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Hyperlipidemia and its treatment

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ABSTRACT: Hyperlipidemia is characterised by elevated concentrations of one or more plasma lipids, including low-density and Exceptionally low concentration lipoproteins, phospholipids, triglycerides, cholesterol and increasedelevated high-density lipoprotein values. The increase in lipoprotein levels is a prominent hazard component associated withheart conditions. Mainly two forms of hyperlipidemia exist. Primary hyperlipidemia, which is typically hereditary and results from genetic abnormalities, is the initial form. Secondary hyperlipidemia is an alternative form that arises from predisposing factors such as chronic renal failure, obesity, thyroid dysfunction, intoxication, or hypothyroidism. As a second-line treatment, PCSK9 inhibitors are presently administered to patients whose lipid levels are unregulated despite treatment with statins or statin combinations. Evinacumab and other ANGPTL3 inhibitors have received clearance from the FDA and the EMA to treat familial hypercholesterolemia. This article serves as a concise overview of novel agents presently in use or under development for the purpose of lowering lipid levels. The primary objective of this research endeavour is to ascertain potential therapeutic targets for hyperlipidemia and establish a correlation between the clinical presentation of hyperlipidemia and the most recent advancements in this rapidly expanding discipline. Additionally, the role of nutraceuticals in hyperlipidemia treatment is discussed.

Keywords: Hyperlipidemia, lipoprotein, chylomicrons, PCSK9 inhibitors, ANGPTL3 inhibitors, statins, ezetimibe, evinacumab.

I. INTRODUCTION:

Disruptions in blood lipid levels are a defining feature of dyslipidemia. Hyperlipidemia (HL) is the most prevalent form of dyslipidemia. LDL-C, TG, and total cholesterol (TC) levels increased while HDL values decreased in subsequent blood tests[1]. It significantly affects atherosclerosis and is believed to be an important risk indicator for cardiovascular diseases[2]. The following conditions increase the risk of diabetes progression: coronary heart disease, myocardial infarction, cerebrovascular illnesses, and stroke[3]. The liver is the principal source of the increased blood cholesterin levels. Over 80% of the body's entire production is carried out by the liver. Although fish, pork, and eggs are rich in cholesterol, other foods also comprise this dietary component[4,5].

Atherosclerosis' principal clinical manifestation, coronary artery disease (CAD), continues to be the foremost cause of mortality and morbidity for individuals of all genders on a global scale [6]. Nevertheless, atherosclerosis gives rise to peripheral artery disease, cerebrovascular illness, and ischemic heart disease[7]. Additionally, it is critical to bear in mind that endovascular therapies are indispensable in the management of atherosclerotic diseases. Despite this, their effectiveness is constrained by restenosis, thereby necessitating recurrent interventions.

Table 1: Ideal cholesterol readingsin human body[10].

Lipoproteins	Normal range	Risk condition
LOW DENSITY LIPOPROTEIN (LDL)	Under 100 mg/dl	160 and high
HIGH DENSITY LIPOPROTEIN (HDL)	>60 mg/dl	Below 40-50 mg/dl
TRIGLYCERIDES	<150 mg/dl	More than 200 mg/dl
VERY LOW-DENSITY LIPOPROTEIN (VLDL)	2 & 30 mg/dl	More than 30 mg/dl
TOTAL CHOLESTROL(TC)	Under 200 mg/dl	240 mg/dl and above

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LIPOPROTEIN CLASSIFICATION:

Large molecules comprised of proteins and lipids are called lipoproteins. They are employed in the process of making proteins and lipids water-soluble. Different kinds of molecules make up lipids. Lipids and other types of molecules make up a portion of these molecules.

1. Low-density lipoproteins (LDL).
2.Intermediate-density lipoproteins (IDL)
3. Very low-density lipoproteins (VLDL)
4. High-density lipoproteins (HDL)
5. Chylomicrons (CM)[11]

1. Chylomicrons (CM): Large chylomicrons serve as carriers for dietary lipids as they travel from the intestinal lumen to the circulation, where they undergo degradation into IDL, which are denser and more compactVLDL particles aren't manufactured solely in the liver. While the liver is the primary production site, the intestine also contributes a smaller amount of VLDL. These lipoprotein packages act as delivery trucks for transporting fats throughout the body. They come equipped with various proteins called apolipoproteins, such as A-I, A-II, and C-III, which help them ferry their cargo and interact with cells[12].

2. VLDL (Very low-density lipoproteins): It consist of chylomicrons in greater abundance than triglycerides, are smaller particles secreted by the liver. A sterol-containing low-density lipoprotein that travels from the tissues and organs of the body to the liver. These are formed through the combination of triglycerides and cholesterol[13]

3. High-Density Lipoproteins (HDL): In popular culture, they are often referred to as "good cholesterol". After being synthesized there, they are returned to the liver to break down lipids, including cholesterol. HDL also plays an important role in preventing atherosclerosis[14].

4. Intermediate Low-Density Lipoproteins (ILDL): Lipase enzymes in adipose tissue and muscle capillaries lyse VLDL particles, resulting in intermediate-density lipoprotein.

Hyperlipidemia classification:

1. Considering the type of lipid:

Hyper-triglyceridemia: - Triglycerides make up a large portion of its composition.

Hyper-cholesterolemia: - Cholesterol levels are high in this.

2. Based on the causative element:

Primary hyperlipidaemia: - The factors that lead to the development of hyperlipidemia can be used to distinguish between primary and secondary cases[15]. Fredrickson distinguished five types of familial hyperlipidaemia based on lipoprotein patterns obtained by ultracentrifugation or electrophoresis[16] .

- **Type I:** High cholesterol and triglycerides
- **Type II:** High cholesterol, normal triglycerides
- **Type III:** Elevated triglycerides and cholesterol
- **Type IV:** Increased risk factors for atherosclerosis (artery hardening) including high triglycerides, high uric acid, and potentially abnormal cholesterol levels
- **Type V:** Primarily high triglycerides[17].

Acquired (Secondary) hyperlipidemia: Secondary dyslipoproteinemias, or acquired hyperlipidemias, are disorders resulting from changes in the metabolism of lipoproteins and plasma lipid[18].

Risk factors of hyperlipidemia:

Exogenous	**ketogenic diets, alcohol, beta blockers, corticosteroids, anti-retrovirals, obesity, isotretinoin, thiazide diuretics, anticonvulsants, anabolic steroids, and estrogen**
Endocrine	Cushing syndrome, hypothyrodism, hypopituitarism, diabetes mellitus, and lipodystrophy
Gastrointestinal	Pancreatitis, Hepatitis, Cirrhosis, and Cholestasis
Renal	Syndrome Nephrotic, failure of the kidneys, syndrome of hemolysis and urea, Nervous system anorexia
Storage diseases	storing cysteine, illnesses related to glycogen storage, Tay-Sachs disease, Gaucher disease, Alternating periodic porphyria and Neumann-Pick disease
other factors	nervosa anorexia, starvation, Systemic lupus erythematous, progeria, and idiopathic hypercalcemia

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Lipid metabolism:

Lipid metabolism affects a wide range of physiological processes, including as hormone regulation, energy storage, nerve impulse transmission, and the transport of fat-soluble nutrients.. Lipids provide 9 kcal of energy, which is a high caloric density when compared to protein and carbs. Moreover, lipids allow the body to store 100,000 kcal of energy, which allows it to function for 30 to 40 days without eating as long as it drinks enough water. An essential organ in the process of metabolizing fats is the liver[19]. Biochemical lipids are stored in adipose tissue, which is a type of connective tissue found in cells throughout the body. Lipids provide structural integrity to vital human organs, including the spleen, liver, heart, and kidneys[20].

The intestinal lumen absorbs almost all dietary lipids, which are then moved to the intestinal lymph. Encased in chylomicrons within the intestinal lymph. Once these lipoproteins reach the circulation, they undergo hydrolysis by endothelial lipoprotein lipase. This enzyme catalyses the conversion of triglyceride into non-esterified fatty acids and glycerol. Subsequently, theleftover chylomicrons are absorbed by the liver, which then mixes them with cholesterol, cholesteryl esters, and ApoB100 to produce VLDL.Hepatic lipase and lipoprotein lipase, two enzymes, convert VLDL into IDL as soon as it enters the bloodstream. During this process, apolipoproteins and phospholipids transform back into HDL. More apolipoproteins are lost when hepatic lipase hydrolyzes IDL, converting it to LDL[21].

The liver produces these HDLs at first, then releases them into the bloodstream.Through the action of LCAT, HDL cholesterol is esterified to cholesteryl ester in the circulation. After esterification, it travels to chylomicrons and VLDL and subsequently returns to the liver through the LDL receptor. CETP enables the movement of cholesterol ester to Low Density Lipoprotein particles, which are then acquired by endocytosis by LDL receptors. Choleryl esters are finally broken down into cholesterol, which is subsequently excreted from the body as bile acid[22].

Pathophysiology of hyperlipidemia:

Due to the increased mortality and morbidity associated with hyperlipidemia, scientists and researchers have conducted a vast number of studies in an effort to elucidate the disease's precise pathophysiology in greater depth. This is done so that active treatment and early disease detection can be implemented to prevent complications and enhance patient health. Based on current research and literature reviews, hyperlipidemia originates from endothelial damage in the blood vessels, which causes nitric oxide to be lost at the site of injury.Lipids build up in the endothelium wall's lowest layer as a result of this depletion, which also causes an inflammatory reaction in the region of the afflicted location. During this process, the lipids are consumed by macrophage cells, which then combine them with cholesterol to produce foam cells.Foam cell development will result in necrosis, apoptosis, and mitochondrial malfunction. Simultaneously, the smooth muscle cells encapsulate the foamy cells, thereby impeding their destruction and generating fibrotic plague. Conversely, platelet activity is stimulated by tissue factors, which leads to plague rupture and thrombosis[23]. Poisoning of the blood vessels can develop either abruptly, causing arterial obstruction, or gradually, leading to venous stenosis. In both mechanisms, lipid plague continues to be the primary cause of cardiovascular disease progression and patient health deterioration.Individuals diagnosed with hyperlipidemia may also encounter tendon dysfunction, namely in the patellar tendon, with cardiovascular illness. This phenomenon occurs due to the progressive accumulation of macrophages in tendon tissues caused by hyperlipidemia, which damages collagen fibres and substitutes lipid for collagen, ultimately leading to tendons that are less robust and more susceptible to injury[24].

Pharmacotherapy for Hyperlipidemia:

Drug treatment:

In primary prevention, lipid-lowering medication is initiated primarily on the basis of Low Density Lipoproteins levels of cholesterol and the anticipated danger of coronary heart disease events [25][26][27]. Drug treatment is advised in patients who have established atherosclerotic cardiovascular disease, diabetes mellitus, monogenic hyperlipidemia, and severe hyperlipidemia without undergoing a multifactorial risk assessment. Pregnancy and breastfeeding are both contraindicated periods for lipid modification therapies.

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Medications that reduce the level of serum lipoproteins:

Anti-hyperlipidemiamedications employ complementary mechanisms to address the issue of elevated serum lipids. Certain agents inhibit the synthesis of lipoprotein carriers that transport triglyceride and cholesterol, while others promote lipoprotein degradation. Others increase cholesterol excretion from the body directly or decrease cholesterol absorption.

Inhibitors of HMG-COA reductase

AGENTS OR DRUGS: rosuvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, and atorvastatin[28].

STATINS:

3-hydroxymethyl-glutaryl-CoA reductase is primarily inhibited in the liver by statins. This enzyme restricts the rate of cholesterol biosynthesis. Enhanced hepatic LDL receptor expression results from the subsequent reduction in intrahepatic cholesterol, which subsequently leads to a decline in circulating LDLc[29].Since they minimize the risk of the disease by around one-fifth for every one mmol/l decrease in LDL cholesterol, they are the most effective way to prevent cardiovascular disease (CVD) without influencing LDL cholesterol levels[30].

Therapeutic uses: These drugs effectively lower plasma cholesterol levels, regardless of the type of hyperlipidemia. Conversely, these drugs are less effective for those with homozygous familial hypercholesterolemia because they lack LDL receptors.Although cholesterol-lowering drugs provide protection, about 25% of patients still have coronary incidents while taking these meds. This raises the possibility that supplemental drugs, increased physical activity, or dietary adjustments are required.

Pharmacokinetics: When taken orally, pravastatin and fluvastatin are almost completely absorbed, but lovastatin and simvastatin are absorbed 30–50% of the time. The same holds true for pravastatin and fluvastatin; they do not need hydrolysis to their acid forms to be active, unlike lovastatin and simvastatin. Mainly the liver is affected by these drugs due to first-pass extraction. Even after being biotransformed, several of the chemicals retain some degree of action. Even while pee does its share of elimination, bile and faeces do the bulk of the heavy lifting. Their half-life ranges from one and a half to two hours. Several statin features are summarised in Figure 1.

Characteristics	Simvastatin	Atorvastatin	Pravastatin	lovastatin	Fluvastatin	Rosuvastatin
Serum LDL cholesterol reduction produced (%)	41	50	34	34	24	50
The percentage of serum triacylglycerol that was reduced	18	29	24	16	10	18
Increase in serum HDL cholesterol generated (%)	12	6	12	9	8	8
Plasma half-life (hr)	1-2	14	1-2	2	1-2	19
Interaction with the central nervous system	Yes	No	No	Yes	No	No
Renal excretion of the dosage absorbed (%)	13	2	20	10	<6	10

Figure 1: An overview of inhibitors that bind to 3-hydroxy-3-methylglutaryl coenzyme (HMG CoA)[31].

Adverse effects:

Liver:HMG CoA reductase inhibitors have been linked to biochemical abnormalities in liver function. Testing liver function and keeping an eye on blood transaminase levels are therefore recommended. Following discontinuation of drug treatment, these return to normal.. [Note: Drug buildup may be caused by hepatic insufficiency.]

Muscle: Myopathy and rhabdomyolysis, or the breakdown of muscle, are very rare occurrences.The most common causes of these occurrences were either specific medications such cyclosporine, erythromycin, niacin, or gemfibrozil,

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or patients with renal failure. The levels of plasma creatine kinase ought to be monitored often.
Drug interactions: Warfarin levels may also rise as a result of HMG CoA reductase inhibitors. It is crucial to regularly assess INR times as a result.
Contraindications: It is not advised to use these drugs while pregnant or nursing. Use of them is not advised for minors or teenagers[31].

Nicotinic acid derivative (niacin): Research has shown that the water-soluble B vitamin niacin may decrease cardiovascular morbidity and all-cause mortality; When treating hyperlipidemia, it was the first drug to decrease cholesterol. decreases total, LDL, and triglyceride cholesterol[32]. Niacin is either the primary or second choice for treating diabetic dyslipidemia and hypertriglyceridemia. However, dizziness, flushing of the skin, or itching are common side effects of niacin[33].

Niacin exerts its cholesterol-lowering effects through a two-pronged mechanism:

1. **Inhibition of lipolysis and free fatty acid mobilization:** Niacin impedes the breakdown of triglycerides, the main storage form of fat in the body. This translates to a decrease in circulating free fatty acids, which serve as precursors for LDL cholesterol synthesis within the liver.

2. **Suppression of hepatic VLDL and LDL production:** By limiting the availability of free fatty acid substrates, niacin reduces the liver's capacity to synthesize very-low-density lipoprotein (VLDL) particles. VLDL is a precursor to LDL cholesterol, so this reduction in VLDL production consequently leads to decreased LDL levels[34].

3. **Niacin treatment has been hampered by inadequate patient adherence:** Over three-quarters of patients experience severe skin erythema, pruritus, headache, and in certain cases, vertigo and abdominal distress, which are the most frequent adverse effects. Additionally, niacin elevates liver enzymes[35].

Fibric acid derivatives:
DRUGS: Fenofibrate, Gemfibrozil, Clofibrate, Benzafibrate, Ciprofibrate.

Antihyperlipidemic agents of this nature induce a substantial reduction in plasma triglyceride levels while only marginally affecting LDL sterol levels. Gradually, HDL cholesterol levels increase. The presence of fibrates increased plasma HDL-C concentration by approximately 20%, while fibrate-class medications has the potential to 50% lower plasma triglyceride levels[36].

Peroxisome proliferator-activated receptor-α (PPAR-α) activity in the hepatic tissue is the main way that fibrillates work [37]. Consequently, hepatic triglyceride output reduces, fatty acid β-oxidation in the liver increases, and lipoprotein lipase activity rises. Therefore, there is a net increase in the clearance of HDL, VLDL, and residual particles[38]. Although fibrates inhibit the synthesis of very low-density lipoproteins derived from the liver, they have no effect on the rate of chylomicron secretion. TG concentrations are significantly influenced by the presence or absence of a functional lipoprotein lipase (LPL) pathway. In monogenic chylomicronemias, coagulants are ineffective due to the absence or severe impairment of LPL activity[39].

Ezetimibe:

Ezetimibe selectively blocks the absorption of cholesterol. Because of its creation and formulation, The treatment of hypercholesterolemia has been greatly improved by ezetimibe, the first drug of a class of drugs that blocks the intestinal absorption of cholesterol and phytosterols. Small intestine cholesterol absorption is restricted, even when the fat-soluble vitamin's plasma concentrations remain unchanged[45].In the upper small intestine, ezetimibe, the only known inhibitor of cholesterol absorption, decreases LDL-C levels by preventing Niemann-Pick C1-like protein 1[46]. By incorporating ezetimibe into the treatment regimen, an additional 21% to 27% reduction in LDL-C is achieved[47]. Furthermore, this drug is characterised by its commendable safety record and comparatively affordable price.
Mechanism of action: Ezetimibe works by essentially preventing the absorption of cholesterol from bile and the brush border of the villi in the small intestine. As a consequence, there is a decrease in the quantity of cholesterol being carried from the colon to the liver, as well as a drop in the cholesterol levels seen in liver cells. Furthermore, it improves the removal of cholesterol from the bloodstream[48,49].
Adverse effect: Although ezetimibeis is generally well tolerated, dizziness, abdominal pain, and diarrhoea are the most frequent adverse effects.

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Ezetimibe has been observed to induce increases in liver function assays, specifically in the levels of alanine transaminase and aspartate transaminase[50].

PCSK9 Inhibitors:

Volanesorsen inhibits ANGPTL3 expression, whereas inclisiran inhibits PCSK9 expression. A portion of these products has received FDA clearance.Even though BA is authorized to treat patients with existing atherosclerotic cardiovascular disease or heterozygous FH, it is unable to diminish LDL-C levels in this instance as intended. The inflammatory marker C-reactive protein (CRP), which is measured by oral administration of BA, is only little affected[40]. Several clinical trials have shown promise for lowering bad cholesterol levels with a new family of lipid-lowering medications called protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. The lowering of LDL receptors is significantly aided by PCSK9. The liver cells, or hepatocytes, help filter out LDL cholesterol from the blood because they have receptors for it. The PCSK9 protein attaches to the LDL receptor and initiates the receptor's degradation process, which raises LDL cholesterol levels. Antibodies such as evolocumab or alirocumab, which are monoclonal antibodies, have the ability to stop PCSK9 from binding to LDL receptors. This process increases LDL receptor recycling and improves LDL cholesterol absorption while indirectly reducing circulation LDL cholesterol levels[41].Due to higher levels of immunogenicity and injection site responses than the previous two antibodies, bonocizumab, the third monoclonal antibody in its class, had its clinical trials terminated[42]. Once every two weeks, monoclonal antibodies, such as evolocumab and alirocumab, are administered subcutaneously as part of the current treatment. The recommended dosage ranges from seventy-five milligrams to three hundred milligrams, depending on the initial levels of low-density lipoprotein (LDL) cholesterol. I should emphasize that four to six weeks after the commencement of therapy, steady concentrations of evolocumab and alirocumab were reached [43, 44].

ANGPTL3 Inhibitors:

Lipidology-related pharmacological research is currently concentrating ona achievable new target for the management of dyslipidemia is ANGPTL3. To target ANGPTL3, many research groups have used varied methods, such as antisense oligonucleotides and monoclonal antibodies. The enzymes endothelial lipase (EL) and lipoprotein lipase (LPL) are inhibited in their activity by ANGPTL3[51]. Because both LPL and EL are required for the formation of triglycerides and LDL cholesterol, inhibiting the ANGPTL3 protein results in their disinhibition, which decreases levels of these substances in the blood[52,53].

The FDA and the European Medicines Agency approved evinacumab, an ANGPTL3 monoclonal antibody, to treat familial hypercholesterolemia, marking the beginning of the development of angiopTPL3 inhibitors. A 15 mg/kg body weight dose given intravenously every four weeks is the recommended dosage. A Phase III clinical trial determined evinacumab's efficacy by the fact that blood LDL cholesterol levels decreased by 47.1% in individuals treated with the medicine, whereas they increased by 1.9% in patients given a placebo. Upper respiratory tract infections and influenza-like symptoms make up the bulk of evinacumab's side effects. Evanacumab, like other injectable medications, may cause severe allergic responses, including anaphylaxis [54].

Agonists for the peroxisome proliferation activated receptor (PPAR):

PPARs: Orchestrating Cellular Function

Peroxisome proliferator-activated receptors (PPARs) are a subfamily of nuclear receptors, belonging to the larger superfamily with over 48 members. These ligand-dependent transcription factors play a critical role in regulating gene expression and influence a diverse array of cellular processes [55].

Upon ligand binding, PPARs heterodimerize with the retinoid X receptor (RXR) and subsequently bind to specific DNA sequences known as peroxisome proliferator response elements (PPREs) located in the promoter regions of target genes [57]. This complex then modulates the transcription of genes involved in:

- **Maintaining cellular homeostasis**
- **Directing morphogenesis (cell development)**
- **Regulating lipid and glucose metabolism**
- **Controlling cell proliferation and differentiation**

By regulating these essential processes, PPARs exert a profound influence on overall health and disease development.

Three mammalian PPARs have been found; they are referred to as PPAR-α, -ω, and β-. Target gene expression is regulated by the binding of PPAR response elements to DNA sequences.

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PPAR-α activation controls the expression of many genes that control lipoprotein content, reduce inflammation, and promote free fatty acid oxidation [58].

PPAR- and PPAR-ligands prevent atherosclerosis by preventing macrophages from forming foam cells. Research has demonstrated that PPAR agonists exhibit promising potential as agents with both antihyperlipidemic and antihyperglycemic effects [59].

New possible targets for therapy:

ACAT:(Acyl-CoA cholesterol acyl transferase inhibitors)

ACAT is the enzymatic catalyst responsible for facilitating the choline esterification process from intracellular cholesterol. Two isomers of ACAT are designated ACAT1 and ACAT2.

One of the factors that contributes to the development of atherosclerosis is the production of foam cells, which is assisted by the attraction of monocytes that have been converted into foam cells in the artery wall by oxidized LDL. As a result, it is possible that ACAT-1 inhibitors may have an antiatherogenic effect, and that ACAT-2 inhibitors will have a major impact on lowering intestinal cholesterol absorption [60]. Furthermore, the significance of ACAT stems from its pivotal role in the assembly and secretion of lipoproteins that incorporate apolipoprotein B in the intestines and liver[61].

Avasimibe and Eflucimibe inhibit ACAT to lower plasma cholesterol levels and stop atherosclerosis from progressing.[62,63].

CETP inhibitors:(Cholesteryl ester transfer protein inhibitors)

CETP mediates proatherogenic action by inducing reverse cholesterol transfer. It helps the liver convert cholesteryl ester from proatherogenic lipoproteins, such as VLDL and LDL, to anti-atherogenic HDLs that include apolipoprotein B. Furthermore, most research has shown that CETP inhibition inhibits the development of atherosclerosis[64].

Phase III clinical trials have shown that anacetrapib and dacletrapib belong to a new class of pharmaceuticals. Without changing LDL levels, dacetrapib raised HDL cholesterol levels by 31% and reduced CETP activity by 50%[65].

MTP inhibitors: (Microsomal triglyceride transfer protein inhibitors)

Apart from controlling the production of cholesterol esters and moving neutral lipids across membrane vesicles, MTP contributes to the synthesis of CD1 and antigen-presenting molecules. As a result, when MTP is inhibited, plasma triglycerides, LDL cholesterol, and VLDL cholesterol are considerably decreased. These findings suggest that MTP inhibitors could be useful in reducing atherogenic lipoprotein levels[66].

Squalene-synthase inhibitors:

The initial stage of the sterol synthesis process involves catalysis by SqS., including cholesterol, and it catalyses the conversion of farnesyl pyrophosphate to squalene. When it comes to creating new medications to treat hyperlipoproteinemia, pharmacologists see SqS inhibitors as very promising lead molecules[67]. A possible SqS inhibitor, BMS-188,494, was shown to reduce the levels of plasma cholesterol in rats after oral administration, per the report [68].

ATP citrate lyase inhibitors:

ATP citrate lyase (ACL) is the primary enzyme that produces cytosolicacetyl-CoA and oxaloacetate. Cytosolicacetyl-CoA and oxaloacetate synthesis are critical steps in the production of fatty acids and cholesterol. This is why treating dyslipidemia by inhibiting ACL is an interesting strategy[69]. BMS-303141, the best inhibitor of the enzyme ACL in the 2-hydroxy-N-arylbenzene sulfonamides family, was chronically given to high-fat fed rats in order to reduce weight gain, triglycerides, plasma cholesterol, and glucose[70].

Role of Nutraceuticals in treatment of hyperlipidemia:

Stephen DeFelice first used the term "nutraceutical" in 1989. It combines the definitions ofnutrient and pharmaceutical.The concept is that, similar to medications, these goods may be utilized to treat pathological illnesses. A product or component of a diet that offers health advantages, such as illness prevention and treatment, is what these are called[72]. An increasingly relevant and widely discussed possibility is the implementation of a non-pharmacological nutraceutical based therapy for hyperlipidemia[73].

A class of naturally occurring compounds with a broad variety of phenolic structures are

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called flavonoids. They may be found in many foods and beverages, such as fruits, cereals, bark, vegetables, roots, flowers, stems and tea. The active ingredients were determined to be flavonoids. Flavones, flavanones, catechins, and anthocyanins are some of the main categories of flavonoids, among more than 4000 variants. Because of their antioxidant characteristics, flavonoids are expected to significantly impact the cardiovascular system. When oxygen radicals oxidise low-density lipoprotein (LDL), they damage the endothelium wall and lead to hyperlipidemia, which in turn accelerates atherosclerotic processes. The inclusion of tannins, proanthocyanidines, flavonoids, and other polyphenolic chemicals in the ethanol extracts may be responsible for the action, since they inhibit the oxidation of LDL-c[74].

Polyphenols, which originate from plants and include several phenolic groups, are famous for their antioxidant capabilities. Many plants contain polyphenols that have therapeutic qualities. Green tea, grapes, olives, fruits, and vegetables are great sources of these components. They are hypocholesterolemic because they may inhibit HMG-CoA reductase, microsomal triacylglycerol transport protein, and acetyl-CoA acetyltransferase[75].

II. CONCLUSION:

An extensive literature search yielded the data used to compile this review on hyperlipidemia and its management. That is because hyperlipidemia is the root cause of a plethora of complex disorders. Among all diseases that contribute to death, hyperlipidemia ranks first globally. One of the major contributors to the onset and advancement of CVD is abnormalities in lipid metabolism. Reasonable prevention and treatment of CVDs can only be organised with timely and accurate diagnosis, as well as evaluation of concurrent risk factors for CVD development. Although statins have greatly decreased cardiovascular events, there is still a high residual risk, and some individuals have intolerance to them, usually as a result of myalgia. When treating hyperlipidemia, other than statins, other options include niacin, fibric acid derivatives, ezetimibe, PCSK9 inhibitors, and ANGPTL3 inhibitors. More treatment alternatives are required, particularly for severe and hereditary hyperlipidemias. Some examples of more recent medical developments and pharmacological strategies include ACET inhibitors and other treatments that target CETP. Additionally, antihyperlipidemic and antioxidant properties were discovered in natural crude medicines that are abundant in medicinally active components including polyphenols and flavonoids. Treatment of hyperlipidemia with nutraceuticals is gaining more and more attention and is thought to be crucial.

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