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MINIREVIEW

NATURAL PRODUCTS WITH HYPOGLYCEMIC, HYPOTENSIVE, HYPOCHOLESTEROLEMIC, ANTIATHEROSCLEROTIC AND ANTITHROMBOTIC ACTIVITIES

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Summary

This article reviews compounds of botanical origin which are capable of lowering plasma levels of glucose and cholesterol and blood pressure, as well as compounds inhibiting atherosclerosis and thrombosis. Hypoglycemic natural products comprise flavonoids, xanthones, triterpenoids, alkaloids, glycosides, alkyldisulfides, aminobutyric acid derivatives, guanidine, polysaccharides and peptides. Hypotensive compounds include flavonoids, diterpenes, alkaloids, glycosides, polysaccharides and proteins. Among natural products with hypocholesterolemic activity are β-carotene, lycopene, cycloartenol, β-sitosterol, sitostanol, saponin, soybean protein, indoles, dietary fiber, propionate, mevinolin (β-hydroxy-β-methylglutaryl coenzyme A reductase inhibitor) and polysaccharides. Heparins, flavonoids, tocotrienols, β-hydroxy-β-methylglutaryl coenzyme A reductase inhibitors (statins), garlic compounds and fungal proteases exert antithrombotic action. Statins and garlic compounds also possess antiatherosclerotic activity.

Key Words: hypoglycemic, hypotensive, hypocholesterolemic, antiatherosclerotic, antithrombotic, natural products

Introduction

The serious health risks posed by hyperglycemia, hypertension and hypercholesterolemia need little elaboration, Diabetes mellitus, which manifests itself in hyperglycemia and other symptoms, would lead, if untreated, to a myriad of complications including retinopathy, neuropathy, coronary heart disease, stroke, etc. Hypertension and hypercholesterolemia may also result in cerebrovascular accident and myocardial infarction if not well taken care of.

Athrerosclerosis is thickening and hardening of the vessel walls due to soft deposits of intra-arterial fat and fibrin that harden over time. Hypertension results if atherosclerosis increases systemic vascular

resistance. Atherosclerosis contributes to coronary artery and cerebrovascular disease. Thromboembolic disease ensues if there is a fixed (thrombus) or moving (embolism) clot which obstructs flow within a vessel, reducing nutrient supply to tissues. Clots occuring in the brain, heart or lungs may cause death. In view of the untoward side effects that some of the drugs currently in use for therapy of the aforementioned disorders may produce, there is a need to search for new drugs. Natural products furnish a good source for such search. In fact, the fungal product mevinolin, a competitive inhibitor of β-hydroxy-β-methylglutaryl CoA reductase, is used to treat hypercholesterolemia (1), and a host of related drugs (statins) with antiatherosclerotic and antithrombotic properties has been developed. Biguanides such as metformin, which has been in use for the treatment of non-insulin-dependent diabetes mellitus, are derived from guanidine, another natural product (2,3). This article focuses on natural products with hypoglycemic, hypotensive, hypocholesterolemic, antiatherosclerotic and antithrombotic activities.

(A) Plants with Hypoglycemic Activity and Active Principles

Acacia arabica

Wadood et al (4) demonstrated that *Acacia arabica* seeds contained a substance(s) which depressed the blood glucose level in normoglycemic but not in alloxan-diabetic rabbits, suggesting that the mechanism of action involved release of insulin from pancreatic beta-cells.

Artemisia herba alba

Aerial parts of *Artemisia herba alba*, which is used in Iraqi folk medicine as an anti-diabetic therapeutic agent, exerted a significant hypoglycemic action on normoglycemic and alloxan-diabetic rats (5).

Cleome droserifolia

An extract of the plant suppressed the basal blood glucose level and also postprandial hyperglycemia in rats rendered glucose-intolerant with tetracycline. Potentiation of peripheral and hepatic insulin sensitivity and reduction of intestinal glucose absorption were implicated in the mechanism of hypoglycemic action of the plant extract. Additionally, the extract might possess anti-atherogenic activity in view of its ability to elevate the ratio of high density lipoprotein-cholesterol to low density lipoprotein-cholesterol in the blood (6).

Eugenia jambolana

The pulp extract as well as the seed extract of *E. jambolana* fruits displayed hypoglycemic activity although the action of the extract was much more speedy. Serum insulin level rose after oral administration of the extracts in normoglycemic and streptozotocin-induced diabetic rats. Insulin secretion from isolated islets of Langerhans from normal and diabetic rats was augmented after incubation with the extracts (7).

Ficus bengalensis

Similarly the bark extract of *F. bengalensis* possessed hypoglycemic activity. Insulin secretion was augmented as in the case of *E. jambolana* pulp and seed extracts (7).

A flavonoid which is a leucodelphinidin derivative was isolated from *F. bengalensis* by Geetha et al (8). Its hypoglycemic activity in normal and alloxan-induced diabetic rats was compared with that of the sulfonylurea glibenclamide.

Glossostemon bruguieri

Mucilage from the moghat *G. bruguieri* roots exerted a pronounced hypoglycemic action on diabetic rats, bringing the glucose level down to half of the pre-treatment level within 15 days. It is noteworthy that the powdered root of the plant has been in use traditionally in Eastern countries because of its nutritive and therapeutic value (9).

Lagerstraemia speciosa

Colosolic acid isolated from the plant activated glucose transport into Ehrlich ascites tumor cells and possessed hypoglycemic activity (10).

Lythrum salicaria

Torres and Suarez (11) reported the hypoglycemic activity of extracts of this plant. Lamela et al (12) subsequently reported that ethereal extracts of the stems and flowers induced hypoglycemia and enhanced insulin secretion in normoglycemic rats.

Momordica charantia

A polypeptide with 66 amino acid residues, designated polypeptide-P, was isolated from the fruits and seeds of *M. charantia*. It elicited hypoglycemia in gerbils, langurs and humans when administered subcutaneously (13). Two polypeptides from the seeds, with a molecular weight of approximately 90,000 and amino acid compositions distinct from that of insulin, displayed insulin-like (i.e. antilipolytic and lipogenic) activities in isolated rat adipocytes (14,15). Ali et al (16) examined the fruit pulp, seed and whole plant extracts of *M. charantia* for hypoglycemic activity in normal and diabetic rats. Saponin-free methanolic extract of pulp juice elicited hypoglycemia in normal rats and glucose-fed normal rats but was devoid of similar effects in streptozotocin-induced diabetic rates and glucose-fed normal rats either in the fasting or postprandial state. Similarly prepared extracts of seeds and the whole plant were ineffective. The results suggest that non-sapogenin compounds in the *M. charantia* fruit pulp produced hypoglycemia by augmenting insulin secretion from β cells or by potentiating the action of insulin.

Opuntia cactus

The plant extract brought about a lowering of blood glucose in pancreatectomized rabbits as well as normal rabbits. The plant has been traditionally used in Mexico for treating diabetes (17).

Panax ginseng

Ng and Yeung (18) reviewed the hypoglycemic and insulinomimetic principles in ginseng. Glycans designated panaxans A to E had been demonstrated to elicit hypoglycemia in both normal and diabetic mice. A fraction designated DPG-3-2 exerted its hypoglycemic action or provoked insulin secretion in diabetic and glucose-loaded normal mice while having no effect on normal mice. Adenosine, a carboxylic acid, and a peptide with a molecular weight of 1400 inhibited catecholamine-induced lipolysis in rat epididymal fat pads. EPG-3-2, a fraction related to DPG-3-2, also exhibited antilipolytic activity.

Petiveria alleaceae

Extracts of leaves and stems of the plant brought about over 60% reduction in blood glucose concentration one hour after oral administration in male Balb/c mice which had been fasted for 48 hours (19).

Phaseolus vulgaris

Hypoglycemic activity of the vegetal complex of *P. vulgaris* in experimental diabetes was demonstrated by Khaleeva et al (20).

Swertia chirayita

Swerchirin (1,8-dihydroxy-3,5-dimethoxyxanthone), a xanthone from the hexane fraction of *S. chirayita*, produced hypoglycemic activity in fasted, fed, glucose-loaded and tolbutamide-pretreated rats (21). Centipiperalone induced in normal rats hypoglycemia, elevation of plasma immunoreactive insulin level and β-cell degranulation. It was also active in streptozotocin-induced severely diabetic rats (22).

Swertia japonica

Five xanthones and two triterpenoids from the ethyl acetate-soluble fraction of *S. japonica* with hypoglycemic activity were isolated. Thysanolactone was a triterpene first isolated from *S. japonica*. One of the xanthones, bellidifolin, manifested a potent hypoglycemic activity in streptozotocin-induced diabetic rats (23).

Tecoma stans

T. stans is an allegedly antidiabetic medicinal plant in Mexico. Intravenous administration of *T. stans* infusion in normal dogs evoked an early hyperglycemic response probably due to hepatic glycogenolysis, followed by a slow decline of blood glucose level (24).

Teucrium polium

An aqueous decoction of the aerial parts of *T. polium* produced a decline in blood glucose level 4 hours after intravenous administration and 24 hours after intraperitoneal injection, probably by increasing peripheral metabolism of glucose and not by augmenting insulin release (25).

Other Hypoglycemic Plants and Active Principles

Day and Clifford (26) have compiled a list of plants with hypoglycemic activity and their active principles. They include polysaccharides produced by *Aconitum carmichaeli* root (designated aconitan A), *Anemarrhena asphodeloides* rhizome (designated anemaran A), *Dioscorea japonica* rhizophor (designated dioscoran C), *Lithospermum erythrorhizon* root (designated lithospermum B), *Panax ginseng* root (designated panaxan) and *Saccharum officinarum* stalk (designated saccharan C), *Amorphophallus korjac* tuber (glucomannan) and *Cyamopsis tetragonolobus* seed (galactomannan). Epicatechin (flavoniod) from *Pterocarpus marsupium* heartwood, alkaloids from leaves of *Catharanthus roseus*, *Coccinia indica* and *Tecoma stans*, *Lupinus terminis* seeds, glycosides from *Ficus bengalensis* bark, *Ficus religiosa* root bark and *Gymnema sylvestre*, leaves and aerial part of *Momordica charantia* were the other hypoglycemic products. Alkyldisulfides from *Allium cepa* and *Allium sativum* bulbs, hypoglycins (aminopropylpropionic acid dervatives) from unripe fruits of *Blighia sapida*, aminobutyric acid derivative from *Emericella quadrilineata* fruiting bodies and guanidine from *Galega officinalis* leaves were among the remaining anti–diabetic compounds cited. Of the aforementioned compounds, guanidine is toxic at high doses. However, biguanides and the antidiabetic agent metformin are derived from guanidine (2). Alkyl disulfides lack stability and hypoglycins are toxic, hence limiting their usefulness. Hypoglycemic polysaccharides may act within the intestinal tract to retard glucose absorption but they can also suppress blood glucose level when administered parenterally, suggesting a distinct site of action (see 26).

The papers referred to below (27-48) contain detailed information about the antidiabetic compounds covered in the article of Day and Clifford (26).

The following antidiabetic plants contained anti-hyperglycemic principles. *Cucurbita ficifolia, Guaiacum coulteri, Lepechinia caulescens, Crataegus pubescens, Cynodon dactylon, Calea zacatechichi, Buddleia americana, Bauhina divaricata, Coix lachryma, Marrubium vulgare, Psacalium peltatum* (49,50). *Opuntia streptacantha, Slanum verbascifolum, Teucrium cubense, Cecropia obtusifolia, Phaseolus vulgaris, Tecoma stans, Erivobotrya japonica, Salpianthus macrodonthus, Aloe barbadensis* (51), *Eleutherococus rhodiola* (52), *Trigonella foenum* (53), *Spinacea oleraceae, Cucumis sativis* and *Cuminum cyminum* (54). The structures of the active principles have yet to be elucidated. The reviews of Atta-ur-Rahman (55) and Bailly and Day (56) also include plants with antidiabetic activity.

Fungi with Hypoglycemic Activity

An acidic polysaccharide, composed of mannose, xylose, glucuronic acid and glucose in the molar ratio of 4:2:1:0.3 and possessing a molecular weight of 1500 kDa, was isolated from the hot-water extract of the fruiting bodies of *Tremella aurantia*. It demonstrated pronounced hypoglycemic activity in normal mice, streptozotozin-induced mice and genetically diabetic mice. No harmful effects were noted (57).

A highly branched glucuronoxylomannan from the fruiting bodies of *Tremella fuciformis* exerted a dose-dependent hypoglycemic action in normal as well as streptozotocin-induced diabetic mice. Plasma insulin level and hepatic activities of hexokinase and glucose-6-phosphate dehydrogenase were elevated while hepatic glucose-6-phosphatase activity was depressed (58).

A highly branched galactomannan elaborated by a *Pestalotiopsis* species, after intraperitoneal administration, expressed hypoglycemic activity in streptozotocin-induced diabetic mice and affected oral glucose tolerance in normal mice (59). It had a molecular weight of 24 kDa and a galactose: mannose ratio of 1:7. In addition to α-D-mannopyranosyl residues of a yeast mannan type, it possessed β-(1→3)–linked D-galactofuranosyl and non-reducing terminal β-D-galactofuranosyl residues.

TABLE 1
Some Hypoglycemic Natural Products

Name of compound	Type of compound	Plant of origin	Reference
Aconitan A	Polysaccharide	*Aconitum carmichaeli*	26
Anemaran A	Polysaccharide	*Anemarrhena asphodeloides*	26
Bellidifolin	Xanthone	*Swertia japonica*	23
Colosolic acid		*Lagerstraemia speciosa*	10
Dioscoran C	Polysaccharide	*Dioscorea japonica*	26
Emeriamine	Aminobutyric acid derivative	*Emericella quadrilineata*	26
Epicatechin	Flavonoid	*Pterocarpus marzupium*	26
Hypoglycins	Aminopropylpropionic acid derivatives	*Blighia sapida*	26
Leucodelphihidin derivative	Flavonoid	*Ficus bengalensis*	8
Lithospermum B	Flavonoid	*Lithospermum erythrorhizon*	26
Panaxan	Polysaccharide	*Panax ginseng*	18,26
Polypeptide-P	Peptide	*Momordica charantia*	13
Saccharan C	Polysaccharide	*Saccharum officinarum*	26
Swerchirin	Xanthone	*Swertia chirayeta*	23
	Polysaccharide	fungi	57-60

Kiho et al. (60) demonstrated hypoglycemic activity of a polysaccharide from cultured mycelia of *Cordyceps sinensis* in genetically diabetic mice, streptozotocin-induced diabetic mice and normal mice. However, plasma insulin level was unaffected. The polysaccharide was composed of galactose, glucose and mannose in the molar ratio of 62:28:10 and possessed a molecular weight of 45 kDa.

Some of the aforementioned hypoglycemic compounds are highlighted in Table 1.

(B) Plants with Hypotensive Activity and the Active Principles

Table 2 presents some of the natural products with known hypotensive action.

Andrographis paniculata

The n-butanol extract of the plant evoked in Sprague-Dawley rats a dose-dependent fall in mean arterial blood pressure without influencing the heart rate. The hypotensive action was not altered by propranolol, atropine and captopril, indicating that it was not mediated through effects on the β-adrenoceptor, muscarinic cholinergic receptor and angiotensin-converting enzyme. The hypotensive action was mediated by α-adrenoceptors, autonomic ganglion and histaminergic receptors because of the attenuating effect of phentolamine, hexamethonium, pyrilamine and cimetidine (61).

TABLE 2
Some Hypotensive Natural Products

Name of compound	Type of compound	Plant of origin	Reference
Chrysanthetriol	Sesquiterpene	*Chrysanthemium indicum*	64
Coleonol	Diterpene	*Coleus forskohlii*	65
Dicentrine	Aporphine derivative	*Lindera megaphylla*	69
Dihydrocorynantheine	Indole alkaloid	*Uncaria rhyncophylla*	76
Forskolin	Diterpene	*Coleus forskohlii*	66
Fusaric acid		*Fusarum spp.*	82
Gambirine	Alkaloid	*Uncaria callophylla*	75
Hyperin	Flavonoid	*Taxillus yadoriki*	74
Hirsutin, hirsuiteine	Indole alkaloids	*Uncaria rhynchophylla*	76
13-Hydroxylupanine	Alkaloid	*Cadia ellisiana*	62
2-pyrrolecarbonic acid			
Isorhynchophylline	Indole alkaloid	*Uncaria rhynchophylla*	76
Lectins	Protein	*Flowering plants and mushrooms*	77,81
Niaziminin A and B		*Moringa oleifera*	70
Quercitrin	Glycoside	*Taxillus yadoriki*	74
4(3H) Quinazolinone		*Strobilanthes cusia*	73
Rhynchophylline	Indole alkaloid	*Uncaria rhynchophylla*	76
Isorhyncophylline			
Dihydrocorynantheine			
Tetramethylpyrazine		*Ligusticum wallichii*	68
Yangambin		*Ocotea duckei*	71
β-Yohimbine	Indole alkaloid	*Amsonia elliptica*	
4[(4-O-acetyl-α-L-rhamnosyloxyl)-benzyl] isothiocyanate		*Moringa oleifera*	70

Cadia ellisana

The hypotensive potency of the alkaloid 13-hydroxylupanine-2-pyrrolcarbonic acid ester from the plant was higher in anesthetized dogs, monkeys and rats than that in conscious animals. In the isolated rabbit heart with intact accelerator nerves, perfusion with the alkaloid reduced norepinephrine release from nerve endings, diminished the positive inotropic effect and decreased the rise in heart rate brought about by electrical stimulation of the accelerator nerve. The alkaloid inhibited transmission of sympathetic impulse and attenuated sympathetic circulatory reflexes. The antifibrillatory effect of the alkaloid was also demonstrated (62).

Casimiroa edulis

An aqueous extract of the seeds suppressed rat aortic ring contractions induced by norepinephrine, serotonin and prostaglandin. An intact vascular endothelium was not required and histamine antagonists had no effect (63).

Chrysanthemum indicum

This is a traditional drug used for hypotensive purposes. Chrysanthetriol, a sesquiterpene, has been isolated. Whether it is the hypotensive principle remains to be elucidated (64).

Coleus forskohlii

The diterpene coleonol isolated from it lowered blood pressure in the anesthetized cat and the spontaneously hypertensive rat due to relaxation of vascular smooth muscle (65). The diterpene forskolin potentiated the effect of adenosine on coronary relaxation (66).

Cynomorium coccineum

Fresh juice and its water-soluble fraction displayed strong depressor activity (67).

Ligusticum wallichii

A calium antagonist, tetramethylpyrazine, was isolated. It blocked the entry of extracellular calcium through calcium channels and inhibited the release of intracellularly stored calcium in the vascular smooth muscle cell (68).

Lindera megaphylla

Dicentrine, an aporphine derivative and α_1-adrenoceptor antagonist, was isolated. Intravenous administration of dicentrine elicited a dose-related decrease in mean arterial pressure in anesthetized normotensive rats without affecting heart rate, cardiac output and stroke volume but markedly increasing tail blood flow (69).

Moringa oleifera

Niaziminin A, niaziminin B and 4-[(4'-O-acetyl-α-1-rhamnosyloxyl) benzyl] isothiocyanate from the ethanolic extract of *M. oleifera* leaves exhibited hypotensive activity (70).

Ocotea duckei

A specific platelet-activating factor (PAF) receptor antagonist, yangambin, was isolated. Yangambin pretreatment curtailed PAF-induced cardiovascular changes and thrombocytopenia (71).

Phyleanthus amarus

A preparation of the entire plant produced hypotensive effects on human subjects with mild hypertension (72).

Strobilanthes cusia

The alkaloid 4 (3H)-quinazolinone isolated from the whole plant exhibited hypotensive action (73).

Taxillus yardoriki

From the Japanese mistletoe *T. yadoriki* two known flavonoid glycosides, hyperin and quercitrin, were prepared. Their hypotensive activity was investigated (74).

Uncaria callophylla

The alkaloid gambirine produced a dose-dependent drop in systolic and diastolic blood pressures and heart rate. It exhibited a prompt onset of action (75).

Uncaria rhyncophylla

Indole alkaloids including hirsutine., hirsuteine, rhyncophylline, isorhyncophylline and dihydrocorynantheine produced hypotensive action in rats. Hirsutine manifested an antiarrhythmic action (76).

Some lectins from plants such as ricin, wheat germ agglutinin, concanavalin A and lentil lectin also manifested hypotensive activity (77).

Some of the more popular western herbs for treatment of hypertension include barberry, black cohosh, feverfew, mistletoe, motherwort, saffron and valerian (78). Plants with hypotensive, antiatheromatic and coronarodilating action include garlic, hellebore, olive, hawthorn and periwinkle (79, 80).

Extracts of various edible mushroom species including *Ganoderma lucidum*, *Grifolia frondosa*, *Lentinus edodes*, *Pleurotus sajor-caju* and *Volvariella volvacea* elicited a lowering of blood pressure in rats (see 81). One of the lectins, TML-1, isolated from cultured mycelia of the edible mushroom *Tricholoma mongolicum*, also possessed hypotensive action which was not mediated via autonomic ganglion transmission, α-adrenoceptors, β-adrenoceptors, cholinergic receptors, histaminergic receptors, nor the renin-angiotensin system. Its hypotensive action was probably mediated through vasorelaxation via adenosine A2 receptors and/or nitric oxide (endothelium-derived relaxing factor) (81).

The mycotoxin fusaric acid (5-butylpicolinic acid) elaborated by several *Fusarum* species exerted hypotensive activity (82).

The hypotensive activity of marine algae has been reported (83-84).

(C) Natural Products with Hypocholesterolemic Activity and the Active Principles

Beta-carotene and Lycopene

The hypocholesterolemic effect of beta-carotene and lycopene was studied by Fuhrman et al (85). Cholesterol synthesis from [3H]-acetate but not that from [14C] mevalonate in the macrophage cell line J-774A.1 was suppressed by beta-carotene or lycopene (10μM) and the hydroxymethylglutaryl (HMG)-CoA reductase inhibitor fluvastatin (10μg/ml). The activity of the macrophage low density lipoprotein (LDL) receptor was enhanced by all three compounds. Dietary supplementation with lycopene or carotenoids brought about a decline in plasma LDL-cholesterol level, probably by inhibiting macrophage HMG CoA reductase activity.

Extract of the Plant Cleome droserifolia

The plant extract reduced LDL-cholesterol and elevated the high density lipoprotein (HDL)-cholesterol/low density lipoprotein (LDL)-cholesterol ratio, indicating that it had anti-atherogenic value (6).

Cycloartenol and β-sitosterol

Ikeda et al (86) investigated the action of the trimethylsterol, cycloartenol, on cholesterol absorption and serum cholesterol level in rats. No synergism of cycloartenol with β-sitosterol in lowering plasma cholesterol level was discernible when both were included in a cholesterol (0.5%)-enriched diet. However, co-administration of cycloartenol and β-sitosterol ameliorated the reduction in apolipoprotein A-1 due to cholesterol feeding more effectively than β-sitosterol alone. Dietary β-sitosterol mitigated, and a combination of cycloartenol and β–sitosterol brought about a slightly greater reduction of hepatic deposition of cholesterol. Cycloartenol was less effective than β-sitosterol in correcting lipid abnormalities induced by dietary cholesterol. Intestinal cholesterol absorption was not affected by cycloartenol.

The plant sterol β-sitosterol lowered hepatic cholesterol level in rats and mice (87).

Lee et al (88) showed that plant sterols inhibited cholesterol absorption and reduced plasma cholesterol level in patients with type II hyperlipoproteinemia.

Sitostanol

Gylling et al (89) examined the efficacy of including sitostanol ester in margarine as a dietary treatment for children with familial hypercholesterolemia (FH). It was found that serum total cholesterol, intermediate density lipoprotein-cholesterol and LDL-cholesterol levels fell while the HDL-cholesterol/LDL-cholesterol ratio was elevated. The proportions of delta 8-cholesterol, lathosterol 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.

Miettinen and Vanhanen (90) studied the effects of small amounts of sitosterol, sitostanol and sitostanol esters dissolved in rapeseed oil on serum lipids and cholesterol metabolism in patients with

TABLE 3
Some Hypocholesterolemic Natural Products

Compound	Source	Reference
β-carotene	Carrots etc.	85
Lycopene	Tomatoes etc.	85
Indole-3-carbinol	Plants	99
β-sitosterol and sitostanol	Plants	90
Saponin	Plants	91
Silicon dioxide	Plants	91.,92
Soybean protein	Soybean	98
Dietary fiber	Beans etc.	93-97
Mevinolin	*Aspergillus terreus*	101
Polysaccharide	Fungi	58,60

primary hypercholesterolemia and various apolipoprotein E phenotypes on a rapeseed oil diet. A diminution in total cholesterol and LDL-cholesterol levels in serum was observed. Cholesterol absorption was reduced while there was a compensatory rise in cholesterol synthesis. The effects were most consistent in subjects with epsilon 4 allele.

Saponin

Price et al (91) have authored a review of saponins which are common in the plant kingdom. Among the diverse biological activities of saponins is their hypocholesterolemic action. Story et al (92) commented that saponin – cholesterol interaction was an important part of the hypocholesterolemic action of alfafa but interactions of bile acids with other components of alfafa might be equally important. Alfafa plant and sprout saponin bound significant amounts of cholesterol.

Soybean Protein

Nagata et al (93) demonstrated that soybean protein induced a reduction in serum apo A-1 and apo B with the relative concentration of HDL-cholesterol remaining at the higher level. The hepatic concentration of cholesterol was lowered. Forsythe et al (94) showed that plant proteins (50% from soybean meal and 25% each from corn and wheat) lowered plasma cholesterol level in young male pigs compared with animal proteins (90% from casein and 10% from lactalbumin). Carroll et al (95) observed that plasma cholesterol levels were lower when soybean protein was included in the diet of young, healthy, normolipidemic women. However, Neves et al (96) found that soy and alfafa proteins did not affect plasma total cholesterol and HDL-cholesterol when compared with purified animal proteins (casein, egg albumin, lactalbumin) and crude animal proteins (fish meal and blood meal).

Mokady and Liener (97) 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, no LDL, and a higher level of HDL.

Silicon Dioxide (Silica)

Silica occurs in plant cell walls and interstitial spaces. It decreased plasma total cholesterol, very low density lipoprotein (VLDL)-cholesterol and LDL-cholesterol (98).

Plant Indoles

Indole-3-carbinol induced a lowering of serum cholesterol level, and serum LDL-cholesterol/VLDL-cholesterol ratio (99).

Unsaturated Fatty Acids

Trans and cis fatty acids block fatty acid metabolism by competitively inhibiting delta-6-desaturase. On the basis of the available evidence, Booyens et al (100) commented that unnatural dietary trans and cis unsaturated fatty acid isomers should be reckoned as a definite risk factor in the etiology of coronary disease, despite an early report about the hypocholesterolemic activity of unsaturated fatty acids of plant origin.

Dietary Fiber

Fiber from food including khejri beans *(Prsopsis cinceria),* prepalbanti *(Ficus religiosa),* barbanti (*Ficus glomerata*) and teent (*Capparis decidua*) comprises cellulose, lignin, hemicellulose, teent and pectin. They affected the total lipid, cholesterol, triglycerides and phospholipids of the liver. Teent exerted the most conspicuous hypocholesterolemic effect, probably by increasing fecal excretion of cholesterol and bile salts (101).

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 decreased serum cholesterol and liver triglyceride level. No changes in hepatic histology in response to propionate intake were detected (102).

Mevinolin

Mevinolin, produced by the fungus *Aspergillus tereus*, competitively inhibits β-hydroxy-β-methylglutaryl Co A reductase, a key enzyme in the cholesterol biosynthetic pathway, and thereby lowers cholesterol level (1).

Fungal Polysaccharides

Polysaccharide CS-F30 from cultured mycelia of *Cordyceps sinensis* decreased plasma cholesterol level in mice (60). The glucuronoxylomannan from *Tremella fuciformis* fruiting bodies brought about a decline in plasma cholesterol level in mice (58).

Algal Extract

An extract of *Spirulina*, a unicellular filamentous blue-green alga for human consumption in Mexico and Central Africa, had hypocholesterolemic activity (103-104).

(D) Natural Products with Antiatherosclerotic and Antithrombotic Activities

Fenwick and Hanley (105) reviewed the antiatherosclerotic effect of onion and garlic (genus *Allium*) and their essential oils. Beretz and Cazenave (106) reviewed natural products with antithrombotic activity. Garlic (*Allium sativum*) inhibits platelet aggregation *in vitro* and *in vivo*, Flavonoids inhibit cyclic nucleotide phosphodiesterase and hence platelet aggregation. Hirudin, a polypeptide with 65 amino acid residues from the medicinal leech *Hirudis medicinalis*, potently inhibits thrombin.

The statins (HMG CoA reductase inhibitors) exhibit antiatherosclerotic and antithrombotic activities (107). They reduce the incidence of ischemic strokes in patients with a history of coronary artery disease (107) and slow pregression of coronary heart disease (108).

Palm oil tends to decrease thrombus formation. Tocotrienols, which are vitamin E-active constituents of palm oil, possess antithrombotic activity (109).

Heparins are a group of naturally occurring glycosaminoglycans characterized by anticoagulant activity. Unfractionated heparin and low molecular weight heparins such as dalteparin and tinzaparin (113) have been used in the prevention and treatment of thromboembolic disorders. The flowers of *Filipendula ulmaria* contained heparin bound to plant proteins. The neutralizing effect of protamine sulfate on the anticoagulant activity of the plant heparin was demonstrated (114). Bode and Franz (115) described the derivatization and anticoagulant activities of three heparinoid substances derived from three different types of plant polysaccharides. A non-proteinaceous sulfur-containing anticoagulant with electrophoretic, chromatographic and spectral properties resembling heparin was isolated from peony roots. It inhibited platelet aggregation (116). An anticoagulant factor with a molecular weight of 60 kDa was isolated from the leaves of a West African plant, *Aspilia africana* (117). The proteases tricholysine (triase) and longolytin isolated from the culture media of two lower fungi, *Tricholthecium roseum* and *Arthrobotrys longa*, displayed anticoagulant and fibrinolytic activities (118).

TABLE 4
Some Antiatherosclerotic and Antithrombotic Natural Products

Compound	Source	Activity	Reference
Onion and garlic compounds	Onion and garlic	Antiatherosclerotic and antithrombotic	105,106
Flavonoids	Plants	Antithrombotic	106
HMG CoA reductase inhibitors	Fungi and synthetic	Antiatherosclerotic and antithrombotic	107-108
Tocotrienols	Palm oil	Antithrombotic	109
Heparin	Plants	Antithrombotic	110-116
Streptokinase	Bacteria	Antithrombotic	106-118
Tricholysine	*Trichothecium roseum*	Anticoagulant	106-118
Longolytin	*Anthrobotrys longa*	Anticoagulant	118

The first generation of antithrombotic agents includes bacterial streptokinase and human urine urokinase (116-118). These molecules lack specificity for the fibrin clot, and thus an effort has been made to produce agents with higher fibrin clot selectivity using recombinant DNA technology (118).

Conclusion

Compounds with disparate structures but with the same pharmacological activity (i.e. hypoglycemic, hypotensive, hypocholesterolemic, antiatherosclerotic or antithrombotic activity) can be isolated from different plant species. Some of these compounds have been abandoned due to toxicity but other compounds apparently are devoid of adverse effects. Some of these active principles originate from edible plants. The inclusion in the diet of substances with hypoglycemic, hypotensive, hypocholesterolemic, antiatherosclerotic and antithrombotic activities would undoubtedly be of some value. It is hoped that as new additions are made to the list of these active compounds, researchers may one day come across compounds with the desired efficacy and devoid of or causing only minimal untoward side effects. The availability of more sophisticated chromatographic techniques will hopefully expedite the discovery of such drugs. In fact, cardiac drugs have been successfully developed from natural products. Besides, better QC/QA techniques, more sophisticated functional assays and high-throughput chip technologies could help to accelerate the commercial uses of these natural products.

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