Review Article

Chinese herbal medicine for treatment of dislipidemia

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Abstract Prevalence of dislipidemia is increasing rapidly in China and there has been a growing interest in Chinese herbal medicine for the treatment of hyperlipidemia both inside and outside China. In this article, lipids regulating effects of 9 herbs or their extracts and 5 herbal formulae which have been published in English-language literature are reviewed. Although evidence from animals and humans consistently supports the therapeutic activities of these Chinese herbal medicines, few multi-center large-scale clinical trials have been conducted to confirm the efficacy and evaluate their safety. (J Geriatr Cardiol 2009; 6:119-125)

Key words dislipidemia; traditional Chinese medicine; herbal medicine

Introduction

Serum levels of lipids and lipoprotein lipids are among the most potent and best substantiated risk factors for atherosclerotic diseases, particularly coronary heart disease (CHD).¹ In China, due to the rapidly changing in lifestyle, the prevalence of dislipidemia is increasing dramatically. Proper recognition and management of dislipidemia can reduce cardiovascular and total mortality rates.² Current lipids modulating medications include bile-acid sequestrants, fibrates, nicotinic acid, cholesterol absorption inhibitors, cholesteryl ester transfer protein inhibitors, phytosterols, oil fish and HMG-CoA reductase inhibitors.³ Clinically, statins have been the most widely prescribed drugs for hypercholesterolemia. Statins effectively lower the plasma concentration of low density lipoprotein (LDL) cholesterol (LDL-C) and reduce mortality and morbidity from CHD. However, many patients under statin treatment alone do not achieve the LDL-C goal suggested by the recent guidelines of the National Cholesterol Education Program’s Adult Treatment Panel III (ATP III). In addition, intensive statin therapy has been associated with increased incidence of discontinuation, hepatotoxicity and myalgia.⁴ Therefore, further lowering of LDL or non-high density lipoprotein (HDL) cholesterol (HDL-C) might require combination therapies or novel drugs.⁵

Dislipidemia is a modern disease. Most common dyslipidemias themselves only rarely cause symptoms or produce clinical signs that are evident on physical examination and require laboratory tests for detection. Thus, there were no counterpart records of dislipidemia in traditional Chinese medicine (TCM) literatures. During the past decades, however, there has been a growing interest in TCM treatment of hyperlipidemia and different TCM theories for the pathogenesis and pathology of hyperlipidemia have been proposed. In addition, hundreds of Chinese herbal medicines, whether in the form of monomers, compounds, crude extracts, single-herbs or formulae have been reported to be effective for the prevention and treatment of hyperlipidemia. In this article, we will limit our review only to those studies published in English. Although there have been extensive investigation to the mechanisms of actions by which herbal medicines regulating lipids metabolism, these, however, will be reviewed in a separate article.

Single herbs and extracted monomers with hypolipidemic effects

Up to now, hundreds of single Chinese herbs and extracted monomers have been reported to be able to affect lipid metabolism. Unfortunately, most of the studies were of inadequate or poor quality and had not been replicated by other researchers. Studies on several herbs, however, are relatively extensive.

Gynostemma pentaphyllum and gypenoside

Gynostemma pentaphyllum (Jiaoulan) is a perennial creeping herb, which belongs to the Cucurbitaceae family. The earliest record of the plant is in the book “Herbs for Famine,” which was published in the Ming Dynasty (1368-1644 A.D).⁶ In TCM, G pentaphyllum is indicated for heat clearing, detoxification, and as an anti-tussive and expectorant for relieving cough and chronic bronchitis. Gypenoside is a saponins extract derived from the G pentaphyllum.⁶ In poloxamer P407 induced hyperlipidemia rat model, Megalli and colleagues⁷ showed that acute (4
days) and chronic (12 days) pretreatment by gypenoside extract (250 mg/kg) significantly reduced triglyceride (TG) (53% and 85%, respectively) and total cholesterol (TC) levels (10% and 44%, respectively). In addition, Gynostemma reversed the P407 inhibition of lipoprotein lipase (LPL) activity in a concentration-dependent manner, with a 2-fold increase at ~10 μg/ml.

**Hawthorn fruit and triterpenic acids**

Hawthorn fruit has a long history of use as a medicinal plant in both China and Europe. In China, it has been documented as a food as early as the 700 B.C. The history and traditional uses of dry hawthorn in TCM are to relieve fullness that follows overeating or consumption of a fatty meal. Hawthorn extract has been used to treat the early stages of congestive heart failure and angina pectoris. It was also clinically effective in reducing blood pressure. In addition, hawthorn fruit significantly inhibited thromboxane A2 biosynthesis and platelet adhesion, thus reducing the formation of atheroma and thrombosis.

Several earlier studies showed that hawthorn decreased serum TC, LDL-C and TG in hyperlipidemic patients. Zhang et al. reported that in rabbits fed diet with high cholesterol diet (1 g/100 g, HC), hawthorn supplementation (2 g/100g) led to decreases in serum TC and TG of 23.4% and 22.2%, respectively, 50.6% less cholesterol accumulation in aorta and 23-95% greater excretion of neutral and acidic sterols. Hawthorn is rich in triterpenic acids [i.e. oleanolic acid (OA) and ursolic acid (UA)] and polyphenols (e.g. epicatechin, procyanidin B2, procyanidin B5, procyanidin C1, hyperoside, isoquercitrin and chlorogenic acid) (13). Recently, Lin, et al. demonstrated that OA and UA are particularly responsible for the cholesterol lowering effect of hawthorn.

**Danshen**

Danshen (Salvia miltiorrhiza) is one of the most versatile Chinese herbal drugs that have been used for hundreds of years in the treatment of numerous ailments including cardiovascular diseases. The lipids lowering effects of danshen had been reported in Chinese in dozens of animal experiments and clinical studies in the mainland of China. A recent study by Ji and Gong showed that the purified S.miltiorrhiza extract (PSME) at 150 mg/kg • d significantly lowered the concentrations of plasma TC, CDC-C and triglycerides, as well as concentrations of liver TC and TC in rats fed on high-fat/high-cholesterol diet, accompanied. PSME treatment also increased the concentration of serum HDC-C.

**Red yeast rice**

Red yeast rice is produced by solid-state fermentation of washed and cooked rice using the fungus Monascus purpureus. It has been used in China as a food preservative and colorant and for its medicinal properties since the Tang Dynasty (800 A.D). The extracts from red yeast rice contain starch, sterols, isoflavones, and monounsaturated fatty acids and other compounds and may contain lovastatin. Xuezhikang (XZK) and Zhibituo, two proprietary medicines independently developed in China, are capsules containing pulverized powder of fermented rice and yeast and are now used widely in the mainland of China as lipids lowering drugs.

A meta-analysis including 9,625 participants and three preparations (Cholestin, Xuezhikang and Zhibituo) showed significant reduction of serum TC levels (weighted mean difference -0.91 mmol/L, 95% confidence interval-1.12 to 0.71), TG levels (-0.41 mmol/L, -0.6 to -0.22), and LDL-C levels (-0.73 mmol/L, -1.02 to -0.043), and increase of HDL-C levels (0.15 mmol/L, 0.09 to 0.22) by red yeast rice treatment compared with placebo. The lipid modification effects appeared to be similar to pravastatin, simvastatin, lovastatin, atorvastatin, or fluvastatin. Compared with non-statin lipid lowering agents, red yeast rice preparations appeared superior to nicotinate and fish oils, but equal to or less effective than fenofibrate and gemfibrozil. In the China Coronary Secondary Prevention Study, a randomized, double-blind, placebo-controlled clinical trial, which enrolled nearly 5,000 patients who experienced a previous myocardial infarction to receive either placebo or to XZK daily for an average of 4.5 years, major coronary event that included nonfatal myocardial infarction and death from CHD were 10.4% in the placebo group and 5.7% in the XZK-treated group, with absolute and relative decreases of 4.7% and 45%, respectively. Treatment with XZK also significantly decreased CV and total mortality by 30% and 33%, the need for coronary revascularization by 1/3, and lowered TC and LDL-C lipoprotein cholesterol and TG, but raised HDC-C levels. A subgroup analysis of 1,445 elderly patients (aged 65 to 75 years) showed even more significant effects in reducing death from coronary events and all-cause mortality.

**Huanglian and berberine**

Huanglian (Rhizoma Coptidis) was recorded as a medication as early as 200 A.D. in The Herbal Classic of the Divine Plowman (Shen Nong Ben Cao Jing). In TCM, the major therapeutic activity of Rhizoma Coptidis is claimed for the treatment of infection and inflammation.

Berberine is the main bioactive compound in Rhizoma Coptidis. The content of berberine in Rhizoma Coptidis is 5.2%-7.7%. Since Rhizoma Coptidis is expensive, most berberine used in clinical application is prepared from herbs other than Rhizoma Coptidis, such as Berberis amurensis Rupr. and Phellodendron amurense Rupr. Berberine has many chemical forms, and berberine hydrochloride is the most common form. In China, berberine is an over-the-counter drug for the treatment of gastrointestinal infections, such as bacteriae diarrhea.

Effects of berberine on lipid metabolism have been
evaluated in animals and human subjects. In rats fed on high-fat diet, berberine was shown to decrease serum TG. TG deposition in liver and muscle was reduced significantly, and liver steatosis was prevented by berberine administration. In animal, berberine was shown to decrease TG, serum cholesterol and LDL-C markedly in hamster or diabetic rats fed with high-cholesterol diet. However, berberine seems to have little or no effects on HDL level.19, 20 Recently, berberine was demonstrated to reduce cholesterol. Two clinical trials demonstrated that berberine was able to decrease TG by 35% and 22%, serum cholesterol by 29% and 16%, and LDL-C by 25% and 20% in subjects with dyslipidemia.21, 22

Ginseng and ginsenosides

Ginseng is one of the most popular Chinese herbal medicines. In TCM, ginseng is only referred as the root of Panax ginseng C. A. Mey. However, the root of Panax quinquefolium L. (American ginseng) is also called ginseng sometimes. Ginseng contains many bioactive compounds. The representative compounds are ginseng-specific saponins (ginsenosides), which have clear bioactivities in the regulation of blood glucose and blood pressure. The total contents of ginsenosides are 2.6-6.6% of dry weight of ginseng roots in Asian ginseng, red ginseng (heated and marinated Asian ginseng) and American ginseng. The ginsenosides are divided into several different compounds, such as Rb1, Rb2, Rc, Rd, Re and Rg1.23

The lipid metabolism by ginseng was reported more than 20 years ago.24, 25 In one study, ginseng was administrated through diet supplement. American ginseng and Chinese red ginseng led to reduction of cholesterol and TG levels in liver and serum of avian. In rats and patients fed on high-cholesterol diet to generate hyperlipidemia, administration of red ginseng powder reduced plasma TC, TG, FFA, platelet adhesiveness, and increased HDL-C significantly.26 In a clinical trial, administration of ginseng extract led to reduction of TC, TG and LDL-C, and induction of HDL. These effects were attributed to the potent antioxidant effect of ginseng.27

Ginsenosides are considered as the active components in the regulation of lipid metabolism and body weight. In mice with diet-induced hyperlipidemia, ginsenosides had an additive effect to aerobic exercise in the regulation of lipid metabolism, and antioxidant capacity. In obese animals fed on a high-fat diet, ginsenosides isolated from ginseng are able to reduce food intake, fat composition and serum leptin level, prevent weight gain and increase in serum TG. 27, 28 However, opposite results were obtained by another group using mice. Injection of ginsenosides prepared from Korean red ginseng impaired lipid metabolism through inhibition of PPARα function.29 Thus, more experiments are required to evaluate the efficacy of ginseng on lipid metabolism.

Turmeric and curcumin

Turmeric (Curcuma longa) is a rhizomatous herbaceous perennial plant of the ginger family, Zingiberaceae. In TCM, turmeric has been used for the treatment of rheumatic diseases and dysmenorrhea for more than 1,000 years. Curcumin, a major active component of longa, has many pharmacologic activities including anti-inflammatory properties, powerful antioxidant activity, and cancer-preventive properties.30 Recent study showed that curcumin lowered blood glucose and glycated hemoglobin levels by lowering oxidative stress in diabetic rats, improved insulin resistance and glucose homeostasis in db/db mice.31 Ramirez-Tortosa et al.32 reported that in rabbit model fed on high cholesterol diet, oral administration of a turmeric extract at doses of 1.66 and 3.2 mg/kg body weight lower the level of TC. Interestingly, the lower dosage (1.6-mg) group had lower levels of cholesterol, phospholipids and TG in LDL than the higher (3.2-mg) dosage group. Asai and colleagues33 investigated the effects of dietary supplemented curcuminoids on lipid metabolism in rats and found liver TG and cholesterol concentrations were significantly lower in treatment rats than in controls. Plasma TG in the VLDL fraction were also lower in treatment group than in control group. Manjunatha and Srinivasan also showed the hypolipidemic and antioxidant effects of curcumin (0.2%, wt/wt) in high-fat (30%)-fed rats.34 More recently, Jang et al.35 reported that curcumin exhibits an obvious hypolipidemic effect by increasing plasma paraoxonase activity, ratios of HDL-C to TC and of apo A-I to apo B, and hepatic fatty acid oxidation activity with simultaneous inhibition of hepatic fatty acid and cholesterol biosynthesis in high-fat-fed hamsters.

Gegen and puerarin

There are two components of Pueraria lobata (or in Japanese, Kudzu) that are utilized in traditional medicine, including the flower, Flos Puerariae, and root, Radix Puerariae (gegen). Gegen is one of the earliest medicinal plants used in TCM. Gegen has been demonstrated to have effects on treatment of fever, liver diseases and cardiovascular diseases. In China, gegen is also used as a health supplement for reducing risk factors of cardiovascular diseases.36 Puerarin is one of the major isoflavonoid compounds isolated from gegen. Puerarin has been reported to stimulate bone formation, prevent cell injury in rodent diabetic models, act as a nerve growth factor, and exert a vasodilatory influence.37

Yan et al.39 reported that in Sprague-Dawley rats fed with hypercholesterolemic diet, oral administration of puerarin (300 mg/kg/day) markedly attenuated the increase in TC in both serum and liver and caused a significant reduction in the atherogenic index. Guan and colleagues40 compared the hypolipidemic activity of Gegen phytoestrogens with that of soybean phytoestrogen in es-
trogen-and androgen-deficient hamsters. They randomly divided ovariectomized female or castrated male hamsters into groups receiving soybean or Gegen phytoestrogen extracts (30 mg/kg of body weight) per day. Their results showed that the ovariectomized hamsters orally given soybean and Gegen phytoestrogen extracts had significantly decreased serum TC and non-HDL-C with HDL-C being unaffected in ovariectomized female. Administration of Gegen phytoestrogen extracts did not significantly lower serum TC in castrated male rats, but caused redistribution of cholesterol among lipoproteins, leading to a significant decrease in the ratio of non-HDL-C to HDL-C.

Soy and soy isoflavones

Perhaps the most extensively studied and most widely used herb or diet supplement for cardiovascular disease prevention in recent years, soy bean also has a long history of medicinal use in China, mainly for its effect of detoxification. An early meta-analysis demonstrated the consumption of soy protein rather than animal protein significantly decreased serum concentrations of TC, LDL-C, and TG. The result showed that ingestion of 47 g soy protein/d reduced serum TC by 9.3%, LDL-C by 12.9% and TG by 10.5% and increased HDL-C by 2.4%. More recently, another meta-analysis of 11 studies published from 1990 to 2006 showed that soy isoflavones significantly decreased serum TC by 0.10 mmol/L (3.9 mg/dl or 1.77%) and LDL cholesterol by 0.13 mmol/L (5.0 mg/dl or 3.58%), but no significant changes in HDL-C and TG were found. Furthermore, the results showed that soy protein that contained enriched isoflavones significantly decreased LDL-C by 0.18 mmol/L (7.0 mg/dl or 4.98%) and increased HDL-C by 0.04 mmol/L (1.6 mg/dl or 3.00%). Ingesting 102 mg soy-derived isoflavones/d, independent of the amount of soy protein ingested, for 1-3 months would lower TC by a mean of 0.10 mmol/L (1.77%) and LDL-C by a mean of 0.13 mmol/L (3.58%). The reductions in LDL-C were larger in the hypercholesterolemic subgroup than in the normocholesterolemic subgroup.

Herbal formula in the treatment of hyperlipidemia

For many diseases, such as cancer and many other complex diseases, treatment regimen containing multiple drugs with distinct but related mechanisms can usually amplify the therapeutic efficacies of each agent, leading to maximal therapeutic efficacy with minimal adverse effects. Studies have shown that for the treatment of hyperlipidemia, combination of different agents, such as niacin lovastatin and ezetimibe atorvastatin, might result in a more global improvement of lipid profile.

TCM prefers combining different medical herbs into one therapy through formulae. According to TCM, a disease may have a set of identical symptoms among different patients, but the background for development of the same disease is quite different in patients. In the individualized treatment, multiple herbs are often prescribed to form a special formula and single herb is not often used individually. This individualized approach to treatment, or treatment based on syndrome differentiation, is one of the characteristics of TCM. Typically, formulae consist of several types of medicinal herbs or minerals, in which one represents the principal component, and others serve as adjuvant ones to assist the effects or facilitate the delivery of the principal component. It is believed that, at least in some formulae, multiple components could hit multiple targets and exert synergistic therapeutic efficacies.

Currently, one of the widely accepted TCM theories for the pathogenesis of dislipidemia is the so-called “turbid-phlegm and blood stasis theory”. According to this theory, lipid metabolism disorders mainly involve with two organs, namely, Shen (肾) and Pi (脾). The pathological changes originate from Gan (肝)-Shen deficiency or congenital Pi-deficiency which causes inner accumulation of dampness-phlegm to block Qi circulation and further leads to blood stasis. One of us (Guo J), based on clinical observation of thousands of patients with dislipidemia, proposed that the organ “Gan” could play a pivotal role in the development of dislipidemia, and stagnation of “Gan-Qi” is the underlying mechanisms. Several formulae were designed according to this hypothesis and clinically used for the treatment of hypercholesterolemia, hypertriglyceridemia, and their related diseases. Several observational studies have shown excellent efficacy and safety and a large, randomized clinical trial is ongoing to test this theory.

In addition to dozens of herbal formulae that were reported in Chinese-language journals, several recipes of Chinese herbal medicine which have lipsids regulating effects have been experimentally explored outside China, although few have been clinically observed.

Kangen-karyu

Kangen-karyu (Guanyuan Keli) is a traditional Chinese herbal prescription which has been widely used and extensively investigated in Japan for more than two decades. It comprises six crude drugs: Paeoniae Radix (Baishao), Rhizoma Cnidii (chuaxiong), Carthami Flos (Honghua), Rhizoma Cyperi (xiangfu), Radix Aucklandiae (Muxiang), and Radix Salviae Miltiorrhizae (Danshen). This prescription is now available in granule and is commonly used to treat symptoms related to “blood stasis”. In addition, it has received much attention due to its numerous biological activities, such as inhibition of platelet aggregation, suppression of hypertension and anti-aging.

In a study using diet-induced hypercholesterolemic rat model, Yokozawa et al. found that serum levels of LDL-C were lowered and the HDL-C level was significantly increased by administration of Kangen-karyu extract. The same group also found that Kangen-karyu extract could improve...
hyperglycemia, hyperlipidemia, and hypertension in fructose-induced metabolic syndrome or streptozotocin-induced diabetic rat model and might play a protective role against metabolic syndrome or diabetes.\textsuperscript{51}

**Danggui-Buxue-Tang**

Danggui-Buxue-Tang (DBT) is a very popular TCM prescription which contains Angelica sinensis (danggui) and Astragalus membranaceus (huangqi) at a ratio of 1: 5. DBT is used widely in China for stimulating red blood cell production and enhancing cardiovascular function.\textsuperscript{52} Zhang et al.\textsuperscript{53} found that oral administration of DBT (3 or 6g/kg/day for 4 weeks) could regulate blood lipid, decrease TC, TG, and LDL-C in diabetic atherosclerosis rats which were induced by nitric oxide inhibition (L-NAME in drinking water, 1mg/ml) plus high-fat diet.

**Da-Chaihu-Tang**

Da-Chaihu-Tang (DCT) is an ancient Chinese herbal prescription that has been used for the treatment of acute abdominal diseases, including acute cholecystitis and cholangitis for almost 2 thousand years.\textsuperscript{54} It is now often used as an anti-obese drug, particularly in Japan. Early studies suggested that DCT might reduce hypercholesterolemia induced by a high cholesterol diet or that associated with aging in rats. Yoshie et al.\textsuperscript{55} investigated the antihypercholesterolemic effects of DCT in female heritable Kuroswa and Kusanagi-hypercholesterolemic (KHC) rabbits. They found that plasma TC levels were significantly decreased in the groups administered DCT 1.0 g/kg per day or pravastatin for 4-24 weeks, whereas there were no change with plasma phospholipid and TG levels. DCT treatment also significantly decreased plasma LDL-C levels, but had no effect on either VLDL- or HDL-cholesterol levels. Two other studies, however, did not show significant effects of DCT on serum lipids levels, either in high-fat diet-fed male KK/ Ta mice or in spontaneous familial hypercholesterolemia (FH) model and KHC rabbits.\textsuperscript{56, 57}

**Guizhi-Fuling-Wan**

Guizhi-Fuling-Wan (GFW, or in Japanese, Keishibukuryogan) is composed of 5 herbs: Cinnamomum cassia Prese (Cortex Cinnamomomi), Paeonia lactiflora Pallas (Radix Paeoniae), Paeonia suffruticosa Andrews (Cortex Moutan Radicis), Prunus persica Batsch (Semem Persicae) and Poria cocos Wolf (Hoelen). Traditionally, it was used for the treatment of pelvic inflammatory disease or tumor in women in China, and for blood stagnation (including atherosclerosis) in Japan.\textsuperscript{58}

Nakagawa et al.\textsuperscript{59} have examined the effects of GFW on glucose and lipids metabolism in Otsuka Long-Evans Tokushima Fatty (OLETF) rats, an animal model of type 2 diabetes. They found that oral administration of GFW produced significant improvement against impaired glucose tolerance while fasting serum glucose and insulin levels, and the homeostasis index of insulin resistance did not change by GFW treatment. GFW significantly lowered serum TC and TG levels and hepatic TC level. Using cholesterol-fed non obese rabbit model of non-alcoholic fatty liver disease, Fujimoto and colleagues\textsuperscript{60} also found that treatment with 1% GFW were associated with significant amelioration of lipid profiles, including decreased TC, LDL-C, and TG levels, but no difference of HDL-C level was observed between the GFW treated group and controls. However, an earlier study by Sekiya et al., also using cholesterol-fed rabbit, did not found treatment with GFW for 8 weeks could affect serum lipids levels of rabbit.\textsuperscript{61}

**Daming Capsule**

Among dozens of Chinese herbal prescriptions claimed with hypolipidemic effect, few have been investigated in randomized clinical trial. Recently, Yang et al. reported a randomized, multi-center, open-label, parallel-group trial of Daming capsule (DMC), which composed 6 herbal medicines (Rheum officinale Baill. Cassia obtusifolia L. Salvia miltiorrhiza, Citrus reticulata Blanco, Ginseng, Poria cocos Wolf), in Chinese patients with hyperlipidemia. Sixty enrolled patients with hyperlipidemia allocated to six medical centers were randomly divided into two groups. One group received DMC 2g b.i.d. for 6 weeks, and the other received pravastatin 10mg o.d. for 6 weeks. Serum TC, TG, LDL-C and HDL-C were measured before and after drug treatment. Their results showed that serum TC and LDL-C levels in the DMC-treatment group were significantly decreased compared with those before treatment ($P < 0.05$), while TG and HDL-C levels did not change much. Eight patients experienced diarrhea during DMC treatment and two experienced myalgia and epigastric discomfort during pravastatin treatment.

**Conclusions**

Historically, natural products have provided an endless source of medicine. As a unique system in complementary and alternative medicine, TCM holds great potential in the control of lipid metabolism and is promising to provide new effective therapies. The hypolipidemic activities of many Chinese herbal medicines have been proved in well-designed animal experiments. Mixtures of interacting compounds produced by plants may provide important combination therapies that simultaneously affect multiple pharmacological targets and provide clinical efficacy beyond the reach of single compound-based drugs. At present, what seems most important is to evaluate their efficacy and safety by well-designed, large-scale clinical trials, and then to investigate the underlying mechanisms using cutting edge technology.
References

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