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Hyperlipidemia: An Updated Role Of Cytochrome P450, Explored Plants And Screening Animal Models For Hyperlipidemia

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Abstract: As a result of high levels of triglycerides, cholesterol and other lipids in the bloodstream, hyperlipidemia is a disorder that may lead to heart disease and stroke. Increased levels of plasma lipids are the root cause of many cardiovascular illnesses. A major part of this study is devoted to the function of cytochrome and plant extracts, as well as animal screening models. Hyperlipidemia may be treated with a combination of over-the-counter drugs and dietary adjustments, as well as frequent exercise and a healthy diet. It also discusses the different hyperlipidemia screening models that are now available..

Introduction:

Hyperlipidemia is a disease, an abnormal metabolism in blood stream with increased level of fatty substances called lipids. Lipids are basically present in cholesterol and triglycerides[1]. Hyperlipidemia is also termed as hyperlipiprotenemia, due to the presence of fatty substances in the blood stream, which further attach to the lipids and form large molecules called lipoproteins. Hypercholesterolemia and hypertriglyceridemia are subcategory of hyperlipidemia. It is a condition where there is increased level of total cholesterol and increased level of triglycerides respectively in the blood[2].

LIPIDS:

Lipids are biological substances found in blood that are soluble in organic solvents but insoluble in water.

Lipids are classified as[3]:

1. Triglyceride
2. Phospholipids
3. Cholesterol
4. Free fatty acid.

Triglycerides:

Triacylglycerol is another name for triacylglycerides, which are well-known compounds. Adipocytes have the highest concentrations of these lipids, making them the most prevalent lipids in the body. Plant and animal cells have the capacity to store lipids. There is an overabundance of fat, alcohol and sugar in the body that is turned into triglycerides, which are deposited in fat cells. As a source of energy, triglycerides also play a vital function in metabolism. Synthesis occurs mostly in the liver and adipose tissue4. There are three fatty acid molecules in the structure of triglycerides. The table below5 shows the range and value of triglyceride based on data retrieved from the National Institutes of Health:

Phospholipids:

Phospholipids (PL) play a significant role since they are found in high concentrations throughout the body's main organs and tissues, including the brain. Covalently bonded lipids with phosphate-containing polar head groups linked to hydrocarbon chains are known as phospholipids. In the liver, lipoproteins limit fat formation by controlling membrane permeability and maintaining the mitochondrial electron transport chain, hence it is known as a lipotropic factor. Reverse cholesterol transport is helped by this process, which is facilitated by the creation of eicosanoid precursors. Cholesterol may be dissolved in this compound6,7.

Cholesterol:

Considering its role in tissue mobility, cholesterol is an essential component of all mammalian cell membranes. Steroid hormones and bile acids are two examples of this family of chemicals. As a free fatty acid or in the form of numerous fatty esters, it is found in animal cells, but not in plant lipids. For example, it protects nerve fibres and forms progesterone, testosterone, estradiol, and cortisol, the sex hormones known as progesterone, testosterone, and estradiol. Bile salts, which aid in the digestion of food, are also produced by the liver. Vitamin D production in the skin is aided by the presence of cholesterol.8

Lipoproteins:

By combining with proteins, lipoproteins carry cholesterol and triglyceride throughout the body. Cholesterol esters and triglycerides are examples of non-polar lipids found in the hydrophobic centre of these big particles. Phosphatidylcholine (PC), free cholesterol (FC), and apolipoproteins9 make up the hydrophilic membrane surrounding the hydrophobic core.

Types of Lipoproteins:

It is broadly of six types namely as depicted below:

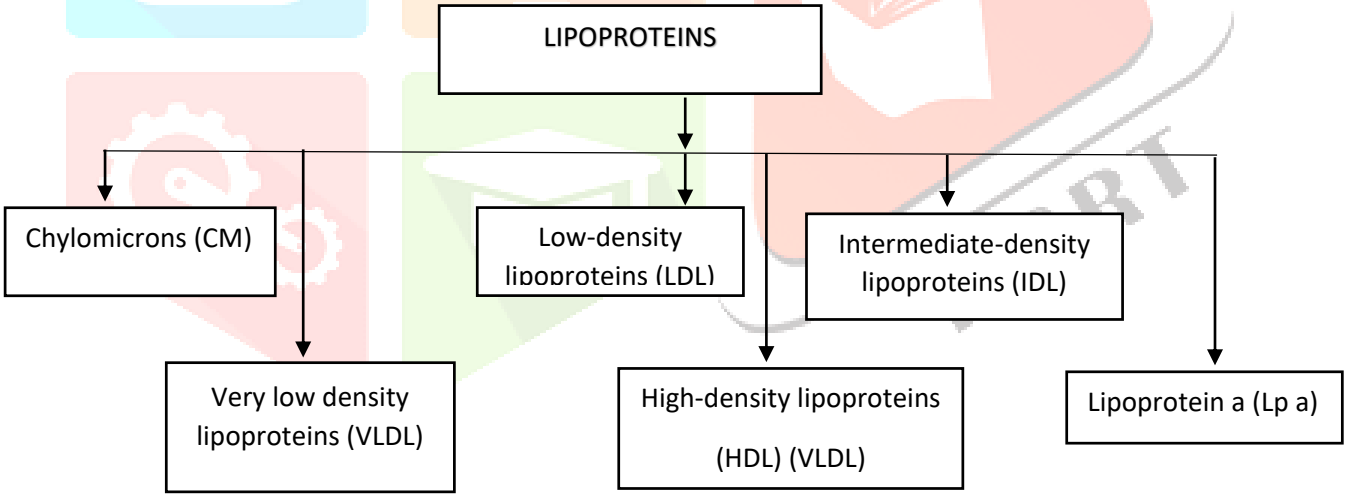

Fig 1:0 Types of lipoprotein

Chylomicrons:

In terms of both size and density, these are the biggest plasma proteins in the bloodstream. Dietary fats are solubilized in bile, and bile acid concentration is a good predictor of this compound's concentration.

VLDL:

Lipoproteins with a very low triglyceride content, known as very low-density lipoproteins, are smaller than chylomicrons. They're produced in the liver and transport triglycerides from the liver into the bloodstream. Cholesterol and triglycerides are the building blocks of these substances.

IDL:

Lipase, an enzyme found in the capillaries of adipose and muscle tissue, degrades VLDL particles, forming intermediate density lipoproteins.

LDL:

Lipoprotein lipase and intestinal chyle12 produce low-density lipoproteins from VLDL.

HDL:

HDL is known as the "good" cholesterol because it actively seeks for and eliminates LDL. The liver and small intestines produce HDL. The liver is responsible for the breakdown of lipids in the body's tissues and the subsequent return of these lipids to the tissues13. It has an anti-inflammatory effect.

Lp(a):

The liver is responsible for releasing it. Atherosclerosis is connected to lipoprotein (a), a cholesterol-rich plasma lipoprotein. There was also a statistically significant rise in Lp(a) plasma level concentration in females with age, according to studies by Nago et al. As compared to non-drinkers, alcohol drinkers had decreased Lp(a) plasma levels, which was also shown to be true 14.

Free Fatty Acid:

Free Fatty Acid:

It is one of the simplest forms of lipids that may be found as esters, and it is made up of free fatty acids (FFAs). Because FFAs are water insoluble and very minimally available at albumin binding sites, it is considered a considerable energy store. Large quantities of energy are released as ATP when mitochondria-containing cells absorb FFAs from the bloodstream and oxidise them to produce CO2 and H2O.

Classification of free fatty acids based on aliphatic tail length:

Free fatty acid	**No. of carbon atom**
Fatty acids with a short chain (SCFAs)	Carbon atoms with less than six
MCFAs (Medium Chain Fatty Acids)	6–12 atoms of carbon
Fats with long chains (LCFAs)	Carbon atoms with a mass ranging between 6 and 12

Table 1.3: Classification of free fatty acids based on aliphatic tail length

Functions of free fatty acids:

Systemic fuel energy homeostasis is regulated by receptor signalling, gene expression, and metabolic gene expression in physiology.

Many physiological and pathological processes are regulated by the functional receptors of FFAs, such as the fatty acid binding protein (FABP) and the peroxisome proliferator activated receptor (PPAR).

Classification of hyperlipidemia

Hyperlipidemia may be divided into two major categories:

Based on the kind of lipids:

In hypercholesterolemia, the total cholesterol level is excessive. In hypertriglyceridemia, the triglyceride levels are elevated.

On the basis of causing factor:

Because of a hereditary flaw, this kind of hyperlipidemia is known as familial (or primary). The lipoprotein electrophoresis or ultracentrifugation pattern is used by Fredrickson to classify familial hyperlipidemia. 17

Type I–Excessively high amounts of triglycerides in the blood.

High cholesterol and normal triglyceride levels in Type II.

Type III–Excessive levels of cholesterol and triglycerides.

Uric acid, atheroma, and elevated triglycerides characterise type IV diabetes.

This kind of triglyceride is raised.

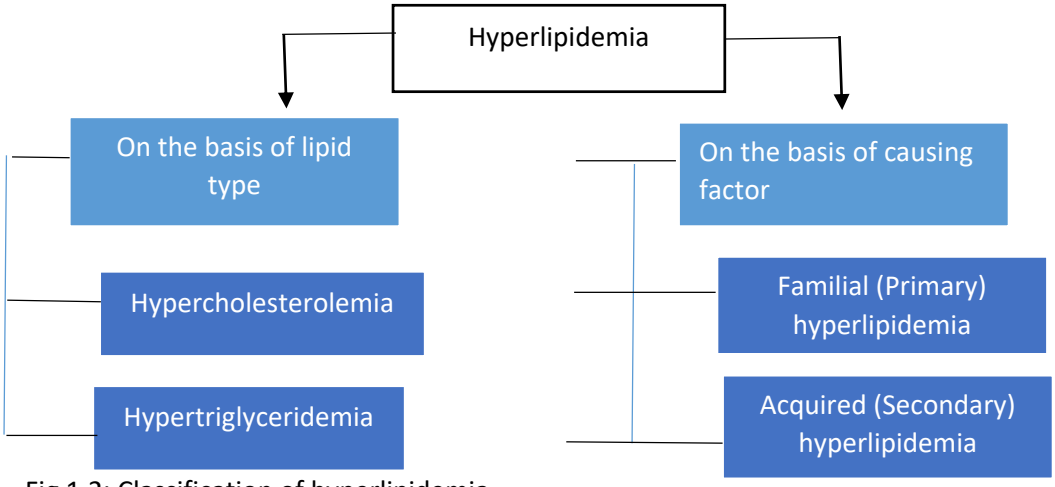

Fig 1.2: Classification of hyperlipidemia

Hyperlipidemia secondary to a medical condition acquired over time Acquired means that it is a consequence of underlying conditions. Changes in the metabolism of plasma lipoproteins18 are caused by the development of acquired hyperlipidemia. The combination of acquired hyperlipidemia with substantial hyper triglyceridemia may lead to an increased risk of early atherosclerosis, pancreatitis, and other consequences of the chylomicronemia syndrome.

Causes of acquired hyperlipidemia
Diabetes Mellitus
Use of drugs such as diuretics, β-blockers and estrogens.
Alcohol consumption.
Some rare endocrine disorders and metabolic disorders.
Hypothyroidism
Renal failure
Insulin Resistance Type 2 Diabetes
using diuretics, -blockers, and estrogens.
Consumption of alcohol.
There are a few uncommon endocrine and metabolic conditions.
Hypothyroidism
failure of the kidneys
Syndrome of nephrosis

Table 1.4: Causes of acquired haemophilia

Symptoms of hyperlipidemia

Although there are no evident signs of hyperlipidemia, it is generally discovered through routine medical examinations. Hyperlipidaemia is also often seen in patients who have had a stroke or heart attack. There are just a few circumstances in which hyperlipidemia is present:

-Hyperlipidemia on few cases leads to atherosclerosis, characterised with chest pain (angina), further which the body may undergo heart attack or stroke[20].

-Xanthomas, deposits of cholesterol is develop in patient with familial form or high blood cholesterol level under the skin, more specifically under the eye[21].

-The high level of triglycerides may form nodules on the knees[22].

-Hyperglycaemia is also associated with swollen liver and pancreas.

- Vessels of brain and heart may be blocked.

Complications of hyperlipidaemia:

Atheosclerosis:

Cholesterol, fat, and calcium buildup in the arterial walls is a frequent ailment. Large and medium fibrous plaques occur as a consequence of this deposit in the arteries. The pathophysiology of atherosclerosis is said to be influenced by cholesterol. Atherosclerosis, the leading cause of cardiovascular disease, is thought to be exacerbated by hyperlipidemia, which is a key risk factor for this illness.

Coronary Artery Disease:

Atherosclerosis, the buildup of lipids in the arterial walls that results in fibrous plaque, is the primary cause of coronary artery disease. The myocardial receives its blood via the arteries, which get narrowed as a result of lipid buildup, reducing the amount of blood and oxygen available to the heart. In the long term, the heart muscle will be damaged because of the irregular blood supply. Consequently, a rise in lipids has been linked to coronary artery disease.

Myocardial Infraction:

Myocardial Infarction (MI) is a condition, where there is lack of oxygen required by the myocardium to supply blood to the coronaries. It is further characterised by chest pain or discomfort extending to shoulder, arm, back, neck and/or jaw[27].This lack of blood and oxygen supply further results in cardiac cell damage or death of cardiac cell[28].

Ischemic stroke or cerebrovascular accident:

Essentially, it's a disorder in which part or all of the brain's blood supply is cut off. Brain health depends on the oxygen and other nutrients carried by the blood. When the brain's blood supply is cut off, the brain's neuron brain cells die and cease to perform their duties. When an artery is blocked by a stroke-causing clot in the brain, the condition is known as a stroke. Stroke risk may be lowered by a reduction in low density lipoprotein and total cholesterol, according to research done in clinical trials29.

Angina Pectoris:

Angina is a symptom, not a disease of the heart. Chest pain, uneasiness, and/or a pressing sensation are common symptoms. To put it another way, it's when there's a lack of blood flow to the heart muscle. Heart disease, specifically occlusion of a coronary artery, causes a reduction in blood flow.30

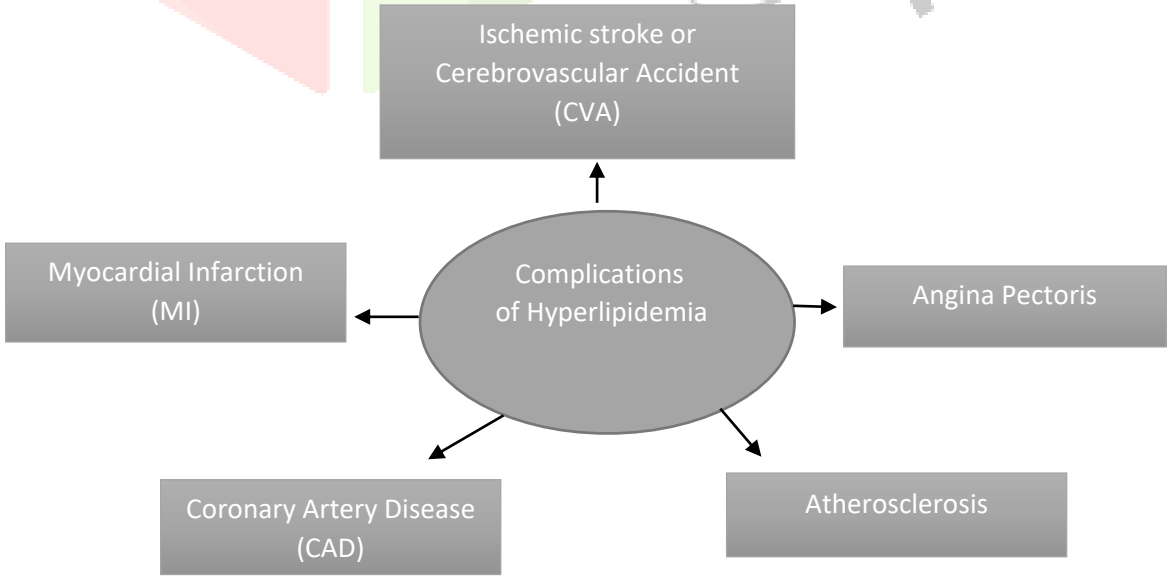

Fig 1.3: Complications of hyperlipidemia

Pathophysiology of hyperlipidemia:

Primary and secondary hyperlipidemia are the two main forms of hyperlipidemia pathogenesis.

Primary hyperlipidemia's aetiology:

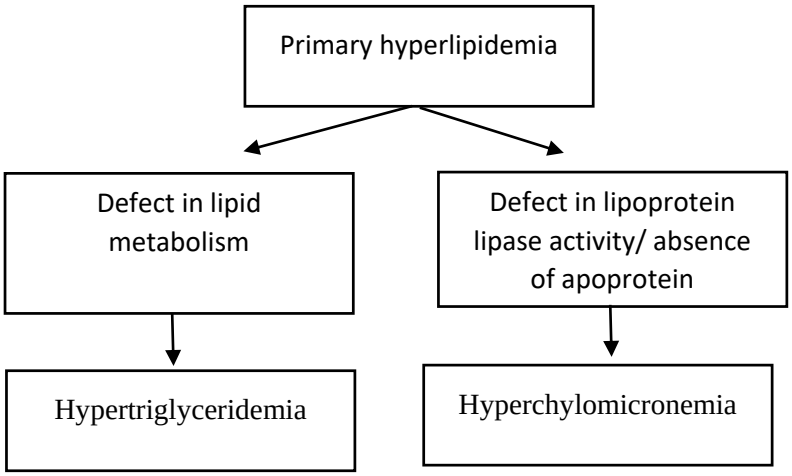

Fig 1.4: Pathophysiology of primary hyperlipidemia

Pathophysiology of secondary hyperlipidemia:

Fat containing meal increases serum triglycerides for about 3-10 hours as the after food chylomicrons absorption from the GI tract occurs after 30-60 minutes[31]. Hyperlipidemia is seen in diabetic patients due to low LPL activity causing the liver to synthesis VLDL. Hypercholesterolemia and hypertriglyceridemia are caused by the liver's increased production of VLDL in hyperadrenocorticism32. The conversion of cholesterol to bile acids is reduced in hypothyroidism. The atherosclerotic lesions form as a result of LDL being transported and retained in the extracellular matrix of endothelial cells. LDL enter the artery wall and undergo oxidation which attaches monocytes into the artery wall the monocytes accelerates oxidation of LDL when transformed into macrophage. Oxidized LDL have inflammatory responses which is mediated by cytokines[33].

Cholesterol hypothesis: Cholesterol enters the bloodstream in the form of complexes of lipids and proteins, which are degraded into bile acids before being expelled in the form of biliary secretions. Acetyl coenzyme A is used to synthesise cholesterol (acetyl-CoA). –ketothiolase also condenses two acetyl-CoA molecules into acetoacetyl-CoA. 3-Hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA) is the limiting enzyme in the production of cholesterol from squalene and cytochrome P450 51 controls the post-squalene section of the process (CYP51). The CYP51 enzyme removes the 14-methyl group of lanosterol as the initial sterol precursor in the process of cholesterol production. A protein similar to Niemann-Pick C1 and ATP-binding cassette (ABC) transporters ABCG5 and ABCG8 work together to transport cholesterol into the enterocyte. triglycerides are hydolyzed in the blood by lipids to release cholesterol, which is then released into the bloodstream as very low density lipoproteins (VLDLs) (VLDL). Once released into the bloodstream, very low density lipoproteins (VLDL) lose their lipid content and become IDLs and then low density lipoproteins (LDLs) (LDLs). LDLs are responsible for transporting cholesterol to peripheral tissues, where it is subsequently hydroxylated by the lysosomal enzyme to release free cholesterol. Atherosclerotic plaques are caused by the activation of the enzyme, acyl cholesterol acyltransferase (ACAT), which is activated by free cholesterol and then re-esterifies cholesterol for storage. CYP27A1 or CYP46A1 are expressed in neural tissues that hydroxylate excess cholesterol to eliminate it.

CYP7A1 : A significant part of the liver's daily clearance of 400–600 mg of cholesterol is due to this crucial predictor of plasma cholesterol levels. Cholesterol is converted to 7-hydroxycholesterol by CYP7A1. There was an increase in total cholesterol in three people who were deficient in cholesterol 7 hydroxylase, and they were shown to be resistant to statin therapy35,36.

CYP27A1: Only 18–20 mg of cholesterol are excreted by CYP27A1.

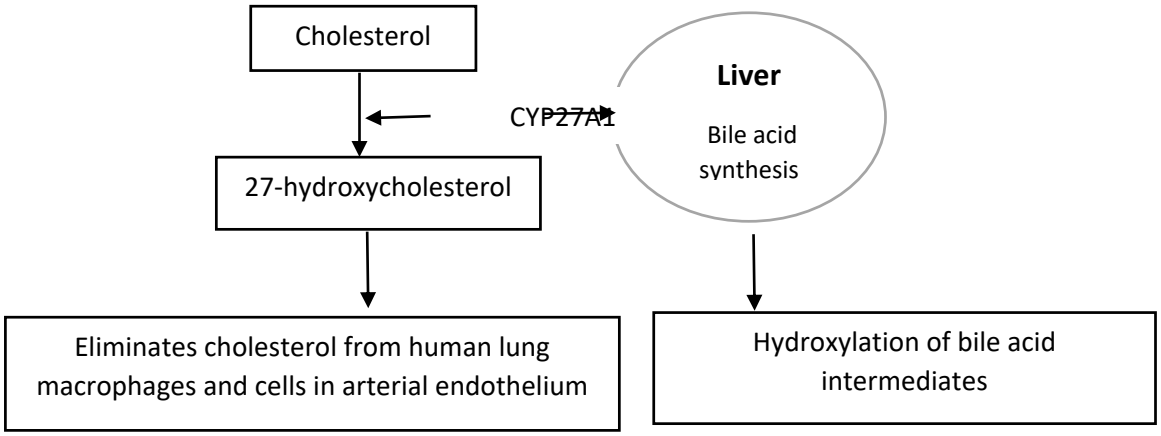

Fig: Mechanism of CYP27A1 for cholesterol lowering[37].

The CYP27A1 activity of a person with CYP7A1 deficit was twice as high as that of a control participant with no CYP7A136 mutation. Slowly increasing cerebrotendinous xanthomatosis (CTX) is characterised by many symptoms such as early atherosclerosis38 in those who are deficient in this enzyme.

CYP46A1:

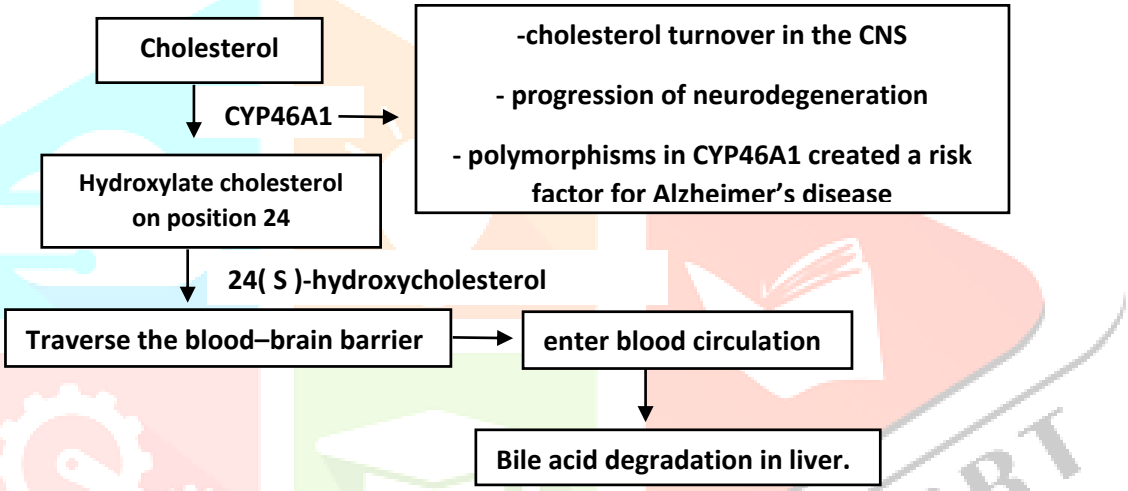

Fig: **Mechanism of CYP46A1 for cholesterol lowering[38,39,40].**

Factors affecting hyperlipidemia:

-Age: When it comes to cardiovascular disease risk, persons with familial hypercholesterolemia are more likely to have very high LDL-C values, whereas those with genetic polymorphisms have a much lower risk than the general population.

-**Environment**: Environmental tobacco smoke (ETS) and hyperlipidemia were the focus of a Taiwanese research that looked at how stress at work affected both variables. An increased risk of hyperlipidemia was shown to be associated with both poor dietary choices and high levels of work-related stress, according to the findings. Non-obese, non-smoking individuals who have been exposed to ETS as well as those who have experienced work-related stress have an increased chance of developing hyperlipidemia.

Because cadmium absorbed by soil is hazardous to human health, soil cadmium contamination is a significant source of pollution. An increase in high-density lipoprotein (HDL) function led to hyperlipidemia, inflammation, and alterations in the liver's fatty composition in zebrafish models given a high cholesterol diet containing cadmium41.

There is a role for trace elements in physiological processes and in the metabolism of food. A zebrafish model's ability to maintain homeostasis of lipids was shown to be influenced by iron ingestion in studies using HCD-fed zebrafish after only 24 weeks of iron consumption42.

- **Racial/ethnic differences in lipid profiles:** Compared to Whites, African–Americans have a greater lipid profile. Decreased hepatic lipase activity and lower triglyceride levels have been reported in African–Americans44. When it comes to lipoprotein (a), which has an extra disulfide-linked glycoprotein known as ApoA, African–Americans have lower levels than whites.45,46

Diagnosis of hyperlipidemia

Hyperlipidemia does not show any symptoms at an early stage and later result in stroke or other cardiac disorder. Hyperlipidemia can be detected by a blood test, namely termed as lipid profile test. Normal levels for a lipid profile[47,48] are listed below (table)

Lipids	Desirable value	Borderline	High risk
Cholesterol	Less than 200 mg/dl	200-239 mg/dl	240 mg/dl
Triglycerides	Less than 140 mg/dl	150-199 mg/dl	200-499 mg/dl
HDL cholesterol	60 mg/dl	40-50 mg/dl	Less than 40 mg/dl
LDL cholesterol	60-130 mg/dl	130-159 mg/dl	160-189 mg/dl
Cholesterol/HDL ratio	4	5	6

Table 1.5: Normal levels for a lipid profile Review of NIHARIKA VERMA's article, "Introduction to Hyperlipidemic Disorder and Treatment,"

Prevention of hyperlipidemia

-Review of NIHARIKA VERMA's article, "Introduction to Hyperlipidemic Disorder and Treatment,"

-Soluble fiber-rich foods include oats, beans, and certain fruits.

-Maintaining a healthy weight requires frequent exercise.

Treatment of hyperlipidemia:

An individual's lipid levels and stage of hyperlipidemia affect the therapy options. Regular physical activity, a low-fat diet, and weight loss and smoking cessation are also recommended by doctors as a starting point for therapy. Monotherapy or combination therapy is used based on the severity of hyperlipidemia to further develop the treatment. Ayurveda therapy, on the other hand, falls under the umbrella of holistic medicine, which emphasises well-being via food, nutrition, herbs, yoga, meditation, and seasonal rituals. In addition to pharmaceutical and Ayurveda treatments, home remedies may help decrease fat and cholesterol levels in the body by using just a few items.

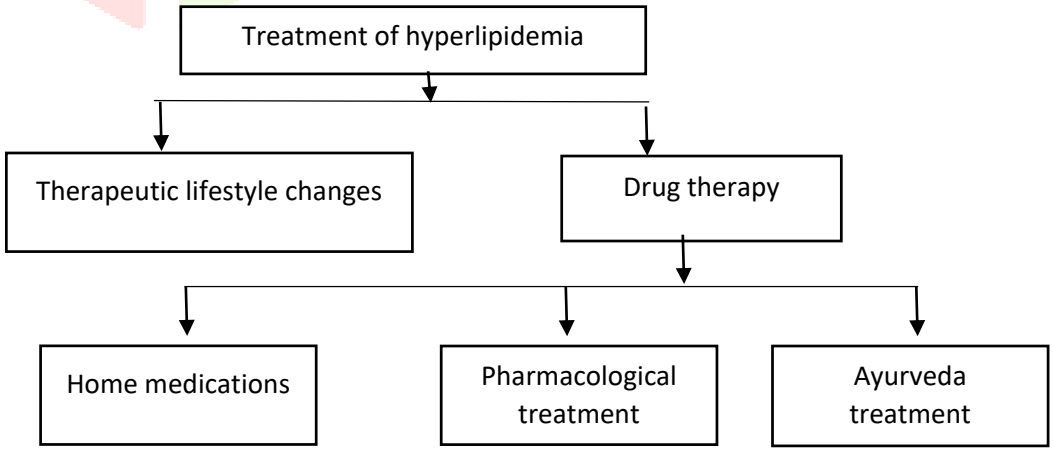

Fig 1.5: Treatment of hyperlipidemia

Therapeutic lifestyle changes

Change in lifestyle is the initial treatment recommended to lower the lipids level. Few of the recommended lifestyle changes for improving the health in relation to hyperlipidemia are:

-Diet modification with less intake of fats.

- Regular physical activity

-Smoking cessation

-Weight management.

Drug therapy

The initiation of a drug qualifies in presence of high LDL with the presence of risk factors. The lipid lowering drugs available are listed below[49]:

Drug	Mechanism of action
HMG-CoA reductase inhibitors Lovastatin Simvastatin Atorvastatin Rosuvastatin	↓ CH synthesis by inhibition of rate limiting HMG-CoA reductase
Bile acid sequestrants Cholestyramine Colestipol	↓ bile acid absorption, ↑ hepatic conversion of CH to bile acids, ↑ LDL receptors on hepatocytes
Fibric acid derivatives Gemfibrozil Bezafibrate Fenofibrate	↑ Activity of lipoprotein lipase, ↓ release of fatty acids from adipose tissue
Nicotinic acid	↓ Production of VLDL, ↓ lipolysis in adipocytes

Plants having hypoglycaemic activity:

Hyperlipidemia may be prevented using hypolipidemic medications, although these medications have side effects. For the treatment of hyperlipidemia, there is a need for novel molecules with fewer side effects. There is no comparison between herbal hypolipidemic medications in terms of potency or negative effects. Because of their hypolipidemic properties, these natural compounds are sought after by patients. Listed below are a few hypoglycemic therapeutic plants:

S.NO	Plant name	Family	Plant part	Reference
1	Abelomoschus esculentus	Malvaceae	Whole plant	50
2	Amaranthus Spinosus	Amaranthaceae	Leaves	51
3	Crotalaria juncea	Fabaceae	Leaves	52
4	Chlorophytum Borivilianum	Liliaceae	Leaves	53
5	Ougeinia oojeinensis	Fabaceae	Bark	54
6	Bauhinia purpurea	Fabaceae	Leaves	55
7	Glycyrrhiza Glabra	Fabaceae	Root	56
8	Hibiscus cannabinus	Malvaceae	Fresh mature leaves	57
9	Withania Somnifera	Solanaceae	Root	58
10	Moringa oleifera	Moringaceae	Leaves, roots, seeds	59
11	Luffa aegyptiaca	Cuccurbitaceae	Fruit	60
12	Rhinacanthus nasutus	Acanthaceae	Whole plant	61
13	Eclipta prostrate	Asteraceae	Plant juice	62

Table 1.6: Medicinal plants with hypolipidemic activity.

Screening models available for hypolipidemia Study:

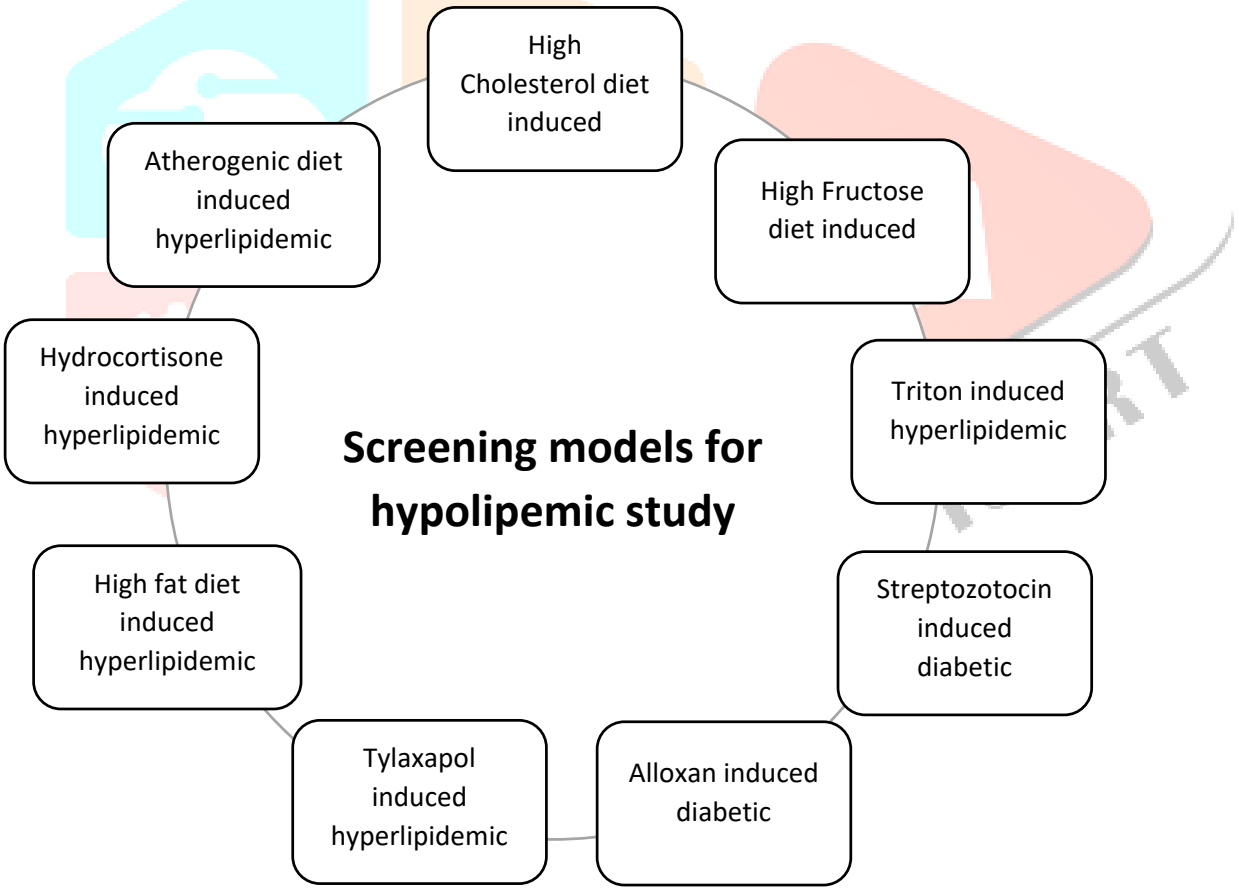

Fig 1.6: Screening models available for hypolipidemia Study

SL.No	Model	Reference
1	High Cholesterol diet induced method	63
2	High Fructose diet induced method	64
3	Triton induced hyperlipidemic method	65
4	Streptozotocin induced diabetic method	66
5	Alloxan induced diabetic method	67
6	Tylaxapol induced hyperlipidemic method	68
7	High fat diet induced hyperlipidemic method	69
8	Hydrocortisone induced hyperlipidemic method Diabetic induction by streptozotocin Diabetic induction by alloxan Hyperlipidemia caused by Tylaxapol Hyperlipidemia caused by a high-fat diet is one option. Method for inducing hyperlipidemia using hydrocortisone	70
9	Hyperlipidemic method produced by an atherosclerotic diet	71

Table1.7: Screening models for hypolipidemic study.

SL.No	Other Models
1	Hereditary hypercholesterolemia in experimental animals like rats
2	Hereditary hyperlipidemia in rabbits.
3	Transgenic animals- apoprotein E knock out model
4	Fructose induced hypertriglyceridemia in laboratory animal rats

Table 1.8: Other Screening models for hypolipidemic study.

Zebrafish as a model for screening effective Antihyperlipidemic drugs

Zebrafish fish was used as a model for hypolidipemic study due to the similar development and metabolic processes to mammals[72]. The zebrafish is generally small in size, a low cost for maintenance and develops rapidly[73]. It has been reported that zebrafish was also used to analyze the and observe the lipid metabolism[74]. In a research that used zebrafish as a model for antihyperlipidemia, it was revealed that the lipid levels of High Fat Diet zebrafish were dramatically elevated and that atorvastatin, fenofibrate, and ezetimibe exhibited lipid-lowering effects to some extent75. Dyslipidaemia and its accompanying illnesses have also been studied using Zebrafish models76.

Lxr Mutant Zebrafish:

Lxrα and Lxrβ are liver X receptor genes in mammals responsible for cholesterol metabolism. In zebrafish, Lxrα is present and knocked out result in LDL elevation in a High cholesterol diet or high at diet. This result in increased cholesterolemia and hepatic steatosis[77].

Apoc2 Mutant Zebrafish

APOC2 is lipoprotein lipase activator having a role in lipid metabolism[78]. Deletion of apoc2 Zebrafish via TALEN technology revealed chylomicronemia and severe hypertriglyceridemia [79]

CONCLUSION: Hyperlipidemia, a leading cause of coronary heart disease, is the subject of this review. The management, symptoms, kinds, categorization, and pathophysiology of hyperipidemia are discussed in this article. Plants with hypolididemic properties are among the many treatments available, including psychotherapy and pharmacology. The numerous screening methods for hypolipidemic activity are also discussed in the text.

REFERENCE

1. Xiao C, Dash S, Morgantini C, Hegele RA, Lewis GF. Pharmacological targeting of the atherogenic dyslipidemia complex: the next frontier in CVD prevention beyond lowering LDL cholesterol. Diabetes. 2016 Jul 1;65(7):1767-78.
2. Keating GM. Evolocumab: a review in hyperlipidemia. American Journal of Cardiovascular Drugs. 2016 Feb 1;16(1):67-78.
3. Fahy E, Subramaniam S, Brown HA, Glass CK, Merrill AH, Murphy RC, Raetz CR, Russell DW, Seyama Y, Shaw W, Shimizu T. A comprehensive classification system for lipids1. Journal of lipid research. 2005 May 1;46(5):839-61.
4. Smelt AH. Triglycerides and gallstone formation. Clinica chimica acta. 2010 Nov 11;411(21-22):1625-31.
5. Verma N. Introduction to hyperlipidemia and its treatment: A review. Int J Curr Pharm Res. 2016;9(1):6-14.
6. Feingold KR, Grunfeld C. Lipids: a key player in the battle between the host and microorganisms1. Journal of lipid research. 2012 Dec 1;53(12):2487-9.
7. Sundaram M, Yao Z. Recent progress in understanding protein and lipid factors affecting hepatic VLDL assembly and secretion. Nutrition & metabolism. 2010 Dec;7(1):1-7.
8. Rhee EJ, Kim HC, Kim JH, Lee EY, Kim BJ, Kim EM, Song Y, Lim JH, Kim HJ, Choi S, Moon MK. 2018 Guidelines for the management of dyslipidemia in Korea. Journal of Lipid and Atherosclerosis. 2019 Sep 1;8(2):78-131.
9. Costet P. Molecular pathways and agents for lowering LDL-cholesterol in addition to statins. Pharmacology & therapeutics. 2010 Jun 1;126(3):263-78.
10. Ridker PM, Genest J, Boekholdt SM, Libby P, Gotto AM, Nordestgaard BG, Mora S, MacFadyen JG, Glynn RJ, Kastelein JJ, JUPITER Trial Study Group. HDL cholesterol and residual risk of first cardiovascular events after treatment with potent statin therapy: an analysis from the JUPITER trial. The Lancet. 2010 Jul 31;376(9738):333-9.
11. Danesh J, Collins R, Peto R. Lipoprotein (a) and coronary heart disease: meta-analysis of prospective studies. Circulation. 2000 Sep 5;102(10):1082-5.
12. Schade DS, Shey L, Eaton RP. Cholesterol Review: A Metabolically Important Molecule. Endocrine Practice. 2020 Dec 1;26(12):1514-23.
13. Pichot R, Watson RL, Norton IT. Phospholipids at the interface: current trends and challenges. International journal of molecular sciences. 2013 Jun;14(6):11767-94.
14. Drescher S, van Hoogevest P. The Phospholipid Research Center: Current Research in Phospholipids and Their Use in Drug Delivery. Pharmaceutics. 2020 Dec;12(12):1235.
15. Kimura I, Ichimura A, Ohue-Kitano R, Igarashi M. Free fatty acid receptors in health and disease. Physiological reviews. 2019 Oct 30.
16. Sieber J, Jehle AW. Free fatty acids and their metabolism affect function and survival of podocytes. Frontiers in endocrinology. 2014 Oct 27;5:186.
17. Elkins RC, Milnor WR. An Official Journal of the American Heart Association.
18. Shattat GF. A review article on hyperlipidemia: types, treatments and new drug targets. Biomedical and Pharmacology Journal. 2015 May 3;7(1):399-409.
19. Chait A, Brunzell JD. Acquired hyperlipidemia (secondary dyslipoproteinemias). Endocrinology and metabolism clinics of North America. 1990 Jun 1;19(2):259-78.
20. Wouters K, Shiri-Sverdlov R, van Gorp PJ, van Bilsen M, Hofker MH. Understanding hyperlipidemia and atherosclerosis: lessons from genetically modified apoe and ldlr mice. Clinical Chemistry and Laboratory Medicine (CCLM). 2005 May 1;43(5):470-9.
21. Gofman JW, Lindgren F, Elliott H, Mantz W, Hewitt J, Strisower B, Herring V, Lyon TP. The role of lipids and lipoproteins in atherosclerosis. Science. 1950 Feb 17;111(2877):166-86.
22. Haffner SM. Diabetes, hyperlipidemia, and coronary artery disease. The American journal of cardiology. 1999 May 13;83(9):17-21.
23. Gao W, He HW, Wang ZM, Zhao H, Lian XQ, Wang YS, Zhu J, Yan JJ, Zhang DG, Yang ZJ, Wang LS. Plasma levels of lipometabolism-related miR-122 and miR-370 are increased in patients with hyperlipidemia and associated with coronary artery disease. Lipids in health and disease. 2012 Dec;11(1):1-8.
24. Azab AE, Elsayed AS. Acute myocardial infarction risk factors and correlation of its markers with serum lipids. J Appl Biotechnol Bioeng. 2017;3(4):00075.
25. Nickolas TL, Radhakrishnan J, Appel GB. Hyperlipidemia and thrombotic complications in patients with membranous nephropathy. InSeminars in nephrology 2003 Jul 1 (Vol. 23, No. 4, pp. 406-411). WB Saunders.

26. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. The Lancet Neurology. 2009 May 1;8(5):453-63.
27. Nelson RH. Hyperlipidemia as a risk factor for cardiovascular disease. Primary Care: Clinics in Office Practice. 2013 Mar 1;40(1):195-211.
28. Mauch DH, Nägler K, Schumacher S, Göritz C, Müller EC, Otto A, Pfrieger FW. CNS synaptogenesis promoted by glia-derived cholesterol. Science. 2001 Nov 9;294(5545):1354-7.
29. Jeong J, McMahon AP. Cholesterol modification of Hedgehog family proteins. The Journal of clinical investigation. 2002 Sep 1;110(5):591-6.
30. Schaefer EJ, Levy RI. Pathogenesis and management of lipoprotein disorders. New England Journal of Medicine. 1985 May 16;312(20):1300-10.
31. Armstrong C. Endocrine society releases guidelines on diagnosis and management of hypertriglyceridemia. American family physician. 2013 Jul 15;88(2):142.
32. FOR EP, CHILDREN RR. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011 Dec;128(Suppl 5):S213.
33. Ngoc TH, Ngoc QN, Tran A, Phung NV. Hypolipidemic effect of extracts from Abelmoschus esculentus L.(Malvaceae) on tyloxapol-induced hyperlipidemia in mice. J Pharm Sci. 2008;35(1-4):42-6.
34. Pikuleva IA. Cholesterol-metabolizing cytochromes P450: implications for cholesterol lowering. Expert opinion on drug metabolism & toxicology. 2008 Nov 1;4(11):1403-14.
35. Russell DW. The enzymes, regulation, and genetics of bile acid synthesis. Annual review of biochemistry. 2003 Jul;72(1):137-74.
36. Pullinger CR, Eng C, Salen G, Shefer S, Batta AK, Erickson SK, Verhagen A, Rivera CR, Mulvihill SJ, Malloy MJ, Kane JP. Human cholesterol 7α-hydroxylase (CYP7A1) deficiency has a hypercholesterolemic phenotype. The Journal of clinical investigation. 2002 Jul 1;110(1):109-17.
37. Duane WC, Javitt NB. 27-hydroxycholesterol: production rates in normal human subjects. Journal of lipid research. 1999 Jul 1;40(7):1194-9.
38. Bjorkhem I. Inborn errors in bile acid biosynthesis and storage of sterols other than cholesterol. The metabolic and molecular basis of inherited disease. 1995.
39. Kotti TJ, Ramirez DM, Pfeiffer BE, Huber KM, Russell DW. Brain cholesterol turnover required for geranylgeraniol production and learning in mice. Proceedings of the National Academy of Sciences. 2006 Mar 7;103(10):3869-74.
40. Abildayeva K, Jansen PJ, Hirsch-Reinshagen V, Bloks VW, Bakker AH, Ramaekers FC, De Vente J, Groen AK, Wellington CL, Kuipers F, Mulder M. 24 (S)-hydroxycholesterol participates in a liver X receptor-controlled pathway in astrocytes that regulates apolipoprotein E-mediated cholesterol efflux. Journal of Biological Chemistry. 2006 May 5;281(18):12799-808.
41. Kim JY, Kim SJ, Bae MA, Kim JR, Cho KH. Cadmium exposure exacerbates severe hyperlipidemia and fatty liver changes in zebrafish via impairment of high-density lipoproteins functionality. Toxicology in Vitro. 2018 Mar 1;47:249-58.
42. Kim JY, Lee EY, Choi I, Kim J, Cho KH. Effects of the particulate matter2. 5 (PM2. 5) on lipoprotein metabolism, uptake and degradation, and embryo toxicity. Molecules and cells. 2015 Dec 31;38(12):1096.
43. Vega GL, Clark LT, Tang A, Marcovina S, Grundy SM, Cohen JC. Hepatic lipase activity is lower in African American men than in white American men: effects of 5′ flanking polymorphism in the hepatic lipase gene (LIPC). Journal of lipid research. 1998 Jan 1;39(1):228-32.
44. Sumner AE, Vega GL, Genovese DJ, Finley KB, Bergman RN, Boston RC. Normal triglyceride levels despite insulin resistance in African Americans: role of lipoprotein lipase. Metabolism. 2005 Jul 1;54(7):902-9.
45. Utermann G. The mysteries of lipoprotein (a). Science. 1989 Nov 17;246(4932):904-10.
46. Danesh J, Collins R, Peto R. Lipoprotein (a) and coronary heart disease: meta-analysis of prospective studies. Circulation. 2000 Sep 5;102(10):1082-5.
47. Girija K, Lakshman K. Anti-hyperlipidemic activity of methanol extracts of three plants of Amaranthus in triton-WR 1339 induced hyperlipidemic rats. Asian Pacific Journal of Tropical Biomedicine. 2011 Sep 1;1(1):S62-5.
48. Dhaliya S, Surya A, Dawn V, Betty C, Arun K, Sunil C. A review of hyperlipidemia and medicinal plants. Int JA PS BMS. 2013 Oct;2(4):219-37.
49. Visavadiya NP, Narasimhacharya AV. Ameliorative effects of herbal combinations in hyperlipidemia. Oxidative medicine and cellular longevity. 2011 Sep 15;2011.

50. Velmurugan C, Sundaram T, Sampath Kumar R, Vivek B, Sheshadrishekar D, Ashok Kumar BS. Anti diabetic and hypolipidemic activity of bark of ethanolic extract of Ougeinia oojeinensis (ROXB.). Med J Malaysia. 2011 Mar 1;66(1):23.
51. Lakshmi BV, Neelima N, Kasthuri N, Umarani V, Sudhakar M. Antihyperlipidemic activity of Bauhinia purpurea extracts in hypercholesterolemic albino rats. Int J Pharm Tech Res. 2011;3(3):1265-72.
52. Visavadiya NP, Narasimhacharya AV. Ameliorative effects of herbal combinations in hyperlipidemia. Oxidative medicine and cellular longevity. 2011 Sep 15;2011.
53. Pradeep K, Gagandeep K, Nanjaian M. Antihyperlipidemic effect of hydroalcoholic extract of Kenaf (Hibiscus cannabinus L.) leaves in high fat diet fed rats. Annals of biological research. 2010;1(3):174-81.
54. Rajanandh MG, Satishkumar MN, Elango K, Suresh B. Moringa oleifera Lam. A herbal medicine for hyperlipidemia: A pre–clinical report. Asian Pacific Journal of Tropical Disease. 2012 Jan 1;2:S790-5.
55. Thayyil AH, Surulivel MK, Ahmed MF, Ahamed GS, Sidheeq A, Rasheed A, Ibrahim M. Hypolipidemic activity of Luffa Aegiptiaca fruits in cholesterol fed hypercholesterolemic rabbits. Int J Pharm Appl. 2011 Jan 1;2(1):81-8.
56. Desu BS, Saileela CH. Anti-hyperlipidemic activity of methanolic extract of Rhinacanthus nasutus. Int J Res Pharm Chem. 2013;3(3):708-11.
57. Zhao Y, Peng L, Lu W, Wang Y, Huang X, Gong C, He L, Hong J, Wu S, Jin X. Effect of Eclipta prostrata on lipid metabolism in hyperlipidemic animals. Experimental gerontology. 2015 Feb 1;62:37-44.
58. Ónody A, Csonka C, Giricz Z, Ferdinandy P. Hyperlipidemia induced by a cholesterol-rich diet leads to enhanced peroxynitrite formation in rat hearts. Cardiovascular research. 2003 Jun 1;58(3):663-70.
59. Horne RG, Yu Y, Zhang R, Abdalqadir N, Rossi L, Surette M, Sherman PM, Adeli K. High Fat-High Fructose Diet-Induced Changes in the Gut Microbiota Associated with Dyslipidemia in Syrian Hamsters. Nutrients. 2020 Nov;12(11):3557.
60. Schurr PE, Schultz JR, Parkinson AT. Triton-induced hyperlipidemia in rats as an animal model for screening hypolipidemic drugs. Lipids. 1972 Jan;7(1):68-74.
61. Maiti R, Das UK, Ghosh D. Attenuation of hyperglycemia and hyperlipidemia in streptozotocin-induced diabetic rats by aqueous extract of seed of Tamarindus indica. Biological and Pharmaceutical Bulletin. 2005;28(7):1172-6.
62. Ojiako OA, Chikezie PC, Ogbuji AC. Blood glucose level and lipid profile of alloxan-induced hyperglycemic rats treated with single and combinatorial herbal formulations. Journal of traditional and complementary medicine. 2016 Apr 1;6(2):184-92.
63. Ngoc TH, Ngoc QN, Tran A, Phung NV. Hypolipidemic effect of extracts from Abelmoschus esculentus L.(Malvaceae) on tyloxapol-induced hyperlipidemia in mice. J Pharm Sci. 2008;35(1-4):42-6.
64. Sampathkumar MT, Kasetti RB, Nabi SA, Sudarshan PR, Swapna S, Apparao C. Antihyperlipidemic and antiatherogenic activities of Terminalia pallida Linn. fruits in high fat diet-induced hyperlipidemic rats. Journal of Pharmacy and Bioallied Sciences. 2011 Jul;3(3):449.
65. Meng X, Chen X, Wu L, Zheng S. The hyperlipidemia caused by overuse of glucocorticoid after liver transplantation and the immune adjustment strategy. Journal of immunology research. 2017 Jan 17;2017.
66. Sikarwar MS, Patil MB. Antihyperlipidemic activity of Salacia chinensis root extracts in triton-induced and atherogenic diet-induced hyperlipidemic rats. Indian journal of pharmacology. 2012 Jan;44(1):88.
67. Chen K, Wang CQ, Fan YQ, Xie YS, Yin ZF, Xu ZJ, Zhang HL, Cao JT, Wang Y, Gao L. Model design for screening effective Antihyperlipidemic drugs using zebrafish system. Pakistan journal of pharmaceutical sciences. 2017 Sep 1;30(5).
68. Dooley K, Zon LI. Zebrafish: a model system for the study of human disease. Current opinion in genetics & development. 2000 Jun 1;10(3):252-6.
69. Streisinger G, Walker C, Dower N, Knauber D, Singer F. Production of clones of homozygous diploid zebra fish (Brachydanio rerio). Nature. 1981 May;291(5813):293-6.
70. Walters JW, Anderson JL, Bittman R, Pack M, Farber SA. Visualization of lipid metabolism in the larval zebrafish intestine reveals a relationship between NPC1L1 mediated cholesterol uptake and dietary fatty acids. Chemistry & biology. 2012 Jul 27;19(7):913.
71. Chen K, Wang CQ, Fan YQ, Xie YS, Yin ZF, Xu ZJ, Zhang HL, Cao JT, Wang Y, Gao L. Model design for screening effective Antihyperlipidemic drugs using zebrafish system. Pakistan journal of pharmaceutical sciences. 2017 Sep 1;30(5).

72. Ka J, Jin SW. Zebrafish as an Emerging Model for Dyslipidemia and Associated Diseases. Journal of Lipid and Atherosclerosis. 2021 Jan;10(1):42.
73. Goodman C. Medical technology assessment directory: A pilot reference to organizations, assessments, and information resources.
74. Stone NJ. Secondary causes of hyperlipidemia. Medical Clinics of North America. 1994 Jan 1;78(1):117-41.
75. Castilla-Guerra L, del Carmen Fernández-Moreno M, Álvarez-Suero J. Secondary stroke prevention in the elderly: new evidence in hypertension and hyperlipidemia. European journal of internal medicine. 2009 Oct 1;20(6):586-90.
76. Pahan K. Lipid-lowering drugs. Cellular and molecular life sciences CMLS. 2006 May;63(10):1165-78.
77. Vedder VL, Aherrahrou Z, Erdmann J. Dare to compare. Development of atherosclerotic lesions in human, mouse, and zebrafish. Frontiers in Cardiovascular Medicine. 2020:109.
78. Wolska A, Dunbar RL, Freeman LA, Ueda M, Amar MJ, Sviridov DO, Remaley AT. Apolipoprotein C-II: New findings related to genetics, biochemistry, and role in triglyceride metabolism. Atherosclerosis. 2017 Dec 1;267:49-60.
79. Baggio G, Manzato E, Gabelli C, Fellin R, Martini S, Enzi GB, Verlato F, Baiocchi MR, Sprecher DL, Kashyap ML. Apolipoprotein C-II deficiency syndrome. Clinical features, lipoprotein characterization, lipase activity, and correction of hypertriglyceridemia after apolipoprotein C-II administration in two affected patients. The Journal of clinical investigation. 1986 Feb 1;77(2):520-7.