MEDICINAL PLANTS FOR THE PREVENTION AND TREATMENT OF CORONARY HEART DISEASE

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Summary

Statistics from the World Health Organization indicate that the burden of chronic diseases, including coronary heart disease, cancers, diabetes and obesity contributes 59% of the 56.5 million deaths reported in 2001. With coronary heart disease (CHD) ranking as the primary contributor to morbidity and mortality worldwide, it is not surprising that a great deal of research is now focused on identifying new therapeutic alternatives to prevent and treat this disease. With the caveat that the most consistent recommendations from a public health perspective involve multiple changes in diet and exercise, medicinal plants are also a viable option for the treatment and prevention of CHD. While there are literally hundreds of plants used around the globe used traditionally for the treatment of CHD, very few of these plants have been thoroughly scientifically investigated. However, some medicinal plants have sufficient pre-clinical and more clinical data, indicating that these botanical dietary supplements and their constituents have a possible use in strategies to reduce the prevalence and mortality of cardiovascular disease either in the general population or subsets of individuals at high risk. Some well-investigated examples include artichoke, garlic, ginkgo, guggul, hawthorn, and tea. For these plants significant preclinical and clinical data exist indicating that these botanicals may be beneficial in the prevention and treatment of CHD. The focus of this review will be primarily on those medicinal plants used traditionally to treat CHD that have some evidence of effect in human studies or that have a preclinical data base sufficient to warrant clinical evaluations.

1. Introduction

According to the World Health Organization, the burden of chronic diseases, including coronary heart disease (CHD), cancers, diabetes and obesity contributed 59% of the 56.5 million deaths reported worldwide in 2001. With CHD ranking number one as the main contributor to morbidity and mortality worldwide, there is a significant interest in identifying plants that have cardioprotectant and cardiotonic activity, as well as the phytochemicals responsible for these activities. To date, the evidence suggests that the health benefits of complex plant constituents are even more considerable than we

thought due to the large numbers of phytochemicals present in each plant. New evidence suggests that in order to understand the health benefits of plant-based supplements and foods, we will need to take into account the fact that complex mixtures of phytochemicals found in foods and other botanicals may act synergistically. These new revelations may in time dispel the "magic bullet theory", which suggests that only pure compounds are the most efficacious. There is also no doubt that the emerging new fields of nutrigenomics and pharmacogenomics will play an important role in determining the interaction of these complex substances with the genetic variability of individuals and will determine the individual response and its magnitude to phytochemicals.

1.2. Coronary Heart Disease and treatment

Coronary heart disease includes all diseases of the circulatory system including acute myocardial infarction, ischemic heart disease, valvular heart disease, peripheral vascular disease, arrhythmias and stroke. While the dietary association with CHD is clearly important, several genes and variants have been associated with increased CHD risk, including some encoding components for the renin angiotensin system, and mutations in the genes encoding the hepatic low-density lipoprotein LDL receptor protein, apolipoprotein E, lipoprotein lipase and interleukin-6 and leptin. Thus, future food and medicinal plant research should focus on the assessment of how phytochemical constituents interact or regulate the expression of these genes.

Globally, there are literally hundreds of plant-based medicines used in traditional systems of medicine for the treatment of CHD and its sequelae. The majority of these plants are used alone or in combination with other herbs. Most of these plant-based medicines have not been scientifically investigated and there is little scientific or clinical data supporting their therapeutic use. However, for some specific botanicals (dietary supplements and herbal medicinal products) there are significant clinical data suggesting that the use of these products may reduce chronic disease prevalence and mortality either in the general population or subsets of individuals at high risk. With the caveat that the most consistent recommendations to the general public for CHD prevention includes multiple changes in diet and exercise, several botanical dietary supplements including: artichoke (*Cynara scolymus*), garlic (*Allium sativus*), ginkgo (*Ginkgo biloba*), guggul (*Commiphora mukul*), hawthorn (*Crateagus* species), red wine (*Vitis vinifera*), saffron (*Crocus sativa*), and tea (*Camellia sinensis*) may also be beneficial and will be highlighted in this review.

2. Artichoke (*Cynara scolymus*).

Officially, medicinal artichoke products consist of the dried radical leaves of *Cynara scolymus* L. (Asteraceae). However, the fresh lower part of the flower head is also official in the African Pharmacopoeia and is used in African traditional medicine. Artichokes, while native to Mediterranean northern Africa, southern Europe, and the Canary Islands, are cultivated in other subtropical regions of the world. The plant contains up to 6% phenolic acids, including 3-O-caffeoquinic acid (chlorogenic acid), caffeic acid, 4-O-caffeoquinic acid, 5-O-caffeoquinic acid, 1,3-di-O-caffeoquinic acid, 1,5-di-O-caffeoquinic acid (cynarin); up to 5% sesquiterpene lactones, with cynaropicrin being the primary component followed by dehydrocynaropicrin,

grosheimin and their derivatives; and flavonoids (0.35-0.75%) including scolymoside, cynaroside and cyanotrioside (see Figure 1). While the plant and its preparations are commonly used to treat dyspepsia, it is also used traditionally for the prevention and treatment of atherosclerosis and kidney dysfunctions (diuretic).

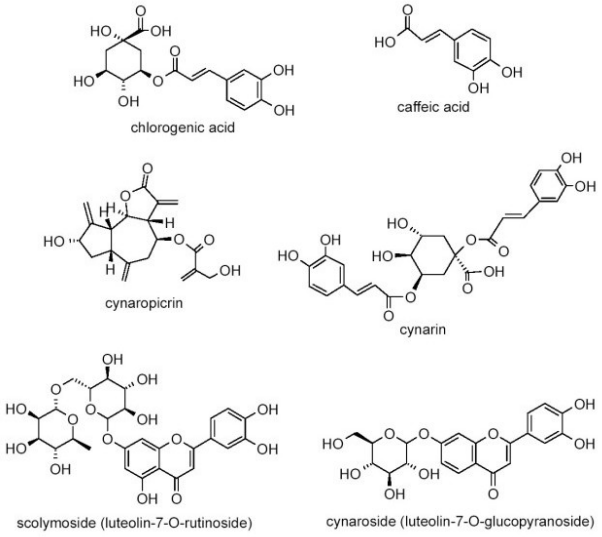

Figure 1. Structures of phytochemicals from artichoke.

2.1. Clinical studies

Two randomized controlled clinical trials assessed the effects of an artichoke extract on cholesterol levels in 187 patients. In a double-blind, randomized, placebo-controlled comparative study, the lipid lowering effect of an extract of the crude drug was assessed in 44 healthy volunteers. The volunteers were randomly assigned to receive either 640 mg of the extract or placebo for 12 weeks. No significant difference was observed in total cholesterol levels in healthy subjects treated with placebo or the extract for twelve weeks. However, in a subset of patients with a cholesterol level above 220 mg/dl, treatment with the extract reduced total serum cholesterol levels.

A second placebo-controlled trial assessed the safety and efficacy of an extract of the leaves (crude drug/extract ratio 25-35:1, aqueous extract) as coated tablets containing 450.0 mg extract (CY450). Patients (n = 143) with hyperlipoproteinemia having an initial total cholesterol of > 7.3 mmol/l (> 280 mg/dl) received 1.8 g artichoke dry extract per day or placebo over 6 weeks. Changes of total cholesterol and low-density lipoprotein (LDL)-cholesterol from baseline to the end of the six-week treatment period showed a statistically significant superiority (P = 0.0001) of artichoke dry extract over placebo. Observed reductions in total cholesterol levels were 18.5% in the extract treated group and 8.6% in the group treated with placebo. LDL-cholesterol decrease in the CY450 group was 22.9% and 6.3% for placebo. LDL/HDL ratio showed a decrease of 20.2% in the CY450 group and 7.2% in the placebo group. There were no drug related adverse events reported.

Several uncontrolled studies found that cynarin, a chemical constituent of artichoke, reduced total serum cholesterol in patients after treatment with oral doses of 750 to 1500 mg per day. Oral administration of cyanarin in a dose of 1000 mg/day for 4 weeks

resulted in a significant decrease (15%, $P < 0.005$) in total cholesterol in 17 patients. In a controlled trial 2 groups of 30 patients presenting various dislipidemic pictures were treated for 50 days with either 3,5-dihydroxy-1,4-bis-(3,4-dihydroxy-cinnamoyloxy)-cyclohexan-carbonic acid (cynarin) or placebo. Cynarin proved to be able to induce a significant reduction of the hypercholesteremia, the level of pre-beta-lipoproteins, the beta/alpha-lipoprotein ratio and patients' body weight. A post-marketing survey was conducted and involved 557 patients treated with 1.5 g of the extract for an average treatment period of 43.5 days. In patients whose cholesterol levels were routinely determined ($n = 302$), serum cholesterol and triglyceride levels were significantly decreased ($P < 0.001$).

2.2. *In vitro* and *in vivo* studies

Aqueous artichoke extracts inhibit cholesterol biosynthesis from ^{14}C-acetate in primary cultured rat hepatocytes in a concentration-dependent biphasic manner with moderate inhibition (approximately 20%) between 0.007 and 0.1 mg/ml and stronger inhibition at 1 mg/ml. Replacement of ^{14}C-acetate by ^{14}C-mevalonate largely prevented the inhibitory effects of the extracts indicating an inhibition of the activity of hydroxymethylglutaryl-CoA-reductase (HMGCoA-reductase). Stimulation of HMGCoA-reductase activity by insulin was effectively blocked by the extract at the same concentrations. Cynaroside, a flavonoid glycoside and its aglycone luteolin, both constituents of the extract, were primarily responsible for the inhibition of HMGCoA-reductase activity.

In vivo, the effect of an artichoke extract on the progression of atherosclerosis was investigated in rats (four groups of 10) fed a high cholesterol diet. One group received 110.0 mg/kg body weight (bw)/d of the powdered leaves, another 80.0 mg/kg bw/d of powdered *Cynara cardunculus*, the 3rd group 10.0 mg/kg bw/d heparaxal, and the 4th served as the control. Tissue examination after 120 days of treatment showed that the extract prevented formation of atherosclerotic changes, prevented serum cholesterol increase, caused a decrease in lipid phosphate, slightly increased the level of glycoproteins in the blood, prevented serum γ-globulin increase, decreased albumin, glycoproteins, and liver cholesterol, and increased γ-globulin and γ-globulin fractions. *C. cardunculus* showed a similar, but 60% weaker action. A methanol extract of the crude drug was shown to reduce serum triglyceride levels in olive oil-loaded mice. Oral administration of the extract, at a dose of 125 to 500 mg/kg bw/d, significantly suppressed serum triglyceride (TG) elevation 2 h after administration of olive oil. In contrast, 6 h after administration of olive oil, increases in TG level were observed in the groups that received the extract at doses of 125 and 250 mg/kg bw/d. Orlistat, a lipase inhibitor, completely suppressed the serum TG elevation at 250 mg/kg bw/d. Clofibrate, a hypolipidemic medicine, also suppressed the TG level at 250 and 500 mg/kg bw/d. Three sesquiterpenes, cynaropicrin, aguerin B, and grosheimin were isolated as the active components of the artichoke extract.

Aqueous and ethanol artichoke extracts also reduced intracellular oxidative stress stimulated by inflammatory mediators such as tumor necrosis factor alpha (TNFα) and lipopolysaccharide (LPS), as well as ox-low density lipoprotein (oxo-LDL) in endothelial cells and monocytes. Both extracts inhibit basal and stimulated reactive

oxygen species (ROS) production in endothelial cells and monocytes in a dose dependent manner. In endothelial cells, the ethanol extract (50.0 µg/ml) significantly reduced ox-LDL-induced intracellular ROS production by 60% ($P < 0.001$) and the aqueous extract (50.0 µg/ml) reduced ox-LDL-induced intracellular ROS production by 43% ($P < 0.01$). The ethanol extract (50.0 µg/ml) reduced ox-LDL-induced intracellular ROS production in monocytes by 76% ($P < 0.01$). Effective concentrations of 25 to 100 µg/ml were well below the cytotoxic levels of the extracts which started at 1 mg/ml as assessed by LDH leakage and trypan blue exclusion. An extract of the crude drug was studied in human leukocytes to assess its activity against oxidative stress. The extract produced a concentration dependent inhibition of oxidative stress when cells were stimulated with agents that generate reactive oxygen species (ROS): hydrogen peroxide, phorbol-12-myristate-13-acetate (PMA), and N-formyl-methionyl-leucyl-phenylalanine (fMLP). Cynarin, caffeic acid, chlorogenic acid, and luteolin, constituents of artichoke leaf ext., also show a concentration-dependent inhibitory activity in the above models, contributing to the antioxidant activity of the extract in human neutrophils.

3. Garlic (Allium sativum)

Garlic (*Allium sativum*, Liliaceae), also known as “the spice of life”, was one of the earliest documented examples of a food plant also used for the prevention and treatment of disease. The plant is a perennial, erect bulbous herb, with the bulb, giving rise to a number of narrow, keeled, grass-like leaves above ground. The medical history of garlic dates back at least 4000 years, where its medical uses were described in the ancient Chinese, Indian and Sumerian literature. Discorides, a Roman physician, recommended garlic to clean the arteries, and Hippocrates (460-370 BC), the father of modern medicine, was known to prescribe garlic for a wide variety of ailments. Garlic has been used as a food and medicine for thousands of years, and more recently has been the focus of numerous clinical studies, primarily for its cardiovascular benefits.

3.1. Clinical studies

3.1.1. Antihypercholesterolemic activity

Garlic contains a number of disulfide and trisulfide organosulfur compounds that appear to be the active constituents. More than 35 randomized trials have been reported in which the effects of garlic on cardiovascular endpoints have been examined. Overall, there is evidence from randomized controlled trials (RCT) in adults that use of garlic preparations can lead to a small but statistically significant reduction in total cholesterol levels as compared with controls. Thirty-seven randomized trials, all but one in adults, consistently showed that compared with placebo, various garlic preparations led to small, statistically significant reductions in total cholesterol at 1 month (range of average pooled reductions 1.2 to 17.3 milligrams per deciliter [mg/dL]) and 3 months (range of average pooled reductions 12.4 to 25.4 mg/dL). Garlic preparations that were studied included standardized dehydrated tablets or non-commercial enteric-coated tablets, "aged garlic extract™," oil macerates, distillates, raw garlic, and combination tablets. Eight placebo-controlled trials reported total cholesterol outcomes at 6 months; pooled analyses showed no significant reductions of total cholesterol with garlic compared with placebo. Statistically significant reductions in low-density lipoprotein

levels (LDL) (range 0 to 13.5 mg/dL) and in triglycerides (range 7.6 to 34.0 mg/dL) also were found in pooled analyses at 3 months. No significant changes in high-density lipoprotein levels (HDL) were seen in pooled analyses at 1 and 3 months. One multicenter trial involving 98 adults with hyperlipidemia found no differences in lipid outcomes at 3 months between persons who were given an antilipidemic agent and persons who were given a standardized dehydrated garlic preparation. Interpreting the lipid results is difficult at best since trials often had unclear randomization processes, short durations, and no intention-to-treat analyses.

3.1.2. Antihypertensive activity

Twenty-seven small, randomized, placebo-controlled trials, all but one in adults and of short duration, reported mixed effects of various garlic preparations on blood pressure. Most studies did not show any significant differences between persons randomized to garlic compared with those randomized to placebo. The one small trial (n=40) that directly compared a standardized dehydrated garlic preparation with an active antihypertensive agent found no differences in blood pressure between groups. Because of unclear randomization processes, lack of intention-to-treat analyses, missing data, and variability in blood pressure measurement techniques, no firm conclusions can be drawn from these trials.

3.1.3. Effects on platelet aggregation and myocardial infarction

Ten small, randomized trials, all but one in adults and of short duration, showed promising effects of various garlic preparations on platelet aggregation and mixed effects on plasma viscosity and fibrinolytic activity. Because the trials had only 409 participants, short follow-up periods, unclear randomization processes, no intention-to-treat analyses, missing data, and variability in techniques used to assess outcomes, no firm conclusions can be drawn. There were insufficient data to confirm or refute effects of garlic on clinical outcomes such as myocardial infarction. One 3-year randomized trial with 492 participants found no statistically significant decreases in numbers of myocardial infarctions and deaths when placebo was compared with 6 to 10 grams of garlic ether extract.

Overall, the data suggests that the reductions, averaging between 12-25 mg/dl were the greatest in patients treated with the garlic products for 3 months. Decreases in LDL and TG levels also have been reported. However, for some placebo-controlled trials, no significant garlic-associated reductions in total cholesterol were observed even after 6 months of treatment. The conflicting data regarding garlic's hypocholesterolemic actions may be due to flawed trial design, differences in types of garlic preparations used, doses administered, duration of use and heterogeneity in subject profiles. Of interest is a recent report examining whether improved delivery of bioactive garlic constituents could explain discordant findings. When men and women were collectively evaluated following ingestion of a garlic oil preparation, only total antioxidant indices were significantly improved after 6 weeks treatment. Yet when evaluated by gender, HDL-C and total cholesterol were significantly improved for women only. Thus gender and bioavailability of preformed bioactives may also explain disparate results. In addition to lipid-lowering actions, garlic preparations have been studied in humans for

other potential cardiovascular disease (CVD) benefits. Blood pressure reduction, normalization of glucose and insulin response, and frequency of myocardial infarctions have been evaluated to a very limited degree with no consistent conclusions.

4. Guggul (Commiphora mukul)

Guggul is a lipophilic extract prepared from the resin of trunk and branches of *Commiphora mukul* (Jacq.) Engler (Burseraceae), commonly referred to as the mukul myrrh tree. The medicinal use of guggul dates back to 600 BC, when it was employed for the treatment of obesity, atherosclerosis, and various inflammatory conditions. Preparations of resin have also been used in traditional medicine as mouthwashes, a dentifrice, for treatment of ulcers of mouth and pharynx, for foul and indolent ulcers, for wound healing in veterinary practice. The plant sterols E- and Z-guggulsterone (Figure 2) are believed to be the bioactive compounds. Recent research indicates that guggulsterones are antagonists of the farnesoid X receptor and the bile acid receptor, two nuclear hormone receptors involved in bile acid regulation and cholesterol metabolism. According to the recent WHO Monograph for guggul, the plant is useful for the treatment of hyperlipidemia and hypercholesterolemia.

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Biographical Sketch

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