

Antihyperlipidemic and cardioprotective effects of plant natural products: A review

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Abstract

The present review article explains antihyperlipidemic and cardioprotective effects of various plant natural products. These are antioxidants which found in vegetable oils, fruits, seeds, plant leaves, stem, and plant roots. This article emphasizes therapeutic potential of sulfur-containing compounds, anthraquinones, thiosulfates and ajoenes, tricin, quercetin, Kaikasaponin III and tectorigenin, polyphenols, vitamins and minerals, flavonoid, and phenolics mainly naringenin; aglycone, flavanone (+)-catechin, (–)-epicatechin, and procyanidin B2, quercetin, kaempferol, myricetin, rutin, naringenin, catechin, fisetin, and gossypetin, thymol and carvacrol, ceramidine B (limonoid), ginsenoside Rb1 and Rb2, naphthalenic compounds 6-methoxysorigenin and its glycosides, acylates, madecassoside (terpenoids), Miroestrol (phytoestrogen), quercetin rutinoid (rutin), tournefolal, and tournefollic acids A and B. Few other compounds such as thiobarbituric acid, niacin, hederagenin monodesmosides, kalopanaxsaponin A (KPS-A) and sapindoside C, abietane and seco-abietane diterpenes, lycopene, Curcubitacins A, B, C, D, E, I, J, K, and L, and Colocynthisides A and B were found active. For a healthy life regular intake of plant natural products or herbal diets significantly reduce the cardiovascular risks. Before use, well-designed clinical trials are essentially required to explore real efficacy and safety of these plant products. For management of cardiovascular risks lipid profile is highly needful at an earlier stage. In addition, microlevel biomolecular changes responsible for multiple morbidities affiliated to CVD diseases must be measured to find minor changes at an earlier stage.

Key words: Antilipidemic herbal preparations, cardiovascular diseases, hyperlipidemia, LDL cholesterol, plant natural products

INTRODUCTION

Today, due to bad food habits hyperlipidemia, diabetic cardiomyopathy and cardiovascular diseases (CVDs) become serious global health problems. Cases related to obesity, hyperlipidemia, atherosclerosis, and diabetic cardiomyopathy (DCM) are increasing day by day and large numbers of deaths are occurring worldwide.^[1] There are two important reasons of these CVD diseases and disorders; first one is metabolic storage of excess fat/lipids (adipogenesis) in body tissues after dietary use, second genetic or heredity-related disorders. Hyperlipidemia is the main cause of generation of CVDs myocardial infarction and strokes. It is a major pathological condition associated with disrupted lipid levels and physiological redox homeostasis. Increased cholesterol levels create problems in streaming of blood through blood vessels. This hypercholesterolemic state causes multiple risks to cardiovascular system impose excessive release of reactive oxygen species

(ROS) that lead to enhanced lipid peroxidation.^[2] It also aggravates atherosclerosis and oxidative stress in patients.^[2] Today, most of the people are affected due to obesity induced blood pressure, blood vessel inflammation arteriosclerosis, and diabetic cardiomyopathy (DCM). This is a more common and severe complication of diabetes that is causing high mortality in association of blood pressure.^[3]

Cardiovascular diseases (CVDs) and other associating disorders such as myocardial infarction, hypertension, peripheral vascular diseases, coronary heart disease, cardiomyopathies, and dyslipidemias become significant health burden and most frequent causes of morbidity and mortality in man [Figure 1].^[4] More especially in vascular

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diseases like atherosclerosis atherogenic plaques are formed as a result of accumulation of lipids and fibrous elements in the subendothelial space of large arteries and subsequent formation of lesions inside the coronary and cerebral arteries.^[5] Pathogenesis of atherosclerosis is multifactorial, and many modifiable and non-modifiable risk factors have been identified.^[6] Atherosclerosis is a chronic multifactorial disease characterized by mainly changes of blood lipids profile and inflammation in vessel wall. It is well known that lipid peroxide in low-density lipoprotein (LDL) plays an important role in atherosclerosis and atherosclerotic diseases. Therefore, timely prevention and therapy of atherosclerosis is highly essential to reduce the risk of the development of its clinical manifestations.^[7] These risk factors collectively contribute to the development, progression, and rupture of atherosclerotic plaque.^[8]

Natural plant products can be used for the treatment or prevention of cardiovascular and metabolic disorders.^[9] These plant-derived antioxidants^[7,10] can play an essential role in the prevention of cardiovascular diseases^[11-13] mainly atherosclerosis.^[14] Due to its strong free radical scavenging activity, rejuvenation of health is possible if used in dietary supplements. Plant natural products become valuable source of less toxic, highly efficacious, and safe multitarget drugs. These are rich in antioxidants if used in dietary supplements. Plant flavonoids stop hardening and narrowing of the arteries in atherosclerosis and also act as anti-atherogenic, hypotensive, lipid-lowering, and anti-thrombotic agents. These subsequently reduce the chance of strokes, heart attacks, and peripheral vascular diseases [Figure 2]. Thus, herbs can potentially reduce serum lipid profile if include in dietary habits.^[14]

Natural products promote health and successfully prevent cardiovascular and metabolic disease. No doubt these are valuable source for the discovery of new drugs [Figure 2]. However, there is a need to explore the cellular and molecular cardioprotective mechanisms of herbs used in treatment

CVDs and their risk factors. However, before its use, lipid profile mainly serum concentrations of total cholesterol, LDL-C, HDL-C, triglycerides, apoA and apoB, SGOT, SGPT, glucose, and insulin must be checked.^[14] It is advised that only pharmacologically approved herbs should be prescribed for therapeutic use. More often, herb-drug interactions should be investigated and checked thoroughly for their efficacy, safety, and toxicity.^[15] This review emphasizes safe use of natural plant products and herbal medicines for the treatment of hypercholesterolemia and CVDs.

SOURCE OF INFORMATION

For writing this comprehensive research review on antihyperlipidemic and cardioprotective effects of various plant natural products, various databases were searched. For collection of relevant information, specific terms such as medical subject headings (MeSH) and key text words, such as “antihyperlipidemic and cardioprotective,” “natural plant products,” and therapeutic uses” published till 2020 were used in MEDLINE. Most specially for retrieving all articles pertaining to the natural plant products and herbal medicines for the treatment of hypercholesterolemia and CVDs, electronic bibliographic databases were searched and abstracts of published studies with relevant information on the venom toxins/allergens were collected. Furthermore, additional references were included through searching the references cited by the studies done on the present topic. Relevant terms were used individually and in combination to ensure an extensive literature search. For updating the information about a subject and incorporation of recent knowledge, relevant research articles, books, conferences proceedings, and public health organization survey reports were selected and collated based on the broader objective of the review. This was achieved by searching databases, including SCOPUS, Web of Science, and EMBASE, PubMed, PMC, Publon, Swiss-Prot, and Google searches. From this common methodology, discoveries and findings were identified and summarized in this final review.

USE OF VEGETABLE OILS

Vegetable oils are edible and typical dietary component and predominantly used for cooking purposes. These are extracted from some seeds, nuts, cereal grains, and fruits and remain in liquid state at ambient temperatures.^[16] Vegetable oils are mainly triacylglycerols (92–98%), polar lipids (phospholipids and galactolipids), monoacylglycerols, and diacylglycerols. These also contain free fatty acids and polyisoprenoids in minor amounts.^[17] Other minor components are tocopherols/tocotrienols (up to 900 mg kg⁻¹) and phytosterol esters/phytosterols (up to 1%). Plant oils contain wide variety of fatty acids which are nutritionally beneficial to human health. ALA (alpha-linolenic acid), another omega-3 fatty acid, is found in plant sources such as nuts and seeds mainly flaxseed.

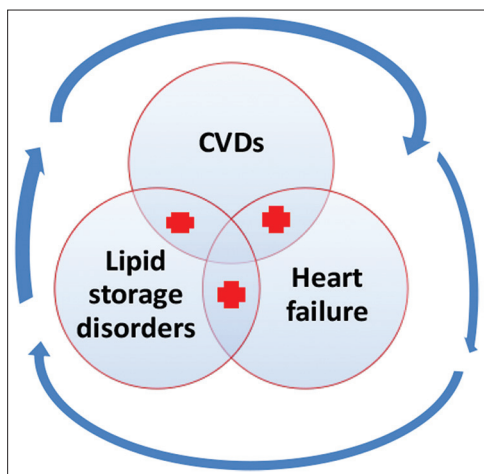


Figure 1: Inter-relationship between CVD, lipid storage disease, and heart failure

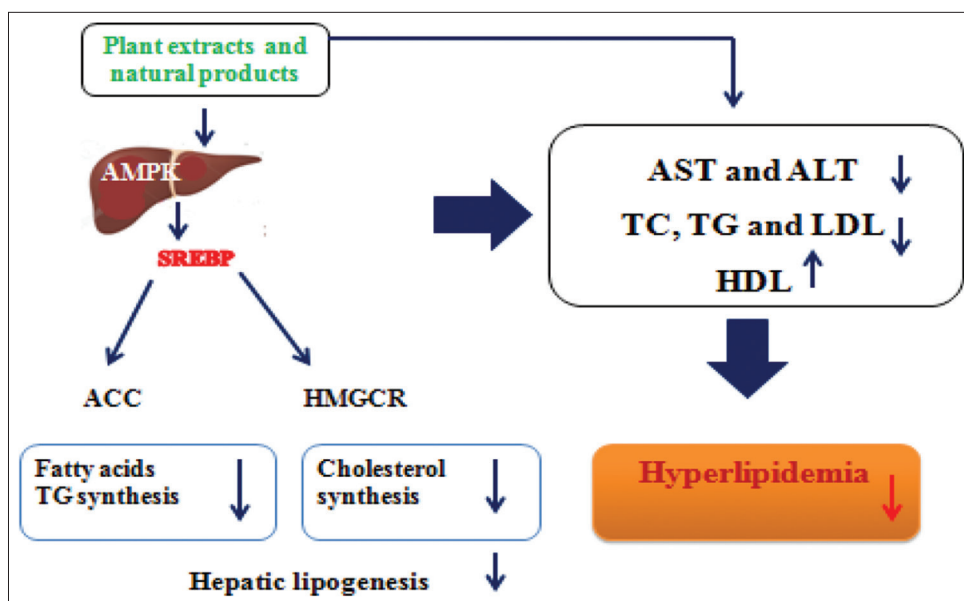


Figure 2: Possible mechanisms in hepatic tissues showing action of plant natural products that prevent hyperlipidemia through AMPK pathway and regulation of lipid metabolism. *AMPK – Adenosine monophosphate-activated protein kinase, ACC – Acetyl-CoA carboxylase, HMG-CoA reductase, AST – Aspartate transaminase, ALT – Alanine transaminase, CVD – Cardiovascular disease, LDL – Low-density lipoprotein cholesterol, TC – Total blood cholesterol (TC) and TG – Triglyceride

Vegetable oils contain non-volatile organic compounds (VOCs) which are less toxic and less dissolving power of non-polar and polar bioactive components with the function of fatty acids and/or lipid classes in vegetable oils, other minor components.^[18] Natural products can be used to have new drugs as they possess a variety of pharmacological targets.^[19] Vegetable oils are source of unsaturated fatty acids which can replace deposited fat; vegetable oils also possess natural antioxidants which can extract out or sequestration of bad cholesterol and fats. Plant oils can easily leach out deposited fat from tissue adipocytes [Figure 2]. Peroxisome proliferator-activated receptor γ (PPAR γ), the chief regulator of adipogenesis, has been acutely investigated as a molecular target for natural products in the development of antiobesity treatments. Due to their susceptibility to oxidation from the exposure to oxygen, heat and light, resulting in the formation of oxidation products, such as peroxides and hydroperoxides and plant oils rich in polyunsaturated fatty acids have a limited shelf life.^[20,21]

Most vegetable oils are unstable during storage or cooking due to the oxidation of their polyunsaturated fatty acids. Therefore, partial hydrogenation is frequently applied to improve the flavor and oxidative stability of vegetable oils by reducing the content of the highly unsaturated linolenic and linoleic acids.^[20,21] Vegetable oils contain predominantly unsaturated (light, liquid) fatty acids of two kinds: Monounsaturated (oleic acid – mainly in extra virgin olive oil) and polyunsaturated (linoleic acid and linolenic acid – in oils extracted from oil seeds). Plant origin short-chain omega-3 fatty acids are ALA (alpha-linolenic acid) mainly EPA eicosapentaenoic acid and DHA docosahexaenoic acid extend big health benefits. These are extracted

from flaxseed.^[20,21] Besides, plant oils “Fish oil” are also nutritionally and medically important as they contain long-chain polyunsaturated fatty acids. Omega-3 fatty acids are found in fatty layers of cold water fish and shellfish, plant, and nut oils. Fish are low in saturated fat. These provide benefits to cardiovascular disease patients [Figure 3].^[20,21]

USE OF NATURAL ANTIOXIDANTS

Plants contain natural antioxidants mainly flavonoids phenolic oligomeric proanthocyanidins (OPC) and pterostilbene (PT) with niacin (NA). These natural antioxidants blends show potential antihyperlipidemic effects and assist in reduction in lipid peroxidation, decrease cellular damage, and contribute cardioprotective activity.^[22] This is the main reason that medicinal plants constitute a principal health-care resource. Due to their multitarget therapeutic action, there is a gradual increase in acceptance at the global level. Today, there are number of herbal medicines which are used for the treatment of hypercholesterolemia and cardiovascular problems mainly CVDs. There are confirmed scientific reports on usage of herbal medicines which prove their therapeutic efficacy. These simple natural antioxidants blends present in drug formulations can help in mitigating chronic illnesses in general populations.

CONSUMPTION OF VEGETABLES AND FRUITS

Vegetables and fruits are source of variety of polyphenols, vitamins, and minerals which act as natural antioxidants and

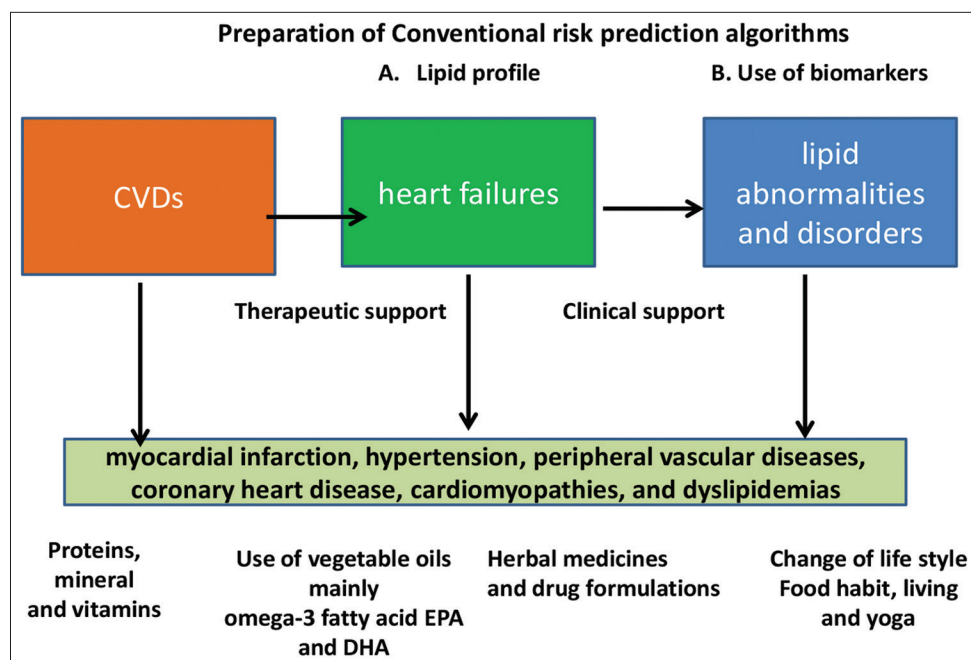


Figure 3: Management of hyperlipidemia mainly CVDs, heart failure, and lipid abnormalities using various natural plant products

assist in prevention of hyperhomocysteinemia. Drinking juices are a potential way to improve cardiovascular health.^[23] Herbal tea (ZHT) for antihypercholesterolemic and antilipidemic perspectives in decrease of serum LDL cholesterol (5.6%) and TG (12.5%) was also observed after consumption of T3 at day 60.^[24] *Pistacia atlantica* subsp. *Kurdica* shows antihyperlipidemic and antioxidative activity in streptozotocin-induced diabetic mice.^[25] Blue-green algae (*Nostoc commune*) inhibit cholesterol absorption in mice and lower down plasma total cholesterol and triglyceride (TG) levels compared with controls.^[26] Interestingly, kombucha inhibit absorption of LDL cholesterol and triglycerides and cause a significant increase in HDL cholesterol life.^[27] Both zedoary (*Curcuma zedoaria* Roscoe.) and *Xanthium strumarium* L. (Asteraceae) plant extracts showed antilipidemic effects [Figure 3].^[28]

USE OF HERBAL MEDICINES

The use of medicinal herbs continues to be an alternative treatment approach for several diseases including CVDs. At present, use of herbal preparations has been increased because of their therapeutic efficacy. Herbal preparations and drugs are cost effective and show big therapeutic promise compared to standard modern therapies. Due to their easy usage and less toxic, there is a general belief among people that they are safe. Polyherbal formulations prepared using different proportions of *Commiphora mukul* (Hook ex Stocks) Eng., *Salacia reticulata* Wight, *Terminalia arjuna* (Roxb.) Wight and Arn, and *Curcuma longa* Linn. showed antilipid-peroxidative effects.^[29] Today, statins and biguanides are two prominent representatives of natural products which are mostly used against metabolic disease.

There is going on a large search for lipid-modifying agents. Few of them are statins, fibrates, niacin, and ezetimibe that significantly reduce the risk of atherosclerotic morbidities. These are established herbal drugs used in CVD treatments. There are important approaches such as inhibition of proprotein convertase, inhibition of the synthesis of apolipoprotein (apo) B, and microsomal triglyceride transfer protein to block the formation of atherogenic lipoproteins which occur are atherosclerosis. Other approaches are inhibition of adenosine triphosphate citrate lyase to inhibit the synthesis of cholesterol, inhibition of the synthesis of lipoprotein, apoC-III to reduce triglyceride-rich lipoproteins, and cholesteryl ester transfer protein to enhance high-density lipoprotein (HDL) functionality.^[30] Plant natural products inhibit cholesterol absorption in mice and lower down plasma total cholesterol and triglyceride (TG) levels [Figure 3].^[31]

Various types of herbs can potentially reduce serum lipid levels through different metabolic pathways. More specially, the herb-drug interactions may decrease the morbidity if well-tested anti-hyperlipidemic drug formulations are being provided life.^[32] However, GSTC3 successfully decreased the serum total cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), triglycerides, and phospholipids similar to standard atorvastatin while maintaining high-density lipoprotein (HDL) at normal levels at dose of 100 mg/kg body weight. Significantly lower values of LDL, VLDL, and atherogenic index of plasma as well as higher HMG-CoA/mevalonate ratios demonstrate significant hypolipidemic effect for GSTC3. It may be possibly due to partial inhibition of HMG-CoA reductase activity in experimental animals [Figures 2 and 3].^[32]

USE OF ANTILIPID PEROXIDATION NATURAL PLANT EXTRACTS

Different solvent extracts prepared from aerial parts of various plant species such as Bael leaf extracts,^[33] *Talinum triangulare* (Jacq.) Willd.,^[34] *Momordica charantia* fruit extract Linn.,^[35] and use of *Aloe vera* also decreases LDL cholesterol levels by 45%, 3%, and 69%, respectively, in experimental rats.^[36] Dietary use of onion (*Allium cepa* L.) significantly cut down the hyperlipidemia, hypertension, and diabetes.^[37] Similar antilipid peroxidation activities are also reported in *Padina boergerensis*,^[38] *Maytenus royleanus*,^[39] *Phyllanthus emblica* leaves,^[40] Tunisian *Zizyphus lotus*,^[41] and *Terminalia chebula* Retz. (Combretaceae) fruits.^[42] *Hypericum x moserianum* and *Hypericum ericoides* show potential antilipid peroxidation activities.^[43] Methanolic extract of the bark of *Ficus amplissima* (FAB) shows significant antilipid-peroxidative effect in the pancreas of STZ-induced diabetic rats.^[44] Similar antilipid peroxidation activities also found in *Sanguisorba officinalis* methanolic,^[45] and aqueous or ethanolic extracts,^[46] *Apocynum venetum* (AVLE),^[47] *Piper trioicum* Roxb. and *Physalis minima* L.,^[48] and Tunisian *Rhamnus alaternus*.^[49] Various solvent extracts prepared from different plant species i.e. *Phaseolus trilobus*,^[22] *O. basilicum* and *T. foenum-graecum*,^[50] *Asparagus racemosus* (AR) and *Premna integrifolia*^[51] Linn, *Murraya koenigii*,^[52] *Gongronema latifolium*,^[53] (Utazi), and *Jasminum grandiflorum* Linn.^[54] *Gongronema latifolium* (Utazi),^[54] *Jasminum grandiflorum* Linn. extracts. Extracts prepared from fruit pulp of the Chakapat lychee (*Litchi chinensis* Sonn.),^[55,56] *Rosa davarica* Pall.,^[57] *Aegle marmelos* (AMFEt), and *Momordica charantia* Linn. Fruits showed antilipid-peroxidative activity in streptozotocin diabetic rats.^[58] Hamsters fed on 3% or 9% tomato paste showed reduced rates of serum TC and LDL levels.^[59]

Strong antilipid peroxidation activity is also reported in *Pinus morrisonicola* Hay.^[60] and *Selaginella involvens* (Sw.) Spring, a wild fern water extract.^[61] The oral consumption of Gel-Et for 4 weeks caused significant reduction total cholesterol levels by 11%, 17%, and 25%, and LDL cholesterol levels by 69%.^[62] Similarly, SCBe showed antilipidemic activity as evidenced by significant decrease in serum TC, TG, and LDL-C levels and significant increase in HDL-C level in antilipidemic activities of *S. cochinchinensis* bark methanolic extract (SCBe) in streptozotocin (STZ)-induced diabetic rats life.^[63] Hypolipidemic activities are reported in *Averrhoa bilimbi* Linn. leaves (Oxalidaceae, Common name: Bilimbi),^[64] *Phyllanthus urinaria*,^[65] radix *Angelica sinensis*,^[66] Yam (*Dioscorea batatas*) tuber mucilage,^[67] *Nardostachys jatamansi*,^[68] and *Cortex Phellodendri*.^[69] Radix *Aconiti Preparata* and *Radix glycyrrhizae* can significantly suppress lipid peroxidation of myocardial homogenate^[70] and *Ficus carica* leaves also showed antilipidemic effects [Figure 3].^[71]

ANTIHYPERLIPIDEMIC EFFECTS

Garlic (*Allium Sativum*)

Garlic is widely used in Asian countries for dietary purposes. Both aged and processed garlic are used for the treatment of cardiovascular and diabetic patient's life.^[72,73] It contains fructooligosaccharides which have potential benefits on health life.^[74] Homemade green garlic preparations possess cardioprotective potential to prevent cardiovascular diseases. This is the main reason that Mediterranean people who have a noted lower mortality rate due to cardiovascular diseases life.^[75] Garlic shows multiple protective effects and improves functioning of cardiovascular system.^[76-78] It removes off atherosclerosis and does reduction of serum lipids.^[78] It shows inhibition of platelet aggregation and enhancement of fibrinolysis. Wild garlic (*Allium ursinum*) has been reported to contain similar amounts of sulfur-containing compounds,^[79] thiosulfates and ajoenes from garlic, exert similar effects on cyclooxygenase, 5-lipoxygenase, angiotensin-converting enzyme, and platelet aggregation.^[34] DADS show strong antilipidemic effects [Table 1].^[80]

Garlic products showed positive effects on lipid metabolism in cholesterol-fed rats^[81] and cut down lipid contents in experimental animals.^[82-84] Possibly, it may occur through inhibition of 3-hydroxy-3-methyl-glutaryl-CoA reductase or other enzymes.^[85-87] More specifically, garlic-derived organosulfur diallyl di- and trisulfide compounds inhibit cholesterol biosynthesis in primary rat hepatocyte cultures.^[88-89] Moreover, garlic ingredients increase loss of bile salts in feces and mobilization of tissue lipids into circulation. Garlic does lowering of blood lipids, blood sugar, and fibrinogen and induces fibrinolytic activity in patients with coronary artery diseases. Garlic essential oil shows profound effect on postprandial hyperlipidemia and does prevention of atherosclerosis [Figures 2 and 3].^[90]

Wild garlic (*A. ursinum*) causes decrease hepatocyte cholesterol synthesis *in vitro*.^[91] Aged garlic extract and its constituent SAC have been found to protect vascular endothelial cells from injury caused by oxidized LDL.^[92] More often, aged garlic extract, "Kyolic," and essential oil^[93] showed anti-atherosclerosis-related effects.^[94] Garlic products affect lipid content in normal and atherosclerotic human aortic cells.^[95] Garlic products show long-term effect on the development of plaque formation in the carotid branches of both femoral arteries^[96] and lower down blood lipid level in cholesterol-fed rabbits.^[97] Daily supplementation of aged garlic extracts lowers down lipoprotein oxidation susceptibility^[98] and protects against LDL malfunction.^[99,100] Garlic contains oil-soluble organosulfur compounds which affect on doxorubicin-induced lipid peroxidation.^[101] Garlic extracts cut down vascular tissue lipids, fatty streak formation, and atherosclerotic plaque size.^[102] Garlic extract significantly normalizes the ratio of serum LDL to HDL

Table 1: Important bio-organic ingredients isolated from various plant species which show antihyperlipidemic and cardioprotective activity

Plant natural product	Plant species	Plant part	Biological effects
Sulfur-containing compounds	<i>Allium sativum</i> , garlic	Bulbs	Hypolipidemic and cardioprotective
Thiosulfinates and ajoenes	Oil-macerated garlic extract	Bulbs	Antihyperlipidemic
Umbelliferon- α -D-glucopyranosyl-(2I \rightarrow 1II)- α -Dglucopyranoside	<i>Aegle marmelos</i>	leaf	Antihyperlipidemic
Anthraquinones	<i>Radix Rhizoma Rhei</i>	Leaf and buds	Antihyperlipidemic
Methyl ferulate, methyl p-hydroxycinnamate, p-hydroxybenzaldehyde, tricetin, and quercetin 3,4'-dimethyl ether	<i>Sorghum bicolor</i> .	Stem	Antihypercholesterolemia and protective to CVD
Kaikasaponin III and tectorigenin	<i>Pueraria thunbergiana</i>	Flowers	Antilipid-peroxidative effects
N-acetylcysteine	<i>Allium</i> species	Bulbs	Antihypercholesterolemic
Gallic acid (trihydroxybenzoic acid)	Gallnuts, sumac, witch hazel, tea leaves, oak bark	Stem bark	Antihypercholesterolemic
Polyphenols, vitamins, and minerals	Leafy green vegetables	Vegetables and fruits	Hyperlipidemic and cardioprotective
Oligostilbenes	<i>Vitis amurensis</i>	Leaf and stem	Antioxidant and LOX-1 inhibitory effects.
Flavonoid and phenolics	<i>Hypericum androsaemum</i> L.	Leaf	Higher radical scavenging and antilipid peroxidation activity
Naringenin; aglycone flavonoid, flavanone	Grapefruits	Fruit	Antilipid peroxidation
(+)-catechin, (-)-epicatechin, and procyanidin B2	<i>Tamarindus indica</i>	Seed	Antioxidant and antilipid peroxidation
Quercetin, kaempferol, myricetin, rutin, naringenin, catechin, fisetin, and gossypetin (flavonoids)	<i>Citrullus colocynthis</i> , <i>Kelussia odoratissima</i> Mozaff., and <i>Carum copticum</i> L.	Leaf and seed	Antilipid peroxidation
Thymol and carvacrol	<i>Thymus vulgaris</i>		Antilipid peroxidation
Ceramicine B (limonoid)	<i>Chisocheton ceramicus</i>	Leaf	Antilipid droplets accumulation activity
(6)-paradol phenolic constituent	Ginger <i>Zingiber officinale</i>	Stem and bud	Antilipid peroxidation
Lycopene	<i>Lycopersicum</i> species	Fruit	Decrease cardiovascular risks
Ginsenoside Rb1 and Rb2	<i>Cudrania cochinchinensis</i>		Antilipid peroxidative effect
Naphthalenic compounds 6-methoxysorigenin and its glycosides, acylates	<i>Rhamnus nakaharai</i>	Leaves	Antilipid peroxidation assay
Madecassoside (terpenoids)	<i>Centella asiatica</i>	Leaves	Antilipid peroxidation
Thiobarbituric acid	<i>Atalantia ceylanica</i>	Leaves	Antilipid peroxidation
Miroestrol (phytoestrogen)	<i>Pueraria mirifica</i>	Tuberous root	Antilipid peroxidation

(Contd...)

Table 1: (Continued)

Plant natural product	Plant species	Plant part	Biological effects
Benzenoids, tournefolal, tournefolic acids A and B, and B ethyl ester, and salvianolic acid A, and rosmarinic acid	<i>Tournefortia sarmentosa</i>	Stems	Anti-LDL-peroxidative activity
quercetin rutinoside (rutin)	<i>Capparis sicula</i> , <i>Capparis orientalis</i>	Aerial parts	Antilipidemic activity
Methyl ferulate, quercetin 3,4'-dimethyl ether	<i>Terminalia chebula</i>		Antilipid peroxidation activity
Hederagenin monodesmosides, kalopanaxsaponin A (KPS-A), and sapindoside C	<i>Kalopanax pictus</i>	Stem barks	Antilipid peroxidation effects
Abietane and seco-abietane diterpenes	<i>Salvia candelabrum</i>	Stem and leaves	Antilipid peroxidation
Curcubitacins A, B, C, D, E, I, J, K, and L and Colocynthisides A, and B	<i>Citrullus colocynthis</i>	Fruit and leaves	Anti-inflammatory and antilipidemic
Phthalides and steroids	<i>Centaurium erythraea</i> L. fam.	Stem and leaves	Antilipid peroxidation
Total phenolic and flavonoid contents	<i>Aloe barbadensis</i> Miller.	Fleshy leaves	Antilipid peroxidation

level in rat fed with hypercholesterolemia diet^[103] [Table 1, Figures 3 and 4].

Bel (*Aegle Marmelos*)

A. marmelos leaf extract shows antihyperlipidemic activity in rats in a dose-dependent manner. It causes a significant reduction in total cholesterol, triglycerides, low-density lipoprotein, very low-density lipoprotein, and significantly increased high-density lipoprotein life.^[104] Its unripe fruits also shows antidyslipidemic effect against ISO-induced cardiac stressed rats and restore ISO-induced myocardial infarction [Figures 2 and 3] life.^[105] *A. marmelos* leaf extract pre-treatment increased the activity of Na(+)K(+) ATPase and decreased the activity of Ca(2+) ATPase in the heart and aorta simultaneously^[106] [Table 2].

Onion (*Allium Cepa*)

Onion (*Allium cepa* L.) belongs to family: Liliaceae (lilies). It is an easily digestible aromatic vegetable which is used throughout the world. Onions contain phenolics and flavonoids that have potential anticholesterol and antioxidant properties. Onion contains numerous sulfur compounds including thiosulfates and thiosulfonates; cepaenes; S-oxides; S, S-dioxides; mono-, di-, and trisulfides; and sulfoxides. Onion contains sulfur compounds, including S-methyl cysteine sulfoxide and allyl propyl disulfide showed hypolipidemic effects life.^[107] These compounds also showed anti-atherosclerotic and antithrombotic effects in experimental animal's life.^[108] Bioactive compounds found in onion play an important role in the prevention of cardiovascular diseases and cancer [Table 1].

Kareel (*C. decidua*)

Capparis decidua (CD) is a xerophytic or desert dominating shrub found in desert region of Rajasthan showing strong climatic adaptations. It is a densely branched, thorny plant with smaller scanty and caduceus leaves having pink to red flowers and green berry fruits. Its fruit and shoot extract possesses very strong hypolipidemic efficacy and significantly cut down human plasma triglycerides, total lipids, and phospholipids [Table 1].^[109-111] Plant fruit shows antiatherosclerotic effect^[112] (and its regular use can restore cardiovascular activity).^[113]

Toddalia aculeata

Toddalia aculeata is an important medicinal plant widely used for the treatment of several diseases and disorders. Plant shows antihyperlipidemic activities in high-fat diet fed hyperlipidemic rats.^[114] Plant contains aculeatin that causes lipolysis of 3T3-L1 adipocytes^[115] and assists in restoration of cardiovascular system.^[116] Plant also acts as smooth muscle relaxant^[117] [Table 1].

Ocimum sanctum

Tulsi (*Ocimum sanctum* Linn.) is an aromatic plant belongs to family Lamiaceae. It is traditionally used for the preparation of various Ayurvedic formulations for the treatment of cough, cold, bronchitis, influenza, and asthma. Tulsi leaves show lipid-lowering and antioxidative activities.^[118] It has also been shown to counter metabolic stress does normalization of blood glucose, blood pressure, and lipid levels. It assists in relieving from psychological stress and exerts positive effects

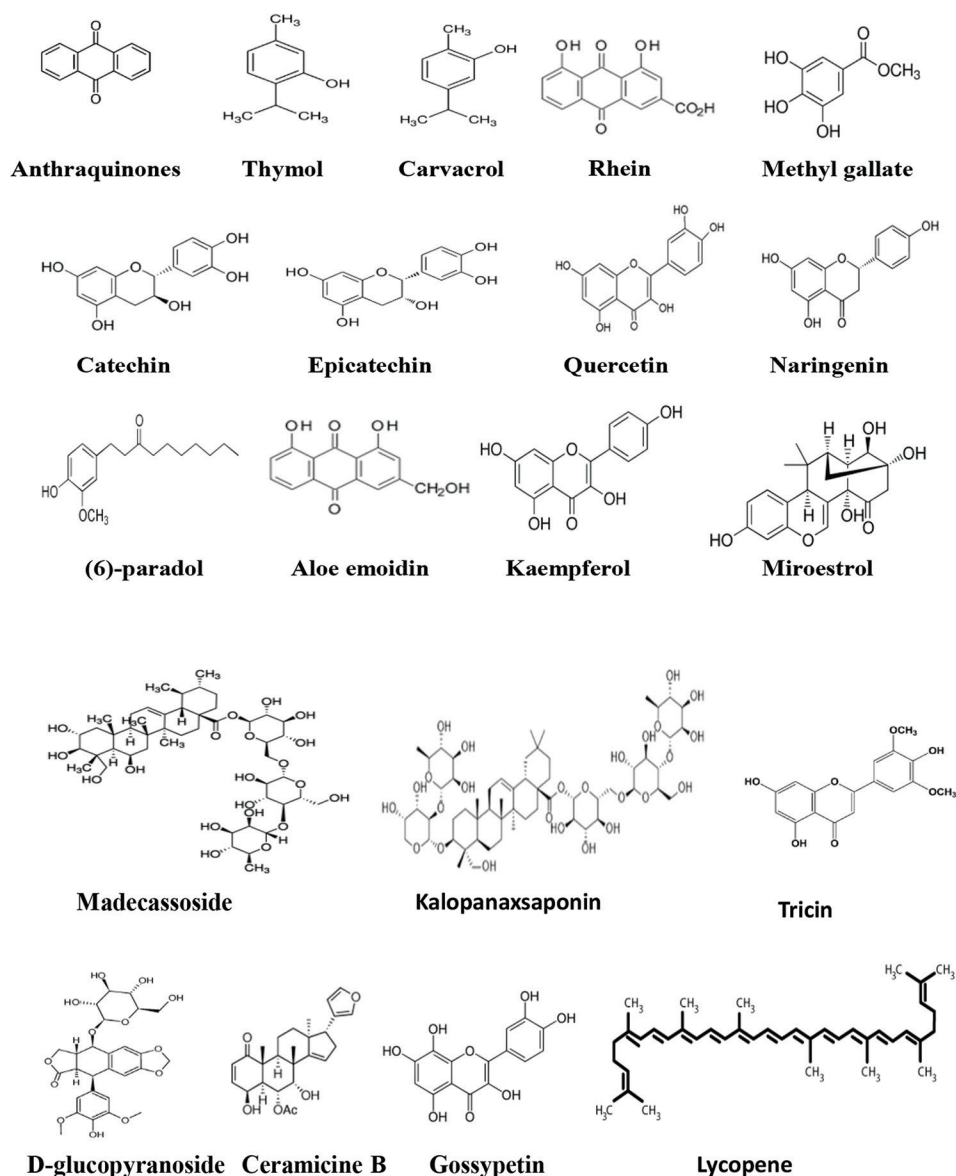


Figure 4: Various antihyperlipidemic bio-organic compounds isolated from various plant species

on memory and cognitive function through its anxiolytic and antidepressant properties.^[119]

OS, commonly known as Holy basil/Tulsi, has been traditionally used to treat cardiovascular diseases (CVD) and manage general cardiac health. OS leaves significantly change the blood lipid profile after a dose 1 g for 4 weeks in albino rabbit.^[120] This resulted in significant lowering in serum total cholesterol, triglyceride, phospholipid, and LDL cholesterol levels and significant increase in the HDL cholesterol and total fecal sterol contents. OS contains phenolic compounds and eugenol (EUG) which are traditionally used for treating CVD.^[121] Tulsi (OS) polyphenolic extracts were found to have the inherent capacity to inhibit the transcriptional expression of genes, that is, LDLR, LXR alpha, PPARs (alpha, gamma), CD-36, and c-myc which control lipid metabolism, cytokine production, and cellular activity within the arterial wall [Table 1] [Figures 3 and 4].

ANTILIPIDEMIC PLANT NATURAL PRODUCTS

Anthraquinones and Sulfur Compounds

Anthraquinones isolated in ethanolic fractions of total *Radix Rhizoma Rhei* significantly reduce blood levels of total cholesterol, triglycerides, HDL, and LDL.^[122] Gallic acid, a trihydroxybenzoic acid, also demonstrates robust anti-obesity capabilities.^[123] Utilization of niacin and ergosterol may prevent the hypercholesterolemia and incidence of coronary heart diseases [Table 1].^[124] Similar anti-hypercholesterolemic effect is also reported in N-acetylcysteine (NAC) and sesame oil administration in diet-induced hypercholesterolemic mice.^[125] Five major compounds methyl ferulate, methyl p-hydroxycinnamate, p-hydroxybenzaldehyde, triclin, and quercetin 3,4'-dimethyl ether were isolated from EtOAc

Table 2: Antihyperlipidemic activity in solvent extracts from various plant species

Scientific name	Plant common name	Plant part extracts/ compound	Biological activity
<i>Gouania longipetala</i>		Methanol leaf extract	Antilipidemic activities
<i>Citrullus colocynthis</i> (L.) Schrad.		Leaf extract	Antilipidemic activities
<i>Symplocos cochinchinensis</i>			Antidiabetic and antilipidemic activities
Edible oil produced from <i>Punica granatum</i> L.		Seeds	
<i>Momordica charantia</i>		Fruit extract Linn.	Significant lowering of cholesterol and triglyceride levels while elevating HDL cholesterol levels
<i>Ficus carica</i>		leaves	Antilipidemic and antidiabetic effects of ficusin isolated from
<i>Capparis orientalis</i>		Stem	These rutin-rich extracts exhibited pronounced dose-dependent enzyme inhibitory activities toward pancreatic lipase.
<i>Aegle marmelos</i> leaf extract			Shows hyperlipidemic activity in rats dose-dependent reduction of total cholesterol triglycerides, LDL, VLDL, and significantly increased HDL
Garlic		And cut down lipid contents in experimental animals	Products showed positive effects on lipid metabolism in cholesterol-fed rats
<i>Bipolaris</i> sp. <i>Bipolaris</i> sp., and <i>Phoma</i> sp. also exhibited significantly		Higher flavonoid and phenolic contents	Exhibited significantly higher radical scavenging and antilipid peroxidation activity than the other isolates
Wild garlic		<i>Allium ursinum</i>	Wild garlic (<i>Allium ursinum</i>) causes decrease hepatocyte cholesterol synthesis <i>in vitro</i>
<i>Padina boergesenii</i>		Plant extract	New secondary metabolite, padinolic acid
<i>Piper trioicum</i> Roxb. and <i>Physalis minima</i> L. extracts			Antilipid peroxidation activity of
<i>Hypericum androsaemum</i> L.			content of phenolics and flavonoids
<i>Rhizoma rhei</i> anthraquinones, total <i>Radix et Rhizoma Rhei</i> could		Anthraquinones	Significantly reduce blood levels of total cholesterol, triglycerides, HDL, and LDL
<i>Phyllanthus emblica</i> leaves		Methanol extract of	
<i>S. cochinchinensis</i> bark		Antilipidemic activities of	Methanolic extract (SCBe) in streptozotocin (STZ)-induced diabetic rats
Ginger			Lipid peroxidation chemopreventive potential of (6)-paradol, a pungent phenolic constituent of
<i>Premna integrifolia</i> Linn. Mant. (Verbanacea)		Roots of	Antilipid peroxidation
		Berberine, suppression of CYP1A expression, and lipid peroxidation by	Beta-naphthoflavone a major isoquinoline alkaloid in herbal plants induced
<i>Terminalia arjuna</i> (Roxb.) Wight and Arn, and <i>Curcuma longa</i> Linn. extracts			Antilipid-peroxidative effects on serum and platelets <i>in vitro</i>
<i>Terminalia chebula</i> Retz.		Fruit	Antilipid peroxidative

(Contd...)

Table 2: (Continued)

Scientific name	Plant common name	Plant part extracts/ compound	Biological activity
<i>Cudrania tricuspidata</i>		Root bark flavonoids	Antilipid peroxidation efficacy on human low-density lipoprotein
Tomato		Tomato paste	Antilipid peroxidative
<i>Atalantia ceylanica</i>		Plant extract	Antilipid peroxidation
<i>Chisocheton ceramicus</i>			Ceramicine B, a limonoid with antilipid droplets accumulation activity from
<i>Apocynum venetum</i>		Leaves extract of	Antioxidant and antilipid peroxidation effects
<i>Rhamnus alaternus</i>			Antilipid peroxidation
<i>Premna integrifolia</i> Linn. Mant.		Roots	Antilipid peroxidation
<i>Agrimonia pilosa</i>			Natural antioxidant sources, prevent oxidation-related diseases
<i>O. basilicum</i>		Leaves	Antilipid peroxidation effects, potent antioxidant effects
<i>Sida acuta</i> Burm. f.			Oxygen species/nitrogen species
<i>Jasminum grandiflorum</i> Linn.			Chemopreventive efficacy and antilipid-peroxidative potential
<i>Rosa davurica</i> Pall.		Fruit	Prevent the lipid peroxidation
<i>Pueraria thunbergiana</i>			Antilipid-peroxidative effect
<i>Kalopanax pictus</i>		MeOH extract of stem barks	Antilipid-peroxidative effect
<i>Salacia oblonga</i> Wall.			Hypoglycemic and antioxidant activity
<i>Phyllanthus urinaria</i> may			Antilipid peroxidation

fraction of *Sorghum bicolor* stem [Table 1]. All five compounds showed antilipid peroxidation activity (IC₅₀ values of 0.5, 0.4, 0.3, and 0.3 microM, respectively).^[126] Two compounds kaikasaponin III and tectorigenin isolated from *Pueraria thunbergiana* (Leguminosae) flowers showed potent antilipid-peroxidative effect.^[127] Guar gum shows antihypercholesterolemia, antihyperglycemia, and antiobesity activity.^[128]

Mozaff. and *Carum copticum* L. contain thymol and carvacrol which show antilipidemic effects^[137] Ceramicine B, a limonoid isolated from *Chisocheton ceramicus*, showed antilipid droplets accumulation activity.^[138] (6)-*paradol* a pungent phenolic constituent of ginger shows antilipid peroxidation and chemopreventive potential.^[139] Similarly, oligostilbenes isolated from the leaf and stem of *Vitis amurensis* potential antioxidant and LOX-1 inhibitory effects [Table 1].^[140]

FLAVONOID AND PHENOLIC COMPOUNDS

Flavonoid and phenolic compounds found in *Hypericum androsaemum* L. (Hypericaceae) and *Bipolaris* sp. show significantly high radical scavenging and antilipid peroxidation activity.^[129,130] Naringenin (NRG), the aglycone flavonoid found in grapefruits, shows antilipid peroxidation activity.^[131] Antioxidant and antilipid peroxidation activities are also reported in (+)-catechin, (–)-epicatechin, and procyanidin B₂,^[132] berberine.^[133] D-threo-guaiacylglycerol 8-O-beta-D-(6'-O-galloyl)glucopyranoside, 9-methoxy-D-threo-guaiacylglycerol 8-O-beta-D-(6'-O-galloyl)glucopyranoside, 6''-O-galloyl salidroside, methyl gallate, and quercetin.^[134] Plant flavonoids such as quercetin, kaempferol, myricetin, rutin, naringenin, catechin, fisetin, and gossypetin showed antiatherosclerotic effects.^[135] *Citrullus colocynthis*^[136] and *Kelussia odoratissima*

LYCOPENE

Lycopene is known to decrease cardiovascular risks. Madecassoside also shows protective effect against myocardial ischemia reperfusion injury and effects of antilipid peroxidation.^[141] GSTC3 decreased serum total cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), triglycerides, and phospholipids at a dose of 100 mg/kg body weight.^[29] It causes hypolipidemic effect due to partial inhibition of HMG-CoA reductase activity.^[29] Ginsenoside Rb1 and Rg1 isolated from *Cudrania cochinchinensis* var. gerontogea,^[142] naphthalenic compounds 6-methoxysorigenin, and its glycosides [i.e., 6-methoxysorigenin-8-O-glucoside, alpha-sorinin, and 6-methoxysorigenin-8-rutinoside], two acylates (peracetate and perpropionate) from *Rhamnus nakaharai* showed antilipid peroxidation activity.^[143] Madecassoside (MA)

one of the principle terpenoids in *Centella asiatica* shows protective effects against myocardial ischemia-reperfusion injury antilipid peroxidation.^[144] *Atalantia ceylanica* leaves contain thiobarbituric acid showed antilipid peroxidation.^[145] Miroestrol (MR) is a potent phytoestrogen from the tuberous root of *Pueraria mirifica*, antilipid peroxidation; and normalizes the superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase activity on glutathione content in the livers and uteri of β -naphthoflavone (BNF)-treated mice.^[145] Anti-LDL-peroxidative activity was detected in benzenoids, tournefolal, tournefolic acids A and B, and B ethyl ester, together with salvianolic acid A, isosalvianolic acid C, lithospermic acid, salvianolic acid F, and rosmarinic acid isolated from the stems of *Tournefortia sarmentosa*.^[146] *Capparis sicula* subsp. *sicula* and *Capparis orientalis* aerial parts showed antilipidemic activity due to the presence of quercetin rutinoid (rutin).^[147] *Terminalia chebula* RETZ contains methyl ferulate^[148] and *Kalopanax pictus* stem barks contain two hederagenin monodesmosides, kalopanaxsaponin A (KPS-A) and sapindoside C, which exhibit significant antilipid peroxidation effects.^[149] *Salvia candelabrum* shows antilipid peroxidation activity due to the presence of abietane and seco-abietane diterpenes [Table 1].^[150]

CARDIOPROTECTIVE EFFECTS

Bel is used for the preparation of various Ayurvedic traditional medicines. It has wide ethnomedicinal uses because of its strong cardioprotective activity.^[151] The leaf extract of *A. marmelos* shows preventive effect in isoprenaline isoproterenol (ISO)-induced myocardial infarction in rats.^[106] It restores creatine kinase and lactate dehydrogenase activity in the heart of isoprenaline-treated rats. Bel is also used as a cardiac depressant^[152-154] and found biologically active against several major diseases including cancer, diabetes, and cardiovascular diseases.^[155] Its leaf extract shows antihyperglycemic and antihyperlipidemic activities and minimizes the cardiovascular risk factors associated with diabetes.^[156] Lanosteryl triterpenes isolated from *Protorhus longifolia* act as a cardioprotective agent in diabetic cardiomyopathy and ischemic heart diseases.^[157] Periplogenin-3-O-Dglucopyranosyl-(1 \rightarrow 6)-D-glucopyranosyl-(1 \rightarrow 4)-Dcymaropyranoside, isolated from *A. marmelos*, shows protective effects against DOX-induced cardiovascular morbidities and hepatotoxicity in rats.^[158] Plant polyphenols are also used for the prevention of heart diseases.^[159] Garlic-derived allicin shows cardiovascular benefits and antioxidant properties.^[160] It also shows significant anti-atherosclerotic potential and unique vascular protective properties.^[161] Both processing and cooking conditions of *Allium* sp. induced antiplatelet activity and thiosulfinate content.^[162]

Raw garlic and its essential oil show serum fibrinolytic activity and anti-clotting effects that could become a solution of cardiovascular diseases^[163] for patients suffering from coronary artery disease.^[46] The long-term use of garlic causes significant improvement in ischemic heart diseases. Both raw

garlic and fried garlic improve microhemovascular system^[164] and increase fibrinolytic activity in patients if continued therapy is provided [Table 1, Figures 3 and 4].^[165] Garlic shows endothelium mediated vasorelaxant response in isolated rat aorta which tone up heart physiology.^[166] Garlic may act on the nitric oxide system and exert effects on the elastic properties of vasculature.^[166] It restores systemic blood pressure^[167a,b] and shows protective effect in aorta of the elderly patients.^[168] It may be endothelium dependent and independent. Garlic powder put positive effect on cutaneous microcirculation of diseased^[167a] and healthy persons.^[167b] Similarly, dried ethanol-water extract of garlic shows acute effect on the microhemovascular system of the skin^[167a,b] and restores function of conjunctival vessels^[168] [Table 1, Figures 3 and 4].

However, potent activation of nitric oxide synthase by garlic may be highly useful in multiple therapeutic applications.^[169] Both allicin and ajoene, compounds derived from garlic, induce nitric oxide synthase system^[170] that prevents hypertension.^[171] Garlic does pulmonary vasorelaxation due to the presence of allicin.^[172] Similarly, aqueous garlic extract shows beneficial effect on the blood vascular system of streptozotocin diabetic rats.^[173,174] Onions bulbs contain flavonoids which provide relief in heartburn^[175] cardiovascular problems.^[176] Onion (*Allium cepa*) leaves also showed cardioprotective and antioxidant activity in doxorubicin (DOX)-induced cardiotoxicity in rats.^[176,177] Its use can restore and control ambulatory blood pressure and endothelial function in overweight-to-obese patients affected with severe hypertension.^[178] Onion extract and onion soup showed inhibitory activity toward platelet aggregation.^[179-182] This activity is due presence of quercetin, in green onion prohibit bulbs.^[183,184] However, the use of green onion in salads successfully decreases blood pressure in hypertensive subjects.^[178] It extends immense cardiovascular benefits in human subjects. Thiosulfates dimethyl- and diphenyl-thiosulfate slow down thrombocyte biosynthesis.^[181,182] *Cynodon dactylon* significantly decreased the total cholesterol, low-density lipoprotein, and triglyceride levels in blood serum of alloxan-induced diabetic rats^[185] [Figures 3 and 4].

Ginkgo biloba extract (EGb) shows cardioprotective protective effect against myocardial impairment in diabetic rats.^[186] It assists in repairing (EGb) of damages induced by lysophosphatidylcholine in vascular endothelial cells *in vitro*.^[187] Similar cardioprotective potential is also found in few other plant species, that is, *Rauvolfia serpentina*, *Terminalia arjuna*, *Coriandrum sativum*, *Elettaria cardamomum*, *Piper nigrum*, *Allium sativum*, *Crataegus oxyacantha*,^[188] and *Sida rhombifolia* (L.).^[189] In addition, cardioprotective effects are also reported in puerarin isolated from *Pueraria lobata* Ohwi., and Danshensu isolated from the Chinese herb, *Salvia miltiorrhiza*. These bio-organics are used for the treatment of acute ischemic myocardial injury ischemic heart disease.^[190] Addition of dietary fibers decreases serum cholesterol, triglycerides, increasing the high-density lipoprotein cholesterol level, and the management of glycemic

indices and obesity.^[128] Gum guggul is used as a therapeutic agent in the treatment of hyperlipidemia and associated cardiac disorders such as hypertension and ischemia.^[191]

At global level, there is a rapid increase which has been observed in coronary heart disease (CHD) and cardiovascular diseases. This global increase in cases of hyperlipidemia is due to unhealthy eating habits, obesity, and physical inactivity.^[192] In India, 17% of total deaths occurred were due to hyperlipidemia. Few lipid-soluble drugs inhibit the enzymes responsible for the synthesis of cholesterol and cut down its level significantly.^[193] It could be contributed by antihyperlipidemic natural plant products, that is, acetone extract of the fruits of *Capsicum frutescens*.^[194] Ethanolic extract of *C. tamala* leaves is showed hypoglycemic and antihyperglycemic activities.^[195] Administration of *C. tamala* leaves extract in diabetic rats restored the level of blood glucose to near normal levels. In addition, total cholesterol, TG, LDL, and VLDL cholesterol levels in diabetic rats were a significantly increased.^[196] Regular dietary use of *C. tamala* leaves can cure diabetes associated with hyperlipidemia. No doubt leaf extract promotes the insulin release from the undestroyed β -cells.^[197] *Cinnamomum verum* shows positive cardioprotective effects and reduces blood pressure, plasma glucose, obesity, and ameliorating dyslipidemia. *Cinnamomum cassia* extracts are also used to cure gastritis, diabetes, blood circulation disturbance, and inflammatory diseases [Figures 3 and 4].^[198] *C. cassia* contains coumarin, trans-cinnamic acid, cinnamaldehyde, 2-hydroxycinnamaldehyde, 2-methoxycinnamaldehyde (6), 2-hydroxy-cinnamylalcohol, benzoic acid, (+)-syringaresinol, and phenethyl (E)-3-[4-methoxyphenyl]-2-propenoate bio-organic compounds with antihyperlipidemic activity.^[199]

CONCLUSION

There are thousands of plant species which possess antioxidants that could be used for antihyperlipidemic drug formulations. Before use herbal preparations, their safety, potency, toxicity, life-threatening adverse effects, and possible herb-drug interactions must be evaluated, analyzed, and critically discussed. In particular, before use of any herbal drug formulation, there is immense need to determine clinical and therapeutic dose level. Its efficacy and side effects by testing them in 2-fold blind placebo experiments in animal models. For making public health index, conventional risk prediction algorithms must prepare to identify intensive risk factors, microlevel changes in various biomolecules, function of enzymes, and their metabolic pathways. For more appropriate judgment of CVDs, there is a need to check lipid profile, triglyceride to HDLp (high-density lipoproteins) ratio, lipoprotein cholesterol ratio, lipid-lipoprotein ratio, LDL cholesterol level, HDLp and apolipoprotein levels, lipoprotein and LTPs ratio, sphingolipids, omega-3 index, and ST2 level. However, major cardiovascular risks can be identified by measurement of non-HDL cholesterol, total

HDL cholesterol and triglyceride, and HDL cholesterol ratios. There is also an urgent need of new more authentic, appropriate, and reliable diagnostic and therapeutic markers to confirm CVDs, well in time to start the clinical aid to the patients. Well-designed clinical trials are required to test action of herbal drugs on tissues, cells, and organ system of patient to lower down usage specific adverse effects.

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