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Recent Advances on the Nutritional Effects Associated with the Use of Garlic as a Supplement

Intake of Garlic and Its Bioactive Components[1]

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ABSTRACT The health benefits of garlic likely arise from a wide variety of components, possibly working synergistically. The complex chemistry of garlic makes it plausible that variations in processing can yield quite different preparations. Highly unstable thiosulfinates, such as allicin, disappear during processing and are quickly transformed into a variety of organosulfur components. The efficacy and safety of these preparations in preparing dietary supplements based on garlic are also contingent on the processing methods employed. Although there are many garlic supplements commercially available, they fall into one of four categories, i.e., dehydrated garlic powder, garlic oil, garlic oil macerate and aged garlic extract (AGE). Garlic and garlic supplements are consumed in many cultures for their hypolipidemic, antiplatelet and procirculatory effects. In addition to these proclaimed beneficial effects, some garlic preparations also appear to possess hepatoprotective, immune-enhancing, anticancer and chemopreventive activities. Some preparations appear to be antioxidative, whereas others may stimulate oxidation. These additional biological effects attributed to AGE may be due to compounds, such as *S*-allylcysteine, *S*-allylmercaptocysteine, N^{α}-fructosyl arginine and others, formed during the extraction process. Although not all of the active ingredients are known, ample research suggests that several bioavailable components likely contribute to the observed beneficial effects of garlic. J. Nutr. 131: 955S–962S, 2001.

KEY WORDS: • *garlic* • *extraction* • *process* • *S-allylcysteine* • *allicin*

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Preclinical and clinical studies reveal a close relationship between dietary habits and the occurrence of disease. Diets high in fat may increase the risk of heart disease and some forms of cancer. On the contrary, increased intake of fruits, vegetables, herbs and some of their constituents reduces risks and may even prevent some diseases. Alliums such as garlic have been studied extensively for their health benefits. More than a thousand publications over the past decade alone reveal the widespread interest in this class of foods. Several of the allium foods have been shown to reduce risks and/or modulate metabolism to favor the prevention of diseases. Garlic, in particular, is considered to be one of the best disease-preventive foods because of its potent and widespread effects. Although some studies have cast doubt on the benefits of garlic extract, careful examination of such data emphasizes the need to clarify the influence of processing on the benefits of garlic. An array of garlic preparations is available on the market. This article will clarify the effects of garlic supplements and the chemical and biological differences among commercial preparations.

Health benefits of garlic and current confusion

The potency of garlic (*Allium sativum*) has been acknowledged for >5000 years. In ancient times, the Babylonians, Egyptians, Phoenicians, Vikings, Chinese, Greeks, Romans and Hindus used garlic frequently (Block 1985). They took garlic as a remedy for intestinal disorders, flatulence, worms, respiratory infections, skin diseases, wounds, symptoms of aging and many other ailments. The use of garlic to treat wounds surfaced repeatedly through the middle ages into World War II, when garlic was used to treat the wounds of soldiers (Essman 1984). Garlic was ground or sliced and was applied directly to wounds to inhibit the spread of infections.

Garlic thus acquired a reputation in the folklore of many cultures over the centuries as a formidable prophylactic and therapeutic medicinal agent. To date, >3000 publications from all over the world have gradually confirmed the traditionally recognized health benefits of garlic. Many favorable experimental and clinical effects of the consumption of garlic preparations, including garlic extract, have been reported. These biological responses include reduction of risk factors for cardiovascular diseases and cancer, a stimulation of immune function, enhanced foreign compound detoxification, radio-

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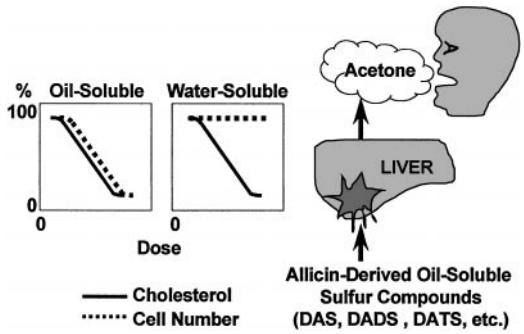

FIGURE 1 Comparison of efficacy and safety of oil-soluble and water-soluble sulfur compounds in garlic. The reduction in cholesterol seen from oil-soluble sulfur compounds [e.g., diallyl sulfide (DAS), diallyl disulfide (DADS) or diallyl trisulfide (DATS)] appears to be due to toxicity as revealed by increased lactate dehydrogenase from exposed hepatocytes (Liu and Yeh 1999) and release of acetone in the breath after oral consumption by humans (Lawson and Abrams 1998). Water-soluble sulfur compounds, although effective at reducing cholesterol, were not cytotoxic. Therefore, extraction by aqueous ethanol solution (aging process) reduces damage to the liver.

protection, restoration of physical strength, resistance to various stresses and potential antiaging effects.

It has long been known that extraction of a food can increase its potency and eliminate unpleasant characteristics. The irritating, acidic and oxidizing compounds in raw garlic can be eliminated or modified by extraction. In fact, in some cultures, garlic is soaked or extracted with alcohol, wine, milk or vinegar before use. Many adverse reactions to garlic can be attributed to an excess of oil-soluble organosulfur constituents. For example, the lipid-lowering effects of some oil-soluble sulfur compounds in hepatocytes coincide with cytotoxicity, as revealed by increased lactate dehydrogenase release from cells (Liu and Yeh 1999). Water-soluble sulfur compounds, on the other hand, although effective at reducing cholesterol, were not cytotoxic (**Fig. 1**). An array of water-soluble constituents, including *S*-allylcysteine (SAC),[3] may account for the reduced toxicity of the hydroalcoholic extracts of garlic compared with raw preparations. (Kanezawa et al. 1984, Nakagawa et al. 1980, 1984a and 1984b, Sumiyoshi et al. 1984, Yoshida et al. 1984).

Garlic preparations have been shown to exhibit hypolipidemic, antiplatelet and procirculatory effects. Aged garlic extract (AGE), along with other garlic preparations, has been reported to possess hepatoprotective, immune-enhancing, anticancer and chemopreventive activities. Furthermore, AGE exhibits antioxidative activities, whereas raw or heated garlic stimulates oxidation (Imai et al. 1994). Thus, not all garlic preparations can be assumed equivalent in their composition and, more importantly, in the biological response they may precipitate.

Several clinical reports, including meta-analyses, have revealed a cholesterol-lowering effect of garlic in humans (Lau et al. 1987, Neil et al. 1996, Silagy and Neil 1994, Warshafsky et al. 1993). These reports have promoted public awareness about the cholesterol-lowering effects of garlic. However, recent publications (Berthold et al. 1998, Breithaupt-Grögler et al. 1997, Isaacsohn et al. 1998, McCrindle et al. 1998, Neil et al. 1996, Simons et al. 1995) suggested that not all preparations may be hypocholesterolemic. These negative publications have caused confusion within both the public and academic domains. Although the reason for these inconsistencies remains unknown, it likely relates to components occurring in the preparation, the quantity of the preparation provided and/or the duration of the study.

[3] Abbreviations used: AGE, aged garlic extract; DADS, diallyl disulfide; DAS, diallyl sulfide; SAC, *S*-allylcysteine; SAMC, *S*-allylmercaptocysteine.

Chemistry of garlic

The chemistry of garlic is quite complex and likely developed as a self-protective mechanism against microorganisms and other insults. The primary sulfur-containing constituents in whole, intact garlic are the γ-glutamyl-*S*-alk(en)yl-L-cysteines and *S*-alk(en)yl-L-cysteine sulfoxides, including alliin. The γ-glutamyl peptides are biosynthetic intermediates for corresponding cysteine sulfoxides (Lancaster and Shaw 1989). Whole garlic typically contains ~1% alliin, together with (+)-*S*-methyl-L- cysteine sulfoxide (methiin) and (+)-*S*-(trans-1-propenyl)-L-cysteine sulfoxide. *S*-(2-Carboxypropyl)glutathione, γ-glutamyl-*S*-allyl-L-cysteine, γ-glutamyl-*S*-(trans-1-propenyl)-L-cysteine and γ-glutamyl-*S*-allyl-mercapto-L-cysteine are also present in garlic cloves (Fenwick and Hanley 1985, Sugii et al. 1964). During storage of garlic bulbs at cool temperatures, alliin accumulates naturally. On average, a garlic bulb contains up to 0.9% γ-glutamylcysteines and up to 1.8% alliin. In addition to these main sulfur compounds, intact garlic bulbs also contain a small amount of SAC, but no allicin. SAC is formed from γ-glutamyl cysteine catabolism (**Fig. 2**) and has been reported to contribute to the health benefits of some garlic preparations.

Garlic is famous for its characteristic odor, arising from allicin and other oil-soluble sulfur components. Typical volatiles in crushed garlic and garlic essential oil include diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide, methyl allyl disulfide, methyl allyl trisulfide, 2-vinyl-1,3-dithiin, 3-vinyl-1,2-dithiin (Fenwick and Hanley 1985) and *E*,*Z*-ajoene (Block et al. 1984). Once garlic is processed by cutting or crushing, compounds in the intact garlic are converted into hundreds of organosulfur compounds in a short period of time. When garlic is "damaged," i.e., attacked by a microbe, crushed, cut or chewed, or when it is dehydrated, pulverized and then exposed to water, the vacuolar enzyme, alliinase, rapidly lyses the cytosolic cysteine sulfoxides (alliin) to form the cytotoxic and odiferous alkyl alkane-thiosulfinates (Fig. 2). The transiently formed compound, allicin, an oily

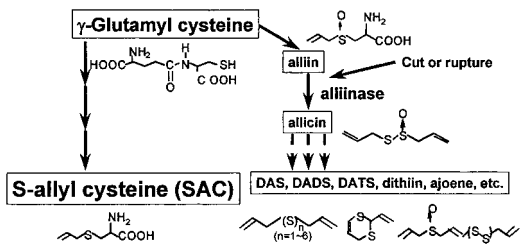

FIGURE 2 Chemical change in garlic. Intact garlic bulbs contain high amounts of γ-glutamylcysteines. These reserve compounds can be hydrolyzed and oxidized to form alliin, which accumulates naturally during storage of garlic bulbs at cool temperatures. After processing, such as cutting, crushing, chewing or dehydration, the vacuolar enzyme, alliinase, rapidly lyses the cytosolic cysteine sulfoxides (alliin) to form the cytotoxic and odoriferous alkyl alkane-thiosulfinates such as allicin. Allicin and other thiosulfinates instantly decompose to other compounds, such as diallyl sulfide (DAS), diallyl disulfide (DADS) and diallyl trisulfide (DAT), dithiins and ajoene. At the same time, γ-glutamyl-cysteines are converted to *S*-allylcysteine (SAC) via a pathway other than the alliin/allicin pathway. SAC contributes heavily to the health benefits of garlic.

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colorless liquid, comprises 70–80% of the thiosulfinates. Typically, alliin is converted to allicin by alliinase.

Allicin is an odorous and extremely unstable compound that decomposes to sulfides, including ajoene and dithiins. Allicin is sometimes mislabeled as "garlic oil" because it is not present in intact garlic or garlic products (Freeman and Kodera 1995). Although allicin has been shown to be an effective antimicrobial agent in vitro, its effects in vivo are questionable. Recent studies reveal that the bioavailability of allicin is poor (Lawson et al. 1992, **Table 3**). Allicin was actually discovered to be a component of garlic by Cavallito and Bailey (1944)(**Table 1**). At that time, the use of antibiotics to treat infectious diseases was just being discovered. The discovery of allicin in garlic was so sensational that garlic was patented in the United States for its antibiotic and antifungal effects. However, the plan of medicinal or antiseptic use of allicin soon faded because of its instability. Within a few minutes after adding allicin to blood, it can no longer be detected (Freeman and Kodera 1995). Allicin cannot be detected in the blood or urine after the ingestion of raw garlic or pure allicin (Lawson et al. 1992). Although freshly crushed garlic may contain limited amounts of allicin, no commercially available processed garlic preparations contain allicin. The acidity of the stomach would be expected to prevent the conversion of allium to allicin (Freeman and Kodera 1995). As seen in Table 3, no allicin was detected in human blood after oral intake of commercially available products standardized for allicin potential or allicin yield. These findings clearly indicate that allicin does not contribute to the in vivo effects of garlic. Freshly crushed garlic is chemically unstable and has been shown to cause undesirable side effects, such as stomach disorders (Desai et al. 1990, Nakagawa et al. 1980) and allergic reactions (Lybarger et al. 1982).

Processed garlic contains a variety of sulfur-containing compounds other than those found naturally in intact garlic cloves, depending on the conditions applied (Fenwick and Hanley 1985, Lawson 1993). Sulfur-containing compounds in commercial garlic preparations vary, depending on their manufacturing processes.

In addition to odoriferous oil-soluble compounds, less odorous water-soluble organosulfur compounds have been shown to be biologically active in various areas. SAC has an array of biological effects including a reduction in carcinogen bioactivity and a depression in oxidative damage (Amagase and Milner 1993, Imai et al. 1994, Lee et al. 1994, Li et al. 1995, Numagami et al. 1996, Sumiyoshi and Wargovich 1990).

The nonvolatile sulfur-containing compounds, SAC and SAMC are present in several garlic preparations, although the content varies considerably (Imai et al. 1994, Lawson 1993).

Additional constituents of intact garlic include the following: steroidal glycosides (Matsuura et al. 1988), lectins (Kaku et al. 1992), prostaglandins, fructan, pectin, essential oil, adenosine, vitamins B-1, B-2, B-6, C and E, biotin, nicotinic acid, fatty acids, glycolipids, phospholipids, anthocyanins, flavonoids, phenolics and essential amino acids (Fenwick and Hanley 1985). The importance of the constituents in explaining the health benefits of garlic remains to be resolved.

TABLE 1

History of allicin

Discovered in 1944, antifungal activity, U.S. patent
Never developed as a drug for the following reasons:
Instability
Inability to be absorbed
Offensive odor
Determined to be of limited value inside the body
New concept: Allicin is simply a transient compound.
Rapidly decomposes to other compounds

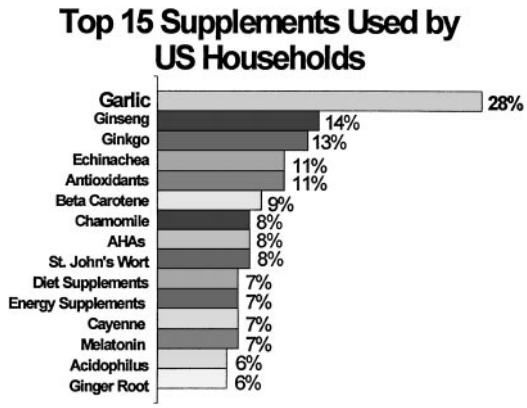

FIGURE 3 Top supplements used by U.S. households in 1997. Of 91 herbal supplements, garlic was found to be used more than twice as much as other supplements. Research conducted by Hartman and New Hope (Wyngate 1998).

Garlic supplements and intake of garlic

According to the USDA National Agricultural Statistics Service, the amount of garlic produced in the United States in 1998 was ~252,000 metric tons. Over 60% of the garlic consumed worldwide is produced in California. In 1997, the U.S. garlic market was valued at $261 dollars. Australians consume ~3000 metric tons of garlic annually, two thirds of which is imported from the United States (Woodward 1996). Garlic products have experienced increasing popularity in the last decade. The top supplements used by U.S. households are presented in **Figure 3** (Wyngate 1998). This market research, conducted in 1997, clearly showed that garlic products were the most popular of 91 dietary supplements. The dozens of brands of garlic on store shelves can be classified into four groups, i.e., essential oil, garlic oil macerate, garlic powder and garlic extract (**Table 2**). As indicated previously, the manufacturing process can markedly influence the composition of the garlic product. Clearly, manufacturers must ensure that garlic products are safe, stable and effective. Documentation of the safety and effectiveness is crucial in the evaluation of all products, including garlic, that are proposed for use for health promotion.

Although there is no standard intake of garlic, the 1988 German Kommission E monograph (1988) proposed that daily intake of ~1–2 cloves garlic or ~4 g of intact garlic may have health benefits. Unfortunately, this recommendation is not substantiated with a scientific reference. In many recent clinical studies, the daily dose of dehydrated garlic powder has been ~900 mg. Aged garlic extract intakes ranging from 1 to 7.2 g/d have been used with success. Studies showing immune enhancement in humans have shown as little as 1.8 g to as much as 10 g/d of AGE to be effective (Abdullah et al. 1989, Kandil et al. 1987 and 1988). Interestingly, no severe toxic side effects were reported in these clinical studies, even at high dosages. Other garlic supplements do not have studies of toxicity or safety, and few have any clinical studies to confirm their efficacy.

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TABLE 2

Garlic products on the market

Type of product	Main compounds and characteristics[1]
Garlic essential oil	Only 1% oil-soluble sulfur compounds (e.g., DAS or DADS) in 99% vegetable oil No water-soluble fraction No allicin[2] Not well standardized No safety data
Garlic oil macerate	Oil-soluble sulfur compounds and alliin No allicin[2] Not well standardized No safety data
Garlic powder	Alliin and a small amount of oil-soluble sulfur compounds No allicin[2] Not well standardized Results on cholesterol are not consistent. No safety data
Aged garlic extract	Mainly water-soluble compounds (e.g. SAC, SAMC or saponins) Standardized with SAC Small amount of oil-soluble sulfur compounds Various beneficial effects Well-established safety Heavily researched (200+ papers)

[1] Abbreviations: DAS, diallyl sulfide; DADS, diallyl disulfide; SAC, *S*-allyl cysteine; SAMC, *S*-allyl mercaptocysteine.

[2] Allicin is a highly unstable and reactive compound that decomposes rapidly to other compounds. For this reason, no garlic product on the market contains a detectable amount of allicin (<1 ppm) (Freeman and Kodera 1995).

Essential oil

Garlic essential oil is obtained by steam distillation of garlic. The essential oil content of garlic cloves is 0.2–0.5% and consists of a variety of sulfides, such as DADS and diallyl trisulfide (Block 1985, Yan et al. 1992). Whole garlic cloves, ground in water, are heat-distilled or extracted in an organic solvent (e.g., hexane) to obtain the oil fraction. Water-soluble compounds are totally eliminated by this process. Allicin is also completely eliminated from the oil. Commercially available garlic oil capsules generally contain vegetable oil and a small amount of garlic essential oil because of pungent odors. More attention to the ingredients in these products is warranted.

Dehydrated powder

Garlic powder is mass-produced as a flavoring agent for condiments and processed foods. Garlic cloves are sliced or crushed, dried and pulverized into powder. Garlic powder is thought to retain the same ingredients as raw garlic; however, the proportions and amounts of various constituents differ significantly (Iberl et al. 1990b). For example, the main sulfur compound in both raw garlic and garlic powder is alliin. On average, garlic cloves contain ~0.8% alliin. A pure dehydration process, with no loss of ingredients, would result in a 2–2.5 mg/g alliin content in the powder. However, garlic powders contain only 1% alliin at most, indicating that more than half of the alliin is lost during dehydration. Crushed raw garlic is high in allicin, containing ~3.7 mg/g (Lawson et al. 1992). Although allicin is often emphasized in dehydrated powder, many preparations contained no allicin, possibly reflecting its instability (Freeman and Kodera 1995, Yan et al. 1993). Therefore, although dehydrated garlic powders contain some constituents similar to those of raw garlic, amounts may vary significantly.

Although no product on the market contains a detectable amount of allicin (<1 ppm) (Freeman and Kodera 1995), some garlic powder products claim to be able to generate a certain amount of allicin (so-called "allicin potential" or "allicin yield"). However, only a very small amount of allicin (<5%) has been produced in simulated gastric fluid compared with water (Freeman and Kodera 1995), demonstrating that is not generated in appreciable amounts. This is likely due to the inactivation of alliinase, the enzyme that catalyzes the conversion of alliin to allicin at ≤pH 3 (Lawson and Hughes 1992). When dehydrated garlic powder was exposed consecutively to simulated stomach fluids and simulated intestinal fluids, which would occur when a garlic powder is consumed orally, a 99% loss in allicin production was observed (Freeman and Kodera 1995). Therefore, allicin cannot be the active compound in dehydrated garlic powders, nor is it an appropriate marker compound for all garlic preparations. As stated previously, some dehydrated powder products are reported to be ineffective at reducing plasma cholesterol in humans (Berthold et al. 1998, Breithaupt-Grögler et al. 1997, Isaacsohn et al. 1998, McCrindle et al. 1998, Neil et al. 1996, Simons et al. 1995). Part of this inconsistency in the literature may relate to poor standardization of products tested.

Oil macerate

Oil macerates were originally developed for use as condiments. Oil macerate products are made of encapsulated mixtures of whole garlic cloves ground into vegetable oil. During the manufacturing process, some alliin is converted to allicin. Because allicin is unstable and decomposes quickly, oil macerate preparations contain allicin-decomposed compounds such as dithiins, ajoene and sulfides, residual amounts of alliin and other constituents in garlic (Block 1985, Iberl et al. 1990a). Standardization for ingredients in macerates has not been explored adequately.

Extract

For garlic extract, whole or sliced garlic cloves are soaked in an extracting solution (e.g., purified water and diluted alcohol) for varying amounts of time. After separation of the solution, the extract is generally concentrated and used. Powdered forms of the extract are also available. The extract, especially AGE, contains mainly the water-soluble constituents in garlic and a small amount of oil-soluble compounds (Weinberg et al. 1993). The extract is characterized by water-soluble sulfur-containing compounds, including SAC and SAMC (Imai et al. 1994). Aged garlic extract is processed in a different way from the other three types of garlic products. As the name indicates, this extract is aged for up to 20 mo. During this aging process, the odorous, harsh and irritating compounds in garlic are converted naturally into stable and safe sulfur compounds. Aged garlic extract contains primarily water-soluble sulfur compounds such as SAC and SAMC, as well as a variety of oil-soluble sulfur compounds. SAC can be used for standardization because it is bioavailable (Nagae 1994). Further, the safety of AGE has been confirmed by various toxicological studies (Kanezawa et al. 1984, Nakagawa et al. 1980, 1984a and 1984b, Sumiyoshi et al. 1984, Yoshida et al. 1984).

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Bioavailability of garlic compounds

Bioavailability of active ingredients in garlic is likely essential. SAC is one of the water-soluble organosulfur compounds in garlic. Its concentration increases during extraction/aging. The pharmacokinetics of SAC are well established (Nagae et al. 1994). SAC can be detected in the plasma, liver and kidney after oral intake (Nagae et al. 1994). The bioavailability of SAC is 103.0% in mice, 98.2% in rats and 87.2% in dogs (Nagae et al. 1994). *N*-Acetyl-SAC has been identified as a metabolite of SAC in the urine of dogs and humans. This suggests that SAC could be transformed by *N*-acetyltransferase. SAC and its metabolite(s) are possible compliance-markers for clinical studies involving garlic (Steiner and Li 2001). Because SAC is found in many preparations, it might be used for standardization and/or used to compare various sources.

The oil-soluble organosulfur compounds in garlic, including allicin, sulfides, ajoene and vinyldithiins, are not found in blood or urine, even after consumption of a large amount of garlic (**Fig. 4**; Lawson et al. 1992). As shown in Table 3, a preliminary study with garlic products, including enteric-coated products, revealed that no allicin was found in blood after oral ingestion. Allyl mercaptan and DAS were the first compounds identified as the components that produce the strong odor detectable after ingestion of garlic (Laakso et al. 1989, Minami et al. 1989). Allicin, perfused into isolated rat livers, showed a remarkable first-pass effect and is metabolized to DADS and allyl mercaptan, whereas ajoenes and vinyldithiins were recovered in the effluent (Egen-Schwind et al. 1992b). Allicin disappeared very rapidly when incubated with liver homogenate (Egen-Schwind et al. 1992a). No allicin was detected in either serum or urine from 1 to 24 h after ingestion of 25 g of raw garlic (~90 mg allicin) (Fig. 4; Lawson et al. 1992). Comparing the content of garlic products for their ability to inhibit platelet aggregation on the basis of ajoene and dithiin content (Lawson et al. 1992) may be inadequate because other compounds may act synergistically or independently to bring about an effect. For example, AGE, which contains neither ajoene nor dithiin, significantly reduced platelet aggregation and adhesion in two double-blind, placebo-controlled clinical studies (Rahman and Billington 2000, Steiner and Lin 1998). Thus, the concentration of various compounds and their effects in vitro may not determine effectiveness. Preclinical or, preferably, clinical studies are required to confirm or refute the effectiveness of a product in question, whatever its chemical composition.

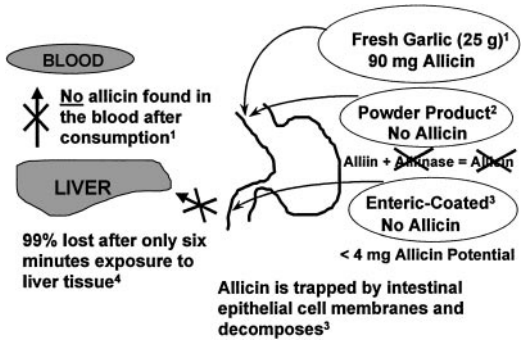

FIGURE 4 Fate of allicin. *1*) No allicin is found in the blood after oral consumption of 90 mg allicin (Lawson et al. 1992). *2*) Garlic products do not contain allicin (Freeman and Kodera 1995), nor can they produce allicin from alliin because alliinase is destroyed by stomach acid (Lawson et al. 1992). *3*) Enteric-coated garlic powder bypasses stomach acid. However, intestinal fluid inhibits production of allicin from powder by 40% (Freeman and Kodera 1995). Further, intestinal epithelial cells decompose allicin (Freeman and Kodera 1995). Any allicin produced may destroy both good and bad bacteria (Shashikanth et al. 1985) and aggravate the intestinal lining and stomach (Kodera 1997). According to the clinical study in Table 3 (in this article), theoretical amounts of allicin delivered to the intestinal tract from enteric-coated garlic powder still do not reach the blood stream. *4*) Even if any allicin were to reach the liver from the intestinal tract, it would be transformed in liver tissue (Egen-Schwind et al. 1992a). Whether the garlic preparation/product contains allicin or not, allicin is not detected in the bloodstream in the body. Therefore, allicin is not bioavailable and cannot reach target organs via circulation.

TABLE 3

Allicin in human blood from commercially available products[1]

Product	Allicin μg/mL plasma
Product A	ND[1]
Product B	ND
Product C (Enteric-coated)	ND
Product D (Enteric-coated)	ND

[1] In-house clinical data: Allicin was not detected in human blood from commercially available products. Allicin was measured as previously reported (Freeman and Kodera 1995). Product A: Kwai (Lichtwer Pharma, Lot #X96030100); product B: Quintessence (Pur Gar, Lot #608116); product C: Garlicin (Nature's Way, Lot #609018); product D: Garlinase 4000 (Enzymatic Therapy, Lot #227Y180F).

DADS is a metabolite of allicin (Egen-Schwind et al. 1992b). The maximum concentration of radiolabeled DADS in the liver of mice occurred 90 min after intraperitoneal administration (Pushpendran et al. 1980). Seventy percent of the radioactivity, which was no longer DADS, was distributed in the liver cytosol, of which 80% was metabolized to sulfate. DADS, like allicin, was not detected in human blood or urine from 1 to 24 h after oral ingestion of 25 g of crushed raw garlic (Lawson et al. 1992).

Because allicin, ajoene, vinyldithiins and DADS are not found in the blood or urine after garlic consumption, they are likely not the active compounds per se. The instability and/or metabolism of such compounds likely contribute to the inconsistent results found in the clinical cholesterol studies using garlic oil (Berthold et al. 1998) and garlic powder products (Berthold et al. 1998, Breithaupt-Grögler et al. 1997, Isaacsohn et al. 1998, McCrindle et al. 1998, Neil et al. 1996, Simons et al. 1995).

SAC is a stable, odorless, water-soluble compound with the ability to lower cholesterol (Yeh and Yeh 1994), serve as an antioxidant (Ide et al. 1997, Imai et al. 1994), inhibit the cancer process (Amagase and Milner 1993, Li et al. 1995) and protect the liver from toxins (Nakagawa et al. 1988). AGE, a product standardized for SAC, has shown cholesterol-lowering effects in several clinical studies (Lau et al. 1987, Steiner et al. 1996, Yeh et al. 1995). Other metabolites of garlic constituents, such as *N*-acetyl-*S*-(2-carboxypropyl)-cysteine, *N*-acetylcysteine and hexahydrohippuric acid, have been detected in human urine after ingestion of garlic (Jandke and Spiteller 1987). After consumption of garlic, *N*-acetyl-*S*-allyl-cysteine is found in human urine. At present, SAC is the only reliable human compliance marker used for studies involving garlic consumption because it is detectable and increases quantitatively in the blood after oral intake of garlic capsules (Steiner and Li 2001).

Overall, the active principles in garlic have not been fully characterized. It is assumed that the bioavailability of these

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sulfur-containing compounds will play an important role in determining the biological response to various garlic preparations.

Safety and quality control of garlic preparations

The effectiveness of garlic may be in prevention rather than therapy. To obtain the preventative benefits of garlic, however, long-term supplementation may be necessary. Long-term use of supplements raises issues about toxicity. The general attitude of the public regarding safety is one of the important concerns associated with long-term use of any product. As mentioned previously, garlic preparations vary in constituents, necessitating toxicological tests of each product to ensure its safety. It is essential that safety be considered a major part of the quality control of all garlic preparations

Although garlic has been used safely in cooking as a popular condiment or flavoring and used traditionally for medicinal purposes, it is commonly known that excessive consumption of garlic can cause problems. Garlic odor on breath and skin (Mader 1990) and occasional allergic reactions (Siegers 1992) are recognized. Reports since 1932 have revealed the following adverse effects associated with raw garlic and garlic powder: *1*) stomach disorders and diarrhea (Caporaso et al. 1983, Desai et al. 1990, Nakagawa et al. 1980); *2*) decrease of serum protein and calcium (Miyamoto 1938, Shashikanth et al. 1986); *3*) anemia (Katsunuma 1932, Kuzutani 1934, Nakagawa et al. 1980); *4*) bronchial asthma (Lybarger et al. 1982, von Kirsten and Meister 1985); *5*) contact dermatitis (Burden et al. 1994, Garty 1993, Lembo et al. 1991, McFadden et al. 1992, Mitchell 1980, Parish et al. 1987); and 6) inhibition of spermatogenesis (Dixit and Joshi 1982, Qian et al. 1986).

Oil-soluble sulfur compounds are known irritants and allergens; topically applied DAS is the most allergenic (Papageorgiou et al. 1983). Imada (1990) reported the following toxicity effects of garlic: *1*) allicin is one of the major irritants in raw garlic; *2*) oil-soluble sulfur compounds are more toxic than water-soluble compounds; and *3*) when garlic is extracted in a certain period, its toxicity is greatly reduced.

Crushed raw garlic is high in allicin (3.7 mg/g) (Lawson et al. 1982). Enteric-coated garlic products are designed to deliver allicin (1–5 mg, depending on the product label claim) directly into the intestinal tract. However, allicin can be an oxidizing agent that not only impedes bacterial growth (Shashikanth et al. 1985) but also can damage the intestinal lining and the stomach (Kodera 1997). As shown in **Figure 5**, raw garlic juice (0.5 mL) caused significant damage to the epithelial mucosal membrane after 2 h in rats. After 24 h of exposure, ulcers, shrinkage and bleeding in the epithelial mucosa were detected. When three kinds of commercially available enteric-coated garlic preparations, i.e., Garlicin, Garlique and Garlinase 4000, were used at dosages of 133, 108 and 60.5 mg/rat, respectively, each caused severe damage to the duodenal mucosa after 2 h of exposure (Fig. 5). Saline controls showed no damage to ligated duodenums. According to this study, enteric-coated garlic powder products, which are designed to generate allicin in the delicate intestine, may be hazardous to the intestinal tract.

On the other hand, a number of toxicological and clinical studies of AGE have been performed with no adverse effects. The safety of AGE has been well established by the following studies: *1*) acute and subacute toxicity tests (Nakagawa et al. 1984a and 1984b); *2*) chronic toxicity test (Sumiyoshi et al. 1984); *3*) mutagenicity tests (Yoshida et al. 1984); *4*) general toxicity tests (Kanezawa et al. 1984, Nakagawa et al. 1980); *5*) teratogenicity tests (Segments I, II, and III); 6) toxicity test conducted by the U.S. Food and Drug Administration; and *7*) clinical studies conducted on >1000 subjects (Hasegawa et al. 1983, Kawashima et al. 1989, Steiner et al. 1996).

One of the active ingredients of garlic preparations, includ-

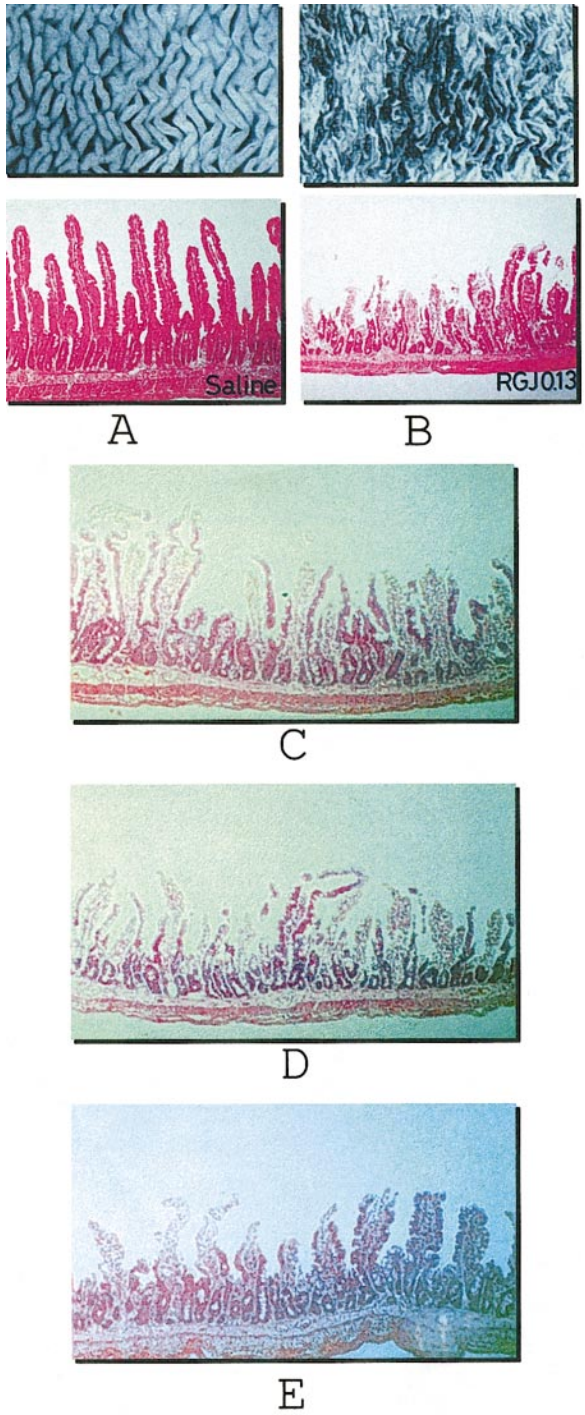

FIGURE 5 Effects of garlic on the intestinal mucosa of rats. Freshly prepared raw garlic juice (0.5 mL), high in allicin, injected into the ligated duodenum of rats (*B*) resulted in significant damage to the epithelial mucosal membrane after 2 hof exposure. Ligated duodenum exposed to saline alone (*A*) showed no damage. Three kinds of commercially available enteric-coated garlic preparations, i.e., Garlicin (*C*), Garlique (*D*) and Garlinase 4000 (*E*), were injected into ligated duodena at dosages of 133, 108 and 60.5 mg/rat, respectively. All of these products caused severe damage to the duodenal mucosa after 2 h of exposure.

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ing AGE, is SAC. SAC is a very useful compound that has been well researched for its pharmacologic effects. The United States National Cancer Institute tested the toxicity of SAC vs. other typical garlic compounds and found that it has 30-fold less toxicity than allicin and DADS (Imada 1990). The 50% lethal oral dose for allicin in mice is as follows (mg/kg body): male 309, female 363; for DADS: male 145, female 130; and for SAC: male 8890, female 9390.

Documentation of safety and effectiveness are crucial in the evaluation of products used for health purposes, such as drugs and food supplements. As mentioned above, different garlic preparations comprise different constituents, which necessitates detailed toxicological and biological tests of each product to ensure safety and efficacy.

U.S. Pharmacopoeia (USP) and other organizations are developing a monograph dealing with garlic as part of a series on botanicals. USP did not list allicin as a reference standard in its garlic and garlic powder monograph (USP 1999). Label statements on dietary supplements must be based on science that can help consumers make informed decisions.

Summary

- Garlic has many health benefits and has been traditionally used worldwide over the centuries.
- The chemistry of garlic is complicated and the quality of garlic products is dependent on the manufacturing process.
- Although allicin has been thought to be an active component of garlic, allicin does not account for the proposed health benefits of garlic.
- Inconsistency in the efficacy of garlic supplements may be due to the incorrect standardization and the overlooking of other truly active compounds.

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