A Comprehensive Review on Recent Progress in *Invivo* and *Invitro* Models for Hyperlipidemia Studies

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ABSTRACT:

Hyperlipidemia refers to an abnormality in plasma lipid levels. Research conducted in India indicates that the prevalence of elevated cholesterol is greatest in the country's metropolitan areas. Lifestyle factors, inactivity, and a diet heavy in saturated fat are at the root of most cases of hyperlipidemia. It's classified in two ways. Hypercholesterolemia and hypertriglyceridemia, as well as hereditary and acquired forms, may be distinguished. Modifying one's diet and way of life is often sufficient to cure hyperlipidemia. If they're too high, medication (allopathic or ayurvedic) will be required. Statins and fibrates are the two medications that get the most use. Plasma lipids may be boosted by inducing agents. Triton X100, Triton WR 1339, and Methionine are three of the most common inducing agents used in in vitro and in vivo studies. Hyperlipidemia may be treated with a change in diet; therefore, effective natural home treatments are available.

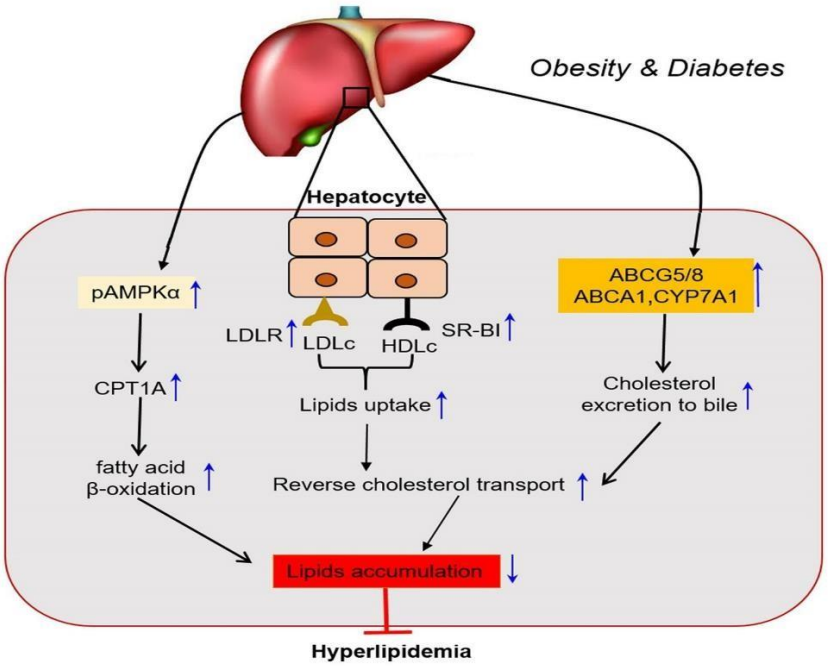
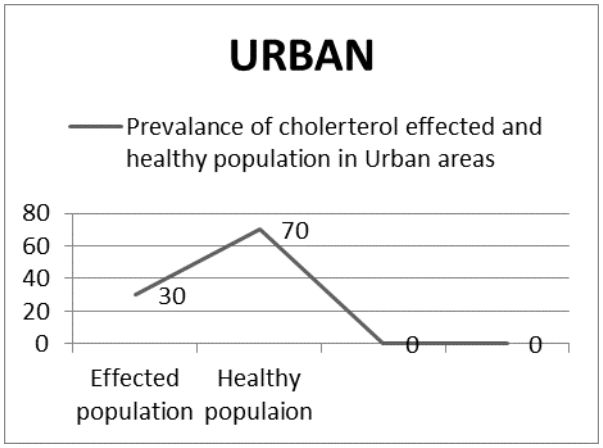


Fig: 1-Graphical abstract

KEYWORDS: Hyperlipidemia, Lipoproteins, Chylomicrons, Triton X 100, Methionine.

INTRODUCTION

An increase in blood levels of lipids such as cholesterol, cholesterol ester, triglycerides, and phospholipids are known as hyperlipidemia [1, 2, 3]. There will be a buildup of fat in the artery walls, liver, and other organs as a result of this abnormal increase in lipid levels in the circulation. This is a prelude to a wide variety of potentially fatal diseases [4,5], including atherosclerosis, cardiovascular disease, cerebrovascular accidents, etc. The majority of cardiovascular illnesses are caused by hyperlipidemia [6]. It is predicted that this will become the primary factor in the rising hyperlipidemia-related death rate [1, 2].
There are an estimated 2.6 million fatalities and 29.7 million impairments worldwide caused by high cholesterol levels [7, 8]. Cholesterol is obtained from foods like milk, cream, yoghurt, butter, ghee, etc. that are high in fat. The liver is responsible for producing and storing some cholesterol in the body. Around 80% of the cholesterol in our bodies is made in the liver, according to most estimates [9, 10, 11].



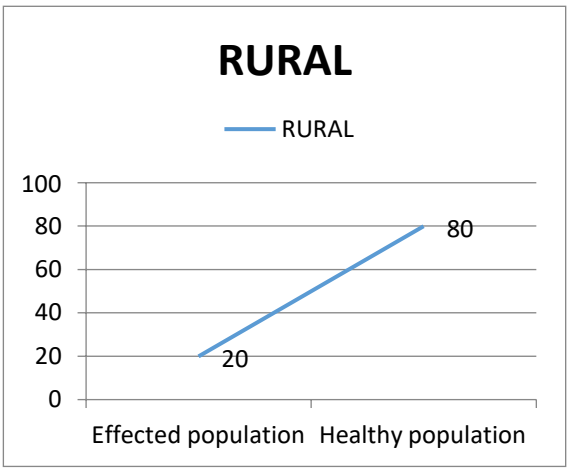


Fig: 2- It illustrates the disparity between urban and rural populations' cholesterol levels.

The percentage of Indians living in urban areas vs. those living in rural areas with hyperlipidemia is seen in the following pie chart (data from). The different types of lipoproteins that make up cholesterol are high-density (HDL) and low-density (LDL). Low-density lipoprotein (LDL) cholesterol is the culprit in many cardiovascular diseases. HDL, on the other hand, is considered good cholesterol since it helps rid the body of LDL. Hyperlipidemia [9] occurs when these levels are outside of the normal range. Cholesterol is a precursor to several hormones and steroids.
High cholesterol is linked to 2.6 million deaths and 29.7 million health problems . Cholesterol is obtained from foods like milk, cream, yoghurt, butter, ghee, etc. that are high in fat. The liver is responsible for producing and storing some cholesterol in the body. Around 80% of the cholesterol in our bodies is made in the liver, according to most estimates[11].

Table1: It indicates the normal and risk range of cholesterol in our body [12]

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

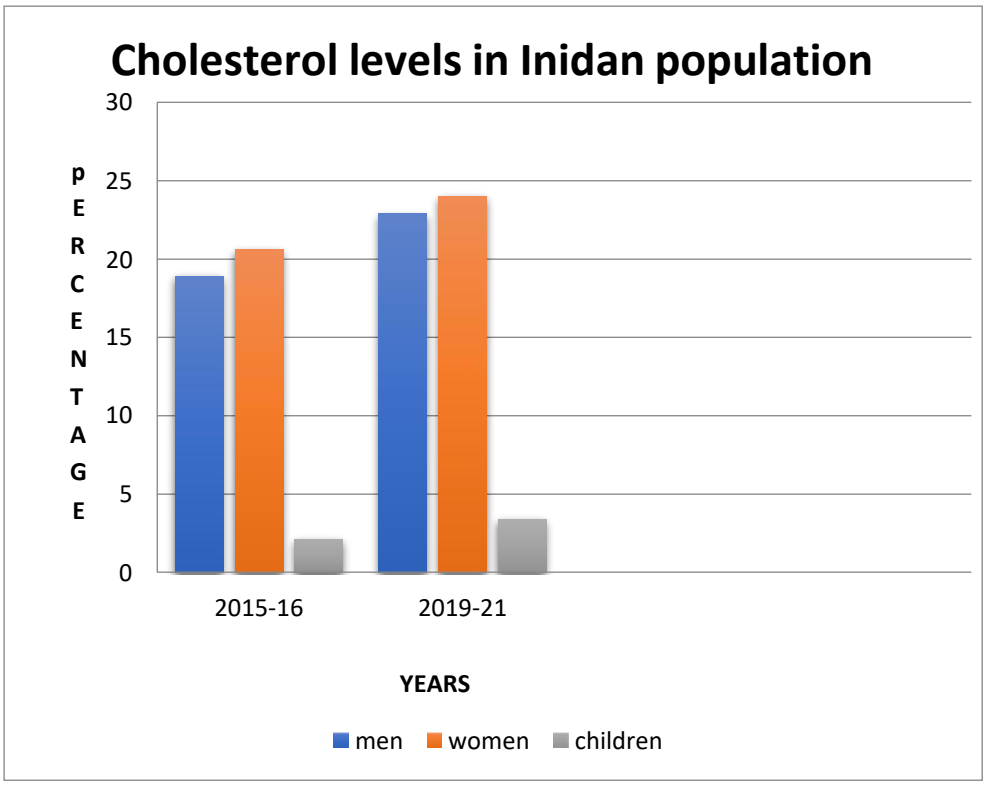


Fig: 3 Negative effect It's a statistical representation of information on Indians' cholesterol levels. cts:

The steady increase in Indians' cholesterol levels is graphically shown here. The information shown here is for the years 2015–2016 and 2020–2021. Inactivity, heredity, and unhealthy eating habits are major contributors to this [13].

CLASSIFICATION OF HYPERLIPIDEMIA:

Hyperlipidemia is classified based on 2 factors [14]. They are:

ON THE BASIS OF LIPID TYPE

High blood cholesterol levels, often known as hypercholesterolemia, are a medical condition in and of themselves. When this number is more than 200, it means that there is an excess of cholesterol in the blood serum. Hypercholesterolemia is a major contributing factor in the development of atherosclerosis and other atherosclerosis-related disorders. Two basic classes of factors are at play here. Primary causes and secondary causes are the two types. Obesity, poor nutrition, and genetics all have a role in the development of type 2 diabetes, while other variables such as diabetes mellitus, renal disease, hypothyroidism, Cushing syndrome, family history, lack of physical exercise, etc. play supporting roles [15].

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

Mild TG level (150-199mg/dl)

High TG levels (200-499mg/dl)

Very high >500mg/dl

HTG is caused by both hereditary causes and high triglyceride levels. Health problems are another contributor [16].

DEPENDING ON THE PRIMARY CAUSE

Inherited There is a genetic predisposition to have high LDL cholesterol.

Acquired,

A sedentary lifestyle combined with an unhealthy diet may lead to hyperlipidemia, which is an abnormal rise of triglycerides and cholesterol in the blood.

CLASSIFICATION OF LIPOPROTEINS:

Including both lipids and proteins, lipoproteins are very big molecules. Their purpose is to improve the solubility of lipids and proteins in water. The molecules that make up lipids are varied. There are lipids and other compounds in here somewhere. Simply put, lipids are fat molecules. Their molecular compositions vary. Molecules like lipids and others are used to construct some of them. To put it simply, lipids are fatty acids. Their molecular compositions vary. Lipids and several other compounds are used to construct some of these macromolecules. To put it

simply, lipids are fatty acids. Several kinds of molecules compose them. There are lipids and other compounds in here somewhere. Chylomicrons, very low-density lipoproteins, intermediate-density low-density lipoproteins, high-density lipoproteins, and low-density lipoproteins are all types of lipoproteins [16].

Chylomicrons (CM):

Once in the bloodstream, dietary lipids are broken down into smaller, denser particles called intermediate-density lipoprotein (IDL) through a process called chylomicron phagocytosis (IDL). A-I, A-II, A-IV, B-48, C-1, C-2, C-3, and E are only some of the apolipoproteins that are bound to them. Intestinal production of very low-density lipoprotein (VLDL) is secondary to liver production [18].

Lipoproteins with a very low density (VLDL):

Smaller than chylomicrons and triglycerides, the liver secretes very low-density lipoproteins (VLDLs). The liver stores cholesterol, but VLDLs carry it to the rest of the body. Cholesterol and triglycerides make up the bulk of their composition [17].

Cholesterol that is intermediate in size, or ILDL:

Intermediate-density lipoprotein is made when lipase enzymes in the capillaries of fat and muscle break up VLDL particles.

High-density lipoproteins (HDL):

The term "good cholesterol" is frequently used to refer to high-density lipoproteins (HDL). They are created in the liver and transport lipids like cholesterol back there for breakdown after leaving the tissues. The prevention of atherosclerosis is another essential function of HDL [18].

METABOLISM OF LIPOPROTEINS:

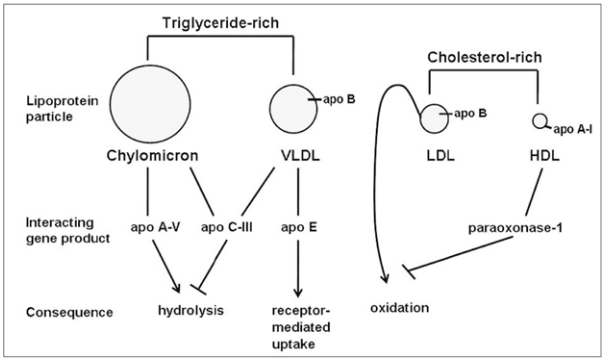


Fig.4 Metabolism of Lipoproteins

Excessive dietary fat and cholesterol cause a buildup of triglycerides in the liver's lymphatic system. The formation of chylomicrons begins in the colon and continues in the liver's capillaries. These chylomicrons go into the capillaries, where they leave behind residue chylomicrons, which travel to the liver to be processed into VLDL, which then travel to the capillaries, where they are broken down into remnants and IDL (intermediate density lipoproteins), which in turn convert into LDL (low-density lipoproteins), which in turn bind to the LDL receptor and convert into cholesterol, which in turn travels to the endocrine glands to be used in the synthesis of steroid hormones. Peripheral tissue cholesterol is transformed into LDL and HDL by plasma LCAT (lecithin-cholesterol acyltransferase), an enzyme that transforms free cholesterol into cholesteryl ester. Triacylglycerols are transformed.

PATHOGENESIS:

As blood monocytes and platelets stick to a damaged artery wall, they make mediators like platelet-derived growth factors. These promote the growth of smooth cells in the intima and media of the vessel, as well as the production of collagen, the absorption of cholesterol, and the formation of plaque. Plaque rupture can cause sudden symptoms like unstable angina, myocardial infarction, and sudden heart death [19, 20,21].

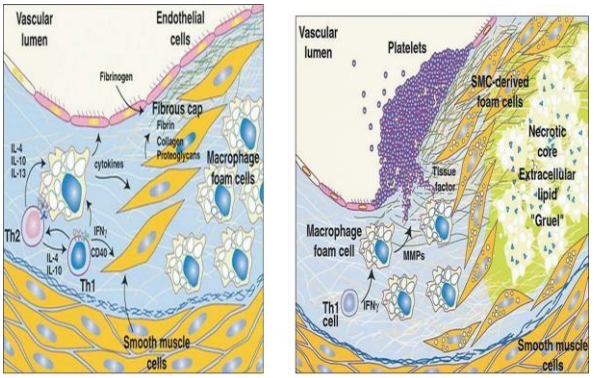


Fig. A & B

Fig.5 (The figures 5 A and B show the process of atherosclerosis and unstable plaque in the role of inflammation.)

SYMPTOMS:

➢ Atherosclerosis is a disease caused by the buildup of fatty deposits in the arterial walls. It causes the heart to get an inadequate flow of blood and oxygen.

- Two conditions that cause heart attacks include atherosclerosis (hardening of the arteries) and coronary artery disease (CAD).
- A myocardial infraction, in which oxygen flow to the heart is cut off, is the third. The buildup of fat is to blame for this occurrence.
- A stroke caused by arterial blockage is called an ischemic stroke.
- Vascular diseases obstruct arterial or venous blood flow.
- Cholesterol buildup in the artery walls causes hypertension, a disorder characterised by increased blood pressure.
- Ischemic injury to the pancreatic acinar is caused by large, triglyceride-rich lipoprotein particles called primary chylomicrons [22,23]. This disease is known as pancreatitis.

CAUSES:

Defects in lipid metabolism are the most common cause of hyperlipidemia. It manifests itself because to a lack of Apo protein C-11 and a deficiency in lipoprotein lipase function.

- Lifestyle choices, lack of exercise, and eating a high-fat diet are among the environmental variables that contribute to hyperlipidemia after inherited disorders.
- Mutations in the low-density lipoprotein receptor induce familial hypercholesterinemia by preventing the liver from taking up low-density lipoprotein from the bloodstream.
- Due to a decline in low-density lipoprotein receptors, less Apo B gets cleared from the body and more of it builds up in the tissues.
- Due to a lack of Apo 2, VLDL levels rise while excretion decreases, and plasma Apo cl levels rise, leading to a greater Apo-mediated inhibition of LDL and triglycerides hydrolysis [24,25,26].

RISK FACTORS:

There are two distinct categories of risk factors for hyperlipidemia.

1. Age, gender, and heredity are non-modifiable risk variables. Chronic disorders are another.

Medicines, poor diet, and lack of exercise all count as modified risk factors [27].

DIAGNOSIS:

A lipid profile is a blood test used to diagnose hyperlipidemia. The levels of LDL, HDL, VLDL, and triglycerides in the blood are measured. Hyperlipidemia may be diagnosed with periodic blood work [28].

Preventative Strategies for Hyperlipidemia and Related Disorders

Follow this diet plan to lower levels of fatty acids and cholesterol in your blood:

- Eat more oats, legumes, and some fruits to increase your soluble fiber intake.
- Consume a wide range of veggies and fruits.
- Have fish at least twice a week [29].

Changing Having a good Way of Life

In moderate instances of hyperlipidemia and in those who do not have CHD or CHD risk equivalents with fewer than two risk factors, therapeutic lifestyle adjustments are indicated as first-line therapy. Saturated fatty acids should account for less than 7% of calorie consumption, and daily cholesterol intake should be capped at 200 milligrams. Preferred are soluble fiber and plant sterol esters [30].

Ayurvedic drugs:

The practice of Ayurvedic medicine dates back thousands of years. The principles of Ayurvedic medicine are grounded in the natural order. Her strategy for health and well-being is predicated on a recognition of the connection between mental and emotional states and physical health. Ayurvedic medicine seeks to integrate and balance these factors in order to prevent illness and improve health via the use of dietary and nutritional practices, medicines, yoga, meditation, and the observance of seasonal rituals [31].

Changes in the diet:

Intake of muesli lowers LDL by 12-24 percent.

Consuming orange juice has been shown to reduce blood cholesterol levels.

Seeds of the coriander plant reduce levels of triglycerides and cholesterol.

Reduced triglyceride and cholesterol levels are a benefit of eating soybeans, honey, fish oil, and honey. Lessen the body's ability to produce cholesterol.

Including foods like brown rice, brinjal, coconut oil, ratio, and turmeric into your diet will help reduce your LDL cholesterol levels. Improves the LDL/HDL ratio and increases HDL while reducing LDL [32].

The use of plants for treating hyperlipidemia:

Medicinal plants have been used for a long time to help people stay healthy and make money all over the world because they have a lot of healing properties and are all natural. Because of the exorbitant price of Western pharmaceuticals and healthcare, many people in underdeveloped nations turn to herbal remedies instead [33].

TREATMENT:

Hyperlipidemia is treated with a wide variety of lipid-lowering medications. Myocardial infarction prevention medicines may have little utility in her current CHD patients, according to a pharmacological study [34].

In addition to TLC, people with high LDL, CHD, and other risk factors should think about developing new drugs to treat their conditions. Statins, ezetimibe, bile acid sequestrates or bile-binding resins, niacin, fatty acid derivatives, and plant sterols are some of the current medications used to reduce cholesterol levels. Medication aimed to reduce blood cholesterol levels may be recommended if dietary modifications are insufficient [35].

Fibrates (fabric acid derivatives):

Common antihyperlipidemic medicines include fibrates like clofibrate, gemfibrozil, fenofibrate, and bezafibrate, which reduce plasma triglycerides and LDL sterols to varying degrees. Elevated HDL cholesterol is seen over time. Angiographic tests showed that fibrates are crucial in preventing the development of coronary atherosclerosis and relieving symptoms in existing cases.

Mechanism of action:

Research on rodents and humans' points to four main fibrate mechanisms:

Fibrates are predominantly ligands for the PPAR-nuclear transcription receptor, which stimulates lipolysis of lipids. They upregulate Apo, a lipolysis enzyme, and downregulate Apo C-III, an inhibitor of lipolysis. Apo AI and Apo AII expression were both upregulated in vertebrates, leading to higher HDL cholesterol levels [36].

Raising hepatic fatty acid intake and lowering hepatic triglyceride generation, dietary fibre promotes the creation of fatty acid transport proteins and acyl-CoA synthetization, both of which lead to enhanced hepatic fatty acid uptake.

Fibrates seem to speed up the breakdown of LDL through a pathway involving receptors. This makes LDL particles bigger, more lipid-rich, and more attracted to receptors.

The process of making HDL is sped up, and cholesterol is moved in the opposite direction. Fibrates cause more Apo A-1 to be made, which leads to higher levels of HDL cholesterol in the liver, plasma, and blood and better transport of reverse cholesterol [37].

A Derivative of Nicotinic Acid (niacin)

The water-soluble B vitamin niacin was the first lipid-lowering drug used to treat hyperlipidemia, and it has been linked to a decreased risk of cardiovascular disease and death overall. Cholesterol and LDL cholesterol and triglyceride levels are lowered [38].

Mechanism:

By stopping hormone-sensitive lipase from working, niacin slows down the breakdown of triglycerides, which is the main source of free fatty acids in the blood. The liver plays a crucial role in the synthesis of triacylglycerol from these typically circulating fatty acids. Hence, niacin prevents the formation of VLDL and lessens the output of LDL [39].

Adverse impacts Patients' poor adherence has hampered the effectiveness of niacin treatment. More than 75% of patients have at least one adverse event, most often skin redness, itching, headache, and, in rare cases, nausea and gastrointestinal pain. Niacin also raises enzyme levels in the liver [28].

Cholesterol absorption-inhibiting agent selective (ezetimibe)

Ezetimibe was the first of a new class of medicines made to treat hypercholesterolemia. It stops plant sterols and cholesterol from being absorbed in the intestines. It blocks sterols from entering the bloodstream via the small intestine but has no effect on ADEK vitamin plasma levels.

By inhibiting the human sterol transporter Niemann-Pick C1-like 1 protein, ezetimibe lowers cholesterol transportation from the gut to the liver and prevents cholesterol absorption in the small intestine (NPC1L1). This improves sterol elimination from the body.

Adverse reactions:

The majority of people have no adverse reactions to ezetimibe. Headache, stomach discomfort, and diarrhoea are the most typical adverse reactions. Functional assays, such as those for alanine transaminase and aspartate transaminase, show that

ezetimibe is associated with an increase in liver enzyme levels [40].

Potentially New Targets and Therapeutic Approaches

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

Cholesterol acyltransferase inhibitor (ACAT): Acyl-coenzyme A-CoA cholesterol acyltransferase (ACAT) is an enzyme that catalyses 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) have multiple functions, including transport of neutral lipids between membrane vesicles, CD1 biogenesis, antigen-presenting molecules, and regulation of cholesterol ester biosynthesis.

Blocker of the protein involved in the transfer of cholesterol esters: CETP in the liver promotes a shift of cholesteryl esters from antiatherogenic HDL to proatherogenic lipoprotein B-containing lipoproteins, including VLDL and LDL. Also, most studies have shown that there is evidence that CETP may contribute to atherosclerosis by taking part in the transport of cholesterol in the opposite direction. This suggests that blocking CETP slows the progression of atherosclerosis. There is support for the idea [41].

Inhibiting lanosterol synthase: Lanosterol synthase (LSS) catalyzes the cyclization of 2,3-oxidosqualene to lanosterol, the first sterol in the cholesterol synthesis pathway [42].

NEW MEDICATIONS 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.

***INVITRO*-INDUCING MODELS**

Table 2: The table below shows the inducing agents of *In-vitro* models.

S.no	Agents	Dose	No. of days	Cell lines	Mechanism of action
1	Triton x 100	0.01%	Single induction	Hematoma cells	Triton x 100 accelerates hepatic cholesterol synthesis and intestinal lipid absorption suppresses the action of lipoprotein lipase circulation by extrahepatic tissue resulting in blood lipid concentration and causing hyperlipemia.
2	Triton WR-1339	10mg/ml	Single induction	Hepatoma cells	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 ACH

3	Methionine	1%(w/w)	Single induction	Hepatoma cells	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 hyperlipidaemia
4	D fructose	0.55mM	Single induction	Hepatoma cell	High fructose diet which increases hepatic secretion of very low-density lipoproteins this decreases the plasma clearance which causes hyperlipidaemia

EIGHT MODELS THAT INFLUENCE IN VIVO

Table 3: Agents used as inducers in in vivo models are listed below.

S.no	Agents	Dose	No. of days	ROA	Animals	Mechanism of action
1	Triton X 100	1.5 and 3mg/kg	21	I.P	Rats	Triton X-100 tends to increase hyperlipemia and blood lipid concentration by stimulating hepatic cholesterol synthesis and inhibiting intestinal lipid absorption by extra hepatic tissue.
2	Triton WR-1339	400mg/kg	7	I.P	Male Wistar rats	The enzymatic lipid lipase is inhibited by Triton WR -1339, leading to an increase in triglyceride and very low density lipoprotein accumulation and an increase in hepatic cholesterol biosynthesis.
3	Poloxamer -407	0.5 and 1g/kg	12	I.P	Rats	Hyperlipidaemia is caused by poloxamer 407 because it raises serum lipoprotein levels and blocks the lipoprotein lipase responsible for triglyceride hydrolysis.
4	Doxorubicin	6mg/kg	5 weeks	I.V	Rats	
5	D-Galactosamine	400mg/kg	1	Oral	Male albino rats	Hyperlipidaemia is caused by poloxamer 407 because it raises serum lipoprotein levels and blocks the lipoprotein lipase responsible for triglyceride hydrolysis.
6	Cyclosporin A	25mg/kg	28	I.P	Male rats	
7	Adriamycin	1.5mg/kg	Weekly twice	I.P	Male lewis inbred rats	This results in hyperlipidemia due to an increase in blood levels of

						cholesterol, phospholipids, and triglycerides. Nephropathy
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	Elevated levels of triglycerides, HDL, VLDL, and VDL cholesterol lead to hyperlipidemia.

CONCLUSION

For this review, I read a lot of articles that talked about hyperlipidemia and different ways to cause it in vitro and in vivo. Given that hyperlipidemia is a major contributor to a wide variety of serious illnesses, Worldwide, hyperlipidemia kills more people than any other single disease. The monitoring indicates an annual rise in cholesterol levels. It is one of the most significant threats to heart health. We pay special attention to hyperlipidemia and its treatment because of its role in disease prevention. Recent shifts in treatment recommendations are giving more direction for the management of hyperlipidemia, as stated by Kosisochukwu J. Ezeh and Obi-ora Ezeudemba et al., 2021. The first line of defence against high cholesterol is statins. The therapeutic effect of medicinal plants is 100 percent. The latest FDA-approved medications are also included. This review also serves as a primer on the various induced models employed in the lab. Experimental studies typically employ Triton X 100 and Triton WR 1339, as stated by JM Ahh, SJ Kim, et al., 1997; Ashiyanaparwin, Abulkalam Najami; and Mohd Akhtar et al., 2018. It also explains the mechanisms of action of the various invitro and in vivo inducing models that have been studied. For research purposes, this article is invaluable.

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DECLARATIONS

Conflict of Interest:

The authors declare no potential conflicts of interest.

Ethical approval:

This Article does not contain any studies with human participants or animals performed by the author.

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