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Article 1

Potential Health Benefits of Garlic (*Allium Sativum*): A Narrative Review

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Potential Health Benefits of Garlic (*Allium Sativum*): A Narrative Review*

Peter B. Bongiorno, Patrick M. Fratellone, and Pina LoGiudice

Abstract

A member of the Liliaceae family, garlic (*Allium sativum*) is highly regarded throughout the world for both its medicinal and culinary value. Early men of medicine such as Hippocrates, Pliny and Aristotle encouraged a number of therapeutic uses for this botanical. Today, it is commonly used in many cultures as a seasoning or spice. Garlic also stands as the second most utilized supplement. With its sulfur containing compounds, high trace mineral content, and enzymes, garlic has shown anti-viral, anti-bacterial, anti-fungal and antioxidant abilities. Diseases that may be helped or prevented by garlic's medicinal actions include Alzheimer's Disease, cancer, cardiovascular disease (including atherosclerosis, strokes, hypertension, thrombosis and hyperlipidemias) children's conditions, dermatologic applications, stress, and infections. Some research points to possible benefits in diabetes, drug toxicity, and osteoporosis.

KEYWORDS: garlic, atherosclerosis, herbal medicine, botanical medicine, children, cardiovascular disease, Alzheimer's, cancer

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INTRODUCTION

A member of the Liliaceae family, garlic (*Allium sativum*) is a cultivated food highly regarded throughout the world. Originally from Central Asia, garlic is one of the earliest of cultivated plants. The Ebers Codex, and Egyptian medical papyrus dating to about 1550 B.C.E. mentions garlic as an effective remedy for a variety of ailments. Early men of medicine such as Hippocrates, Pliny and Aristotle espoused a number of therapeutic uses for this botanical (Murray 2005). Today it is commonly used in many cultures as a seasoning or spice.

According to the US Food and Drug Administration survey of 900 people, garlic stands as the second most utilized supplement (behind Echinacea), with almost 17% of the population using a garlic supplement in the preceding 12 months (Timbo et al. 2006). Most of the garlic eaten today comes from China, South Korea, India, Spain, and the United States. In addition to its reputation as a healthy food, garlic has shown anti-viral, anti-bacterial, antifungals and antioxidant capacities. Additionally, anti-atherosclerotic and anti-cancer properties have also been demonstrated. The genus *Allium* includes garlic, scallions, onions, chives, and leeks. These contain the sulfur compounds which are medicinally active.

Teardrop shaped cloves are encased in dry skin-like papers that unite to create the bulb. The garlic bulb is the part of the plant used most often for cooking and medicinal uses. Garlic can be eaten raw. Most often it is used raw after being chopped, minced, sliced, or juiced. More often, it is cooked where it enhances flavor as well as adds nutritional benefit.

GARLIC

The majority of reported medicinal effects of this botanical appear to come from the sulfur containing compounds, high trace mineral content, and enzymes. Most of the sulfur found in whole garlic cloves are of two types found in equal quantities: the *S*-alkylcysteine sulfoxides and the γ -glutamyl-*S*-alkylcysteines. The most abundant sulfur compound in garlic is alliin (*S*-allylcysteine sulfoxide), which is present at 10 mg/g in fresh garlic or 30 mg/g dry (Lawson 1998). Recent studies from Korea has further elucidated novel sulfur containing nitrogenous compounds responsible for the greening process of crushed or bruised garlic. These compounds are not released when the garlic is finely peeled and have been found to differ significantly from other green plant pigments (Lee et al. 2007). It is clear that even with a plant medicine as well characterized as garlic, there is still much to be learned.

Typical garlic food preparation includes chopping, mincing, or crushing the garlic. When these traumas occur the odor-free cysteine sulfoxides are exposed to the allinase enzymes, and quickly convert to thiosulfanates, which give off garlic's characteristic aroma. The main thiosulfanate is allicin, which has a half-life of up to 16 hours at room temperature, or two and a half days when kept as a juice or crushed form. Other thiosulfanates include alliin, allyl cysteine and allyl disulfide. The allinase enzyme responsible for thiosulfanate conversion becomes inactivated below a pH of 3.5 or with heating. Microwave radiation will destroy allinase activity within one 1 minute. (Pedrazza-Cheverri et al. 2006). Up until recently, the therapeutic value of garlic has been attributed to the low-molecular weight thiosulfates. Although allicin is considered the major antioxidant and scavenging compound, studies are showing that other compounds may play stronger roles (Chung 2006). In addition, newer research has characterized some polar compounds of phenolic and steroidal origin, which proffer various pharmacological properties. These latter compounds, in contrast to the thiosulfates, are without odor, and are also heat stable (Lanzotti 2006). Furthermore, some of the scavenger properties of garlic are not affected by heating or cutting (Pedraza-Chaverri).

CONDITIONS

CARDIOVASCULAR DISEASE

Garlic is a popular supplement well-perceived as a healthy choice among people looking to increase cardiovascular wellness. Approximately 4% of all cardiovascular disease patients and 30% of cardiovascular patients who use herbal supplements take garlic (Yeh et al. 2006). Known risk factors for cardiovascular disease include inflammation, high cholesterol, high homocysteine, high blood pressure, diabetes and dementia, including its most common form, Alzheimer's disease. Indeed, as early as the 1920's and 1930's (Rahman 2001, Schlesinger 1926, Taubman 1934), numerous studies do bear the beneficial cardiovascular effects. Garlic is well reported to scavenge oxidants, increase superoxide dismutase, catalase, glutathione peroxidase, and glutathione levels, as well as inhibit lipid peroxidation and inflammatory prostaglandins. Garlic also reduces cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl-CoA. Garlic has been shown to inhibit LDL oxidation, platelet aggregation, arterial plaque formation, decrease homocysteine, lower blood pressure, and increase microcirculation, which is important in diabetes, where microvascular changes increase heart disease and dementia risks. Garlic may also help prevent cognitive decline by protecting neurons from neurotoxicity and apoptosis, thereby

preventing ischemia- or reperfusion-related neuronal death and by improving learning and memory retention (Borek 2006). Garlic may also possess anti-inflammatory abilities to suppress the nuclear factor-kappaB activation pathway (Aggarwal et al. 2004).

ALZHEIMER'S DISEASE

Known for its neuroprotective abilities in vitro (Peng et al. 2002), aged garlic has been looked to for multiple benefits that some researchers believe may address a number of underlying mechanisms which contribute to the classic Alzheimer beta-amyloid plaque. According to one author, garlic:

“is expected to produce cumulative benefits and exhibit enhanced neuroprotection by virtue of being “natural statin”, “natural NSAID”, “natural anti-oxidant”, “natural anti-apoptotic agent” and “memory enhancer”, a combination of many single-ingredient synthetic pharmaceutical drugs currently used for Alzheimer's therapy, only with least adverse effects (Chauhan 2006).”

Unfortunately, there is a dearth of clinical studies showing of aged garlic extract in relation to Alzheimer's pathology, except for reports showing improved behavior in senescence accelerated mice after garlic treatment (Nishiyama et al. 2001). Given the multiple-mechanistic possibilities and minimal risk associated with its use, garlic seems a prudent recommendation for prevention and treatment. Since aged garlic is best studied in relation to Alzheimer's it may be the best form to employ.

ATHEROSCLEROSIS and HYPERLIPIDEMIA

Health claims touting garlic's universal ability to lower cholesterol is ubiquitous. The research also bears this out, but there are a number of conflicting studies. Garlic's main benefits are due to its ability to lower cholesterol and decrease lipid peroxidation in order to inhibit plaque formation. In vitro studies clearly show the ability of several garlic components to suppress LDL oxidation and short-term supplementation of garlic in human subjects has demonstrated an increased resistance of LDL to oxidation (Lau 2006).

Results from controlled human studies are mixed, with studies performed in the early 1990's showing effective results (Jain et al. 1993, Steiner et al. 1996) whereas a number of studies from the past six years have not shown efficacy to lower cholesterol. (Peleg et al. 2003, Isaacsohn et al. 1998, Gardner et al. 2001). Morris et al. reviewed five clinical trials on garlic's effect on the cardiovascular system. All of these studies showed garlic to be of no benefit (1995). As many studies that have shown garlic to have no effect on the cardiovascular system,

there are studies that have shown garlic to be cardio-protective. Lau et al. (1987) found that aged garlic extract was effective in lowering serum cholesterol and triglycerides. The most recent study by Mahmoodhi et al. (2006) was conducted on 30 volunteer individuals with blood cholesterol higher than 245 mg/dl. The subjects ingested 5g raw garlic twice a day for 42 days and then refrained from garlic for next 42 days. After 42 days of garlic consumption the mean of blood total cholesterol ($p<0.001$) triglycerides ($p<0.01$) and FBS ($p<0.01$) were reduced significantly, while HDL-C significantly increased ($p<0.001$). Following 42 days of no garlic consumption total cholesterol ($p<0.001$), triglycerides and FBS ($p<0.05$) were significantly increased and HDL-C ($p<0.01$) decreased. The authors of this study concluded that consumption alone can decrease serum lipids and may be effective in mild cases, but should probably not be relied on as the main therapeutic agent for hyperlipidemia. Other recent animal work also corroborates the beneficial effect of using boiled or raw garlic, the forms most often used most commonly (Gorenstein et al. 2006).

As more research is conducted, newer processes to extract garlic are being employed. A small recent Japanese study of 15 hypercholesterolemic patients evaluated a material produced from garlic fermented with the mold *Monascus pilosus*. This preparation significantly reduced serum total cholesterol and low-density lipoprotein cholesterol levels at when checked 2 and 4 weeks after beginning treatment. The level of triglycerides had a tendency towards reduction in hypertriglyceridemic patients as well, whereas high-density lipoprotein cholesterol was unchanged, and triglycerides (Sumioka et al. 2006).

Finally, some studies suggest that food context may also play a role. A very small Indian study of 32 hypercholestermic subjects paired fish oil with garlic ingestion. Significant reductions for the test group in all the lipid parameters (save high-density lipoprotein, which was increased). After 60 days of supplementation, total cholesterol, low-density lipoprotein, serum triglyceride, very low-density lipoprotein, and total cholesterol were reduced by 20%, 21%, 37%, 36.7%, and 23.4%. The protective high-density lipoprotein increased by 5.1% (Jeyaraj et al. 2006). The potential of garlic may be enhanced by the concomitant intake of other anti-oxidants, such as lycopene and vitamin E (Fuhrman et al. 2006).

At this time, we recommend that for hyperlipidemia, garlic is best used raw or boiled for no longer than 20 minutes before ingestion, and that it may be more effective to take with fish oils and other foods known to be high in antioxidants. Use of enteric coated tablets in one study conferred no benefit for cholesterol reduction over placebo (Tanamai et al. 2004).

DIABETES

A number of animal studies support the effectiveness of garlic in reducing blood glucose in streptozotocin-induced as well as alloxan-induced diabetes mellitus in rats and mice. Most of the studies showed that garlic can reduce blood glucose level in diabetic mice rats and rabbits (Banerjee et al. 2004). One Iranian study evaluated oral administration of garlic extract for 14 days on the level of serum glucose, total cholesterol, triglycerides, urea, uric acid, creatinine, in normal and streptozotocin-induced diabetic rats. Administrations of the garlic extract significantly decreased serum glucose, total cholesterol, triglycerides, urea, uric acid, creatinine, aspartate amino transferase and alanine amino transferase levels, while increased serum insulin in diabetic rats but not in normal rats ($p < 0.05$). Interestingly, a comparison was made between the action of garlic extract and glibenclamide, a well-known antidiabetic drug. The antidiabetic effect of the garlic was more effective than that observed with glibenclamide (Eidi et al. 2006). Unfortunately, the effect of garlic on humans with diabetes is not well studied as is fraught with conflicting results (Zhang et al. 2001, Jain et al.).

FIBRINOGEN

There has been much controversy regarding the association of fibrinogen and cardiovascular disease. The Northwick Park Heart Study in England was the first study to demonstrate a correlation. The four-year follow-up revealed an association between cardiovascular deaths and fibrinogen levels were more significant than that of cholesterol levels. Other studies have demonstrated this association (Ernst 1994). The clinical significance of these studies reveals that garlic, in a treatment protocol designed to promote fibrinolysis, may offer significant benefit in the prevention of cardiovascular diseases, including myocardial infarctions and strokes.

HOMOCYSTEINE

Elevated plasma homocysteine concentrations have been associated with an increased risk of vascular disease as high homocysteine is known to inhibit endothelial cell proliferation (Seyar 2007, Weiss et al. 2006) and contribute to atherothrombotic events. In one animal study by Yeh et al., the addition of aged garlic extract decreased plasma total homocysteine concentration by 30% (2006). However, marked lowering of homocysteine concentrations by folic acid and B-vitamin supplementation seems to play no bearing on inflammatory and immune cytokine responses and may not reduce risk of cardiovascular events (Peeters et al. 2007, Heart Outcomes Prevention Evaluation 2 Investigators 2006).

Accordingly, it is premature to state that garlic's hypohomocysteinemic effect would solely help protect cardiovascular function. Possibly, the effect of B vitamins, garlic and other healthful interventions would collectively create a more protective response.

HYPERTENSION

Garlic has probably been most popularized as a complementary therapy for blood pressure control, as it is used by approximately 50% of patients who have hypertension (Capraz et al. 2006). Recent in vitro studies by Benavides et al. (2007) have confirmed the vasoactive ability of garlic's sulfur compounds whereby red blood cells convert garlic's organic polysulfides into hydrogen sulfide, a known endogenous cardioprotective vascular cell signaling molecule. In one pilot study, a high dose of garlic tablet (2400 mg, containing 31.2-mg allicin) had been used and overall blood pressures decreased at approximately 5 h after the dose, including a 16 mm drop in diastolic pressure (McMahon et al. 1993). One meta-analysis pooled the data from 415 patients from eight controlled trials of garlic for high blood pressure. Reductions of 7.7 mm Hg systolic and 5 mm diastolic were noted. The authors concluded that these doses may be useful for mild hypertension but higher doses may be needed for moderate or severe pressures (Silagy et al. 1994). In a more recent meta-analysis of 23 placebo-controlled trials, one trial showed a reduction in systolic pressure, while three studies showed significant decreases in diastole (Ackerman et al. 2001). Although garlic may have benefits in regards to blood pressure, more consistency with regard to garlic preparation and study duration will need to be addressed in order to confirm benefits or inefficacy. Given the available research and its safety profile, it seems reasonable to include garlic in a regimen of dietary changes and exercise to yield the best effects on blood pressure control.

THROMBOSIS

In one clinical study, researchers found that the daily consumption of 1 clove of fresh garlic for 6 months resulted in an 80% decrease in serum thromboxane B₂ in middle-aged men (Ali et al. 1995). A recent insitu study in a rat model has demonstrated overall antithrombotic effects of garlic by modulation of fibrinolytic activity through increased plasminogen activation and by inhibiting thrombin formation (Fukao et al. 2007). The antithrombotic effects of garlic are attributed to the allyl propyl disulfide, diallyl disulfide, and other sulfur compounds present in the essential oil. Although the exact mechanism by which these compounds

alter platelet function is not known, in vitro studies suggest that they may act via inhibition of platelet lipooxygenase and cyclooxygenase enzymes, which in turn suppresses the production of thromboxane B₂ (Rajaram et al. 2003).

CANCER

Of the many favorable actions of garlic, inhibition of the growth of cancer is perhaps the most notable. Various forms of garlic, including fresh garlic extract, aged garlic, garlic oil and a number of organosulphur compounds, appear to offer protection against some cancers. Garlic likely has several synergistic biological effects that either prevent or possibly may fight cancer. The chemopreventive activity has been attributed to the ability to modulate the activity of several metabolising enzymes that activate (cytochrome P450s) or detoxify (glutathione *S*-transferases) carcinogens and inhibit the formation of DNA adducts in several target tissues (Hassan 2004). Also, garlic was shown to stimulate immune effector cells including T- and natural killer cell number and activity. Numerous epidemiological, clinical and laboratory studies have demonstrated the role of garlic in cancer prevention (Milner 2001, Flieischauer et al. 2001, Galeone et al. 2006, Setiawan et al. 2005) especially in relation to digestive tract cancers, including esophageal and stomach cancers (Gao et al. 1999, Berspalov et al. 2004). There is also promising research evaluating the use of garlic in leukemic (Hassan), melanoma (Taylor et al. 2006) and neuroblastoma (Karmakar et al. 2007) cell lines.

In the Iowa Women's Health Study, 41,387 middle age women have been tracked regarding their dietary, lifestyle and general health. It was found that those women eating garlic were less likely to develop colon cancer (Steinmetz et al. 1994). Other Dutch Research in the Netherlands Cohort Study found a significant decrease in the development of stomach cancer in those consuming garlic's close relative, onion. Interestingly, garlic capsules did not confer any benefit. Garlic as a food was not directly studied (Dorant et al. 1996). Garlic reduces risk of patients with prostate cancer, especially those with localized disease. Men in the highest of three intake categories of total allium vegetables (>10.0 g/day) had a statistically significantly lower risk (odds ratio = 0.51, $P < .001$) of prostate cancer than those in the lowest category (<2.2 g/day). Similar comparisons between categories showed reductions in risk for men in the highest intake categories for garlic specifically (odds ratio = 0.47, $P < .001$). The reduced risk of prostate cancer was independent of body size, intake of other foods, and total calorie intake and was more pronounced for men with localized than with advanced prostate cancer (Hsing et al. 2002). As a note, prostate specific antigen serum markers had significant decreases during short term ingestion, but returned

to baseline after 4 weeks (Mehraban et al. 2006). This should be kept in mind when using serum diagnostics to determine clinical treatment options.

DERMATOLOGIC APPLICATIONS

A 42-person study examined the topical use of two different garlic extracts of for wart and corn treatment. Five volunteers utilized a water extract of garlic while 23 volunteers applied lipid extract to appropriate areas twice a day. Five controls applied a neutral solvent. All lipid extract volunteers experienced complete resolution of warts within one to two weeks and this topical resolved 80% of corns. The water extract seemed to be less potent, with complete dissolution of smaller warts and corns, and only partial dissolution of larger ones. Controls showed no improvement from baseline. The lipid extract did cause some burning, redness, blistering and skin darkening, which resolved after conclusion of use (Dehghani et al. 2005). Given that there are other documented cases of garlic burns from topical use (Parish et al. 1987), caution is advised when using garlic as a topical, and may be contraindicated in diabetic patients, and patients with poor circulation.

ANTI MICROBIAL

During World War I, the success of garlic in treating wounds and dysentery was well known. However its antibiotic properties remained a mystery until Sandoz Pharmaceuticals isolated a compound, alliin. When garlic is chopped, crushed or bruised the alliin converts to the active ingredient, allicin. Garlic exerts broad-spectrum antimicrobial activity against many species of bacteria, virus, parasites, protozoan and fungi (Adetumbi et al. 1983, Koch 1993, Hughes et al. 1991).

Garlic is active against the bacterias *Shigella dysenteriae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus spp*, *Salmonella spp*, and *Proteus mirabilis*. It is also active against viruses, herpes simplex, HIV and influenza. B. Singh and Shukla (1984) have repeatedly shown that garlic is active against strains of bacteria that are highly resistant to antibiotics. As far back as 1944, Cavallito et al. demonstrated that both garlic juice and allicin inhibited the growth of *Staphylococcus*, *Streptococcus*, *Bacillus*, *Brucella* and *Vibrio* species using fresh and vacuum- dried powdered garlic preparations which were found to be effective against *Citrobacter*, *Klebsiella* and *Mycobacterium* species, in addition to *Staphylococcus*, *Streptococcus* and *Proteus* species (Sharma et al. 1977, Elnima et al. 1983). Despite the many garlic trials, only a few have demonstrated efficacy in animal and human studies against the leading causes of dysentery. The drug resistant strains included *Shigella dysenteriae* type 1, *Shigella flexneri*, enterotoxigenic *Escherichia coli* and *Vibrio cholerae*. Other

studies demonstrate activity of garlic against amebic, toxoplasmosis and cryptosporidium. Garlic oil, powder and other constituents have been shown to exert potent antibacterial effects on *Helicobacter pylori* (Sivam et al 2001, You et al. 1998). This may explain epidemiological evidence for protection against gastric cancers. In one preliminary study by Tanaka et al. (2006), double-blinded randomized clinical trial studying colorectal adenoma, 2.4mL per day of aged garlic extract was used to evaluate suppressive effects on this condition. For the thirty-seven patients (19 in the active group, 18 in the control group) who completed the study, the number of adenomas increased linearly in the control group, but the aged garlic extract group significantly suppressed both the size and number of colon adenomas in patients after 12 mo of high-dose treatment ($P=0.04$).

It has been said that if only one herb could be used to combat an epidemic spread of antibiotic resistant bacteria, garlic would be the choice.

FUNGAL INFECTIONS

Ajoene is an active compound in garlic that may also play a role as a topical fungal agent (Ledezma et al. 2006, Ghandi et al. 1988). Garlic has shown to inhibit growth of fungal elements equally along with the drug ketoconazole, when tested on the fungi *Malassezia furfur*, *Candida albicans*, other *Candida* sp. as well as 35 strains of various dermatophyte species (Shams-Ghahfarokhi et al. 2006). In 1980 there was a preliminary report of the benefit if garlic 21 cases of cryptococcal meningitis (Anonymous, 1980).

DRUG TOXICITIES and PHARMACOKINETICS

Glutathione is a compound necessary for liver detoxification. It has been hypothesized that garlic organosulfur compounds may be able to prevent glutathione depletion. Patients who experience increases in reactive oxygen species-induced stress on liver function may be protected by garlic ingestion (Sabayan et al. 2006). It was found in *Escherichia coli* cultures that aged garlic extract, S-allylcysteine, diallyl sulfide and diallyl disulfide do not interfere with the antibiotic activity of gentamycin but may ameliorate gentamycin-induced nephrotoxicity (Maldonado et al. 2005). Aged garlic has also been shown to reverse oxidant effects of nicotine toxicity in rat studies (Sener et al. 2005). One observational Phase IV study slated to conclude in July of 2008 will report on whether various garlic supplements may have an effect on the drug-metabolizing enzyme cytochrome P450 and the drug transporter, P-glycoprotein in order to ascertain whether garlic itself may affect the pharmacokinetics pharmaceutical drugs (www.clinicaltrials.gov). More research is needed, but in

the future, garlic may be a unique choice to help minimize the toxic effects of therapeutic drugs.

NURSING and CHILDREN'S CONDITIONS

Garlic preparations have a long history of utilization as safe and effective treatments for children. Two studies in breast feeding mothers even show that infants prefer the milk from mother's who eat garlic (Menella et al. 1993a Menella et al. 1993b). In this author's clinical experience (PL), a child's digestive system can potentially react to garlic as an irritant from the breast milk hence causing colic to occur even though the child is not directly allergic to garlic. For use with children, garlic is often prepared in syrup forms, honeys or oils (Bove 2001). A double blinded evaluation of 180 children revealed that a naturopathic ear drop preparation of calendula, St. John's wort, and verbena in olive oil with essential oils of garlic, lavender and vitamin E at 5 drops 3 times a day for children with ear pain secondary to otitis media found statistically significantly greater pain relief on both days 2 and 3 of treatment in the patients who were given ear drops alone than in the patients who were given ear drops and antibiotics (Sarrell et al. 2003). It is unknown which individual components may have had the greatest effect or if it a synergistic effect of these botanicals allowed for the reduction in pain.

Garlic tablets have been studied in an open label study of 172 children with acute respiratory infections. This study used 600mg per day of a time released garlic tablet was compared against 472 controls. The garlic reduced acute respiratory infections by 170% compared to placebo and 240% versus benzimidazole-treated children (Andrianova et al. 2003).

To study the effect of oral garlic on arterial oxygen pressure, garlic powder in a capsule form was given to 15 Iranian children who had contrast echocardiogram-confirmed hepatopulmonary syndrome (10 boys and 5 girls with a mean age of 9.4+/-3.9 years). The underlying factors of their disease were: biliary tract atresia (4 patients), autoimmune hepatitis (4 patients), cryptogenic cirrhosis (4 patients) and pre-sinusoidal portal hypertension (3 patients). Patients were evaluated clinically and by arterial blood gas every four weeks. Eight patients (53.3%) showed an increase of 10 mmHg in their mean arterial oxygen pressure. The baseline partial oxygen pressure was 65.6+/-12.1 mmHg in the responder group and 47.1+/-11.2 mmHg in non-responder group. At the end of treatment the mean partial pressure of oxygen in responders and non-responders was 92.2+/-7.75 mmHg and 47.5+/-11.87 mmHg, respectively ($P<0.01$). In conclusion, the authors suggested that garlic can reduce the severity of hepatopulmonary syndrome and that arterial oxygen pressure is increased after treatment with garlic (Najafi et al. 2006). Further studies are needed to fully

evaluate the garlic therapy for hepatopulmonary syndrome in children, but these preliminary results are promising.

Although a number of adult studies have been conducted, only one study has been performed in a pediatric population to determine whether garlic extract therapy is efficacious and safe in children with familial hyperlipidemia. McCrindle et al's randomized, double-blind, placebo-controlled clinical trial involving 30 pediatric patients, 8 to 18 years of age, who had familial hyperlipidemia and a minimum fasting total cholesterol level >4.8 mmol/L (>185 mg/dL) assessed the effect of a commercially available garlic extract (1998). The patients were treated with the extract at a dose of 300 mg (containing 0.6 mg of allicin), three times a day, or an identical placebo, for 8 weeks. The main outcomes measured included absolute and relative changes in fasting lipid profile parameters. The groups were equivalent at baseline and compliance was similar in the two groups ($P = .45$). The results of this trial showed no significant relative attributable effect of garlic extract on fasting total cholesterol or low-density lipoprotein. In addition, no significant effect was observed on the concentrations of high-density lipoprotein, triglycerides, apolipoprotein B-100, lipoprotein-a, fibrinogen, homocysteine, or blood pressure. There was a small effect on apolipoprotein A-I. There were no differences in adverse effects between groups. The study concluded that garlic extract therapy has no significant effect on cardiovascular risk factors in pediatric patients with familial hyperlipidemia.

OSTEOPOROSIS

Garlic may also confer phytoestrogenic effects to counter bone loss. One fascinating animal study examined the effects of garlic extracts on the intestinal movement of calcium in rats as well as to study garlic's possible role in maintaining the bone mineral content and bone tensile strength in an ovariectomized rat model of osteoporosis. The results suggest that, in this experimental model, oil extract of garlic promotes intestinal transference of calcium by modulating the activities of both intestinal alkaline phosphatase and Ca^{2+} activated ATPase. Also, the observed low bone mineral content and low bone tensile strength in these rats were significantly restored by garlic oil supplementation. Furthermore, garlic oil supplementation was able to revive partially the bilateral ovariectomy-induced decrease in the serum estrogen titer. Interestingly, the serum parathyroid hormone level, was found unaltered in these rats. The garlic oil supplemented partial recovery in serum estrogen titer in bilaterally ovariectomized rat was found to be persistently associated with enhanced calcium transference and better preservation of bone mineral content (Mukherjee et al. 2006). It may then be useful to use garlic as a treatment strategy in post-menopausal women with osteoporotic

tendency or for pre-mature menopausal women who have sustained low estrogen levels.

STRESS

Among its many uses, garlic appears to have the fortunate capacity for protecting against the ravages of stress that affects the autonomic nervous and neuroendocrine system. Rats that were trained with endurance exercises to physical fatigue enjoyed improved parameters of aerobic glucose metabolism, attenuated oxidative stress, and vasodilation, when given garlic at a dosage of 2.86 g/kg 30 minutes before exercise (Moriwaka et al. 2006). In rats exposed to psychologically stressful situations, aged garlic extracts significantly prevented the decreases in spleen weight seen in control animals. Additionally, the garlic significantly prevented the reduction of hemolytic plaque-forming-cells in spleen cells and anti-SRBC antibody titer in serum caused by this psychological stress. Moreover, a reduction in NK activities was observed in the psychological stress-exposed mice as compared with normal mice (non-stress), whereas NK activities in the garlic administered mice were almost equivalent to the mice not exposed to stressors (Kyo et al. 1999). Garlic was able to block the lipopolysaccharide induced immune cytokine and plasma corticosterone and catecholamine changes following cold water immersion stress (Nance et al. 2006). Aged garlic extract is also effective to prevent adrenal hypertrophy, hyperglycemia and elevation of corticosterone in hyperglycemic mice induced by immobilization stress (Kasuga et al. 1999). Given the extreme chronic stress many people now face during daily life, garlic may prove useful to counter the negative impact this stress has on human physiology.

DOSAGE

A commercial garlic product should provide a daily dose equal to at least 4000mg (one to two cloves) of fresh garlic. The cloves may be diced and mixed with wildflower honey for palatability. This dosage translates to at least 10mg alliin or a total allicin potential of 4000ug (Murray et al. 2006). In dried form this would be 300-mg of garlic powder tablet (standardized to 1.3 percent alliin or 0.6 percent allicin yield) two to three times per day, or 7.2 g of aged garlic extract per day (Tattelman 2005). In tincture form from fresh bulb as a 1:2 in 95 % alcohol, the dosage can be 40 drops up to six times per day.

SIDE EFFECTS/ CONTRAINDICATIONS

The main side effect commonly associated with garlic intake is breath odor, especially when raw forms of the herb are used. According to Mitchell, when garlic is taken before meals, the odor is decreased (2003). Odorless garlic formulations are available. However, odorless garlic is often prepared either by adding chemical substances to mask the odor or by cooking the garlic, which may destroy some of the active ingredients. Nausea and vomiting are other major side effects. Care should be taken in consuming high quantities. Although an entire bulb produces little juice, it is potent and can act a strong emetic, in even small quantities.

Although garlic generally poses little in terms of safety issues, there are isolated cases of topical garlic burns (Friedman et al. 2006) and anaphylaxis (Yin et al. 2007) documented in the literature. Although rare, garlic allergy has been attributed to the protein alliin lyase, which has induced IgE mediated hypersensitivity responses from skin prick testing (Kao et al. 2004). Those testing positive may need to refrain from exposure to all members of the *Allium* family, including garlic, onions and shallots.

Consumption of garlic also has been reported to be associated with decreased platelet aggregation and bleeding events (Chagan et al. 2004). As a result, the literature has generally cautioned against using garlic while using anti-coagulant therapy (Saw et al. 2006). There is a reported case of spontaneous spinal or epidural hematoma in a 87-year-old man, with associated platelet dysfunction related to excessive garlic ingestion. This patient eventually recovered (Rose et al. 1990).

However, a recent double-blinded placebo controlled pilot study by Macan et al. (2006) of 48 patients tested administration of aged garlic extract with concomitant use of warfarin (Coumadin®) and found no evidence of increased hemorrhage in either the placebo or the garlic users. The authors from UCLA determined that “the results suggest that AGE is relatively safe and poses no serious hemorrhagic risk for closely monitored patients on warfarin oral anticoagulation therapy. Although the risk-benefit ratio of AGE use needs to be considered carefully when warfarin therapy is necessary, its positive effects may be beneficial to people with a high-risk background or who are taking cardiovascular medications.”

CONCLUSIONS

Garlic, from crushed to capsules, is consumed throughout the world. This abstract demonstrates by documented studies the benefits of garlic for its anti-microbial , antioxidant and anti-inflammatory potential. It has been used to treat cardiovascular diseases, including atherosclerosis, strokes, hypertension, thrombosis and hyperlipidemias, as well as uses in Alzheimer's, diabetes, and cancer. Most impressive and unique are its use and safety in children. Although some studies show medicinal benefits of garlic, there are others which do not. Clearly more studies are needed. Fresh and powdered garlic are popular for food seasoning and should continue to be used. Today, with the ever-growing resistant organisms, garlic, taken alone or with other herbal antibiotics such as grape seed extract or ginger, remains a powerful antimicrobial agent. Clearly more studies are needed to refine the use and improve the efficacy of this important plant medicine.

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