PLANT PRODUCTS WITH HYPOCHOLESTEROLEMIC POTENTIALS

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I. INTRODUCTION

Cholesterol levels have become the source of health concerns, even though cholesterol is one of the most valuable substances in the human body. Over the past few years, the amount of cholesterol information and dietary advice bombarding the public has grown exponentially. Atherosclerosis is a complex multi-cellular process involving oxidation of cholesterol and the intracellular accumulation of oxidized cholesterol. This accumulation causes a cascade of inflammatory processes, resulting in an unstable atherosclerotic plaque that ultimately bursts, causing myocardial infraction. Botanical dietary supplements (herbs) can ameliorate this process and help to prevent cardiovascular disease at different steps in the process (Herber, 2001). Epidemiological and experimental evidence indicates that elevated plasma cholesterol carries a high risk of atherosclerotic diseases (AD). Risk begins to increase with cholesterol levels above 4 mmol/l, and then increases up to 6–6.5 mmol/l; persons with cholesterol levels persistently above 6–6.5 mmol/l require energetic management to bring down their lipid levels to the optimal range. The advantages of bringing down lipids to satisfactory levels have been confirmed by several experimental, animal and interventional studies indicating lowered morbidity and mortality in AD commensurate with reduction of serum cholesterol and/or improvement in high density lipoprotein (HDL)-cholesterol (Ginsberg, 1990; Havel and Kane, 1995; Tripathi, 1995; Mary *et al.*, 2000). An excessive concentration of lipids in plasma may alter the lipoprotein metabolism and lead to hypercholesterolemia, hypertriglyceridemia or both (Ginsberg, 1990;

Havel and Kane, 1995). Circulating plasma lipoproteins, known as HDL, low density lipoprotein (LDL) and very low density lipoprotein (VLDL) or chylomicrons, can be elevated by environmental causes, such as diet, or by inherited genetic defects in the synthesis or degradation of these compounds. Dyslipidemia or hypercholesterolemia is characterized by a combination of abnormalities in the plasma levels of triglycerides and HDL. Cholesterol, with or without elevated LDL cholesterol levels, affects many persons with premature coronary artery diseases (CAD). However, both qualitative and quantitative abnormalities in circulating triglyceride-rich lipoproteins (TRLPs) may particularly be a key factor in the development of CAD (Miek, 1999; Henry and Ginsberg, 2002). The lipoproteins play an essential role in the transport of endogenous lipids from the liver to the non-hepatic tissues through an endogenous pathway, while peripheral and hepatic chylomicrons transport dietary lipids from the intestine to the peripheral and hepatic tissues through an exogenous pathway (Figure 1).

A. CURRENTLY AVAILABLE THERAPY FOR HYPERLIPIDEMIA

Hypercholesterolemia and hyperlipidemia can be associated with a variety of clinical conditions as well as poor dietary practices. The proper management of hypercholesterolemia and hyperlipidemia is considered appropriate to prevent consequences that might develop including CAD and other conditions associated with extremely high levels of circulating triglycerides (Anonymous, 2000). For the management of hypercholesterolemia and hyperlipidemia, several drug therapies are available which are explained later (Rang *et al.*, 1999):

1. Bile acid sequestrates are anion-exchange resins, which sequester bile acid in the intestine. Cholestyramine and colestipol are the most commonly used in this category, which by this mechanism prevents bile acid re-absorption and causes decreased absorption of exogenous cholesterol and increased metabolism of endogenous cholesterol into bile acid in the liver by preventing enterohepatic recirculation. This leads to an increased expression of LDL receptors in liver and causes increased removal of LDL from blood and reduces the LDL cholesterol in the plasma.
2. Nicotinic acid inhibits hepatic triglyceride production and VLDL secretion, which lowers the plasma level of LDL and increases HDL. Nicotinic acid is mostly used to treat elevated LDL and VLDL by decreasing VLDL synthesis.
3. HMG (β-hydroxy-β-methylglutaryl)-CoA reductase is a rate-limiting enzyme, which catalyzes the conversion of HMG-CoA to mevalonic acid.

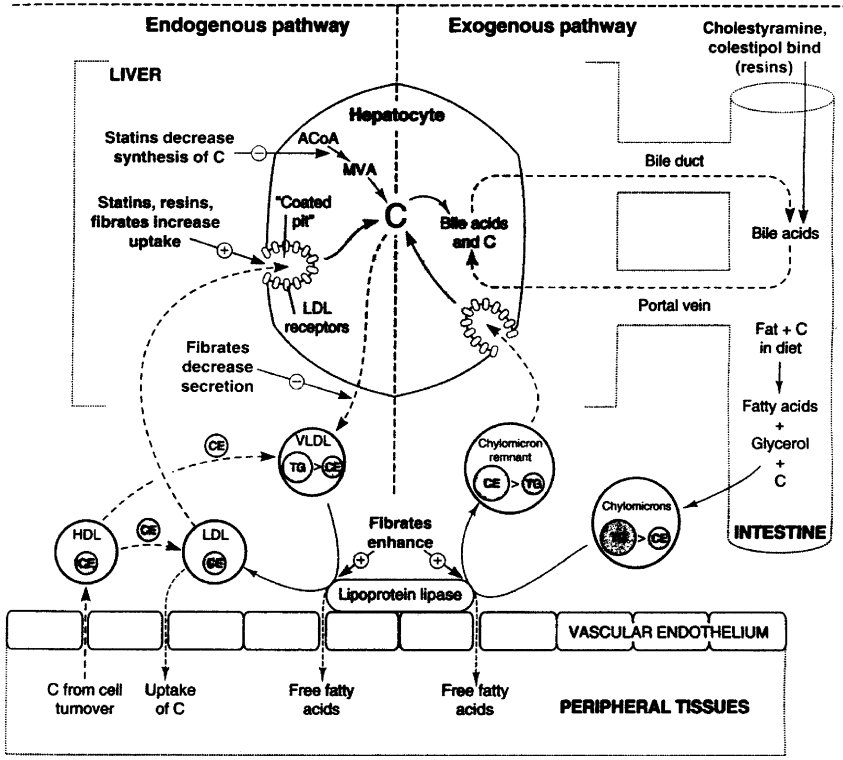

FIG. 1 Schematic diagram of cholesterol transport in the tissues, with sites of action of the main drug affecting lipoprotein metabolism (C = cholesterol; CE = cholesteryl ester; TG = triglycerides; MVA = mevalonate; HMG-CoA reductase = 3-hydroxy-3-methyl-glutaryl-CoA reductase; VLDL = very low density lipoproteins; LDL = low density lipoproteins; HDL = high density lipoproteins). (Reprinted from Rang *et al.* (1999), with permission from Elsevier Science.)

The HMG-CoA reductase inhibitors (Statins like simvastatin, lovastatin, pravastatin, fluvastatin, etc.) inhibit the enzyme and thereby decrease the hepatic cholesterol synthesis and increase the synthesis of LDL receptors causing increased clearance of LDL and a reduced concentration of LDL cholesterol in plasma. HMG-CoA reductase inhibitors are used to treat elevated LDL which also causes a small reduction in plasma triglycerides and an increase in HDL cholesterol.

4. Fibrates like gemfibrozil, clofibrate, ciprofibrate, etc. are fibric acid derivatives which stimulate lipoprotein lipase, an enzyme that breaks down lipids in lipoproteins and causes an increase in the hydrolysis of

triglycerides in chylomicrons and VLDL particles, thus liberating free fatty acids for storage in fat or metabolism in striated muscles. They also reduce hepatic VLDL and increase hepatic LDL uptake. Thus, they decrease VLDL synthesis and are used to treat elevated triglycerides and elevated lipoproteins by stimulating lipoprotein lipase.

5. Probucol lowers the concentration of both LDL and HDL in the plasma. It inhibits the oxidation of cholesterol thereby lowering the development of atherosclerosis.

Besides drugs, dietary factors play a key role in the development of cardiovascular disease. Epidemiological studies have shown that diets rich in fruits, herbs and spices are associated with a low risk of cardiovascular disease. Several dietary and nutritional herbs can be used to facilitate the metabolism of cholesterol. Potential therapeutic foods include garlic, artichoke, wheat germ, alfalfa sprouts, buckwheat, watercress, rice polishings, apple, celery, and cherries. Fresh juices such as carrot and pineapple with honey, liquid chlorophyll, parsley, alfalfa and spinach, beet and celery are also beneficial. Several reports on the use of dietary fibers and other food products have proved the efficacy of natural products of plant origin for the treatment of hypercholesterolemia (Agarwal and Chauhan, 1988; Glore *et al.*, 1994; Anderson, 1995; Navab *et al.*, 1996). Details on the various aspects of the cholesterol-lowering efficacy of the phytoconstituents as well as the individual plant products are explained in the subsequent sections.

II. PHYTOCONSTITUENTS WITH HYPOCHOLESTEROLEMIC POTENTIALS

Compounds with different structures but with the same therapeutic activity isolated from different plant species act as active moieties for the treatment of particular diseases. Some of these compounds have been abandoned due to toxicity but these compounds apparently do not cause serious adverse effects. Some of these active principles originate from edible plants and their inclusion in the diet would undoubtedly be of some value because of their hypocholesterolemic potential. Several phytoconstituents including inulin, pectin, gugglu lipids, flavonoids, ginkoloids, saponins, tannins, and others obtained from various plant sources have proven hypolipidemic potentials as has been further explained in Tables I and II. The chemical structures of a few potential phytoconstituents with hypolipidemic activity are shown in Figure 2. It is hoped that as new additions are made to the list of these active compounds causing only minimum untoward side effects, these naturally

TABLE I

SOME HYPOCHOLESTEROLEMIC, ANTI-ATHEROSCLEROTIC AND ANTI-THROMBOTIC NATURAL PRODUCTS

Constituents	Source	Activity	References
β-Carotene	Carrots, etc.	Hypocholesterolemic	Fuhrman *et al.* (1997)
Lycopene	Tomatoes, etc.	Hypocholesterolemic	Fuhrman *et al.* (1997)
Indole-3-carbinol	Brassica species	Hypocholesterolemic	Peluso and Schneeman (1994)
β-Sitosterol and sitostanol	Many plants	Hypocholesterolemic	Gylling and Miettinen (1996)
Saponin	Fenugreek, *Bupleurum chinense*, *Gyrostemma pentaphyllum*, etc.	Hypocholesterolemic	Miettinen *et al.* (1995)
Soybean protein	Soybean	Hypocholesterolemic	Mokady (1992)
Dietary fiber	Beans, *Hordeum vulgare*, *Juglans nigra*, etc.	Hypocholesterolemic	Story *et al.* (1984)
Mevinolin	*Aspergillus terreus*	Hypocholesterolemic	Booyens *et al.* (1984)
Polysaccharide	Fungi	Hypocholesterolemic	Kiho *et al.* (1996)
Sulfur compounds	Onion and garlic	Anti-atherosclerotic and anti-thrombotic	Wang and Ng (1999)
Flavonoids	Many plants	Anti-thrombotic	Wang and Ng (1999)
HMG-CoA reductase inhibitors	*Monasceus purpuries*; also from fungi and synthetic source	Anti-atherosclerotic and anti-thrombotic	Wang and Ng (1999)
Tocotrienols	Palm oil	Anti-thrombotic	Wang and Ng (1999)
Heparin	*Hipendula ulmaria*	Anti-thrombotic	Wang and Ng (1999)

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TABLE II

PHYTOCONSTITUENTS WITH HYPOLIPIDEMIC ACTIVITY

Name of the phytoconstituents	Family	Name of the plant	References
Inulin	Compositeae	*Chicorium intybus* L.	Roberfrodid (1999)
	Asteraceae	*Arctium lappa* L.	Iwakami *et al.* (1992)
Pectin, citrus flavonoids	Rutaceae	*Citrus lemon* L.	Carper (1988); Potter (1995); Bruneton (1995)
	Moraceae	*Oputia tuna mill Oputi ficus-indica*	Der Marderosian and Beutler (2002)
Gugglu lipids	Burseracaea	*Commiphora mukul*	Der Marderosian and Beutler (2002)
Gums	Fabaceae	*Cyamopsis tetragonolobus* (L). Taub	Robbers *et al.* (1996); Todd *et al.* (1990); Der Marderosian and Beutler (2002)
	Sterculiaceae	*Sterculia urens* Roxb.	Der Marderosian and Beutler (2002)
Flavonoids, polyphenolic compounds, isoflavones	Rosaceae	*Crataegus oxyacantha* L., *C. laevigata (Poir.) DC*, *C. monogyna Jacquin*	He (1990); Chen *et al.* (1995); Rajendran *et al.* (1996)
	Euphorbiaceae	*Emblica officinalis* Gaertin	Thakur and Mandal (1984); Thakur (1985); Mathur *et al.* (1996); Jacob *et al.* (1988)
	Ginkgoaceae	*Ginkgo biloba* L.	DeSmet *et al.* (1997)
	Leguminosae	*Glycine max*	Barnes (1998); Der Marderosian and Beutler (2002)
	Asteraceae	*Arctium lappa* L.	Sun (1992)
	Gramineae	*Avena sativa* L.	Anderson *et al.* (1984); Der Marderosian and Beutler (2002)
	Combretaceae	*Terminalia arjuna*, *T. bellirica*, *T. chebula*	Chevallier (1996); Thakur *et al.* (1988)
	Vitaceae	*Vitis vinifera V. labrusca V. rotundifera*	Der Marderosian and Beutler (2002)
	Zingiberaceae	*Zingiber officinale* Roscoe	Kiuchi *et al.* (1992)
Guar gum	Compositae	*Silybum marianum* L.	Der Marderosian and Beutler (2002)

(*continued on next page*)

TABLE II (*continued*)
PHYTOCONSTITUENTS WITH HYPOLIPIDEMIC ACTIVITY

Name of the phytoconstituents	Family	Name of the plant	References
	Rutaceae	*Citrus lemon* L.	Carper, 1988; Potter (1995); Bruneton (1995)
Alkaloid—Rhynchophylline	Rubiaceae	*Uncaria tomentosa* DC	Jones (1994); Hemingway and Phillipson (1974))
Fibers	Polyporaceae	*Grifola frondosa*	Kabir *et al.* (1987); Kubo and Nanba (1996); Kubo and Nanba (1997)
	Juglandaceae	*Juglans nigra*	Zambon *et al.* (2000); Potter (1995)
	Germineae	*Hordeum vulgare* L.	Lupton *et al.* (1994)
Saponins	Umbelliferae	*Bupleurum chinense* DC	Bone (1996); Der Marderosian and Beutler (2002)
	Cucurbitaceae	*Gynostemma pentaphyllum* (Thunb.) Makino	Der Marderosian and Beutler (2002)
	Leguminosea	*Medicago sativa* L.	Malinow *et al.* (1977,1978,1981); Cohen *et al.* (1990)
	Liliaceae	*Ruscus aculeatus* L.	Capelli and Nicora (1988)
	Araliaceae	*Panax quinquefolius* L. *Panax ginseng* C.A. mayer	Chen (1996)
Sterols	Combretaceae	*Terminalia arjuna, T. bellirica, T. chebula*	Chevallier (1996); Thakur *et al.* (1988)
	Leguminosea	*Medicago sativa* L.	Cohen *et al.* (1990)
Fixed oil and volatile oil	Euphorbiaceae	*Emblica officinalis*	Mathur *et al.* (1996); Jacob *et al.* (1988)
Essential fatty acids	Lamiaceae	*Perilla frutescens* (L) Britt.	Der Marderosian and Beutler (2002)
	Portulacaceae	*Portulaca oleracea* L	Reid (1986)
	Linaceae	*Linum usitatissimum* L.	Robinson (1991)
	Onagraceae	*Oenothera biennis* L.	Horrobin and Manku (1983); Puolakka and Makarainen (1985)
	Oleaceae	*Olea europaea*	Carper (1988); Aviram (1996)

TABLE II (*continued*)
PHYTOCONSTITUENTS WITH HYPOLIPIDEMIC ACTIVITY

Name of the phytoconstituents	Family	Name of the plant	References
Lycophene	Solanaceae	Ripe fruit of tomatoes	Der Marderosian and Beutler (2002)
Sulfur-containing principles	Liliacea	*Allium cepa*	Augusti and Mathew (1974); Lata *et al.* (1991); Der Marderosian and Beutler (2002)
Konjac mannan (Glucomannan)	Araceae	*Amorphophallus konjac* Koch	Der Marderosian and Beutler (2002)
Mono and oligosaccharides	Gramineae	*Avena sativa* L.	Anderson *et al.* (1984); Der Marderosian and Beutler (2002)
Triterpenes	Umbelliferae	*Bupleurum chinense* DC	Bone (1996); Der Marderosian and Beutler (2002)
Psyllium mucilloid (Metamucil)	Plantaginaceae	*Plantago lanceolata* L.	Greaves *et al.* (2000)
Stevia's glycosides (Rebaudioside A) Steviobioside	Asteraceae	*Stevia rebaudiana* Bertoni	Der Marderosian and Beutler (2002)

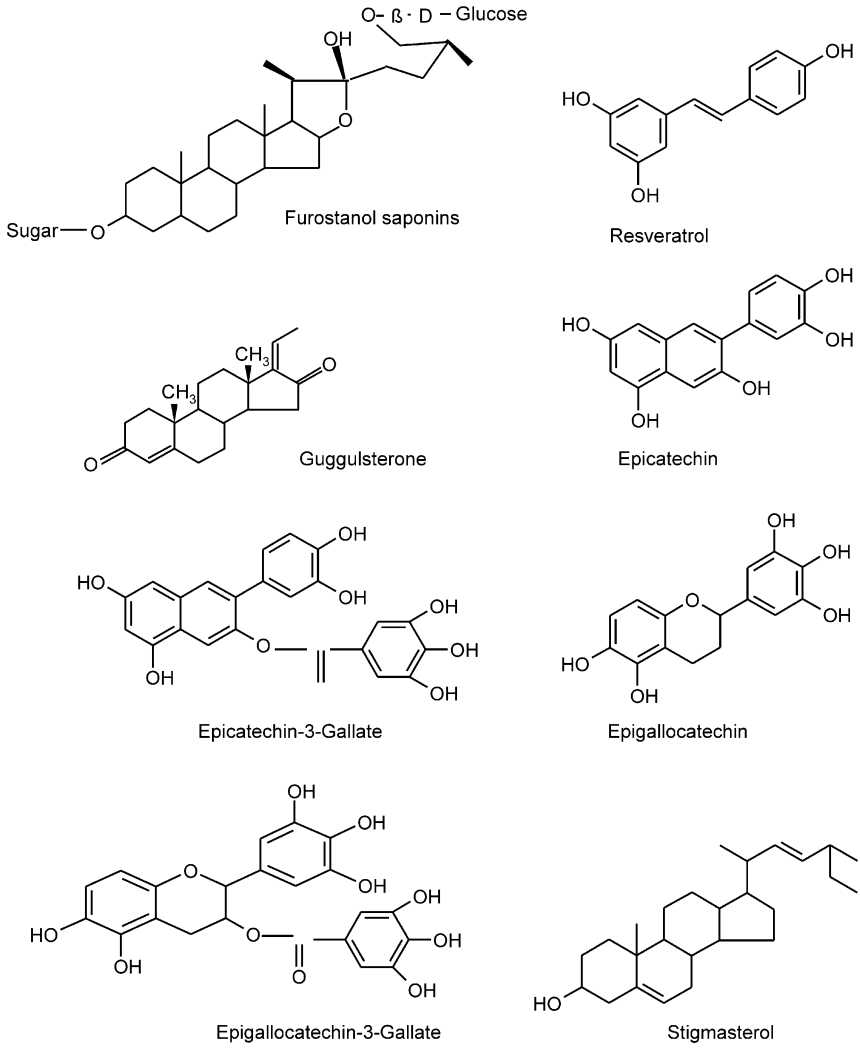
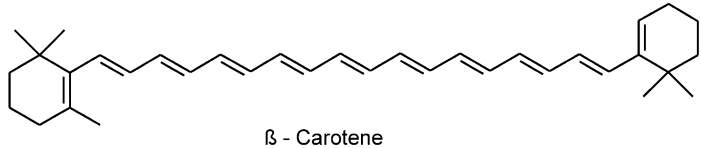
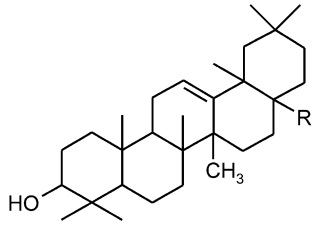


FIG. 2 Some hypocholesterolemic phytoconstituents.

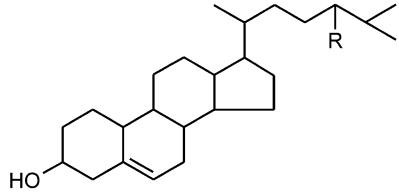
occurring components will definitely help in the development of therapeutically potent hypocholesterolemic drugs in the future and will also expedite the discovery of such drugs. Alternatively, several of these plants may be useful as nutraceutical ingredients. Several groups of plant constituents possessing significant therapeutic potentials as hypocholesterolemic agents are delineated in the following section.



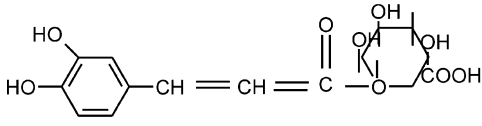
ß - Carotene



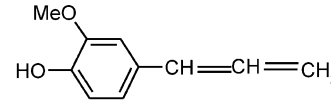
ß - Amyrin
Oleanolic acid (R = COOH)



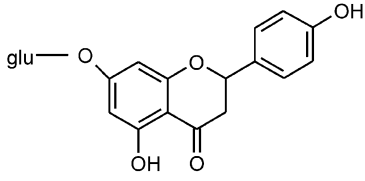
Sitosterol (R = Et), Campesterol (R = Me)



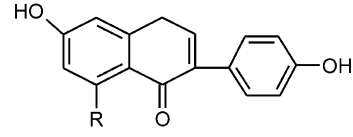
Chlorogenic acid



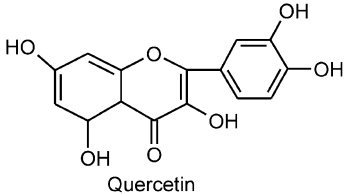
Eugenol



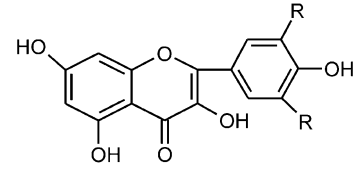
Naringin



Daidzein (R = H)
Genistein (R = OH)



Quercetin



Kaempferol (R = H)
Myricetin (R = OH)

FIG. 2 (*continued*)

A. FIBERS

Hordeum vulgare, *Juglans vigra*, *Amorphophallus konjac*, and *Grifolia frondosa* are rich in dietary fibers. Dietary fiber, especially soluble, viscous fibers effectively decrease serum cholesterol and LDL cholesterol concentrations (Anderson, 1995). Most soluble or viscous fibers have hypocholesterolemic effects (Glore *et al.*, 1994; Anderson, 1995). In general, these soluble fibers, such as psyllium, oat bran, guar and pectin, decrease serum cholesterol and LDL cholesterol concentrations without affecting serum triglycerides. LDL has a central role in the pathogenesis of atherosclerosis (Navab *et al.*, 1996). Oxidation of LDL in the sub-endothelial space of arteries sets the stage for macrophage uptake of LDL, foam cell development, and ultimately, fatty streak and atheroma formation (Navab *et al.*, 1996). Decreasing the LDL cholesterol concentrations is one of the most effective means of decreasing the risk for coronary heart disease (CHD). Often, consumption of these soluble fibers is accompanied by distinct reductions in serum HDL cholesterol concentrations (Glore *et al.*, 1994; Anderson, 1995). The cholesterol-lowering effects of soluble or viscous fibers relate to their gel-forming properties (Navab *et al.*, 1996). Soluble fibers such as psyllium and oat bran appear to exert their principal effects on cholesterol metabolism through decreases in bile acid absorption. These soluble fibers bind bile acids in the small intestine, alter micelle formation and decrease their absorption in the small intestine. Consequently, more bile acids are excreted with the feces. Acting somewhat like bile acid binding resins, these soluble fibers deplete the bile salt pool and divert cholesterol synthesis from lipoprotein precursors to bile acid synthesis (Glore *et al.*, 1994; Navab *et al.*, 1996). Fiber comes in many forms, including oats (*Avena sativa*), guar gum, and pectin. Recently, the U.S. Food & Drug Administration (FDA) made history by ruling in the first federally sanctioned health claim for manufactured foods that oat-rich cereals and other foods are permitted to advertise their products as "cholesterol lowering." Beta glucan, a viscous gel in the soluble fiber of oats, surrounds cholesterol-rich bile acids and limits their re-absorption by blood, shuttling them off into fecal excretion. Less bile is consequently returned to the liver which causes the liver to secrete more bile acids, the production of which uses up more cholesterol from the blood.

Guar gum, similar to pectin, is well documented regarding its ability to lower cholesterol levels. However, its principal drawback is its extreme viscosity, making foods containing guar gum very unpalatable. Non-viscous forms have been created via partial enzymatic hydrolysis of the gum's polysaccharide component, but there is some controversy regarding whether these processing techniques actually inhibit the guar gum's lipid-lowering

effects by reducing its digestibility rather than inhibiting bile acid re-absorption.

Chitosan is a form of fiber that absorbs dietary fat in the gut and can also inhibit LDL cholesterol while boosting desirable HDL cholesterol levels. The mechanism behind its action may be explained by chitosan's ability to bind both bile acids and phospholipids, reducing their absorption from the intestines and increasing fecal excretion of cholesterol. Chitosan has been shown to significantly lower plasma cholesterol and reduce the development of atherosclerotic plaques. Other fiber sources from food including kherjri beans (*Prosopsis cinceria*), prepalbanti (*Ficus religiosa*), barbum (*Ficus glomerata*) and teent (*Capparis decidua*) comprise cellulose, lignin, hemicelluloses, teent and pectin. These fiber sources affected the total lipid, cholesterol, triglycerides and phospholipids of the liver. Teent exerted the most conspicuous hypocholesterolemic effect probably by increasing the fecal excretion of cholesterol and bile salts (Agarwal and Chauhan, 1988).

B. PLANT STEROLS

The plant kingdom contains a number of sterols that differ from cholesterol by having ethyl or methyl groups or unsaturation in the side-chain. The predominant ones are sitosterol, stigmasterol, and campesterol. The most prominent is β-sitosterol, which differs from cholesterol in that it has an ethyl group at C-24 of the side-chain. Phytosterols belonging to the family of 4-desmesmethylsterols include β-sitosterol, campesterol and stigmasterol that are found mostly in plant oils such as soybean, canola, and sunflower. Phytosterols are natural components of plants and they play an important role in the cell membrane, analogous to that of cholesterol in animals. The 4-desmesmethysterols noted are the major phytosterols and comprise roughly 50% of the sterols in the western diet, with the remainder being cholesterol (Subbiah, 1971). β-Sitosterol is a natural extract from soybeans; sitostanol is a hydrogenated phytosterol found in extract from pine wood pulp.

The esterification of either of the sterols enhances its solubility in a hydrophilic environment. This modification makes the phytosterol a more active ingredient when used to fortify edible products that lower serum cholesterol. The cholesterol-lowering action of β-sitosterol was first reported more than 40 years ago (Farquhar *et al.*, 1956). The differences between the plant sterols and the cholesterol include the addition of an ethyl group to the aliphatic side-chain of both sterols. Saturation of the double bond in the second ring of β-sitosterol yields sitostanol. The presence of the ethyl group on the side-chain increases the hydrophobicity of both phytosterols such that it is greater than the hydrophobicity of the base molecule, cholesterol. This increase in hydrophobicity is expected to decrease the absorption of

these phytosterols into the body (Heinemann *et al.*, 1991, 1993). The low solubility of both native β-sitosterol and sitostanol in aqueous solutions leads to the use of the fatty acid esterified forms of these compounds, thus enabling their incorporation into food products. The esterification of the phytosterols is an important advance because it allowed more consistent and enhanced delivery of the sterols to the small intestine, the major site of cholesterol absorption (Mattson *et al.*, 1982). Delivery to the site of cholesterol absorption also enhanced its activity to inhibit absorption of the sterol.

It was found that the addition of sitosterol to the diet of cholesterol-fed chickens or rabbits lowered cholesterol levels in both species and inhibited atherogenesis in the latter (Ling and Jones, 1995). Sitosterol or mixtures of soy sterols were studied extensively as cholesterol-lowering agents (Compassi *et al.*, 1997). The mode of action appears to involve inhibition of cholesterol absorption, although the plant sterols themselves are absorbed very poorly (Tilvis and Miettinen, 1986). The mechanism of inhibition of cholesterol absorption is believed to be through crystallization and co-precipitation. Ingestion of 1 g of sitosterol reduced the absorption of cholesterol by 42% in a meal containing 500 mg of cholesterol (Mattson *et al.*, 1982). The decrease in plasma cholesterol is probably due to an increase in LDL receptor activity. However, the decline in plasma cholesterol is relatively lesser than the decrease in absorption, presumably because of a compensatory increase in cholesterol synthesis. Sitostanol, a saturated sitosterol derivative, reduced the intestinal absorption of cholesterol and serum cholesterol more effectively than sitosterol at doses below those of sitosterol (Heinemann *et al.*, 1986). In a recent study, sitostanol was interesterified with margarine, and the resultant product (1.9–2.6 g sitosterol per day) exhibited a hypocholesterolemic effect in a population with mild hypercholesterolemia (Miettinen *et al.*, 1995). The sitostanol was not absorbed and did not appear to interfere with the absorption of fat-soluble vitamins.

The use of plant sterols—β-sitosterol and sitostanol in consumer products to decrease cholesterol is supported by numerous clinical studies that document their efficacy in lowering mild hyperlipidemia (Jones *et al.*, 1998; Hallikainen and Uusitupa, 1999). Although the normal diet contains plant sterols that range from 160 to 360 mg/day, a 5- to 10-fold increase is required to exert a cholesterol-lowering effect. Consumer products with increased amounts of phytosterols that exceed the content found in the diet have been made available to the consumer. In evaluating the efficacy of including sitostanol ester in margarine as a dietary supplement for children with familial hypercholesterolemia (FH), it was found that serum total cholesterol (TC), intermediate density lipoprotein-cholesterol and LDL-cholesterol levels fell while the HDL-cholesterol/LDL-cholesterol ratio was elevated.

The proportions of delta 8-cholesterol and desmosterol in the serum rose while those of cholestanol, campesterol and sitosterol dropped, implying a decreased absorption of cholesterol and a compensatory increase in its synthesis. High basal precursor sterol proportions were predictive of a large decrement in titer of LDL cholesterol. It appeared that partial substitution of normal dietary lipid consumption with sitostanol was a safe and effective therapeutic measure for children with FH (Lees *et al.*, 1977; Wang and Ng, 1999). The effect of a small amount of sitosterol, sitostanol and sitostanol esters dissolved in rapeseed oil on serum lipids and cholesterol metabolism in patients with primary hypercholesterolemia and various apolipoprotein E phenotypes on a rapeseed oil diet showed a diminution in TC and LDL-cholesterol levels in the serum (Gylling and Miettinen, 1994).

Squalene, a sterol precursor also found in plant products, was originally suggested to have a cholesterol-lowering effect, but earlier studies in animals showed that it had no positive influence on atherosclerosis (Ling and Jones, 1995). Sitosterols and squalene are present in both monounsaturated and polyunsaturated vegetable oils and thus may be responsible for some of the variable cholesterol-lowering effects observed in studies using these products. Other cholesterol-lowering alcohols in rice bran oils include esters of triterpene alcohols that inhibit hepatic cholesterol esterase and tocotrienols that inhibit HMG Co-A reductase (Rukmini and Raghuram, 1991); however, there is conflicting evidence as to whether rice bran oil decreases plasma cholesterol levels in humans (Lichtenstein *et al.*, 1994).

Gugulipid, the oleoresin form of *Commiphora mukul*, is a mixture of diterpenes, sterols, steroids, esters and higher alcohols. The active ingredients responsible for the well known hypolipidemic effects of the plant are the guggulsterones, specifically guggulsterone E and guggulsterone Z. Fenusterols, commonly known as furostanol saponins from fenugreek seeds, are found to possess hypolipidemic activity. The principal furostanol saponin in fenugreek is diosgenin. Diosgenin has been proven to have various effects on cholesterol metabolism, specifically in lowering LDL plasma cholesterol levels. Other furostanols in fenugreek include gitogenin, tigogenin, smilagenin, sarsasaponin, etc. In light of the effect which furostanol saponins exert on appetite stimulation and hormone release, fenugreek seeds are traditionally used in appetite stimulation where the resulting increase in food intake ultimately triggers anabolism. Animal model studies have revealed that the furostanol saponin fraction is responsible for the anabolic effects of fenugreek seeds. In addition, the furostanol classes of plant steroids have pronounced immunostimulating and luteinizing hormone (LH) releasing properties. LH in turn signals the pituitary gland to produce more testosterone and high-testosterone levels have been correlated with improved athletic performance. The mechanism of hormone

releasing action of furostanols is linked to the conversion of cholesterol into active hormones, resulting in the simultaneous reduction of plasma cholesterol levels.

C. β-CAROTENE AND LYCOPENE

Dietary carotenoids are a family of about 600 fat-soluble plant pigments that serve as natural colors. The carotenoids, which have been studied most in this regard, are β-carotene, lycopene, lutein and zeaxanthanin; the former two belong to the carotene class, whereas the latter two belong to the xanthophylls. Xanthophylls are more polar than the carotenes as they contain one hydroxyl group (Johnson, 2002). β-Carotene is the most widely studied carotenoid and is one of the major carotenoids in our diet. It has been reported that dietary supplementation with lycopene or carotenoids like β-carotene cause a decline in plasma LDL cholesterol levels (Fuhrman *et al.*, 1997). Cholesterol synthesis from [3H]-acetate but not that from [14C] mevalonate in the macrophage cell line J-774A.1 has been reported to be suppressed by β-carotene or lycopene (10 μM) and the HMG-CoA reductase inhibitor, fluvastatin (10 μg/ml). The activity of the macrophage LDL receptor is enhanced by these three compounds. Thus, the hypocholesterolemic effect of β-carotene and lycopene is probably associated with the inhibition of HMG CoA reductase activity (Peluso and Schneeman, 1994).

D. FLAVONOIDS

Flavonoids might represent another beneficial group of naturally occurring hypolipidemic compounds. Flavonoids are widely distributed in the vegetable plant kingdom and exhibit distinctive pharmacological properties. Chemically flavonoids are the derivatives of 2-phenyl-1-benzopyran-4-one with varied chemical structures that are present in fruits, vegetables, nuts, and seeds (Kuhnau, 1976; Cook and Samman, 1996). The flavonoids can be widely classified into different categories like flavonols, flavones, catechins, flavanones and appear to have intensive biological properties that promote human health and help to reduce the risk of disease. Flavonoids act as antioxidants, protect LDL cholesterol from oxidation, inhibit platelet aggregation, and act as anti-inflammatory and anti-tumor agents (Smith and Yang, 1994; Cook and Samman, 1996; Manach *et al.*, 1996). Oxidative modification of LDL cholesterol is thought to play a key role during atherosclerosis. Plants such as *Camellia chinensis*, citrus fruits, *Ginkgo biloba*, soya beans, etc. contain large amounts of these polyphenolic compounds and exhibit various biological properties. These polyphenolic

compounds can inhibit oxidation of LDL cholesterol. Cells of the arterial wall including macrophages, smooth muscle cells, and endothelial cells can oxidize or otherwise modify LDL (Heinecke, 1997; Russell, 1999). Modified LDL can be a ligand for receptor-mediated processes leading to significant accumulation of cholesteryl esters (CE) in macrophages and smooth muscle cells (Heinecke, 1997; Russell, 1999). These CE-rich cells, known as foam cells, are the hallmark of the early atherosclerotic lesion. Flavonoids are usually present within the subendothelial space of the arterial wall in concentrations sufficient to protect lipoproteins such as LDL from oxidation. There is some evidence to suggest that flavonoids can be incorporated into lipoproteins within the liver or intestine and subsequently be transported within the lipoprotein particle (Fuhrman *et al.*, 1995; Kerry and Abbey, 1998). Flavonoids have been shown to inhibit the oxidation of LDL *in vitro* and, furthermore, the addition of the flavonoids, quercetin and catechin, to the diet have been shown to reduce LDL oxidation *ex vivo* in rats and was found to decrease the atherosclerotic lesion area in apoE-deficient mice (de Whalley *et al.*, 1990; Hayek *et al.*, 1997; da Silva *et al.*, 1998; Fremont *et al.*, 1998; Borradaile *et al.*, 1999). The mechanisms whereby flavonoids inhibit LDL oxidation are unclear. They may protect α-tocopherol in LDL from oxidation, possibly by being preferentially getting oxidized themselves, or they may reduce the formation or release of free radicals. Flavonoids can react with superoxide anions (Kuhnau, 1976), hydroxyl radicals (Husain *et al.*, 1987) and lipid peroxy radicals (Torel *et al.*, 1986). These compounds may also act by chelating iron, which is thought to catalyze processes leading to the formation of free radicals (Afanas'ev *et al.*, 1989; Morel *et al.*, 1993). A number of reports have suggested that these compounds may also influence atherogenesis through an effect on lipid and lipoprotein metabolism (Sharma, 1979; Basarkar and Nath, 1983; Choi *et al.*, 1991a,b; Jahromi *et al.*, 1993; Anthony *et al.*, 1997a; Yotsumoto *et al.*, 1997; Wilcox *et al.*, 1998; Borradaile *et al.*, 1999). In addition to direct oxidant scavenging, flavonoids may inhibit the enzymes involved in generating pro-oxidant molecules. For example, flavonoids have been shown to inhibit the generation or release of free radicals derived from lipoxygenase (LOX) (Huang *et al.*, 1997). It has been suggested that LOX is involved in the early events of atherosclerosis by inducing plasma LDL oxidation in the subendothelial space of the arterial wall (Huang *et al.*, 1997). While the majority of research focused on the anti-oxidant roles of flavonoids, studies in rats have shown that the flavonoids such as quercetin (Fuhrman *et al.*, 1995), hesperidin (Collins *et al.*, 1997), marsupin (Jahromi *et al.*, 1993), pterosupin (Jahromi *et al.*, 1993), liquiritigenin (Jahromi *et al.*, 1993), biochanin A (Anthony *et al.*, 1997), formononetin (Anthony *et al.*, 1997), and pratensein

(Anthony *et al.*, 1997) cause significant reductions in serum TC and triglyceride (TG). In non-human primates, dietary genistein, the isoflavone significantly reduces plasma LDL and VLDL cholesterol levels (Anthony *et al.*, 1997).

1. *Citrus flavonoids*

Naringin (naringenin-7-rhamnoglucoside), the bitter principle of grapefruit (*Citrus paradisi*) is found in the juice, flower, and rind of the fruit. Naringin and other naringenin glycosides can be found in a variety of other sources including propolis (Nagy *et al.*, 1985) and *Prunus davidiana* (Husain *et al.*, 1987). *Monotes engleri* contains a prenylated form of naringenin (6-(1,1-dimethylallyl)naringenin) (Seo *et al.*, 1997). The chemical name of naringenin is 2,3-dihydro-5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one. Naringenin is derived from the hydrolysis of the glycone forms of this flavanone, such as naringin or narirutin (Prasad, 1999). Another predominant flavonoid present in citrus fruit is hesperidin. Naringin exhibits anti-atherogenic property by inhibiting lipid peroxidation at 465–565 mM (Laughton *et al.*, 1991; Saija *et al.*, 1995), auto-oxidation of rat cerebral membranes at 322 mM (Saija *et al.*, 1995), LOXs and cyclooxygenases at $>$200 mM (Corvazier and Maclouf, 1985; Laughton *et al.*, 1991) and myeloperoxidase at 150 mM (Divi and Doerge, 1996). It also inhibits thromboxane B2 production at 175–200 mM (Corvazier and Maclouf, 1985) and platelet aggregation at 90–500 mM (Landolfi *et al.*, 1984; Corvazier and Maclouf, 1985). It has a significant effect on lipid metabolism by reducing apo-B secretion from hepatocytes at 50–100 mM (Wilcox *et al.*, 1998; Borradaile *et al.*, 1999) and inhibits acyl-CoA: cholesterol acyltransferase at 50–100 mM (Wilcox *et al.*, 1998).

E. TEA POLYPHENOLICS

Tea is a rich source of polyphenolics; green tea leaves consist specifically of catechins and black tea leaves contain theaflavins (catechin dimers). When rats were fed green tea polyphenols, blood cholesterol concentrations declined in hypercholesterolemic animals (Dreosti, 1996). These effects may be explained by the capacity of green tea catechins and gallate esters to reduce intestinal cholesterol absorption, lower blood coagulability, and inhibit proliferation of human aortic smooth muscle cells. It has been reported that LDL-cholesterol oxidation is inhibited by exposure to tea flavonoids, specifically the catechins from green tea leaves or theaflavins from black tea leaves (Dreosti, 1996). Catechin, epigallocatechin gallate provided the maximum protection and was more protective than vitamin E, whereas

the theaflavins exerted even stronger inhibitory effects than the catechins. In human epidemiological studies, green tea consumption was inversely associated with serum levels of TC and LDL-cholesterol, but had no significant correlation with levels of HDL-cholesterol or triglycerides (Kono *et al.*, 1996). Catechins are considered to lower cholesterol by a mechanism that suppresses cholesterol absorption in the intestine (Fukuyo *et al.*, 1986; Chisaka *et al.*, 1988; Ikeda *et al.*, 1992; Ishikawa *et al.*, 1997; Matsumoto *et al.*, 1998; Valsa *et al.*, 1998). In studies of animals fed high-fat or high-cholesterol diets, tea catechins reduced serum cholesterol and/or lipid levels in rats (Muramatsu *et al.*, 1986; Valsa *et al.*, 1995) mice (Matsuda *et al.*, 1986), and hamsters (Chan *et al.*, 1999), and increased fecal excretion of neutral steroids and bile acids in hamsters (Chan *et al.*, 1999). In rats fed a normal diet, a dose of 10 mg/kg of catechin produced the maximum reduction in plasma cholesterol and the maximum increase in excretion of fecal neutral steroids and bile acids (Valsa *et al.*, 1995). Thus tea polyphenols play an effective role in lowering elevated cholesterol levels.

F. SAPONIN

Among their diverse biological activities, saponins possess effective hypocholesterolemic action (Price *et al.*, 1992). Saponin–cholesterol interaction is an important part of the hypocholesterolemic action of alfalfa but interactions of bile acids with other components of alfalfa might be equally important. Alfalfa plant and sprout saponin have been found to be effective in binding significant amounts of cholesterol (Wang and Ng, 1999).

G. SOYBEAN PROTEIN

The cholesterol-lowering effects of soy protein have been recognized for more than 90 years (Anderson *et al.*, 1995a,b). It has been reported that soybean protein induced a reduction in serum apo A-1 with the relative concentration of HDL-cholesterol remaining at a higher level (Forsythe *et al.*, 1980). It has been observed that plant protein (50% from soybean meal and 25% each from corn and wheat) lowered plasma cholesterol levels in young male pigs compared with animal proteins (90% from casein and 10% from lactalbumin) (Forsythe *et al.*, 1980). Carroll *et al.* (1978) observed that plasma cholesterol levels were lower when soybean protein was included in the diet of young, healthy normo-lipidemic women. Studies over the past 20 years have shown that the daily consumption of 30–60 g of soy protein contributes to a decrease in total and LDL cholesterol level between 10 and 20% in individuals with elevated serum cholesterol (Caroll, 1991). An intake of 30–60 g of isolated soy protein in muffins, breads,

cookies and other commonly eaten bakery items effectively lowers raised cholesterol (Potter *et al.*, 1993). Mokady (1992) reported that rats fed a diet containing 10% protein derived from soy protein, wheat gluten, or wheat gluten supplemented with lysine and threonine possessed lower serum cholesterol and triglyceride levels with no LDL and a higher level of HDL.

H. PLANT INDOLES

Indole 3-carbinol induced a lowering of serum cholesterol levels and the serum LDL-cholesterol/VLDL cholesterol ratio (Mokady, 1992).

I. UNSATURATED FATTY ACIDS

Booyens *et al.* (1984) reported that unnatural dietary *trans* and *cis* unsaturated fatty acid isomers are a definite risk factor in the etiology of coronary disease, despite an early report about the hypocholesterolemic activity of unsaturated fatty acids from plant origin.

J. RESVERATROL

Resveratrol (*trans*-3,4′,5-trihydroxystilbene) is a phytopolyphenol isolated from the seeds and skins of grapes. In plants, resveratrol functions as a phytoalexin that protects against fungal infection (Hain *et al.*, 1990). Because of its high concentration in grape skin, significant amounts of resveratrol are present in wine. Recent studies indicate that resveratrol can block the process of multi-step carcinogenesis, namely, tumor initiation, promotion and progression. Resveratrol can also reduce the risk of cardiovascular disease in man. The molecular mechanisms of resveratrol in chemoprevention of cancer and cardiovascular disease are interesting and are under intensive investigation. *In vivo*, *ex vivo* and many animal experiments have shown that resveratrol possesses many biological attributes that favor protection against atherosclerosis, including anti-oxidant activity, modulation of hepatic apo-lipoprotein and lipid synthesis, inhibition of platelet aggregation (Soleas *et al.*, 1997). It has been suggested that it plays a role in the prevention of heart disease, as it inhibits platelet aggregation, alters eicosanoid synthesis and modulates lipid and lipoprotein metabolism (Soleas *et al.*, 1997). Platelets have a critical role in initiating the chemical signals that set in motion complex cellular events, resulting in atherosclerosis. Platelets adhere to the endothelial surface of arteries and trigger luminal occlusion leading to acute CHD (Renaud *et al.*, 1992). Gehm *et al.* (1997) reported a new facet of resveratrol, where, on the basis

of its structural similarity with the synthetic estrogen–diethylstilbosterol, they hypothesized that it might be a phytoestrogen (Gehm *et al.*, 1997).

K. PROPIONATE

A metabolic product of fiber fermentation, propionate may mediate some of the hypocholesterolemic effects of certain soluble plant fibers. In cholesterol-fed rats, propionate decreases serum cholesterol and liver triglyceride level where no changes in hepatic histology in response to propionate intake have been detected (Wang and Ng, 1999).

L. MEVINOLIN

Mevinolin produced by the fungus *Aspergillus tereus*, competitively inhibits HMG-Co-A reductase, a key enzyme in the cholesterol biosynthetic pathway, and thereby lowers cholesterol level (Wang and Ng, 1999).

M. FUNGAL POLYSACCHARIDES

Polysaccharides CS-F30, from cultural mycelia of *Cordyceps sinensis* decreased plasma cholesterol in mice (Jones *et al.*, 1998). The glucuronoxylomannan from *Tremella fuciformis* fruiting bodies brought about reduction in the plasma cholesterol level in mice (Wang and Ng, 1999).

N. ALGAL EXTRACT

An extract of Spirulina, unicellular filamentous blue-green algae for human consumption has been reported to have potential hypocholesterolemic activity (Chamorro *et al.*, 1996).

O. RICE BRAN OIL

Rice bran oil is made from the pericarp and germ of the *Orzya sativa* seed. It constitutes 10% of the rough rice grain and 18–22% oil. Pharmacological properties of rice bran oil and its active component, oryzanol, have been established for varied therapeutic potential including hypolipidemic, neuroendocrinological, gastroenterological and dermatological effects (Suzuki and Oshima, 1970). Rice bran oil and its varied components have a demonstrated ability to improve the plasma lipid pattern of rodents, rabbits, non-human primates and humans reducing total plasma cholesterol and triglyceride concentrations, and increasing the HDL cholesterol level (Cicero and Gaddi, 2001).

P. SULFUR-CONTAINING COMPOUNDS

Allium cepa and *Allium sativum* are rich in naturally occurring sulfur-containing compounds which influence plasma cholesterol and atherosclerosis. Garlic oil was in the pharmacopeia of the Babylonians and other ancient people (Kritchevsky, 1991). Garlic contains a number of compounds, but the most active are diallyl disulfide (DADS) and its mono *S*-oxide (allicin). Allicin was identified initially as the active compound responsible for anti-atherosclerotic effect. It has also been observed that water-soluble organosulfur compounds, especially *S*-allyl cysteine (SAC), present in aged garlic extract (AGE) and DADS, present in garlic oil are also potent inhibitors of cholesterol synthesis. Garlic oil or garlic has been shown to be hypolipidemic in humans, with a recent meta-analysis suggesting that one-half clove of garlic per day lowered serum cholesterol by approximately 9%. The same amount of garlic was shown to reduce cholesterol levels and severity of atherosclerosis in cholesterol-fed rabbits. The mechanism of hypocholesterolemia may be the inhibition of cholesterol synthesis (Yu-Yan and Liu, 2001). Abramovitz *et al.* (1999) investigated the effect of allicin as an active component of garlic on the formation of fatty streaks in the aorta and lipid profile in mice. While no significant differences were observed between the blood lipid profiles, the microscopic evaluation of the formation of fatty streaks in the aortic sinus showed that values for mice in the allicin treated groups were significantly lower by nearly 50% (Abramovitz *et al.*, 1999).

III. HERBS USEFUL IN HYPERCHOLESTEROLEMIA

Herbs are generally considered as a safe way to strengthen and tone the human body system. Herbs may be used as dried extracts or tinctures (alcohol extracts) or in any other dosage form, singly or in combination, as noted (Mukherjee, 2001). Currently available hypolipidemic drugs like gemfibrozil, bezafibrate, lovastatin, and nicotinic acid are not totally safe particularly when used for prolonged periods. Viewed in this context, the hypolipidemic potentials of medicinal plants need critical study. Several plant species have been reported to possess anti-hypercholesterolemic action. For example, garlic (*A. sativum*) has the effect of reducing cholesterol. It is most effective when included in the diet in the raw form, or taken in capsules. Herbs that support the claim to be used for their hypocholesterolemic effects include *Cicer arietinium*, *Commiphora mukul*, *Curcuma longa*, *Emblica officinalis*, *Inula racemosa*, *Terminalia* species of plants like *Terminalia arjuna*, *Terminalia chebula*, *Trigonella foenum graecum*, milk thistle (*Silybum marianum*), dandelion root (*Taraxacum officinale*), burdock root

(*Arctium lappa*), blue flag (*Iris versicolor*), greater celandine (*Chelidonium majus*), blue vervain (*Verbena bastata*), and hawthorn berries (*Crataegus oxyanthoides*). These herbs help to lower high blood pressure, promote cholesterol metabolism and suppress cholesterol synthesis as well as strengthening connective tissue and cardiac muscle. Ginger (*Zingier offiicinalis*), Alfalfa (*Medicago sativa*) and several other herbs have been shown to lower cholesterol levels (Sharma, 1997; Wang and Ng, 1999; Mukherjee, 2002). The hypolipidemic potentials of the various plant species has been further explained in Table III. Details on several plants including their general habits, pharmacognositical, pharmacological and clinical properties with hypolipidemic potential are discussed in the next section.

A. *PHYLLANTHUS NIRURI*

Phyllanthus niruri (Family—Euphorbiaceae) is a small herb distributed throughout the tropical and subtropical regions of both hemispheres. This plant is of medicinal importance for numerous ailments like dysentery, influenza, and diabetes and possesses diuretic, anti-hepatotoxic and anti-viral effects (Chopra *et al.*, 1986; Qian, 1996). The lipid-lowering activity of *P. niruri* has been studied in Triton-induced and cholesterol-fed hyperlipemic rats. Serum lipids were lowered by *P. niruri* extract orally fed (250 mg/kg b.w.) to the Triton WR-1339 induced hyperlipemic rats. Chronic feeding of this plant (100 mg/kg) in animals simultaneously fed with cholesterol (25 mg/kg) for 30 days caused lowering of the lipids and apoprotein levels of VLDL and LDL in experimental animals. The anti-hypercholesterolemic effect of this plant may be mediated through the inhibition of hepatic cholesterol biosynthesis, increased excretion of fecal bile acids, and enhanced plasma lecithin: cholesterol acyl transferase activity (Khanna *et al.*, 2002). *P. niruri* enhances the excretion of bile acids through feces and this contributes to the regress of cholestersteosis in liver damage. Disorders of lipid metabolism are associated with peroxidative degradation of membrane lipids and, like picroliv, this may also act as an anti-oxidant to inhibit lipid peroxidative liver damage (Chander *et al.*, 1988).

B. *CORAINDRUM SATIVUM*

Almost all the spices exhibit a wide range of physiological and pharmacological effects (Beena *et al.*, 1995, 1996) and thus are useful as domestic remedies for many of the human disorders (Nadkarni and Nadkarni, 1976; Chopra *et al.*, 1986). *Coraindrum sativum* popularly known as coriander seed is a very commonly used spice in Indian cuisines. The biochemical effects of this seed on lipid parameters in 1,2-dimethyl hydrazine (DMH) induced colon

TABLE III
PLANTS POSSESSING HYPOLIPIDEMIC POTENTIALS

Name of the plant	Family	Plant parts used	References
Achyranthus aspera	Amaranthaceae	Leaves, roots	Khanna *et al.* (1992)
Aegle marmelos	Rutaceae	Fruits, root, bark, leaves, flowers	Sharma and Dwivedi (1997)
Agave vera	Amaryllidaceae	Roots, leaves, gum	Sharma and Dwivedi (1997)
Alchemilla xanthochlora	Rosaceae	Leaf	Filipek (1992); Der Marderosian and Beutler (2002)
Allium cepa	Liliacea	Under ground bulb	Augusti and Mathew (1974); Lata *et al.* (1991); Der Marderosian and Beutler (2002)
Allium stivum	Liliacea	Bulb, oil	Sharma and Dwivedi (1997)
Aloe barbadensis	Liliacea	Leaves	Sharma and Dwivedi (1997)
Amorphophallus konjac Koch.	Araceae	Flour	Der Marderosian and Beutler (2002)
Apocynum venetum	Apocynaceae	Leaves, roots	Kim *et al.* (2000)
Arctium lappa L.	Asteraceae	Seeds, roots, leaves	Iwakami *et al.* (1992)
Avena sativa L.	Gramineae	Inner husk of the grain	Anderson *et al.* (1984); Der Marderosian and Beutler (2002)
Azadirachta indica	Meliaceae	Leaf	Mukherjee *et al.* (1995)
Bambusa arundunaceae	Gramineae	Leaves	Sharma and Dwivedi (1997)
Bidens pilosa	Asteraceae	Leaves	Dimo *et al.* (2001)
Bosswellia serrata	Burserraceae	Gum	Sharma and Dwivedi (1997)
Brassica varcapitata	Cruciferae	Oil	Sharma and Dwivedi (1997)
Bupleurum chinense DC	Umbelliferae	Roots	Bone (1996); Der Marderosian and Beutler (2002)
Cajanus cajan	Fabaceae	Seeds	Sharma and Dwivedi (1997)
Camellia sinensis L. *Kuntze* (*Green tea*)	Theaceae	Leaves	Yokozawa and Dong (1997); Tijburg *et al.* (1997)
Lycopersicon esculentum	Solanaceae	Ripe fruit of tomatoes	Der Marderosian and Beutler (2002)
Capparis deciduas	Capparaceae	Leaves, fruits, stem	Sharma and Dwivedi (1997)
Capsicum frutescens	Solanaceae	Fruits	Sharma and Dwivedi (1997)
Carthamus tinctorius L.	Compositae	Flower	Der Marderosian and Beutler (2002)

TABLE III (*continued*)

PLANTS POSSESSING HYPOLIPIDEMIC POTENTIALS

Name of the plant	Family	Plant parts used	References
Carum capaticum	Umbeliferae	Fruits, roots	Sharma and Dwivedi (1997)
Celastrus paniculatus	Celastraceae	Seed oil, bark, root, fruit	Sharma and Dwivedi (1997)
Cicer arietinum	Papillionaceae	Seeds, leaves	Sharma and Dwivedi (1997)
Cichorium intybus L.	Compositae	Root	Roberfrodid (1999)
Citrus lemon L.	Rutaceae	Fruit	Carper (1988); Bruneton (1995)
Cimicifuga racemosa (L.) *Nutt.*	Ranunculaceae	Root and rhizomes	Greaves *et al.* (2000)
Commiphora mukul	Burseracaea	Exudates	Der Marderosian and Beutler (2002)
Crataegus oxyacantha L. *C. laevigata* (Poir.) *C. monogyna* Jacquin	Rosaceae	Flowers, leaves, fruits	Chen *et al.* (1995); Rajendran *et al.* (1996)
Curcuma amada	Zinziberaceae	Rhizome	Sharma and Dwivedi (1997)
Curcuma longa	Zinziberaceae	Rhizome	Sharma and Dwivedi (1997)
Cyamopsis tetragonolobus (L.) Taub.	Fabaceae	Indian cluster bean	Todd *et al.* (1990); Der Marderosian and Beutler (2002)
Cynara scolymus L.	Compositae	Leaf	Gebhardt (1998); Anonymous (1999)
Emblica officinalis Gaertin.	Euphorbiaceae	Fruit	Thakur and Mandal (1984); Thakur (1985); Jacob *et al.* (1988); Mathur *et al.* (1996)
Emblica ribes	Myrsinaceae	Seeds, fruit, bark	Sharma and Dwivedi (1997)
Eleutherococcus senticosus Maxim	Araliaceae	Root and leaf	Der Marderosian and Beutler (2002)
Eugenia caryophyllata Thunb.	Myrtaceae	Buds	Der Marderosian and Beutler (2002)
Forsythia suspense (Thunb)	Oleaceae	Ripe fruit	Iwakami *et al.* (1992)
Ganoderma lucidum Karst.	Polyporaceae	Whole plant	Lininger (1998)
Ginkgo biloba L.	Ginkgoaceae	Leaves	DeSmet *et al.* (1997)
Glycine max	Leguminosae	Beans	Barnes (1998); Der Marderosian and Beutler (2002)
Grifola frondosa	Polyporaceae	Whole mushroom	Kabir *et al.* (1987); Kubo and Nanba (1996, 1997)

(*continued on next page*)

TABLE III (*continued*)
PLANTS POSSESSING HYPOLIPIDEMIC POTENTIALS

Name of the plant	Family	Plant parts used	References
Gynostemma pentaphyllum (Thunb.) Makino	Cucurbitaceae	Whole plant	Der Marderosian and Beutler (2002)
Hordeum vulgare L.	Gramineae	Barely grain flour	Lupton *et al.* (1994)
Juglans regia L.	Juglandaceae	Fruit	Chi (1982); Potter (1995)
Juglans nigra	Juglandaceae	Nuts	Der Marderosian and Beutler (2002)
Juniperus communis	Cupressacea	Berries and fruits	Tunon *et al.* (1995)
Linum usitatissimum L.	Linaceae	Seed	Robinson (1991)
Medicago sativa L.	Leguminosea	Leaves and sprouts	Malinow *et al.* (1977, 1978, 1981); Cohen *et al.* (1990)
Momordica charantia L.	Cucurbitaceae	Fruits, leaves and seeds	Der Marderosian and Beutler (2002)
Monascus purpureus		Fermented cooked rice	Der Marderosian and Beutler (2002)
Moringa oleifera	Moringaceae	Leaves	Ghasi *et al.* (2000)
Mucuna pruriens	Papilionacea	Roots, seeds, fruit	Sharma and Dwivedi (1997)
Musa sapientum	Musaceae	Fruits, root, stem, flower, leaves	Sharma and Dwivedi (1997)
Napeta hidostama	Labiatae	Whole plant	Sharma and Dwivedi (1997)
Oenothera biennis L.	Onagraceae	Seeds	Horrobin and Manku (1983); Puolakka and Makarainen (1985)
Olea europaea	Oleaceae	Fruit	Carper (1988); Aviram (1996)
Oputia tuna Mill *Oputi ficus*—Indica		Raw plant	Der Marderosian and Beutler (2002)
Oryza sativa	Gramineae	Rice bran oil	Seetharamaiah and Chandrasekharan (1989)
Panax quinquefolius L. *Panax ginseng* C.A.	Araliaceae	Root	Chen *et al.* (1995)
Paullinia cupana	Sapindaceae	Seeds	Bydlowski *et al.* (1991)
Persea Americana	Lauraceae	Fruit	Der Marderosian and Beutler (2002)
Perilla frutesceus (L.)	Lamiaceae	Seeds	Der Marderosian and Beutler (2002)
Phaseolus aureus	Fabaceae	Seed	Sharma and Dwivedi (1997)

TABLE III (*continued*)

PLANTS POSSESSING HYPOLIPIDEMIC POTENTIALS

Name of the plant	Family	Plant parts used	References
Phaseolus mungo	Fabaceae	Seed	Sharma and Dwivedi (1997)
Phyllanthus niruri	Euphorbiaceae	Whole plant	Khanna *et al.* (2002)
Picrorhiza kurroa	Scrophulariaceae	Root	Sharma and Dwivedi (1997)
Piper nigram	Piperaceae	Leaves	Sharma and Dwivedi (1997)
Polygonum multiflorum	Polygonaceae	Root, stem and leaf	Chevallier (1996); Reid (1986)
Portulaca oleracea L	Portulacaceae	Whole herb	Low and Rodd (1994); Reid (1986)
Pterocarpus marsupium	Papalionaceae	Gum, leaves	Sharma and Dwivedi (1997)
Plantago lanceolata L.	Plantaginaceae	Seeds	Greaves *et al.* (2000)
Ruscus aculeatus L.	Liliaceae	Root	Capelli and Nicora (1988)
Ruta graveolens L.	Rutaceae	Aerial parts	Chevallier (1996); Duke (1989)
Saussuraea lappa	Asteraceae	Root	Sharma and Dwivedi (1997)
Silybum marianum L.	Compositae	Seeds	Der Marderosian and Beutler (2002)
Stevia rebaudiana Bertoni.	Asteraceae	Leaf	Der Marderosian and Beutler (2002)
Tanacetum parthenium	Asteraceae	Leaves	Der Marderosian and Beutler (2002)
Terminalia arjuna Terminalia bellirica Terminalia chebula	Combretaceae	Bark and fruit	Chevallier (1996)
Thevatia nerifolia	Apocynaceae	Leaves	Sharma and Dwivedi (1997)
Tinospora cordifolia	Menispermaceae	Root	Der Marderosian and Beutler (2002)
Trachyspermum ammi L.	Apiaceae	Fruit	Srivastava (1988)
Trichosanthes dioca	Cucurbitacea	Fruit powder	Sharma and Dwivedi (1997)
Trigonella foenumgraecum	Leguminosae	Leaves, seeds	Sharma and Dwivedi (1997)
Tussilago farfara L.	Compositae	Buds	Hwang *et al.* (1987)
Uncaria tomentosa DC	Rubiaceae	Bark	Cohen *et al.* (1990); Hemingway and Phillipson (1974)
Vitis vinifera V. labrusca V. rotundifera	Vitaceae	Grapes and leaves	Der Marderosian and Beutler (2002)
Zingiber officinale Roscoe	Zingiberaceae	Rhizome	Kiuchi *et al.* (1992)

cancer in rats has been reported (Chitra and Leelamma, 2000). The level of cholesterol decreased in the coriander-fed group compared with the DMH control group at the end of the 30-week period. Cholesterol and its metabolites, namely the secondary bile acids stimulate the proliferative activity of the colonic epithelium resulting in tumor promotion (Takano *et al.*, 1981). The observed decrease in the level of cholesterol in the experimental group may be due to lower cholesterogenesis (Petrovich *et al.*, 1984) as well as increased excretion of sterols and their metabolites. The cholesterol/phospholipids ratio is closely related to membrane fluidity. The lower ratio of cholesterol/phospholipids in the spice-fed group is closely associated with membrane stability. A change in the concentration of cholesterol will greatly affect the fluidity of the membrane and thereby can bring about abnormal changes in the membrane properties and function. The spice also prevents changes in the ratio of cholesterol/phospholipid, thereby maintaining the membrane fluidity, integrity and function. Thus, the inclusion of this spice in the daily diet plays a significant role in the protection of colon against chemical carcinogenesis (Marsch *et al.*, 1976; Chitra and Leelamma, 2000).

C. *MORINGA OLIEFERA*

Moringa oliefera Lam (English-horse radish plant or drumstick tree) commonly known as 'Sajna' is a very well known botanical used in traditional medicine in India. It is native to South Asia, but grows in tropical Africa and Latin America. The leaves are eaten commonly as a food in India (Ramachandran *et al.*, 1980; Pal *et al.*, 1996). A crude extract of the leaf of *M. oliefera* Lam has been shown to possess hypocholesterolemic activity (Ghasi *et al.*, 2000). A dose of 1 mg/g extract when co-administered with a high-fat diet, daily for a period of 30 days, had a cholesterol-reducing effect in the serum, liver, and kidneys, compared to the high-fat-fed group. The presence of the phytosterol, β-sitosterol, has been established in the leaf of this plant which is presumably the bioactive component that lowers the plasma concentration of LDL and exerts the cholesterol-lowering property (Ghasi *et al.*, 2000).

D. *APOCYNUM VENETUM*

Apocynum venetum L. known as Luobuma in China and Rafuma in Japan has been used for a long time in traditional Chinese medicine (TCM) for the treatment and prevention of hypertension, bronchitis, common cold and other ailments. The therapeutic potential of the leaves of this plant as an anti-hypertensive, anti-aging and anti-hyperlipidemic has been reported (Muramatsu *et al.*, 1986; Ma and Chen, 1989). This when used as a

tea product drink is useful as an anti-hypercholesterolemic and anti-atherosclerotic (Matsuda *et al.*, 1986; Muramatsu *et al.*, 1986). Luobuma extracts decreased the serum TC and LDL-cholesterol levels and the atherogenic index, as well as the hepatic TC level in hypercholesterolemic rats, but they increased the HDL-cholesterol level. Clinical report on the Luobuma extract indicates that it decreases TC and triglyceride levels of patients with hyperlipidemia (Ma and Chen, 1989).

E. *CICER ARIETINUM*

This plant belongs to the papillionaceae family and commonly known as *Channa* in Hindi and Bengal gram in English. It is rich in amino acids like cystene, lysine, methionine, tryptophan, arginine and glutamic acid. *C. arietinum* has been found to have highly significant hypocholesterolemic action in rats and rabbits. It lowered both ester and free cholesterol contents of beta-lipoproteins. The hypocholesterolemic property was detected in lipid extracts of the plant as well as in the defatted portion, the former being more potent in this respect. Its lipid-lowering action could possibly be attributed to inhibition of the synthesis of cholesterol in the liver, and increased catabolism and excretion of cholesterol end products in the feces (Mathur *et al.*, 1968a,b). In patients fed a high-fat diet, supplementation of *C. arietinum* has been reported to lower serum lipids significantly. The hypocholesterolemic effect was associated with a statistically significant increase in 24-h fecal excretion of total bile acids without any significant increase in neutral sterols (Mathur *et al.*, 1968c). *C. arietinum* has been observed to have a very significant anti-artherogenic effect in rabbits. The atherosclerotic process is delayed in onset and is also less severe in degree in rabbits treated with *C. arietinum*. It has also been reported that the cholesterol content of the aortic wall in the control animals was significantly higher in the cholesterol-fed rabbits in comparison to *C. arietinum* (Mathur *et al.*, 1968b). In albino rats having egg-yolk induced hypercholesterolemia, supplementation of *C. arietinum* decreased the serum cholesterol level due to the isoflavone, biocharin, present in germinating *C. arietinum* (Madhavan *et al.*, 1971; Sharma, 1997).

F. *COMMIPHORA MUKUL* (SYNONYM: *C. WIGHTII*)

This plant is commonly known as ‘Indian Bdellium Tree’ and ‘Guggul’ in Ayurveda. Gum resin excreted from the plant is mostly used. Guggul is a spiny shrub or small tree with many branches, usually growing 2 or 3 m high and found in the arid, rocky tracts of Rajasthan, Gujarat and Karnataka in India. A healthy tree yields 250–500 g of resin in one season, and guggul plants typically begin yielding resin after 5 years (Raghunathan and

Mittra, 1982). The tree of *C. mukul* is mostly found in Sindh, Rajasthan, Hyderabad, Karnataka, Madhya Pradesh, Assam and Bangladesh regions of the Indian subcontinent. The medicinal activity has been attributed to the oleogum resin (guggul) of the stem bark, which has been in use for thousands of years. Ayurvedic literature is full of praise for guggul and its divine actions, right from healing bone fractures and inflammations to treating cardiovascular disease, obesity and lipid disorders. In Tibetan medicine, the plant is used for skin diseases, anemia, edema, salivation and heaviness of the stomach and has been proven helpful for regulating cholesterol levels. The plant's lipid-lowering properties have been noted among practitioners of Ayurvedic medicine, while modern scientific research is validating these observations. Guggul works to balance conditions of both low and high cholesterol whether brought on by diet, lack of exercise, chronic stress, or genetic predilection.

Gum guggul has been found to act as hypocholesterolemic and hypolipidemic agents in experimental animals like pigs, chicks, rabbits and rats (Arora *et al.*, 1972). Preliminary clinical studies carried out on 22 patients of hypercholesterolemia with associated obesity, ischemic heart disease, hypertension and diabetes showed a fall in total serum cholesterol and serum lipids in all cases treated with guggul (Dwarakanath and Satyavati, 1970). In another study, guggulipid, an oleoresin and mixture of several steroid lipids, in the dose of 1.2 g/day for 6 weeks reduced cholesterol by 15% and triglycerides by 20%. When guggulipid was administered in a dose of 1.5 g/day for 12 weeks, it brought down the levels of cholesterol by 16.9% and triglycerides by 27%. The effect of guggul powder (8 g/day) in 135 patients with ischemic heart disease for a duration of 12 weeks showed reductions in serum cholesterol (27%), serum triglycerides (36%), phospholipids (20%), and free fatty acids (37%) (Sharma, 1997). It is believed that the lipid-regulating effects of guggul resulted from its thyroid-regulating action, and its combined effects of inhibiting the biosynthesis of cholesterol's thyroid hormones. *Z*-guggalsterone, a ketosteroid and a component of guggul is such an agent. The plant is especially useful where T3 (Triiodothyronine) values of the thyroid are low. Guggul's thyroid stimulating property also explains the traditional use of the plant for thyroid-related problems. The hypolipidemic action of the gum resin of *C. mukul* is well accepted in Indian systems of medicine that can be explained on the following basis (Satyavati *et al.*, 1976):

- Significant increase in the rate of removal/extraction of cholesterol from the body.
- Mobilization of cholesterol from the tissues (as evident clinically by the resolution of xanthomas).
- Decrease in input/synthesis of cholesterol.

- Increase in the rate of degradation of cholesterol by activating the thyroid gland.
- Crude plant extracts contain ion-exchange resins, which combine with the bile acids and thereby trap cholesterol out of entero-hepatic circulation.

The oleoresin from *C. mukul* has been mentioned in the ancient Indian texts Atharvaveda, and in the early medical texts of Charaka, Sushruta, the Samhitas and Nighantus describing the old treatise, which are over a thousand years old. Textbooks of Ayurvedic Medicine distinguish between fresh and old varieties of guggul. The oleoresin contains 0.37% essential oil containing mainly myrecene, dimyrecene and polymyrecene. Alcohol extraction gives a soluble resin and an insoluble carbohydrate gum. The ethyl acetate-soluble portion of guggul was found to possess hypolipidemic and anti-inflammatory properties. The active ingredients responsible for the use of the plant in the maintenance of healthy cholesterol levels, are the guggulsterones, specifically guggulsterone *E* and guggulsterone *Z*, standardized to contain a minimum of 2.5% guggulsterones *E* and *Z*. The limits for the maximum level of guggulsterones (*E* and *Z* to 4.0–6.0%) in a soft extract have been specified in an official book (Anonymous, 1966). The extract of *C. mukul* was found to confer significant protection to albino rats against the development of experimental atherosclerosis; the extract not only prevented deteriorating changes in serum cholesterol, triglycerides, and plasma fibrinogen level but also favorably increased the plasma fibrinolytic activity (Nityanand *et al.*, 1973).

While performing clinical studies on 20 patients with hyperlipidemia who were administered with 4.5 g of purified gum guggul in two divided doses daily for 16 weeks, serum cholesterol and serum triglyceride levels were observed to decrease at the end of the 4th–8th week. HDL cholesterol showed a gradual increase while VLDL and LDL cholesterol showed a significant decrease at all time points (Satyavati *et al.*, 1969). Thus due to its use from ancient times, over the years, it has become well known for the lowering of blood cholesterol levels. It may also be used as part of a weight reduction program. Scientists have been studying the hypolipidemic activity of guggul for over 20 years. It began with animal trials in the late 1960s and because of its success, quickly progressed to human clinical studies. Guggul proved extremely effective in regulating cholesterol, triglycerides, and phospholipids in both types of research. Extracts of guggul have been shown to lower the serum cholesterol level in chicks and have shown similar effects in rabbits, rats and domestic pigs (Nityanand *et al.*, 1973; Satyavati *et al.*, 1976). Another study performed in India in the late 1970s researched the long-term effects of lipid-regulating substances on humans. The two substances compared were clofibrate—an effective and frequently used hypolipidemic drug, and an ether extract of guggul resin. The guggul extract (1.5 g per day)

was taken orally by 41 of the 51 subjects suffering from elevated cholesterol triglycerides while the remaining 10 took clofibrate (2.0 g per day). It was observed that cholesterol and triglyceride levels fell significantly, progressively, and equally in both groups. In a 1986 study, an ethyl acetate extract of guggul showed similar benefits to those highlighted in the study above. In this particular trial, the guggul extract compared favorably with other hypolipidemic drugs, significantly lowering serum cholesterol and triglyceride levels in 78.9% of the test subjects and it produced no noticeable side effects. Another study of guggul found that serum cholesterol and triglyceride levels were lowered by an average of 17.5 and 30.3%, respectively (Tripathi *et al.*, 1968; Satyavati *et al.*, 1976).

G. *CURCUMA LONGA*

Turmeric (*Curcuma longa*), synonymous with curcumin, is a native East Indian and Southeast Asian herb and one of the medicinal plants listed in an Assyrian herbal text dating from about 600 BC. *C. longa* is a perennial herb belonging to zingiberace family. It is 2–3 ft high with a short stem and tufted leaves (Panda, 1986). The rhizomes are short and thick. In India it is popularly known as haldi, halud, turmeric or halder. Turmeric was used by ancient practitioners in India as a stomachic, tonic and carminative. It is used as a household remedy for local application in inflammatory conditions and other painful affections. Its anti-platelet activity is equal to that of aspirin, but unlike aspirin does not increase prostacyclin synthesis. Studies on the effect of alcoholic and ethereal extracts of the rhizomes of *C. longa* and *C. amada* on the cholesterol level in experimental hypercholesterolemic rabbits revealed that the ethereal extract of *C. amada* lowered the blood cholesterol level (Pachauri and Mukherjee, 1970). Rhizome has been reported to contain the important coloring matter curcumin, which belongs to the dicinimolymethane group. Curcumin, isolated from the rhizomes of *C. longa*, caused a sharp but transient fall in blood pressure (Malhotra and Ahuja, 1974). It has also been reported that sodium curcuminate isolated from *C. longa* is an active choleretic which causes an increase in total excretion of bile salts, bilirubin and cholesterol. Ethanol extracts of *C. longa* (tuber) and *Nardostachyas jatamansi* (whole plant) feeding elevate the HDL cholesterol/TC ratio (Chaudhuri, 1998). The extract also caused a significant reduction in the ratio of TC/phospholipids. *C. longa* exhibited better cholesterol and triglyceride lowering activity (Ch = −85%, TG = −88%) as compared to *N. jatamansi* in Triton-induced hyperlipidemia. The cholesterol-lowering effects of curcumin span all levels of lipid-lowering mechanism, including lowering total and LDL cholesterol (by 11% normally), increasing HDL cholesterol (by 29% normally), and reducing

lipid peroxidation, thereby limiting the oxidation of LDL cholesterol rats (Pachauri and Mukherjee, 1970; Sharma, 1997; Kokate *et al.*, 1998).

H. *EMBLICA OFFICINALIS*

E. officinalis belonging to the Euphorbiaceae family is popularly known as amlaor, amlaki in India. It is cultivated in the Deccan region, Coastal districts and Kashmir region, Uttar Pradesh and the central part of India. Though all its parts including dried fruit seeds, leaves, root, bark and flower are used for medicinal purposes; its dried fruit seeds have been mainly in use for therapeutic purposes (Panda, 1986). *E. officinalis* has been reported to exert hypolipidemic activity. *E. officinalis* has been found to reduce serum TC, aortic cholesterol and hepatic cholesterol significantly, without any effect on the serum triglyceride levels in both normal and cholesterol induced hypercholesterolemic rabbits. The effect of *E. officinalis* on total serum cholesterol and its lipoprotein fractions was also studied in normal and hypercholesterolemic individuals aged 35–55 years. When the supplement was given for a period of 28 days in the raw form, both normal and hypercholesterolemic subjects showed a decrease in cholesterol levels. Two weeks after withdrawing the supplement, the total serum cholesterol levels of the hypercholesterolemic subjects rose significantly almost to the initial levels (Tewari *et al.*, 1968; Sharma, 1997).

I. *INULA RACEMOSA*

Inula racemosa belongs to the Asteraceae family and is commonly known as 'pushkarmool.' It is extensively cultivated in Jammu and Kashmir and abundantly found in Himalayan regions of India. Roots of this plant are used for medicinal purposes. The root powder of *I. racemosa* has been reported to be a hypolipidemic agent in clinical and experimental studies (Tripathi *et al.*, 1984). It has been investigated to have potential biochemical effects on isoprenaline-induced changes in rat's serum glutamic oxaloacetate transaminase, lactic dehydrogenase and creatinine phosphokinase. It has been found to possess a propranolol-like beneficial effect in prevention of coronary ischemia and has been reported for its potent hypolipidemic and cardioprotective activity (Sharma, 1997).

J. *TERMINALIA ARJUNA*

T. arjuna commonly known as 'arjun' in India belongs to the Combretacea family and is a large deciduous tree attaining a height of 66 ft. Its bark has been used as medicine in heart disease since 500 BC. The main constituents of

bark powder include glycosides (Arjunine, Arjunetin, Arjunoside I, Arjunoside II, Triterpene-*o*-glycoside). The alcoholic decoction of this bark powder significantly increases euglobin lysis time, prolongs prothrombin time and lowers the serum cholesterol levels in ischemic heart disease patients. The bark powder lowered the systolic blood pressure and body mass index, and increased the HDL-cholesterol. The administration of the bark powder of *T. arjuna* causes a significant decrease in circulating catecholamine levels, while in adrenal glands its concentration goes up. It might be acting by inhibiting the catecholamine release from adrenal glands into the circulation, thus protecting the heart from catecholamine toxicity (Sharma, 1997; Gauthamna *et al.*, 2001). The hypolipidemic action of *T. arjuna* coupled with the enhancement of PGE_2-like activity, negative inotropic, chrontropic, anti-arrhythmic, anti-hypertensive and HDL cholesterol-raising properties make it an imminently cardio-protective product for the overall management of CAD (Gauthamna *et al.*, 2001).

K. *TRIGONELLA FOENUMGRAECUM*

Fenugreek, otherwise known as *Trigonella foenumgraecum* has a rich 3000-year-old history of medicinal use in Egypt, Southern Europe, India, Asia, and Northern Africa. Fenugreek is mentioned in a variety of ancient writings, like the papyri found in Egyptian tombs and the records of the Roman emperor. The seeds of fenugreek (*T. foenumgraecum*), a condiment in India, are high in fiber content and are reported to have anti-diabetic and hypercholesterolemic properties in both animal models and humans. It is an aromatic herb, commonly known as 'Methi' in Hindi and fenugreek in English, belongs to family—leguminosae, and is cultivated in many parts of India. It has been used for many years as an insect repellent by agriculturists to protect gram from insect attacks. It was traditionally used to minimize the symptoms of menopause and arthritis, control diabetes, reduce cholesterol, control coughs and fevers, as an anti-inflammatory, and to improve heart and vascular health. Overall, fenugreek is an herb with a rich history in healthcare (Nadkarni and Nadkarni, 1976; Bruneton, 1995). The hypolipidemic effects of fenugreek seed on animals have been reported by many workers including effects on noninsulin-dependent diabetic patients; these studies have proven the potent thereapeutic potential of fenugreek in the treatment of hypercholesterolemia (Sharma, 1984, 1986a,b, 1996; Sharma *et al.*, 1990). The oral administration of *T. foenumgraecum* showed significant hypocholesterolemic and hypotriacylglycerolemic effects in cholesterol-induced hyperlipidemic rabbits, restoring the normal serum lipid levels and substantially lowering the tissue

lipids (Stark and Madar, 1993; Stark and Zechiaria, 1993; Sharma, 1997; Sowmya and Rajyalakshmi, 1998).

Several more recent animal and human clinical trials have confirmed the therapeutic application of fenugreek seeds. Antioxidant activity preventing lipid peroxidation has been reported for the seeds of fenugreek (Anuradha and Ravikumar, 1998). 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. Fenugreek is endowed with a variety of natural therapeutic compounds. The seeds contain an excellent source of mucilaginous fiber mainly composed of galactomannans. Galactomannans are glyconutrients that help to slow the absorption of carbohydrates, help to create a feeling of fullness and also act to improve organ health at the cellular level. Fenugreek seeds contain 45–60% fiber. Fenugreek seeds are also rich in protein (20–30% of the seed) and free amino acids, such as arginine (which plays a key role in cardiovascular health), histidine, lysine and tryptophan (Sauvaire *et al.*, 1984, 1991, 1998). Fenugreek seeds also contain a unique amino acid called 4-hydroxyisoleucine (Fowden *et al.*, 1973; Hardman and Fazli, 1972). Recent scientific research has confirmed that this rare compound can actually mimic and stimulate the release of insulin thereby helping to control blood glucose levels (Ali *et al.*, 1995). This explains fenugreek's unique ability to help control diabetes. Fenugreek is also rich in flavonoids such as apigenin, luteolin, orientin, quercetin, vitexin, and isovitexin. These flavonoids act as powerful natural antioxidants and help to strengthen the immune system, improve cellular health and reduce the signs of aging. Even more impressive is the content of saponins in the seeds. Fenugreek contains natural saponins that can bind to cholesterol and fat in our diet and remove them from the body (Hardman and Fazli, 1972; Gupta *et al.*, 1986; Benichou *et al.*, 1999). Some of these saponins such as yamogenin, tigogenin, and neotigogenin can also act as natural phytoestrogens and help to support hormonal balance. In addition, fenugreek seeds contain vitamins A, B1, C, and nicotinic acid, therapeutic oils, pyridine-type alkaloids, such as trigonelline, choline, gentianine, and carpaine, and volatile oils such as *n*-alkenes and sesquiterpenes. Thus, fenugreek offers a diverse and effective natural therapeutic compound for curing so many ailments.

L. *APIUM GRAVEOLENS*

Apium graveolens known as celery belongs to the family Umbelliferae and is a biennial plant that is native to Europe. Celery generally grows about 1–2 ft tall, has tough-ribbed green stems and segmented dark green leaves containing toothed leaflets. It is high in mineral content, and contains pheromone steroids identified as boars and parsnips (Claus and Hoppen, 1979).

Besides this, it also contains isovalerinic aldehyde, propionic aldehyde and acetaldehyde (Leung, 1980). It has long been recommended in TCM orally for dizziness, headache and high blood pressure. In rats fed a high-fat diet for 8 weeks to induce hyperlipidemia, those given a celery juice supplement were reported to have significantly lower TC, LDL-cholesterol and triglycerides. An aqueous celery extract significantly lowers the systolic blood pressure (Leung, 1980).

M. *CICHORIUM INTYBUS*

Cichorium intybus, commonly known as 'Chicory' of the family Compositae or Astraceae, is a perennial plant indigenous to Europe, India and Egypt. Chicory flowers contain chichorin, which is 6,7-glucohydroxycoumarin. The root contains up to 8% inulin (a polysaccharide), a bitter principal containing one part protocatechuic aldehyde to three parts inulin (Balbaa *et al.*, 1973). Chicory's oligosaccharides are probiotic and are beneficial in maintaining healthy gastrointestinal flora. This plant is our best source of the cholesterol-lowering phytochemical, inulin. In France and Italy, the roots are not only consumed as a drink, but are also considered as a vegetable. Inulin is also reportedly lipolytic and may thereby decrease obesity and act as one of the contributors to cardiopathy. Improved lipid metabolism was demonstrated in rats fed an inulin containing chicory extract, possibly due to the changes in absorption or synthesis of cholesterol (Kim and Shin, 1996; Roberfroid and Delzenne, 1998; Roberfrodid, 1999).

N. *OENOTHERA BIENNIS*

Oenothera biennis, commonly known as Evening Primrose of the family Onagraceae, is a large delicate wild flower native to North America. It is not a true primrose; the blooms usually last for only one evening. Seeds of *O. biennis* contain 14% of a fixed oil known as OEP. This oil contains 50–70% *cis*-linoleic acid and 7–10% *cis*-gamma-linoleic acid (GLA) (Leung, 1980). Essential fatty acids are important as cellular and structural elements, and as precursors of prostaglandins, which help to regulate metabolic function. GLA may inhibit a number of cardiovascular pathologies, including cardiac arrhythmia, hypertensive responses, platelet aggregation and hyperlipidemia. Linoleic acid can reduce elevated serum cholesterol levels, but GLA has cholesterol-lowering activity about 170 times greater than the parent compound. GLA, the major active ingredient in the evening primrose oil (also in borage, currant and hempseed oil), inhibits platelet aggregation, reduces blood pressure and restores the motility of red blood cells (Marderosian and Lawerence, 1998).

O. *CRATAEGUS SPP.*

Crataegus spp. (*Crataegus oxyacantha*, *Crataegus laevigata*, and *Crataegus monogyna*), commonly known as Hawthorn of Rosaceae family, is a spiny bush or small tree that grows up to 7.5 m in height. The leaves, flowers, bark, and fruit contain the flavonoid pigments, hyperoside and vitex rhamnoside. The flavonoid constituents from hawthorn have been frequently reported (Fisel, 1965, 1966; Lewak, 1969). Hawthorn has been frequently studied in the prevention and treatment of atherosclerosis. A hawthorn preparation, when administered to animals, resulted in the lowering of blood viscosity and the fibrinogen level. Another report found that the tincture of hawthorn increased bile acid excretion and decreased the cholesterol synthesis in rats. The mechanisms involve an upregulation of hepatic LDL receptors, resulting in a greater influx of cholesterol into the liver. Hawthorn has also been found to enhance cholesterol degradation (He, 1990; Rajendran *et al.*, 1996).

P. *VITIS VINIFERA*

Vitis vinifera, which is commonly known as grapes, is a deciduous climbing plant, native to southern Europe and western Asia but is cultivated in warm temperature regions through the world (Ensminger *et al.*, 1994). Grapes are a rich source of polyphenolic compounds and flavonoids including quercetin, catechins, myricetin, kaempferol, and the isomers of resveratrol are the main constituents (Soleas *et al.*, 1995; Stein *et al.*, 1999). Flavonoids in red wine, especially quercetin, are said to be far more effective than vitamin E in preventing the oxidation of LDL cholesterol, which is a contributor to the development of atherosclerosis. Proanthocyanins in red wine are both radical scavengers and xanthine oxidase inhibitors. *In vivo* lipid peroxidation has been implicated in many coronary malfunctions, including atherosclerosis and other ailments like aging and cancer. Phenolic constituents also inhibit cyclooxygenase and LOX in platelets and macrophages, thereby reducing thrombotic tendencies.

Q. *PORTULACA OLERACEA*

Portulaca oleracea commonly known as purslane belongs to the family Portulacaceae and is an herbaceous cosmopolitan weed. *P. oleracea* is one of the major sources of omega-3 fatty acids and was found to produce beneficial effects on cholesterol and triglyceride levels in heart disease and in strengthening the immune system. The plant also possesses marked antioxidant activity (Reid, 1986; Chevallier, 1996; Hocking, 1997).

R. *CYNARA SCOLYMUS*

Cynara scolymus, also known as artichoke, belongs to the family Compositae and is a perennial herb widely cultivated in the Mediterranean regions and adjoining parts of central Europe. Artichoke is found to contain high amounts of flavone glycosides (Hammouda, 1993; Fleming, 1998; Gebhardt, 2001), volatile oils (Hammouda, 1993), bitter sesquiterpene principles (Gebhardt, 1998), phytosterol, tannins, and sugars (Hammouda, 1993). An *in vitro* study determined that artichokes inhibit cholesterol biosynthesis by indirectly modulating and inhibiting HMG-CoA reductase, the key enzyme in the biosynthetic pathway for cholesterol synthesis. The cynaroside and particularly the aglycone, luteolin, were mainly responsible for HMG-CoA reductase inhibition (Brown and Rice-Evans, 1998; Gebhardt, 1998; Anonymous, 1999; Gebhardt, 2001). The flavonoid of artichoke, luteolin, demonstrated anti-oxidant properties (Brown and Rice-Evans, 1998). A prospective study investigating 143 patients with TC greater than 280 mg/dl reported that patients given 1800 mg of dry antichoke extract per day versus placebo over a 6-week period experienced statistically significant changes in total and LDL cholesterol. TC was decreased by 18.5 versus 8.6% for the placebo, while TC was reduced 22.9 versus 6.3% for the placebo. Thus, dry artichoke extract was recommended to treat hypo-lipoproteinemia thereby reducing the risk of atherosclerosis and CHD (Brown and Rice-Evans, 1998).

S. *VACCINIUM MYRTILLUS*

Vaccinium myrtillus, commonly known as bilberry fruit, originates mainly from northern and central Europe (Bisset, 1994). This well known plant is rich in flavonoids, the polyphenolic compounds that promote anti-oxidant activity (Bisset, 1994). A study conducted on the antioxidative potential of *V. myrtillus* showed potent protective action on LDL particles during *in vitro* copper-mediated oxidation. The study concluded that this extract may be more potent than either ascorbic acid or butylated hydroxy-toluene in the protection of LDL particles from oxidative stress (Mitcheva, 1993; Bisset, 1994).

T. *GLYCINE MAX*

The soybean plant, *Glycine max*, belongs to the family Leguminosae, and is found to possess a number of health benefits including anti-carcinogenic effects and improvements in cardiovascular and intestinal problems. The mechanisms responsible for the effect of soy on serum lipoproteins are not well known. Caroll (1991) and Potter (1995) reviewed various hypotheses

which include the amino acid composition of soy protein, interruption of the intestinal 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, and the effects of components such as isoflavones, fiber and saponins in soybeans. The cholesterol-lowering effect may be due to another constituent associated with soy protein that is either lost or liberated during the hydrolysis of the protein (Potter, 1995). Greaves *et al.* (2000) have reported that a soy protein diet decreased both plasma cholesterol concentrations and intestinal cholesterol absorption. However, the addition of a semi-purified soy extract rich in isoflavones to casein-lactalbumin protein did not improve plasma lipids or reduce cholesterol absorption. Furthermore, the addition of a conjugated equine estrogen to casein-lactalbumin protein did not improve plasma lipids or affect intestinal cholesterol absorption. Thus, a bioactive component of soy protein other than or in addition to the isoflavones such as the saponins, phytic acid, protein components, or the amino acid composition of the soy protein or the protein–isoflavone interaction may be involved in the lipid-lowering effects (Greaves *et al.*, 2000).

U. *PLANTAGO PSYLLIUM*

Plantago psyllium, commonly known as plantain, belongs to the family Plantaginacea and is a perennial weed with worldwide distribution. About 250 different varieties are available which are mostly herbs and/or shrubs characterized by basal leaves and inconspicuous flowers (Greaves *et al.*, 2000). Plantain constituents include various acids like benzoic, caffeic, vanillic, and ursolic acids; alkaloids like boschniakine and amino acids. Flavonoids found in plantain include apigenin, baicalein, sctellarein and others (Greaves *et al.*, 2000; Der Marderosian and Beutler, 2002). Many reports on psyllium have concluded that it can be helpful in treating various hyperlipidemias (Der Marderosian and Beutler, 2002). In animal studies, plantain lowered the total plasma lipids, cholesterol and triglycerides in atherosclerotic rabbits (Der Marderosian and Beutler, 2002). In a study of 28 patients who took 3 doses (3.4 g/dose) per day compared with placebo for 8 weeks, the psyllium-treated patients showed decreases in total serum cholesterol levels compared with the placebo group after 4 weeks. Decreases were also seen in LDL cholesterol and LDL/HDL ratio. At the end of 8 weeks, values for TC, LDL cholesterol and the LDL/HDL ratio were 14, 20, and 15%, respectively, below baseline. This study suggested that a high-cholesterol level could be managed safely and easily by including psyllium preparations in the diet (Katcher and Koda, 1987). Psyllium seed was found to be more effective than *P. ovata* husk in reducing serum cholesterol in

normal patients. A report in 20 hypercholesterolemic pediatric patients on low-fat diets, however, found psyllium seed to be ineffective in lowering cholesterol or LDL levels (Der Marderosian and Beutler, 2002). A polyphenolic compound from the psyllium leaves was found to exhibit hypocholesterolemic activity, perhaps by the enhancement of cholesterol elimination as fecal bile acids (Der Marderosian and Beutler, 2002).

V. RED YEAST RICE

Red yeast dates back to 800 AD where it was described in the ancient Chinese Pharmacopoeia published during the Ming dynasty (Der Marderosian and Beutler, 2002). The yeast is grown on rice so that the crimson organism permeates the rice; then it is ground to a powder. It is a mild non-poisonous yeast thought to be useful for gastric problems such as indigestion. *Monascus purpureus* yeast is made by a fermentation process using cooked non-glutinous rice. It has been used traditionally in China as food and medicine (Der Marderosian and Beutler, 2002). The commercial product contains 0.4% naturally occurring HMG-CoA reductase inhibitors of which lovastatin and biologically active hydroxyl acids are the most abundant. One of the most significant aspects of red yeast rice is its 9 HMG-CoA reductase inhibitors, as well as the isoflavones, unsaturated fatty acids and trace elements such as selenium (Katcher and Koda, 1987). Over two dozen clinical studies demonstrate its effectiveness. For example, a TC decrease of 17% and a 22.4% decrease in LDLs were demonstrated in a clinical trial conducted at UCLA. Hypercholesterolemia is treated aggressively with statin drugs, very potent inhibitors of HMG-CoA reductase, and the rate-limiting enzyme in cholesterol biosynthesis at the mevalonate level. Lovostatin's action is its conversion to mevinolin in the body. Mevinolin is the active principle found in red yeast rice, which enzymatically inhibits mevalonate, thus lowering cholesterol. It also has anti-oxidant properties. Numerous clinical trials suggest that red yeast rice (*Monascus purpureus*) has comparable therapeutic effects without the side effects of the statin drugs (Der Marderosian and Beutler, 2002).

W. MILK THISTLE (*SILYBUM MARIANUM*)

Silybum marianum is commonly known as milk thistle or holy thistle. Silybum is indigenous to Kashmir, India but is also found in North America. It grows to a height of 5–10 ft and has large prickly leaves. The milk thistle seed extract contains a bioflavonoid complex known as Silymarin, which consists of silybin, silidianin, and silicristin (Leung, 1980; Katcher and Koda, 1987). Silybin is the most biologically active component with regard to its

anti-oxidant and hepatoprotective properties (Arnone *et al.*, 1979). It exerts anti-oxidant and membrane-stabilizing activities, attributes important for liver secretion and uptake of plasma lipoproteins. Inhibition of HMG-CoA reductase *in vitro* has been demonstrated with therapeutic application of milk thistle, implying its possible direct influence on liver cholesterol metabolism. Milk thistle can be compared to probucol, a hypocholesterolemic anti-oxidant drug. In contrast to probucol, milk thistle caused an increase in HDL lipoproteins and a decrease in liver cholesterol content, both additional benefits. Administration of silymarin at 420 mg/day for 3 months to 14 type II hyperlipidemic patients resulted in a slight decrease in TC and HDL-cholesterol levels (Benda *et al.*, 1980). The biliary cholesterol and phospholipid concentrations in rats were also slightly reduced. The silybin-induced reduction of biliary cholesterol both in rats and humans may be due in part to the decreased liver cholesterol synthesis (Lorenz *et al.*, 1982; Feher *et al.*, 1989; Schulz *et al.*, 1998).

X. *LINUM USITATISSIMUM*

Linum usitatissimum, commonly known as flaxseed, belongs to the family Linaceae. Flaxseed is the richest food source of lignans, one of the major groups of phytoestrogens (Thompson *et al.*, 1991) and is incorporated into human diets because of its reported health benefits. Lignans have been implicated as having anti-tumorigenic (Thompson *et al.*, 1996), estrogenic and/or anti-estrogenic, and antioxidant (Collins *et al.*, 1997; Prasad, 2000) properties. Prasad (2000) reported that rabbits receiving secoisolariciresinol diglucoside, the major lignan found in flaxseed, had reduced total and LDL-cholesterol concentrations. Lignans have also been shown to modulate activities of 7-hydroxylase and acyl CoA cholesterol transferase (Kitts *et al.*, 1999), two of the key enzymes involved in cholesterol metabolism. Sanghvi *et al.* (1984) concluded that the reduction in hypercholesterolemic atherosclerosis induced by flaxseed is due to a decrease in total serum cholesterol and LDL cholesterol and that the anti-atherogenic activity of flaxseed is independent of its linolenic acid content. However, the hypocholesterolemic effects of whole flaxseed can also be attributed, in part, to its linolenic acid and fiber components (Bierenbaum *et al.*, 1993; Cunnane *et al.*, 1995; Prasad, 1997; Jenkins *et al.*, 1999). The hypocholesterolemic effects of linolenic acid have been reported in both animals (Garg *et al.*, 1989) and humans (Chan *et al.*, 1991). Garg *et al.* (1989) demonstrated that feeding a linolenic acid-rich diet to rats lowered serum cholesterol levels more effectively than a diet rich in linoleic acid. Flaxseed reduced serum levels of both apo B and apo A-1 (Jenkins *et al.*, 1999). The soluble fiber mucilage present in flaxseed may also contribute to the observed

hypocholesterolemic properties (Edralin *et al.*, 2002; Brown *et al.*, 1999; Prasad, 1999; Lucas *et al.*, 2002).

Y. *ALLIUM SATIVUM*

1. Usage in medicine

Allium sativum, commonly known as garlic, is a perennial herb having bulbs with several cloves enclosed in a silky white or pink envelope of the skin. It is a popular spice added to several edible preparations all over the world since ancient times. It has also found its use as a folk remedy for a variety of ailments. The hypolipidemic effect of *A. sativum* is well documented. Garlic acquired a reputation in the folklore of many cultures over centuries as a formidable prophylactic and therapeutic medicinal agent. To date, many favorable experimental and clinical effects of garlic preparations, including garlic extract, have been reported. Some of the earliest references to this medicinal and culinary plant are found on Sumerian clay tablets dating from 2600 to 2100 BC (Banerjee and Maulik, 2002). Garlic was an important medicine to the ancient Egyptians listed in the medical text *Codex Ebers* (ca. 1550 BC), especially for the working class involved in heavy labor (Moyers, 1996; Lawson, 1998). There is evidence that during the earliest Olympics in Greece, garlic was fed to the athletes for increasing stamina (Lawson, 1998). In ancient Chinese medicine, garlic was prescribed to aid respiration and digestion, and most importantly, for treating diarrhea and worm infestations (Woodward, 1996). Three ancient medical traditions in India, i.e., Tibbi, Unani and Ayurveda, made extensive use of garlic as a central part of the healing efficacy of plants (Moyers, 1996). The leading Indian ancient medical text, *Charaka-Samhita* recommends garlic for the treatment of heart disease and arthritis. In another ancient Indian medical textbook, *Bower Manuscript* (~300 AD), garlic was used for fatigue, parasitic disease, digestive disorders, and leprosy (Rivlin, 1998). With the onset of the Renaissance period, increasing attention was paid in Europe to the medical use of garlic. A leading physician of the 16th century, Pietro Mattiali of Siena, prescribed garlic for digestive disorders, infestations with worms, and renal disorders, as well as to help mothers during difficult childbirth (Moyers, 1996). In England, garlic was used for toothache, constipation, dropsy, and plague (Rivlin, 1998). In the modern era, scientists have been trying to validate many of these properties of garlic, especially in terms of the identity of the active components, their mechanisms of action, and the exploration of the potential benefits as food supplements. The effects of *A. sativum* juice, as well as that of the essential oil extract of an equivalent amount of *A. sativum*, was studied on alimentary hyperlipidemia, blood coagulation time, and serum cholesterol

levels; both the juice and the essential oil of *A. sativum* were found to have significant protective action against fat-induced fibrinogen. Both garlic products caused a decrease in fibrinolytic activity as well as coagulation time. Both raw and boiled forms of *A. sativum* were reported to decrease total serum cholesterol (Sharma, 1997).

2. *Phytoconstituents in garlic*

Raw garlic homogenate has been the major preparation of garlic subjected to intensive scientific study because it is the commonest form for garlic consumption. Raw garlic homogenate is essentially the same as an aqueous extract of garlic, which has been used in various scientific studies. Allicin (allyl 2-propenethiosulfinate or diallyl thiosulfinate) is thought to be the principal bioactive compound present in aqueous garlic extract or raw garlic homogenate. When garlic is chopped or crushed, allinase enzyme, present in garlic, is activated and acts on alliin (present in intact garlic) to produce allicin. Other important sulfur-containing compounds present in garlic homogenate are allyl methyl thiosulfonate, 1-propenyl allyl thiosulfonate and γ-L-glutamyl-*S*-alkyl-L-cysteine. The adenosine concentration increases several-fold as the homogenate is incubated at room temperature. The enzyme allinase responsible for converting alliin (*S*-allyl cysteine sulfoxide) to allicin is inactivated by heat. Thus, the water extract of heat-treated garlic contains mainly alliin. Since garlic powder is simply a dehydrated, pulverized garlic clove, the composition, especially the allinase activity of garlic powder is identical to that of fresh garlic. However, the dehydration temperature should not exceed 60°C, above which allinase is inactivated (Lawson, 1998). Another widely studied garlic preparation is AGE. Sliced raw garlic stored in 15–20% ethanol for 20 months is referred to as AGE. This whole process is supposed to cause considerable loss of allicin and increased activity of certain newer compounds, like *S*-allylcysteine (SAC), *S*-allylmercaptocysteine, allixin and selenium which are stable, highly bioavailable and have significant antioxidant activity (Borek, 2001). Another recently identified antioxidant compound of AGE is *N*-α-(1-deoxy-D-fructos-1-yl)-L-arginine (Fru-Arg), which is not present in raw or heat-treated garlic (Ryu *et al.*, 2001). Medicinally used garlic oil is mostly prepared by steam-distillation process. Steam-distilled garlic oil consists of the diallyl (57%), allyl methyl (37%) and dimethyl (6%) mono- to hexasulfides. A typical commercial preparation of garlic oil contains diallyl disulfide (DADS, 26%), diallyl trisulfide (DATS, 19%), allyl methyl trisulfide (15%), allyl methyl disulfide (13%), diallyl tetrasulfide (8%), allyl methyl tetrasulfide (6%), dimethyl trisulfide (3%), pentasulfide (4%) and hexasulfide (1%). Oil-macerated garlic oil contains the vinyl-dithiins and ajoenes. Ether extracted garlic oil (essential oil) contains

nine times as much of the vinyl-dithiins (5.7 mg/g) and allyl sulfides (1.4 mg/g) and four times as much of the ajoenes (0.4 mg/g) (Lawson, 1998).

Garlic and its various preparations have been widely recognized as agents for prevention and treatment of atherosclerosis, hyperlipidemia, thrombosis, hypertension and diabetes. The effectiveness of garlic in the treatment of cardiovascular diseases appeared to be encouraging in experimental studies, which prompted several clinical trials. The efficacy of garlic for the treatment of various diseases has been increasingly subjected to rigorous scientific investigations. Garlic appears to be the cheapest way to prevent hyperlipedemia as well as cardiovascular disease (Banerjee and Maulik, 2002).

3. Therapeutic effect of garlic in hyperlipidemia and atherosclerosis

Garlic is best known for its lipid-lowering and anti-atherogenic effects. In cases where dietary therapy may not be sufficient to control lipid levels, natural compounds can lower cholesterol levels and, in general, are less expensive than drugs. The composition and method of preparation of garlic supplements may contribute to efficacy of garlic preparations in lowering cholesterol levels. There are conflicting studies on the effectiveness of garlic. Since the 1980s, four out of five studies have shown that garlic lowers cholesterol. Allicin, the major component of garlic imparting the characteristic garlic odor is mainly responsible for the hypolipidemic activity. The commercially prepared alliin or odorless garlic is converted to allicin in the body. Garlic reduces atherosclerosis by inhibiting platelet aggregation, increasing fibrinolysis, enhancing antioxidant activity, and reducing serum lipids in general to lower cholesterol levels and other significant risk factors for CAD (Banerjee and Maulik, 2002). Several animal and human studies have proven the efficacy of garlic as a herbal remedy to reduce a multitude of risk factors, which play a decisive role in the genesis and progression of arteriosclerosis including decreases in total and LDL-cholesterol, a decrease in HDL-cholesterol, a reduction of serum triglyceride and fibrinogen concentrations, the lowering of arterial blood pressure and the promotion of organ perfusion, and, finally, enhancement in fibrinolysis, inhibition of platelet aggregation, and diminution of plasma viscosity (Jain, 1975). Several groups of investigators (Jain, 1975, 1977; Bordia *et al.*, 1977; Chang and Johnson, 1980; Kamanna and Chandrasekhara, 1984; Mand *et al.*, 1985; Schwartz *et al.*, 1993) studied the effects of long-term (2–9 months) feeding of garlic and garlic preparations (2% garlic powder in diet) on experimental atherosclerosis induced by a high-cholesterol diet in rabbits. Most of these studies reported a statistically significant reduction in atheromatous lesions, particularly in the aorta, that averaged about 50%. The chronic effects of garlic on lipid metabolism in rats were also encouraging. The duration of

these studies was at least 4 weeks. Garlic (1–4% in diet) and garlic protein administration in hypercholesterolemic rats induced by a high-cholesterol diet, significantly reduced serum cholesterol, triglyceride and LDL cholesterol levels (Chang and Johnson, 1980; Rajasree *et al.*, 1999; Mathew and Daniel, 1996; Qureshi *et al.*, 1983; Kamanna and Chandrasekhara, 1982; Chi, 1982; Chi *et al.*, 1982) but had no effect on serum HDL. Total lipid content and cholesterol levels in liver were also decreased in rats after chronic garlic consumption. Since 1975, there have been more than 46 human studies on the lipid-lowering effects of garlic and garlic preparations. These studies were mostly randomized, double blind, and placebo-controlled using garlic powder rather than raw garlic for periods of 4–16 weeks, in hyperlipidemic patients. Most of these studies showed a significant decrease in serum cholesterol and serum triglyceride (Banerjee and Maulik, 2002). Only about one-third of these studies measured lipoproteins, where significant favorable changes in the LDL-cholesterol level (11–26% decrease) were consistently observed. A few studies using garlic powder (having low allicin yields) failed to show any lipid-lowering effects (Lutomski, 1984; Luley *et al.*, 1986). During the last decade, 18 clinical studies have been published regarding the hypolipidemic effect of garlic. Nine studies showed negative results, and garlic powder was used in seven of these studies (Simons *et al.*, 1995; Berthold and Sudhop, 1998; Isaacsohn *et al.*, 1998; McCrindle *et al.*, 1998; Byrne *et al.*, 1999; Rahman and Billington, 2000; Superko and Krauss, 2000; Gardner *et al.*, 2001; Ziaei *et al.*, 2001). The differences in the composition and quantity of sulfur components of different garlic preparations used in various studies could account for the inconsistent findings. It highlights the need for standardization of different garlic preparations. Other factors might also have affected the inconsistent results including subject recruitment, the duration of study, dietary control, lifestyle, and methods of lipid analyses (Warshafsky *et al.*, 1993; Silagy and Neil, 1994).

Four meta-analysis of randomized, placebo-controlled human studies on the hypocholesterolemic effects of garlic are available (Warshafsky *et al.*, 1993; Silagy and Neil, 1994; Neil *et al.*, 1996; Stevinson *et al.*, 2000). The analyses further detected that the extent of the cholesterol-lowering properties of garlic differed markedly from one study to another. Warshafsky and his colleagues deduced from five randomized clinical trials that hypercholesterolemic patients treated with garlic had a mean plasma cholesterol concentration that was 9% lower than that of patients treated with placebo (Warshafsky *et al.*, 1993). Silagy and Neil analyzed 16 trials, with data from 952 subjects in a meta-analysis (Silagy and Neil, 1994). Garlic, in powder and non-powder form, significantly lowered serum lipid levels over a 1–3 month period. Serum cholesterol fell by 8% with dried powder preparations and 15% with non-powder preparations. The serum triglyceride level also dropped

significantly, while HDL-cholesterol was essentially unchanged. Amongst the garlic powder preparations, these effects appeared to be similar across the daily dose-range of 600–900 mg. Another meta-analysis (Neil *et al.*, 1996) revealed that there was no significant difference in the mean concentrations of serum lipids, lipoproteins or apo A1 or B amongst the groups receiving garlic (900 mg/day of dried garlic powder standardized to 1.3% allicin) and placebo. In this meta-analysis, garlic was less effective in reducing TC than suggested by previous meta-analyses. However, in a more recent meta-analysis of 13 trials (Stevinson *et al.*, 2000), garlic reduced the TC level from baseline significantly more than placebo, while six diet-controlled trials with the highest scores for methodological quality revealed a nonsignificant difference between garlic and placebo groups. The available data suggest that garlic is superior to placebo in reducing TC levels. However, the size of the effect is modest, and the robustness of the effect is debatable. Therefore, the hypocholesterolemic effect of garlic remains to be firmly established (Banerjee and Maulik, 2002). The protective effect of garlic on atherosclerosis has been attributed to its capacity to reduce the lipid content of the arterial wall. Garlic causes direct anti-atherogenic (preventive) and anti-atherosclerotic (causing regression) effects at the level of the artery wall (Orekhov and Grunwald, 1997). Garlic depressed the hepatic activities of lipogenic and cholesterogenic enzymes such as malic enzyme, fatty acid synthase, glucose-6 phosphate dehydrogenase and HMG-CoA reductase (Yu-Yan and Liu, 2001). Garlic also increased the excretion of cholesterol, as manifested by enhanced excretion of acidic and neutral steroids after garlic feeding (Chi *et al.*, 1982). LDL isolated from human subjects given AGE (Munday *et al.*, 1999) and aqueous garlic extract (Lewin and Popov, 1994) was found to be significantly more resistant to oxidation. These data indicate that suppressed LDL oxidation may be one of the powerful mechanisms accounting for the benefits of garlic in atherosclerosis (LauBenjamin, 2001). The first investigated, active compound responsible for the anti-atherosclerotic effect was alicin, however, recent *in vitro* studies revealed that water-soluble organosulfur compounds, especially SAC, present in AGE and DADS, present in garlic oil are also potent inhibitors of cholesterol synthesis (Gebhardt and Beck, 1996).

IV CONCLUSION

Atherosclerosis is a complex disease, characterized by an excessive inflammatory, fibro-fatty, proliferative response to damage of the artery wall involving several cell types, particularly smooth muscle cells, monocyte-derived macrophages, T-lymphocytes and platelets (Schwartz *et al.*, 1993).

Hyperlipidemia constitutes a major etiopathological factor for atherosclerosis. Most recent findings indicate a multi-faceted cause to the problem of cardiovascular disease, including excessive intake of saturated fats, carbohydrate metabolic dysfunction, nutritional deficiencies, hormonal imbalance, and a high-stress lifestyle. Different people seem to oxidize cholesterol differently. In addition, certain mechanisms in the body may have gone awry, such as impaired liver LDL receptor uptake in FH. Lowering, but not eliminating, the intake of saturated fats is advisable. Nature has provided specific compounds capable of augmenting dietary and lifestyle changes for improved cardiovascular health and may afford a way to lower cholesterol without resorting to synthetic drug preparations and their potential side effects.

Atherosclerosis results from multiple complex interactions among injurious stimuli and the healing or reparative response of the arterial wall occurring in a hyperlipidemic and dyslipoproteinemic environment (Schwartz *et al.*, 1993). Events in the atherogenic cascade involve both environmental and genetic factors (Epstein, 1992). Despite the decline in rates of mortality due to heart diseases during the past two decades, cardiovascular diseases remain the most frequent cause of death (Carlson *et al.*, 1979). Several large clinical trials have established that regulation of dyslipidemia through diet or diet plus pharmacotherapy reduces the incidence of CHD events (Carlson and Bottiger, 1985). The association of raised serum cholesterol with cardiovascular disease is well known. Some studies suggest that elevated serum triglyceride may also be a risk factor (Carlson *et al.*, 1979; Carlson and Bottiger, 1985) especially in individuals with diabetes, since there is often a marked hyperlipidemia in diabetes (Beteridge, 1989). Moreover, diabetic patients experience a two-to-three-fold increase in cardiovascular morbidity and mortality when compared with nondiabetics. The beneficial effect of lowering elevated serum cholesterol levels on the prevention of CHD has been well established (Lipid Research Clinic Program, 1984). Dietary intervention has been recommended for all subjects with a LDL level of more than 160 mg/dl (Huttunen *et al.*, 1991). In addition to the quantity of fat and the polyunsaturated/saturated fat ratio, other dietary factors also play a role in the management of hyperlipidemia. Several studies have shown that dietary fiber, particularly soluble fiber, has considerable influence on serum cholesterol levels (Dreher, 1987; Miettinen, 1987).

Herbs have been used as medical treatments since the beginning of civilization and some herbal derivatives (e.g., aspirin, reserpine, and digitalis) have become a mainstay of human pharmacotherapy. For cardiovascular diseases, herbal treatments have been used in patients with congestive heart failure, systolic hypertension, angina pectoris, atherosclerosis, cerebral insufficiency, venous insufficiency, and arrhythmia. Scientific validation of several plant species has proved the efficacy of the botanicals in reducing the

cholesterol levels. From the reports on their potential effectiveness against hypercholesterolemia, it is assumed that the botanicals have a major role to play in the management of hyperlipidemia, which need further exploration for necessary development of drugs and nutraceuticals from natural resources (Mukherjee, 2001, 2002). However, many herbal remedies used today have not undergone careful scientific assessment, and some have the potential to cause serious toxic effects and major drug-to-drug interactions. Continuing research is necessary to elucidate the pharmacological activities of the many herbal remedies now being used to treat hyperlipidemia, atherosclerosis and other cardiovascular diseases.

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