Garlic

Allium sativum L.

[Fam. *Liliaceae*]

Overview

Garlic consists of various dosage forms of the fresh or carefully dried bulbs of *Allium sativum*. In the U.S. and Western Europe, most of garlic's popularity is based on the extensive traditional use of this herb, and on scientific research suggesting that cardiovascular benefits are associated with ingesting garlic as a conventional food and a dietary supplement. More than 3,000 scientific articles have been published on the chemistry, pharmacology, toxicology, and clinical uses of garlic.

Primary Uses

- Hyperlipidemia
- Atherosclerosis

Other Potential Uses

- Hypertension, mild
- Peripheral arterial occlusive disease (PAOD)
- Decreased platelet function
- Colon cancer prevention
- Stomach cancer prevention
- Coughs, colds, catarrh, and rhinitis (These traditional uses are not supported by clinical trials.)

Pharmacological Actions

Garlic reduces total cholesterol and serum triglycerides; elevates high density lipoproteins (HDL); prevents platelet aggregation and thrombus formation; stimulates fibrinolysis; prolongs clotting time; reduces low-density lipoprotein oxidation; reduces systolic and diastolic blood pressure; attenuates age- and blood pressure-related increases in aortic stiffness; has immunomodulating activity; reduces blood glucose levels; is antifungal and fungistatic against *Cryptococcus neoformans;* antioxidant; anticancer; antimicrobial; inhibits anion transport and sickle cell dehydration and restricts dense cell formation in sickle cell patients.

Dosage and Administration

For the prevention of atherosclerosis and prophylaxis and treatment of peripheral arterial vascular diseases, long-term treatment is generally advised. Epidemiological findings support long-term, consistent use to aid in preventing stomach and intestinal cancers.

FRESH HERB: 4 g (1 clove) minced bulb daily.

INFUSION: 4 g in 150 ml of hot water.

FLUID EXTRACT: 4 ml [1:1 (*g/ml*)].

TINCTURE: 20 ml [1:5 (*g/ml*)].

GARLIC POWDER (standardized): 200–300 mg, 3 times daily.

AGE™ AGED GARLIC EXTRACT (standardized): 300–800 mg, 3 times daily, or 1–5 ml daily.

Contraindications

None known according to the German Commission E and other European scientific bodies. According to the World Health Organization, patients with a known allergy to garlic and those taking warfarin (and presumably other anticoagulants) should use caution in ingesting garlic. However, a clinical trial on a proprietary aged garlic extract (AGE) showed no prolonged bleeding in patients taking warfarin. Reports of increased clotting time suggest that patients avoid garlic at least one week prior to surgery.

PREGNANCY AND LACTATION: There are no restrictions on using garlic during pregnancy and lactation. A controlled trial showed that garlic's major sulfur-containing volatile compounds are transmitted to human milk, leading to infants' improved drinking habits.

Adverse Effects

Garlic odor may permeate the breath and skin. Gastrointestinal symptoms and intestinal flora changes or allergic reactions are rare. In separate single case reports, excessive ingestion of garlic was associated with postoperative bleeding, spontaneous spinal epidural hematoma, and platelet dysfunction. Occupational exposure to crushed garlic products and the topical application of garlic to treat wounds or infections may cause allergic contact dermatitis. For garlic and various generic garlic preparations, reported allergic reactions included burns, zosteriform dermatitis, induction of pemiphigus (blisters), allergic asthma and rhinitis, contact urticaria, and protein contact dermatitis; but no adverse effects were reported for AGE according to toxicological and clinical studies. Garlic preparations can increase clotting time, which is sometimes beneficial, but in some cases can contribute to an adverse event. Cross-sensitivity may occur with onions and tulips.

Drug Interactions

Concurrent use of garlic and antiplatelet agents (e.g., aspirin) and anticoagulants (e.g., warfarin) might increase the potential for prolonged bleeding. One report showed that clotting time doubled for 2 patients taking warfarin and garlic simultaneously, although there was insufficient information to properly assess these cases. A controlled trial on AGE resulted in no interaction with warfarin. A small trial suggests possible serum reduction of saquinavir, an anti-HIV drug.

Clinical Review

Of 32 studies (45,694 total participants) on garlic's impact on cardiovascular and arterial health, cancer, immunity, and circulation, all but four demonstrated positive effects.

Two reviews concluded that garlic preparations might have small, positive, short-term effects (< 3 months) on lipids and promising antithrombic effects. Insignificant effects on blood pressure and no effect on glucose levels were observed. However, data was insufficient to draw conclusions about certain clinical cardiovascular outcomes (e.g. myocardial infarction), antithrombic activity, or cancer prevention. Due to the marginal quality and short duration of many trials and the unpredictable release and inadequate definition of active constituents of many garlic preparations used in the studies, conclusions regarding clinical significance are limited.

Lipid-lowering effect

Thirteen trials (795 participants) demonstrated a positive correlation between lipid-lowering effects and garlic oil, powder, or capsules. Six randomized, double-blind, placebo-controlled (R, DB, PC) studies and four DB studies supported garlic use in treating elevated lipid conditions including hyperlipidemia and hypercholesterolemia. One R, open, parallel group, comparison (O, PG, Cm) study (70 participants) found garlic powder to have a significant impact over garlic oil in lowering blood-lipid counts and blood pressure and in increasing a sense of overall well-being. An R, PC study involving 35 renal transplant patients found a garlic product to have positive effects on hyperlipidemia. One O study (82 participants) found a positive impact of garlic on coronary heart disease, in addition to its lipid-lowering effects.

A meta-analysis on garlic's effect on total serum cholesterol levels found a statistically significant reduction in total cholesterol levels. Another study assessed and subsequently reassessed clinical data from 952 patients and 16 trials and found that all data demonstrated a significant reduction of total cholesterol when comparing garlic to placebo. Three studies on the allicin-standardized garlic powder tablets failed to show a significant reduction in elevated serum cholesterol. It was later determined that allicin released from the tablets varied significantly, and that the lack of expected allicin release possibly led to negative results. A study of 24 brands of enteric-coated tablets found that 83% of the brands released less than 15% of their allicin potential. Subsequently, the researchers recommended that manufacturers standardize supplements to dissolution of allicin release, not to allicin potential. (For non-allicin products, e.g., AGE, the standardization is to bioavailable compounds, e.g., S-allycysteine [SAC].) In the most recent and comprehensive meta-analysis (13 R, DB, PC trials), researchers showed a significant difference ($p<0.01$; 5.8%) in the reduction of total cholesterol levels between baseline and placebo. The authors concluded that current evidence indicates that any specific lipid-lowering effect is small, and the clinical outcome may not be meaningful; however, there were several problems identified with the meta-analysis, indicating that conclusions can only be applied to the specific brands tested and not to the general effectiveness of garlic.

Antihypertensive effect

Two R, DB, PC studies and one R, O, PG, Cm study (159 total participants) showed garlic's antihypertensive effects. A systematic review and meta-analysis of 8 R, C trials (415 participants) was conducted to determine garlic's effect on blood pressure. Of the 7 trials that compared garlic with placebo, 3 demonstrated a significant reduction in systolic blood pressure (SBP), and 4 in diastolic blood pressure (DBP). The authors concluded that more rigorously designed trials might provide evidence to recommend hypertension treatment with garlic.

Antiplatelet effects

One R, DB, PC, crossover (CO) study and 2 DB, PC studies (214 total participants) indicate the potential use of garlic as a coronary disease preventative due to its positive impact on platelet functions.

Anti-atherosclerotic effect

Garlic's positive influence on arterial and fibrinolytic activities was shown in two studies (354 participants). The longest clinical trial on garlic to date, a R, DB, PC, 4-year study (152 participants), showed that garlic had an anti-atherosclerotic impact, decreasing age-related arterial plaque. In one epidemiological, cross-sectional, observational (E, CS, OB) study (202 participants), standardized garlic powder was found to have positive effects on arterial activities, including elastic vascular resistance, pulse wave velocity, and systolic blood pressure.

Anticancer/Chemoprevention

Anti-cancer and chemopreventative qualities of garlic were shown in 5 studies (44,044 subjects). One E study of 15 years demonstrated that stomach cancer incidents were reduced with use of raw and cooked garlic. Two E studies (42,325 subjects) found that garlic intake significantly decreased colon cancer risks. Two OB studies demonstrated garlic's chemopreventative potential through the improvement of arachidonic acid and acetaminophen metabolism. A meta-analysis of E studies on the association between garlic consumption and risk of stomach, colon, head and neck, lung, breast, and prostate cancers concluded that raw and cooked garlic use might have a protective effect against stomach and colorectal cancers.

Other

One pilot study involving 7 HIV+ patients demonstrated a positive impact on natural killer cell activity and improvement in conditions such as diarrhea, genital herpes, and candidiasis. One R, DB, PC study showed that garlic did not negatively impact bleeding potential in warfarin therapy patients. Garlic's impact on peripheral circulation was observed in two studies: one R, CO, Cm study showed immediate improvement in hand and foot circulation; and one DB, PC study showed a significant increase in walking distance in persons with peripheral arterial occlusive disease (PAOD). The latter was the only study to meet the Cochrane Library's inclusion criteria for its review on garlic use for PAOD. Because the one study reviewed was small, of short duration (12 weeks), and found no significant overall improvement in patients with PAOD, the Cochrane Review disagreed with the author's findings and concluded that further trials on garlic's effects on PAOD are warranted.

Garlic

Allium sativum L.
[Fam. *Liliaceae*]

Overview

In the U.S. and Western Europe, garlic is one of the most popular substances used to reduce various risks associated with heart disease. Most of garlic's popularity is based on the herb's well-known folk uses and scientific research on the benefits of garlic for heart health. These health-promoting benefits may be experienced by using garlic as both a food ingredient and a dietary supplement.

Uses

For slightly reducing elevated levels of cholesterol in the blood; prevention of hardening of the arteries; improvement of blood flow; mild hypertension (high blood pressure); possible prevention of stomach and colon cancer; supportive therapy for peripheral arterial occlusive disease (PAOD, poor circulation to the legs causing tightness and pain in the calves when walking).

Dosage

Long-term treatment is generally advised in the prevention of atherosclerosis and in the prevention and treatment of peripheral arterial vascular diseases. Epidemiological findings (population studies) support long-term, consistent use for the possible prevention of stomach and intestinal cancers.

Fresh, minced garlic: 1 clove daily.

Infusion: 1 clove in 150 ml of hot water.

Garlic powder (standardized): 200–300 mg, 3 times daily (in pill or tablet form).

AGE™ aged garlic extract (standardized): 300–800 mg, 3 times daily or 1–5 ml daily (in capsules).

Contraindications

None known according to the German Commission E and other leading scientific bodies. According to the World Health Organization, patients with a known allergy to garlic and those taking anticoagulant drugs like warfarin (Coumadin®) should be cautious about ingesting garlic. Garlic should not be taken prior to surgery (at least one week) as it may interfere with blood clotting.

Pregnancy and Lactation: There are no known restrictions during pregnancy or lactation. However, some of garlic's properties are transmitted to human milk, leading to improved drinking habits in infants.

Adverse Effects

Being a commonly used food, garlic is relatively safe. Adverse effects are rare, but there may be gastrointestinal symptoms and changes to the intestinal flora (beneficial bacteria that aid in digestion). Allergic reactions have been reported for garlic and various generic preparations, but no adverse effects were reported for AGE according to toxicological and clinical studies. According to one report, garlic was associated with unusual bleeding after an operation. Garlic preparations can increase clotting time, which is sometimes beneficial, but in some cases can contribute to an adverse event. Also, garlic may produce a characteristic odor on the breath or skin.

Drug Interactions

Taking garlic with antiplatelet agents, like aspirin, and anticoagulants, like warfarin, may increase the potential for prolonged bleeding.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.

Garlic

Allium sativum L.

[Fam. *Lilaceae*]

Overview

In the United States and Western Europe, garlic is one of the most popular substances used to reduce various risks associated with cardiovascular disease. Most of garlic's popularity is based on the extensive traditional use of this herb and on scientific research suggesting that cardiovascular benefits are associated with ingesting garlic as both a conventional food and dietary supplement (Blumenthal *et al.*, 2000). Garlic preparations have been one of the top-selling herbal supplements on the U.S. market for many years (Brevoort, 1998), ranking third in retail sales in the mainstream market in 2000, and generating revenues over $61 million (Blumenthal, 2001). To date more than 3,000 scientific papers have been published investigating the activities of garlic and garlic compounds, including chemical, toxicological, pharmacological, clinical, and epidemiological studies (Amagase *et al.*, 2001). Garlic preparations with uniquely different chemical compositions, including powdered dried garlic products standardized to allicin yield and aged garlic extract (AGE™) products that are standardized to S-allylcysteine (SAC), have been the subject of numerous clinical studies. Determining which forms are the most effective remains controversial and is an ongoing subject of study and debate. Medical literature includes positive outcomes in clinical studies involving several types of garlic preparations.

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Description

Garlic preparations consist of the fresh or dried bulbs (main bulb and secondary bulbs or cloves) of *Allium sativum* L. [Fam. *Lilaceae*], and various dosage forms (Blumenthal *et al.,* 1998). Garlic oil is not present in fresh or dried garlic bulbs; instead, the oil is produced by converting water-soluble thiosulfinates to oil-soluble sulfides via steam distillation. Aged garlic involves long-term extraction in dilute ethanol for up to 20 months, then drying; pickling garlic involves immersion in vinegar (5% acetic acid) (Amagase *et al.*, 2001; Lawson, 1998a).

Primary Uses

Cardiovascular

- Hyperlipidemia (Isaacsohn *et al.*, 1998; Lash *et al.*, 1998; McCrindle *et al.*, 1998; Steiner *et al.,*1996a, 1996b; Yeh *et al.*, 1995; De A Santos and Johns, 1995; Steiner and Lin, 1994; Jain *et al.*, 1993; Grünwald *et al.,* 1992; Holzgartner *et al.*, 1992; Mader, 1990; Vorberg *et al.,* 1990; Lau *et al.*, 1987; Bordia, 1981)
- Atherosclerosis (Koscielny *et al.*, 1999)

Other Potential Uses

Cardiovascular

- Hypertension, mild (Steiner *et al.*, 1996; Auer *et al.*, 1990)
- Peripheral arterial occlusive disease (PAOD) (Koscielny *et al.*, 1999; ESCOP, 1997; Kiesewetter *et al.*, 1993b)

Hematology

- Decreased platelet function (Rahman and Billington, 2000; Steiner *et al.*, 2001; Steiner *et al.*, 1996; Kiesewetter *et al.*, 1991; Kiesewetter *et al.*, 1993a)

Chemopreventative

- Colon cancer preventative (Steinmetz *et al*, 1994; Witte *et al.,* 1996)
- Stomach cancer preventative (You *et al.*, 1989)

Miscellaneous

- Garlic has traditionally been used to relieve cough, colds, catarrh, and rhinitis, although clinical trials do not support such uses (ESCOP, 1997)

Dosage

Internal

Crude Preparations

FRESH HERB: 4 g daily (1 clove) minced bulb or equivalent preparations (Blumenthal *et al.*, 1998). [NOTE: Some authors have suggested that this dosage level should be revised downward to approximately 2,700 mg of fresh garlic, equivalent to the 900 mg of garlic powder used in some clinical trials that studied the ability of garlic to prevent and/or reverse atherosclerotic plaque build-up (Schulz *et al.*, 2001).]

INFUSION: 4 g in 150 ml of hot water (Blumenthal *et al.*, 2000).

FLUID EXTRACT: 1:1 (*g/ml*), 4 ml (Blumenthal *et al.*, 2000).

TINCTURE: 1:5 (*g/ml*), 20 ml (Blumenthal *et al.*, 2000).

Standardized Preparations

GARLIC POWDER (Kwai®): 200–300 mg, 3 times daily (Warshafsky *et al.*, 1993).

AGE ™ (Kyolic®) aged garlic extract: 300–800 mg, 3 times daily or 1–5 ml daily (Steiner 2001; Steiner *et al.*, 1996; Rahman and Billington, 2000; USP, 2002; Lau *et al.*, 1987).

Duration of Administration

Long-term treatment is generally advised in the prevention of atherosclerosis (Koscielny *et al.*, 1999), and the prophylaxis and treatment of peripheral arterial vascular diseases (ESCOP, 1997). Epidemiological observations support the long-term consistent use for prevention of cancer in the stomach and intestines (You *et al.*, 1989).

Chemistry

Crude Preparations

Fresh garlic bulbs contain about 65% water, 28% carbohydrates (fructans), 2.3% organosulfur compounds (OSC), 2% protein, and 1.2% free amino acids. The main OSC in whole garlic are the cysteine sulfoxides (1% alliin and 0.1% cycloalliin) and the γ-glutamylcysteines (0.6% γ-glutamyl-S-trans-1-propenylcysteine and 0.4% γ-glutamyl-S-allylcysteine). When the bulb is bruised, crushed, chewed, or minced, the alliin, in the presence of the enzyme alliinase, is converted to allicin (ESCOP, 1997). One mg of alliin produces 0.458 mg of allicin, which is considered to be responsible for some of garlic's biological activity and is a precursor to some thiosulfinates, which also have been shown to be active (Lawson 1998a; Block, 1985; Bradley, 1992; Budavari, 1996; ESCOP, 1997). However, allicin is unstable and decomposes to other volatile sulfur compounds (the half-life of allicin is not more than 24 hours), so the extent of allicin's activity has been questioned. Intact garlic cloves (the sections that comprise the garlic bulb) also contain S-allylcysteine (SAC), but no allicin. SAC is formed from gamma-glutamyl cysteine catabolism and has been reported to contribute to the health benefits of some garlic preparations (Amagase *et al.*, 2001). Fresh and aged garlic extract (AGE, see below) also contain steroidal saponins (Matsuura, 2001).

Standardized Preparations

Processed garlic preparations contain a variety of sulfur-containing compounds other than those found naturally in intact garlic cloves, depending on the conditions applied (Lawson, 1998a; Fenwick and Henley, 1985). Sulfur-containing compounds in commercial garlic preparations vary, depending on their manufacturing process. Powdered preparations of dried garlic contain alliin and compounds derived from its subsequent transformation, but no allicin. Enteric coatings protect these powdered preparations from conversion while in the stomach. Garlic oil yields neither alliin, nor allicin as the converting enzyme is destroyed by heat. It does contain diallyl disulfide, diallyl trisulfide, and allyl methyl trisulfide. Macerated garlic-derived oil contains vinyldithiins, ajoene, and diallyl trisulfides (Lawson, 1998a). Garlic extract and odorless AGE are listed in the *United States Pharmacopeia/National Formulary* (USP, 2002). The most abundant sulfur compound in AGE is SAC; it is standardized to not less than 0.05% SAC (USP, 2002).

Pharmacological Actions

Human

Garlic reduces total cholesterol (TC) and serum triglycerides (TG) and elevates high density lipoproteins (HDL) (Auer *et al.*, 1990; Barrie *et al.*, 1987; Lau *et al.*, 1987; Bordia, 1981; De A Santos and Johns, 1995; Silagy and Neil, 1994a); prevents platelet aggregation and thrombus formation (Rahman and Billington, 2000; Barrie *et al.,* 1987; Kiesewetter *et al.,* 1993a; Kiesewetter *et al.,* 1993b; Legnani *et al.,* 1993); stimulates fibrinolysis, prolongs clotting time (Chutani and Bordia, 1981; Gadkari and Joshi, 1991; Harenberg *et al.,* 1988; Legnani *et al.,* 1993); reduces low-density lipoprotein (LDL) oxidation (Ide and Lau, 2001; Lau, 2001; Munday, 1999; Steiner and Lin, 1994; Harris *et al.*, 1995; Phelps and Harris, 1993); reduces systolic blood pressure, diastolic blood pressure, and mean blood pressure from baseline (Steiner *et al.,* 1996a, 1996b; De A Santos and Johns, 1995; Silagy and Neil, 1994b; Grünwald *et al.,* 1992; Auer *et al.,* 1990;); attenuates age- and blood pressure-related increases in aortic stiffness (Breithaupt-Grögler *et al.,*1997); stimulates peripheral microcirculation (Okuhara, 1994); is antifungal and fungistatic against *Cryptococcus neoformans*, the organism that causes cryptococcal meningitis (Anon., 1980; Davis *et al.,* 1990); may decrease the risk of gastrointestinal cancers (Gail *et al.*, 1998; You *et al.*, 1991, 1989, 1988; Reuter *et al.,* 1996; Buiatti *et al.*, 1989; Lau, 1989); modulates immune system activity (Brosche and Platt, 1993; Kandil *et al.,* 1988; Lawson, 1998a; Reuter *et al.,* 1996); reduces blood glucose levels (Kiesewetter *et al.,* 1991). Garlic does not inhibit *H. pylori* bacteria in the stomach (Graham *et al.*, 1999). Although one study concluded that garlic extracts had no statistically significant impact on how far patients with peripheral vascular disease (PVD) can walk (Kiesewetter *et al.*, 1993b), AGE has been reported to exhibit stimulation of peripheral circulation in human subjects (Okuhara, 1994; Kikuchi *et al.*, 1994). One pilot clinical trial (Ohnishi *et al.,* 2000) indicated an effect of AGE and other antioxidants in the potential treatment of sickle cell anemia patients.

Animal

Garlic lowers elevated levels of serum homocysteine (Yeh, 1999); lowers serum cholesterol and lipids (Bordia *et al.,* 1975; Kamanna and Chandrasekhara, 1982; Chi *et al.*, 1982); is antithrombotic (Bordia *et al.*, 1975); increases fibrinolysis and clotting time (Bordia *et al.,* 1975; Reuter *et al.,* 1996); reduces blood pressure (Sial and Ahmad, 1982; Ruffin and Hunter, 1983); is antioxidant (Han *et al.,* 1992; Lawson, 1998a); modulates immune system (Kyo *et al.*, 1999, 1998; Lawson, 1998a; Reuter *et al.,* 1996); reduces blood glucose levels and increases insulin levels (Augusti, 1975; Chang and Johnson, 1980); is anti-allergenic (Kyo *et al.,* 1997); exhibits antitumor activity against transitional cell carcinoma of the bladder with AGE (Lau *et al.,* 1986; Riggs *et al.,* 1997); reduces breast cancer incidence (Amagase and Milner, 1993; Liu *et al.,* 1992; Kröning, 1964); decreases incidence of hepatic tumors in the *Bufo regularis* toad (El-Mofty *et al.,* 1994).

In vitro

Antithrombotic

The rational clinical application of garlic necessitates demonstrating the association between garlic consumption and important clinical outcomes such as atherosclerosis. *In vivo* and *in vitro* studies suggest garlic extracts and several garlic constituents have a significant antithrombotic effect (Ariga *et al.,* 1981; Boullin, 1981; Srivastava, 1986; Mohammed and Woodward, 1986). Garlic has been shown to increase fibrinolysis and prolong clotting time (Reuter *et al.,* 1996). Adenosine in AGE and its constituents are the most potent antiplatelet constituents of garlic. Allicin was thought an active compound in garlic due to its highly reactive and oxidative characteristics, but it is rapidly metabolized in human blood (in *in vitro* culture) and therefore might not contribute to the *in vivo* antithrombotic effect of garlic (Freeman and Kodera, 1995; Koch and Lawson, 1996).

Ajoene is found in small amounts in garlic oil-macerates, but not in commercial garlic preparations and garlic powders.

Bioavailability of ajoene has not yet been established. Antithrombotic and vasodilatory actions of garlic might be due to adenosine deaminase and cyclic AMP phosphodiesterase, which can be found in garlic extracts. The decrease of thromboxane B2 (TXB2) levels is another possible explanation for garlic's antithrombotic effects. Most of the above explanations are based on *in vitro* and *in vivo* experiments (Berthold and Sudhop, 1998; Rahman and Billington, 2000; Bordia *et al.,* 1996; Agarwal 1996).

Koscielny *et al.* (1999) reported a slowing and reversal of atherosclerotic plaque formation. AGE has been shown to protect vascular endothelial cells against hydrogen peroxide-induced lipid peroxidation and biomembrane damage (Yamasaki *et al.,* 1994); prevent oxidized LDL-induced membrane damage, loss of cell viability, and lipid peroxidation (Ide and Lau, 1997b); and demonstrate antihypertensive activity (Lawson, 1998a; Steiner *et al.*, 1996; Koch *et al.,* 1992a; Sendl *et al.,* 1992).

Anticancer

Garlic inhibits the induction and growth of cancer (Milner, 1996; Lea, 1996). The effect on tumor initiation and promotion has been documented, and both the oil-soluble and water-soluble OSCs such as methyl propyl disulfide and propylene sulfide, SAC, S-allylmercaptocysteine (SAMC), and allicin reduce the proliferation of neoplasms and inhibit the development of liver glutathione S-transferase placental (GST-P) positive tumor foci and other indications of cancer in different organs. In contrast, OSCs such as diallyl sulfide, diallyl trisulfide, and allyl methyl trisulfide enhance the formation of liver tumor foci.

However, in rats, diallyl disulfide shows the following activities: inhibits the potential for colon and renal tumor development (Fukushima *et al.*, 1997); inhibits the growth of human prostate cancer cells (Pinto *et al.,* 1997a); demonstrates cytotoxic activity against MBT2 bladder tumor cells (Riggs *et al.,* 1997); is antiallergenic (Kyo *et al.,* 1997); stimulates macrophage activity, natural killer cells, and LAK cells. It may also increase production of interleukin (IL-2), tumor necrosis factor (TNF) and interferon gamma, which are cytokines associated with beneficial antitumor responses. AGE protects against the immunosuppression induced by chemo- and radiation therapy (Lamm and Riggs, 2000; Lau, 1989) and UV light (Reeve *et al.*, 1993a, 1993b).

Antimicrobial effects

Antibacterial activity against *Escherichia, Salmonella, Staphylococcus, Streptococcus, Klebsiella, Proteus, Bacillus, Mycobacterium, Clostridium*, and resistant strains (Adetumbi and Lau, 1983; Farbman *et al.,* 1993; Hughes and Lawson, 1991; Lawson 1998a; Reuter *et al.,* 1996); antifungal activity against *Candida* and *Cryptococcus* (Anon., 1980; Caporaso *et al.,* 1983; Hughes and Lawson, 1991; Lawson, 1998a); antiulcer/antibacterial against *Helicobacter pylori* (Sivam, 2001; Sivam *et al.*, 1997); antifungal, antiparasitic (Ankri and Mirelman, 1999). The main antimicrobial effect of allicin is limited when in direct exposure to the microorganisms due to its chemical reaction with enzymes (e.g., alcohol dehydrogenase, thioredoxin reductase) and RNA polymerase. This reaction can affect the essential metabolism of cysteine proteinase activity involved in the virulence of *Entamoeba histolytica*. An aqueous extract of garlic cloves, standardized for its thiosulfinate concentration tested positively for its antimicrobial activity against *H. pylori* (Sivam *et al.*, 1997). Minimum inhibitory concentration was 40 mcg thiosulfinate per ml. It is possible that the sensitivity of *H. pylori* to garlic extract at such low concentrations may be related to the reported low risk of stomach cancer in those populations with high allium vegetable intake. However, an uncontrolled trial involving 20 patients with positive urea breath tests, taking 300 mg tablets of dried garlic powder, three times daily for eight weeks, did not eradicate *H. pylori* (Fennerty *et al.*, 1999).

Hematology effects

In vitro studies (and a pilot clinical trial) have indicated an effect of AGE and other antioxidants in the potential treatment of sickle cell anemia patients (Ohnishi *et al.*, 2000, 2001; Ohnishi and Ohnishi, 2001).

Mechanism of Action

Lipid-lowering

- One possible mechanism is thought to be attributed to allicin/thiosulfinates (Lawson, 1998a; Reuter *et al.*, 1996) but a recent study revealed water-soluble OSC, e.g., SAC and SPC, may be the active compounds inhibiting cholesterol synthesis (Liu and Yeh, 2001). However, oil-soluble OSC, e.g., diallyl disulfide (DADS) and others, decomposed from thiosulfinates including allicin, actually killed the cells, thus indirectly inhibiting cholesterol synthesis (Liu and Yeh, 2001).
- Increases catabolism of fatty acid-containing lipids, especially triglycerides (Yeh *et al.*, 1995; Yeh and Yeh, 1994; Lawson, 1998a).
- Inhibits cholesterol biosynthesis at the level of β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) reductase (Yeh *et al.*, 1995; Yeh and Yeh, 1994; Gebhardt *et al.,* 1994; Gebhardt, 1993).
- Inhibits cholesterol biosynthesis at later steps, as evidenced by accumulation of the cholesterol precursors, lanosterol and 7-dehydrocholesterol, although this latter effect may be of minor therapeutic significance (Gebhardt *et al.,* 1994; Gebhardt, 1993).
- Enhances palmitate-induced inhibition of cholesterol biosynthesis (Gebhardt, 1995).
- Inhibits cholesterol biosynthesis by targeting squalene monooxygenase, an enzyme that catalyzes the downstream pathway in cholesterol synthesis (*in vitro* study on fresh garlic extract) (Gupta and Porter, 2001).
- Lipid-lowering activity may be due to the presence of steroid saponins in fresh garlic and AGE, which may interfere with the absorption of total and LDL cholesterol from the intestine lumen, thereby reducing plasma levels (40–57% in test animals), without adversely affecting HDL levels. Saponins are known to inhibit intestinal absorption of cholesterol, suggesting possible hypocholesterolemic effect (Matsuura, 2001).

Antithrombotic

- Garlic inhibits platelet aggregation and stimulates fibrinolysis; this may be attributed to allicin/thiosulfinates at lower garlic doses and cycloalliin at higher garlic doses (*in vitro*) (Lawson, 1998a; Reuter *et al.*, 1996). However, since it is argued that allicin/thiosulfinates may not be bioavailable, other compounds may be responsible (Amagase *et al.*, 2001).
- Inhibits normal arachidonate metabolism (Ariga *et al.*, 1981; Makheja *et al.*, 1980; Makheja *et al.*, 1981; Reuter *et al.*, 1996).

- Inhibits the lipoxygenase and cyclo-oxygenase pathways of the arachidonic acid cascade, thereby inhibiting the synthesis of prostaglandins and thromboxanes (PGE2, PGD2, PGI2, TXB2) (Rahman and Billington, 2000; Reuter *et al.*, 1996; Ariga *et al.,* 1981; Makheja *et al.,* 1981, 1980).
- Inhibits fatty acid lipoxygenase (Liu and Yeh, 2001; Reuter *et al.*, 1996; Ariga *et al.,* 1981; Makheja *et al.*, 1981, 1980).
- Ajoene affects fibrinogen-induced human platelet aggregation and inhibits binding of fibrinogen to adenosine diphosphate (ADP) stimulated platelets *in vitro* (Reuter *et al.*, 1996).

Antihypertensive

- Action is thought to be attributed to γ-glutamylcysteines and fructans; allicin is not involved (Lawson, 1998a; Reuter *et al.,* 1996).
- γ-glutamylcysteines can inhibit angiotensin-converting enzyme (ACE), thus inhibiting angiotensin II (a hormone that increases vasoconstriction) (Lawson, 1998a; Sendl *et al.,* 1992).
- Fructans can inhibit adenosine deaminase in isolated cells, thus increasing adenosine and its associated blood vessel dilatory activity (Lawson 1998a; Koch *et al.,* 1992).
- Increases nitric oxide through activation of nitric oxide synthase activity (Das *et al.,* 1995).

Antimicrobial

- Action is *in vitro* or externally thought to be attributed to allicin/thiosulfinates (Lawson, 1998a; Reuter *et al.,* 1996).
- Allicin disrupts cellular metabolic processes *in vitro* through inactivation of proteins by oxidation of essential thiols to disulfide, competitive inhibition of enzymes containing cysteine in their active sites by reacting with the sulfhydryl (-SH) group, and noncompetitive inhibition of enzymes by reacting with -SH groups at allosteric sites (Adetumbi and Lau, 1983; Cavallito *et al.*, 1944; Lawson, 1998a).
- Garlic extract inhibits *H. pylori* bacterial *in vitro* at moderate concentrations, thereby suggesting mechanism for antigastric ulcer effect (Sivam, 2001; Sivam *et al.*, 1997).

Anticancer

- Action is thought to be attributed to any number of garlic compounds: SAC, SAMC, thiosulfinates, γ-glutamylcysteines, and other unknown compounds (Lawson, 1998a; Pinto *et al.*, 1997b; Reuter *et al.,* 1996, Amagase and Milner, 1993; Liu *et al.,* 1992) although the thiosulfinates (e.g., allicin) are questioned due to their instability.
- Decreases the amount of nitrate-reducing bacteria in the stomach, thus reducing the formation of carcinogenic nitrosamines (Dion and Milner, 1996; Mei *et al.,* 1985, 1982).
- Inhibits the induction and growth of cancer, which may be mediated by modulation of carcinogen metabolism (Lea, 1996).
- Stimulates macrophage activity, natural killer cells, and LAK cells, and might increase the production of IL-2, TNF, and interferon gamma, which are cytokines associated with beneficial antitumor response (Lamm and Riggs, 2000; Lau *et al.*, 1991; Lau, 1989; Abdullah *et al.,* 1989).

Antiallergenic

- Inhibits antigen-specific histamine release from mast cells *in vitro* (Kyo *et al.,* 1997); decreases antigen-specific IgE mediated skin reactions *in vivo* (Kyo *et al.,* 1997); and reduces antigen-specific, late-phase reaction by modulating the production and release of cytokines from activated T-lymphocytes *in vivo* (Kyo *et al.,* 1997).

Antioxidant

- Action is thought to be attributed to primarily water-soluble OSC (e.g., SAC and SAMC) in addition to fructosyl-arginine, other Maillard reaction compounds in AGE, and other compounds (Ryu, 2001; Imai, 1994); some authors suggest action may be due to the allicin/thiosulfinates (Lawson, 1998a; Reuter *et al.,* 1996).
- Decreases oxidation of LDL cholesterol in humans (Ide and Lau, 2001; Lau, 2001; Munday, 1999; Steiner and Lin, 1994; Harris *et al.,* 1995; Phelps and Harris, 1993).
- Increases the activity of several enzymes (including glutathione peroxidase and catalase) involved in antioxidative processes and decreases the concentration of lipid peroxides in the blood (Ide and Lau, 1999; Steiner and Lin, 1994; Geng and Lau, 1997; Han *et al.,* 1992).
- Increases intracellular glutathione (GSH) (a potent intracellular antioxidant and detoxifier), modulates the activity of the GSH redox cycle, and increases activity of superoxide dismutase (SOD, a potent intracellular antioxidant) activity (Ide and Lau, 2001; Wang *et al.*, 1999; Hatono *et al.*, 1996; Geng and Lau, 1997).

Immunomodulatory

- Action thought to be attributed to protein fraction of garlic (Moraika *et al.*, 1993; Lau *et al.*, 1991; Hirao *et al.*, 1987).
- Inhibits activation of nuclear factor kappa B (NF-κB) in human T-cells that are involved in immune and inflammatory reactions (Geng *et al.,* 1997).
- Increases phagocytosis, natural killer cell activity, antibody titer, and lymphocyte counts (Brosche and Platt, 1993; Kandil *et al.,* 1988; Lawson, 1998a; Reuter *et al.,* 1996).

Hematological (AGE)

- Inhibits anion transport and sickle cell dehydration (Ohnishi *et al.*, 2001), restricts dense cell formation (Ohnishi and Ohnishi, 2001) and 4.0 mg/mL was shown to inhibit dense cell formation by 50% (Ohnishi *et al.*, 2000). A U.S. patent has been granted to Wakunaga of America, Mission Viejo, CA for the "Therapeutic Uses of Specially Processed Garlic for Sickle Cell Disease" (Ohnishi and Tsuyoshi, 2001).
- Increased natural killer cell activity and improved helper suppressor T-cell ratios in AIDS patients (Abdullah *et al.*, 1989).

Contraindications

None known according to the German Commission E and other leading European scientific bodies (Blumenthal *et al.*, 1998; ESCOP, 1997). The World Health Organization (WHO) cautions against the use of garlic by patients with a known allergy to garlic, and those taking warfarin (and presumably other anticoagulants) (WHO, 1999). However, AGE has been tested in a placebo-controlled, double-blind clinical trial in patients taking Coumadin® (warfarin); there was no demonstrated interaction

with Coumadin® and no prolonged bleeding (Rozenfeld *et al.*, 2000). Several case reports of increased clotting time suggest that patients should discontinue use prior to surgery (Brinker, 2001), usually by at least one week.

PREGNANCY AND LACTATION: None known (Blumenthal *et al.*, 1998; ESCOP, 1997). A controlled trial showed that major sulfur-containing volatiles from garlic are transmitted to breast milk, leading to improved drinking habits of infants (ESCOP, 1997; Mennella and Beauchamp, 1991). In Japan, AGE is an ingredient in pharmaceutical products that are used in nutritional nourishment for pregnant and lactating women.

Adverse Effects

The most commonly reported adverse effect of garlic is that its odor may pervade the breath and skin (Blumenthal *et al.*, 1998). Raw garlic has a stronger odor and higher levels of high molecular weight sulfur compounds than cooked garlic, but malodorous breath tested in humans who ingested raw garlic showed higher levels of low molecular weight sulfur compounds and different constituents than those associated with common halitosis (Tamaki and Sonoki, 1999). Differences in the frequency of other adverse effects caused by various garlic preparations have not been completely determined (Mulrow *et al.*, 2000), such adverse effects being dependent upon the method of preparation. Gastrointestinal symptoms and changes to the intestinal flora or allergic reactions are rare but are occasionally reported (Lembo *et al.*, 1991). In separate, single-case reports, garlic was associated with postoperative bleeding (Burnham, 1995), spontaneous spinal epidural hematoma, and platelet dysfunction from excessive ingestion (Rose *et al.*, 1990). Occupational exposure to crushed garlic products and the topical application of garlic to treat wounds or skin infections may cause allergic contact dermatitis (Lee and Lam, 1991; Bojs and Svensson, 1998). Allergic reactions including burns (Roberge *et al.,* 1997), zosteriform dermatitis (Farrell and Staughton, 1996), induction of pemphigus (blisters) (Brenner and Wolf, 1994), allergic asthma and rhinitis, contact urticaria, and protein contact dermatitis have been reported for garlic and various generic garlic preparations (WHO, 1999; DeSmet, 1992), but no adverse effects were reported for AGE according to toxicological and clinical studies (Miyoshi *et al.*, 1984; Nakagawa *et al.*, 1984, 1980; Sumiyoshi *et al.*, 1984). Cross-sensitivity may occur with onions and tulips (Siegers, 1992; WHO, 1999). Garlic preparations can increase clotting time (Chutani and Bordia, 1981; Gadkari and Joshi, 1991; Harenberg *et al.,* 1988; Legnani *et al.,* 1993), which is sometimes beneficial, but in some cases, can contribute to an adverse event.

Drug Interactions

Concurrent use of garlic and antiplatelet agents (e.g., aspirin) and anticoagulants (e.g., warfarin) might increase the potential for prolonged bleeding. One report showed that clotting time (International Normalization Ratio) doubled for two patients taking warfarin and garlic simultaneously (Sunter, 1991); however, this report lacks adequate data to assess causality (Rotblatt and Ziment, 2001). Further, a controlled clinical trial on AGE showed no interactions with warfarin (Rozenfeld, 2000). Another trial on nine HIV-negative individuals produced significant decreases in serum levels of the anti-HIV drug saquinavir (Piscitelli *et al.*, 2002); however, this study has design problems rendering the results uninterpretable.

American Herbal Products Association (AHPA) Safety Rating

CLASS 2C: Not to be used while nursing (McGuffin *et al.*, 1997). However, a controlled trial indicated a positive therapeutic use during lactation (ESCOP, 1997; Mennella and Beauchamp, 1991).

Regulatory Status

CANADA: Drug or possibly "New Drug" if claims made. Food in absence of claims (HPB, 1993). Schedule OTC "Herbal and Natural Products" and "Homoeopathic Products" have marketing authorization with Drug Identification Numbers (DIN) assigned (Health Canada, 2001).

EUROPEAN UNION: Powder, freeze-dried, or low temperature dried (<65°C), containing not less than 0.45% allicin, official in *European Pharmacopoeia* 3rd ed. Suppl. 2001 (Ph.Eur., 2001).

FRANCE: Traditional Herbal Medicine (THM) permitted for treatment of minor circulatory disorders (Bradley, 1992). Essential oil is dispensed as an aromatherapy drug (Goetz, 1999).

GERMANY: Fresh or carefully dried bulb is approved by Commission E as non-prescription drug (Blumenthal *et al.*, 1998). Fresh bulb for preparation of mother tincture official in the *German Homoeopathic Pharmacopoeia* (GHP, 1993).

GHANA: Monograph for fresh whole bulb occurs in *Ghana Herbal Pharmacopoeia* (GHP, 1992).

INDIA: Bulb and oil are approved single drugs dispensed in Unani system of medicine (CCRUM, 1997).

JAPAN: OTC drug for fatigue (Okada and Miyagaki, 1983). AGE approved for nourishment of pregnant and lactating women.

SWEDEN: Classified as 'Natural Remedy' for self-medication requiring pre-marketing authorization from Medical Products Agency (MPA). One product (e.g. Bio-Garlic Pharma Nord) is listed in the "Authorised Natural Remedies" with the approved indication "Traditionally used for the relief of cold symptoms" (MPA, 2001a; Tunón, 1999). Homoeopathic dilutions (e.g., Radiotron AB) are also registered drugs (MPA, 2001b).

SWITZERLAND: Powdered garlic in tablets, standardized powdered extract in tablets, oily macerate in capsules, and multiple-herb preparations containing standardized garlic extract have positive classification (List D) by the *Interkantonale Konstrollstelle für Heilmittel* (IKS) and corresponding sales category D, with sales limited to pharmacies and drugstores, without prescription (Morant and Ruppanner, 2001). Twenty-eight garlic phytomedicines and two homoeopathic medicines are listed in the *Swiss Codex* 2000/01 (Ruppanner and Schaefer, 2000).

U.K: Herbal medicine on the *General Sale List* (GSL), Table A (internal or external use), Schedule 1 (requires full product license) (GSL, 1989).

U.S.: Dietary Supplement (USC, 1994). Fresh or dried compound bulbs, powdered garlic, fluidextract and extract are official in the U.S. *National Formulary* 19th edition (USP, 2002). Tincture of mature bulb, 1:10 (*w/v*) in 55% alcohol (*v/v*), is a Class C OTC drug of the *Homoeopathic Pharmacopoeia of the United States* (HPUS, 1989).

Clinical Review

Thirty-two studies, including 45,694 participants, are outlined in the following table, "Clinical Studies on Garlic." All but four of the studies (Berthold *et al.*, 1998; Isaacsohn *et al.*, 1998; McCrindle *et al.*, 1998; Simons *et al.*, 1995) demonstrated positive effects on conditions including cardiovascular and arterial health, cancer, immunity, and circulation. Studies from the table are categorized and discussed in the following six sections. In addition to the studies in the table, this Clinical Review discusses numerous reviews and meta-analyses that are not listed in the table.

Based on the Agency for Healthcare Research and Quality's (AHRQ) review and summary of clinical studies on garlic (Mulrow *et al.*, 2000), researchers concluded that garlic preparations may have small, positive, short-term effects (less than three months) on lipids, and promising antithrombic effects. However, the data was insufficient to draw conclusions about certain clinical cardiovascular outcomes (e.g., myocardial infarction), antithrombic activity, or cancer prevention. No effects on glucose or insulin sensitivity, or consistent decreases in blood pressure were found. Case-control studies suggest that consuming large amounts of garlic in the diet may reduce the risks of laryngeal, gastric, colorectal, and endometrial cancers, and adenomatous colorectal polyps (Mulrow, *et al.*, 2000). A subsequent review of 45 randomized trials by some of the same researchers concluded that the trials suggest possible small short-term benefits of garlic preparations on some lipid and antiplatelet factors, insignificant effects on blood pressure, and no effect on glucose levels (Ackermann *et al.*, 2001). Conclusions regarding clinical significance are limited due to the marginal quality and short duration of many trials, as well as the unpredictable release and inadequate definition of active constituents in many of the garlic preparations used in the studies.

Lipid-lowering effect

Thirteen trials involving a total of 795 participants demonstrated a positive correlation between garlic oil, powder, or capsule intake and lipid-lowering effects. Six randomized, double-blind, placebo-controlled (R, DB, PC) studies (Yeh *et al.,* 1995; Jain *et al.,* 1993; Rotzsch *et al.,* 1992; Auer *et al.,* 1990; Mader *et al.,* 1990; Vorberg *et al.,* 1990), as well as two DB, multi-center studies (Grünwald *et al.,* 1992; Holzgartner *et al.,* 1992) supported the use of garlic in treating elevated lipid conditions including hyperlipidemia and hypercholesterolemia. Three studies showed the positive impact of taking Kyolic® capsules specifically for improving hypercholesterolemia conditions (Steiner *et al.,* 1996; Steiner and Lin, 1994; Lau *et al.,* 1987). One R, open, parallel group, comparison (O, PG, Cm) found garlic powder to have a significant impact over garlic oil on lowering blood lipid counts and blood pressure, as well as increasing the overall sense of well-being in 70 subjects (De A Santos and Johns, 1995). An R, PC study involving 35 renal transplant patients found the garlic product, Pure-Gar®, to have positive effects on hyperlipidemia (Lash *et al.,* 1998). One O study involving 82 subjects (Bordia, 1981) found garlic to have, in conjunction with the lipid-lowering effects, a positive impact on patients with coronary heart disease.

A meta-analysis on the effect of garlic on total serum cholesterol levels found a statistically significant reduction in total cholesterol levels (Warshafsky *et al.*, 1993). Another analysis assessed clinical data from 952 patients and 16 trials, indicating a decrease in total cholesterol levels (Silagy and Neil, 1994b). A subsequent reanalysis of all data still demonstrated a significant reduction of total cholesterol compared to placebo (Warshafsky *et al.*, 1993). Three studies on the allicin-standardized garlic powder tablets (Kwai®) failed to show a significant reduction in elevated serum cholesterol (Isaacsohn *et al.*, 1998; McCrindle *et al.*, 1998; Simons *et al.*, 1995). It was later determined that the allicin release from the tablets varied significantly, and that negative studies were possibly due to the lack of expected allicin release (Lawson *et al.*, 2001). A study of 24 brands of enteric-coated tablets found that 83% of the brands released less than 15% of their allicin potential (Lawson and Wang, 2001). Therefore, the researchers recommend that manufacturers standardize supplements to dissolution of allicin release, not to allicin potential. (For non-allicin releasing products, e.g., AGE, the standardization is to other compounds, e.g., SAC.) In a recent, comprehensive meta-analysis of 13 R, DB, PC trials researchers demonstrated a significant difference ($p<0.01$) in the reduction of total cholesterol levels between baseline and placebo, equivalent to a 5.8% reduction in total cholesterol levels. The authors concluded that current evidence indicates that any specific lipid-lowering effect is small, and the clinical outcome may not be meaningful (Stevinson *et al.*, 2000). However, there were several problems identified with the meta-analysis, indicating that the conclusions can only be attributed to the specific brands tested and not the effectiveness of garlic in general. In particular, the brand used in 10 of the trials did not protect allinase from exposure to gastric acid. Another tested supplement was spray-dried, resulting in the loss of alliin. The study on the garlic oil that showed no effect utilized a form that has demonstrated low bioavailability; therefore the conclusions of the meta-analysis need to be considered within this context (Lawson, 2001). Several of these products are not standardized to a bioavailable marker compound. Clinical studies with positive outcomes using AGE standardized with bioavailable SAC have shown significant levels of SAC in human blood during the study period (Steiner and Li, 2001).

Antihypertensive effect

Two R, DB, PC studies and one R, O, PG, Cm study (159 total participants) demonstrated the antihypertensive effects of garlic (De A Santos and Johns, 1995; Jain *et al.*, 1993; Auer *et al.,* 1990). A systematic review and meta-analysis of randomized controlled trials was conducted to determine the effect of garlic on blood pressure. Eight trials, including 415 participants, were identified. Of the seven trials that compared the effect of garlic with a placebo, three demonstrated a significant reduction in systolic blood pressure (SBP), and 4 in diastolic blood pressure (DBP). The authors concluded that more rigorously designed trials can provide evidence to recommend the clinical application of garlic in the treatment of hypertension (Silagy and Neil, 1994b).

Antiplatelet effects

One R, DB, PC, crossover (CO) study and 2 DB, PC studies involving a total of 214 subjects indicate the potential use of garlic as a coronary disease preventative due to its positive impact on platelet functions (Steiner and Li, 2001; Kiesewetter *et al.,* 1991; 1993a).

Anti-atherosclerotic effect

In the longest clinical trial on garlic to date, garlic's ability to prevent and possibly reverse atherosclerosis was tested in a R, DB, PC, four-year study in which 152 men and women were given 900 mg garlic powder as tablets (Kwai®) per day (Koscielny *et al.*, 1999). The subjects possessed significant plaque buildup and at least one additional cardiovascular risk factor (e.g., high LDL

levels, hypertension, diabetes, and/or history of smoking). After the four years, garlic subjects had an average 2.6% reduction in plaque volume while the placebo group's plaque increased 15.6%. Researchers concluded that garlic has a preventive and possibly curative role in arteriosclerosis therapy. In one epidemiological, cross-sectional, observational (E, CS, OB) study with 202 participants, standardized garlic powered was found to have positive effects on arterial activities including elastic vascular resistance, pulse wave velocity, and systolic blood pressure (Breithaupt-Grogler, 1997).

Anticancer/Chemoprevention

Anti-cancer and chemopreventative qualities of garlic were demonstrated in five studies involving a total of 44,044 subjects. One E study spanning over a period of 15 years, demonstrated that raw and cooked garlic use had a significant impact on decreasing stomach cancer incidents (You *et al.*, 1989). Two other E studies found that garlic intake significantly decreased the risk of colon cancer in 42,325 participants (Witte *et al.*, 1996; Steinmetz *et al.*, 1994). Garlic's chemopreventative potential was demonstrated in two OB studies through the improvement of arachidonic acid and acetaminophen metabolism (Dimitrov and Bennink, 1997; Gwilt *et al.*, 1994). Case-control studies suggest that consuming large amounts of garlic in the diet may reduce the risks of laryngeal, gastric, colorectal, and endometrial cancers and adenomatous colorectal polyps (Mulrow, *et al.*, 2000).

Several reviews of E studies have examined the cancer-preventive effect of garlic, including garlic ingested as a food (Dorant *et al.*, 1993; Fleischauer *et al.*, 2000). A meta-analysis of the epidemiological evidence on the association between garlic consumption and risk of stomach, colon, head and neck, lung, breast, and prostate cancers concluded that raw and cooked garlic consumption might have a protective effect against stomach and colorectal cancers (Fleischauer *et al.*, 2000). An earlier review of *in vitro*, *in vivo*, epidemiologic, and case-control studies suggested that the evidence is not conclusive to support chemoprevention in humans, but further research is warranted (Dorant *et al.*, 1993); however, this review preceded much of the salient research in this area.

Other

One pilot study involving 7 HIV+ patients demonstrated a positive impact on natural killer cell activity as well as improvement in conditions such as diarrhea, genital herpes, and candidiasis (Abdullah *et al.,* 1989). One R, DB, PC study showed that garlic did not negatively impact bleeding potential in patients undergoing warfarin therapy (Rozenfeld, *et al.*, 2000). Two studies involving 92 subjects demonstrated garlic's positive impact on peripheral circulation: one R, CO, Cm study showed an immediate improvement in hand and foot circulation (Okuhara, 1994); and one DB, PC study involving 80 subjects with peripheral arterial occlusive disease (PAOD) showed a significant increase in walking distance (Kiesewetter *et al.,* 1993b). This last study was the only study to meet the inclusion criteria established by the Cochrane Library for its review on the use of garlic for PAOD. The Cochrane Review concluded that further trials on garlic's effectiveness on PAOD are warranted because the one study reviewed was small, of short duration (12 weeks), and found no significant overall improvement in patients with PAOD. The discrepancy between the conclusions of the study and those of the review is a result of the study's analysis of the mean difference between the garlic and placebo groups instead of analyzing the mean change within the groups' pre- and post-treatment.

Branded Products*

AGE™ (Aged Garlic Extract): Wakunaga of America Co., Ltd. / 23501 Madero / Mission Viego, CA 92691 / U.S.A. / Tel: (800) 421-2998 / www.kyolic.com. This refers to a proprietary garlic extract with stable sulfure compounds standardized to bioavailable components (e.g., SAC) in various types of formulations. See Kyolic® below.

Höfel's® Garlic Pearles One-A-Day: Seven Seas Ltd., a division of the Merck Group / Hedon Road / Marfleet / Hull / England / HU9 5NJ / U.K. / Tel.: +44-1482-37-5234 / Fax: +44-1482-37-4345 / Email: info@hofels.com or Info@Seven-Seas.ltd.uk / www.hofels.com. A gelatin or glycerin capsule containing 2 mg garlic oil, and soybean oil.

Kwai® forte 300 mg LI 111: 1. Lichtwer Pharma AG / Wallenroder Strasse 8-14 / 13435 Berlin / Germany / Tel: +49-30-40-3700 / Fax: +49-30-40-3704-49 / www.lichtwer.de. One sugar-coated tablet (dragée) contains: garlic bulb powder 300 mg. Other components: lactose monohydrate, cellulose, highly dispersive silicon dioxide, magnesium stearate, castor oil, Macrogol 6000, Hypromellose, saccharose, talcum, gelatin, Povidon K25, carnauba wax, bleached wax, yellow quinoline E104, indigo carmine E132.

Kwai®N LI 111: Lichtwer Pharma AG. One tablet contains 100 mg dried powder from *Allium sativum* (garlic bulb) standardized to contain 1.3% allicin (yielding 0.6% allicin). Inactive ingredients: lactose, magnesium stearate, powdered cellulose, colloidal anhydrous silica, methylhydroxypropylcellulose, polyethylene glycol 6000, castor oil, talc, polyvinylpyrrolidone 25, sucrose, gelatin, quinoline yellow E 104, indigotine E 132, carnauba wax, cera alba.

Kyolic® Liquid: Wakunaga of America Co., Ltd. Aged Garlic Extract™ in water and residual alcohol from extraction.

Kyolic® Reserve: Wakunaga of America Co., Ltd. 600 mg Aged Garlic Extract™ per capsule.

Kyolic® Super Formula 100: Wakunaga of America Co., Ltd. 300 mg Aged Garlic Extract™ per capsule plus whey.

Kyolic® Super Formula 101: Wakunaga of America Co., Ltd. 270 mg Aged Garlic Extract™ per capsule, plus brewer's yeast, kelp, and whey.

Kyolic® Super Formula 102: Wakunaga of America Co., Ltd. 350 mg Aged Garlic Extract™ per capsule, plus food enzymes: amylase, protease, lipase, and cellulase (30 mg).

Kyolic® Super Formula 103: Wakunaga of America Co., Ltd. 220 mg Aged Garlic Extract™ per capsule, plus Ester C® (105 mg), *Astragalus membranaceous* (100 mg), and calcium (23 mg).

Kyolic® Super Formula 104: Wakunaga of America Co., Ltd. 300 mg Aged Garlic Extract™ per capsule, plus 190 mg lecithin.

Kyolic® Super Formula 105: Wakunaga of America Co., Ltd. 200 mg Aged Garlic Extract™ per capsule, plus beta-carotene (6 mg), vitamin C (120 mg), vitamin E (60 IU), selenium (25 mg), and green tea (45 mg).

Kyolic® Super Formula 106: Wakunaga of America Co., Ltd. 300 mg Aged Garlic Extract™ per capsule, plus hawthorn berry (50 mg), cayenne pepper (10 mg), and vitamin E (100 IU).

Pure-Gar® Garlic Powder A-2000: Essentially Pure Ingredients™, c/o Pure Gar L.P. / 21411 Prairie Street / Chatsworth, CA 91311 / U.S.A. / Tel: (800) 537-7695 /

www.essentiallypure.com. Dried powder from *Allium sativum* (garlic bulb): allicin yield 2,000 ppm min.; total thiosulfinates yield 2,100 ppm minimum; allian 7,500 ppm minimum; gamma-glutamylcysteines 10,000 ppm minimum.

Pure-Gar® Garlic Powder A-5000: Essentially Pure Ingredients™ / 21411 Prairie Street / Chatsworth, CA 91311 / U.S.A. / Tel: 818-739-6046 / www.essentiallypure.com. Dried powder from *Allium sativum* (garlic bulb): allicin yield 5,000 ppm minimum; total thiosulfinates yield 5,000 ppm minimum; allian 11,000 ppm minimum; gamma-glutamylcysteines 10,000 ppm minimum; total sulfur 6,500 ppm minimum.

Pure-Gar® Garlic Powder A-8000: Essentially Pure Ingredients™. Dried powder from *Allium sativum* (garlic bulb): allicin yield 8,000 ppm minimum; total thiosulfinates yield 8,000 ppm minimum; allian 18,000 ppm minimum; gamma-glutamylcysteines 8,000 ppm minimum.

Pure-Gar® Garlic Powder A-10000: Essentially Pure Ingredients™. Dried powder from *Allium sativum* (garlic bulb): allicin yield 10,000 ppm minimum; total thiosulfinates yield 10,000 ppm minimum; allian 23,000 ppm minimum; gamma-glutamylcysteines 8,000 ppm minimum.

Sapec®: Lichtwer Pharma AG. 300 mg tablet of dried garlic powder standardized to contain 1.3% allicin (yielding 0.6% allicin).

Tegra®: Hermes Fabrick Pharma / Georg-Kalb-Str. 5-8 / 82049 Grosshesselohe / Germany. Steam-distilled garlic oil (does not contain allicin, fructans, agrinine, or gamma-glutamylcysteines).

*American equivalents, if any, are found in the Product Table beginning on page 398.

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Clinical Studies on Garlic (*Allium sativum* L.)

Cardiovascular

Hyperlipidemia/Hypercholesterolemia/Hypertension/Related Risk Factors

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Berthold *et al*., 1998	Hypercholesterolemia (mean TC 291 mg/dl and mean LDL 207 mg/dl)	R, DB, PG n=25 (diet not controlled)	12 weeks following a 4-week washout period	5 mg, 2x/day or placebo (with meals)	Tegra® garlic oil (oil bound to b-cyclodextrin for slow release)	The garlic preparation did not influence serum lipoproteins, cholesterol, absorption, or cholesterol synthesis. Garlic oil could not be recommended for hypercholesterolemia. The study was criticized for slow-release aspect that has been found to greatly reduce total absorption and because the oil preparation contained a different chemical profile than preparations used in other studies.
Isaacsohn, 1998	Hyperlipidemia (LDL<160 mg/dL; TG <350 mg/dL)	R, PC, PG, MC n=50 (n=28 taking garlic; n=22 taking placebo) subjects on the NCEP Step 1 diet 8 weeks before and during treatment	12 weeks	300 mg, 3x/day	Sapec®, Kwai® garlic powder	No significant lipid or lipoprotein changes between the two groups. Compliance to diet was same for both groups; however, effect of diet on lipid/lipoprotein levels prior to treatment may have influenced treatment. Another factor possibly influencing the results is the alleged change made to the tablets' enteric coating in 1992–1993 (Lawson, 1998).
Lash *et al*., 1998	Hyperlipidemia in renal transplant patients (TC>185 mg/dl; LDL> 160 mg/dl)	R, PC n=35 (garlic n=19; placebo n=16) (NCEP Step 1 diet during treatment)	12 weeks	680 mg, 2x/day	Pure-Gar®	At 6 weeks, there was a significant decrease from baseline of 14 mg/dL in TC ($p<0.05$) and 12 mg/dL in LDL ($p<0.05$). Authors noted that although garlic showed benefit, patients still required drug therapy to treat hyperlipidemia. They suggested that garlic may be used to decrease the required dosage of HMG-CoA reductase inhibitors.
McCrindle *et al*., 1998	Hypercholesterolemia in children (TC >185 mg/dL)	R, DB, PC n=30 (garlic n=15; placebo n=15) NCEP Step 2 diet for 6 months prior to treatment	8 weeks	300 mg, 3x/day	Kwai® garlic powder	There was no significant reduction attributed to garlic for cardiovascular risk factors, with the exception of a small increase in apolipoprotein A-I levels. Authors note that adult studies have yielded positive results.
Steiner *et al*., 1996	Hypercholesterolemia (men) (TC=220–280 mg/dL)	DB, PC, C n=41	6 months, crossed over for 4 months (placed on NCEP Step 1 diet 4 weeks prior to start/ throughout)	3 capsules (800 mg each) 3x/day	Kyolic® AGE capsules vs. placebo capsules	Total cholesterol (TC) levels were reduced 6.1–7% compared to placebo period or baseline ($p=0.0001$), respectively. No difference noted for total glycerides (TG) or HDL ($p=0.004$). LDL decreased 4% and systolic blood pressure (SBP) decreased 5.5% ($p=0.0001$) with the garlic and modes decreased in diastolic blood pressure (DBP). Authors concluded AGE garlic supplementation has beneficial effects on lipid profile and BP in moderately hypercholesterolemic patients.
Yeh *et al*., 1995	Hypercholesterolemia (TC=220–285 mg/dL)	DB, PC, R n=34 (garlic n=17; placebo n=17) men (35–55 years old)	5 months	3 capsules, (800 mg each) 3x/day	Kyolic® AGE capsules vs. placebo capsules containing common food ingredient	At 4th and 5th month, TC levels in AGE group 6% and 7% lower, respectively, than baseline value and no change in placebo group. Plasma HDL-cholesterol and triglyceride levels not altered by AGE or placebo. Compared with placebo, LDL-cholesterol level significantly lower in AGE group (145 ± 25 vs. 165 ± 24 mg/dl). AGE supplementation has significant mild cholesterol lowering effect in hypercholesterolemic men.
De A Santos and Johns, 1995	Garlic powder vs. garlic oil on blood lipids, blood pressure, and well-being	R, O, PG, Cm, n=70 (garlic powder n=36; or garlic oil n=34)	16 weeks	200 mg, 3x/day	Garlic powder: Kwai® (tablet), Garlic oil: Höfel's® Original Garlic Oil Capsules	Lipid-lowering effect for garlic powder=11% vs. 3% for oil. LDL lowered by 16% vs. 1% respectively. HDL did not change significantly and TG did not change. Also noted was a decrease in blood pressure with garlic powder but not for oil. Well-being assessment improved for powder but not for oil. Garlic powder appears to be superior to oil in reducing cholesterol, BP, and improved well-being.

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Clinical Studies on Garlic (*Allium sativum* L.) (cont.)

Cardiovascular (cont.)

Hyperlipidemia/Hypercholesterolemia/Hypertension/Related Risk Factors (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Simons *et al.*, 1995	Hypercholesterolemia (mild to moderate) (5.5–8.05 mmol/L)	R, DB, PC, CO n=28	12 weeks after 28 day baseline dietary period; 28 day washout at end	300 mg, 3x/day	Kwai® garlic powder	No demonstrable effect of garlic on oxidizabilty of LDL, on ratio of plasma lathosterol/cholesterol (a measure of cholesterol synthesis), nor on LDL receptor expression in lymphocytes. No effect on ingestion of lipids and lipoproteins.
Steiner and Lin, 1994	Hypercholesterolemia (TC=230–290 mg/dL)	DB, CO, R n=45 men (30–70 years old)	10 months	700 mg, 3 capsules, 3x/day	Kyolic® AGE capsules vs. placebo capsules	66% of subjects in garlic group showed modest reduction (about 8%) of total and LDL cholesterol but no change in HDL. Significant reductions in measured platelet adhesion (34–58%) and aggregation (10–25%). Study suggests that AGE supplementation has beneficial effects on lipids, especially platelets, that may lead to cardiovascular risk reduction.
Jain *et al.*, 1993	Serum lipids, lipoproteins, glucose, and blood pressure	R, DB, PC n=42	12 weeks	300 mg, 3xday, or placebo	Garlic powder in tablet form	Experimental group experienced a 6% reduction in TC ($p<0.01$) vs. placebo group (1%) reduction. LDL decreased 11% and 3% respectively ($p<0.05$). No changes in HDL, TG, serum glucose, or blood pressure noted (subjects were normotensive).
Grünwald *et al.*, 1992	Hypercholesterolemia (TC>6.5 mmol/L)	DB, MC n=48	18 weeks	200 mg, 3x/day Subjects maintained a normal diet and medications	Kwai® garlic powder	After garlic treatment and compared to baseline, mean serum TC decreased by 8% ($p<0.001$); LDL decreased by a non-significant 5%; HDL increased by 5%; LDL: HDL improved by 12% ($p<0.05$); TG levels decreased by a non-significant 11%. 23 patients with mild hypertension experienced a significant decrease of 7% in SBP ($p<0.05$) and a non-significant 4% in DBP.
Holzgartner *et al.*, 1992	Hyperlipoproteinemia (TC or TG >250 mg/ml) garlic vs. Bezafibrate	R, DB, MC, Cm n=98 (6-week prephase treatment w/placebo and NCEP Step I diet)	12 weeks (NCEP Step I diet maintained throughout study)	900 mg/day or 600 mg Bezalfibrate/ day	Garlic powder preparations equivalent to Sapec®, Kwai® garlic powder	Compared to baseline, both medications caused a significant decrease in TC (26%) ($p<0.001$), LDL (32%) ($p<0.001$), and TG (30%) ($p<0.01$), as well as a significant increase in HDL (51%) ($p<0.001$) with no difference between their efficacies. No differences were observed between the two regimens.
Rotzsch *et al.*, 1992	Alimentary hypertriglyceridemia (after intake of fatty meals)	R, DB, PC n=24	6 weeks	300 mg/day or placebo and fatty meal	Sapec®, Kwai® garlic powder; fatty meal contained 100g butter	The postprandial increase of TG was reduced significantly in garlic group, and was up to 35% less compared to placebo. HDL-2 cholesterol tended to increase with garlic more than placebo.
Auer *et al.*, 1990	Mild hypertension (DBP 95–104 mmHg; TC >250; TG>200)	R, DB, PC, C n=47 (garlic n=24; placebo n=23) (n=21 taking blood pressure medication)	12 weeks (after 7 week acclimation period)	200 mg/day or placebo	Kwai® garlic powder	Results indicated 13% decrease in DBP in garlic group vs. 4% for placebo ($p<0.01$). SBP decreased by 11% in garlic compared with 5% in the placebo group ($p<0.05$). Serum cholesterol and TG were significantly decreased after 8 and 12 weeks in garlic group vs. placebo ($p<0.05$).
Mader *et al.*, 1990	Hyperlipidemia (TC >200mg/dL)	R, DB, PC, PG, MC n=221 (garlic n=111; placebo n=110)	16 weeks	200 mg/day or placebo	Kwai® garlic powder	Experimental group experienced a 12% reduction in TC vs. a 3% reduction in placebo group ($p<0.001$). TG decreased by 17% vs. 2% respectively ($p<0.0001$). The best effect was noted in patients with TC levels 251–300 mg/dL.
Vorberg *et al.*, 1990	Hypercholesteriolemia	R, DB, PC, PG n=40 (garlic n=20; placebo n=20)	16 weeks	300 mg, 3x/day	Sapec®, Kwai® garlic powder	Garlic group resulted in a significantly lower TC ($p<0.001$), TG ($p<0.05$), BP ($p<0.001$), than placebo. A self-evaluation revealed a greater feeling of "well being" ($p<0.05$).

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Clinical Studies on Garlic (*Allium sativum* L.) (cont.)

Cardiovascular (cont.)

Hyperlipidemia/Hypercholesterolemia/Hypertension/Related Risk Factors (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Lau, *et al.*, 1987	Hypercholesterolemia and hypertriglycerides	DB, C, CC n=15	6 months	1 g/day	Kyolic® AGE capsules	Serum cholesterol level (220–440 mg/dl) significantly dropped (12–31%) with AGE compared to baseline. Serum LDL and triglycerides were also significantly reduced (p<0.05) with AGE.
Bordia, 1981	Blood lipids in subjects with coronary heart disease	O (n=20) healthy volunteers or (n=62) patients with coronary heart disease	10 months	0.25 mg/kg of body weight/day or placebo	Garlic essential oil in gelatin capsules	Patients taking garlic experienced a decrease in serum cholesterol (p<0.05) and LDL (p<0.05), while an increase was observed in the HDL fraction (p<0.05).

Arterial and Fibrinolytic Activity

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Steiner and Li, 2001	Effects on platelet function	DB, CO, PC, R n=34 normal healthy men and women	44 weeks (6-week baseline period; 18-week supplementation, 18-week crossover; 2-week washout)	3 capsules (800 mg each) 3x/day 1st 6 weeks; 800 mg, 6x/day 2nd 6 weeks; 800 mg, 9x/day 3rd 6 weeks	Kyolic® AGE capsules vs. placebo capsules	Compared with baseline and placebo, threshold level of platelet aggregation was significantly increased, i.e., AGE significantly (p<0.05) inhibited platelet aggregation, especially induced by collagen and epinephrine. Adherence of platelets inhibited by AGE in dose-dependent manner. AGE exerted selective inhibition on platelet aggregation and adhesion, suggesting potential use as cardiovascular disease prevention.
Koscielny *et al.*, 1999	Arterial plaque (in patients with advanced atherosclerotic plaque)	R, DB, PC n=152	4 years	300 mg, 3x/day	Kwai® garlic powder	In placebo the atherosclerotic plaque (in carotid and femoral artery) increased by 15.6% over 4 years while decreasing 2.6% in experimental group (p<0.0001). Garlic diminished the age-related decrease in plaque volume by 6–13% over 4 years (p<0.001). Assessed by high-resolution ultrasound. Results substantiate a preventive and curative role for garlic powder for atherosclerosis.
Breithaupt-Grogler, 1997	Age-related stiffening of the aorta (healthy adults)	E, CS, OB n=202 (matching pairs technique)	≥2 years	≥300 mg/day	Standardized garlic powder	Pressure-standardized elastic vascular resistance was lower in garlic groups than age-matched controls (p<0.0001). Pulse wave velocity (PWV) correlated with age (r=0.44 garlic, r=0.52 control) and systolic blood pressure (SBP) (r=0.48 garlic group, r=0.54 control group) for both groups, but in garlic group an increase in age or SBP was associated with a smaller rise in PWV vs. controls. No difference noted in blood pressure, heart rate, and plasma lipid levels in both groups. Chronic garlic powder consumption attenuated age-related increase in aortic stiffness.
Kiesewetter *et al.*, 1993a	Platelet aggregation (juvenile ischemic attack)	DB, PC, PG n=60	4 weeks (following a 4-week washout period)	200 mg, 4x/day or placebo	Kwai® garlic powder	A significant decrease (p<0.01) in circulatory platelet aggregates (down 10.3%) and spontaneous platelet aggregates (down 56.3%) was observed in garlic group. Garlic group also decreased in DBP, plasma viscosity, and serum cholesterol.
Kiesewetter *et al.*, 1991	Platelet aggregation	DB, PC n=120	4 weeks	400 mg, 2x/day or placebo	Garlic powder	Observations in garlic group include spontaneous platelet aggregation disappearance, increase of 47.6% microcirculation of the skin, 3.2% decrease in plasma viscosity, mean DBP decrease from 74 to 67 (p<0.05), and a drop in the mean fasting blood glucose concentration from 89.4 to 79.

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Clinical Studies on Garlic (*Allium sativum* L.) (cont.)

Anticancer/Chemoprevention

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Dimitrov and Bennink, 1997	Effect on arachidonic acid metabolism	PS, O n=8 healthy female volunteers	3 months	10 mL extract/day mixed with orange or V8 juice in morning	Kyolic® aged garlic hydroalcoholic liquid extract	Compared to baseline, after 3 months of taking Kyolic® substantial decrease in serum PGE2 levels in majority of subjects. Results indicate that ethanol-water soluble extract is capable of modulating PGE2 and PGF2a.
Witte *et al.*, 1996	Colon cancer	E, CC n=488	4 years	≥3 servings/week	Serving size unspecified	A reduction of 37% occurrence in pre-cancerous cells and colorectal polyps was observed. (Odds ratio = 0.63.)
Gwilt *et al.*, 1994	Effect on metabolism of acetamino-phen	O n=16 males (healthy, non-smoking)	3 months	10 ml extract/day mixed with 120 ml orange juice	Kyolic® aged garlic hydroalcoholic liquid extract plus acetamin-ophen (500 mg Tylenol®)	Garlic treatment had no discernible effect on oxidative metabolism, but was associated with slight increase in sulfate conjugation of acetaminophen. Study suggests that AGE has limited potential as a chemopreventive agent.
Steinmetz *et al.*, 1994	Colon cancer	E, CH n=41,837	5 years	≥ 1 servings/week	Unspecified as to the quantity of a serving size	The study showed that risk of colon cancer in women ages 55–69 decreased with garlic consumption (rr=0.68).
You *et al.*, 1989	Stomach cancer	E n=564 patients with stomach cancer, n=1,131 controls	15 years	0 kg/year; 0.1–1.5 kg/y; >1.5 kg/y	Raw and cooked garlic	Significant trends were shown for the decrease of stom-ach cancer with garlic use. Odds ratio (95% CI) for highest compared with lowest garlic consumption was 0.7 (0.4–1.0, p=0.03).

Other

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Rozenfeld *et al.*, 2000	Bleeding potential of combined garlic and warfarin therapy	DB, PC, R n=8 patients (INR therapeutic for at least 2 months)	4 weeks	1,200 mg/day or placebo	Kyolic® AGE capsules	All patients took Coumadin®. No INR differences between groups noted (p>0.05). Compared to baseline, no significant changes in INR values within each group (p>0.05). No patients developed urine or stool bleeding. Kyolic® did not worsen side effects of Coumadin®.
Okuhara, 1994	Peripheral circulation	Cm, CO, R n=12 healthy male volunteers	5 months (Jan~May 1994)	Single-admin-istration test: 1.6 ml GE or GEC/day or continuous administration test: 0.8 ml GE or GEC 2 x/day	Kyolic® aged garlic hydroal-coholic liquid extract (GE) vs. heat-treated liquid prepara-tion of garlic (GEC)	After single administration, skin temperatures in GE (garlic) group peaked at 60 minutes on backs of hands (p<0.01) and 90 minutes on backs of feet (p<0.01). In GEC (control) group, peaked at 30 minutes on backs of hands and feet. After 14 days continuous use, higher skin temperatures in GE group on backs of hands and feet and on only backs of feet in GEC group. Study suggests improved blood flow with GE.
Kiesewetter *et al.*, 1993b	Intermittent claudication (Peripheral Arterial Occlusive Disease Stage II)	DB, PC n=80	12 weeks	200 mg, 4x/day or placebo	Kwai® garlic powder	A significant increase (p<0.05) was observed in walking distance by the 5th week and correlated to a simultane-ous decrease in spontaneous platelet aggregation in gar-lic group vs. placebo. Garlic group also had decrease in diastolic blood pressure (DBP), plasma viscosity, and serum cholesterol.
Abdullah *et al.*, 1989	Effects on natural killer (NK) cell activity in HIV+ patients	PS n=7	12 weeks	5 g/day 1st 6 weeks; 10 g/day 2nd 6 weeks	Aged processed garlic prepara-tion: Special Garlic Preparation (SGP)	After 6 weeks, 6 of 7 qualified patients had normal NK activity, and all had normal NK activity at 12 weeks. Helper/suppressor ratio improved in 4 of 7 patients. Conditions of diarrhea, genital herpes, candidiasis and pansinusitis with recurrent fever also improved during the study.

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