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Review Article

A Brief Report on Hyperlipidemia and its Inducing Models

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ABSTRACT

Hyperlipidemia is a condition of having abnormalities in plasma lipids. According to the surveys done in India, urban populations are more affected by higher cholesterol levels than rural populations. Hyperlipidemia is mainly caused due to lifestyle, lack of exercise, and high-fat diet intake. It is classified based on two factors. They are on the basis of lipid type i.e., hypercholesteremia and hypertriglyceridemia, and on the basis of causing factors i.e., familial and acquired factors. In general, Hyperlipidemia can be treated by lifestyle and dietary changes. If the levels are high, medication is needed (Ayurvedic or Allopathic). The most commonly used drugs are statins and fibrates. Inducing agents are used to increase plasma lipids. These are used in *in vitro* and *in vivo* experiments mostly used inducing agents are Triton X100, Triton WR 1339, and methionine. As hyperlipidemia can be cured by switching to a healthy diet, natural home remedies can show a high impact.

Keywords: Hyperlipidemia, Lipoproteins, Chylomicrons, Triton X100, Methionine

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ABBREVIATIONS

HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; VLDL: Very Low-Density Lipoprotein; ApoB: Apoprotein B; TG: Triglyceride; IP: Intra Peritoneal; IV: Intravenous; ROA: Route of Administration; IDL: Intermediate-Density Lipoprotein; Apo-2: Apoprotein-2; CHD: Chronic Heart Disease; TLC: Therapeutic Lifestyle Changes; FA: Fatty Acids; PPAR: Peroxisome Proliferator-Activation Receptor; NPCIL-1: Niemann-Pick C1-Like 1 protein; ACATI: Acetyl-coA Cholesterol Acyl Transferase Inhibitor; MTP: Microsomal Triglyceride transfer Protein; CETP: Cholesterol Esterase Transfer Proteins; LS: Lanosterol Synthase; FDA: Food and Drug Administration; ApoC-3: Apoprotein C3; ApoA1: Apoprotein A1; ApoA4: Apoprotein A4; GST: Glutathione S-Transferase; SOD: Superoxide Dismutase; GSH: Glutamyl-L-cysteinyl-glycine; CAT: Catalase; PX: Peroxidase

INTRODUCTION

Hyperlipidemia is a health condition that results in the chronic elevation of cholesterol, cholesterol ester, triglycerides, and phospholipids in the blood (Shattat GF, 2015; Mishra PR, *et al.*, 2011; Jeyabalan S and Palayan M, 2009). Due to this abnormal elevation of lipid contents in blood and it will get deposited in the walls of arteries, the liver, and other organs. This acts as a precursor for many hazardous health diseases such as Atherosclerosis, heart attacks, strokes, etc., (Ezeh KJ and Ezeudemba O, 2021; Altmann SW, *et al.*, 2004). Hyperlipidemia is liable for most cardiovascular diseases (Brouwers MC, *et al.*, 2012). It is estimated that this will become the major cause of the increase in mortality rate due to hyperlipidemia in the coming years (Shattat GF, 2015; Mishra PR, *et al.*, 2011).

Overall deaths due to elevated levels of cholesterol are found to be 2.6 million deaths and 29.7 million disabilities (Noubiap JJ, *et al.*, 2015; Mendis S, *et al.*, 2011). The food source of cholesterol from high-fat dairy products like milk, cream, yogurt, butter and ghee, etc., Liver in our body also produces and stores some amount of cholesterol. On average estimation, our liver can produce 80% of cholesterol (Mumthaj P, *et al.*, 2021; Singh R and Nain S, 2018; DuBroff R and de Lorgeril M, 2015) (*Figure 1*).

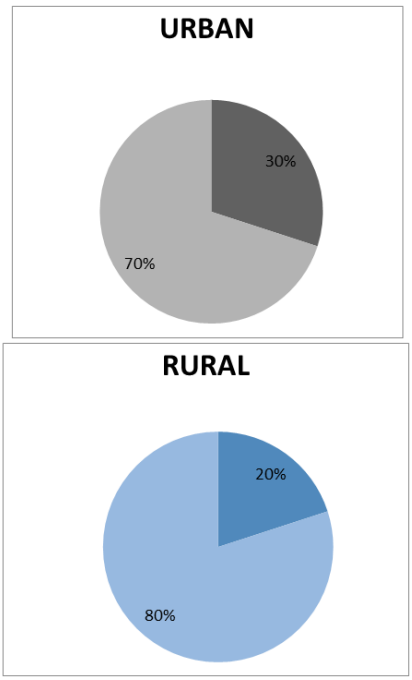

Figure 1: Cholesterol levels in urban and rural population, (■): Effected population; (■): Healthy population; (■): Effected population; (■): Healthy population

The above pie chart shows the data of urban and rural population that is 30% and 20% suffering from hyperlipidemia in India (Gupta R, *et al.*, 2017).

Cholesterol includes Low-Density Lipoproteins (LDL), High-Density Lipoproteins (HDL). LDL is the bad cholesterol that leads to a disorder such as strokes, carotid artery disease, and peripheral arterial disease whereas, HDL is good cholesterol, as it eliminates LDL from the body. Any deviation in these levels results in hyperlipidemia (Mumthaj P, *et al.*, 2021). Many hormones and steroids are produced from cholesterol (*Table 1* and *Figure 2*).

Table 1: Normal and risk range of cholesterol in human body (Mumthaj P, *et al.*, 2021)

Lipoproteins	Normal range	Risk condition
LDL	Under 100 mg/dl	160 and high
HDL	Greater than 60 mg/dl	Under 40-50 mg/dl
VLDL	2 and 30 mg/dl	Above 30 mg/dl
Triglycerides	Less than 150 mg/dl	Above 200 mg/dl
Total	Under 200 mg/dl	240 mg/dl and higher

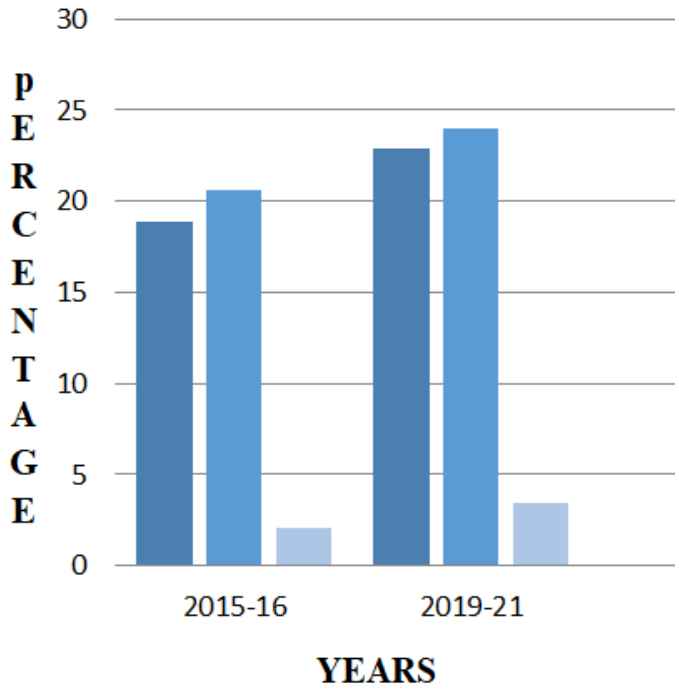

Figure 2: Data on cholesterol levels in the Indian population, ( ): Men; ( ): Women; ( ): Children

This bar graph clearly shows the rise in cholesterol levels in the Indian population. This data is from the years 2015-2016 and 2019-2021. This is mainly due to lack of physical exercise, genetical inheritance, and improper diet (Pandey G, 2022).

LITERATURE REVIEW

Hyperlipidemia is classified based on 2 factors (Joseph D, 2011). They are:

On the basis of lipid type

Hypercholesterolemia: Hypercholesterolemia is described as high levels of cholesterol in the blood. It indicates the blood serum cholesterol levels of 200 mg/dl or more in blood serum levels. Many atherosclerosis and atherosclerosis conditions such as ischemic cerebrovascular disease, coronary heart diseases, etc., are caused by hypercholesterolemia. There are mainly two types of causes. They are primary causes and secondary causes. The primary causes include environmental causes such as obesity, dietary choices, and genetic factors whereas secondary factors include diabetes mellitus, kidney diseases, hypothyroidism, Cushing syndrome, family history, less physical activity, etc., (Pattis P and Wiedermann CJ, 2008).

Hypertriglyceridemia: It is described as high levels of triglycerides in the blood. HTG is classified based on TG levels:

- Mild TG level (150-199 mg/dl)
- High TG levels (200-499 mg/dl)
- Very high>500 mg/dl

The main reasons for HTG are genetic factors and elevated levels of triglycerides. The other causes include medical conditions (Karachi H, *et al.*, 2022).

On the basis of causing factor (Mumthaj P, *et al.*, 2021)

Hereditary factors: It is a condition that increases the levels of LDL that is passed down across families.

Acquired factors: It is a condition of abnormal elevation of lipids including triglycerides and cholesterol in the blood due to a sedentary lifestyle and unbalanced diet.

Classification of lipoproteins

Lipoproteins are large molecules made of lipids and proteins. They are used to make lipids and proteins compatible with water. Lipids are made up of different types of molecules. Some of these molecules are made up of lipids and other types of molecules.

Lipoproteins are classified as Chylomicrons, Very Low-Density Lipoprotein, Intermediate Density Lipoprotein, High-Density Lipoprotein, and Low-Density Lipoprotein (Sharma A, *et al.*, 2019).

Chylomicrons (CM): Chylomicrons are large particles that transport dietary lipids from the intestine to the bloodstream, where they are broken down into smaller and denser Intermediate-Density Lipoprotein (IDL). They have a variety of apolipoproteins attached, including A-I, A-II, A-IV, B-48, C-I, C-II, C-III, and E. Very Low-Density Lipoprotein (VLDL) particles are primarily formed in the liver, but also in the intestine to a lesser degree (Sundaram M and Yao Z, 2010).

Very Low-Density Lipoproteins (VLDL): Very Low-Density Lipoproteins (VLDLs) are smaller particles than chylomicrons and triglycerides, and are secreted from the liver. VLDLs transport cholesterol from the liver to organs and tissues in the body. They are composed of a mixture of cholesterol and triglycerides (Sundaram M and Yao Z, 2010).

Intermediate Low-Density Lipoproteins (ILDL): The lysis of VLDL particles by lipase enzymes in the capillaries of adipose tissue and muscle results in Intermediate-Density Lipoprotein.

High-Density Lipoproteins (HDL): High-Density Lipoproteins (HDL) are commonly referred to as "good cholesterol". They are synthesized in the liver and carry cholesterol and other lipids from tissues back to the liver for degradation. HDL also plays an important role in protecting against atherosclerosis (Ridker PM, *et al.*, 2010).

Metabolism of lipoproteins

Intake of high dietary fat and cholesterol leads to the deposition of fat in the liver lymph (*Figure 3*). Chylomicrons are formed in the intestine as it enters the liver through capillaries. These chylomicrons enter into the capillaries and form remnant chylomicrons and enter into the liver and form VLDL these enter into the capillaries and form remnants and IDL (Intermediate Density Lipoproteins) then the remnant convert into LDL (Low-Density Lipoproteins) this LDL binds to the LDL receptor and convert into cholesterol this form HDL (High-Density Lipoproteins) and passes to endocrine glands for steroid hormone synthesis. Cholesterol in the peripheral tissue from remnant through plasma LCAT (Lecithin-Cholesterol Acyltransferase, which is an enzyme that converts free cholesterol into cholesteryl ester) and gets converted into LDL and HDL. Triacylglycerols go through hydrolysis in capillaries and form glycerol and fatty acid. Glycerol returns to the liver for glucose synthesis. Some of the fatty acids get resynthesis and are stored mainly in adipose tissue and the remaining fatty acids go through beta-oxidation in the peripheral tissue and are transported by serum albumin.

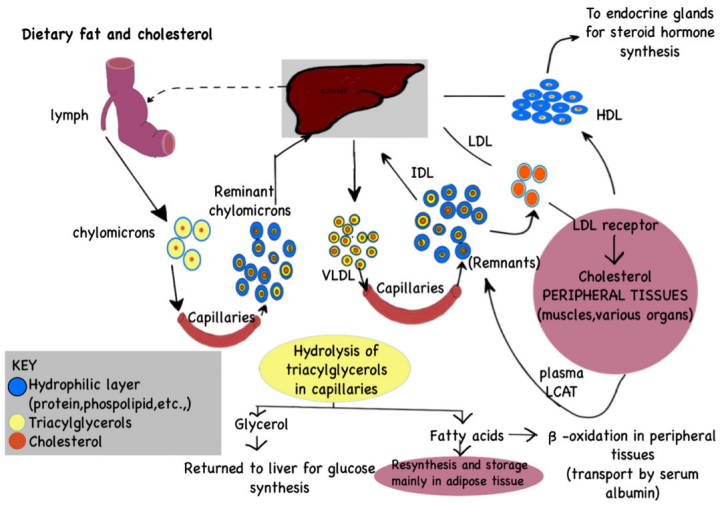

Figure 3: Metabolism of lipoproteins

Pathogenesis

The pathogenesis of hyperlipidemia begins when blood monocytes and platelets attach to a damaged vessel wall, the release of mediators such as platelet-derived growth factors stimulate the growth of smooth cells in the intimal and medial lining of the vessel, as well as collagen synthesis, cholesterol uptake, and plaque formation. Plaque rupture can lead to acute syndromes such as unstable angina, myocardial infarction, and sudden cardiac death (Mumthaj P, *et al*., 2021; Murphy SL, *et al*., 2013).

Symptoms

Atherosclerosis: It is a condition in which the accumulation of lipids in the walls of the arteries. It leads to insufficient blood and oxygen supply to the heart.

Coronary artery diseases: It is a condition in which the accumulation of lipids in the walls of the arteries which leads to the narrowing of the arteries.

Myocardial infraction: It is a condition in which there is a decrease in oxygen supply to the heart. This is due to the accumulation of lipids.

Ischemic stroke: It is a condition due to the blockage of the artery.

Vascular diseases: It blocks the blood flow in the arteries or veins.

High blood pressure: It is a condition where cholesterol gets deposited in the walls of the arteries which leads to the narrowing of the arteries.

Pancreatitis: It is a condition in which large triglycerides-rich lipoproteins particles primary chylomicron; prevent capillary circulation and causes ischemic damage to the pancreatic acinar (Kumar G, *et al*., 2013).

Causes

- The primary reason for hyperlipidemia is a defect in lipid metabolism. It effects by the defect of lipoprotein lipase activity and the absence of Apo protein C-11.
- The secondary cause of hyperlipidemia includes genetic abnormalities and environmental factors which includes-
- Lifestyle and exercise
- High-fat diet intake.
- Low-Density Lipoprotein plays an important role in maintaining the hepatic uptake of Low-Density Lipoprotein from plasma mutation in the Low-Density Lipoprotein receptor causes familial hypercholesterinemia.
- Decrease LDL receptor and increased Apo B.
- Decrease in the level of Low-Density Lipoprotein receptors is responsible for decreased clearance of Apo B will deposit in the body.
- Defect in Apo 2-synthesis.
- Increase in Very Low-Density Lipoprotein and decrease in excretion.
- Apo cl accumulated in the plasma leading to an increase in Apo-mediated inhibition of Low-Density Lipoprotein and triglycerides hydrolysis (Nirosha K, et al., 2014; Millar JS, et al., 2005; Dhingra S and Bansal MP, 2005).

Risk factors

Risk factors of hyperlipidemia are of two types-

1. Non modified risk factors include

- Age, gender and genetics
- Chronic diseases

2. Modified risk factor includes

- Medications
- Nutrition
- Physical inactivity (Nouh F, *et al*., 2018)

Diagnosis

Hyperlipidemia can be detected with a blood test called a lipid profile. This test checks for LDL, HDL, VLDL, and Triglyceride levels in the blood. Regular testing is recommended to diagnose hyperlipidemia (Cunningham AB, 1988).

Preventive measures

To lower fatty acid and cholesterol levels, adopt the following diet:

- Increase intake of foods high in soluble fiber such as oats, beans, and certain fruits.
- Eat pears, apples, bananas, etc.
- Consume fish twice a week (Verma N, 2016).

Dietary changes: Dietary changes include-

- Oatmeal-LDL is reduced by 12%-24%.
- Orange juice-Lowers cholesterol levels in the blood.
- Coriander seeds-Lower triglyceride and cholesterol levels.
- Soybeans, honey and fish oil-Lowers the levels of triglycerides

- Brown rice, brinjal, coconut oil, turmeric-Lower the levels of LDL cholesterol, improves the LDL/HDL ratio and raises HDL (Verma N, 2016).

Treatment

Many lipid-lowering drugs are marketed to treat hyperlipidemia. A drug project suggests that drugs used to prevent myocardial infarction are relatively ineffective in existing CHD patients (Russell DW, 2003; Edeoga HO, *et al*., 2005).

Elevated LDL, presence of risk factors, and documented CHD should qualify drug therapy development along with TLC. Current lipid-lowering drugs include statins, ezetimibe, bile acid sequestrates or bile-binding resins, niacin, fabric acid derivatives, and plant sterols. If dietary changes prove inadequate, medications specifically designed to lower blood cholesterol levels may be prescribed (Safeer RS and laCivita CL, 2000).

Fibrates (Fabric acid derivatives): Fibrates, which include clofibrate, gemfibrozil, fenofibrate, and bezafibrate, are a commonly used class of antihyperlipidemic agents that result in a significant decrease in plasma triglycerides and a modest decrease in LDL sterols. HDL cholesterol levels rise gradually. Angiographic experiments revealed that fibrates play the most important role in slowing the progression of coronary atherosclerosis and reducing the occurrence of coronary artery disease.

Data from rodent and human studies suggest four major fibrate mechanisms:

Lipid lipolysis stimulation: Fibrates primarily act as ligands for the PPAR-nuclear transcription receptor. They increase the expression of lipoprotein lipase, Apo, and decrease the expression of Apo C-III, a lipolysis inhibitor. Fibrates also increased HDL cholesterol levels by increasing the expression of Apo AI and Apo AII (Elmore S, 2007).

Increasing hepatic Fatty Acids (FA) uptake: While decreasing hepatic triglycerides production Fibrates promote the formation of fatty acid transport protein and acyl-CoA synthetize, which contribute to increased fatty acid uptake by the liver and a lower availability of fatty acids for triglyceride formation (Keshetty V, *et al*., 2009).

Increase LDL particle removal: Fibrates appear to increase LDL catabolism *via* the receptor-mediated pathway, LDL particles became larger and more lipid-rich, and thus had a higher affinity for receptors (da Rocha JT, *et al*., 2009).

High-density lipoprotein formation: It is accelerated and reverse cholesterol transport is stimulated. Fibrates increase Apo A-1 formation contributing to increase the liver, plasma concentrations of Apo A4, HDL-cholesterol and a more effective reverse cholesterol transport (Girija K and Lakshman K, 2011).

Nicotinic acid derivative (niacin): Niacin, a water-soluble B vitamin, was the earliest lipid-lowering agent used to treat hyperlipidemia and has been shown to reduce cardiovascular morbidity and all-cause mortality. Reduces Total Cholesterol, LDL Cholesterol, and Triglycerides (Irudayaraj SS, *et al*., 2013).

Niacin inhibits hormone-sensitive lipase and reduces lipid dissolution of triglycerides, the major producers of circulating free fatty acids. For these normally circulating fatty acids, the liver plays an important role in the formation of triacylglycerol. Niacin, therefore, inhibits the secretion of VLDL and reduces the production of LDL (Ragheb A, *et al*., 2011).

Treatment with niacin has been plagued by low patient compliance. The most common side effects are severe skin redness, itching, headache, and in some patient's nausea and abdominal discomfort, affecting more than three of quarters of patients. Niacin also increases liver enzymes (Safeer RS and laCivita CL, 2000).

Selective cholesterol absorption inhibitor (ezetimibe): The discovery and development of ezetimibe, the first in a family of drugs that inhibit intestinal absorption of plant sterols and cholesterol, has improved the treatment of hypercholesterolemia. Inhibits the absorption of sterols from the small intestine and does not affect plasma levels of vitamins A, D, E, K.

Ezetimibe selectively inhibits cholesterol absorption in the small intestine and reduces cholesterol delivery from the intestine to the liver by blocking the human sterol transport protein Niemann-Pick C1-Like 1 Protein (NPC1L1). This increases the clearance of sterols from the bloodstream (Carvalho FS, *et al*., 2014).

Ezetimibe is generally a well-tolerated drug. The most common side effects are headache, abdominal pain, and diarrhea. Ezetimibe appears to cause elevated liver enzymes. Functional tests include elevated alanine transaminase and aspartate transaminase.

Lifestyle changes: Therapeutic lifestyle changes are recommended as initial treatment for mild cases of hyperlipidemia and people without CHD or CHD risk equivalents with fewer than two risk factors. The diet should be restricted to 25%-35% of energy intake, with saturated fatty acids making up less than 7%, and cholesterol intake limited to 200 mg a day. Plant sterol esters and soluble fiber are preferred (Verma N, 2016).

Ayurvedic treatment: Ayurvedic medicine is one of the oldest medical systems in the world. Ayurvedic therapy is based on the "laws" of nature. This approach to wellness is based on an understanding of the interrelationship between body, mind, and spirit. The goal of Ayurvedic medicine is to integrate and balance these elements to prevent disease and promote health through diet, nutrition, herbs, yoga, meditation, and seasonal daily routine (Belay B, *et al*., 2007).

Plant's role in the treatment of hyperlipidemia: Medicinal plants have always been considered a source of healthy life for all peoples and international trade due to their rich therapeutic benefits and 100% natural nature. The regular use of herbal medicines in many developing countries is largely due to the high cost of Western medicines and healthcare (Bersot TP, 2011).

New potential targets and treatment options

Recently, a number of clinical studies have revealed new potential agents with promising antihyperlipidemic activity, which include:

Acyl-coA Cholesterol Acyl Transferase inhibitor (ACAT): Acyl-coA Cholesterol Acyl Transferase (ACAT) is an enzyme that catalyzes the conversion of intracellular cholesterol to cholesteryl esters. ACAT has two isomers called ACAT1 and ACAT2.

Inhibitor of Microsomal Triglyceride transfer Protein (MTP): Microsomal Triglyceride transfer Proteins (MTPs) has multiple functions, including transport of neutral lipids between membrane vesicles, CD1 biogenesis, antigen-presenting molecules and regulation of cholesterol ester biosynthesis.

Cholesterol Ester Transfer Protein (CETP) inhibitor: CETP in the liver promotes a shift of cholesteryl esters from antiatherogenic HDL to proatherogenic lipoprotein B-containing lipoproteins, including VLDL and LDL. Furthermore, most studies have shown that there is evidence that CETP may play a proatherogenic role by participating in reverse cholesterol transport, suggesting that inhibition of CETP slows atherosclerosis progression. There is support for the idea.

Lanosterol synthase inhibitor: Lanosterol Synthase (LSS) catalyzes the cyclization of 2,3-oxidosqualene to lanosterol, the first sterol in the cholesterol synthesis pathway.

Recent drugs for hyperlipidemia: The FDA has approved two new non-statin drugs that have been shown in clinical trials to potentially help lower high cholesterol. Nexretol and Nexlyzet can be used with statins with reduced or minimal side effects. Two new drugs have some side effects that differ from statins (*Tables 2 and 3*).

Table 2: Inducing agents of *in vitro* models

S.no	Agents	Dose	No. of days	Cell lines	Mechanism of action	References
1	Triton X100	0.01%	Single induction	Hepatoma cells	Triton X100 accelerates hepatic cholesterol synthesis and intestinal lipid absorption suppresses the action of lipoprotein lipase circulation by extra hepatic tissue resulting in blood lipid concentration and causing hyperlipidemia.	Ahn JM, *et al.*, 1997
2	Triton WR-1339	10 mg/ml			Triton WR-1339 increased oxidative stress through an elevation in that associated with depletion in glutathione activates the GST, SOD, GSH, PX and CAT in plasma, liver and brain then triton WR induced into DNA fragments and inhibit Acetylcholine (ACH)	Tacherfiout M, *et al.*, 2018; Yamamoto K, *et al.*, 1984
3	Methionine	1% (w/w)			Methionine increases serum triglycerides and total concentration of cholesterol activity in tissue by decreases lipoprotein lipase activity in tissue dietary methionine increase bile acid secretion which excreted into the faeces which enhance hepatic cholesterol which causes hyperlipidemia.	Hidiroglou N, *et al.*, 2004; Kawasaki M, *et al.*, 2008
4	D-fructose	0.55 mM			High fructose diet which increases hepatic secretion of very low-density lipoproteins this decreases the plasma clearance which causes hyperlipidemia	Huang D, *et al.*, 2011

Table 3: Inducing agents used in *in vivo* models

S.no	Agents	Dose	No. of days	ROA	Animals	Mechanism of action	Reference
1	Triton X100	1.5 and 3 mg/kg	21	I.P	Rats	Triton X100 accelerates hepatic cholesterol synthesis and intestinal lipid absorption suppresses the action of lipoprotein lipase circulation by extra hepatic tissue resulting in blood lipid concentration and causes hyperlipidemia.	Parwin A, *et al.*, 2019
2	Triton WR-1339	400 mg/kg	7	I.P	Male wistar rats	Triton WR-1339 inhibit the activity of lipoprotein lipase enzyme, this result in accumulation of triglycerides and very low density lipoproteins it increases the hepatic cholesterol biosynthesis	Zarzecki MS, *et al.*, 2014; Kumar G, *et al.*, 2013
3	Poloxamer-407	0.5 and 1 g/kg	12	I.P	Rats	Poloxamer 407 increase serum lipoprotein and inhibit the lipoprotein lipase which facilitates the hydrolysis of triglycerides which result in hyperlipidemia	Johnston TP and Palmer WK, 1993; Chaudhary HR and Brocks DR, 2013
4	Doxorubicin	6 mg/kg	5 weeks	I.V	Rats	Doxorubicin decreases L carnitine and causes hyperlipidemia nephropathy	Badary OA, *et al.*, 2000
5	D-Galactosamine	400 mg/kg	1	Oral	Male albino rats	D galactosamine induced fatty liver and significantly increases cholesterol free fatty acids, triglycerides and phospholipids and causes hyperlipidemia	Arivu I and Muthulingam M, 2015
6	Cyclosporin A	25 mg/kg	28	I.P	Male rats	Cyclosporine A inhibits ApoB and VLDL transportation over the endoplasmic reticulum so that reduction and the efficiency of lipid by inhibition of MTP	Afshari AT, *et al.*, 2005; Kockx M, *et al.*, 2012
7	Adriamycin	1.5 mg/kg	Weekly twice	I.P	Male lewis inbred rats	This increases the cholesterol, phospholipids and triglycerides which causes hyperlipidemia nephropathy	Kunitomo M, *et al.*, 1985
8	High fat diet	20% sucrose, 15% lard, 1.2% cholesterol, 0.2% bile salts, 10% casein, 0.6% calcium hydro phosphate, 0.4% mountain flour	Six weeks	Oral	Male Sprague Dawley rats	Increase the VDL, HDL, VLDL, triglycerides level and causes hyperlipidemia	Kim MH, *et al.*, 2016; Duan R, *et al.*, 2021

DISCUSSION AND CONCLUSION

This review is based on a study of many articles that gives information about hyperlipidemia and *in vitro*, *in vivo* inducing models. As hyperlipidemia is the main cause of many complicated diseases. Hyperlipidemia is the top disease that causes mortality throughout the world. According to the surveillance, this is an increase in the cholesterol level yearly. It is one of the major risk factors that affect heart structure and functions. We mainly focus on the prevention and treatment of hyperlipidemia and also it helps in preventing complicated diseases. According to Ezeh KJ and Ezeudemba O, recent changes in treatment recommendations are providing greater guidance for the management of Hyperlipidemia. Statins are the frontline treatment for hyperlipidemia. Medicinal plants give a 100% therapeutic effect. This also gives information about new drugs approved by FDA. This review is also an overview of inducing models used in experimental studies. According to Ahn JM and Parwin A, Triton X100 and Triton WR1339 are most widely used for experimental studies. It also provides information about the various inducing models used in *in vitro* and *in vivo* with their mechanism of action. This article is useful for future studies.

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