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Hypocholesterolemic Effect of Indian Medicinal Plants - A Review

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Abstract

Indian medicinal plants have potent effects in treating diseases such as hypercholesterolemia. This review was performed on published Indian articles on hypocholesterolemic effect of Indian medicinal plants through literature search using Cochrane Library Database, Embase, Sci-finder, Pubmed with MeSH keywords and abstracts of Medicinal and Aromatic plants. All databases were searched from their respective inception until April 2011. About 15,620 papers were obtained using related titles and keywords through the electronic databases as well as various other sources. Therefore, 110 papers were finalized on native and naturalized Indian medicinal plants (24) belonging to various families and were then reviewed. Hypocholesterolemic effect of Indian medicinal plants was furnished with available animal models and clinical trials, which contribute to design new strategies to manage hypercholesterolemia.

Keywords: Hypercholesterolemia; Cardiovascular disease; Coronary heart disease; HMG-CoA reductase and bile acids

Introduction

Hypercholesterolemia is a major risk factor for the development and progression of atherosclerosis and related cardiovascular disease (CVD). Epidemiological, clinical, genetic and experimental studies indicate that high serum level of low density lipoprotein cholesterol (LDL-C) is associated with the cause [1]. Coronary heart disease (CHD) was first reported in European countries around 1980s, but now the prevalence has increased in the developing Asian countries due to changes in life style [2]. The Scandinavian Simvastatin Survival Study Group (4S), LIPID study and CARE study have clearly demonstrated that the reduction in cholesterol level reduces the risk of CHD in both normal and diabetic patients. Current projections suggest that by the year 2020, India will have the largest CVD burden in the world. One of the major initiating events in atherosclerosis is oxidative damage to the cholesterol component of the LDL, known as LDL oxidation, which forms atheromatous plague progressing to CVD. The World Health organization (WHO) estimates that 80% of the people of developing countries rely on traditional medicines, mostly plant-derived drugs, for their primary health needs. India is well known for its rich traditional systems of medicine, that is, Ayurveda, Siddha and Unani besides a vast reservoir of living traditions of ethnomedicine. Several modern drugs in use such as statins, fibrates, nicotinic acid and resins [3], lower blood cholesterol level, either by inhibiting endogenous synthesis and/or by lowering cholesterol absorption from the intestine [4]. Owing to their side effects, people are looking for safer alternatives, and the search for new drugs capable of reducing and regulating serum cholesterol level has gained interest resulting in numerous reports on significant activities of natural agents. In this review, the hypocholesterolemic property of Indian medicinal plants is enumerated.

Methods

Literatures pertaining to hypocholesterolemic potential of medicinal plants were obtained using Cochrane Library Database, Embase, Sci-finder, Pubmed with MeSH keywords and abstracts of Medicinal and Aromatic plants. All databases were searched from their respective inception until April 2011.

Results

About 15,620 papers were obtained using related titles and keywords through the electronic databases as well as various other sources. Therefore, 110 papers were finalized on native and naturalized Indian medicinal plants (24) belonging to various families and were then reviewed. This review shows the hypocholesterolemic effect of Indian medicinal plants with available animal models and clinical trials. The findings are summarised below.

Allium cepa L. (Family: Alliaceae)

Hindi–Piyaj; English–Onion

Allium cepa is commonly cultivated throughout India; its bulb is used as food constituent. The therapeutic uses of onion such as antibiotic, antioxidant, antidiabetic, antiatherogenic, anticancer and fibrinolytic have been studied. Furthermore, juice of onion is also useful in treating jaundice, fever and chronic bronchitis (Wealth of India, 1985). Onion contains many sulfur containing active principles, which takes part in biological activities, mainly in the form of cysteine derivatives, namely, S-alkyl cysteine sulfoxides that decompose into a variety of thiosulfinates and polysulfides by the action of an enzyme allinase on extraction [5]. As allyl and related sulfoxides are inhibiting thiol group enzymes, alliums are to be used only in limited quantities [6].

Allium sativum L. (Family: Alliaceae)

Hindi–Lasan; English–Garlic

The botanical name *Allium* is derived from the Celtic word ‘all’, which means pungent. It is cultivated and commonly used as food ingredient. Garlic has been used as stimulant, carminative, antirheumatic and antihelmintic. The preventive role also extends against asthma, intestinal complaints, gout, diseases of lungs, high blood pressure and besides improves the immune system [7]. The essential oil fraction of garlic comprises 60% of diallyl disulphide (DADS) which showed hypocholesterolemic activity according to [8] Kamanna & Chandrasekhara. In a study, Rai, Sharma, & Tiwari [9] showed that sysnthesised DADS anologues showed activity equally effective as the statins and hence provide a new therapeutic approach for the treatment of CVD.

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Garlic has been investigated extensively for health benefits, resulting in more than 1000 publications over the last decade alone, and it is considered one of the best disease-preventive foods, based on its potent and varied effects. The major sulfur-containing compounds in intact garlic are γ-glutamyl-S-allyl-L-cysteines and S-allyl-L-cysteine sulfoxides (alliin). Both are abundant as sulfur compounds, and alliin is the primary odorless, sulfur-containing amino acid, a precursor of allicin. Alliinase is the key enzyme that facilitates the transformation of cysteine sulfoxides to thiosulfinates such as allicin. γ-Glutamyl-S-allyl-L-cysteines are converted into S-allylcysteines (SAC) through an enzymatic transformation with γ-glutamyltranspeptidase. Several clinical reports and meta-analyses have revealed the cholesterol-lowering effects of garlic supplementation in humans [10]. Warshafsky, Kamer, & Sivak [11] have reported that neither garlic oil nor dehydrated garlic powder affects cholesterol levels. However, Amagase, Petesch, Matsuura, Kasuga, & Itakura [12] clarified that allicin or allicin potential is not a correct marker for controlling the quality of garlic supplements. Allicin is thought to be a transient compound that rapidly decomposes into other sulphur-containing compounds such as diallyl disulfide (DADS), diallyl sulphide (DAS), diallyl trisulfide and sulfur dioxide and is not a genuine active compound of garlic. Freeman & Kodera [13] also reported that no processed garlic preparations contain allicin, and it should not be a meaningful chemical evaluation for garlic products. One study concludes that the lack of effect is due to varied levels of allicin potential in the dehydrated garlic powder supplements used in the clinical studies [14].

SAC is the water-soluble organosulfur compound in garlic, which effectively reduces cholesterol synthesis and has been proven to be safe in toxicological studies. SAC is one of the active ingredients of aged garlic extract (AGE); a widely studied garlic preparation. Sliced raw garlic stored in 15-20% ethanol for 20 months is referred to as AGE. Many clinical, preclinical, and in vitro studies have shown that allicin-free garlic products, such as AGE, have clear and significant biological effects [15]. Based on the above evidences, water-soluble organosulfur compounds such as SAC should be considered reliable compliance markers for human clinical studies because they are among the active compounds of garlic, are stable, and have many biological effects in addition to their bioavailability. Thus, the standardization of garlic preparations using SAC as a chemical marker is scientifically reasonable and well justified [16].

Semecarpus anacardium L. (Family: Anacardiaceae)

Hindi–Bhilawa; English–Marking nut

Semicarpus anacardium is a deciduous tree found in the sub-Himalayan and tropical regions of India. Ripe fruit is regarded as stimulant, digestive, nervine and escharotic. It is used in the treatment of syphilis, rheumatism, piles, dyspepsia, epilepsy and other diseases of nervous system [7]. Ethanol extract of nut shell (500 mg/kg) decreased serum LDL-C and very low density lipoprotein cholesterol (VLDL-C) levels on 60 days of treatment in atherogenic male rabbits. Cholesterol mobilization from liver and prevention of deposition in peripheral tissues were observed and the inhibition of cholesterol absorption at intestine may be considered as the possible mode of action [17].

Coriandrum sativum L. (Family: Apiaceae)

Hindi–Dhania; English–Coriander

Coriandrum sativum is extensively cultivated in India for its seeds. Dried fruit is generally used for sore throat, flatulence, indigestion, vomiting and bilious complaints. Fresh plant is used in erythema and bleeding piles [7]; it is popularly known for its cooling and apetite increasing properties. *C. sativum* showed significant increase in hydroxy methyl glutaryl CoA (HMG-CoA) reductase and plasma lecithin cholesterol acyl transferase (LCAT) activity in hypercholesterolemic rats and enhanced degradation of cholesterol to faecal bile acids and neutral sterols. Concurrently, there was a decrease in VLDL-C and LDL-C levels with observed increase in high density lipoprotein cholesterol (HDL-C) level compared to control group [18].

Commiphora mukul (Hook.ex Stocks) (Family: Burseraceae)

Hindi–Guggul; English–Indian bedellium

Commiphora mukul grows abundantly in the arid and rocky areas of India. The *Sushruta Samhita* (600 B.C.), a well-known Ayurvedic medical text, describes the usefulness of the gum resin from the tree *C. mukul* in the treatment of a number of ailments, including obesity and disorders of lipid metabolism [19]. In Indian traditional system of medicine, the gum resin from *C. mukul* has been used in the treatments of rheumatism, nervous disorders, skin diseases, anaemia, cystitis, gonorrhoea and chronic bronchitis [7]. Inspired by a strong correlation between the modern concepts of atherosclerosis and obesity and descriptions in the *Sushruta Samhita*, Satyavati [20] studied the effect of gum guggul on the lipid levels of hyperlipidemic rabbits. Following her studies, a wide range of efforts have confirmed the hypolipidemic effect of gum guggul and lead to identification of the compounds such as E- and Z-guggulsterone the isomers of gum guggul as the active hypolipidemic agents.

Several mechanisms have been proposed for the effects of guggul. It may decrease hepatic steroid production, ultimately increasing the catabolism of plasma LDL-C. Alternatively, the proposed active components of guggul, guggulsterones E and Z, may increase hepatic binding sites for LDL-C, thus increasing LDL-C clearance. Still another possibility is prevention of cholesterol synthesis in the liver by ketonic steroids. Guggulsterones E and Z are effective antagonists of the bile acids receptor, farnesoid X receptor (FXR), which is primarily expressed in the liver, kidney, and small intestine; it regulates the expression of genes involved in cholesterol/bile acids homeostasis, allowing more cholesterol catabolism and excretion from the body [21]. Studies of the efficacy of guggul for hypercholesterolemia have produced conflicting results and information currently available indicates that guggul may be effective for lowering total cholesterol and triglycerides in patients on a non-Western diet.

Since, hypercholesterolemia is a chronic disease, the long-term effects of guggul should be assessed and it may depend on dietary practices [22]. Szapary et al. [23] have reported that 8 weeks of treatment with guggulipid did not appear to improve levels of serum cholesterol among adults with hypercholesterolemia and in fact appeared to increase levels of LDL-C. Participants in their trial consumed on average 181 mg/day of dietary cholesterol, which was less than a "typical American diet", and also less than the baseline dietary cholesterol (212 mg/day) from an Indian study of guggulipid that reported positive results [24] guggulsterones may be effective only in individuals who have an excessive dietary intake of cholesterol.

Terminalia arjuna Weight & Arn (DC.) (Family: Combretaceae)

Hindi–Arjun; English–Arjuna

Terminalia arjuna is seen in lower Himalayas, central and southern parts of India. The thick, white-to-pinkish-gray bark has been used in India's native Ayurvedic medicine for over three centuries, primarily as a cardiac tonic. Clinical evaluation of this botanical medicine indicates that it can be of benefit in the treatment of CAD, heart failure, and possibly hypercholesterolemia [25]. The bark is astringent, tonic and also used to treat diarrhea, dysentry and bilious infections. It is further recommended for kapa, pitta and vayu [7]. The main constituents of the bark powder include glycosides (Arjunine, Arjunetin, Arjunoside I, Arjunoside II, Triterpene-*o*-glycoside). Ethanolic extract of bark of *T. arjuna* (100 and 500 mg/kg) treated to atherogenic albino rabbits reduced TC after 60 days. Both the dosage forms were observed effective in decreasing TC and LDL-C levels, whereas the TC: HDL ratio was influenced by the higher dose [26]. In a randomized placebo-controlled trial, *T. arjuna* tree bark powder (500 mg) significantly decreased TC level in 105 successive CAD patients [27]. The hypolipidemic action of *T. arjuna* coupled with the enhancement of prostaglandin E2 (PGE2) like activity, anti-arrhythmic, anti-hyperrtensive and HDL-C raising properties make it an imminently cardio-protective product for the overall management of CAD [28].

Emblica officinalis L. (Family: Euphorbiaceae)

Hindi–Amla; English–Indian gooseberry

Emblica officinalis is a deciduous tree cultivated in hill slopes and plains in the Deccan region, coastal districts and northern parts of India. Leaf, bark and fruit have potential efficacy against diseases such as inflammation, cancer, age-related renal disease, diabetes, anemia, jaundice, diarrhea and peptic ulcer [29]. Amla extract given (10 and 20 mg/kg) to hypercholesterolemic rabbits had the ability to prevent LDL oxidation; besides it decreased synthesis of cholesterol and enhanced reverse cholesterol transport by elevating HDL-C level [30].

Phyllanthus niruri L. (Family: Euphorbiaceae)

Hindi–Bhuiamla; English–Niruri

Phyllanthus niruri is a small herb distributed commonly in central and southern parts of India. This plant has medicinal properties for dysentry, influenza, diabetes, jaundice, genito-urinary infections and viral infections [7]. Supplementing *P. niruri* plant (100 mg/kg) with cholesterol (25 mg/kg) to rats for a period of 30 days, lowered lipids, VLDL-C and LDL-C levels [31]. The anti-hypercholesterolemic effect of this plant was assessed to be mediated through the inhibition of hepatic cholesterol biosynthesis, increased excretion of bile acids and enhanced plasma LCAT activity.

Cicer arietinum L. (Family: Fabaceae)

Hindi–Chana dal; English–Bengal gram

Cicer arietinum is cultivated in southern India; it is given for skin and lipid disorders, indigestion, vomiting, diarrhoea, dysmenorrhoea and for fever [7]. The increase in membrane cholesterol of erythrocytes because of hypercholesterolemic diet leads to osmotic fragility, which was reflected in packed cell volume and erythrocyte count. A direct relation in decrease of allosteric enzyme (Na^+-K^+)-ATPase (membrane bound enzyme) activity was noticed. This condition was reversed by treating with dietary fibre of bengal gram [32]. Conflicting reports have appeared concerning the beneficial effect of legume fibre on cholesterogenesis [33,34]. One of the difficulties in assessing the physiological role of fibres relates to the fact that their composition may vary widely. However, it is now fairly well established that dietary fibre is composed of a hydrophilic component and a more hydrophobic or ionic component that have been ascribed to the ability to hydrate or to behave as a weak ion exchanger, which can sequester bile acids and other sterols by preventing reabsorption, thereby decreasing body cholesterol stores [35].

Bengal gram fibre exhibited maximum hypocholesterolemic and hypolipidemic effect as the water absorption and holding capacity of the fibre was useful in assessing their hypocholesterolemic effect with bile acids [36]. Menon and Kurup [37] have proposed that the fibre in bengal gram especially pectin may lower cholesterol levels by absorbing bile acids. The consequent loss of bile acids by faecal excretion is then offset by an increase in hepatic conversion of cholesterol into bile acids. The protective role appears to be rendered by the hydroxyl and carboxyl groups of uronic acid present in the pectin molecule. Bengal gram consists of isoflavones Biocharin A and Formononetin in high amounts, which were estrogen-like compounds and most probably the active compounds responsible for lowering serum cholesterol level [38].

Cyamopsis tetragonoloba (L.) Taub. (Family: Fabaceae)

Hindi–Guar; English–Cluster bean

Cyamopsis tetragonoloba is a vegetable cultivated throughout India. It is rich in polysaccharide and dietary fibre consumed frequently. The pods are sweet, cooling, laxative, digestive and appetizer. It is useful in treating constipation, dyspepsia, anorexia, agalactia, nyctolopia and vitiated conditions of pitta [39]. Aqueous, alcoholic and petroleum ether extracts and residual seed meal of guar were fed to hypercholesterolemic albino rats for 3 months. Among them, petroleum ether extract exerted a significant hypocholesterolemic effect [40]. Cluster bean powder (0.5% and 2.5%) showed reduction in serum cholesterol level in 7 weeks when administered to albino rats [41]. Guar gum (15 g) given with normal diet to overweight adults for 6 weeks produced a significant reduction in plasma LDL-C and TC: HDL-C ratio [42].

Glycine max (L.) Merr. (Family: Fabaceae)

Hindi–Bhat; English–Soya bean

Glycine max is an important global crop; it is native to East Asia and provides oil and protein [43]. Fibre of soy bean showed maximum plasma cholesterol lowering effect in hypercholesterolemic male albino rats compared with fibres of cereals and pulses isolated from the seed coat when administered for 4 weeks [44]. Caroll and Potter [45,46] reviewed various hypotheses on the effects of components such as isoflavones, fibre and saponins in soy beans which include, interruption of the intetstinal absorption of bile acids and dietary cholesterol, direct effects on the hepatic metabolism of cholesterol, alteration of the concentration of the hormone involved in cholesterol metabolism. *In vitro* bile acids binding capacity was evident with legume fibres than with cereal fibres and the presence of soy phytoestrogens (isoflavones: genistein and daidzein) in soya was suggested as the agents responsible for reducing serum cholesterol level.

Glycyrrhiza glabra L. (Family: Fabaceae)

Hindi–Muleti; English–Licorice

Glycyrrhiza glabra is found in India; its root decoction is given for sore-throat, asthma, dysuria and used as tonic and laxative [7]. When the root powder of *G. glabra* (5% and 10%) was administered to hypercholesterolemic male albino rats for 4 weeks, it decreased plasma and liver cholesterol levels, whereas the HMG-CoA reductase activity and HDL-C levels were significantly increased [47] and in another study [48], the effect of roots of *G. glabra* has been seen (5%, given for 4 weeks) to reduce plasma and hepatic lipid profiles and increased faecal excretion of cholesterol, neutral sterol, and bile acids in hypercholesterolemic rats.

Trigonella foenum-graecum L. (Family: Fabaceae)

Hindi–Methi; English–Fenugreek

Trigonella foenum-graecum is cultivated in many parts of India. It is an aromatic herb rich in fibre; hence the seeds and green leafy parts are used in cooking. Seeds are given to treat flatulence, diarrhea, dyspepsia, chronic cough, gout and diabetes [7]. Several more recent animal and human clinical trials have confirmed the therapeutic application of fenugreek seeds. Combined with its long history of safe use, it is no surprise that fenugreek is gaining a reputation as a promising herbal supplement for optimal health. The seed contain an excellent source of mucilaginous fibre mainly composed of galactomannans. Even more impressive is the content of saponins in the seeds that can improve bile acids and neutral sterols excretion as well as faecal weight [49]. Fenugreek powder (15%, 30% and 60%) mixed with hypercholesterolemia inducing diet and fed to rats for 4 weeks showed decrease in serum LDL-C and VLDL-C levels. In another study, fenugreek seed powder (5%, 10% and 15%) showed antilithogenic effect in mice. Cholesterol gallstones (CGS) were induced by providing lithogenic diet (0.5% cholesterol) for 10 weeks. Fenugreek seed offers health-beneficial antilithogenic potential by virtue of its favourable influence on cholesterol metabolism by decreasing serum, hepatic and biliary cholesterol levels [50].

*Vigna aconitifolia (*Jacq.) Marechal (Family: Fabaceae)

Hindi–Moth; English–Mat bean

Vigna aconitifolia, a perennial or annual herb, is found throughout India. The tender pods are used as vegetable and the plant is used as fodder for live stock [51]. The hypocholesterolemic effect of moth bean protein was compared with pigeon pea and casein in albino rats. After 45 days of treatment, the moth bean protein significantly lowered total and LDL-C levels and markedly increased HDL-C level [52].

Vigna mungo (L.) Hepper (Family: Fabaceae)

Hindi–Urad dal; English–Black gram

Vigna mungo has been in cultivation since ancient times and it is one of the most highly prized pulses of India. Ground into flour or paste, it is extensively used in culinary preparations and green pod is consumed as vegetable. It is given to patients with enlarged spleen and liver, for fistula and to relieve heat and burning sensation of eyes [7]. The fibre-rich polysaccharide from black gram decreased cholesterol level in serum, liver and aorta of rats fed with normal and high fat cholesterol diet [37].

Neutral detergent fibre (NDF) residue of black gram showed higher enzyme activity (HMG-CoA reductase: mevalonate ratio) in male albino rats; hence, the rate of degradation of cholesterol in liver was greater than the rate of cholesterogenesis resulting in higher concentration of bile acids production. A decrease in bile acids return through enterohepatic circulation was observed as a result of binding of NDF to bile acids in the intestine [53]. But, hydroalcoholic extract of the seeds of *V. mungo* showed decreased HMG-CoA reductase activity, increased biliary excretion, and decreased absorption of dietary cholesterol in poloxamer 407-induced hyperlipidemic rats [54].

Vigna unguiculata (L.) Walp. (Family: Fabaceae)

Hindi–Lobhia; English–Cowpea

Vigna unguiculata is a sub-erect, bushy annual found in warmer parts of India [50]. It is given for anorexia, constipation, helminthiasis, agalactia, jaundice and general debility [55]. The green pods and leaves are eaten as food. It is a good fodder for milk cows. Studies were carried out in atherogenic albino rats treated with whole, defatted and hexane extracts of cowpea; among them hexane-extract was effective in lowering the serum and liver cholesterol levels and increased bile acids excretion in faeces. The presence of neutral lipids in the extract possibly exhibited hypocholesterolemic effect [56].

Ocimum sanctum L. (Family: Labiateae)

Hindi–Tulsi; English–Holy basil

Ocimum sanctum is a widely grown sacred plant of India. Each part of the plant has a medicinal value; especially the juice of the plant is diaphoretic, expectorant, relieves headache and is used for skin disorders, malaria, cholera and chronic fever [7]. *O. sanctum* seed oil (0.8 g/kg) showed decrease in TC, triglycerides, LDL-C and VLDL-C levels from second to fifth week in male albino rabbits; decrease in lipid peroxidation and improvement in antioxidant status were observed [57]. Geetha & Vasudevan [58] showed inhibition of erythrocyte lipid peroxidation and protection of liver and aortic tissue of hypercholesterolemia-induced male albino rabbits by feeding aqueous extracts of Ocimum.

Linum usitatissimum L. (Family: Linaceae)

Hindi–Alsi; English–Linseed

Linum usitatissimum is grown at the eastern Mediterranean region of India. It is given for cold, cough, bronchial infections, cystitis, gonorrhea, diarrhea and dysentry [7]. Prasad [59] reported that rabbits receiving secoisolariciresinol digluside, the major lignan found in flaxseed, had reduced TC and LDL-C concentrations. Lignans have also been shown to modulate activities of 7-hydroxylase and acyl CoA cholesterol transferase, two of the key enzymes involved in cholesterol metabolism [60]. Flaxseed oil (1g/kg bw), when administered to male albino rats along with high fat diet (HFD) for 60 days, however, decreased LDL-C, VLDL-C, TC: HDL-C and LDL-C: HDL-C ratios. Flax seed oil contained 51%–55% alpha-linolenic acid (18:3 n–3 fatty acid) that resulted in higher cholesterol secretion into bile leading to a depletion of intrahepatic pool of cholesterol [61].

Moringa oleifera Lam. (Family: Moringaceae)

Hindi–Sajna; English–Drumstick

Moringa oleifera is a very well-known botanical used in traditional medicine in India; generally all parts of the tree are eaten. Juice of the root is used for asthma, gout, lumbago, rheumatism, epilepsy and hysteria. Leaves are given for scurvy and applied topically for dog bites [7]. The crude extract of leaves (1 mg/g) given with high fat diet for a period of 30 days led to decrease in cholesterol levels in serum, liver and kidney. The presence of phytosterol and β-sitosterol in the leaf is presumably the bioactive component with cholesterol lowering property [62]. The fruits of *M. oleifera* (200 mg/kg) given along with standard laboratory diet and hypercholesterolaemic diet to rabbits for 120 days were found to lower the serum cholesterol, phospholipid, triglycerides, VLDL-C, LDL-C and atherogenic index, but were found to increase the HDL-C as compared to the corresponding control groups [63].

Sesamum indicum L. (Family: Pedaliaceae)

Hindi–Til; English–Gingelly seed

Sesamum indicum is extensively cultivated in the warmer regions of India mainly for its edible seeds and oil. The seed is beneficial for amenorrhoea and dysmenorrhoea and oil is recommended for psoriasis, prurigo, leucoderma and in promoting hair growth [7]. Sesame seed globulin fraction has low lysine: argenine ratio; when this was administered to male albino rats in an experimental period of 90 days, it decreased LDL-C, VLDL-C and increased the activity of plasma LCAT; this enzyme transports cholesterol from tissues to liver for catabolism [64]. The hypocholesterolemic effect of sesame seed powder administered (5% and 10%) to hypercholesterolemic male albino rats showed decline in plasma LDL-C level, increase in hepatic HMG-CoA reductase activity and enhanced faecal bile acids and cholesterol excretion. The hypocholesterolemic effect appeared to be due to its fibre, sterol, polyphenol and flavonoid contents [65].

Oryza sativa L. (Family: Poaceae)

Hindi–Chawalya dhan; English–Rice

Oryza sativa, an annual or perennial grass, is distributed in the tropical and sub-tropical regions of India. It is the staple diet consumed principally. Rice bran oil (RBO) is extracted from the pericarp and germ of the rice. The oil is reported to prevent cancer in the liver of rats [66]. RBO typically contains 20% saturated fatty acids and approximately equal amounts of oleic and linoleic fatty acids [67]. Attention has begun to focus on the components of RBO, which is richer in triterpene alcohols, tocopherols, sterols, tocotrienols, and oryzanol; the most notable compound is γ-oryzanol, a ferulate ester of triterpene alcohols [68]. The phytosterols, campesterol and β-sitosterol are found at relatively high amounts in RBO. The β-sitosterol structure is more similar to that of cholesterol and it may be more effective in inhibiting cholesterol absorption in the small intestine. In tocotrienols, the major components are the β- and γ-tocotrienols; it is postulated that γ-tocotrienols lower cholesterol through the inhibition of HMG-CoA reductase, the rate-limiting enzyme in endogenous cholesterol synthesis [69].

Most, Tulley, Morales, & Lefevre [70] showed that RBO and not defatted rice bran, exhibited hypocholesterolemic effect in two well-controlled studies in moderately hypercholesterolemic men and women confirming the presence of unsaponifiable substances in RBO. The unsaponifiable substances present in the ether extract of RBO also prevented the increase in mean serum cholesterol level in hypercholesterolemic albino rats [71].

Capsicum annuum L. (Family: Solanaceae)

Hindi–Lalmirch; English–Chilli

Capsicum annuum is one of the most important commercial spice crop grown in tropical and sub-tropical regions of India. With cinchona it is useful in atonic gout, advanced stages of rheumatism and with asafoetida it is used in treating cholera [7]. Capsicum oleoresin (75 mg/kg bw/day) showed reducing effect in serum cholesterol and triglycerides levels in hypercholesterolemic gerbils [72]. The red pepper or its active principle capsaicin showed significant reduction in rise of liver cholesterol and brought enhanced faecal excretion of both free cholesterol and bile acids in female albino rats. The hypocholesterolemic action of capsaicin is likely to be responsible for the presence of common vanillyl moiety [73].

Withania somnifera (L.) *Dunal*. (Family: Solanaceae)

Hindi–Ashvagandha; English–Winter cherry

Withania somnifera grows prolifically in India and is commercially cultivated in Madhya Pradesh. Fruits and seeds are used as diuretic; root is used for constipation, rheumatism, nervous exhaustion and spermatorrhoea [7]. Studies have reported that this plant possesses anti-inflammatory, antitumor, antistress, antioxidant, immunomodulatory and rejuvenating properties [74]. *W. somnifera* showed reduction in cholesterol level of serum in rats fed with high calorie and fat diet [75]. The root powder of *W. somnifera* (0.75 and 1.5 gm/rat/day) when administered to hypercholesterolemic rats showed decrease in serum cholesterol level; on the other hand, significant increase in plasma HDL-C level and HMG-CoA reductase activity were noticed [76].

Curcuma longa L. (Family: Zingiberaceae)

Hindi–Haldi; English–Turmeric

Curcuma longa is a rhizomatous perennial herb, a native of East India. The ancient practitioners in India used turmeric as stomachic, tonic and carminative, as antibacterial, antiseptic and as antihelminthic. It is applied as paste to bruises, wounds and conjunctivitis [7]. Rhizome has been reported to contain the important colouring matter curcumin, which belongs to the dicinimolymethane group. It has also been reported that sodium curcuminate isolated from *C. longa* is an active cholerectic which causes an increase in total excretion of bile salts, bilirubin and cholesterol [77].

The fluidity of the erythrocyte membrane is determined by cholesterol content, fatty acid composition of the membrane phospholipids and the protein matrix. In a hypercholesterolemic situation, the concomitantly higher cholesterol to phospholipids ratio in the blood plasma will have a direct influence on cholesterol transfer from plasma to erythrocytes, resulting in the enrichment of cholesterol in the erythrocyte membrane [78]. The dietary spice principle curcumin (0.2%) given for 8 weeks showed its ability in reversing the deformity and fragility and normalizing the fluidity in the erythrocytes [79]. The hypocholesterolemic activity of curcumin was examined in human hepatoma cell line HepG2. Curcumin treatment caused increase in LDL-receptor mRNA and moderate increase in expression of the sterol regulatory enzyme binding protein (SREBP) genes. But mRNAs of the peroxisome proliferator activated receptor-α (PPAR-α) target genes CD36/fatty acid translocase and fatty acid binding protein 1 were down regulated. These changes in gene expression are consistent with the proposed hypocholesterolemic effect of curcumin [80].

Discussion

Cholesterol is a vital constituent of cell membrane and the precursor of steroid hormones and bile acids. In a healthy organism, an intricate balance is maintained between the biosynthesis, utilization and transport of cholesterol, keeping its harmful deposition to a minimum. The positive association of raised total serum cholesterol levels and of lipoproteins in relation to incidence of atherosclerosis and CHD is well established [81,82]. The protective effect of HDL against atherosclerosis and CHD has also been well documented [83]. The Multiple Risk Factor Intervention Trial (MRFIT) and the Framingham Heart Study have reported an increase in CAD risk by 3% in men and 34% in women with every milligram decrease in HDL level [84]. Furthermore, cholesterol homeostasis is ensured by the coordinated interaction of LDL receptor expression, HMG-CoA reductase and LCAT activity.

Spices form an important class of food adjuncts and are known to exhibit a wide variety of physiological and pharmacological properties; they have been documented to have significant hypolipidaemic influence in a variety of experimental animal systems and are found to be efficacious in human studies too [85]. The structural integrity of RBC was affected by increased osmotic fragility in rats maintained on cholesterol-enriched diet. Spices would beneficially prevent the alteration in erythrocyte membrane lipids and would offer beneficial protective influence on the integrity of erythrocyte membranes.

Catabolism of cholesterol to bile acids is quantitatively the most important pathway of elimination of cholesterol from the body. It is said that changes in the rate of synthesis of bile acids are nearly paralleled by corresponding changes in the rate of cholesterol biosynthesis in the liver [86]. Pulses form an important component of the Indian diet and have been reported to lower the cholesterol levels because of their proteins, carbohydrates and/or fibre content [36]. Dietary fibres appear to interfere with increased excretion of cholesterol and faecal bile acids resulting in depletion of hepatic cholesterol pools and alteration in lipoprotein metabolism [87]. It is known that phytosterols have a greater affinity for micelles than cholesterol because of their greater hydrophobicity, thereby reducing intestinal cholesterol absorption, and consequently reduce hepatic and plasma cholesterol concentrations [88]. Saponins are also capable of precipitating cholesterol from micelles and interfering with enterohepatic circulation of bile acids making it unavailable for intestinal absorption and hence reduce plasma cholesterol levels [89]. The medicinal plants dealt in this review have shown profound effects in the management of hypercholesterolemia in both animal models (Table 1) and clinical trials (Table 2) thus paving way for better therapeutic agents for atherosclerosis and CVD [90-140].

Plant/ Family	Animal Model	Phytoconstituents	Activity	References
Allium cepa/ Alliaceae	white albino rabbits	Onion	Decreased erythrocytes crenation	Vatsala & Singh, 1981
	white albino rabbits	Onion	Decreased erythrocytes crenation	Vatsala & Singh, 1980
	Male albino rats	Onion juice	Hypocholesterolemic	Sharma, Chowdhury, & Sharma, 1975a
	Male albino rabbits	Onion juice	Hypocholesterolemic	Sharma, Chowdhury, & Sharma, 1975b
	Male albino rats	Fibre	Hypocholesterolemic	Vadhera, Punia, & Soni, 1995
Allium sativum/ Alliaceae	Goats	Garlic capsules	Hypocholesterolemic	Kaul & Prasad, 1990
	Male rabbits	Garlic	Anti-atherosclerotic	Mirhadi, Singh, & Gupta, 1991
	Female albino rats	Garlic powder	Hypocholesterolemic	Kamanna & Chandrasekhara, 1982
	Male albino rabbits	Garlic oil	Anti-atherosclerotic	Jain & Konar, 1978
	Male albino rats	Garlic protein	Anti-atherogenic and anti-peroxidative	Rajasree, Rajmohan, & Augusti, 2009
	Wistar rats	Diallyldisulfide	Hypocholesterolemic	Rai, Sharma, & Tiwari, 2009
	Dogs of either sex	Garlic pearls	Hypocholesterolemic	Das, Pramanik, Mitra, & Mukherjee, 1982
	Male albino rabbits	Garlic	Hypercholesterolemic effect during treatment	Gupta, Khetrapal, & Ghai, 1987
Commiphora mukul/ Burseraceae	Male albino rabbits	Alcoholic extract and steroid	Marked hypocholesterolemic effect by steroid	Nityanand & Kapoor, 1971
	Indian domestic pigs	Resin	Hypocholesterolemic	Khanna, Agarwal, Gupta, & Arora, 1969
	Male albino rabbits	Oleoresin fraction	Hypocholesterolemic	Satyavati, Dwarakanath, & Tripathi, 1969
	Male white leg-horn chicks	Steroid, alcoholic extract and terpenoid	Marked hypocholesterolemic effect by steroid	Malhotra, Agarwal, Mehta, & Prasad, 1970
	Normal male rats	Steroid	Hypocholesterolemic	Nityanand & Kapoor, 1973
Emblica officinalis/ Euphorbiaceae	Albino rabbits	Amla	Hypocholesterolemic	Thakur, 1985
Cicer Arietinum/ Fabaceae	Albino rats	Fibre of different pulses	Marked hypocholesterolemic effect by bengal gram	Soni, George, & Singh, 1982
	Albino rats	Lipid extract	Hypocholesterolemic	Mathur, Sharma, & Singhal, 1964a
	Male albino rabbits	Seed coat	Hypocholesterolemic	Mand, Soni, Gupta, Vadhera, & Singh, 1992
	Male albino rats	Whole, defatted and lipid extract	Hypocholesterolemic	Mathur, Singhal, & Sharma, 1964b
	Rabbits	Bengal gram and Biochanin A	Hypocholesterolemic	Gopalan, Gracias, & Madhavan, 1991
	Male albino rats	Tannin, phytic acid and pectin	Marked hypocholesterolemic effect by pectin	Sharma, 1984a
Glycine max/ Fabaceae	Albino rabbits	Defatted soya protein	Anti-atherosclerotic	Thakur & Ali, 1982
Trigonella foenum-graecum/ Fabaceae	Rabbits	Galactomannan	Hypocholesterolemic and anti-atherogenic effect	Boban, Nambisan, & Sudhakaran, 2009
Vigna mungo/ Fabaceae	Male albino rats	Protein	Anti-atherosclerotic	Jayakumari, Nampoothiri, Nambisan, & Kurup, 1978
	Male albino rats	Neutral detergent fibre	Anti-atherosclerotic	Jayakumari & Kurup, 1979
	Male albino rats	Neutral detergent fibre	Hypocholesterolemic	Thomas, Leelamma, & Kurup, 1986
Capsicum annuum/ Solanaceae	Female wistar rats	Capsaicin	Anti-peroxidative	Kempaiah, Manjunatha, & Srinivasan, 2005
Withania somnifera/ Solanaceae	Wistar rats	Aqueous extract of fruits	Hypocholesterolemic	Hemalatha, Wahi, Singh, & Chansouria, 2006
Curcuma longa/ Zingiberaceae	Wistar rats	Curcumin	Hypocholesterolemic	Manjunatha & Srinivasan, 2007
	Male albino mice	Curcumin	Hypocholesterolemic	Soudamini, Unnikrishnan, Soni, & Kuttan, 1992
	Diabetic male albino rats	Curcumin	Hypocholesterolemic	Suresh babu & Srinivasan, 1995
	Female albino rats	Ethanol extract	Hypocholesterolemic	Subba Rao, Chandra Sekhara, Satyanarayana, & Srinivasan, 1970
	Albino mice	Turmeric	Hypocholesterolemic	Godkar, Narayanan, & Bhide, 1996
	Wistar rats	Curcumin	Decreased erythrocytes crenation	Kempaiah & Srinivasan, 2002
	Diabetic rats	Curcumin	Hypocholesterolemic	Babu & Srinivasan, 1997

Table 1: Animal studies on hypocholesterolemic effect of Indian medicinal plants.

Plant/ Family	Study model	Phytoconstituents	Activity	References
Allium cepa/ Alliaceae	10 healthy subjects	Onion extract	Decreased erythrocytes crenation	Singh & Kanakaraj 1985
Allium sativum/ Alliaceae	15 hypercholesterolemic patients of either sex	Aqueous extract	Hypocholesterolemic	Augusti, 1977
	25 healthy males	Garlic	Hypocholesterolemic	Bhushan, Sharma, Singh, Agrawal, Indrayan, & Seth, 1979
	10 healthy volunteers	Garlic	Hypocholesterolemic	Sharma, Sharma, Dwivedi, & Sharma, 1976
	50 normal volunteers	Garlic	Hypocholesterolemic and anti-thrombotic	Gadkari & Joshi, 1991
	32 hypercholesterolemic patients of either sex	Garlic pearls	Hypocholesterolemic	Jeyaraj, Shivaji, Jeyaraj, & Vengatesan, 2005
	20 normotensive and 20 hypertensive patients	Garlic pearls	Anti-hypertensive	Dhawan & Jain, 2004
Commiphora mukul/ Burseraceae	120 hypercholesterolemic patients	Gum and petroleum ether fraction	Hypocholesterolemic	Kuppurajan, Rajagopalan, Koteswara Rao, & Sitaraman, 1978
	205 patients	Guggulipid	Hypolipidemic	Nityanand, Srivastava, & Asthana, 1989
Emblica officinalis/ Euphorbiaceae	15 normal and 20 hypercholesterolemic men	Amla	Hypocholesterolemic	Jacob, Pandey, Kapoor, & Saroja, 1988
	30 patients	Amlamax capsules	Hypocholesterolemic	Antony, Merina, & Sheeba, 2008

Table 2: Clinical studies on hypocholesterolemic effect of Indian medicinal plants.

Conclusion

Herbs have been used in medical treatment since the beginning of civilization and have become a mainstay of human pharmacotherapy. Based on this, many works were carried out in evaluating the hypocholesterolemic effect of plants and from the reports on their potential effectiveness; it is assumed that the botanicals have a major role to play in the management of hypercholesterolemia. Medicinal plants reviewed here have shown great cholesterol reducing property in normal as well as high fat/cholesterol treated animals thus showing protective role in the progression of atherosclerosis. More concentration in evaluating the beneficial effects of medicinal plants certainly will help to utilize the Indian biodiversity and traditional knowledge for prospecting novel compounds as pharmacologically effective products to manage hypercholesterolemia.

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