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MINI-REVIEW

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Antimicrobial properties of *Allium sativum* (garlic)

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Abstract Although garlic has been used for its medicinal properties for thousands of years, investigations into its mode of action are relatively recent. Garlic has a wide spectrum of actions; not only is it antibacterial, antiviral, antifungal and antiprotozoal, but it also has beneficial effects on the cardiovascular and immune systems. Resurgence in the use of natural herbal alternatives has brought the use of medicinal plants to the forefront of pharmacological investigations, and many new drugs are being discovered. This review aims to address the historical use of garlic and its sulfur chemistry, and to provide a basis for further research into its antimicrobial properties.

Background history

The use of garlic as a medicine and condiment predates written history. The oldest recorded literature from the Sumerians is dated at 2600–2100 B.C. In these writings garlic was already widely cultivated, therefore its use must precede this. It is thought to be of Central Asian origin and features highly in the legends of both India and China. No-one knows exactly where the name garlic comes from, but it is assumed that the Anglo-Saxon 'gar' refers to the spear-like foliage and the 'lic' is referring to leek. Botanically, *Allium sativum* is a member of the *Lillaceae* family, along with onions, chives and shallots.

Throughout written history there are always references to garlic. It was part of the staple diet of the Egyptian pyramid builders. Several cloves of garlic were also found in the tomb of Tutankamen. The pharaohs believed that by taking garlic to the afterlife, the food there would always be well seasoned. Garlic was also associated with the Israelites and is mentioned in the bible during the time of the exodus.

"We remember the fish, which we did eat in Egypt freely; the cucumbers, and the melons, and the leeks, and the onions, and the garlick" (Numbers 11:5).

Garlic must have been of high value as is it not a native plant of Egypt and would have to have been imported. The *Codex Ebers*, an Egyptian medical papyrus translated in 1937, contained over 800 medical formulations, 22 of which contained garlic.

The Romans also extolled the virtues of garlic. Pliny the elder, a roman naturalist, described in his *Historia Naturalis* how garlic could be used for gastrointestinal disorders, dog and snake bites, scorpion stings, asthma, madness, convulsions, tumours and consumption. Dioscorides, physician to the Roman army in 1 A.D., also recommended garlic to be used as a vermifuge. Also an integral part of the Babylonian and Greek civilisations, use of garlic has been recorded by Hippocrates 'the father of modern medicine' as a laxative, a diuretic and for the treatment of uterine tumours, by Aristophanes and Galen.

More recently the first evidence of its antimicrobial properties was established in France. During a plague in Marseilles in 1721, four men were employed to remove the dead bodies. During the plague, none of them became infected. The secret was a macerated garlic and wine tincture '*viniagre des quatre voleurs*'. This preparation is still available today (Hann 1996).

Allium chemistry

Although garlic was exalted throughout history, the quest to understand its action began only relatively recently. The German chemist Wertheim (1844) carried out the earliest chemical studies. By a process of steam distillation he was able to obtain a pungent smelling oil from garlic cloves.

He proposed the name allyl for the hydrocarbon contained in the oil and the term is still used to describe the

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CH_2=$CHCH_2$ grouping today. A steam distillate that had antimicrobial properties was also obtained by Semmler (1892).

Cavallito and Bailey (1944) undertook the first definitive study on garlic chemistry. By employing different methods of extraction (Fig. 1), they isolated diallyl disulfide, the major component of the garlic oil; allicin, the component isolated by Semmler; and alliin an odourless precursor. They established that the ethyl alcohol extract displayed the most antimicrobial properties. This distillate, diallyl thiosulfinate, they called allicin. The precursor alliin, a cysteine sulfoxide, and the corresponding alliinase enzyme were isolated 4 years later (Stoll and Seebeck 1948). Several other cysteine sulfoxides and their corresponding thiosulfinates have also been isolated (Lawson 1996).

Allicin itself is very unstable and decomposes rapidly (Brodnitz et al. 1971). Block (1985), using an analogue of allicin S-methyl methane thiosulfinate, elucidated the pathways of decomposition (Fig. 2). Other compounds are obtained from garlic by varying degradation pathways, depending on the environment in which the extract exists; e.g. ajoene and vinyl dithiins have also been isolated.

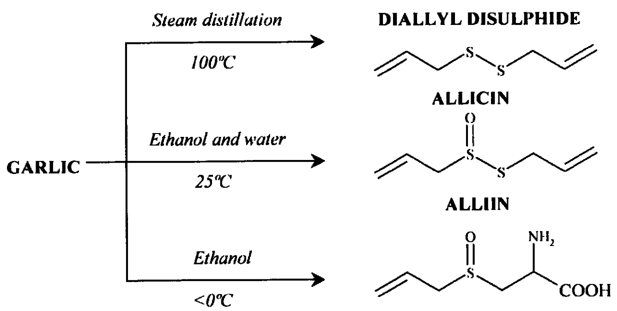


Fig. 1 Sulfur compounds extracted from garlic under various conditions

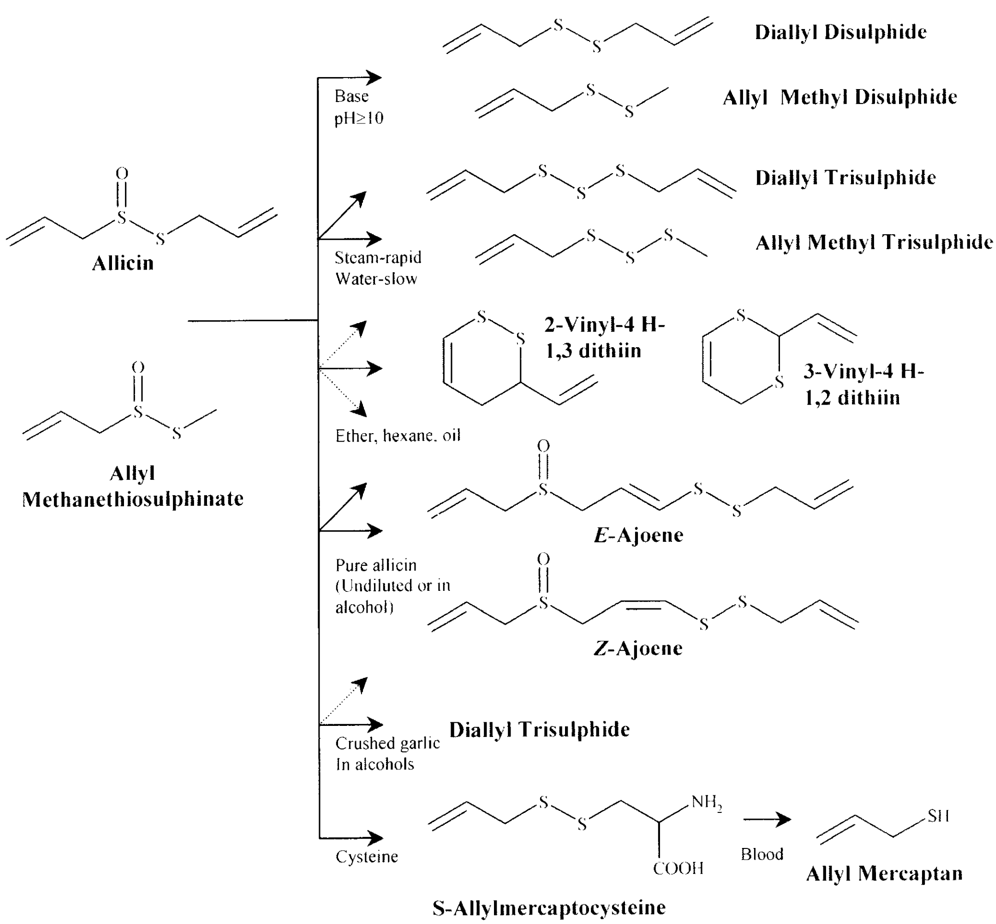
Antimicrobial actions

Principals from garlic have been shown to have antibacterial, antifungal, antiviral and antiprotozoal activities. They also modulate the cardiovascular and immune system as well as having antioxidant and anticancer properties.

Antiprotozoal properties

Very little work has been done to establish the mechanisms of effects of garlic on protozoa. Several studies have shown the extract to be effective against a host of

Fig. 2 Transformation of the principal thiosulfinates in garlic (adapted from Lawson 1996)



protozoa including *Opalina ranarum, O. dimidicita, Balantidium entozoon, Entamoeba histolytica, Trypanosomes, Leishmania, Leptomonas and Crithidia* (Reuter et al. 1996).

Due to the occurrence of unpleasant side effects and increasing resistance to the synthetic pharmaceuticals recommended for the treatment of giardiasis, there has been increasing interest in the quest for natural alternatives. Researchers are looking at plants that have been used for gastrointestinal disturbance by users of alternative therapies for generations.

Early work establishing garlic as a possible treatment for giardiasis was carried out in the former Soviet Union (Kramarenko 1951). Bolton et al. (1982) noted that garlic was often used for gastrointestinal complaints whilst investigating the historical use of garlic. By this time it had already been established that it had antibacterial, antifungal and antiviral properties. This prompted an investigation into its possible use as an antiprotozoal against *Entamoeba histolytica* (Mirelman et al. 1987). Inhibitory activity was noted with crude extract at 25 µg ml^{-1} and the lethal dosage was established as approximately 50 µg ml^{-1}. Encouraged by these results, a clinical trial was carried out on patients that had giardiasis (Soffar and Mokhtar 1991). Garlic was established as an antigiardial, removing the symptoms from all patients within 24 h and completely removing any indication of giardiasis from the stool within 72 h at a dosage of 1 mg ml^{-1} twice daily aqueous extract or 0.6 mg ml^{-1} commercially prepared garlic capsules. No in vitro calculations were possible, as the workers could not culture the protozoa in vitro.

Under certain conditions allicin, a major component of garlic shown to be antibacterial, degrades to diallyl trisulfide. This chemical is more stable than the extremely volatile allicin and is easily synthesised. In China it is commercially available as a preparation called Dasuansu and as been prescribed for *Entamoeba histolytica* and *Trichomonas vaginalis* infections (Lang and Zhang 1981). The antigiardial activity of this garlic component was assessed (Lun et al. 1994). It gave an IC_{50} of 14 µg ml^{-1} and was shown to affect cell morphology.

Allicin, ajoene and organosulfides from garlic are also effective antiprotozoals. It has been suggested that microbial cells are more affected than human cells because they do not have an intracellular thiol content adequate to counterbalance the thiol oxidation by allicin and allicin-derived products. Ajoene has been shown to inhibit phosphatidyl choline synthesis in trypanosomes (Urbina et al. 1993).

Antibacterial properties

Garlic has been used for centuries in various societies to combat infectious disease. In India, garlic has been used to prevent wound infection and food spoilage (Arora and Kaur 1999). In Ireland, at the turn of the twentieth century garlic was used to combat pulmonary infection (Delaha and Garagusi 1985). During World War I garlic was used to alleviate intestinal infections in soldiers stationed in the Balkans.

Historically it is believed that Louis Pasteur first described the antibacterial effect of garlic ‘juices’ in 1858, although no reference is available. More recently garlic has been proven to be effective against a plethora of gram-positive, gram-negative and acid-fast bacteria. These include *Pseudomonas*, *Proteus*, *Staphylococcus aureus* (Cavallito and Bailey 1944), *Escherichia coli*, *Salmonella* (Johnson and Vaughn 1960), *Klebsiella* (Jezowa et al. 1966), *Micrococcus*, *Bacillus subtulis* (Sharma et al. 1977), *Clostridium* (De Witt et al. 1979), *Mycobacterium* (Delaha and Garagusi 1985) and *Helicobacter* (O’Gara et al. 2000). It has been documented that garlic exerts a differential inhibition between beneficial intestinal microflora and potentially harmful enterobacteria (Rees et al. 1993). Inhibition observed in *E. coli* was more than 10 times greater than that seen in *Lactobacillus casei* for the same garlic dose (Skyrme 1997). Exactly why this differential inhibition should occur is not clear, but may be due to differing compositions of bacterial membranes and their permeability to allicin (Miron et al. 2000). The antibacterial activity of garlic is widely attributed to allicin. This is supported by the observation that if stored at room temperature the antibacterial effectiveness of garlic extract is greatly reduced. This reduction occurs to a much lesser extent if the extract is stored at 0–4°C, suggesting thermal instability of the active components. The intracellular effects of allicin are not well understood. It is known that allicin has sulfydryl modifying activity (Wills 1956), and as such is capable of inhibiting sulfydryl enzymes. Cysteine and glutathione counteract the thiolation activity of allicin, and on addition to the reaction mixture the antibacterial activity is reduced. Garlic extract and allicin have been shown to exert bacteriostatic effects on some vancomycin-resistant enterococci. An inhibitory synergism was observed when used in combination with vancomycin (Jonkers et al. 1999). It is thought that allicin modifies the sulfydryl groups on the enzymes of the TN*1546* transposon, which encodes vancomycin resistance, enhancing susceptibility to vancomycin.

Antifungal properties

Antifungal activity was first established in 1936 by Schmidt and Marquardt whilst working with epidermophyte cultures. Many fungi have proven susceptible, including *Candida* (Zubay 1986) *Torulopsis*, *Trichophyton*, *Cryptococcus* (Fromtling and Bulmer 1978), *Aspergillus* (Hitokoto et al. 1980), *Trichosporon* and *Rhodotorula* (Tansey and Appleton 1975). Garlic extracts were shown to decrease the oxygen uptake (Szymona 1952), reduce the growth of the organism, inhibit the synthesis of lipids, proteins and nucleic acids (Adetumbi et al. 1986) and damage membranes (Ghannoum 1988). A sample of pure allicin was shown to be antifungal. Removal of the allicin from the reaction by solvent extraction decreased the antifungal activity (Hughes and Lawson 1991). Activity has also been observed with the garlic constituents, diallyl trisulfide, against cryptococcal meningitis (Cai 1991), and ajoene, against *Aspergillus* (Yoshida et al. 1987). Again thiol addition to the test reduced the activity, suggesting the blocking of thiol oxidation by allicin. Inhibition of respiratory activity is thought to be due to inhibition of succinate dehydrogenase. The adhesion of *Candida* is also greatly reduced in the presence of garlic extract (Ghannoum 1990). Again this effect is diminished by the addition of thiol compounds. The addition of ajoene to some fungal growth mixtures, including *Aspergillus niger*, *C. albicans* and *Paracoccidiodes* (Reimers et al. 1993), has resulted in inhibition at concentrations lower than that experienced with allicin. Studies with aged garlic extract (with no allicin or allicin-derived constituents) showed no in vitro activity. However, when given to infected mice the number of organisms that were seen was reduced by up to 80% (Tadi et al. 1990).

Antiviral properties

In comparison with the antibacterial action of garlic very little work has been done to investigate antiviral properties. The few studies have reported that garlic extract shows in vitro activity against influenza A and B (Fenwick and Hanley 1985), cytomegalovirus (Meng et al. 1993; Nai-lan et al. 1993), rhinovirus, HIV, herpes simplex virus 1 (Tsai et al. 1985) and 2 (Weber et al. 1992), viral pneumonia and rotavirus. Allicin, diallyl trisulfide and ajoene have all been shown to be active (Hughes et al. 1989; Weber et al. 1992). In the case of HIV, it is thought that ajoene acts by inhibiting the integrin-dependent processes (Tatarintsev et al. 1992). Allyl alcohol and diallyl disulfide have also proven effective against HIV-infected cells (Shoji et al. 1993). No activity has been observed with alliin or S-allyl cysteine; it appears that only allicin and allicin-derived substances are active.

Outlook and perspectives

The historical view that garlic is a ‘cure all’ may not be unjustified. Not only have investigations shown that allicin is a potent antimicrobial, but recently it has been recognised that the smaller metabolic breakdown products also exert strong effects. Studies of these smaller constituents are still in their infancy and their modes of action are still being elucidated. With continued investigations we should eventually be able to isolate and exploit the effects of these various compounds. For many years the use of garlic as an antimicrobial has been accepted, and several mechanisms of action are proposed. However, future *Allium* investigations are likely to involve its anticancer effects, its benefits on the cardiovascular and immune systems and perhaps effects yet to be established.

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