol and associated problems because synthetic hyperlipidemic medications, such as fibrates and statins, typically have side effects and contraindications with long-term usage (El-Tantawy et al.,2019). In the general population, gastrointestinal (GI) disorders and symptoms, particularlyirritable bowel syndrome (IBS), are highly prevalent (Ohlsson B et al.,2017). Sedentary behaviours have been linked to elevated blood lipid levels, according to recent research. In fact,watching too much television is linked to lower HDL-C and higher TG, most likely because ituses less energy. In particular, blood pressure, lipid profile, insulin sensitivity, serum glucose levels, and cardiorespiratory fitness are all improved by physical activity. Both healthy grown person and young one with elevated cholesterol level or obesity should engage in regular physical activity to improve BMI, lower TC, LDL-C, and TG, increase HDL-C, and, most importantly, decrease body fat (Mainieri F et al.,2023). In addition to being created by the liver, diet (i.e., items including meat, butter, salami, cheese, egg yolks, and liver that are high in animal fats) can also introduce cholesterol (Zodda D et al., 2018).

Epidemiology

The World Health Organization (WHO) released its most recent monitoring of developments in noncommunicable diseases (NCDs) following 2017, and it states that NCDs account for 70% of all deaths worldwide. Adults under 70 (40%) are the population segment most affected by NCDs (Ramirez AA et al.,2020). About 30 million people worldwide are affected by FH, the most occurred autosomal-dominant genetic illness. FH is characterized by persistently increased levels of LDL cholesterol, which elevate the risk of ischemic heart disease (IHD) (Beheshti SO et al.,2020). With publication bias for the at least 5·2 mmol/L cutoff (appendix), the prevalence was found to be 25·5% (95% CI 20·0–31·4) and 11·0% (7·1–15·5), respectively, when comparing the overall prevalence of elevated total cholesterol concentrations with cutoffs of at least 5·2 mmol/L and at least 6·5 mmol/L. There were significant regional differences in the prevalence, with urban areas having a greater rate than rural ones (Noubiap JJ et al.,2018). Different populations have different rates of HC. In developing nations, the prevalence of HC seems to be rising with time. As an illustration, the population of Nigeria reports a prevalence of 38%, Taiwan reports an estimated 44%, and Korea recorded 19.5% in 2015. Europe had the greatest rate of HC (54%), followed by, South East Asia (29%), America (48%) and Africa (22.6%), according to data from the WHO's Global Health Observatory (Al-Zahrani et al.,2021). In India, the prevalence of hypercholesterolemia ranges from 10 to 15% in rural areas to 25–30% in metropolitan areas (Sharma S et al.,2024). Estimated overall prevalence of hyperlipidaemia is 51.09%; 50.21% in women and 52.04% in men. In China, hyperlipidaemia is 49.3% common. (Rao W et al.,2016).

Pathophysiology

Acyl-CoA: a lipid O-acyltransferase (ACAT) is a crucial enzyme that enterocytes use to re-esterify ingested cholesterol. It is believed to be involved in the development of atherosclerotic lesions and the release of VLDL from the liver. It is engaged in the process of metabolizing cholesterol in macrophages, the liver, the intestine, and the adrenal cortex (Mahamuni SP et al.,2012). Chylomicron remnants carry cholesterol from the colon to the liver where it is absorbed by LDL-receptor-related proteins (LRP). VLDLs, or VLDLs, are the first lipoproteins that the liver produces and enters the bloodstream. Triglycerides are then eliminated by lipoprotein lipase, leaving leftover lipoproteins. LDL receptors (LDL-R) either eliminate the remaining lipoproteins or further metabolize them to LDL, which is subsequently eliminated by these receptors. HDL carry cholesterol from auxiliary cells for the liver. Hepatic lipase in the liver absorbs cholesterol, or cholesterol-ester transport proteins (CETP) recycle it to LDL and VLDL. Bile is the excretion of cholesterol. The five primary lipoprotein disorders—familial combined hyperlipidaemia (FCHL), familial hypertriglyceridemia (FHTG) affect the sites in this process (Jain KS et al.,2007). The production of fatty acids commences with the inclusion of two carbon atoms to acetyl-CoA. While fatty acid synthesis occurs in the cytoplasm, fatty acid oxidation occurs in the mitochondria. of the cell. Adipose tissue and the liver are the primary locations of fatty acid production. Adipose lipolysis (HSL-dependent and ATGL-) and the resulting hepatic VLDL synthesis (substrate-dependent and MTP-) cause hyperlipemia when they outpace the rate at which plasma VLDL is cleared (LPL- and VLDL receptor-dependent) (27 Nouh F et al.,2018). Microvascular function is regulated by a range of lipids, including HDL, LDL, TG, and total cholesterol (TC). Hypercholesterolemia causes capillary endothelial cells to undergo apoptosis, which in turn impairs left ventricular (LV) function and lowers cardiac reserve blood flow and capillary density. It is suggested that elevated cholesterol levels could impact the membrane's lipid bilayer, regulate intracellular calcium ions, and change the myosin heavy chain isoform expression patterns, thereby increasing the susceptibility of the myocardium to external harm (e.g., myocardial ischemia, diabetes, hemodynamic overload) (Yao YS et a.,2020). Since In plasma, cholesterol esters and TG are insoluble, they must be encapsulated as lipoprotein particles must be transported to the tissues like muscle and adipose tissue. The coat of lipoprotein particles is composed of phospholipid, free cholesterol, and apolipoproteins, which are composed of TG and cholesteryl ester in the main. Chylomicrons (CMs), VLDL, LDL, and HDL are the four main types of lipoprotein particles (Rahmany S et al). The pathophysiology of primary hyperlipidemia includes idiopathic hyperchylomicronaemia, which is characterized by a lack of the surface apoprotein CIII31 or a deficiency in lipoprotein lipase function, which results in hypertriglyceridemia and hyperchylomicronaemia. Chylomicrons are absorbed from the gastrointestinal system 30 to 60 minutes after a meal in secondary hyperlipidaemia that contains fat, which can raise serum triglycerides for three to ten hours (Onwe P et al.,2015). Furthermore, Low-density lipoprotein receptor, PCSK9, and apolipoprotein B100 (apoB100) are the three main genes that cause familial hypercholesterolemia (Wal P et al.,2024). The pathophysiology of hyperlipidaemia is depicted in figure 2.

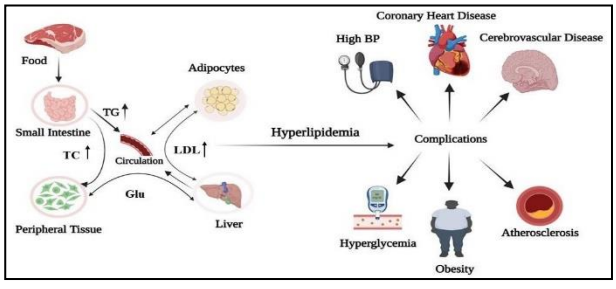


Fig 2: Pathophysiology of Hyperlipidaemia.

Routine Lipid-Lowering therapy:

1.1. HMG-CoA reductase inhibitors:

1.1.1. Statins:

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors that have been shown to be highly effective in lowering primary and secondary cardiovascular outcomes. Patients with dyslipidaemia are advised to take them (Zhang LS et al.,2019; YU HH et al.,2015). Since they are the most often prescribed anti-cholesterol drug due to their lack of side effects, effectiveness in lowering serum cholesterol, and reduction of cardiovascular risk, hydroxy-methylglutaryl-coenzyme A (HMG co-A) reductase inhibitors, or statins, have become one of the most commonly used medications (Cote DJ et al.,2019). Atorvastatin, lovastatin, pravastatin, fluvastatin, pitavastatin, simvastatin, and rosuvastatin respectively are the seven statins that are currently available. The choice of statin is mostly determined by the degree to which it lowers LDL-C, past statin intolerance, and metabolic variations that may indicate drug-drug interactions (Dixon DL et al.,2015). Statins (both lactone and acid forms) must enter in the liver after absorption in order to have the intended effect, such as inhibiting HMG-CoAR, and then be removed by bioconversion. Statins will enter the space of Disse, travel via the endothelial cells' fenestrations, and eventually reach the hepatocytes. Since statins are organic acids, they enter the hepatocyte through membrane carriers of the SLC superfamily, mainly those that belong to the OATP (organic anion transporting polypeptide) subfamily. The active β-hydroxy acid form of simvastatin and lovastatin is produced in the liver cells from the lactone forms which are inactive. The cytochrome P450 isoforms CYP2C9, CYP3A4, and CYP2C8 bio transform statin β-hydroxy acid form to produce hydroxylated metabolites that also help to suppress HMG. -CoAR (36 DU Patrick et al.,2017). Within the cytoplasm and membrane of the ER of almost every human tissue, including the adrenal cortex, liver, intestine, and reproductive organs, cholesterol is synthesized. Rather than coming from food, internal production accounts for the majority of the cholesterol in circulation. The liver produces about 70% of all the cholesterol in the body and blood cholesterol levels will decrease when the liver is unable to manufacture cholesterol (Egom EE et al.,2016). The chemical structures of statin drugs are illustrated in figure 3.

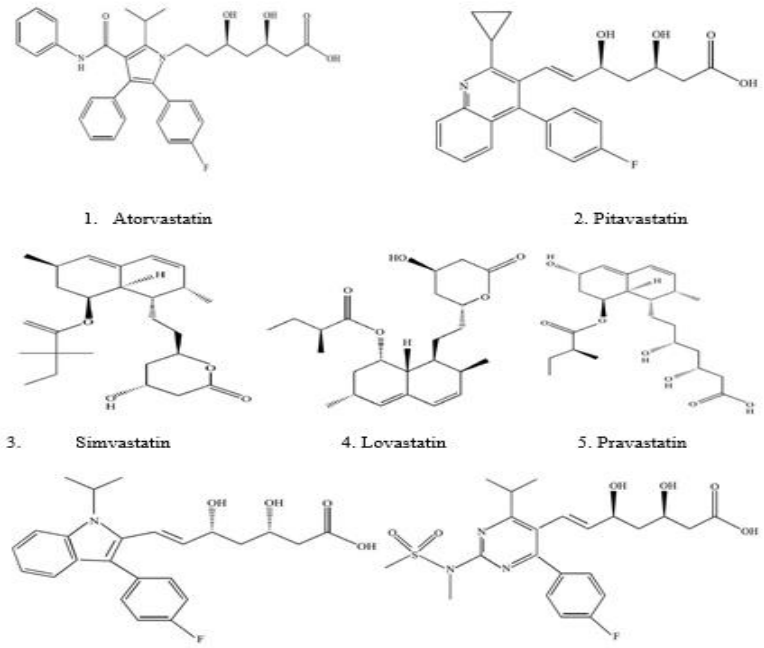


Fig 3: Chemical structures of statins.

1.2. Selective cholesterol – absorption inhibitor:

1.2.1. Ezetimibe:

Monotherapy of Ezetimibe (10 mg/day) considerably lowers levels of LDL-C by about 20%. Furthermore, ezetimibe statistically significantly lowers triglycerides, non- HDL-C, -HDL-C, apolipoprotein B (ApoB), and (hsCRP). (Ferreira AM et al.,2017). When ezetimibe interacts with the Niemann-Pick C1-Like 1 (NPC1L1) protein, it significantly lowers the intestinal absorption of cholesterol. Patients on statins experience an extra 20–25% reduction in LDL-C readings as a result. (Savarese G et al.,2015; Cannon CP et al.,2015). As far as specialized intestinal cholesterol absorption inhibitors go, ezetimibe is the only one available; it is a non-statin lipid-modifying medication. It is a well-tolerated, safe, and effective LDL-lowering drug. Taking 10 mg of ezetimibe daily results in a reduction of 13% to 20% in LDL-C, a reduction of 14% to 19% in non-HDL-C, a reduction of 5% to 11% in triglycerides (TG), and an increase of 3% to 5% in HDL-C. Ezetimibe is recommended for the treatment of homozygous familial hypercholesterolemia in conjunction with atorvastatin or simvastatin; homozygous sitosterolaemia; mixed hyperlipidaemia in combination with fenofibrate, simvastatin, or atorvastatin; and primary hyperlipidaemia alone or in combination with statins (Zhan S et al.,2018). At the jejunal brush boundary of the intestinal epithelium or the liver cells, the protein NPC1L1 is required for the uptake of cholesterol micelles into enterocytes, is known to be blocked by ezetimibe. In clathrin-coated vesicles, ezetimibe can prevent the NPC1L1/sterol complex from interacting with adapt protein 2. Ezetimibe lowers the amount of cholesterol in the liver by decreasing the cholesterol absorption, the production of chylomicrons, and the efflux of cholesterol into the bile. Additionally, it increases the expression of LDL receptors on liver cells, which promotes the elimination of LDL-C derived from blood. Over 90% of the total absorbed dose of ezetimibe was transformed into the pharmacologically active ezetimibe-glucuronide metabolite by the substantial glucuronidation of the 4-hydroxy phenyl group. After being administered, it is quickly absorbed (30 minutes) and takes 1.3 hours to reach its maximum serum concentration (Cmax). The majority of ezetimibe's excretion (78% of the dosage) occurs in faeces. Since ezetimibe has an estimated half-life of 22–24 hours, it is advised to take one dose per day (Kang MK et al.,2021). The chemical structure of Ezetimibe is depicted in figure 4.

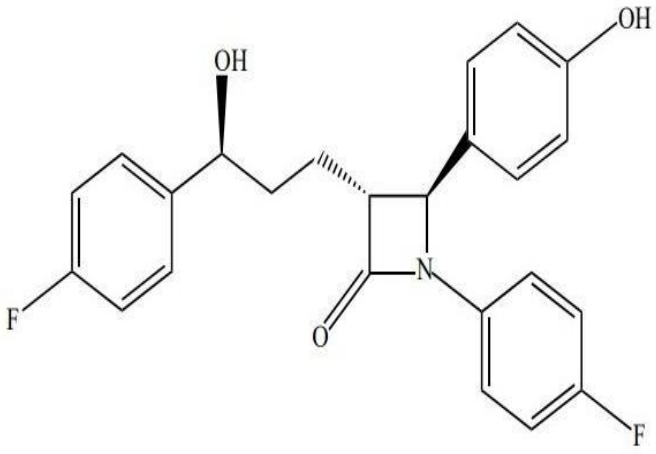
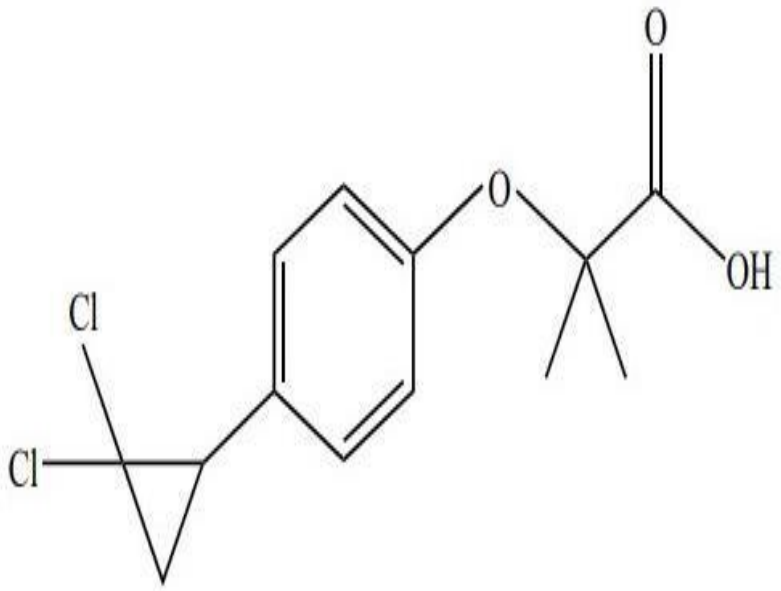


Fig 4: Chemical structure of Ezetimibe.

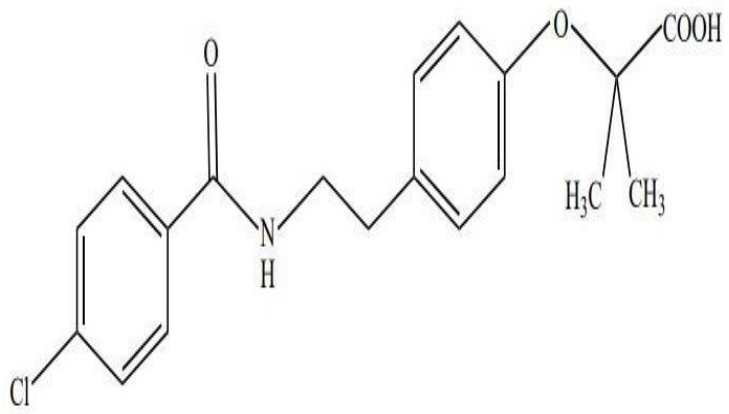
1.3. Antilipemic agents:

1.3.1. Fibrates:

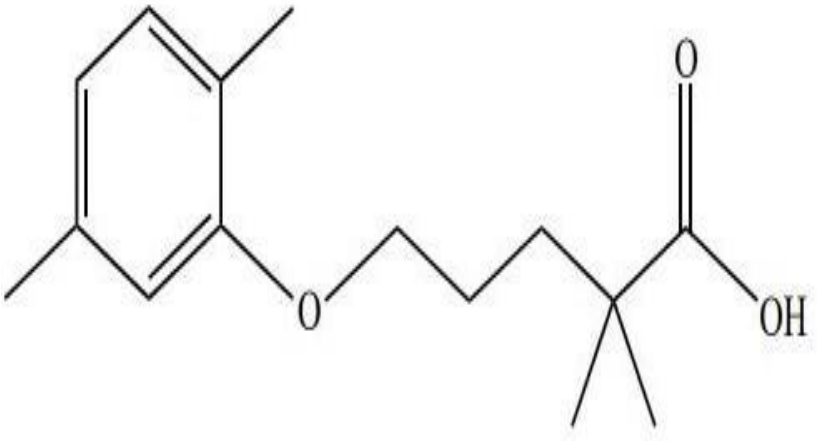
Fibrates, which are derived from fibric acid, have been used for over 40 years to treat lipid problems. The fibrate class of medications now on the market consists of ciprofibrate, bezafibrate, gemfibrozil, and fenofibrate (Okopień B et al.,2018). Fibrates are frequently used to treat hypertriglyceridemia and atherogenic dyslipidaemia. These medications, which are fibric acid derivatives, work primarily by stimulating intracellular PPARs alpha, or peroxisome proliferator-activated receptors. Intracellular/intranuclear receptors with DNA-binding capabilities are called PPARs. The kind of receptor and the ligand determine the site-specific binding. PPAs come in various subtypes: The liver, muscles, and kidneys express alpha receptors, which are generally associated with enhanced lipid metabolism; adipocytes and the liver express gamma receptors in large quantities, which when activated, lower insulin resistance; and lastly, beta/delta receptors, which are engaged in controlling fat metabolism and obesity (Okopień B et al.,2018). The non-hepatic peripheral tissues receive their cholesterol from the liver through LDL, and the excess cholesterol that is not eliminated from these tissues is carried to the liver by HDL where it is degraded and excreted as bile. The reverse cholesterol transport is the term used to describe the latter process. The mechanism of action of the fibrates is thought to involve certain transporter proteins, transcription factors (such PPAR alfa, LXR, etc.), and enzymes (CYP7A1, CEPT, etc.) that are crucial to the reverse lipid transport. The hepatocytes' activation of PPARs, numerous proteins and enzymes linked to fat metabolism are expressed differently (Prasad A et al.,2019). Fibrates influence the metabolism of fatty acids and lipoproteins in the liver, muscle, skeletal and cardiac systems, and kidney by binding and activating PPARα and controlling gene expression. Activated PPARα affects the apoprotein lipase, ATP binding cassette transporter A1, cholesterol ester transfer protein, scavenger receptor class B-type 1, apoprotein (Apo)-A2, Apo-A1, ApoC-3, lipoprotein lipase, and factors primarily influencing HDL and VLDL nutrition. Increased HDL-C concentrations, a more significant TG level reduction, and a somewhat lower LDL-C concentration are the results of fibrate therapy. Additionally, fibrates help avoid the hypertriglyceridemia linked to pancreatitis (Shipman KE et al.,2016). The chemical structures of antilipimic drugs are depicted in figure 5.



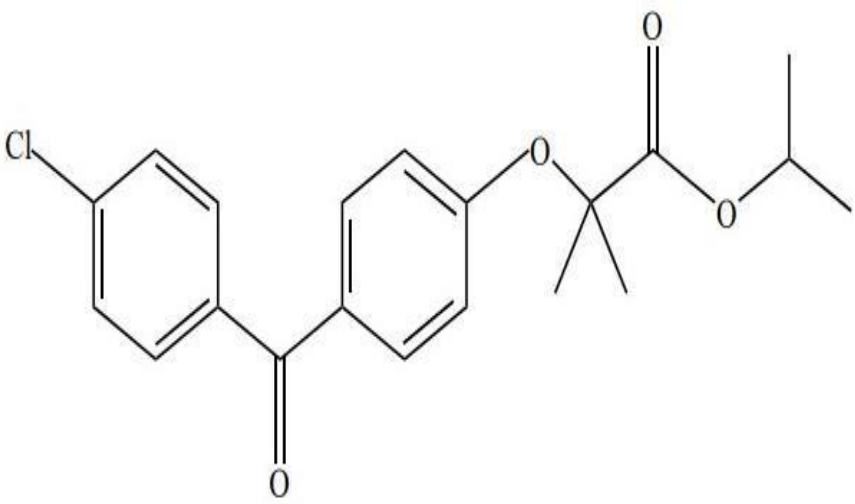
Ciprofibrate



Bezafibrate



Gemfibrozil



Fenofibrate

Fig 5: Chemcial structures of antilipimic drugs.

1.4. PCSK9 Inhibitors:

An enzyme called proprotein convertase subtilisin/kexin type 9 (PCSK9) is crucial to the metabolism of lipoproteins. PCSK9 belongs to the proprotein convertase family and in the liver is secreted. It is an inactive precursor enzyme that has three residues necessary for catalysis (Dadu RT et al.,2014). PCSK9 is indicated in the colon, CNS, and kidney mesenchymal cells in addition to hepatocytes. Recombinant PCSK9 has been shown that investigating the effects of raising the expression of NPC1L1 and CD36 on human intestinal epithelial cells (Caco-2/15 cell line) to enhance cholesterol absorption in vitro, two proteins involved in intestinal cell absorption of cholesterol, as well as by increasing the expression of transporters of cholesterol and lowering cholesterol synthesis (by decreasing HMG-CoA reductase activity). It has been demonstrated that PCSK9 plays a part in triglyceride metabolism and accumulation in visceral adipose tissue. Additionally, it aids in controlling enterocyte cholesterol homeostasis and stimulates chylomicron secretion (Chaudhary R et al.,2017). The serine protease PCSK9 has 692 residues. It is made up of a catalytic domain, prodomain, and histidine-rich C-terminal domain. Prior to being secreted into the extracellular matrix, the PCSK9 zymogen autocatalytically cleaves between the pro and catalytic domains (Coppinger C et al.,2022). There are presently two PCSK9 inhibitors that are authorized for use: evolocumab and alirocumab. The two monoclonal antibodies (mAbs) are entirely human and function by binding free PCSK9 and preventing it from binding to the LDL receptor. Reduced free PCSK9 leads to increased LDL receptor recycling, increased hepatocyte surface LDL receptor density, and substantial decreases in circulating LDL-C, which is consistent with the process where proteins are broken down into short peptides and amino acids (Roth EM et al.,2018). PCSK9 controls how quickly the LDL receptor breaks down in response to the levels of lipids in a cell. An extracellular portion of the LDL receptor is bound by PCSK9. Apolipoprotein-B100, a ligand for the LDL receptor, and a structural protein of LDL bind at a specific site on the LDL receptor. Following internalization into the hepatocyte, the LDL receptor is transported to a lysosome, where it may undergo degradation or be recycled back to the liver cell surface. The LDL receptor is vulnerable to enzymatic degradation because PCSK9 keeps the receptor from adopting a closed shape. Therefore, LDL receptors that do not have PCSK9 attached to they have a higher probability of being recycled back to the cell surface (Page MM et al., 2016).

1.5. ANGPTL 3 Inhibitors:

The liver produces the released protein ANGPTL3. Expression of it raises plasma levels of LDL-C, HDL-C, and TGs Antibodies and antisense oligonucleotides targeting ANGPTL3 are being tested in ongoing clinical trials; these findings could result in the creation of novel therapeutic medications for the management of high cholesterol levels and, consequently, a reduction in the incidence of CAD (Geladari E et al.,2019). The family of secreted glycoproteins known as angiopoietin-like proteins (ANGPTL) (ANGPTL1–8) bears a strong resemblance to angiopoietins, which are involved in the physiology of angiogenesis. Specifically, the high sequence homology ANGPTL3-4-8 model is linked to the inhibition of endothelial lipase (EL) and LPL in different tissues. The illness known as familial mixed hypolipidemia (FCH), which is brought on by mutations that cause ANGPTL3 to lose its function (Kosmas CE et al.,2022). Members 1 through 8 of the angiopoietin family, which vary in tissue expression and regulation, make up the angiopoietin-like proteins (ANGPTLs) protein family. Each one is made up of a linker region, a fibrinogen-like domain (FLD) at the carboxyl's C-terminus, a coiled-coil domain (CCD), and a common domain at the amino terminus (N-terminal). The primary roles of ANGPTL4, ANGPTL8, and ANGPTL3 in lipoprotein metabolism are in the metabolism of TGs, which are rich lipoproteins like chylomicrons and VLDL. They accomplish this by blocking the actions of LPL, LDL, and VLDL, which is

facilitated by endothelial lipase suppression (Sosnowska B et al.,2022). Angptl3 inhibits LPL activity, which raises circulating TG levels (Zhang R et al.,2016). The components of ANGPTL4 and ANGPTL3 are a signal peptide, a fibrinogen-like domain at the C-terminal, and an N-terminal tract with coiled-coil domains. It has been demonstrated that LPL activity is inhibited by both the full-length ANGPTL3 and ANGPTL4 and their N-terminal segments.

The LPL-inhibiting activity of ANGPTL3 and ANGPTL4 was completely eliminated upon deletion of their N-terminal regions (Lee EC et al.,2009). A head-to-head examination of ANGPTL4 and ANGPTL3 made it abundantly evident that while they both increase plasma TG levels and decrease LPL activity, their regulation by nuclear receptors differs. Specifically, ANGPTL4 expression is stimulated in several organs, such as the skeletal muscle and heart, while LPL catalyses the hydrolysis of lipoproteins in circulation to release energy. Repression of LPL activity is the method by which ANGPTL4 overexpression in the heart consistently lowers the utilization of lipoprotein-derived FFA in cardiac tissue (Ruscica M et al.,2020).

Natural Product for controlling Hyperlipidaemia:

Natural products (NPs) are a broad class of heterogeneous chemical substances with a broad range of biological activities that have been applied in a multitude of fields, most notably agriculture, veterinary, and human medicine. They come from marine animals, plants, fungi, and microbes (Yu Y et al.,2022). Among the main causes of risk for the event and seriousness of coronary heart disease is hyperlipidaemia. It is thought that lipid problems linked to hyperlipidaemia are the root cause of atherosclerotic cardiovascular disease. Natural goods andtheir potential to preserve and enhance health and wellness are subjects of increasing attention.Numerous natural products have been demonstrated to be beneficial in reducing the levels of plasma cholesterol and promoting safety profile; the cholesterol-lowering impact of dietary plants has been thoroughly investigated (El-Tantawy WH et al.,2019). In traditional medicine,many treatments are employed for hyperlipidaemia, with medicinal plants playing a crucial role in this process. Food Fibers, sterols, Vitamins, flavonoids, and other antioxidant compounds can lower cholesterol, inhibit LDL oxidation, eliminate oxygen free radicals, and potentially ameliorate metabolic problems and impact the body's defences to treat this illness of the body, according to current studies on dietary supplements and medicinal plants used in ancient medicine (Bahmani M et al., 2015).

Berberine:

Separated from the roots, bark, rhizome, and stems of plants belonging to the genus Berberis, as well as from plants like Hydrastis canadensis (goldenseal) and Coptis chinensis (huanglian in ancient Chinese medicine), berberine is an isoquinolone alkaloid, Chinese traditional medicine has been using berberine for thousands of years. It is believed to enhance the expression of LDL receptors (LDLR) on hepatocytes by stabilizing LDLR mRNA and decrease the production of proprotein convertase substilisin/kexin type 9 (PCSK9) by accelerating the breakdown of hepatocyte nuclear factor 1a (HNF1a) and decreasing PCSK9 mRNA transcription (Koppen LM et al.,2017; Ye Y et al.,2021). Berberine's effects on liver gene expression related to lipoprotein receptors, apolipoproteins, and 3-hydroxy-3-methyl-glutaryl- CoA reductase (HMGR). In contrast to statins, berberine promotes the posttranscriptional expression of the LDLR gene in hepatocytes through stabilization of its mRNA (Kong WJ et al.,2008). To control lipid levels, BBR can coordinate several important targets of lipid metabolism and intestinal flora in the liver and gut. Additionally, it can directly affect blood vessels to treat and prevent AS by reducing endothelial dysfunction, preventing the production of macrophage foam cells, and controlling the migration and

proliferation of vascular smooth muscle cells (VSMCs). Hepatic metabolism mostly converts BBR into thalifendine, jatrorrhizine, demethyleneberberine, and berberrubine. (Cai Y et al.,2021).

Evodiamine:

Evodiae fructus contains the naturally occurring indole alkaloid evodiamine as one of its primary bioactive components (Yu H et al.,2013). Evodiamine, whose chemical formula is C19H17N3O, has a quinazolino carboline skeleton and is present in a range of herbs, including Euonymus europaeus and Evodia rutaecarpa (Sun Q et al.,2020). Evodiamine, a naturally occurring alkaloid, improves the outflow of cholesterol from cultured THP-1-derived macrophages. Evodiamine (20 and 10 mg/kg) administered intra-gastrically for eight weeks significantly improved metabolic lipid profiles by lowering plasma levels of LDL-C, TC, and TG. Additionally, evodiamine dramatically reduced the amount of total bile acids (TBA) and hepatic lipid buildup. Mechanistically, evodiamine up- controlled by the activity of PPARγ, the peroxisome proliferator-activated receptor in the liver and enhanced the mRNA and protein expression of ATP-binding cassette transporter G1 (ABCG1) (Hou X et al.,2021;68 Zha Y et al.,2023). Compared to enriched samples of evodiamine in physical mixture hard capsules, evodiamine in hard capsules has a higher absorption rate (Yu H et al.,2013).

Vine tea:

Herbal teas, such as vine tea (Ampelopsis grossedentata), are widely drunk due to their pleasant taste and ability to promote health. The prospective uses of vine tea and its primary bioactive ingredient, dihydromyricetin, in the fields of food, materials, and medicinal sciences have drawn interest (Carneiro RC et al.,2021). It is shown that the primary bioactive component is flavonoids. In addition to the two most prevalent flavonoids in vine tea, DMY and myricetin, it also includes other common flavonoids as quercetin, kaempferol, hesperidin, apigenin, and rutin (Zhang Q et al.,2021). VT decreased total lipid and glucose levels in the blood (Wan W et al.,2017; Wu J et al.,2022). The three primary species Nekemias cantonensis, Nekemias megalophylla, and Nekemias grossedentata have been employed as the vine tea's origin. All three of these species have woody vines with oblong or oval leaflets, bipinnate compound leaves, and cylindrical twigs. Nekemias grossedentata and Nekemias cantonensis have numerous physical similarities, such as bifurcated tendrils and pronounced longitudinal ridgeson their branches (Zeng T et al., 2023).

Garlic:

For thousands of years, people have utilized garlic, or Allium sativum, for therapeutic purposes. Its therapeutic use dates back around 5,000 years to Sanskrit sources, while Chinese medicine has been using it for at least 3,000 years (Milner JA et al.,1996; Tattelman E et al.,2005). The garlic plant's root bulb is utilized in medicine. It can be utilized as steam-distilled oil, dried, or fresh. Compounds containing sulphur are abundant in garlic. Garlic's impact on cholesterol levels has been the subject of numerous randomized research investigations (Tattelman E et al.,2005). The unique flavour and bioactive qualities of dry bulbs are attributed to the abundance of volatile chemicals found in garlic. Together with antioxidants, minerals, and vitamins, there is also a significant concentration of non-volatile substances with well-known pharmacological and therapeutic qualities (Khokar KM et al.,2023). Allicin is produced when crushed garlic activates alliinase enzymes, which prevent cholesterol from being produced (Saeed MW et al.,2021). HDL maturation and the reverse transport of lipid are facilitated by the process of ester of free lipid, which is catalysed by lecithin cholesterol acyltransferase (LCAT). The primary enzyme in plasma that catalyses the process of ester of lipoproteins rich in triglycerides is called lipoprotein lipase, or LPL. Triglyceride-rich lipoprotein residues can

be taken up and eliminated by the liver with the help of hepatic lipase (HL). These enzymes' heightened activity will lower blood cholesterol levels by promoting lipid metabolism and transformation. Garlic oil has the potential to lower TC and TG levels in hyperlipidemia, most likely through enhancing lipoprotein metabolism and conversion, blocking intestinal cholesterol absorption, delaying hepatic cholesterol synthesis, and hastening the breakdown of TG (Li M et al.,2022).

Curcumin:

Curcuma longa, a rhizomatous herbal plant native to India belonging to the Zingiberaceae family, is well-suited for its medicinal properties. The active ingredients in turmeric known ascurcuminoids may be responsible for its therapeutic effects. The terms "curcuminoids" refer to curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC). The dried, cleaned, cooked, and shiny rhizomes of Curcuma longa are known as turmeric (Rathore S et al.,2020). The primary component of the rhizome is Curcuma longa., an emulsifying molecule with a low molecular weight that is easily able to cross cellular membranes. Based on its molecular makeup, it is classified as a polyphenol. Curcumin's capacity to bind with diverse proteins enables targeted regulation of numerous cellular signalling pathways linked to a range of chronic illnesses (80 Urošević M et al.,2022). Curcumin reduced blood levels of TG, TC, LDL-C, HDL-C, AST, and ALT while fasting (Xia ZH et al.,2020). Curcumin is one possible nutraceutical with lipid-modulating and cell signalling characteristics linked to dyslipidaemia. In particular, new research indicates that curcumin may enhance lipid metabolism and guard against cardiovascular problems brought on by dyslipidemia through a number of mechanisms (Yaribeygi H et al.,2024). After using 180 mg/d of curcumin capsules for six months, there was a noticeable drop in TG levels. Furthermore, elevated activity of serum lipoprotein esterase (LPL), a crucial lipid metabolism-related enzyme, will encourage the hydrolysis of TGs (Zeng Y et al.,2024). Curcumin supplementation exhibited anti-atherosclerotic action by downregulating the expressions of MMP (1, 2 and 9), P-selectin, vascular cell adhesion molecule-1, intracellular adhesion molecule-1, and monocyte chemotactic protein-1. It reduced serum lipid levels and oxidized LDL (Patel SS et al.,2020). It also inhibits TGF-β to prevent cardiac fibrosis (Jyothi MV et al.,2024).

Fenugreek:

The large variety of minerals and bioactive materials found in fenugreek are essential for enhancing the well-being and efficiency of biological systems. Belonging to the Fabaceae family, fenugreek (Trigonella foenum-graecum L.) has been a valuable spice since ancient times. Due to its abundance of phytochemicals, carbohydrates, alkaloid, steroidal saponins, minerals, and amino acid, fenugreek has a variety of uses in medicine, nutrition, nutraceuticals, and therapy (Syed QA et al.,2020; Sarwar S et al.,2020; Sun W et al.,2021). The seeds and leaves have significant therapeutic qualities and are known to lower blood cholesterol (anti-hypercholesterolemic) and blood glucose (anti-diabetic) in both human subjects. Fenugreek has long been used in medicine, both in its leaves and seeds (Hilles AR et al.,2021). These days, effective medications are used to treat hyperlipidaemia, which can considerably lower blood triglyceride (TG) and cholesterol levels; however, due to their high cost and severe side effects, these chemical medications are not always the best option for individuals. Natural products are a rich source of different antioxidants that can help fight against free radicals and prevent oxidative damage. Compared to their synthetic counterparts, natural products are also easier to find, less expensive, and have less side effects. Consumption of fenugreek led to a noteworthy decrease in TG, LDL, and TC (Heshmat-Ghahdarijani K et al.,2020). The table 1 summarizes the various Phyto constituents and their major pharmacological properties.

Table 1: Phyto constituents and their major pharmacological properties

S. No.	Natural Compounds	Major Properties	References
1	Berberine	Stabilize LDLR mRNA to increase the expression of LDL receptors (LDLR) on hepatocytes. Down-regulation of the expressions of intestinal NPC1L1, ACAT2 and ApoB48.	(DoggrellSA et al.,2005; Xiao HB et al.,2012)
2	Evodiamine	Evodiamine, a naturally occurring alkaloid, improves the outflow ofcholesterol from cultured THP-1-derivedmacrophages. It also prevents the absorption of cholesterol in the intestine.	(Zhang Y et al.,2018; Yu Y et al.,2018)
3	Vine Tea	Vine tea decreased total cholesterol and glucose levels in the blood. alters the composition of metabolic intermediates related to the TCA cycle, purine metabolism, amino acid metabolism, and glucose metabolism (including gluconeogenesis and glycolysis).	(Wan W et al.,2017; Zhou X etal.,2022)
4	Garlic	Garlic oil has the potential to lower TC and TG levels in hyperlipidaemia, most likely through enhancing lipoprotein metabolism and conversion, blocking intestinal cholesterol absorption, delaying hepatic cholesterol synthesis, and hastening the breakdown of TG	(Zeng T et al.,2013; Jain AK et al.,1993)
5	Curcumin	Curcumin's capacity to bind with diverse proteins enables targeted regulation of numerous cellular signalling pathwayslinked to a range of chronic illnesses. It reduced serum lipid levels and oxidized LDL	(Sahebkar Aet al.,2014; Saeedi F et al.,2022)
6	Fenugreek	The leaves and seed have significant therapeutic qualities and are known to lower blood cholesterol (anti-hypercholesterolemic) and blood glucose (anti-diabetic)	(AskarpourM et al.,2020)

2. CONCLUSION

Hyperlipidaemia is a disease which not only requires potent therapeutic agents, but strict diet control from the patient's resolve. Because of strong general belief that synthetically derived medicines cause adverse effect, which they often do, either due to misuse or abuse of the medicine or seldom due to patient's ill tolerability towards the drug, patients switch to

relatively less toxic alternative of herbal derived medication, which are also less potent at times. However, both synthetically derived and herbal derived medicines have proven efficacy and helps the patient to achieve quality of life. In this review, we summarized both kind of agents along with their mechanisms of action and pathophysiology of the disease to better understand it, which will help scholars to identify novel therapeutic targets, in order to develop new therapeutic agents.

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