Chapter 14

Garlic: A Review of Its Medicinal Effects and Indicated Active Compounds

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Numerous clinical trials with garlic cloves and standardized garlic powder tablets leave little doubt that modest amounts of garlic have significant cardiovascular effects by reducing serum cholesterol, blood pressure, and platelet aggregation. Epidemiological and animal studies strongly indicate significant anticancer effects, particularly for the intestinal tract. Furthermore, its intestinal and topical antimicrobial activities have been its longest recognized effects. Identification of the compounds essential to the activity of garlic, mostly ascribed to its high content of sulfur compounds, has only been partially resolved. So far, the thiosulfinates, of which allicin is 70-80%, are the only compounds with reasonably proven activity at levels representing normal amounts of garlic consumption. They are clearly responsible for the antimicrobial effects. Several evidences also indicate that they are essential to most of the hypolipidemic, antithrombotic, antioxidant, and hypoglycemic effects of garlic, and for some of its anticancer effects. However, because the thiosulfinates are rapidly metabolized and since their active metabolites have not yet been identified, little is known about their mechanism of action. The compounds responsible for the hypotensive effects and much of the anticancer and immune effects of garlic remain unknown. Until they are known, it is best to consume garlic in whole form, fresh or dried.

Garlic (*Allium sativum* L.) has been used as a medicine for more millennia and by more cultures than perhaps any other plant. Even today, garlic cloves are commonly used as a medication by much of the world, especially in eastern Europe and Asia, while garlic pill supplements are popular in western Europe and growing in popularity in the U.S. In Germany, where most of the clinical research on garlic has taken place and where garlic tablets are the leading non-prescription phytomedicine, 8% of the population regularly consumes garlic supplements, ranking in sales with leading prescription drugs *(1)*. In the U.S., where the total garlic consumption in

In Phytomedicines of Europe; Lawson, L., et al.;
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1994 was 438 million pounds (about 2.5 grams per person per day) *(2)*, garlic ranks in second place behind Echinacea among the best selling herbal supplements *(3)*.

One of the major reasons for the popular medicinal use of garlic is the large amount of scientific research conducted in the 20th century that has confirmed much of the traditional uses of garlic. As of the end of 1996, 1158 pharmacological studies and 650 chemical studies have been published on garlic and garlic products, making it one of the most researched medicinal plants. The pharmacological studies (1202 as of mid-1997; see Table I) have included 208 human studies and have focused mainly on cardiovascular (344), anticancer (221), antimicrobial (252), and antioxidant (60) effects. In addition, 105 toxicology studies and 42 studies on the metabolism of garlic compounds have been published, for a total of 1990 studies on garlic, not including botanical and agricultural studies. Over 40 nations have contributed to this vast literature, with Germany, India, and the U.S. accounting for 63% of the total.

Table I. Pharmacological Studies on Garlic (1900 - 1996)[a]

Effect	Total studies	Human studies
Cardiovascular	344	104 (2)[b]
Blood lipids	179	62
Blood pressure	78	18
Blood fibrinolysis, coagulation, flow	51	18
Platelet aggregation	76	6
Atherosclerosis (plaques)	23	2
Antimicrobial	252	35
Cancer	221	12 (10)[b]
Antioxidant	60	4
Hypoglycemic	28	3
Immune stimulation	15	3
Antiinflammatory	11	1
Gastrointestinal disturbances	43	27
Respiratory	11	5
Heavy metal antidote	28	1
18 Other effects	145	12
Total pharmacological studies	1158	208

[a] Includes only actual studies: human (in vivo), animal, and in vitro studies. Not included are reviews, commentaries, patents, pharmacopoeias. In addition, 44 studies were published in the first half of 1997, 48% of which were on cancer effects.
[b] Epidemiological studies.

The most extensive review of the scientific and historical literature on garlic was published in 1996 by Koch and Lawson *(4)*, a work which includes 2250 garlic references and details the evidence for the identity of the main active compounds for each pharmacological effect. A summary of the book has also been published *(5)*. Other relatively recent reviews includes those of Block on the chemistry of garlic's sulfur and selenium compounds *(6-8)*, Lawson *(9)* on analysis and cardiovascular effects, Sendl *(10)* on analysis of garlic and wild garlic, Reuter *(11)* and Srivastava

(12) on pharmacological effects, Agarwal *(13)* on cardiovascular effects, and short broad reviews by Bradley *(14)*, Leung & Foster *(15)*, and Weiss *(16)*. Older reviews have also been listed by Lawson *(9)*. There is also a new book for general readership by Fulder *(17)* that is very commendable.

To be able to consistently evaluate the pharmacological effects of garlic and to be able to identify the active compound(s) for each effect, a thorough understanding of its composition, and the chemical changes that occur during the production of the commercial products that are often used in the studies, is essential. The purpose of this review is to critically summarize the evidence for the various pharmacological effects of garlic and to present the evidence for the active compound(s) for each effect at doses representing a typical level of garlic consumption. The main emphasis of the review will be upon whole garlic (fresh or dried) and will only touch modestly on commercial oil or extract products.

Medicinal History

The medicinal use of garlic, which began about 5000 years ago (reviewed in *2, 18, 19*), was first recorded by both the Sumerians of Mesopotamia (region of the Tigris and Euphrates rivers) as well as by the people of ancient India. In India it became a part of the popular Ayruvedic medicine and first became recorded in an Ayruvedic medical textbook in 500 AD from much older texts. Garlic was also of great importance in Egypt, where it has been found preserved in Pharaohs' tombs and where its extensive use by pyramid builders was inscribed on the Great Pyramid of Cheops. The Egyptian *Ebers Codex* of 1550 BC mentions the use of garlic in 22 medical formulas. As recorded in the Bible (Numbers 11:5), the Israelites (Jews) mourned for it when they left Egypt about 1400 BC. The popularity of garlic among the Jews has remained even until today, having survived their scattering among other nations, and has, in fact, influenced other nations to use it. China has long used garlic for medicinal purposes, being first recorded in a Chinese medical text about 500 AD. The Greeks used garlic to strengthen Olympic athletes and to treat battle wounds. The Greek physician Hippocrates (460-370 BC), who is considered the "father of medicine," recommended garlic for infections, pneumonia, cancer, digestive problems, increased urine secretion, and improved menstrual flow. Dioscorides, a Greek who lived in the first century AD, and is called the "father of pharmacy," recommended crushed garlic for snake bites, rabid dog bites, coughs, clearing arteries, infections, and leprosy. Some of the most important Roman medical writers (Pliny the Elder, 23-79 AD; Celsus, 25 BC- 50 AD; Galen, 129-199 AD) made similar recommendations. Galen, who was the personal physician of emperor Marcus Aurelius and whose writings greatly influenced Western and Arabic (Unani Tibb system) medicine for a thousand years, called garlic the "theriac (cure-all) of the peasant."

Around 1150, St. Hildegard of Bingen, a German nun who wrote two medical books, strongly encouraged eating raw garlic to improve health and cure the sick. The London College of Physicians recommended garlic to treat poisons, bites, edema, ulcers, and toothaches, as well as for the great plague of London in 1665. Sydenham (1624-1689), a leading English physician, used garlic to cure smallpox. Cholera epidemics of the 1850s in France and Bulgaria were cured with garlic. In

1858, Louis Pasteur showed that garlic and onions could kill the cause of infectious diseases - germs. Albert Schweizer in the early and mid-1900s used garlic in Africa to cure cholera and typhoid fever. In World War I, garlic was widely used in Europe, especially England, to treat battle wounds and dysentery. In World War II, Russia, where garlic use has long been popular, used it again for soldiers' wounds when they ran out of penicillin, which resulted in the nickname of "Russian penicillin."

General Composition of Garlic Cloves

The known composition of the more abundant compounds of garlic cloves are listed in Table II. Although garlic is commonly eaten for both its flavor and health benefits, its content of vitamins and minerals, while average compared to other vegetables on a per weight basis, are much too low (less than 2% of the daily need) at levels normally consumed (2-4 g, or a typical clove) to account for its known health effects. Some unique features of garlic are its low moisture content (62-68% compared to 80-90% for most fruits and vegetables); its high content of fructans, fructose polymers of 10-60 units *(20, 21)* that constitute about 65% of its dry weight; its high content of common free amino acids, which is similar to its protein content and is strongly dominated by arginine; and its very low content of lipids and other oil-soluble compounds. However, its most unique feature is that of its high content of organosulfur compounds, 99.5% of which contain the sulfur amino acid cysteine, even though cysteine itself is absent. The sulfur content of garlic (about 3 mg/g) is four times greater than that of other high sulfur-containing vegetables and fruits, such as onion, broccoli, cauliflower and apricots *(22)*.

Table II. Composition of Garlic Cloves (mg/g fresh weight)

Water	620-680	Adenosine (0 before crush)	0.1 (8 hr)
Water solubles	310-370	Saponins	0.4-1.1
Carbohydrates	260-300	Vitamins	0.15
Fructans	220-250	Ascorbic acid	0.14*
Fiber	15	Thiamine	0.002*
Protein	15-21*	Riboflavin	0.0008*
Amino acids (free, common)	10-15	Minerals	7
Arginine	5-8	Potassium	4.4*
Organosulfur compounds	11-35	Phosphorus	1.8*
Cysteine sulfoxides	6-19	Calcium	0.24*
γ-Glutamylcysteines	5-16	Magnesium	0.18*
S-alkenyl cysteines	0.01-0.03	Sodium	0.11*
Scordinins	0.03	Iron	0.02*
γ-Glutamylphenylalanine	0.4-1.1	Chromium	0.0005*
Lipids	1-2	Selenium	0.0002*
β-Sitosterol	0.015	Germanium	0.00004*
Phenolic acids	0.04	Sulfur	2.3-3.7
Phytic acid	0.8	Nitrogen	6-13

Data from Lawson *(22)*, which also includes additional less abundant compounds.
* Less than 2% of the U.S. Recommended Dietary Allowance in a 3-4 gram clove.

Garlic is also one of the highest selenium-containing foods on a per gram basis *(23)*. Even though the amount of selenium in a single clove is very small, the selenium content of garlic (and likewise the anticancer effects of garlic) can be increased dramatically (up to 2500-fold), when grown in a selenium-enriched soil *(24, 25)*, because selenium, being in the same elemental family as sulfur, will replace sulfur in garlic's cysteine compounds. The most abundant selenium compound in normal garlic is selenocysteine (cys-SeH); whereas in selenium-enriched garlic it is *Se*-methyl selenocysteine *(8, 26, 27)*.

The Sulfur Compounds of Garlic Cloves

The large majority of the analytical and pharmacological research on garlic has focused on its sulfur compounds. This has been the case not only because of their uniquely high abundance in garlic, but also because they are the only known compounds in garlic that have pharmacological activity at doses representing typical levels of garlic consumption, and probably because of the long-recognized pharmacological activity of sulfur-containing drugs such as penicillin, probucol, thiazide, and captopril.

Table III. The Principal Organosulfur Compounds in Whole and Crushed Garlic

Compound	Whole	Crushed
	(mg/g fresh weight)	
***S*-(+)-Alkyl-L-cysteine sulfoxides**		
Allylcysteine sulfoxide (alliin)	6-14	nd
Methylcysteine sulfoxide (methiin)	0.5-2	nd
trans-1-Propenylcysteine sulfoxide (isoalliin)	0.1-1.2	nd
Cycloalliin	0.5-1.5	0.5-1.5
γ-L-Glutamyl-*S*-alkyl-L-cysteines		
γ-Glutamyl-*S*-*trans*-1-propenylcysteine	3-9	3-9
γ-Glutamyl-*S*-allylcysteine	2-6	2-6
γ-Glutamyl-*S*-methylcysteine	0.1-0.4	0.1-0.4
Alkyl alkanethiosulfinates		
Allyl 2-propenethiosulfinate (allicin)	nd	2.5-4.5
Allyl methyl thiosulfinates (2 isomers)	nd	0.3-1.5
Allyl *trans*-1-propenyl thiosulfinates (2 isomers)	nd	0.05-1.0
Methyl *trans*-1-propenyl thiosulfinates (2 isomers)	nd	0.02-0.2
Methyl methanethiosulfinate	nd	0.05-0.1

Nearly all (95%) of the sulfur in intact garlic cloves is found in two classes of compounds in similar abundance—the *S*-alkylcysteine sulfoxides and the γ-glutamyl-*S*-alkylcysteines (see Table III and Figure 1a) *(9, 22)*. Both types of compounds are substituted at the sulfur atom with either allyl (2-propenyl), isoallyl (*trans*-1-propenyl), or methyl groups. The most abundant sulfur compound in garlic is alliin

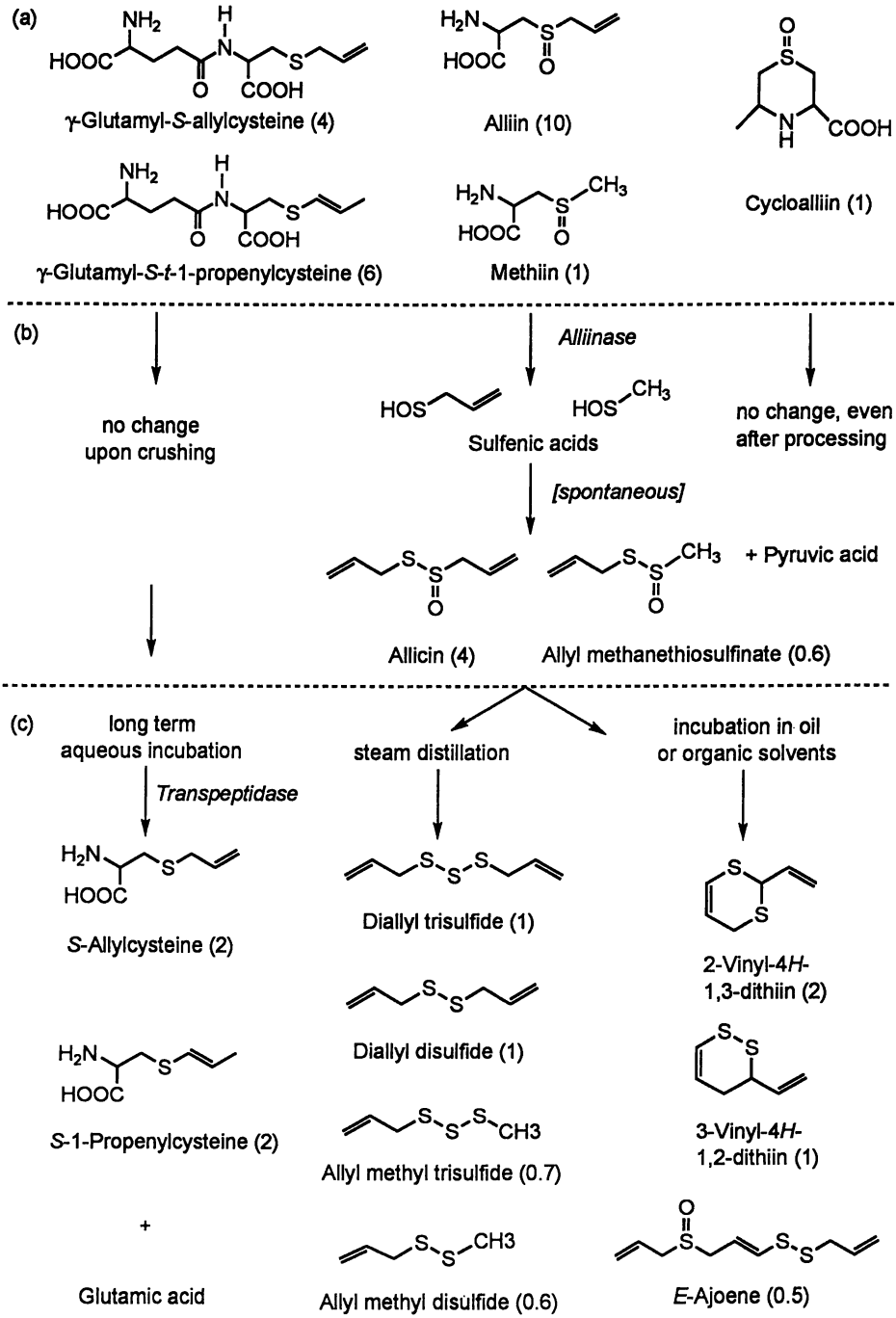

Figure 1. Structures of the main sulfur compounds found (a) in whole garlic cloves and (b) after crushing the cloves and (c) after processing to oils or by aging. Typical quantities ( ) are given as mg/g cloves.

(*S*-allylcysteine sulfoxide), which is typically present at 10 mg/g fresh wt. or 30 mg/g dry wt. (since garlic consistently contains about 65% water, dry weight values are usually three times the fresh weight values) and accounts for about 80% of the total cysteine sulfoxides. It is absent in onions, is less abundant in several other *Allium* species [*A. ursinum* (wild garlic), *A. ampeloprasum* (elephant garlic), *A. tuberosum* (garlic chives/Chinese chives)], and only rarely occurs in small amounts in other plants. The biosynthesis of alliin appears to involve serine and an unknown source of the *S*-allyl group to form the intermediate, *S*-allylcysteine, which is rapidly oxidized to alliin and found only in trace amounts *(22)*. However, the γ-glutamylcysteines act as reserve sources of additional alliin and isoalliin during wintering or sprouting due to γ-glutamyl transpeptidase hydrolysis and subsequent oxidation *(28)*. Although the cysteine sulfoxides are very important parent compounds to many of the pharmacological effects of garlic, the γ-glutamylcysteines have as yet no well-established effect, partly because they have rarely been used in pharmacological studies.

Natural Variation of Garlic's Sulfur Compounds. All plant species vary to some degree in their content, due to soil location and composition, climate, variety differences, harvest date, and post-harvest handling. The extent of these differences, especially for active or suspected active compounds, is important to monitor since they will affect the pharmacological effects. About 85% of the alliin and other cysteine sulfoxides of a garlic plant are found in the bulb, with about 12% in the leaves and 2% in the roots; however, the γ-glutamylcysteines are found only in the bulbs *(22)*. The amount of alliin and γ-glutamylcysteines present in the bulbs increases several-fold in the four weeks prior to harvest time *(29, 30)*. Furthermore, we have found that alliin increases about 25% during the typical curing process (whole plants dried in the shade for at least two weeks) and that extending the normal harvest date ("normal" was judged by appearance factors by two long time commercial growers who independently chose the same date) by 2 weeks—until the plants are almost completely brown—increases the content of these compounds an additional 20% on a dry weight basis (L. Lawson and G. Reynolds, unpublished). Therefore, a careful choice of the harvest date can be very important. In a study with 16 strains of softneck garlic (*A. sativum* var. *sativum*), the type grown in California and most commonly found in grocery stores, and 53 strains of hardneck or topset garlic (*A. sativum* var. *ophioscorodon*) grown on the same 1-acre farm outside Troy, New York by G. Reynolds, there was a 1.8-fold and 2.7-fold variation, respectively, in alliin content and a 1.5-fold and 4.2-fold variation in content of γ-glutamylcysteines *(22)*. Another study of six purchases at grocery stores over four months showed a 2.0-fold variation in alliin *(31)*.

Enzymatic Formation of the Thiosulfinates upon Crushing Garlic. When garlic cloves are cut, crushed, or chewed (or when the powder of dried cloves becomes wet in a non-acid environment), the cysteine sulfoxides, which are odorless and insoluble in organic solvents, are very rapidly converted to a new class of compounds, the thiosulfinates (see Table III and Figure 1b). The thiosulfinates contain two sulfur atoms (being derived from two cysteine sulfoxide molecules with the loss of pyruvate and ammonia), are more soluble in organic solvents than in water, and are somewhat

volatile, which property makes them responsible for the odor of freshly chopped garlic. The formation of thiosulfinates takes place when the cysteine sulfoxides, which are located only in the clove mesophyll storage cells, come in contact with the enzyme alliinase or alliin lyase (EC 4.4.1.4), which is located only in the vascular bundle sheath cells *(32)*. Alliinase is a glycoprotein of MW 55,000 and requires pyridoxal phosphate. It is one of the two most abundant proteins in garlic *(33, 34)* and is active at pH 4.5-8, but is immediately and irreversibly inhibited at acidic pH values below 3.5 *(35-37)*. It is also effectively inhibited by 10 mM amino-oxyacetate and by cooking, but is poorly inhibited by alcohols *(22)*. There appears to be at least two forms of alliinase in garlic, one that is alliin-specific and one that is methiin-specific, the latter being considerably easier to inhibit *(28)*.

With the exception of ring-structured cycloalliin (formed by cyclization of isoalliin), all of the cysteine sulfoxides are lysed by alliinase to form the very transitory sulfenic acids, which self-condense to form the thiosulfinates. Due to the very large abundance of alliinase (10 mg/g fresh *(38)*), the rate of formation of the thiosulfinates is extremely rapid, being complete upon crushing in under 10 seconds for alliin and isoalliin and in about 60 seconds for methiin *(22, 36)*. Because the thiosulfinates result from condensation of three types of sulfenic acids, a total of nine thiosulfinates can be formed; however, only eight are found (Table III), since 1-propenyl 1-propenethiosulfinate is too unstable to exist and has been shown to rapidly form zwiebelanes in onions, where 1-propenyl cysteine sulfoxide (isoalliin) is much more abundant *(39)*. Due to the abundance of alliin, the main thiosulfinate formed upon crushing garlic is allicin, which varies in abundance from 60 to 90% of the total thiosulfinates, with 75% being typical. Most of the methiin is converted to two allyl methyl thiosulfinate regioisomers, allyl methanethiosulfinate and methyl 2-propenethiosulfinate, the former being twice as abundant as the latter *(31, 40)*.

Stability of the Thiosulfinates. The thiosulfinates are self-reactive compounds that can be quite unstable, depending upon the environment (solvent), temperature, and concentration. Since they undergo self-reaction by both monomolecular and bimolecular mechanisms *(6, 41)*, both dilution and the presence of solvents that hydrogen bond with the oxygen atom (water and, to a lesser extent, alcohols) greatly improve their stability. For example, in the absence of solvent or in the presence of low-polarity solvents (hexane, diethyl ether), the half-life of allicin at room temperature is 2-16 hours; however, in crushed garlic (or in garlic juice) it is 2.4 days, increasing to 22 days upon 10-fold dilution with water (60 days upon dilution with 1 mM citric acid; 4 days at 37°C in water), and increasing another 20-fold at 4°C *(20)*. Although allicin is too unstable to be present in any commercial product, it is very sufficiently stable for common home uses (e.g., chopped cloves in a salad or sandwich or stored in a refrigerator).

Composition of Garlic Odor. The odor of both chopped garlic and the breath after eating garlic has always been a salient feature of garlic, both positively and negatively. The odor of fresh cut garlic is mainly due to allicin, although diallyl disulfide becomes the dominant compound after 30 minutes, while the odor of cooked garlic is due mostly to diallyl and allyl methyl trisulfides and lesser amounts of their disulfides *(22, 42)*. When fresh garlic is eaten, the initial breath odor is due

mainly to allyl mercaptan; however, this represents odor from the throat and disappears in about one hour *(43, 44)*. The odor that comes from the lungs *(45)* rises slowly and lasts over 24 hours. It consists mainly of allyl methyl sulfide (87% of the sulfur compounds at nine hours) and dimethyl sulfide (11%) and is due to metabolism of the thiosulfinates *(43,46, 47)*. Dimethyl selenide (methyl-Se-methyl) is also found in the breath at levels that may add to the odor *(43)*. Although the odor of garlic is carried into human breast milk, babies seem to prefer the taste since they nurse longer than when their mothers don't eat garlic *(48, 49)*.

The Sulfur Compounds of Commercial Garlic Products

In addition to the fresh or cooked cloves, garlic is frequently consumed as a spice (garlic powder and garlic salt), as pickled cloves, and as supplements in pill form (garlic powder tablets and capsules; steam-distilled oil capsules; oil-macerate capsules; aged extract tablets, capsules, and liquid). Although the oil products and the aged extracts have all been thought to be extracts, they really should be called transformation products, since none of the main sulfur compounds of these products are significantly found in whole or crushed cloves. These transformations will now be discussed.

Transformation of the Thiosulfinates upon Commercial Processing. The compounds into which the thiosulfinates are transformed depend upon the medium and temperature. In the presence of water, diallyl trisulfide, diallyl disulfide, and allyl methyl trisulfide are the principal products (Figure 1c). Upon steam-distillation of crushed cloves, a commercial oil is produced, in which as many as 30 different sulfides have been found, comprising diallyl (57%), allyl methyl (37%), and dimethyl (6%) mono- to hexasulfides, along with trace amounts of the hepta- and octasulfides and small amounts of the allyl 1-propenyl and methyl 1-propenyl di-, tri-, and tetrasulfides *(50)*. Upon incubation at room temperature in organic solvents, such as hexane, ether, or triglyceride oils (oil-macerated products), two additional types of compounds are formed: the ring-structured vinyldithiins, which are the main compounds formed (70-80%), and lesser amounts (12-16%) of ajoene (*E,Z*-4,5,9-trithiadodeca-1,6,11-triene 9-oxide) *(50-52)*. Some allyl sulfides (diallyl trisulfide, allyl methyl trisulfide and diallyl disulfide) are also formed (4-18%). Except for ajoene, none of the thiosulfinate transformation products retain the oxygen atom. This results in greater volatility (odor) and less solubility in water (e.g., allicin solubility in water is 1%, while for diallyl disulfide it is 0.005% and for diallyl trisulfide it is 0.0006% *(22, 53)*.

Processing Changes During Long Term Incubation (Aging). Among the various types of garlic products, both aged extracts and pickled cloves involve long term incubation. The aged extracts employ chopped cloves that are incubated in dilute (20%) ethanol for 18-20 months prior to drying of the extract *(54, 55)*, while pickled cloves are incubated and permanently packaged in vinegar (5% acetic acid), with the incubation time being dependent on when the cloves are eaten *(22)*. The compositional changes that take place in these products over a two-year period,

especially in the aged extracts, are considerable, as shown in Table IV. The only sulfur compound that is not affected by time is cycloalliin.

For chopped cloves aged in dilute ethanol, the main changes are (1) the initial loss of alliin to thiosulfinate formation, (2) the complete loss of thiosulfinates after 3 months (converted to volatile allyl sulfides which evaporate almost completely), and (3) complete hydrolysis of the γ-glutamylcysteines to the theoretical amounts of *S*-allylcysteine, *S*-1-propenylcysteine (the main sulfur compounds present after 3 months) and glutamic acid (see Figure 1c). There are also substantial increases in cystine (due to protein hydrolysis) and *S*-allylmercaptocysteine (probably due to the reaction of allicin with protein-derived cysteine). The content of *S*-allylcysteine remains constant after 3 months, but *S*-1-propenylcysteine steadily decreases.

Table IV. Compositional changes during aging of a 20% ethanol extract of chopped garlic or of garlic powder in acetic acid (pickling).[a]

Compound	Incubation time (months)				
	0	1	3	12	24
Chopped cloves in 20% ethanol	(mg/g dry extract)				
Alliin	5.0	3.2	2.8	2.9	2.7
Allicin	8.3	4.1	0.4	0	0
Allyl methyl thiosulfinates	2.1	1.3	0.4	0	0
Allyl sulfides	0.19	0.14	0.12	0.09	0.08
Cycloalliin	3.5	3.6	3.5	4.0	3.6
γ-Glutamyl-*S*-allylcysteine	12.7	5.8	1.1	0	0
S-Allylcysteine	0.2	5.9	7.2	7.1	7.2
γ-Glutamyl-*S*-1-propenylcysteine	15.9	3.4	0.5	0	0
S-1-Propenylcysteine	0.5	6.7	8.1	6.5	4.4
S-Allylmercaptocysteine	0.01	0.6	1.2	1.7	1.9
Cystine	0.07	0.5	0.8	0.9	1.2
Total main sulfur compounds	48	34	26	23	21
Glutamic acid	1.1	9.7	14.2	15.8	16.2
Arginine	25	27	28	30	33
Garlic powder in 5% acetic acid					
Alliin	15.3	13.3	12.2	10.4	8.1
Allicin	0	0	0	0	0
γ-Glutamyl-*S*-allylcysteine	11.9	11.1	10.4	8.2	5.9
γ-Glutamyl-*S*-1-propenylcysteine	8.1	6.4	3.6	0.7	0.2
S-Allylcysteine	0.3	0.5	0.6	1.2	1.7
S-1-Propenylcysteine	0.1	0.2	0.2	0.2	0.2

[a] Whole cloves were chopped into small pieces (2x2x1 mm) and placed into a 20% ethanol solution (12 mL/g) in a closed container and stored at room temperature, with samples being removed at the indicated times. Very similar results were also found at 3 mL/g and when using water only. Commercial garlic powder was pickled by incubation in 5% acetic acid at 36 mL/g. The zero time values were measured after 24 h *(22, 56)*.

When garlic powder is incubated in 5% acetic acid (simulates whole cloves in vinegar; similar results were found in commercial products), no thiosulfinates are formed because the acidic pH (3.5) inhibits alliinase. The acidic environment also greatly slows down the hydrolysis of the γ-glutamylcysteines, but it adversely affects the *S*-alkenylcysteines, particularly the *S*-1-propenyl compounds, since only 2% and 42% of the expected *S*-1-propenylcysteine and *S*-allylcysteine, respectively, were found at 24 months.

Composition of Commercial Garlic Products. Table V compares the composition of several brands of the various types of commercial garlic products and supplements with garlic cloves. As can be seen for the range values given, there is a much larger variation in the composition among brands of whole powder tablets (3-fold for standardized products, 35-fold for non-standardized) and oils (50-fold) than among cloves (2- to 3-fold), reflecting differences in manufacturing practices and indicating the need for product labels to declare a specific content/yield value of a compound that represents that product. For the brands that do make specific compound value claims, the values have been found to almost always be fairly accurate.

Garlic Powder Products. Garlic powder is the product most identical with fresh cloves (Table V) since it has only been dehydrated at low oven temperatures (50-60 °C)—at these temperatures there is only a 5-15% loss of allicin-yield *(22)*—and then pulverized; however, the amount of alliin present can vary considerably depending on the care used in slicing and handling of the cloves. The slices can be dried faster if the slices are thinner, but more slicing increases the alliin loss and consequently the odor (allyl sulfides) of the powder. Hence, spice powders have an alliin content (or allicin yield) that is typically about 50% less than that of the powders used to make quality alliin/allicin-standardized tablets *(22)*. Of 29 recently purchased U.S. brands of garlic powder supplements, 11 make specific claims of allicin-yield. The allicin-yield of garlic powder products is fairly stable, with an average 5-year loss of 36% *(22)*.

A very important aspect of the effective quality of garlic powder products is their ability to form allicin after consumption, given the fact that alliinase is rapidly and irreversibly inhibited at the acidic levels typically found in the stomach (pH 1.5-3) *(36, 37)*. When garlic cloves are consumed, allicin formation is not a problem, since it is stable to acid and is formed within 6 seconds of chewing, well before reaching the stomach. Therefore, it is essential that garlic powder products be protected with an acid-resistant coating, either by an enteric-coating or other means. An acid-resistant coating also decreases the breath odor by delaying all allicin formation and release of any allyl sulfides until the tablet is past the stomach. About two-thirds of the U.S. powder supplements claim some type of acid-resistance.

The effectiveness of garlic products in forming allicin in the body is best estimated as the *effective allicin yield*, which is defined in general terms as the amount of allicin formed under simulated gastrointestinal conditions, or in more specific terms as: the amount of allicin formed (or alliin lost) after the products have been agitated at 37 °C in simulated gastric fluid (pH 1.5) for one hour followed by addition of simulated intestinal fluid (pH 7.5) and continued agitation for two hours, according to a modification of U.S.P. protocol #701 for evaluating tablet

disintegration (see Table 3.19 in *(22)*). Of 20 U.S. products tested, eight brands were found to have a *percent effective allicin yield* (yield under simulated gastrointestinal conditions compared to yield when products are dissolved in water) of less than 1%, while only six had effective yields of greater than 70% *(22)*. The effective allicin yield should be the standard of quality for all garlic powder supplements.

Table V. Principal Sulfur-Containing Constituents of Commercial Cloves, Pickled Cloves, Garlic Powders, and Garlic Supplements[a]

Product	Constituent and amount (mg/g product)	Alliin-derived compounds[b]
Garlic cloves	alliin (**10**: 6-14), γ-glutamylcysteines[c] (**10**: 5-15) allicin yield (**3.5**: 2.5-5.1)	**4.8** (3.5-8)
Pickled cloves	alliin (**3.4**: 2.0-4.2) γ-glutamylcysteines (**3.3**:3-4)	**0.0**
Powders[d] for spices	alliin (**11.5**: 10-17), γ-glutamylcysteines (**26**:12-35) allicin yield (**4.5**: 3-7)	**7.3** (4-11)
Powders[d] for tablets	alliin (**21**:7-29), γ-glutamylcysteines (**29**: 14-40) allicin yield (**8.5**: 3-11)	**12.5** (4-17)
Powder tablets		
(allicin-standardized)	alliin (**13**: 7-24), γ-glutamylcysteines (**22**: 7-32) allicin yield (**4.2**: 1.3-8.9)	**5.6** (1.4-12)
(non-standardized)	alliin (**7**: 0.4-14), γ-glutamylcysteines (**12**: 2-31) allicin yield (**1.9**: 0.1-5.7)	**2.6** (0.1-8)
Steam-distilled oil capsules	diallyl disulfide (**1.0**: 0.05-2.8) diallyl trisulfide (**0.7**: 0.04 -2.0) allyl methyl trisulfide (**0.6**: 0.03-1.7)	**3.8** (0.2-11)
Oil-macerate capsules	vinyldithiins (**1.1**: 0.1-4.7), ajoene (**0.2**: 0.02-1.1) diallyl trisulfide (**0.11**: 0.02-0.45)	**1.5** (0.4-6.0)
Aged extract tablets/capsules	alliin (**0.3**: 0.2-0.4) γ-glutamylcysteines (**0.34**: 0.2-0.5) γ-glutamyl-*S*-allylcysteine (**0.25**: 0.1-0.4) *S*-allylcysteine (**0.6**: 0.5-0.7) *S*-allylmercaptocysteine (**0.15**: 0.1-0.2)	**0.15** (0.1-0.2)

[a] Values are given as the **mean** and ranges for several (7-15) brands, or lots of a single brand (aged extract), of each type of product. Adapted from Lawson, 1996 *(22)*.

[b] Total alliin-derived compounds includes allicin and other allyl thiosulfinates (after addition of water), allyl sulfides, vinyldithiins, ajoene, and *S*-allylmercaptocysteine.

[c] The γ-glutamylcysteines values for all products are the sum of the *S*-allyl and *S-trans*-1-propenyl compounds.

[d] To compare powders to cloves, divide powders by three since cloves typically contain 65% water.

Garlic Oil Products. Unlike most plant oils, commercial garlic oils are not actually present in garlic cloves. They are the result of converting the water-soluble thiosulfinates of crushed cloves to oil-soluble sulfides by the use of steam (steam-distilled oil, often erroneously called garlic essential oil) or by incubation in a common plant oil (oil-macerate), such as soybean oil. The steam-distilled oils have been prepared for the past 150 years and are very common, while the oil-macerates, long popular in Europe, have only been in the U.S. (only three brands known) for a few years *(22)*. The composition of these oils has been described previously (see *Transformation of the Thiosulfinates upon Processing*), and the ranges among brands are shown in Table V. All commercial garlic oils have been highly diluted with common plant oils to achieve a content of thiosulfinate transformation products (sulfides) that represents the amount of thiosulfinates in crushed cloves from which they were formed, a standard which has been met by most steam-distilled oils, but only by a few oil-macerates (see Table 3.21 of *(22)*). Currently, no steam-distilled oil product claims a specific amount of sulfides, but 8 out of 22 brands claim a specific amount of "pure garlic oil." Of 11 brands of oil-macerates, only one makes a claim for specific compounds (0.9 mg vinyldithiins and 0.15 mg ajoene per 280 mg capsule). The steam-distilled oils products are stable for at least five years, while the oil-macerates are less stable, due to instability of ajoene after about 18 months (see Table 3.24 of *(22)*).

The only garlic-derived compounds in garlic oils are the thiosulfinate-derived (95% alliin-derived) compounds, compounds which have preserved the important dithioallyl (allyl-SS-) moiety of allicin and the other allyl thiosulfinates. Hence, quality garlic oils represent much of the pharmacological activity of crushed garlic and are useful in providing evidence for the pharmacological activity of allicin.

Aged Extracts and Pickled Cloves. Aged extracts represent a successful attempt to remove the odor-forming ability (alliin, alliin-derived compounds, and active alliinase) of garlic. However, most of the sulfur compounds of garlic are lost in the process (Table V). Their method of preparation and the chemical changes that take place during the aging period were previously described (see *Processing Changes During Long Term Incubation*). They are sold in both dry form and as a liquid containing 10% ethanol. Even though major changes occur with most of the sulfur compounds during the aging period (Table IV), the amount of total *S*-allylcysteine (γ-glutamyl-*S*-allylcysteine plus *S*-allylcysteine) should be nearly the same, on a mole basis, as was present originally in the cloves *(22)*; however, based on a typical total *S*-allylcysteine content in cloves (41 μmole/g dry wt.), the total *S*-allylcysteine content in commercial aged extracts (7.8 μmole/g dry wt. after correcting for 40% excipients) is only 19% of what would be expected, indicating considerable manufacturing losses or the use of cloves of unusually low content of γ-glutamylcysteines. The commercial aged products claim to be standardized on *S*-allylcysteine, but no specific or even minimum amount has ever been declared.

Pickling whole cloves also inactivates alliinase and prevents thiosulfinate and odor formation with only a comparatively modest loss (Tables IV and V) of the original sulfur compounds. Hence, commercial pickled cloves have a total *S*-allylcysteine content of about 22 μmole/g dry wt. Most of the loss is due to diffusion into the pickling solution.

A much shorter and simpler method of preparing a non-odor producing garlic product in which there is little loss of sulfur compounds can be achieved by cooking whole cloves (steam, microwave, or boil) to inactivate alliinase prior to consumption or prior to drying and pulverization. It should be kept in mind, however, that alliinase-inactivated garlic products, while producing little odor, do not possess some of the medicinal benefits of fresh garlic, due to the lack of thiosulfinate yield.

Analysis of Garlic and Standardization of Garlic Products. Allicin is the most important compound upon which to judge the quality of garlic cloves and garlic powders, since thiosulfinates are the only identified compounds from garlic that are reasonably well proven to be essential to the pharmacological activities of garlic at levels representing normal garlic consumption (2-4 g/day). Even though allicin may not be responsible for some of the effects of garlic (see *Summary of the Evidence for the Active Compounds*), it still serves as an important marker compound even for these effects—products that are high in allicin yield are also high in other garlic compounds—until the respective active compounds for these effects are identified.

The allicin yield of garlic cloves (homogenized with 10 mL water/g) and powder (30-60 mL water/g) can only be reliably analyzed by HPLC, preferably by elution with methanol/water (1:1) *(31, 40, 57)*. The allicin standard can be synthesized from pure diallyl disulfide *(*page 56 in ref. *22)* or isolated from cloves or powder by TLC *(31)* and then quantitated by the cysteine-depletion method *(58)*. Since 1 mg allicin is formed from 2.185 mg of alliin, allicin can also be quantitated by adding a known amount of alliin to a filtered garlic homogenate and measuring the amount of increase in the allicin peak area *(59, 60)*. Total thiosulfinates can be determined by the cysteine-depletion method. The alliin content of cloves or products can also be a valuable measure of quality, as long as the activity of alliinase is verified (by rapid depletion of alliin or rapid increase of allicin). The alliin content can be measured by HPLC analysis *(61)* after microwaving cloves for 30 seconds or homogenizing cloves or powder in 10 mM amino-oxyacetate to inhibit alliinase (alcohols have also been used, but do not give complete inhibition). Alliin standard has recently become commercially available (LKT Labs, St. Paul, MN; Indofine, Somerville, NJ; and Extrasynthese, Lyon Nord, France). γ-Glutamylcysteines and S-alkenylcysteines are also analyzed by reversed-phase HPLC *(28)*. The γ-glutamyl-cysteines are not commercially available, but they can be isolated from garlic cloves (*S*-allyl) or onion seeds (*S*-1-propenyl) *(28)*. They can be quantitated by glutamate release upon treatment with γ-glutamyl transpeptidase, and γ-glutamyl-*S*-allylcysteine can also be assayed by *S*-allylcysteine release with the transpeptidase *(28)*. *S*-Allylcysteine (deoxyalliin) can be synthesized *(28)* or purchased (LKT Labs). *S*-1-Propenyl-cysteine is not commercially available.

The sulfides content of steam-distilled garlic oil can be standardized upon diallyl disulfide plus diallyl trisulfide (about 45% of the total sulfides), both of which have recently become available in pure form (>98%, LKT Labs), as determined by HPLC or GC *(50)*. Other sulfides in the oil can be estimated using the relative extinction coefficients *(50)*. The main compounds of the oil-macerate products (vinyldithiins and ajoene) can be analyzed by HPLC *(50, 52)*, but standards are not yet commercially available and are somewhat difficult to prepare in pure form *(50, 52)*. Crude standardization of the oil-products can be achieved by total sulfur content.

Absorption and Metabolic Fate of the Sulfur Compounds

There are only a few reports on the absorption, metabolism, and excretion of garlic's sulfur compounds, insufficient to determine how these compounds might function in the body. For example, until it is known what metabolic form of allicin actually reaches target cells, in vitro studies to determine its mechanism of action have limited use. Furthermore, no marker compound for any of garlic's sulfur compounds have yet been found in human blood.

Allicin is well-absorbed, as indicated by a persistent garlic odor on the breath, skin, and amniotic fluid *(62)* of persons after consumption of fresh cloves. An animal study with ^{35}S-labeled allicin showed at least 79% absorption within 30-60 minutes after oral intake and 65% urinary excretion of the allicin metabolites within 72 hours *(63)*. Furthermore, the antithrombotic activity of fresh garlic (due to allicin, see *Antithrombotic Effects*) is the same in rats whether given orally or intraperitoneally *(64)*. Additionally, as will be presented later, substantial absorption of allicin has been indicated in people, since oral consumption of pure allicin has been shown to significantly increase overall body catabolism of triglycerides.

The metabolic fate of allicin in the body is not well understood; however, our current understanding of what probably takes place up to a certain point is summarized in Figure 2. Neither allicin nor its common transformation products—diallyl sulfides, vinyldithiins, ajoene—can be found in the blood or urine, nor can their odor be detected in the stool, after consuming large amounts of garlic (up to 25 g) *(53)* or of pure allicin (60 mg) (unpublished), indicating that it is rapidly metabolized to new compounds; however, body metabolites of allicin have not yet been identified. The exception to this statement is the presence of allyl methyl sulfide and much lesser amounts of diallyl disulfide in the breath after garlic consumption *(43, 46)*. It has been assumed that these sulfides originate from the thiosulfinates, rather than from other *S*-allyl compounds in garlic. We have recently confirmed this assumption by showing that consumption of pure allicin also results in substantial amounts of allyl methyl sulfide in the breath, accounting for about 10% of the allicin consumed, and demonstrating that the methyl group comes from the body, probably as the reaction product between allyl mercaptan and S-adenosylmethionine (see Figure 2) (unpublished). We also found that consumption of microwave-cooked garlic did not result in allyl methyl sulfide in the breath, showing that the allyl group can only come from allyl thiosulfinates and not from alliin or γ-glutamyl-S-allylcysteine.

In isolated fresh whole human blood, allicin is very rapidly metabolized by the blood cells to allyl mercaptan (allyl-SH) (Table VI) *(9, 65)*. This also appears to occur in the epithelial cells of the throat, since consumption of crushed garlic results in the immediate (15 sec), but short-lived, presence of allyl-SH in the breath *(43, 44)*. However, allyl-SH is probably not the final effective metabolite of allicin, since this highly odorous compound has not been found in measurable quantities in the blood, stool, or urine after oral consumption of 150 mg of allyl mercaptan—nor was it detected, except in the breath, by the most sensitive of all detectors, the sense of smell (limit of detection: 0.1 μg/mL urine) (Lawson & Wang, unpublished). Good possibilities for the identity of the active metabolite of allicin after allyl mercaptan formation would be that of allylsulfinic acid (2-propenesulfinic acid) or allylsulfonic

acid (2-propenesulfonic acid). These compounds are proposed because a similar compound, cysteine, which also has a thiol (SH) group, is metabolized in the body to β-sulfinylpyruvate, which is a sulfinic acid, and to lesser amounts of taurine, which is a sulfonic acid. Furthermore, rat studies with ^{35}S-labeled allicin have shown that most of the ^{35}S-labeled metabolites are highly polar, indicating that they have been oxidized *(63)*, and diallyl sulfide has been shown to be completely metabolized in rats to the oxygenated products, diallyl sulfoxide (DASO) and diallyl sulfone ($DASO_2$) *(66)*.

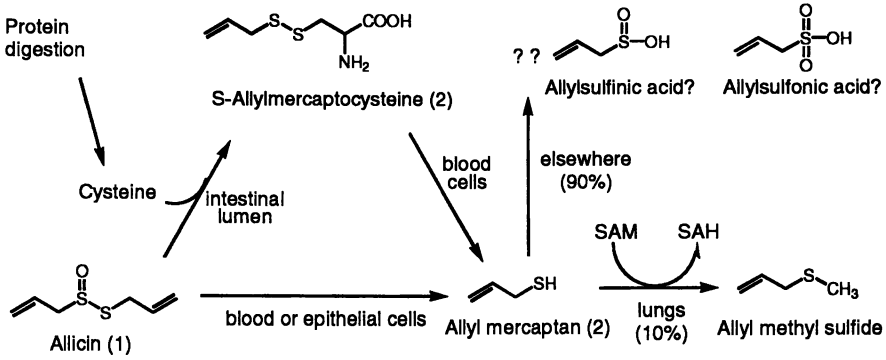

Figure 2. Current understanding of the metabolic fate of allicin in humans. Abbreviations: SAM, *S*-adenosylmethionine; SAH, *S*-adenosylhomocysteine.

Many of the transformation products of allicin that are present in commercial garlic oils are also metabolized initially to allyl mercaptan (Table VI). This is an important observation because it indicates that pharmacological studies with the garlic oils, which contain almost exclusively allicin-derived compounds, have direct implications on the effects of allicin itself.

Alliin from cooked garlic is rapidly absorbed and excreted and can be partially metabolized to diallyl disulfide in animal liver *(63, 67, 68)*, but it is probably not significantly metabolized to diallyl disulfide in humans, since, as was discussed above, consumption of alliin-abundant cooked garlic does not result in the presence of allyl sulfides in the breath. Since the abundant γ-glutamyl-*S*-alkenylcysteines are structurally similar to glutathione, they are probably absorbed intact and then hydrolyzed in the kidney by γ-glutamyl transpeptidase to *S*-allylcysteine and *S*-1-propenylcysteine. Metabolites of these compounds have been found in human urine after garlic consumption and include N-acetyl-*S*-allylcysteine, N-acetyl-*S*-(2-carboxypropyl)-cysteine, N-acetylcysteine, and hexahydrohippuric acid *(69, 70)*. The amount of N-acetyl-*S*-allylcysteine found in a 24 h urine collection accounts for about 25 mole% (own calculation) of the γ-glutamyl-*S*-allylcysteine consumed *(70)*.

Table VI. Fate of Allicin and its Derived Compounds in Whole Blood.[a]

Compound (0.5 mM)	Half-life in blood (minutes)	Reaction product (moles/mole compound)
Allicin	<1	allyl-SH (1.6)
Ajoene	1	allyl-SH (0.8)
S-Allylmercaptocysteine	3	allyl-SH (0.9)
Diallyl trisulfide	4	allyl-SH (0.8)
Diallyl disulfide	60	allyl-SH (0.8)
Diallyl sulfide	NR	
1,2-Vinyldithiin	15	unknown
1,3-Vinyldithiin	NR	
Allyl-SH	NR	
Alliin	NR	

[a] In fresh whole human blood kept at 37°C *(9, 65)*. NR (<10% decrease in 2 hr).

An excellent study on the metabolic fate of large doses of *S*-allylcysteine in three different animals (rat, mouse, and dog) showed that it is rapidly absorbed and is more abundant initially in several tissues, especially kidney, than it is in the blood *(71)*. Its half-life in blood plasma (0.8 to 10.3 hours) and distribution among urinary metabolites varied greatly among the types of animals. The study showed that the bioavailability of *S*-allylcysteine decreased linearly with decreased dose, from 98% at 50 mg/kg body weight to 77% at 25 mg/kg to 64% at 12 mg/kg. Since the highest amount of *S*-allylcysteine that would be ingested from consuming five grams of garlic or any garlic product would not be more than 0.05 mg/kg, the actual bioavailability of *S*-allylcysteine may be very small, indicating a possible advantage of *S*-allylcysteine being present in garlic mainly in the γ-glutamyl form.

Pharmacological Effects and Indicated Active Compounds

The number of publications on the pharmacological effects of garlic cloves and garlic products is truly impressive and includes 1202 in vivo and in vitro studies, of which 208 are human studies, as mentioned in the Introduction and Table I. It is not possible in this short review to discuss each effect in detail; however, a very thorough review of nearly all these studies has recently been published by Reuter et al. *(72)*. After presenting the evidence for each pharmacological effect of garlic, the evidence for the main active compound for each effect is also discussed.

In discussing possible active compounds, it is important to note that the expression "active compound" does not necessarily mean that the compound under consideration is actually causing the effect at the site of action, but rather that the initial presence of the compound is necessary for the effect. This distinction is needed because the metabolic fate of garlic's compounds, as with many herbs, is unknown and since metabolites of the compounds may well be causing the effects. Therefore, the terms "essential to" or "responsible for" or "initially responsible for" are often, but not always, used to more accurately describe an "active compound."

Lipid-Lowering Effect. The most thoroughly studied effect of garlic is that of its ability to favorably influence elevated serum lipids at easily achievable doses. In addition to the 56 animal studies that have been conducted with garlic clove homogenates, allicin, and garlic-derived oils since 1933, 62 human studies have been reported on the lipid-lowering effects of fresh garlic and garlic products, with most of the product studies having been conducted with alliin/allicin-standardized garlic powder tablets (reviewed by Reuter et al. *(72)*). The use of standardized tablets has made it possible to conduct dose-consistent and placebo-controlled studies. Seven open trials with 3-10 g of fresh garlic daily for 3-8 weeks gave an average 16% decrease in cholesterol and 30% decrease in triglycerides (Table VII). Twenty-three trials (13 placebo-controlled and 10 open) from 1986-1994 involving 4600 persons for 6-12 weeks using standardized (3.6-5.4 mg allicin yield), acid-protected garlic powder tablets at a dose (0.6-0.9 g powder) equal to 1.8-2.7 g of fresh garlic, resulted in an average decrease in serum cholesterol of 10.3% (controlled) and 11.3% (open) and in serum triglycerides of 8.5% and 15%, respectively *(72)*.

Table VII. Effects of Garlic and Garlic Products on Elevated Serum Lipids

Study type (# of human studies)	Daily dose	Garlic equivalent	Cholesterol	Triglycerides
Fresh cloves (7)	3-10 g	3-10 g	↓ 16%	↓ 30%
Powders				
•Allicin-standardized tablets[a]				
- placebo-controlled (18)	0.6-0.9 g	2-3 g[b]	↓ 9%	↓ 9%
- non-controlled (10)	0.6-0.9 g	2-3 g[b]	↓ 11%	↓ 11%
•Non-standardized tablets (4)	0.6-1.4 g	2-4 g[b]	↓ 4%	↓ 7%
Oils				
• steam-distilled (2)	10-18 mg	2.5-4.5 g[c]	↓ 10%	↓ 12%
• macerated (4)	2-15 mg	0.5-4 g[c]	↓ 14%	↓ 19%
Aged extracts (2)[d]	---	---	---	---

[a] "Allicin-standardized" means there is a label claim for a specific allicin yield.
[b] Based on the moisture content of whole cloves (65%).
[c] Based on the amount of thiosulfinates needed to produce the oils.
[d] See item 2 under *Evidence that Allicin is Responsible ...* .

Since 1994, five additional placebo-controlled studies have been conducted with alliin/allicin-standardized tablets *(73-78)*, giving an overall cholesterol-lowering effect of 9.1% for the 18 controlled studies, which involved a total of 515 treatment and 557 placebo persons. The effects are greater in individuals with higher initial lipid levels. Of the six controlled and eight open studies that examined lipoproteins, good decreases in LDL-cholesterol were found (8.3% and 14.3%), but only marginal increases in HDL-cholesterol were found (1.3% and 5.3%). A recent diet-monitored placebo-controlled study showed that simultaneous consumption of a standardized garlic powder tablet (0.9 g daily) would reverse the LDL-cholesterol raising effects

of fish oil from an increase of 8.5% to a decrease of 9.5% *(75)*. Two of the recent controlled trials in which the persons were advised to simultaneously reduce fat intake to 30% ("step-1-diet") failed to find an effect on serum lipids *(73, 78)*. Several of the studies have been combined into meta-analyses, which concluded that consumption of the equivalent of one-half to one clove per day results in a 9-12% decrease in serum cholesterol *(78-80)*.

An important clinical trial with the same alliin\allicin-standardized garlic powder tablets compared the efficacy of 0.9 g of garlic powder with 0.6 g of bezafibrate, the most frequently prescribed lipid-lowering drug in Germany, on 94 hyperlipidemic patients who were also advised to adhere to the"step-1 diet" *(81)*. The study revealed very substantial and significant ($p<0.001$) effects in 4-12 weeks and showed that garlic powder was equally as effective as bezafibrate in lowering total cholesterol (initially 284 mg/dL; 10 and 12% decreases in 4 weeks; 25 and 27% decreases in 12 weeks) and LDL-cholesterol (initially 198 mg/dL; 11 and 15% decreases in 4 weeks; 32 and 33% decreases in 12 weeks) and only slightly less effective in raising HDL-cholesterol (initially 35 mg/dL; 11 and 14% increases in 4 weeks; 51 and 58% increases in 12 weeks). The fact that the patients also showed a bias against the effectiveness of garlic compared to the more popular bezafibrate makes the results for garlic even more significant. [Note: The fibrate and statin serum lipid-lowering drugs have been implicated to increase cancer rates at normally prescribed doses *(82)*—however, a major five-year study with simvastatin showed a significant decrease in total death *(83)*—while modest amounts of garlic appear to have substantial anticancer effects (see *Anticancer effects*).]

An interesting new evidence that garlic decreases blood lipids, particularly triglycerides, comes from the finding that consumption of a single dose of raw garlic causes a substantial increase in the level of acetone in the breath, an effect which reaches its peak at about 24 hours *(46)*. Hence, one mechanism by which garlic decreases body lipids is by increasing triglyceride catabolism.

Evidence that Allicin is Responsible for Most of the Serum Lipid-Lowering Effects of Garlic Cloves. There is considerable evidence that allicin is essential for most, but not all, of the lipid-lowering effects of garlic, particularly at low daily doses (2-3 g, representing allicin at 0.05-0.15 mg/kg body weight) of garlic consumption. The evidence has been slow in developing, mainly because the thiosulfinates, due to their somewhat unstable nature and strong taste, have not yet been employed in pure form in human studies, with one exception given below. The evidence is as follows:

1. *Human breath-acetone studies demonstrate increased triglyceride catabolism by garlic and pure allicin, but not by alliinase-inhibited or alliin-free garlic.* The most direct and quickest means to observe the effect of garlic on lipid metabolism is by measuring the 48-hour rise in human breath levels of acetone, which rise is due to increased catabolism of fatty acid-containing lipids, mainly triglycerides *(46)*. In the recent studies shown in Figure 3 (Lawson, L.D. & Wang, Z.J., unpublished), we have demonstrated that consumption of a seven-gram clove of crushed garlic (yielding 38 mg of allicin or 59 mg total thiosulfinates), as well as of the freeze-dried powder from the same cloves, causes substantial increases in breath

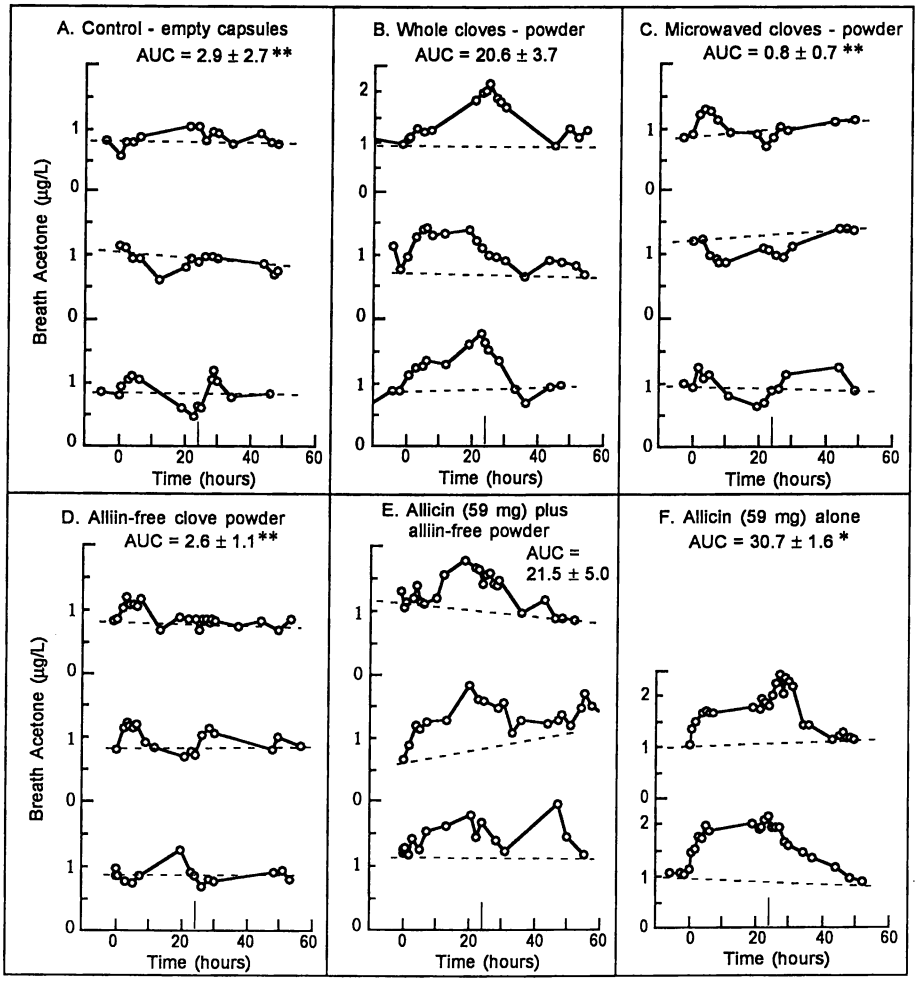

Figure 3. Evidence that allicin (thiosulfinates) plays a major role in the effect of garlic on decreasing body lipids, as indicated by human breath acetone levels. Gelatin capsules (14; 2 every 10 min) were consumed with yogurt over 1 hr starting at time zero and breath acetone measured by GLC. The capsules were either (**A**) empty controls, or they contained (**B**) 2.7 g powder of freeze-dried whole cloves yielding 38 mg of allicin or 59 mg of total thiosulfinates (made from 7 g of fresh cloves; ave. clove wt. 7.6 g), or (**C**) 2.7 g powder of the same cloves that were microwaved (to inactivate alliinase) prior to freeze-drying, or (**D**) 2.7 g of alliin/allicin-free powder prepared by repeated wetting and freeze-drying of powder **B**, or (**E**) 2.7 g of alliin-free powder to which 59 mg of pure (99%) allicin was added (equal to the total thiosulfinates of powder **B**), or (**F**) 59 mg of freshly prepared pure allicin (noticeable effects were also found with 7 mg allicin, not shown). The powders were mixed with 6.5 mL of water before adding to the capsules. The results of 2-3 experiments per treatment are shown. Dashed lines indicate baseline. AUC is the area under the curve to baseline (mean ± s.d.) for 0-48 h. Significant difference from **B** is indicated by * ($P<0.02$) or ** ($P<0.001$). Maximal effects typically occur near 24 hr (vertical lines).

acetone, but that removal of alliin or inhibition of alliinase by microwave cooking eliminates all of the activity. When pure synthetic allicin alone was used or when the allicin was added to the alliin-free garlic at the same original thiosulfinate level, all of the activity was restored. Furthermore, when alliinase-protected enteric-coated garlic powder tablets were also consumed at the same thiosulfinate release level (59 mg) the same amount of breath acetone release was found (not shown), demonstrating the effectiveness of such preparations.

2. *Clinical trials with garlic products not yielding allicin.* The only clinical trials with spray-dried garlic powder (0.7 g/day) failed to show an effect, even when initial cholesterol values were very high (280 mg/dL); however, spray-drying causes nearly complete loss of alliin and allicin-yield *(84, 85)*.

In a recent crossover clinical trial with a dry aged extract which also contains very little alliin and no active alliinase, a dose (7.2 g/day for 5 months) 10 times larger and for a considerably longer time than that needed in the trials with allicin-yielding garlic powder tablets produced only a modest 6% decrease in serum cholesterol and no change serum triglycerides *(86)*. A smaller amount (4 mL daily) of a liquid form of this product, which contained 10% ethanol *(9)*, has been shown to significantly lower serum cholesterol (11%) and triglycerides (15%) by 5-6 months; however, the product caused significant increases in serum lipids in the first two months, an effect not seen with cloves or powders, and the placebo did not contain ethanol *(87)*. It is not possible to compare these two clinical trials with aged extracts to each other or to garlic cloves, since neither were defined by content of any characteristic compounds or by the amount of garlic represented *(88)*.

3. *Animal studies with allicin and with alliinase-inhibited or allicin-depleted preparations.* A recent study with cholesterol-fed rabbits showed that feeding pure allicin at 3 mg/kg for 10 weeks resulted in very significant decreases in serum cholesterol and LDL-cholesterol and increase in HDL-cholesterol, although there was little change in triglyceride *(89)*. A study with normolipidemic rats showed significant decreases in serum cholesterol and triglyceride when fed allicin at 100 mg/kg for 8 weeks *(90)*. Furthermore, fresh garlic has been shown to clear the lipid-turbidity of rabbits fed a high fat diet, but boiled garlic (alliinase inactivated) failed to do so *(91)*. Fresh garlic juice, but not old garlic juice (allicin evaporated) decreased atherosclerotic lesions in cats *(92)*. Lastly, removal of the alliin and thiosulfinates from freeze-dried garlic by distillation completely eliminated the substantial cholesterol-lowering effects of the dried garlic in cholesterol-fed rats, although the oil from the distillation was effective *(93)*.

4. *Clinical and animal trials with allicin-derived garlic oils at doses equivalent to the allicin released from garlic cloves and powder.* As mentioned previously, all garlic oils are derived from the thiosulfinates, mainly allicin. These allicin-derived oils have been shown to be as effective as garlic cloves and garlic powder at similar allicin equivalents (Table VII). Clinical trials with fairly low doses of allicin-derived garlic oils (0.05-0.25 mg/kg, approximately equivalent to the allicin from 1-4 g of raw garlic) have demonstrated a 10-14% reduction in serum cholesterol *(94-99)*, a 12-36% reduction in serum triglycerides, and a 35% decrease in heart attacks *(100)*. Furthermore, a single-dose study found that the ether-extracted oil of homogenized garlic lowered serum cholesterol levels equally as well as the homogenate *(101)*.

Animal studies with garlic oils have also shown substantial cholesterol lowering with steam-distilled oil at 0.2 mg/kg *(102, 103)* and ether-extract oils at 0.5 mg/kg *(104, 105)*. Since both allicin and the main compounds in allicin-derived oils, particularly in the steam-distilled oil, are metabolized in blood to the same compound (see *Absorption and Metabolic Fate*), and since these oils contain no other garlic-derived compounds, these studies provide important evidence for the lipid-lowering activity of allicin. Furthermore, the finding of similar effects in both animals and humans at similar low dose levels provides additional evidence that the effects of garlic on serum cholesterol-lowering found in the clinical trials are real.

5. *In vitro and in vivo inhibition of cholesterol biosynthesis.* The work of Gebhardt *(106-109)* with rat liver cells has shown that allicin, diallyl disulfide, and ajoene are potent inhibitors of cholesterol biosynthesis at low concentrations (5-17 μM), while alliin is inactive. Since metabolites of these compounds, rather than the compounds themselves, actually reach the liver, it is uncertain if they cause direct inhibition of cholesterol synthesis in vivo. Gebhardt has also shown that allicin can decrease cellular biosynthesis of cholesterol by acting on HMGCoA-reductase levels without inhibiting the enzyme directly *(106)*. He has also shown that allicin increases the production of adenosine-generated cyclic-AMP and has concluded that allicin may decrease HMGCoA-reductase by modifying signal transduction pathways *(110)*. Such an effect could account for activity at low doses and for better effects on hyperlipidemics. The activity of liver HMGCoA-reductase has also been shown to be significantly decreased in rats fed a diet of 2.5% garlic powder *(111)*.

6. *No other identified compound* in whole or crushed garlic has indications of significant activity at doses present in normal levels of garlic consumption.

Antithrombotic Effects. The ability of crushed garlic cloves to prevent blood platelets from aggregating (thus reducing the risk of blocked arteries) has been well-established in numerous in vitro and in vivo studies (reviewed in Reuter et al.*(72)*). Eight animal and six human studies have shown in vivo that garlic *(112)*, allicin-standardized garlic powder *(113)* and allicin-derived garlic oils *(96, 115, 116)* at modest doses (equivalent to 2-3 g garlic/person) can prevent platelet aggregation and thrombus formation.

Direct in vivo studies with compounds present in whole or crushed cloves have not been conducted; however, both human and animal studies indicate allicin to be responsible for most of the effect in vivo, since garlic cloves, powders and garlic oils all have similar effects at similar levels of allicin yield or content of allicin-derived compounds *(72)*. Furthermore, serum levels of prothrombotic thromboxane in rats was shown to be significantly decreased by a low oral dose of fresh garlic (equal to 3 g for a person), but not by alliinase-inhibited (boiled) garlic *(64)*. In vitro studies with whole blood clearly show the thiosulfinates (allicin being somewhat more active than the other thiosulfinates) to be responsible for nearly all the activity, with little activity for alliin, and none for *S*-allylcysteine or adenosine, although adenosine is active in the absence of red blood cells. Allicin-derived garlic oils are also effective in vitro, with ajoene, diallyl trisulfide, and 1,2-vinyldithiin having similar activity to allicin *(53)*.

Effects on Fibrinolysis, Blood Coagulation and Blood Flow. In close connection with the platelet antiaggregatory effects of garlic are its effects on increasing fibrinolysis (fibrin breakdown), blood clotting time, and peripheral blood flow rate. The effect on fibrinolysis is one of the more dramatic effects of garlic consumption in people, with noticeable effects occurring in a few hours. To date, 11 clinical trials (3 controlled) have been reported on the fibrinolytic effects of garlic powders, cloves, and allicin-derived garlic oils, revealing an average 70% increase in fibrinolysis for a dose equivalent representing 2-6 g of garlic *(72)*. Improved flow of erythrocytes through the capillaries and decreased plasma viscosity by standardized garlic powder tablets (800 mg dose) has been clearly demonstrated by a novel non-invasive subcutaneous (under the fingernails) technique *(117, 118)*. The effects on increasing blood clotting time have been sufficient for surgeons to ask patients to not eat garlic prior to surgery *(119, 120)*. The active compounds have not been directly proven, nor has cooked (alliinase-inhibited) garlic been tested at a moderate dose, but the effect appears to be mostly due to allicin since the cloves, powder, and allicin-derived garlic oils are equally effective in clinical trials at similar levels of allicin equivalence. However, other active compounds are present, since, at high doses (35 g daily), both raw garlic and fried garlic (alliinase-inhibited) enhanced fibrinolysis almost equally *(121)*. Cycloalliin (Figure 1 and Table III) may account for the activity at higher doses, as it has been shown in two human studies to substantially increase fibrinolysis at 125-250 mg/person, the amount present in about 100 g of garlic *(122, 123)*.

Blood Pressure. Garlic can exert mild hypotensive effects, as shown in 14 human studies (10 placebo-controlled) with allicin-standardized garlic powder tablets (0.6-0.9 g powder), where systolic and diastolic blood pressures decreased by 6.3% and 6.9%, respectively, in the controlled studies in 1-6 months *(72)*. The only studies that showed no effect were those with persons who had normal or only slightly elevated blood pressures. A meta-analysis of eight of the clinical studies concluded that garlic may be of value for persons with mild hypertension *(124)*. Over 30 animal studies have also shown positive effects *(72)*. One mechanism for the effect appears to be stimulation of nitric oxide synthetase *(125, 126)*. There are no good indications of the active compounds. Allicin is not involved since selective removal of the thiosulfinates with organic solvents *(127-129)* or inactivation of alliinase by cooking *(130)* does not change the hypotensive activity in animals. Proteins are also not involved since only the external dialysate has activity *(131)*. The only indications for possible active compounds come from in vitro studies, one of which showed that the γ-glutamylcysteines can inhibit angiotensin converting enzyme *(132)*, a hormone that increases blood pressure; and a second which showed that the fructans of garlic can inhibit adenosine deaminase in isolated cells *(21)*, an effect that could increase levels of adenosine, a compound that acts at purinergic receptors to relax and dilate blood vessel smooth muscles.

Anticancer Effects. The best and almost only evidence for the anticancer effects of garlic in humans comes from eleven epidemiological studies in six countries (Table VIII). They have demonstrated a consistent correlation between garlic clove consumption and decreased risk of gastrointestinal cancers. Indeed, 79% of the 34 epidemiological studies on allium vegetables (garlic, onion, leek) and cancer (mainly

gastrointestinal) have shown a protective effect, a similar percentage as for green vegetables and cruciferous vegetables *(144)*. A study from the Shandong Province of China showed that daily consumption of 20 g (4-6 cloves) of raw garlic was associated with a 92% decrease in stomach cancer compared to consuming less than 1 g daily *(134)*. The effect appears to be due to the killing of nitrate-reducing bacteria (decreased nitrosamines) by the thiosulfinates *(145, 146)*.

An important study for Americans is the Iowa Women's Health Study, a 5-year cohort study which monitored the intake of 127 foods by 41,837 Iowa women, ages 55-69 *(142)*. Garlic was the only food which showed a statistically significant association with decreased colon cancer risk, as demonstrated by a 35% lower risk for consumption of only one or more servings per week. The results of this study have been supported by a second U.S. study with 488 case-controlled Californians, which showed a very significant association between consumption of garlic (3 or more servings/week) and a decrease (37%) in the occurrence of pre-cancerous colorectal polyps *(143)*.

Table VIII. Epidemiological Studies on Garlic Clove Consumption and Cancer

Location/Ref.	Cancer type	Cases/controls	Food	Odds ratio[a]
Argentina *(133)*	colon	110/220	garlic & onions	0.3
China *(134)*	stomach	>100,000 each	raw garlic (20 g/d)	0.08
China *(135)*	stomach	564/1131	garlic (>4 g/d)	0.7
China *(136)*	larynx	201/414	garlic	0.55
Italy *(137)*	stomach	1016/1159	cooked garlic	0.5
Italy *(138)*	stomach	1000/1150	garlic & onions	0.8
Iran *(139)*	esophagus	344/688	pickled garlic	0.6
Switzerland *(140)*	breast	107/318	garlic	0.65
Switzerland *(141)*	endometrium	274/572	garlic	0.6
Iowa women *(142)*	colon	41,837 (cohort)	garlic (≥1 serving/wk)	0.65
California *(143)*	colon polyps	488/488	garlic (≥3 serving/wk)	0.63

[a] Values less than one indicate a protective association; all are statistically significant.

Epidemiological studies in the Netherlands for garlic supplements have failed to find a protective association for colorectal, stomach, or breast cancers *(147-149)*; however, these studies have little relevance since neither brands nor types of supplements were distinguished on the questionnaire and since, as shown in Table V, garlic supplements vary greatly in their composition (much greater than do garlic cloves) depending on both the type of supplement and the brand, even for European brands *(50)*. Furthermore, it is doubtful that supplements are consumed consistently enough over as long of time as are garlic cloves to see an anticancer association.

Although no intervention trials with people have yet been conducted, a large number of animal (carcinogen-induced tumors and DNA aberrations) and in vitro anticancer studies have been conducted with garlic cloves, garlic oils, and aged garlic extract, most of which have shown very positive effects, although large doses have usually been used. Some recent animal studies with lower doses of crushed garlic *(150, 151)*, garlic juice *(152)*, and garlic powder (0.1% of dry diet) *(153)* have shown

good activity at the equivalent of 1.7, 28, 10, and 0.6 g garlic/70 kg person, respectively. The study with garlic powder fed to rats *(153)* indicates a saturation effect around 0.2% of the diet since only a small improvement was seen at 0.5% with no further improvement at 1%. Furthermore, a recent ex vivo study with healthy men showed that consumption of 3 g of raw garlic for 8 days resulted in significantly decreased benzopyrene-induced lymphocyte DNA-adducts *(154)*.

Both allicin and other unidentified compounds in garlic appear to be about equally responsible for the anticancer effects. There are a large number of animal studies which have shown positive effects using pure allicin-derived diallyl sulfides *(72)*. Although most of these studies have used very high concentrations (100-200 mg/kg body wt.), some recent studies with diallyl disulfide at 4-10 mg/kg *(155, 156)* and steam-distilled garlic oil at 2 mg/kg *(151)* have significantly prevented induced tumor growth. In fact, diallyl disulfide was as effective as an equal amount of 5-fluorouracil, the chemotherapy drug of choice *(156)*. The *S*-allyl group is essential to the effect since neither dipropyl sulfides nor *O*-allyl compounds have activity *(157-159)*. Furthermore, diallyl trisulfide is more effective than the disulfide *(160, 161)*, which is more effective than the monosulfide *(162, 163)*. The weak trisulfide bond is also a critical to the mechanism of action for the calicheamicins and esperamicins, natural compounds containing a methyl allylic trisulfide that are among the most powerful antitumor agents known *(164)*. The importance of the allyl group being attached to at least two sulfur atoms (dithioallyl compounds) is also indicated by the much greater antiproliferative effects on cancer cells by allicin-derived *S*-allylmercaptocysteine (allyl-SS-cys) than by *S*-allylcysteine (allyl-S-cys) *(165, 166)*.

On the other hand, in most of the countries where the epidemiological studies were conducted, garlic is mainly eaten in cooked form (alliinase inhibited), indicating that garlic can significantly decrease intestinal cancers in the near absence of allicin or sulfides. Furthermore, positive effects with aged extracts (2-4% of dry diet), which do not form allicin, also indicate important activity by compounds unrelated to allicin; however, the identity of these compounds is unknown. *S*-Allylcysteine has been proposed as a possibility, but its activity as a pure compound accounts for only 0.3-3% of the activity of the extract *(162, 165, 167)* and less than 0.1% of the activity of cloves *(168)*. Since garlic contains much more γ-glutamyl-*S*-allylcysteine than *S*-allylcysteine, it is possible that the former may account for significant activity, particularly since it is probably hydrolyzed to the latter in the kidney. Saponins have also been proposed to account for some of the effects of garlic *(169)*, but their abundance in garlic (1 mg/g) is too small, especially when considering the low amount of garlic normally eaten (1-3 g/d). In contrast, a commonly consumed amount of kidney beans (100 g/d) contains 1400 mg of saponins *(170)*.

Antioxidant Effects. Since antioxidants are important natural means of combating both cancer and atherosclerosis, numerous (42) in vitro studies plus 15 animal and 4 human studies have been conducted with garlic, allicin-derived garlic oils, and allicin *(72)*. They have consistently shown good antioxidant activity as demonstrated by decreased lipid peroxidation, increased free radical scavenging (decreased hydroxyl radicals), and increased glutathione. A recent mouse study showed that diallyl trisulfide—which is metabolized similar to allicin—is much more effective than diallyl sulfide toward increasing tissue glutathione and glutathione-S-transferase

activity *(159)*. Of the four human studies conducted so far (600-900 mg of alliin/allicin-standardized garlic powder per day as tablets), three have shown positive effects on decreasing oxidation of LDL-cholesterol *(171-173)*, while one has not *(73)*. Even though pure allicin can be an oxidizing compound at sufficient concentrations in vitro, the results of 12 animal studies with allicin-yielding garlic powder and allicin-derived garlic oils indicate that allicin is probably responsible for most of the in vivo antioxidant effects of garlic at low doses (0.1-0.5 mg/kg body wt.; equivalent to 1.4 to 8 g garlic for a 70 kg person), while other compounds (alliin, γ-glutamylcysteines, *S*-allylcysteine) appear to have activity only at higher doses (10-50 mg compound/kg body wt.).

Antimicrobial Effects. As one of the most common historical and modern uses of crushed garlic, a large number of antibacterial and antifungal studies (about 250, of which 27 have been human studies), as well as several antiviral (23; 7 human) and antiprotozoal (11) studies, have been reported *(72)*. Crushed garlic or its juice or aqueous extract are effective against a wide range of both Gram positive and Gram negative bacteria, including *Escherichia, Salmonella, Staphylococcus, Streptococcus, Klebsiella, Proteus, Bacillus, Mycobacterium,* and *Clostridium.* Recent reports show that it is also effective against *Helicobacter pylori*, the cause of gastric ulcers *(174, 175)*. Furthermore, it has been shown that crushed garlic is considerably more effective against many of these pathogenic bacteria than against normal flora bacteria, such as *Lactobacillus, Enterococcus,* and *Pediococcus (176, 177)*. A very important aspect of the antibacterial activity garlic is the apparent inability of bacteria to develop resistance to allicin and crushed garlic *(178-181)*. For example, it is almost a thousand times easier for *Staphyloccocus aureus* to develop resistance to penicillin than to allicin *(180)*.

In 1944, Cavallito and Bailey *(182)* were the first to discover that allicin was the main antibacterial agent of garlic. Since then, the thiosulfinate fraction of garlic, which is about 75% allicin, has been shown many times to be responsible for the antimicrobial effects, since selective removal of the thiosulfinates or inhibition of their formation eliminates all of the activity. Allicin-derived compounds present in garlic oils (especially diallyl trisulfide and ajoene) also have antimicrobial activity, although less than for allicin *(72)*. In vitro, allicin is about equally as effective (MIC of 50 μM) as nystatin and ketoconazole against *Candida* fungi *(183)* and more effective than ampicillin or kanamycin against a broad range of pathogenic bacteria *(184)*. Furthermore, Cavallito and Bailey *(182)* showed that while allicin has only 1% of the activity of penicillin against *Staphyloccocus aureus*, it is much more effective than penicillin against Gram negative bacteria. Recently, allicin has been shown in vitro to strongly reduce the pathological effects (50% decrease at 10 μM) of *Entamoeba histolytica*, a major world-wide cause of amoebic dysentery, apparently by inhibition of cysteine proteinases *(185)*. It has long been known that a main mechanism by which allicin exerts its antimicrobial effects is by its rapid reaction with the SH-group of cysteine *(186)* (see Figure 2) in enzymes containing cysteine at their active sites *(187)*.

Most of the antimicrobial studies with crushed garlic or the thiosulfinates have been conducted in vitro. Because most of the antimicrobial uses of garlic are for infections of the skin or intestinal tract, the in vitro studies are probably a fairly

good estimate of the in vivo effects. In fact, several in vivo topical and gastrointestinal studies with animals (10) and humans (6) verify the in vitro effects *(72)*. Furthermore, several studies in animals *(188-191)* and people *(192-196)* demonstrate that orally consumed crushed garlic and allicin-related compounds also have systemic antimicrobial effects in the lungs, kidney, blood, brain, and cerebrospinal fluid.

Immune Effects. A small number of human (3), animal (6), and in vitro (5) studies indicate that low doses of garlic products can stimulate the immune system, as shown by increased numbers of lymphocytes, increased phagocytosis, increased natural killer cell activity, and increased antibody titers *(72)*. The human studies have used (a) daily doses of 0.6 g allicin-standardized garlic powder to show increased phagocytosis and lymphocyte counts *(197)*, (b) 1.8 g of an aged extract to show increased natural killer cell activity *(198)*, and (c) 5-10 g of an undefined garlic extract to show increased natural killer cell activity in AIDS patients *(199)*. Both allicin and other unknown compounds appear to be responsible for the effects, since allicin, allicin-derived sulfides, allicin-depleted garlic extracts, and a protein fraction all have activity *(72)*.

Hypoglycemic Effects. A number of animal studies (25) and a few human studies (3) indicate that garlic can modestly reduce blood glucose and increase insulin levels *(72)*. Although most studies have used large doses for a single day, a recent controlled clinical trial found significant blood glucose reduction (13%) with 0.8 g allicin-standardized garlic powder, the equivalent of 2.5 g fresh garlic, taken for four weeks *(118)*. Allicin appears to be responsible for most of the effect since allicin itself is nearly as effective as the standard drug, tolbutamide *(200)*; whereas, removal of alliin from garlic by spray-drying resulted in no effect *(85)*. Fresh garlic has not yet been compared to cooked (alliinase-inhibited) garlic.

Effects on memory loss and aging. There have been several recent reports with senescence-accelerated mice showing that lifelong consumption of an aged extract of garlic at 2% of the diet (dry wt.) improves learning memory retention, gives a better aging index, and decreases brain shrinkage *(201-204)*. Neither fresh nor cooked garlic have yet been tested in memory or aging studies, although it is expected that similar effects, especially for cooked garlic, may be found at considerably lower doses due to its higher content of garlic compounds (see Table V).

Toxicology

It is common experience that both fresh and cooked garlic are generally well-tolerated when consumed in reasonable amounts and with a meal. Several human studies have shown that long-term consumption of 10-15 grams (2-5 cloves) of fresh garlic daily without noticeable side effects, other than odor on breath and skin *(205)*. Furthermore, in some areas of China, it is common to consume an average of 20 grams of raw garlic daily *(134)*. A recommended safe level for consumption of fresh garlic is 10 grams (2-3 cloves or 3.3 grams dry weight) per day, eaten with meals. However, when consumed without other food or in high amounts, fresh garlic will

irritate the throat and stomach, which effect is due mainly to allicin. Other side effects include skin allergies on the left hand from frequent slicing, skin burns when crushed cloves are placed on the skin for six or more hours (shorter times should be used for treating skin infections), and rare cases of asthma attacks from occupational exposure to garlic dust. Since cooking prevents most of the allicin formation, considerably higher amounts of cooked garlic can be safely consumed. Allicin has an LD50 of 60 mg/kg bw (intravenously), corresponding to 1200 grams fresh garlic for a 70 kg person, as tested in mice (Merck Index), which represents a toxicity level similar to that of ferrous sulfate (a common form of iron supplementation), but about ten times less toxicity than for selenium or Vitamin D. Allicin has been reported to oxidize hemoglobin *(206);* however, such an effect has only been found in vitro near a concentration that is 25,000 times the maximum possible level attainable by consumption of a 3 g clove *(207).* As spices, both garlic and allicin-derived garlic oil have GRAS (generally recognized as safe) status in the U.S. (Federal Register 39, 1994, 34213-34215). The toxicology of garlic has been recently reviewed by Koch *(205).*

Summary of the Evidence for the Active Compounds of Garlic

So far, the thiosulfinates are the only class of compounds with reasonably proven activity at levels representing normal amounts of garlic clove consumption, 2-4 g/day. Allicin is the most important of the thiosulfinates since it is 70-80% of the total and since it has somewhat better antithrombotic and antimicrobial activities than the other thiosulfinates *(53, 182).* Several lines of evidence strongly indicate that the thiosulfinates are responsible for most of the antimicrobial and hypolipidemic/ hypocholesterolemic effects of garlic, while they also appear to be responsible for most of the antithrombotic, antioxidant, and hypoglycemic effects as well as for significant portions of the anticancer and immune-stimulating effects, but not for the hypotensive effects (summarized in Table IX).

Table IX. Summary of the Main Compounds Essential to the Pharmacological Effects of Garlic Cloves at Normal Levels of Consumption

Effect	Good evidence	Some evidence
Antimicrobial	allicin/thiosulfinates	
Hypolipidemic	allicin/thiosulfinates	
Hypotensive	unknown (not thiosulfinates)	γ-glutamylcysteines, fructans
Antithrombotic	allicin/thiosulfinates	
Fibrinolysis	allicin/thiosulfinates	cycloalliin
Antioxidant	allicin/thiosulfinates	
Anticancer	unknown and thiosulfinates	γ-glutamylcysteines
Immune effects	unknown and thiosulfinates	

This does not mean that all of the effects of garlic are due solely to the thiosulfinates, but no other compound has yet been identified with significant activity at levels present in whole or crushed garlic. Likewise, in garlic products, only the

alliin-derived or allicin-derived compounds have been shown to account for most of the activity of these products. Certainly, other active compounds do exist, particularly for the hypotensive, anticancer, and immune effects of garlic, but they have not yet been identified at levels that would account for the activity. Alliin, the parent compound of the thiosulfinates, has no significant activity for any known effect. *S*-Allylcysteine, adenosine, saponins, and a protein fraction have all been proposed to account for some of garlic's activities, but the levels of these compounds are much too small to account for a significant portion of the activity. Cycloalliin may have important activity for both garlic and onions, but it has only been examined for its fibrinolysis effect. The γ-glutamylcysteines and fructans are much more abundant and are good possibilities for future research, although they have as yet only been examined in a few in vitro studies. Pharmacological studies with fractions of garlic of known composition have rarely been conducted for its hypotensive, anticancer, and immune effects, but they will be essential to discovering the identity of garlic's still-unknown active compounds. This is the challenge for the future!

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