Medicinal Plants and Hyperlipidemia

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Abstract

Hyperlipidemia is a well known risk factor for cardiovascular disease (CD). Coronary heart disease, stroke and atherosclerosis are among the primary cause of death. Several drugs are available for the treatment of hyperlipidemia. However, many of these therapeutic agents are associated with serious undesirable effects. Herbal medicine and food supplements can be an alternative approach due to lower cost and minimal adverse effects. Thousands of plants and herbal remedies have been screened for their hypolipidemic action, and several plants have been documented to have significant hypolipidemic effects. However, for the greatest majority of herbal medicine, there is still an inadequate knowledge about their mode of action, contraindications, potential side effects, and interactions with other drugs and other functional foods. The present review will focus only on selected edible medicinal plants for managing dyslipidemia and highlights some important challenges when It comes to safety concerns.

Introduction

Hyperlipidemia, the most common form of dyslipidemia, is a disorder characterized by elevated plasma levels of total cholesterol, triglycerides and low-density lipoproteins cholesterol (LDL-C). Low high-density lipoproteins cholesterol (HDL-C) is also another form of dyslipidemia. (1,2). Mixed dyslipidemia poses a high risk for cardiovascular disease (CVD), which is considered the number one killing disease in the US. Hyperlipidemia is classified into two types, primary or secondary (3, 4). Primary hyperlipidemia is familial and could be due to single gene defect. The secondary hyperlipidemia may develop from diet, certain medical conditions such diabetes, nephritic syndrome, chronic alcoholism, or associated with the use of certain medications like corticosteroids, oral contraceptives and beta blockers.(4,5). The guidelines for hyperlipidemia management have been developed to include pharmacotherapeutics and lifestyle adjustment (5, 3). The most adopted is the 2009 Canadian Cardiovascular Society Dyslipidemia guidelines through introducing the Framingham Risk Scores. (6).

There are several commercially available antilipidemic agents including statins, fibrates, bile acid sequestrants, niacin and ezetimibe. Statins, which are the most commonly used, decrease total cholesterol synthesis by inhibiting the HMG-coAreductase enzyme, but may cause serious adverse effects such as liver dysfunction and myopathy (7). Fibrates cause decrease TG and VLDL cholesterol levels, and increase LPL activity, but may increase the risk of pancreatitis, bile stones, and myopathy (8, 15). Bile acid sequestrants decrease cholesterol levels through increased conversion of cholesterol into bile (8) and can cause TG elevation and constipation. Nicotinic acid reduces TG, TC, LDL-C with an increases of HDL-C, and may cause flushing, hyperglycemia, hepatotoxicity and gout (8,9). Ezetimibe inhibits intestinal cholesterol absorption and usually combined with statins, and this combination may increase the risk of myopathy and hepatotoxicity. As a monotherapy, ezetimibe may cause GI disturbances and very serious hypersensitivity reactions including angioedema. Therefore, the aforementioned

agents are effective in lowering plasma lipids, but very often are associated with intolerable adverse effects. During the last decade, there has been an increase in the use of medicinal plants to treat different ailments including hyperlipidemia. Reported advantages of herbal medicines include effectiveness, safety, and low cost. The review below describes the use of selected edible herbs, and food supplements for the management of hyperlipidemia.

Curcuma longa

Curcumin is produced from Curcuma longa (turmeric) and used as food coloring and flavoring. It has many reported pharmacologic activities including anti-diabetic, anti-inflammatory (10), antioxidant and cancer preventative (11). As antilipidemic, it causes clearance of LDL-C by increasing the expression of LDL receptors and activity in hepatic cells. Curcumin was also reported to act as a scavenger of free radicals. (12). Studies have shown that supplementation of 1 gm/day for 30 days of curcumin led to significant reduction in serum TG levels (13). However, when curcumin was given at 1gm/day for 8 weeks to subjects with metabolic syndrome, it was shown to be more effective than placebo in reducing TC, LDL-C, TG, lipoprotein (a) and elevating HDL-Cconcentration (14) Similarly, hyperlipidemic rats treated for 30 days with 200mg/kg of curcumin exhibited a significant decrease in serum TC, TG, LDL-C and homocysteine levels as well as an increase in HDL-C level (15).investigated and proved to significantly decrease the level of free fatty acids, TC, TG, and leptin (16).

Fenugreek

Fenugreek (Trigonella foenum) is commonly consumed as a spice prepared from the dried seed. The plant is used to lower glucose and cholesterol (17). Recent studies showed significant hypocholesterolemic effects and anti-oxidant activity in cholesterol fed rats (18). Also, a dose of 200mg/kg to hyperlipidemic rats, fenugreek decreased TC (26.2%), TG (36.6%), plasma lipid peroxidation (33.9%), and normalized the activities of anti-oxidative enzymes (19)

Earlier studies suggested that the antilipidemic activity of fenugreek is attributed to its ability inhibit fat accumulation and induction of LDLR upregulation (20). Animal studies showed that fenugreek extract exerted preventive effect on fat accumulation and protection against induced hyperlipidemia and the effect of fenugreek treatment was comparable to that of Orlistat.(21). In humans, defatted and non-defatted fenugreek seeds showed reduction in lipid profile as proved by several clinical studies (22-27). In one study, doses of 25 or 50 grams per day for 20 days lowered significantly TG and TC and increased modestly levels of HDL-C (22). Another study showed that administering 100mg/day for 3 weeks to 15 non obese hyperlipidemic adults lowered both TG and LDL-C from baseline with a slight decrease in HDL-C levels (21). Long term study by the same research team in 60 patients with type 2 diabetes mellitus (DM) given 25 grams of fenugreek seeds per day for 24 weeks noted normal lipid profiles at the end of the study (25, 26). Consumption of 12.5-18 grams of germinated fenugreek seed powder for one month caused a significant reduction in TC and LDL-C without any change in TG, VLDL, and HDL-C levels (27). Similarly, significant decreases in TC and TG and no change in HDL-C, were observed when Bordia et al. investigated the effects of 2.5 grams of fenugreek given twice/day for 3 months to 40 subjects with coronary artery disease and type 2 DM (28). Few transient side effects of fenugreek were noted including gas, diarrhea and dizziness for the first few days (25). Also, some precaution should be exerted in cases of diabetes (23), and since fenugreek preparation may have coumarin derivatives, the risk of hemorrhage should be considered (29).

Cinnamon

Cinnamon *(Cinnamomun verum)* is a spice extracted from the inner bark of the tree. It is commonly used for fragrance and baking. Cinnamon is rich in antioxidants, which protect the body from free radicals. Cinnamaldehyde is a major component of cinnamon and believed to be responsible for the health benefits of the spice. The phenolic and polyphenolic content is similar to those found in berries and dark chocolate (30).

Animal studies showed that rats fed with 200 or 400 mg/kg of cinnamon had significant decreases in TC, TG, LDL-C and significant increase in HDL-C after 8 weeks of treatment (31). In a clinical study conducted by Blevins et al. (32) on individuals with type 2 diabetes, showed that 1 g of cinnamon daily for 3 months did not produce significant changes in fasting glucose, lipid, A1C, or insulin levels. However, an earlier clinical study by Khan et al. (33) showed that 1, 3, and 6 g daily dose of cinnamon were equally effective at lowering fasting glucose, total cholesterol, LDL-C, and TG levels in subjects with type 2 diabetes. A recent study by Chintana Sengsuk et al.(34) on 49 patients with T2DM given 500mg capsules of cinnamon 3 times daily (after meals) for 60 days showed a significant ($p<0.005$) decrease in glucose, TG, TG/HDL-C ratio, whereas HDL-C level was significantly increased ($p < 0.005$), compared to placebo group.

Black seed Nigella

Black seed *(Nigella sativa)*, also known black caraway or black cumin. It is widely used in Asia, Far and Middle East as a spice, food preservative, and for its beneficial health effects (35). The seeds have been reported to ameliorate of oxidative stress through free radical scavenging activity, reduction of blood glucose, and improving dyslipidemia (36). The antilipidemic effects of *N. sativa* were attributed to the inhibition of cholesterol absorption, decreased hepatic cholesterol synthesis, and up-regulation of LDL receptors. Asgary et al. (37) reviewed available literature from 6 clinical trials, where different preparations of N. sativa (100 mg -20 g daily seed powder, 20-800 mg daily of seed oil), and found out that all the preparations produced significant decreases in serum level of TC, TG, LDL-C, while the effect on HDL-C was not significant (37). The study also found out that all doses were well tolerated and without serious side effects. Similar findings were reported by Qidwai and Ashfaq (38) On the other hand, Ibrahim et al. (39) conducted a study on menopausal women supplemented with 1 g dose of *N. sativa* powder capsules after breakfast every day for a period of two months had significantly improved lipid profile in by decreasing TC, TG, and LDL-C while increasing HDL-C compared to placebo. A comparison study was conducted by Muneera et al. (40) to evaluate efficacy and safety between *N. sativa* and simvastatin on hyperlipidemic rats and found that both N. sativa and simvastatin treated groups showed similar significant improvement in lipid profiles. But unlike simvastatin, which was associated with elevated ALT levels, the N. sativa treated group showed normal liver function. These results suggest that N. sativa may be considered as a relatively safe and effective cholesterol-lowering agent.

Ginger

Ginger is the rhizome of the plant *Zingiber officinale* and a widely used spice and folk medicine. The characteristic odor and flavor is due to the mixture of zingerone, shogaols and gingerols. The effect of ginger on lipid levels in patients with hyperlipidemia has also been evaluated by Alizadeh-Navaei et al. (41) Forty five hyperlipidemic patients received ginger capsules 3 g/day in 3 divided doses, and another 40 patients received a placebo (lactose) for 45 days. Significant reductions in TG, TC, LDL-C, and VLDL and an increase in HDL-C were observed in the ginger treated group (41). The results demonstrated the antilipidemic effects of ginger. Ginger has been considered as safe food supplement and classified by US FDA as GRAS "generally recognized as safe". However, there are some reports that ginger cause mild gastrointestinal discomfort and may affect blood pressure and clotting. Animal studies by Shalaby et al. (42) on high fat fed rats given 400mg/kg of ginger caused a significant decrease in lipid profile; an effect was attributed to inhibition of intestinal absorption of cholesterol. When compared to atorvastatin, standard antilipidemic agent, ginger was even more effective in reducing hypercholesterolemia, especially at the 200 and 300 mg/kg doses (43).

Licorice

Licorice is a spice made from the dried root of a shrub *(Glycyrrhiza glabra)* from the legume family. It is native to southeast Europe, Asia and the Mediterranean region and used in the manufacture of licorice candy, chewing gum and a flavoring in sweets. Preclinical studies have shown that the use of licorice in hypercholesterolemic rats, high-fat rats, or high-fructose-fed rats, produced antioxidant, hypocholesterolemic and hypoglycemic actions (44-46). Glycyrrhizin, also known glycyrrhizic acid (GA), was identified as the main bioactive component of licorice. GA was found to possess mineralocorticoid activity and inhibit the enzyme, 11 beta-hydroxylase, involved in the biosynthesis of many steroids, including cholesterol. This could partially explain the rationale for its use to treat various metabolic disorders including dyslipidemia. Couple of clinical studies has evaluated the potential antilipidemic effects of licorice root in humans. The antiatherosclerotic actions of licorice extract been investigated by Fogelman et al. (47), which showed that the supplementation of hypercholesteromic patients with 0.2 g/day of ethanolic extract of licorice root for 12 months produced a decrease in TC and LDL-C with no significant changes in HDL-C compared to control group. The study supports earlier findings and advocates for the antiatherosclerotic actions of licorice and its use in preventive medicine.

Because of the mineralocorticoid activity of glycyrrhizin, some precaution should be exercised while using licorice products in cases of heart failure, hypertension, edema, kidney disease and hypokalemia (48). Patients are advised not to consume more than 4mg/day of pure glycyrrhizin. The content of glycyrrhizin in licorice roots varies from 2 to 20%.

Sage

Sage *(Salvia officinalis)* is an evergreen shrub native to the Mediterranean region and naturalized in all Europe. Sage tea is reported to possess antidiabetic, antiseptic, and anti-inflammatory effect on the oral cavity and gingivitis (49, 50). Clinical studies on 6 healthy females who had sage tea showed an improvement in the lipid profile including decreased TC and LDL cholesterol as well as increased HDL cholesterol, without any adverse effects (51). In a randomized placebo controlled parallel group study conducted on 40 hyperlipidemic type 2 diabetic patients given 500mg capsule of *S. officinalis* leaf extract

3 times per day for 3 months. Levels of HbA1c, TC, TG and LDL cholesterol were significantly decreased in the treatment group by 32.2%, 22.7%, 16.9%, 56.4%, and 35.6% respectively. HDL cholesterol level was increased by 27.6% without serious adverse effects (52). In a similar study, 67 hyperlipidemic patients received one 500mg capsule of sage leaf extract every 8 hours for 2 months. Similar results were observed where on TC, TG, LDL cholesterol, and VLDL levels, as well as increased HDL cholesterol without any significant change of SGOT, SGPT or creatinine. The above results suggest that sage tea/ extract in an effective and safe remedy for hyperlipidemia (53). Animal study by Lima et al. showed that sage tea drinking did not protect against carbon tetrachloride (CCl4) induced liver injury, but increased on the contrary. The study concluded that sage tea did not have a toxic effect on its own; but herb-drug interactions could be possible for such hepatotoxicity (54). However, a recent study on rosmarinic acid-enriched extract of *S. officinalis*, was shown to be effective in suppressing lipid oxidation (55).

Green tea

Green tea is made from unfermented *Camelia sinensis* leaves and subjected to same preparation process of black tea. The plant grows in China, India, Srilanka, Japan, Indonesia, Turkey and Pakistan. Green tea is known to be rich in phenols and polyphenols such as epigallocatechin, epigallocatechingallate, epicatechin, and epicatechingallate (56). Preclinical studies demonstrated the antioxidant and antilipidemic effects of green tea (56, 57, Ikeda, yang). Epigallocatechingallate was found to lower TC, LDL cholesterol and TG (58,59), when it is given for 60 days at a dose of 50mg/kg to high fat fed rats it resulted in a decrease in adipose tissue TG (60, 61). Recently, epigallocatechingallate present in green tea was found to be a potent inhibitor of human 11 beta-hydroxysteroid dehydrogenase enzyme, a microsomal enzyme involved in the steroid biosynthesis (62). A clinical study by Basu et al. (63) showed that consumption of green tea beverage (4 cups/day) and green tea extracts (2 capsules/day) for 8 weeks produced a decreasing trend in LDL-cholesterol and LDL/high-density lipoprotein (HDL), and significant decrease in body weight and body mass index versus controls. Another study by Nagoa et al, (64) showed that consumption of a green tea extract rich in catechins reduces body fat, LDL-C, and cardiovascular disease risks. However, overconsumption of green tea beverage/ extract may cause side effects ranging from mild to serious. Examples of serious side effects include sleep problems, vomiting, diarrhea, irregular heartbeat, tremor, heartburn, convulsions, and confusion. Also, there some evidence that green tea may reduce the intestinal absorption of iron from food (65).

Pursalane

Pursalane, also known as pigweed, is an annual tender plant belongs to the family Portulacaceae. It is common in Europe, Middle East, Asia, and Mexico and maybe eaten as a leaf vegetable with a salty and sour taste (66). The World Health Organization indicated purslane as one of the most widely used medicinal plant (67). The therapeutic value of the plant is related to the presence of high content of omega-3 fatty acids (67, 68). Assessed of lipid profiles before and after 45 days of taking 50-60 g/ day of purslane leaves or Lovastatin 20mg daily showed that the serum levels of TC, LDL cholesterol, and TG decreased significantly in both study groups. However purslane was superior to in decreasing serum TG when compared to Lovastatin (69). Also, in a triple-blinded randomized controlled Trial, the intake of 1 g/day of P. oleracea seeds for 1 month showed decreased levels of TC, LDL cholesterol and TG in dyslipidemic adolescents. This positive effect on serum lipid profile was attributed to the polyphenolic and antioxidant compounds (70).

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