

REVIEW ARTICLE

Hyperlipidemia: Methods of Induction and Possible Treatments

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Abstract

Cardiovascular diseases (CVD) are very serious and can lead to death. The main cause of these diseases is atherosclerosis, which results from the deposition of lipids in the walls of blood vessels. Hyperlipidemia (HL) means an elevation of lipid levels (triglycerides (TG), low density lipoprotein (LDL), and very low-density lipoprotein (VLDL)) with a reduction in high density lipoprotein (HDL) in the blood. Prevention and treatment of HL reflect directly on atherosclerosis and CVD. Many studies have been done to prevent and treat HL, whether by regulating the diet or by using therapies, statins, fibrates, niacin derivatives, bile acid sequestrants, and cholesterol absorption inhibitors are considered the most important treatments used to control HL, and many studies are still being done to discover and evaluate more therapies with fewer side effects for treatment of such a case. For that purpose, induction of HL in lab animals is a must to simulate the naturally occurring CVD. Most of these studies depend on a high-fat diet for induction. The objective of the current review is to provide updated and characterized facts on the methods of HL induction and possible treatments. At the end of this review, we conclude that induction of an experimental hyperlipidemic model for the management of HL is still a goal for evaluating hyperlipidemic drugs. Due to the many problems that result from diet-induced HL, either through its harmful effect on the heart or time consumption, we had to find a new method for induction of HL by using drugs to induce HL within a few days with less harmful effects on the vessels and heart.

Keywords:

Atherosclerosis, Cardiovascular diseases, LDL, HDL, VLDL, and Triglycerides.

Introduction

Dyslipidemia is characterized by an abnormal blood lipid level. The most prevalent kind of dyslipidemia, hyperlipidemia (HL), It is marked by increasing levels of TG, LDL-C, and total cholesterol (TC) in peripheral blood, as well as a drop in HDL level [1]. In reality, HL is linked to a wide range of metabolic illnesses, including type 2 diabetes, hypertension, fatty liver, and atherosclerosis [2,3]. Hewage and Yaodeclared that certain endothelial

dysfunctions are brought on by sustained, extended HL, which is the main risk factor for atherosclerosis with cardiovascular complications [4,5].

HL can be diagnosed by elevated atherogenic indices, significant serum dyslipidemia (LDL, VLDL, TG), values of ischemia-modified albumin, and histopathological examination of the heart tissues [6].

Additionally, HL directly impacts the systolic function and cardiac

electrophysiological response of the heart, which may be connected to the continued buildup of cardiac lipids and the resulting oxidative stress, pro-inflammatory state, and mitochondrial dysfunction throughout the body [5].

A group of fats, or molecules that resemble fats, are found in the blood and are referred to as "lipids". The primary lipids found in blood are phospholipids, triacylglycerol (TAG), fatty acids, cholesterol, and cholesterol esters [7]. Lipoproteins are the particles that carry lipids since they are not soluble in plasma. Due to the heterogeneity of carrier lipoproteins, HL classifications are also based on them.

Types of lipoproteins

Chylomicrons are dietary fat carriers that are rich in triglycerides (TG). The TG-rich carrier of hepatic produced TGs is known as very low-density lipoprotein (VLDL). Low-density lipoprotein (LDL) and Intermediate-density lipoprotein (IDL) particles left over after the lipolysis of triglycerides in VLDL that are high in

cholesterol. HDL is a cholesterol-rich particle that carries cholesterol to the liver for excretion or recycling [8]. The density of lipoproteins grows proportionally to their protein contents but not to their lipid contents as the triglyceride and cholesteryl ester content of the core increases [9].

Hyperlipidemia classification

According to Kanakavalli *et al.* [7], HL can be broadly divided into two types: primary and secondary. The most common kind, often known as familial HL since it results from a genetic abnormality, may be polygenic (many gene faults) or monogenic (a single gene flaw) [10]. The second type, acquired HL, is brought on by other conditions such as hypothyroidism, nephritic syndrome, persistent drinking, diabetes, use of beta blockers, oral contraceptives, and corticosteroids. Pancreatitis can develop as a result of secondary hyperlipidemia and severe hypertriglyceridemia (Table 1).

Table 1: Fredrickson classification of primary hyperlipidemia [10]

Type	Disorder	Cause	Occurrence	Type of lipoprotein increased
I	Primary (monogenic) HL Or Familial hyperchylomicronemia	Altered ApoC2 or deficiency of LPL	Very rare	Chylomicrons
IIa	Polygenic HL Or Familial hypercholesterolemia	Deficiency of LDL receptor	Less common	LDL
IIb	Familial combined HL	increased ApoB and deficiency of LDL receptor	The most common	VLDL and LDL

III	Familial dysbetalipoproteinemia	Defect synthesis of in Apo E- 2	Not common	LDL
IV	Familial hypertriglyceridemia	Decrease excretion of VLDL and Increase its production	Common	LDL
V	Endogenous hypertriglyceridemia	decreased LPL and Increase production of VLDL	Not common	chylomicrons and VLDL

HL, hyperlipemia; ApoC2, apolipoprotein C2; Apolipoprotein lipase; LDL, low density lipoprotein; Apo B, apolipoprotein B; VLDL, very low-density lipoprotein; Apo E- 2, apolipoprotein E-2.

Causes of HL

HL is caused mainly by lifestyle patterns that change with a fat intake of more than 40% of total calories, saturated fats at more than 10% of total calories, cholesterol at more than 300 mg/day, or curable medical disorders. A diet with a high fat percent, along with other unhealthy lifestyle choices like drinking excessive amounts of alcohol, being overweight, not exercising, and smoking contributes to abnormal cholesterol levels. Pregnancy, diabetes, polycystic ovarian syndrome, renal illness, and an underactive thyroid gland are other contributing factors [11].

Higher levels of estrogen and other female hormones have been found to raise or alter cholesterol levels [12]. Previous scientists have noted that age and gender have a significant impact on the genesis and expansion of HL [13].

Signaling pathways of hyperlipidemia actions on myocardium function promoting cardiovascular diseases and their treatment

The main cause of death globally is cardiovascular disease (CVD). Lipids and lipoproteins significantly influence the onset and development of CVD through cellular production, assembly,

transit, plasma concentrations, oxidation, and breakdown [14]. Traditional classifications of lipids include "storage lipids" (such as fatty acids (FAs), sterols, and trans glycerols (TGs) and "structural lipids" (such as glycolipids, phospholipids (PLs), and ceramides) because lipids are essential for various physiological processes supporting biological life. A third group comprises the lipoproteins. The lipoproteins are divided into five categories depending on their density and size. These types are chylomicrons, VLDL, intermediate-density lipoprotein (IDL), LDL, and HDL [15].

Blood cholesterol levels provided the first definitive link between circulating lipids and CVD. Blood cholesterol level was identified as the first direct link between circulating lipids and CVD by the Framingham Heart Study (FHS) [16]. Increased cholesterol levels are associated with an increased 10-year risk of cardiovascular death [17].

High plasma levels of LDL, VLDL, and IDL lead to CVD by encouraging the growth of thrombi and plaque. The oxidised version of native LDL, known as oxLDL, and its post-translational oxidation are what cause atherosclerotic lesions to form. Macrophages within atherosclerotic lesions have scavenger

receptors (SRs) like SR-A1, CD36, and "lectin-like oxLDL receptor-1," which recognise and facilitate the uptake of oxidation-specific epitopes like ApoB-100 modification, cholesteryl ester modification, and PL oxidation on oxLDL but not native LDL[18]. LDL and transformed LDL that have been phagocytosed by macrophages are changed into free cholesterol by the liposomal acid lipase and then into cholesterol esters by the acetyl-coenzyme. Acetyltransferase, which in the endoplasmic reticulum is transformed into unbound cholesterol and released from the cells by cholesterol transporters. Modified LDL is atherogenic because macrophages cannot break it down, which leads to the creation of foam cells[18].

Finding possible therapeutic biomolecules for the prevention and therapy of CVD depends greatly on the synergistic impact of lipids with comparable mechanistic effects. Instead of the conventional categorization of lipids based on their fundamental biological functions, classification of lipids is required based on the mechanistic effect of lipids and lipoproteins on CVD.

Therefore, we advocate grouping lipids and lipoproteins into three distinct categories: (i) enhancing CVDs, (ii) having a conditional influence on CVDs, and (iii) having no known effect on CVDs due to a lack of proof. This categorization, which is consistent with the most recent recommendations for treating CVD [19].

Experimental induction of hyperlipidemia

1- Diet-Induced Hyperlipidemic laboratory animals

The most applicable method for induction of HL in lab animals is diet-

induced, which can be done by mainly two methods:

Cholesterol fed animals: by feeding the animal 8-week diet supplemented with 2% cholesterol[20], or feeding animals with a high-lipid diet enriched with 10% (w/w) lard, 1% (w/w) cholesterol, 1% sodium tauroglycocholate, 5% egg yolk and 0.2% propylthiouracil [21] or feeding animals high-fat diet (cholesterol, coconut oil, and cholestyramine each make up 0.5 g) kg/24 h: for 12 weeks [22] or feeding the animals a diet containing 1.3% cholesterol and 3% saturated fat for 40 days [23].

Due to the fact that a high-cholesterol diet is thought to play a significant role in the onset of cardiac disorders such as atherosclerosis, and ischemic heart disease, using these approaches to induce HL has a number of negative side effects[24]. Numerous research had examined the cellular effects of a diet high in cholesterol on the myocardium; nonetheless, it has been found that intracellular lipid buildup in cardiomyocytes and several changes to the myocardium's structural and functional characteristics have occurred[25].

Casein rich diet induced hyperlipidemia: Casein rich diet without cholesterol may also cause HL in lab animals by giving them a partially pure diet rich in 27% casein. Aortic atherosclerosis and plasma total cholesterol levels rise to 300-800 mg/dL as a result [26]. LDL are the primary increased lipoproteins in casein-fed mice, as opposed to the VLDL that are found in cholesterol-fed animals. Casein-fed animals also developed aortic atherosclerosis substantially less than cholesterol-fed animals [27].

Methionine induced hyperlipidemia

Methionine is a necessary amino acid that is present in a wide range of foods. Methionine helps your body create sulphates, which aid in memory and lower the risk of heart disease, and is used to produce proteins. The good news is that methionine may help prevent osteoporosis while maintaining the condition of your hair, nails, and skin. Concerns regarding the safety of methionine have been expressed [28]. It was found that methionine administration (1 g/kg, po) for 30 days can produce a significant increase in total cholesterol, triglycerides, and LDL with a concomitant decrease in serum HDL. This means that methionine can be used for induction of HL [29].

2- *Spontaneous Hyperlipidemic laboratory animals*

Watanabe Heritable Hyperlipidemic (WHHL) Rabbit

It is a type of rabbit developed by inbreeding from a mutant found in 1973 that has a reliably hereditary hyperlipidemic characteristic [30]. Since LDL functions are genetically absent in WHHL rabbits, they exhibit HL [30]. By deleting four amino acids from the ligand-binding domain of the LDL by an in-frame deletion of twelve nucleotides, it was shown that WHHL rabbits have a defective LDL. The typical rate of transport of mutant LDL to the cell surface is not possible [31]. When the LDL in WHHL rabbits is dysfunctional, there is a reduction in the absorption of LDL by the liver and a corresponding increase in plasma LDL levels that is comparable to HL in humans [32].

Postprandial Hypertriglyceridemic (PHT) lab animals

regular rabbits and the previously mentioned type of rabbits with a hypertriglyceridemia phenotypewere

crossed to create the PHT lab animal [33]. Both postprandial and fasting TG levels were elevated in PHT rabbits. PHT rabbits showed obesity and insulin resistance associated with hypertriglyceridemia [33].

St. Thomas' Mixed Hyperlipidemic (SMHL) Rabbits

The St. Thomas' Hospital rabbit, a possible model of familial mixed hyperlipidemia, was first introduced in the 1980s. It is now known as the SMHL rabbit. On a typical regular diet, these rabbits developed aortic atherosclerosis and revealed high levels of plasma TC (3940 mg/dL, 4- to 5-fold over normal rabbits) with relatively an increased or normal levels of plasma TG (1510 mg/dL, double-fold over normal rabbits) [34]. According to De Roos *et al.* [35], the plasma lipids of low-cholesterol-diet-fed SMHL rabbits were compared with those of WHHL rabbits. After three months of consuming a diet containing 0.08% cholesterol, SMHL rabbits displayed plasma cholesterol and TG levels of 264 and 290 mg/dL, respectively, as opposed to WHHL rabbits, who had TC and TG levels of 791 and 232 mg/dL, respectively [35].

3- *Gene-Manipulated laboratory animals*

Knockout (KO) lab animals: Animals with KO mutations were recently created and used to research HL [36]. On a typical regular diet, ApoE-KO mice displayed mild HL with TC levels at or below 200 mg/dL. When given a cholesterol diet, apo E KO mice shown more vulnerability to HL than did normal animals, and their plasma levels of TG and cholesterol were noticeably higher, with a 5-fold increase in TG and a 6-fold increase in cholesterol in comparison to normal animals [37]. The deletion of *apoE*

gene can be made through the use of one of two genome editing techniques. ApoE is a ligand for both the LDL receptor and lipoprotein receptor-related proteins, and it is crucial for the liver's ability to eliminate leftover lipoproteins. Human type III hyperlipoproteinemia is brought on by genetic *apoE* deficiency. Even when given a chow diet, animals with *apoE* deletion displayed HL[38].

Transgenic animals (TG): human apoE, C-III genes and B-100 are overexpressed within the hepatic tissue, which results in hyperlipidemic TG animals. Plasma TC and TG levels were three times higher in human apo B-100 TG rabbits than in normal rabbits [39]. Although HDL-C and TC levels were unaffected, plasma TG levels in apo C-III TG animals were 3-fold greater than those in normal animals. Elevated TG in apo C-III TG rabbits was scattered in VLDL and CM. according to lipoprotein analyses [40]. There have also been reports of TG animals expressing human apo E2, a variation linked to type III hyperlipoproteinemia, and apo E3, the most prevalent isoform in people. Higher amounts of human apo E3 (>20 mg/dL) expressed in tg animals resulted in marked mixed hyperlipidemia, which is defined by a rise in VLDL and LDL [41].

4- Triton induced hyperlipidemic lab animals

An example of a non-ionic detergent or surfactant is Triton X-100 (TX), which is an octylphenol polyethoxylate with a hydrophilic polyethylene oxide chain [42].

Triton x-100 and Triton wr-1339 were discovered to be the two different forms of triton that can be used in the induction of HL[42].

Triton x-100 induced hyperlipidemic animals:

A single intraperitoneal injection of freshly made Triton-X-100 (100 mg/kg) in physiological saline solution in rats and (200mg /kg) in rabbits can be used to induce HL. After an overnight fast of 18 h, it was shown that the lipid profile was elevated (total cholesterol, triglycerides, LDL, VLDL) one day after the injection [43].

Triton wr-1339 induced hyperlipidemic animals

Triton WR-1339, when dissolved in NS to a final concentration of 4%, can be injected intravenously once to induce HL at a dose of 400 mg/ kg. Triton WR-1339-induced hyperlipidemic rats' serum lipid levels were observed to be significantly elevated, increasing by about 7 folds in TG, 5 folds in TC, and 4 folds in LDL-C [44].

5-Glucocorticoids induced hyperlipidemia

Glucocorticoids are a category of corticosteroids. Since the glucocorticoid receptor is found in practically all cells of vertebrate animals. Glucocorticoids have a role in the immune system's feedback loop, which reduces some elements of immunological function like inflammation. As a result, they are employed in medicine to treat conditions including allergies, asthma, autoimmune illnesses, and sepsis that are brought on by an overactive immune system. The effects of glucocorticoids are very diverse, including some that might be dangerous. They're applied in large doses for treatment of tumors because they also disrupt some of the aberrant pathways found in cancer cells. This includes reducing the negative effects of anticancer medications and having an inhibitory effect on lymphocyte

proliferation, as in the treatment of lymphomas and leukemia [45].

When glucocorticoids attach their receptors, the activated glucocorticoid receptor-glucocorticoid complex increases the expression of anti-inflammatory proteins in the nucleus and suppresses the expression of pro-inflammatory proteins in the cytosol by blocking the translocation of additional transcription factors from the cytosol into the nucleus [45].

Krausz et al. [46] reported that rats kept on a small dosage, (0.5 mg/kg BW) of triamcinolone, one of the glucocorticoids, for 5 days revealed a double fold rise in triglyceride concentration, with subsequent elevation in VLDL components, without marked change in HDL or serum cholesterol. In response to a high dose of triamcinolone (12.5 mg/kg BW), VLDL and triacylglycerol levels decreased to the range of control levels, but HDL and serum cholesterol doubled. The substantial increases in activity of the rate-limiting enzymes of lipogenesis showed that the increase in VLDL was largely attributable to increased hepatic fatty acid production. The triamcinolone treatment caused substantial hyperinsulinemia, which was associated with an increase in the synthesis of fatty acids. The liver responded to this insulin preferentially, in contrast to peripheral tissues, which were generally insulin antagonistic. Small increases in serum glucagon were also brought on by triamcinolone treatment, but these adjustments didn't seem to have any bearing on the bimodal serum lipoprotein perturbations that were being seen. Triamcinolone dosage was observed to affect the pattern of plasma lipid increase, and this was thought to be a potential factor in the variability of glucocorticoid-induced HL [46].

Additionally, it was found that glucocorticoids-treated rabbits exhibit a prominent increase in plasma triglyceride levels, mainly with a decrease in HDL and small increase in other lipids [47].

Pharmacological treatment of hyperlipidemia

The management of HL, which attempts to prevent atherosclerosis and lower the risk of acute coronary events in patients with pre-existing coronary or peripheral vascular disease, relies heavily on dietary therapy in conjunction with hypolipidemic medications [48].

Harvey declared that drugs used for the treatment of hyperlipidemia are classified into five groups [49]:

1. HMG-CoA reductase inhibitors (statins)

Statins include atorvastatin, fluvastatin, lovastatin, and pravastatin. Statins operate by competitively inhibiting HMG-CoA reductase, the rate-limiting step in cholesterol manufacture, which causes the depletion of intracellular cholesterol. Statins and HMG CoA are structurally similar. HMG CoA is the main compound in cholesterol biosynthesis. The cell produces more LDL receptors as a result of this depletion. Plasma cholesterol decreases as a result, which is the final effect. Additionally, statins indirectly increase LDL activity and inhibit VLDL release into the bloodstream [50]. A microscopic iliac-femoral artery lesion treated with statin, particularly atorvastatin, demonstrated anti-atherogenic effects; however, the thoracic aorta gross lesion did not significantly change [51].

It has been demonstrated that statins reduce the risk of heart disease; however, this effect seems to be mostly brought about by a decrease in the risk of acute

coronary syndrome. However, some studies have shown that the use of statins in people with low to moderate cardiovascular risk is related with a decreased risk of coronary heart disease and stroke [52]. Statin use is expected to lower the risk of cardiovascular disease through a number of processes, including lower levels of LDL cholesterol, lessened platelet aggregation, and lower levels of C-reactive protein. These results have led to recommendations for statin usage for all individuals with type 2 diabetes mellitus, high LDL cholesterol, and other cardiovascular disease risk factors who are assessed to be at moderate risk based on age and medical history. Statins reduce LDL levels and the risk of cardiovascular events; however, in randomized controlled studies, they do not lower mortality [53].

2. *Fibrates*

Fenofibrate, gemfibrozil, and clofibrate are a few examples of fibrates. As TG-lowering medications, fibrates used to treat HL decrease TG-rich lipoproteins and enhance the production of the lipoprotein lipase enzyme and the concentration of apolipoprotein CII, which lowers the blood's TAG concentration. The U.S. Food and Drug Administration (FDA) has approved them for the treatment of HL[54]. They can help prevent atherosclerosis in animals fed cholesterol[55]. By lowering triglyceride-rich lipoproteins, also referred to as very low-density lipoproteins, they are thought to reduce the risk of heart disease (VLDL). Clinical investigations have confirmed the positive effects of fibrates [56]. In one trial, fibrates dramatically decreased the risk of cardiovascular disease when combined with a statin drug as opposed to a statin taken alone. Despite being often given, the usage of fibrates has declined recently, probably as a result

of worries about their connection to the liver condition rhabdomyolysis. They are not advised for those who have severe kidney illness, malnutrition, or severe liver disease. Statin therapy ought to be given to these folks instead. If statins are not tolerated, fibrates may be tried for people with mild-to-moderate liver disease [57].

3. *Niacin Derivatives*

Niacin, also known as vitamin B3, is a vitamin that dissolves in water and has been used for many years to treat HL. Niacin derivatives are substances that structurally resemble niacin and influence lipid metabolism similarly. Nicotinic acid, inositol hexanicotinate, and nicotinamide are some of these compounds [58].

The most commonly used niacin derivative for the treatment of HL is nicotinic acid. It functions by preventing lipoprotein lipase from doing its job, which lowers the creation of VLDL and raises the production of high-density lipoprotein HDL. Additionally, nicotinic acid lowers triglyceride levels by reducing the production of VLDL particles in the liver. Additionally, it makes LDL receptors in the liver more active, which increases the number of LDL particles that are cleared from circulation [59].

Another niacin derivative that has been researched for potential use in the treatment of HL is inositol hexanicotinate. Inositol and nicotinic acid are combined to form this substance, which has been demonstrated to lower total cholesterol levels by up to 20%. Additionally, it raises HDL while lowering triglyceride levels. also It has being investigated whether nicotinamide, another niacin derivative, can be used to treat HL. The mechanism of action of this substance is to stop the liver's generation of VLDL and

to prevent the synthesis of fatty acids. Additionally, it raises HDL levels and lowers triglyceride levels [60].

Overall, it has been demonstrated that using niacin derivatives helps individuals with HL lower their triglyceride and total cholesterol levels while raising their HDL levels. The negative effects of these substances, however, can include flushing, itching, nausea, vomiting, and abdominal pain. Therefore, before using any niacin derivatives to treat HL, it's crucial to address any possible hazards with your doctor [60].

4. Bile acid sequestrants (BAS)

Large, positively charged, non-absorbable polymers known as bile acid sequestrants (BAS) are prescribed drugs for the treatment of HL. They reduce the quantity of cholesterol in the blood by attaching to bile acids in the colon and preventing them from being reabsorbed. In general, they are well tolerated and cause few side effects. Cholestyramine, colestipol, and colesevelam are examples of BAS that are often utilised [61,62].

Cholestyramine is a resin that binds to bile acids in the intestine, preventing their reabsorption into the bloodstream. For oral administration, it is offered as a powder or granule that can be diluted with water or other liquids. It has been demonstrated that cholestyramine can lower total cholesterol by up to 20%, LDL cholesterol by up to 30%, and triglyceride levels by up to 40%. Constipation, bloating, nausea, and abdominal pain are typical adverse effects [63].

Colestipol is another resin that binds to bile acids in the intestine and prevents their reabsorption into the bloodstream. For oral administration, it is offered in the form of tablets or granules that can be

dissolved in water or other liquids. Colestipol has been demonstrated to lower triglyceride, LDL, and total cholesterol levels by up to 45%, 25%, and 35%, respectively. Constipation, bloating, nausea, and abdominal pain are typical adverse effects [64].

Colesevelam is a synthetic polymer that binds bile acids in the intestine and prevents their reabsorption into the bloodstream. For oral administration, it is offered in the form of tablets or granules that can be dissolved in water or other liquids. It has been demonstrated that colesevelam can lower triglyceride, total, and LDL cholesterol levels by up to 50%, 30%, 40%, and 40%, respectively. Constipation, bloating, nausea, and abdominal pain are typical adverse effects [65].

5. Cholesterol absorption inhibitors (Ezetimibe)

Inhibitors of cholesterol absorption are a category of drugs used to treat HL, or high cholesterol levels. These drugs work by blocking the absorption of dietary cholesterol in the intestine, thus reducing the amount of cholesterol that enters the bloodstream. Examples of cholesterol absorption inhibitors include ezetimibe [66].

Ezetimibe is a synthetic medication that prevents the small intestine from absorbing dietary cholesterol. Its glucuronyl metabolite is hypothesised to prevent a putative cholesterol transporter in enterocytes, which are found inside the brush-border membrane of the small intestine. It has been demonstrated to lower LDL levels by up to 20% when taken once a day. It can be used alone or in conjunction with statins. Abdominal pain, nausea, and diarrhoea are typical adverse effects [67].

Herbal medicine for the treatment of hyperlipidemia

For decades, herbal remedies have been used to treat HL. Some of the most commonly used herbs include:

1. *Garlic (Allium sativum)*

Garlic, a perennial herb, has played an important medicinal and dietary role throughout history. Garlic is used in numerous forms, such as extracted oil, powdered garlic tablets, or raw garlic [68]. The protective mechanisms of the beneficial effects of garlic in CVDs may be achieved by suppressing LDL oxidation, increasing HDL, and decreasing TC and TG [69].

2. *Guggul (Commiphora mukul)*

Guggul is an Ayurvedic herb; it is an extract from the resin of the mukul myrrh tree (*Commiphora mukul*). It has been used to treat HL. Studies have shown that it can reduce total cholesterol, LDL cholesterol, and triglycerides. The medicinal use of guggul dates back to 600 BC, when it was used for obesity, atherosclerosis, and various inflammatory conditions. The plant sterols E- and Z-guggulsterone are believed to be the bioactive compounds [70]. Recent research indicates that guggulsterones are antagonists of the bile acid receptor (BAR), a nuclear hormone receptor involved in bile acid regulation and cholesterol metabolism [71].

3. *Green Tea (Camellia sinensis) and Gougunao tea*

Green tea contains polyphenols, which can help reduce total cholesterol, LDL cholesterol, and triglycerides. Gougunao tea is made from the young leaves of a famous green tea that is rich in various nutrients and chemical substances, such as trace elements (selenium, zinc, calcium,

magnesium, etc.), polysaccharides, amino acids, vitamins, and tea polyphenols [72]. Many natural polysaccharides have been proven to have ameliorative effects on high-fat diet-induced HL, with fewer side effects. However, similar data on Gougunao tea polysaccharides remains obscure.

The outcomes showed that GTP40 intervention improved the serum/liver biochemical indicators of lipid metabolism in hyperlipidemic mice and prevented aberrant weight gain and excessive lipid droplet accumulation in the livers. The serum's increased amounts of anti-inflammatory cytokines and antioxidant enzymes, as well as the liver's upregulated anti-inflammatory gene. Additionally, research showed a strong relationship between the gut microbiota and SCFAs. In order to prevent fat deposition, oxidative stress, and inflammation while also reestablishing the gut's normal microbial balance in hyperlipidemic mice, GTP40 may be a unique technique [73].

4. *Ginger (Zingiber officinale)*

It is a plant that is used as a popular spice in foods, desserts, and drinks all around the world. This plant has been used since ancient times in the prevention and treatment of many diseases. To date, several properties of ginger, such as antioxidant, anti-inflammatory, and anticoagulation activities, have been studied, and the effect of the plant to reduce pain and improve nausea and vomiting has been established. It was found that ginger has a great effect on improving lipid profiles [74].

5. *Turmeric (Curcuma longa)*

Turmeric is a spice commonly used in Indian cuisine that has anti-inflammatory properties and can help reduce total

cholesterol and LDL cholesterol levels in people with HL[75].

6. *Artichoke Leaf extract (Cynara scolymus)*

The methanolic extract from the leaves of artichoke (*Cynara scolymus* L.) was found to suppress serum triglyceride elevation in mice. In addition, inhibition of gastric emptying was clarified to be partly involved in anti-hyperlipidemic activity[76].

Conclusion

Hyperlipidemia is an excess of lipids or fats in the blood as a result of a variety of reasons that can increase the risk of life-threatening CVD. Induction of an experimental hyperlipidemic model for the management of HL is still a goal for evaluating hyperlipidemic drugs. Due to the many problems that result from diet-induced HL, either through its harmful effect on the heart or time consumption, we had to find a new method for induction of HL by using drugs to induce HL within a few days with less harmful effects on the vessels and heart.

Conflict of interest

Authors have no conflict of interest to declare.

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الملخص العربي

زيادة نسبة الدهون بالدم: طرق الاستحداث والعلاجات الممكنة

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إن أمراض القلب والأوعية الدموية خطيرة جدا ومن الممكن أن تؤدي إلى الوفاة. والسبب الرئيسي في حدوث هذه الأمراض هو تصلب الشرايين والنتاج من ترسيب الدهون في جدران الأوعية الدموية نتيجة لزيادة نسبة الدهون في الدم ولذلك فإن العلاج والوقاية من زيادة نسبة الدهون في الدم يعكس مباشرة على الإصابة بتصلب الشرايين وأيضاً أمراض القلب والأوعية الدموية. ولقد تم عمل العديد من الدراسات لعلاج والوقاية من زيادة نسبة الدهون إما عن طريق تنظيم النظام الغذائي أو عن طريق استخدام الأدوية العلاجية مثل مجموعة الستاتينات والفيبرات و مشتقات النياسين وحواجز حمض الصفراء ومثبطات امتصاص الكوليسترول وكل هذه الأدوية تعتبر أهم العلاجات لزيادة نسبة الدهون وأيضاً العديد من الدراسات مازالت تجرى لاكتشاف وتقييم الأفضل من هذه العلاجات مع تقليل الأعراض الجانبية لها. ومن أجل هذا وجب علينا استحداث زيادة نسبة الدهون في الدم في أحد حيوانات التجارب والتي كانت تحدث في معظم الأبحاث عن طريق إعطاء هذه الحيوانات طعام غني بالدهون. الهدف من هذه الدراسة هو تقديم حقائق محدثة ومميزة حول طرق استحداث زيادة الدهون وطرق علاجها. وفي نهاية هذه الدراسة استنتجنا أن استحداث زيادة نسبة الدهون في الدم لا يزال هدفاً لتقييم أدوية علاج الدهون. نظراً للعديد من المشكلات التي تنتج عن استحداث زيادة الدهون عن طريق تناول غذاء غني بالدهون والكوليسترول، سواء من خلال تأثيره الضار على القلب واستهلاك الوقت، كان علينا إيجاد طريقة جديدة لاستحداث الدهون باستخدام الأدوية لاستحداثها في غضون أيام قليلة مع آثار أقل ضرراً على الأوعية والقلب.