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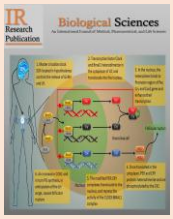

Unwholesome heart (Hypercholesterolemia) and naturally available drugs: A comprehensive review

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ABSTRACT

Hypercholesterolemia is a common disorder in developed countries. It refers to abnormalities in lipid metabolism, plasma lipid transport, or a disorder in the synthesis and degradation of plasma lipoproteins which leads to a high level of fat in the blood. The utilization of natural medicines for the treatment of several diseases and disorders dates back to ancient times. A lot of herbal medicines have got their place on the world market as options to the prescribed drugs to manage and treat various ailments. Hypercholesterolemia contributes a lot to the manifestation and development of atherosclerosis and coronary heart disease (CHD). Hypercholesterolemia prevalence continued to increase annually, requiring the development of drugs capable of lowering blood lipids to check death rate and morbidity due to cardiovascular complications. The current review is designed to gather knowledge about the Management and treatment of hypercholesterolemia, using drugs from Natural sources as the cornerstone instrument. Although synthetic lipid-lowering drugs are useful in treating Hypercholesterolemia, there are several adverse effects. So the use of herbal drugs is eminent as the cornerstone tool, for mitigation, prevention, and treatment of Hypercholesterolemia to address the said ailment. This review aims to provide benefits from numerous lipid-lowering agents with minimal or no side effects from natural sources, where the naturally available drugs can be taken as a means of the normal routine diet without any specific care.

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Introduction

CHD is one of the primary sources of worldwide mortality and morbidity[1]. It is caused by a fluctuation in lipid profile, preferably elevated levels of total cholesterol (TC), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), and triglyceride (TG) concentrations, and a fall in the high-density lipoprotein (HDL) concentration [2]. It

Abbreviations: *ACAT-Sterol O –acyltransferase; AMPK-Activated protein kinase; CHD-Coronary heart disease; HDL-High density lipoprotein; HDLC-High density lipoprotein cholesterol; HMG COA- Hydroxy beta- methyl glutaryl coenzyme A; LDL-Low density lipoprotein; LDL-C- Low-density lipoprotein cholesterol; LDL-R- Low-density lipoprotein Receptor; PPAR- Peroxisome proliferator-activated receptor; TC- serum Total cholesterol; TG- Triglycerides; VLDL -Very low-density lipoprotein*

is well affected by changes in dietary habits. Fluctuation in lipid metabolism or plasma lipid transport or abnormal synthesis and degradation of plasma lipoproteins leads to an elevated level of fat in blood [3]. It may present with the hike in serum [4] (**Figure-1**).

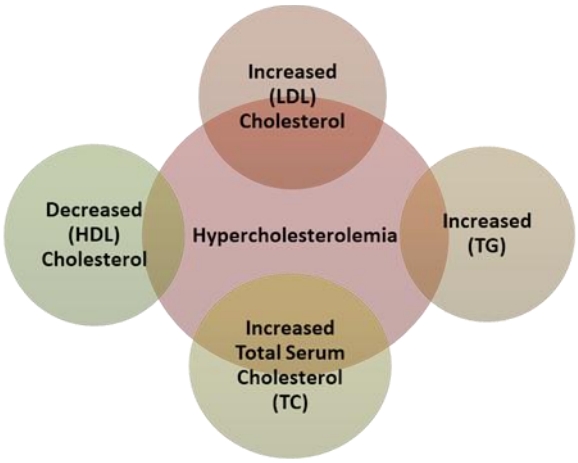

Figure 1. Factors affecting Hypercholesterolemia.

Recent research indicates that familial hypercholesterolemia (FH) is more prevalent than previously reported and is widely recognized as affecting people of all ethnic groups and living in a wide variety of geographical locales. A precise estimate of its global and regional prevalence is required to inform policies aimed at the early detection and prevention of atherosclerotic cardiovascular disease (ASCVD). The purpose of this study is to provide a more comprehensive assessment and more reliable estimation of the prevalence of FH in the general population (GP) and among patients with ASCVD than has previously been possible [5]. The prevalence of hypercholesterolemia rose between 1999 and 2002 (up to 25 percent), 2013–to 16 (up to 17.6 percent), and 2017 to 22 (up to 29.4 percent). Between 2015 and 2016, the prevalence of hypercholesterolemia was 12.2 percent, having decreased by an average annual rate of 0.3 percent since 2010. Between 2015 and 2016, 12.4% of people had elevated total cholesterol and 18.4% had low HDL cholesterol. Between 2013 and 2016, 11.8 percent of individuals had elevated blood total cholesterol, with a mean value of 191 mg/dL [6-9]. Recent studies indicate that 25–30% of urban and 15–20% of rural respondents have elevated cholesterol. This frequency is lower in low-income nations than in high-income ones. In India, the most prevalent dyslipidemias are borderline elevated LDL cholesterol, low HDL cholesterol, and elevated triglycerides.[10] It is revealed in landmark epidemiological studies, that unwholesome lifestyles (smoking, sedentary life, and no refined dietary habits) make around 80% of the population susceptible to CHD threats [4, 11]. Hence, refinement of lifestyle forms the fundamentals for the prevention of CHD. Dietary fatty acids are huge determinants of plasma cholesterol concentrations[12]. Obesity, lack of physical activity, excessive dietary fat intakes, and Medical ailments/diseases that may lead to Hypercholesterolemia are diabetes, kidney disease, pregnancy, and hypothyroidism are the leading causes of CHD [13].

Several experimental studies i.e., clinical trials have manifested the effect of dietary changes on cardiovascular risk factors, including hypercholesterolemia as well [14]. Since then, epidemiologic studies have figured out links between dietary exposures and CHD [15]. Even though there are available medicines, they possess high adverse and unpleasant effects. Natural products in recent years emerged on market for their high benefit to risk ratio and abundance. Some natural products have been discovered linked to hypercholesterolemia. With the help of this review, readers will be able to reap the benefits of a wide variety of natural lipid-lowering agents that have few to no adverse effects in a single article. (Figure-2).

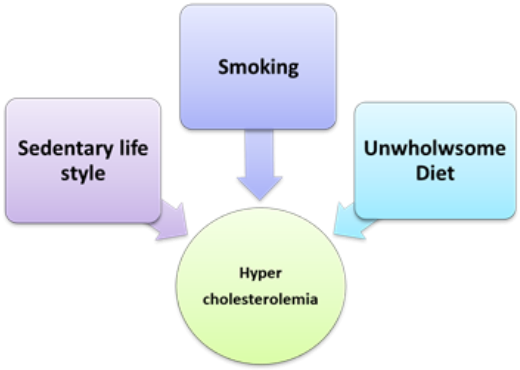

Figure 2. Causative agents in Hypercholesterolemia.

Treatment

There are existing dietary and medicinal approaches to treat the disease. They are discussed briefly

Dietary approach

Eatables like vegetables, fruits, nuts, legumes, whole grains, and also lean protein sources such as white meats, fish, and low-fat dairy products claims of having cardioprotective activity, while foods low in saturated and trans-fatty acids, and foods with a high glycolic index claim of cardioprotective activity either [16, 17]. It is linked with a Lowering of cardiovascular risk in patients with hypercholesterolemia and is supposed to be a first-line treatment in lowering LDL-cholesterol levels (bad cholesterol) in hypercholesterolemic patients [18]. The diet-reducing cholesterol includes margarine, and other food items containing gram quantities of phytosterols or stanols; soluble fiber foods, like psyllium, pectin, and guar gum; red yeast rice and soy protein, etc[19].

Medicinal approach

The newest advances in pharmacological LDL cholesterol-lowering medicines are significant, coming decades after the introduction of the prior LDL cholesterol-reducing pharmaceutical, ezetimibe[20]. Four new LDL-cholesterol-lowering drugs have been approved in recent years. Lomitapide and mipomersen are authorized for homozygous familial hypercholesterolemia but increase hepatic fat [21]. The monoclonal antibodies alirocumab and evolocumab bind to PCSK9 and reduce LDL by 50-60%. These drugs are approved for people with heart disease or congenital hypercholesterolemia whose LDL cholesterol levels are inadequately controlled by conventional drugs [22].

Natural products as drugs

The above approaches are effective for the short period providing symptomatic relief, but they have adverse effects to deal with. In recent years natural products have come to market for their less adverse effect and availability. Some key molecules effective for hypercholesterolemia are mentioned below. (Table 1).

Nuts

Nuts are energy-rich foods as they possess an average of 50% fat, although most fatty acids are unsaturated. It is witnessed from the epidemiological studies and experimental studies (clinical trials) that daily nut consumption does not add up to weight [16]. Adding nuts to the routine foods of humans claims to have a positive effect on health. Nuts are supposed to be "heart-healthy" foods by the U.S. Food and Drug Administration and have given reasons for their utilization for its numerous merits like antioxidant, hypercholesterolemic, cardioprotective, anticancer, anti-inflammatory, and anti-diabetic activity [23, 24].

Nutshell of Semecarpus anacardium

Nutshell extract of *S. anacardium* includes Anacardic acid, Cardol, Catechol, Anacardoside, and Fixed oil [25]. It was provided to rabbits induced with cholesterol, the outcome observed was, a decline in serum cholesterol (-73.3%) and serum LDL-Cholesterol. (-80%).It also manifested a cut down in the Values of cholesterol/triglycerides in the liver, heart muscle, and aorta and it was witnessed that there is a significant decline in plaque (75.3-83.5%) [26]. This outcome declares that S.anacardium exerts hypocholesterolemic activity and limits cholesterol-induced atheroma [27].

Guggul (Commiphora mukul)

Commiphora mukul (guggul) extract has been widely used in Asia as a cholesterol-lowering agent, and its popularity is increasing in the United States. The main active principle of Guggul is Guggulsterones, which are claimed to be potent antagonists of 2 nuclear hormone receptors involved in cholesterol metabolism, establishing a plausible mechanism of action for the hypolipidemic effects of these extracts [28-32].

Olive oil (Olea europaea)

Virgin olive oil, the culinary fat is a pure 'juice' of olives containing both the fat (mainly oleic acid) and the minor bioactive components of olives, such as phytosterols, tocopherols, and phenolic compounds, and is now witnessed as another cardioprotective food, with duo HDL-raising properties and cholesterol-lowering activities [33]. Oleic acid and phenolic compounds are the active ingredients. Olive oil has a cholesterol-reducing effect. Phenolic compounds lend protection against LDL oxidation and aids in the neutralization of free radicals almost similar to vitamin C (ascorbate) and Vitamin E(α-tocopherol). The utilization of olive oil witnesses an elevation in HDL-cholesterol (HDL-C) value, diminishes LDL-cholesterol (LDL-C) value, LDL risk to oxidation, and lipid peroxidation [34]. The decrease in cellular oxidative stress, thrombogenicity, and the development of atheroma plague witnesses the role of olive oil in countering atherosclerosis formation. It cuts the susceptibility to CHD [35].

Rapeseed oil

It is claimed that a feed consisting of monounsaturated fatty acids drops the value of total

Table 1. Phytoconstituents and their active ingredients in hypercholesterolemia.

Natural Product	Active Ingredients	Effect	Reference
Nuts	Unsaturated fatty acids	Hypocholesterolemic, Cardioprotective	[23,24]
Nutshell Of *Semecarpus anacardium*	Anacardic acid, Cardol, Catechol, Anacardosid	Hypocholesterolemic and limits cholesterol-induced atheroma	[27]
Guggul (*Commiphora mukul*)	Guggulsterones	Hypolipidemic	[32]
Olive Oil (*Olea europaea*)	Oleic acid and phenolic compounds	Decrease in cellular oxidative stress, thrombogenicity, and the development of atheroma plague	[35]
Rapeseed Oil	Monounsaturated fatty acids	Prevent the formation of atherosclerosis and linked problems	[37]
Legumes	Phytosterols, fatty acids, polyphenols, carotenoids, glucosinolates, dietary fiber, isoflavones, and lignans	Reduced CHD rates	[39]
Tomato (*Solanum lycopersicum*) and Carrot (*Daucus carota*)	Lycopene, beta-carotene	Blocking macrophage HMG CoA reductase activity	[42]
Cocoa (*Theobroma cocoa)*	Stearic acid, polyphenol	Decline in cholesterol levels, but also results in blood pressure reduction, checks insulin resistance, and anti-inflammatory	[44-47]
Saponin	Glycosides	Hypocholesterolemic	[49]
Fungal Polysaccharides	Polysaccharide CS-F30	Decline in plasma cholesterol	[51]
Aspergillus tereus	Melviolin	Inhibits P-hydroxy-p-methylglutaryl Co A reductase	[52]
Soybean	Essential Carbohydrate and proteins	Increasing HDL	[55]
Algal Extract	Phycocyanin, Sulfated polysaccharides, and γ linolenic acid	Hypocholesterolemic	[56]
Silica	Silicon Dioxide	Declined plasma total cholesterol, VLDL, and LDL-cholesterol	[57]
Dietary Fiber	Fiber	They impacted the total lipid, cholesterol, triglycerides, and phospholipid content	[58]
Whole grains	β-glucan	Promoting fecal excretion of cholesterol and bile salts	[59]
Cleome droserifolia	Essential oils	Lipoprotein-colesterol-C	[66]

Garlic (*Allium sativum*)	Organosulfur constituents	Supplementation cuts down VLDL cholesterol and elevates HDL-C	[67-70]
Red yeast rice (*Monascus purpureus*)	Monacolin K, omega-3 fatty acids, isoflavones, sterols, and saponins.	Inhibits an enzyme i.e., HMG-CoA reductase	[71-75]
Kiwifruit (*Actinidia arguta*), Grapes (*Vitis vinifera*), Dill (*Anethum graveolens*) *longa*)	Polyphenols	Potent -CoA reductase inhibition	[79,80]
Turmeric rhizome (*Curcuma longa)*	Curcuminoids	Inhibits the synthesis of TG and cholesterol	[81,82]
Ginger rhizome (*Zingiber officinale*)	Gingerols and shogaols	Modifies the function of hepatic cholesterol-7-hydroxylase	[83]
Cinnamon (*Cinnamomum cassia*)	Alkaloids	Decline in total cholesterol and LDL Cholesterol	[84,85]
Roselle flower and leaves (*Hibiscus sabdariffa*)	Anthocyanins, flavonols, and protocatechuic acid	Promotes expression of hepatic LDLR and their protection resulting in promoting the elimination of LDL	[86,87]
Fenugreek seeds (*Trigonella foenumgraecum*)	Possesses Mucilage, proteins, fats, fibers, and saponins	Hypocholesterolemic	[90]
Arjun (*Terminalia arjuna*)	Tannins, triterpenoid saponins, flavonoids, proanthocyanidins,	Antiatherosclerotic, Cardioprotective	[92]
Flaxseed/flaxseed oil (*Linum usitatissimum*)	α-Linolenic acid and omega-3 fatty acid	Hypocholesterolemic	[94]
Sesame oil (*Sesamum indicum*)	Lignans (sesamin, sesaminol, and episesamin)	Diminished TG, LDL-C, and increased HDL-C activity	[96]
Vegetable oils	Monounsaturated fats	Inhibits intestinal ACAT and possibly pancreatic cholesterol esterase (pCEase)	[97]
Tea (*Camellia sinensis*)	Catechins and gallate esters	Decline intestinal cholesterol absorption Polyphenolic antioxidants, block lipid peroxidation	[99]
Citrus fruits	Naringenin	Inhibits enzyme HMG-CoA reductase and ACAT	[100]
Nutmeg Fruit (*Myristica fragrans*)	Myristicin	Activates the activated protein kinase (AMPK)	[101,102]
Bitter Gourd (*Momordica charantia*)	Charantin	Activator of PPARs PPAR-α and PPARγ	[103,104]
Fish oil	Omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid)	TGs, but elevates LDL-C declines	[105,106]
Protein concentrate (PC) made from pigeon pea and moth bean (*Phaseolus aconitifolius*)	Casein and legume PCs	Elevation in HDL-C	[107]
Pumpkin (*Cucurbita indica*)	Unsaturated fatty acids, phytoestrogens, and vitamins E.	Hypocholesterolemic	[108]

cholesterol and LDL-cholesterol and may further increase HDL cholesterol. Commonly limited consumption of dietary fat drops the total serum cholesterol and LDL¬ cholesterol in the range of 10% to 15% and prevents LDL oxidation.[36] As hereditary hypercholesterolemia is witnessed at the beginning of absolute childhood rapeseed oil must be included in the usual diet very soon so to prevent the formation of atherosclerosis and linked problems [37].

Legumes

It contains phytosterols, fatty acids, polyphenols, carotenoids, glucosinolates, dietary fiber, isoflavones, and lignans [38]. As witnessed in one of the meta-analyses of ten randomized, controlled trials, regular consumption of one serving of non-soy legumes is linked with mean total and LDL-cholesterol lowering of 12 mg/dl and 8 mg/dl, with a bit elevations in HDL- cholesterol and lowering triglycerides [17]. The utilization of legumes has been linked with reduced CHD rates in prospective studies as well [39].

Tomato (Solanum lycopersicum) and carrot (Daucus carota)

Carrots are rich in Beta-carotene while Tomatoes contain lycopene predominantly [40]. Fuhrman et al (85). Cholesterol synthesis from [3H]- acetate but not that from [14C] mevalonate in the macrophage cell line J-774A. It was inhibited by beta-carotene or lycopene (10 pM) and the HMG- CoA reductase inhibitor fluvastatin [41]. The function of the macrophage LDL receptor was modified by all three compounds. Dietary intake of lycopene or carotenoids resulted in a decline in plasma LDL-cholesterol levels, by blocking macrophage HMG CoA reductase activity [42].

Cocoa (Theobroma cocoa)

Cocoa is the seed that is obtained from the tree Theobroma cocoa and is constituted of nutrients, and minerals found in all seeds. cocoa is a fat-rich edible, and it is abundant in stearic acid, a saturated fatty acid that the organism quickly converts into the monounsaturated oleic acid. Dark chocolate retains constituents of cocoa seeds, so tastes bitter, which is the feature of all polyphenol-rich foods [43]. Many experimental studies i.e., controlled clinical trials reveal that routine consumption of 50–100 g of dark chocolate reduces total and LDL cholesterol between 5 and 10% compared with white chocolate, without significant effects on triglycerides or HDL-cholesterol [44]. prospective studies witness that intake of cocoa feeds prevents a person from CHD, stroke, and diabetes as well. It not only causes a decline in cholesterol levels but also results in blood pressure reduction, checks insulin resistance, and anti-inflammatory effects of flavonoid-rich chocolate products [44-47].

Saponin

One of the fundamental activities of saponins is their hypocholesterolemic action. Story et al declared that saponin - cholesterol interaction was a fundamental part of the hypocholesterolemic action of alfalfa but interactions of bile acids with other components of alfalfa might be equally important [48]. Alfafa plant and sprout saponin bound significant amounts of cholesterol and manifest hypocholesterolemic activity [49].

Fungal Polysaccharides

Polysaccharide CS-F30 source of which is cultured mycelia of *Cordyceps sinensis* brought manifested a decline in plasma cholesterol value in mice [50]. The glucuronoxy and lomannan from *Tremellafuci formis* fruiting bodies manifest a decline in plasma cholesterol levels in mice [51].

Aspergillus tereus

Fungus *Aspergillus tereus* produces Mevinolin, which competitively inhibits P-hydroxy-p-methylglutaryl Co A reductase, a key enzyme in the cholesterol biosynthetic pathway, and causes a decline in cholesterol level [52].

Soybean protein

It is witnessed that soybean protein brought about a rising in serum apo A-I and apo B with the relative concentration of HDL-cholesterol remaining at the peak. The hepatic concentration of cholesterol was lowered. Plant proteins (50% from soybean meal and 25% each from corn and wheat) caused a decline in plasma cholesterol of young male pigs compared with animal proteins (90% from casein and 10% from lactalbumin) [53]. When soybean protein was added to the feed of young, healthy, normolipidemic women, the plasma cholesterol values were reduced. However, soy and alfalfa proteins did not affect plasma total cholesterol and HDL-cholesterol when compared with purified animal proteins (casein, egg albumin, lactalbumin) and crude animal proteins (fish meal and blood meal) [54]. Rats fed a diet containing 10% soy protein derived protein, wheat gluten or wheat gluten mingled with lysine and threonine possessed lower serum cholesterol and triglyceride values, no LDL, and a raised value of HDL [55].

Algal extract

An extract of a unicellular filamentous blue-green alga i.e., Spirulina, for human consumption in Mexico and Central Africa, had hypocholesterolemic activity [56].

Silicon dioxide (Silica)

Silica can be found in plant cell walls and interstitial spaces. It declined plasma total cholesterol, VLDL, and LDL-cholesterol [57].

Dietary fiber

Fiber from numerous eatables like khejri beans (*Prosopis cineraria*), prepalbanti (*Ficus religiosa*), Barbati (*Ficus glomerata*), and teent (*Capparis decidua*) possesses cellulose, lignin, hemicellulose, teent, and pectin. They impacted the total lipid, cholesterol, triglycerides, and phospholipid content [58].

Whole grains

The lipid effects of whole grains are based on their soluble fiber content. Barley Oats and Barley contain β-glucan, a subtype of soluble fiber that forms the liver. Teent manifested the mos apparent cholesterol declining action, by promoting fecal excretion of cholesterol and bile salts [59]. Whole grains such as wheat, oats, corn, barley, psyllium, oat bran, chitosan, cellulose, pectin, guar gum, and lignin. Active constituents are Dietary fibers Beta-glucan. They brought about a decline in cholesterol values by absorbing dietary fats in the GI tract, preventing systemic absorption, and enhancing cholesterol clearing in fecal bile acids [60]. 2-Beta-glucan makes the food more viscous in the stomach and ends up in delayed absorption [61].

Propionate

Propionate is a metabolic product of fiber fermentation. It may assist in some of the hypocholesterolemic effects of some soluble plant fibers. In cholesterol-fed rats propionate declines serum cholesterol and liver triglyceride value. No changes in hepatic histology in response to propionate intake were found [62]. It forms a gel in the intestine and binds bile acids, thereby aiding their fecal loss, but not whole wheat, rye, or rice.[63].

Cleome droserifolia

Extract of essential oils from *Cleome droserifolia* diminishes LDL ¬cholesterol and elevates the HDL/LDL)-cholesterol ratio, revealing that it possesses anti-atherogenic value [64]. An amalgamation of viscous fibers, soy proteins, and almonds causes a decline in low-density lipoprotein-cholesterol-C (LDL-C) resulting from foods with almonds, foods rich in viscous fibers, soy proteins, or plant sterols. The amalgamation of these foods (portfolio diet) shows that the amalgamation of different said foods as a dietary portfolio claims a decline in LDL-C similarly to statins and so increases the high-density lipoprotein-cholesterol-C (HDL-C) [65]. The portfolio diet mentioned by Jenkins and colleagues comprised four key components: soluble fiber abundant food; Soy protein; Plant sterols; Almonds. A combination of these resulted in a total decline of 29% LDL-C, in comparison to a mini dose of a statin[66].

Garlic (Allium sativum)

Organosulfur constituents (Garlic oil, aged garlic, fresh garlic, and garlic powder). active constituents Of garlic inhibit cholesterol synthesis by inhibiting enzymes such as Hydroxy beta- methyl glutaryl coenzyme A (HMG-CoA) reductase, squalene epoxidase, and glucose-6- phosphate dehydrogenase. 2-garlic promotes catabolism of FA-containing lipids preferably TGs. 1- Garlic reduces 515 % of TC. Garlic supplementation cuts down VLDL cholesterol and elevates HDL-C [67-70].

Red yeast rice (Monascus purpureus)

Red yeast rice is Ready to use only when made from cooked non-glutinous white rice fermented by the yeast *Monascus purpureus*, Afer which it is sterilized, dried, grounded, and encapsulated. The active principle encompasses Monacolin K, omega-3 fatty acids, isoflavones, sterols, and saponins. It inhibits an enzyme i.e., HMG-CoA reductase. Red yeast rice is a dietary staple in several Asian countries [71-75].

Kiwifruit (Actinidia arguta), Grapes(Vitis vinifera), Dill (Anethum graveolens)

All of the three possess polyphenols possessing potent -CoA reductase inhibition activity. It is witnessed that almost after two months of consumption of kiwi fruit, there is a significant decline in LDL/HDL-C ratio and total cholesterol/HDL-C ratio, with an elevation in HDL-C. Grapes have the potential of preventing atherosclerosis. The grape polymers enhance fecal excretion of lipids and cholesterol [76-78]. Resveratrol which is having antioxidant properties present in grapes results in a decline in LDL, VLDL, and serum TG levels. Dill results in a well-defined reduction in LDL cholesterol and serum TG and elevates HDL Cholesterol [79, 80].

Turmeric rhizome(Curcuma longa)

Possesses curcuminoids (curcumin 0.3-5.4 %) as the active principle. The lipid declining effects of curcuminoids are due to alterations of cholesterol to bile acid. A level of 0.2 g curcuminoids per 100 g feed witnessed a fall in TC and TGs in the rat. It is witnessed that turmeric inhibits the synthesis of TG and cholesterol.[81, 82].

Ginger rhizome (Zingiber officinale)

Cholesterol declining active constituents include Gingerols and shogaols. They block cholesterol biosynthesis. Ginger modifies the function of hepatic cholesterol-7-hydroxylase. It is the rate-limiting enzyme in the biosynthesis of bile acids, which provokes cholesterol conversion to bile acids, for clearing cholesterol from the body. impact of ginger on serum and hepatic lipid, atherogenic index, blood, and liver lipid peroxidation was found to be hypocholesterolemic[83]

Cinnamon (Cinnamomum cassia)

It shows a decline in total cholesterol and LDL Cholesterol. Its hypocholesterolemic activity shows an improvement in cardiovascular function [84, 85].

Roselle flower and leaves (Hibiscus sabdariffa)

Possesses anthocyanins, flavonols, and protocatechuic acid as active phytoconstituents. It promotes inhibition of intestinal absorption of cholesterol and interrupts lipoprotein production. Also promotes the expression of hepatic LDLR and their protection resulting in promoting the elimination of LDL [86, 87].

Fenugreek seeds (Trigonella foenumgraecum)

Possesses Mucilage, proteins, fats, fibers, and saponins (diosgenin and tigogeninas) as active phytoconstituents. Among these active constituents, diosgenin and tigogenin influence cholesterol metabolism in the liver, Fibres obstruct intestinal absorption of cholesterol by absorbing bile acids which are finally removed by excretion in the feces. An amino acid that is present in fenugreek proteins can significantly cause a declining serum cholesterol value in experimental animals [88]. It was observed that the saponin component of fenugreek seeds interacts with bile salts in the digestive tract and exerts its hypocholesterolemic effect [89].it manifests a decline in serum total cholesterol, TG, and LDL-Cholesterol in hypercholesterolemic patients [90].

Arjun (Terminalia arjuna)

It possesses Tannins, triterpenoidal saponins, flavonoids, proanthocyanidins, and other polyphenols as an active principle. It is claimed that its EtOH extract interrupts the absorption of dietary cholesterol and bile acids as well, from the intestine. It also promotes the removal of fecal sterols and stimulates bile acid synthesis which causes promoted uptake of cellular free cholesterol.it possesses significant antiatherosclerotic activity [91].it also shows a decline in serum biomarker enzyme value, which declares it cardioprotective action [92].

Flaxseed/flaxseed oil (Linum usitatissimum)

Possesses α-Linolenic acid and omega-3 fatty acid as the active ingredients. Regular intake of flaxseeds results in a significant decline in TC and LDL-C [93]. Flaxseed oil modifies serum TG parameters. It is claimed that hypocholesterolemic activity may be due to an increase in LDL receptor mRNA expression and cholesterol catabolism output [94].

Sesame oil (Sesamum indicum)

Possesses active constituents as Lignans (sesamin, sesaminol, and episesamin). It diminishes the value of serum TC. Sesaminol manifests a decline in lipid peroxidase markers and raises the lag time before the lipid peroxidation propagation phase in vitro models. [95] It is witnessed that cholesterol, TG, and LDL-C were cut down. Weight and waist were diminished and HDL-C was raised ($P > 0.05$) [96].

Vegetable oils

Active ingredients include monounsaturated fats. They diminish LDL-C, but not HDL-C. It is observed that it inhibits intestinal ACAT and possibly pancreatic cholesterol esterase (pCEase), which may promote the metabolic potential of the Areca nut extract as regards the absorption of intestinal free cholesterol [97].

Tea (Camellia sinensis)

The active principle of tea is Polyphenolic flavonoids. Green tea catechins and gallate esters decline intestinal cholesterol absorption Polyphenolic antioxidants block lipid peroxidation. It raises the expression of the hepatic LDL-C receptor and promotes the fecal removal of bile acids and cholesterol [98]. in one of the experiments, it was observed that tea constituents manifested a decline in the amount of cholesterol

crystallization. This output makes it clear that tea possesses a goog hypocholesterolemic activity [99].

Citrus fruits

Possesses Flavonoid as naringenin as an active principle. Naringenin declines the plasma hepatic cholesterol concentrations by inhibiting the enzyme HMG-CoA reductase and ACAT. It blocks apoB secretion by inhibiting MTP and modifies LDL-R-mediated containing lipoprotein uptake [100].

Nutmeg fruit (Myristica fragrans)

Its active principle myristicin activates the activated protein kinase (AMPK) enzyme. Nutmeg and its active constituents are used in metabolic disorders like Hypercholesterolemia, obesity, and type-2 diabetes (Nguyen et al 2010). Output observed that administration of M. myristica promoted a reduction in serum TC, TG, and LDL-values, and there manifested an elevation in HDL-C of hypercholesterolemic rats. An increase in serum aminotransferases activities and LPO measure were reversed and amelioration was observed in enzymatic and non-enzymatic antioxidants value in the liver and heart of hypercholesterolemic rats. This experiment claims that M. myristica has cholesterol-reducing properties.[101, 102].

Bitter gourd (Momordica charantia)

Its active constituent charantin acts on the Peroxisome proliferator-activated receptor (PPAR), and thus it is an activator of PPARs PPAR-α and PPARγ. Active principle encompasses Cucurbitane triterpenoids (Charantin). These are activators of key metabolic pathways that limit fatty acid oxidation, adipocyte differentiation, and insulin sensitivity. Also, the bitter gourd oil diet reduced free cholesterol values and brought about an elevation in HDL-C, and no specific changes in total cholesterol [103, 104].

Fish oil

Possesses Omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) as the pharmaceutically active ingredient. Fish oil feeds declines TGs, but elevates LDL-¬C, preferably those of high doses of fish oil [105, 106].

Protein concentrate (PC) made from pigeon pea and moth bean (Phaseolus aconitifolius)

Seeds associated with pigeon pea PC and casein were given a trial in hypercholesterolemic rats. supplements meant for performing a trial containing casein and legume PCs at 10% protein and were administered to albino rats (Wistar strain) for 45 days. In comparision to casein, the two legume PCs witnessed a significant decline in the value of liver total lipid and cholesterol values but pigeon pea PC brought about only a dip in total cholesterols in the heart. While as Moth bean PC brought about an elevation in HDL-C [107].

Pumpkin (Cucurbita indica)

The pumpkin is linked to the Cucurbitaceae family. seeds of pumpkin possess huge amounts of unsaturated fatty acids, phytoestrogens, and vitamins E. its seeds are loaded with significant phytoestrogen compounds (secoisolariciresinol and lariciresinol) that mimic estrogenic-like effects like in the prevention of Hypercholesterolemia and hence prove to be hypocholesterolemic [108].

Conclusion and future perspective

Natural product-based medicine has brought a revolution in the field of medicines. Compounds from natural sources with, hypocholesterolemic activity can be isolated from different plant species or else from nature with least or nil adverse effects in comparison to synthetic drugs available. Most of these active principles originate from edible plants. The inclusion in the diet of substances with, hypocholesterolemic activities is certainly of some value. Drugs can be taken as a Normal routine diet, with no due care. It seems that a broad range of natural substances may have therapeutic benefits in hyperlipidemia, suggesting the possibility of a new generation of anti-hyperlipidemic drugs. Research into the exact mechanisms by which these products reduce cholesterol levels and identifying the active ingredient(s) responsible for these benefits are required to fully understand their hypolipidemic properties. It is hoped that naturally occurring hypocholesterolemic compounds with utmost desired efficacy will overcome the indiscriminate use of synthetic drugs leaving unwanted effects behind. Indeed the better outcome of these naturally existing drugs devoid of or causing the least untoward side effects will speed up the commercial use and cut the adverse effects of the synthetic drugs used otherwise. With the emerging new technologies like nano delivery and targeted drug delivery technology, we can more effectively administer these natural compounds to treat hypercholesterolemia.

Contribution of authors

Both Lahanya Guha, Aashiya Bashir, and Ishfaq Ahmad Bhat have bcontributed equally, in planning, drafting, writing, and analyzing, the write–up.

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Conflict of interest

The author declares no conflict of interest, financial or otherwise.

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