کارگاه‌های آموزشی مرکز اطلاعات علمی

آموزش مهارت های کاربردی در تدوین و چاپ مقاله

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Review Article

Cardiovascular Effects of Allium Sativum (Garlic): An Evidence-Based Review

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Abstract

Garlic has been used since time immemorial as a culinary spice and medicinal herb. Garlic has been cultivated in the Middle East for more than 5,000 years and has been an important part of traditional Chinese medicine. The region with the largest commercial garlic production is central California. China is also a supplier of commercial garlic. The bulb is used medicinally. Garlic has been touted as an herb with numerous health benefits, from treating the common cold to serving as an anticancer agent. Research has proven that garlic is beneficial for those with hypertension. By thinning the blood garlic can lower blood pressure by 5 to 10 percent. It can also lower cholesterol and discourage clot formation. The sulfur compound allicin, produced by crushing or chewing fresh garlic or by taking powdered garlic products with allicin potential, in turn produces other sulfur compounds: ajoene, allyl sulfides, and vinyldithiins. Aged garlic products lack allicin, but may have activity due to the presence of S-allylcysteine. In this review, we focused on the cardiovascular effects of garlic.

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Keywords: Allium sativum • Cardiovascular disease • Garlic • Herbal medicine

Introduction

Herbal medicine has been around and been used for centuries, but only now has it really become so popular and such a big hype. Herbal medicine is the use of herbs for their therapeutic or medicinal value, and although conventional forms of treatment such as prescription medication still ranks in as being far more popular, herbal medicine is definitely starting to catch up. Herbal medicine can be used for a variety of health problems, but today is most commonly used for the treatment of heart disease, high blood pressure, pain, asthma, and related problems. There are certain herbs which are very commonly used in herbalism and garlic for one, which most people do not even realize is considered as being an herb. Garlic use dates back to Old Testament times, when it was a favored food. Drawings of garlic from 3700 BCE were uncovered in Egyptian tombs. Over the centuries, garlic has been used to ward off vampires, demons, witches, and evil beings and was thought to have magical properties. Medicinal uses date back to 1550 BCE, when it was used as a remedy for heart disease, head-aches, and tumors. It has also been used as an aphrodisiac to improve sexual performance and desire, and as a cure-all for everything from hemorrhoids to snake bites.[1–4] In 1997, garlic was the most widely used natural supplement in US house-holds. Garlic was shown to be used more than twice as much as any other natural supplement.[5] Garlic is promoted to lower cholesterol and blood pressure, delay the progression of atherosclerosis, prevent heart disease, improve circulation, prevent cancer, and is used topically for tinea infections.[3,4]

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Scientific and common names

Allium sativum, Allii Sativi Bulbus, Knoblauch, Ail, Ajo, Allium, Camphor of the Poor, Garlic Clove, Nectar of the Gods, Poor Man's Treacle, Rust Treacle, Stinking Rose.[3,6,7]

Recommended daily doses in humans

- 4 g of fresh garlic, approx 1 clove (4–12 mg of allicin or 2–5 mg of allicin)[6]
- Dehydrated garlic powder, 600–1200 mg in divided doses
- AGE, 1–7.2 g/day
- Fresh air-dried bulb, 2–5 g
- Garlic oil, 2–5 mg
- Dried bulb, 2–4 g three times daily
- Tincture (1:5 in 45% alcohol), 2–4 mL three times daily[6]

Side effects

Although herbal medicine is natural and usually very safe, it is important to know that it should not be mixed with any type of prescription medication, because the result could be incredibly dangerous, even potentially life threatening.[8]

Many people enjoy eating garlic. However, some people who are sensitive to it may experience heartburn and flatulence. Because of garlic's anti-clotting properties, people taking anticoagulant drugs should check with their doctor before taking garlic.[9] Those scheduled for surgery should inform their surgeon if they are taking garlic supplements. Garlic appears to be safe during pregnancy and breast-feeding.

Pharmacological/toxicological effects

Cardiovascular effects: Antioxidant and antiatherosclerotic effects

Garlic has been shown to have significant effects on the cardiovascular system. Such areas include improvement in lipids, modest effects on blood pressure, platelet inhibition, antioxidant effects, and a decrease in fibrinolytic activity. In vitro studies have shown that garlic possesses specific antiatherosclerotic effects such as reducing inducible nitric oxide synthase (iNOS) mRNA expression,[10] inhibition of oxidized low-density lipoprotein (LDL)-induced lactate dehydrogenase (LDH) release, and inhibition of oxidized LDL induced depletion of glutathione.[11] Results from a study in nine subjects found that supplementation with AGE at a dose of 2.4g/day significantly inhibited the oxidation of LDL, but ingesting 6 g/day of crushed raw garlic did not have a significant effect. The authors believe that this difference in response may be owing to the fact that the active ingredient in raw garlic is allicin, whereas SAC is believed to be the active component of AGE in preventing atherosclerosis. Nonetheless, when compared to α-tocopherol (Vitamin E), which is well documented at preventing lipid oxidation, both AGE and raw garlic were less effective at inhibiting oxidation ($p<0.05$).[12] In addition, it has been shown that 900 mg/day of garlic powder vs. placebo for 4 years caused a significant decrease in atherosclerotic plaque volume in both men and women with advanced atherosclerotic plaques and at least one cardiovascular risk factor.[13] The effects of garlic as an antioxidant and its ability to alter the atherosclerotic process require additional study. To date, no trials evaluating patient outcomes have been completed.

Antihyperlipidimic effects

Garlic as a lipid-lowering agent is perhaps the most studied topic related to its use in cardiovascular health. The mechanism by which garlic lowers lipoprotein levels is not well understood. Animal data show that garlic significantly decreases hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase activity, and may have some effects on cholesterol α-hydroxylase, fatty acid synthetase, and pentose-phosphate pathway enzyme activity.[14] A recent meta-analysis using multiple databases, from inception until November 1998, compiled all randomized, double-blind, placebo-controlled trials using mono preparations of garlic, to test the effectiveness of garlic in lowering total cholesterol (TC).[15] Inclusion criteria included trials in which participants had elevated TC, defined as 5.17 mmol/L (200 mg/dL) at baseline, and reported TC levels as an end point. Studies were excluded if they did not contain enough data to compute effect size. Of the 39 garlic in hyperlipidemia studies identified, 21 were excluded because they were not placebo-controlled, randomized, double-blind, did not use a mono preparation of garlic, did not report TC, or did not have a baseline TC meeting inclusion criteria. An additional five trials did not include enough data to perform statistical pooling. Of the 13 studies cited in the meta-analysis, 10 used Kwai powder tablets in doses of 600, 800, and 900 mg/day. One study used 700 mg of spray-dried powder per day, another used 0.25 mg/kg body mass of essential oil, and the other study used 10 mg/day of steam-distilled oil. Study duration ranged from 8 to 24 weeks. Of the 13 trials, 10 required a diagnosis of hypercholesterolemia or hyperlipoproteinemia, whereas the other trials required diagnosis of coronary heart disease, hypertension, or healthy participants. A total of 796 participants were involved, and all the trials excluded participants using hypolipidemic drugs. Results showed that TC levels decreased by a modest 5.8% (0.41 mmol/L; 15.7 mg/dL) in participants taking garlic compared to placebo ($p<0.01$). Of the five methodologically similar trials using Kwai 900 mg/day, no significant difference was seen in

reducing total cholesterol with garlic. Additionally, in an analysis of the six trials that controlled for diet, no significant difference was seen in reducing total cholesterol with garlic. The authors also looked at data presented in these studies regarding changes in LDL and high-density lipoprotein (HDL) levels. No significant difference was seen in reducing or increasing these values, respectively.[15] Several more recent studies have confirmed the TC-lowering effect seen in this meta-analysis. A randomized, double-blind, placebo-controlled study in 50 subjects with hypercholesterolemia and LDL levels between 150 and 200 mg/dL, triglycerides less than 300 mg/dL, an average age of 53 years, and who were not using lipid-lowering drugs, evaluated the effect of 300 mg three times daily of garlic powder (Kwai) for 12 weeks. Patients were classified by their LDL pattern A or B. Pattern B LDL has been shown to be more atherogenic than pattern A. This study was designed to not only look at the effect of garlic on lipoprotein levels, but also LDL particle size, LDL and HDL subclass distribution, and the effect on lipoprotein(a) [Lp(a)]. The only significant difference found was a significant decrease in LDL peak particle diameter in LDL pattern A. It is unclear what the implications of this decrease in diameter are. Results showed no significant difference in plasma lipid levels, overall LDL peak particle diameter, LDL or HDL subclass distribution, apolipoprotein B, or Lp (a) in the garlic vs. placebo groups.[16] Another double-blind, placebo-controlled, randomized study of 34 men, average age of 48 years, with total cholesterol levels between 220 mg/dL and 285 mg/dL evaluated the effects of 7.2 g of AGE daily for 5 months. At 2 and 4 months after beginning the study, no significant difference was seen in TC or LDL cholesterol levels. At 5 months, a significant drop (7% in TC, 10% in LDL) was seen in the garlic group vs. placebo. Plasma HDL and triglyceride levels did not change.[17] Overall, there are conflicting data regarding the effects of garlic on serum lipid levels. The diverse nature in the design of these studies makes it difficult to pool data. In addition, the use of various garlic preparations may have differing effects on lipids because of the diverse activity of organosulfide compounds present in each product. However, a larger number of studies have found garlic to provide a significant but small decrease in LDL and total cholesterol when garlic is used for up to 4 months. Further study is needed to determine whether garlic has a prolonged affect on lipids and if the effects are sustainable. Compared to the available lipid-lowering prescription drugs, garlic provides a small-percent decrease in lipid values and has not been shown to have morbidity and mortality benefits in these patients.

Platelet inhibitory and fibrinolytic effects

Platelet inhibition is another widely studied effect of garlic use. Platelet inhibition has been demonstrated in several in vitro and animal studies with fresh garlic cloves,[18] ajoene,[8] garlic oil,[19] and AGE.[20] Mechanisms proven by in vitro studies include a dose-dependent, irreversible inhibition of platelet aggregation through almost complete suppression of thromboxane production,[8,19] a dose-dependent inhibition of collagen-induced platelet aggregation,[21] and inhibition of adenosine diphosphate (ADP) and epinephrine-induced platelet aggregation.[8] Multiple mechanisms may be responsible for the platelet inhibitory affects of garlic. It is thought that the inhibition of thromboxane production is caused by the inhibition of cyclooxygenase, but not lipoxygenase;[8,19] however, some studies question whether garlic inhibits cyclooxygenase. There may be a direct inhibition of thromboxane. β-thromboglobulin release is decreased, which suggests that the effect may be more on the platelet activation phase.[22-23] The specific components of garlic may also have different effects on the various mechanisms of antiplatelet activity. Some forms of garlic may include adenosine, which increases cyclic adenosine monophosphate (CAMP) levels and thus decreases thromboxane formation.[8] The antiplatelet effects of garlic are thought to be caused by allicin, SAC, adenosine, methyl allyl trisulfide (MATS), diallyl disulfide, and diallyl trisulfide.[8,18,21,24] It has been demonstrated that raw garlic extract is more effective than boiled garlic extract in inhibiting platelets ($p<0.001$).[21] Be that as it may, a double-blind, randomized, placebo-controlled study found no significant difference in platelet aggregation when subjects took the equivalent of 15 g raw garlic in capsule form. The garlic preparation consisted of garlic cloves homogenized in water and further processed into an oil extract.[25] Higher doses of garlic may be needed for the inhibition of thromboxane synthesis, whereas lower doses may have other mechanisms. A randomized, placebo-controlled, double-blind crossover study showed that AGE increased the threshold concentrations needed for ADP-, epinephrine-, and collagen-induced platelet aggregation in human blood. Doses of 7.2 g AGE per day significantly increased the threshold of ADP-induced platelet aggregation ($p<0.05$), while lower doses of 2.4 and 4.6 g AGE per day significantly increased the collagen- and epinephrine-induced threshold. Higher doses of 7.2 g AGE per day did not show a significant difference than the lower doses for the latter two substances. Platelet adhesion to collagen-coated surfaces, fibrinogen, and von Willebrand factor were measured. At a dosage of 4.8-7.2 g AGE per day, adhesion to collagen-coated surfaces was significantly reduced ($p<0.05$). All doses significantly decreased adhesion to fibrinogen ($p<0.01$) and only the highest dosage of 7.2 g AGE per day significantly reduced adhesion to von Willebrand factor ($p<0.05$).[20] Similar results were seen in an earlier study of 15 men with hypercholesterolemia.[26] A double-blind, randomized, matching placebo-controlled parallel group investigation was done to evaluate the effect of 800 mg dried garlic powder for 4 weeks (Kwai/Sapec® [Lichter Pharma, Berlin, Germany]; 300-mg tab-lets; contains 1.3% alliin, which corresponds to an Allicin release of 0.6%) in patients with an increased risk

of juvenile ischemic attack owing to increased circulating platelet aggregates. The ratio of circulating platelet aggregates decreased by 10.3%, and spontaneous platelet aggregation decreased by 56.3% during the treatment period compared to baseline ($p<0.01$) and placebo ($p<0.01$). Plasma viscosity also significantly decreased in the garlic group after 4 weeks of treatment compared with baseline and placebo ($p<0.0001$). These levels returned to pretreatment levels 4 weeks after treatment was stopped.[27] In another study, 800 mg of dried garlic powder (Kwai/Sapec) daily for 15 weeks significantly improved pain-free walking distance in patients with arterial occlusive disease. In this randomized, placebo-controlled, double-blind study, 60 patients underwent 15 weeks of physical therapy, 30 of the subjects received garlic, and 30 baseline-matching patients received an identical placebo. After 6 weeks of treatment, pain-free walking distance was significantly farther in the garlic group ($p<0.038$). Cholesterol levels ($p<0.011$), plasma viscosity ($p<0.0013$), and spontaneous thrombocyte aggregation ($p<0.013$) were significantly lower in the garlic group.[28] This is the only published study addressing a clinically relevant outcome associated with platelet inhibition caused by garlic supplements. Fibrinolytic effects of garlic have also been evaluated. Garlic oil was shown to increase fibrinolytic activity by 55% ($p<0.01$) after 3 months of treatment with 2 g twice daily for 3 months. Fibrinogen was not affected.[24] A dried garlic preparation (Sapec) was shown to increase tissue plasminogen activator activity significantly compared to placebo after 1 day and 14 days of treatment.[23] The antiplatelet and antifibrinolytic activity of garlic is of great interest to researchers. Many studies have confirmed these effects as a result of garlic consumption. As with the lipid-lowering effects of garlic, more clinical outcome trials are needed to justify its use in patients with cardiovascular risk factors. In addition, comparative studies with aspirin would be needed to show whether there are any benefits to using garlic instead. Because of the demonstrated antiplatelet effect of garlic, its use should be avoided in patients with bleeding disorders and discontinued 1-2 weeks prior to surgery.

Antihypertensive effects

In addition to its effects on lipids and platelet inhibition, garlic has been studied for its effects on lowering blood pressure. A meta-analysis of the effects of garlic on blood pressure was conducted by Silagy and Neil in1994.[29] Each of the eight randomized studies identified within the analysis used the dried garlic preparation Kwai, 600–900 mg daily (1.8-2.7 g/day fresh garlic) for at least 4 weeks in 415 subjects. Overall, there was an average decrease in systolic blood pressure (SBP) of 7.7 mmHg (95% confidence interval [CI] 4.3-11) and a decrease in diastolic blood pressure (DBP) of 5mmHg (95% CI 2.9-7.1) in those subjects taking garlic. However, only two of the placebo-controlled trials were limited to hypertensive patients. These studies showed an average decrease in SBP of 11.1 mmHg (95% CI 5-17.2) and a decrease in DBP of 6.5 mmHg (95% CI 3.4-9.6) in those subjects taking the garlic preparation. In a pilot study, 2400 mg dried garlic powder (Kwai) containing 1.3% allicin was administered to nine patients with persistent severe hypertension (DBP 115 mmHg). A statistically significant decrease was seen in DBP at 5-14 hours ($p<0.05$), with a maximum decrease at 5 hours after the dose (16±2 mmHg). Although no significant difference was seen in SBP at any time point, a trend was present.[30] Other studies, which had primary outcomes other than blood pressure, have also shown similar findings.

In summary, think of garlic as a basic food that augments the body>s health and lowers blood pressure as well as blood cholesterol. In a nutshell, garlic is an ideal herb for several cardiovascular supplements.

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