ISSN: 2644-2957
DOI: 10.33552/OJCAM.2023.08.000698
Online Journal of Complementary & Alternative Medicine
Iris Publishers

Review Article

Does Allicin Obtained from Garlic Have a Role as An Inhalation Therapy in The Treatment of Covid-19 Infections?

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Received Date: June 26, 2023

Published Date: August 14, 2023

Abstract

Allicin, a derivative of garlic, is known to have broad spectrum antimicrobial and antiviral properties. A review of the scientific literature was undertaken to determine if published evidence supports the proposition that allicin administered via a nebuliser might be of value in the treatment of Covid-19 and secondary pulmonary infections caused by resistant strains of pathogenic microorganisms. The results of the review confirmed that allicin, the principal active ingredient in garlic and garlic extracts, is active against a wide range of viruses including Coronavirus (CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). Results of laboratory studies suggest that it may also be active against Covid-19 by inhibiting protease activity of the virus, a key element in viral replication and infectivity. Additionally, studies using a lung model and clinical isolates of microorganisms, suggest that the extract is likely to be active when administered via a nebuliser. To date no confirmatory clinical studies have been published, although there have been some anecdotal reports on the beneficial use of nebulised allicin. A controlled clinical trial is urgently required to test the hypothesis that nebulised allicin could make a significant contribution to the management of patients suffering from Covid-19 and its sequelae.

Keywords: Garlic; Allicin; Covid-19; Inhalation therapy; Nebulization; Biofilm; Pulmonary infections

Introduction

Garlic (Allium sativum L.; Family: Amaryllidaceae) is an aromatic herbaceous annual spice widely used throughout the world. In 2016, 26.5 million metric tons of garlic were produced, 80% of which was grown in China. Garlic has been used for millennia both to flavor food and treat or prevent of human diseases and metabolic disorders. Sculptures of garlic bulbs were found in ancient Egyptian structures dating back to 3700 BC, while the Ebers papyrus, from around 1500 BC, describes 32 medical applications for garlic.

Garlic extracts, particularly allicin, the principal active ingredient of the bulb, are active against a broad spectrum of bacteria and fungi, including multi-resistant strains. They can also prevent the formation of bacterial biofilms, a major obstacle to successful conventional antimicrobial therapy. Garlic has previously been shown in *in vitro* studies to be active against many different viruses including Coronavirus (CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). New results of molecular binding studies predict that allicin may also interact with Covid-19 active protease sites and thus help to prevent virus replication.

Because allicin rapidly passes through cell membranes and reacts with circulating glutathione, there is some debate concerning its ability to develop sufficient concentrations in tissue, particularly

that of the lung, to exert the desired clinical effect. Fortunately, allicin solution is believed to be effective when delivered by nebuliser. This has been demonstrated in laboratory studies, including one involving the use of a lung model. It is therefore theoretically possible to deliver allicin to the entire inner surface of the lung using an aqueous solution in a nebuliser, with obvious implications for the treatment of Covid-19 and other serious pulmonary infections.

Garlic is considered to be non-toxic when administered via the oral route and few side effects have been reported when garlic has been used medicinally, although consumption of large quantities of raw garlic may cause stomach pain. Isolated instances of tissue damage have been reported if raw garlic is applied to the skin for extended periods. Administration of allicin by nebuliser is not a novel concept as it has formed the subject of anecdotal reports in the literature. However, the results of this review evidence suggest it is an idea worth revisiting in the present pandemic because of the wealth of scientific data now available.

Review Method

The review is based upon references obtained from The National Library of Medicine database PubMed using the search strategy summarised in the following table.

Search term (free text all fields searched)	Number of citations
Garlic OR allicin	6950
Garlic OR allicin AND antibacterial	438
Garlic OR allicin AND antifungal	505
Garlic OR allicin AND antiviral	58
Garlic OR allicin AND covid	29

This search strategy identified a total of 715 potentially relevant references. These were then scanned to identify those which might be relevant to the present study.

Discussion

Chemistry of garlic compounds

Bulbs of A. sativum contain two principal classes of organosulfur compounds, L-cysteine sulfoxides and γ- glutamylcysteine peptides. Detailed information on the chemistry of garlic can be found elsewhere [1-5].

Properties of allicin

An intact garlic bulb has a slight, imperceptible odour, but if sliced or crushed it immediately develops a powerful characteristic smell. An enzyme, alliinase, released by the damage caused to the bulb, converts a family of cysteine sulfoxides to sulfenic acids which spontaneously react together to form allyl-thiosulphinates. In the case of alliin (S-allyl-L-cysteine sulfoxide), which accounts for approximately 80% of the cysteine sulfoxides in garlic, this process results in the production of allicin (S-(2-propenyl)-2-propene-1- sulfinothioate) more commonly referred to as diallyl thiosulphinate, the most studied of the allyl thiosulphinates. Allicin is an oily, colorless, unstable substance, the most biologically active constituent of garlic and the agent responsible for the familiar pungent odour. The conversion process is very rapid and is completed within 10-60 seconds of damaging the bulb. The half-life of allicin produced in this way is 2.5 days at 23°C. Allicin was first isolated from garlic by Cavallito and Bailey [6], and in 1947 it was shown to be responsible for many of the medicinal properties of garlic. It is assumed that the production of allicin by the bulb is a natural defence mechanism which prevents it from becoming spoiled by microorganisms if physically damaged. Alliinase is easily inactivated by heating or boiling and for this reason cooked unpeeled or uncrushed garlic has reduced biological or therapeutic effects, as the alliin cannot be converted to allicin [7].

This has been demonstrated in animal studies. Platelet aggregation was shown to be lost by heating, although crushed garlic retained more anti-aggregatory activity compared to uncrushed garlic [8]. Similarly, the ability garlic fed to rats to protect their DNA against damage caused by a chemical carcinogen was eliminated by first heating the uncrushed garlic cloves [9]. Physically damaging a clove and allowing it to stand for 10 minutes prior to heating preserved some activity. It is recommended therefore that if cooked garlic is consumed as part of the diet for medicinal reasons, it should be allowed to stand briefly after crushing prior to cooking [7]. Allicin itself breaks down in vitro to form a variety of fat-soluble organosulfur compounds including diallyl trisulfide (DATS), diallyl disulfide (DADS), and diallyl sulphide. (DAS) In the presence of oil or organic solvents it produces ajoene and vinyldithiins. Within the body allicin can react with glutathione and L-cysteine to produce S-allylmercaptoglutathione (SAMG) and S-allylmercaptocysteine (SAMC), respectively.

Covid-19 and allicin

Progression and transmission of Covid-19: The symptoms and severity of COVID-19 vary from asymptomatic disease to severe acute respiratory infection. Fever, dry cough, dyspnoea, myalgia, fatigue, loss of appetite, olfactory and gustatory dysfunctions are the most prevalent general symptoms. According to Donma et al. [10], the condition is characterised by decreased numbers of immune system cells such as suppressed regulatory T cells, cytotoxic and helper T cells, natural killer cells, monocytes/macrophages and increased pro-inflammatory cytokines.

As with most viral infections, the crucial event for the viral life cycle of COVID-19 is the entry of genetic material inside the host cell. This is facilitated by a large number of glycosylated spike (S) proteins which cover the surface of the SARS-CoV-2 virus which bind to the host cell receptor. A type 2 serine protease located on the host cell membrane then promotes virus entry into the cell by activating the S protein. Once in the cell the viral RNA is released and polyproteins are translated from the RNA genome. Viral RNA is then replicated and structural proteins are synthesized, assembled, and packaged in the host cell after which more new viral particles are released [11]. All of these stages are achieved by the action of different proteolytic enzymes either of the host or the virus acting

in a concerted fashion to regulate and coordinate specific steps of the viral replication and assembly. It follows therefore that the proteases involved in these three steps are important potential therapeutic targets because molecules which interfere with their activity could help to prevent virus replication [12].

Potential mechanisms by which allicin could prevent disease progression: Khubber et al. [13], predicted that constituents of garlic could inhibit protease activity by the formation of hydrogen bonds with the protease molecule and Thuy et al. [14], used a molecular docking technique to predict the ability of 17 organosulfur compounds found in garlic essential oil to produce an inhibitory effect on the host angiotensin-converting enzyme 2 (ACE2) protein. All the compounds they examined had strong interactions with the amino acids of the ACE2 protein and the main protease of SARS-CoV-2. Similar views on the potential value of allicin and other garlic constituents for the prophylaxis and treatment of COVID-19 infection have been expressed by others [15-17]. Whilst there is yet no direct evidence that Allicin is active against COVID-19, the ability of garlic extracts to kill many different viruses including Coronavirus (CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) has been reported previously [5,18].

Pulmonary bacterial infections and the importance of biofilm formation

Patients with Covid-19 can develop acute respiratory distress syndrome resulting in diffuse alveolar damage with inflammatory infiltrates, potentially predisposing to superinfection [19]. Those on ventilators are particularly susceptible and secondary bacterial infections are a significant cause of morbidity and mortality. Treatment of such infections is complicated by the ability of many bacteria to clump together to form a biofilm within which the cells organize themselves into a coordinated functional community, a process facilitated by the production of a slimy extracellular matrix comprising a polymeric conglomeration of extracellular polysaccharides substances (EPS), proteins, lipids and DNA which forms a protective coating to the cells. A biofilm may contain a single species or a diverse group of microorganisms and its formation may be initiated by many different factors including exposure of planktonic cells to sub- inhibitory concentrations of antibiotics.

The cells within the biofilm matrix are physiologically distinct from planktonic cells of the same organism and are often resistant to treatment with conventional antibiotic therapy. Biofilms are ubiquitous, forming on living or non-living surfaces including the surface of the lung. Pseudomas aeruginosa can cause chronic lung infections, forming biofilm micro-colonies throughout the tissue which are highly tolerant to otherwise lethal doses of antibiotics. The biofilm also protects against the bactericidal activity of polymorphonuclear leukocytes (PMNs).

Effect of allicin on biofilm formation: Biofilm production is influenced by a process termed quorum sensing (QS), by which bacteria interact or 'communicate' with each other by means of small diffusible signalling molecules which pass between cells. These activate the expression of genes which, in addition to biofilm formation, can control functions like bioluminescence and virulence. It follows that quorum sensing inhibitors (QSIs), chemicals which interfere with QS, may offer therapeutic benefits when used alone or in conjunction with antibiotic therapy in the treatment of different pathogens by preventing biofilm formation [20]. In addition to its well-established activity against a broad spectrum of bacteria and fungi, including multi- resistant strains [4], garlic constituents, including allicin, have been shown in numerous studies to be effective QS inhibitors, active against numerous species both in vitro and in vivo.

Lihua et al. [21], investigated the effects of allicin on P. aeruginosa biofilm formation and the production of quorum-sensing controlled virulence factors such as exotoxin A, elastase, pyoverdin and rhamnolipid. They found that allicin inhibited early bacterial adhesion, reduced EPS secretion, and down-regulated the production of virulence factors leading them to conclude that allicin has potential as a therapeutic agent for controlling P. aeruginosa biofilm. Garlic extract was shown to be active against biofilms produced by other bacterial species including Escherichia coli, P. aeruginosa, Klebsiella pneumoniae, Serratia marscens and MRSA. It also exhibited potent activity against systemic and deep tissue infections induced in mice caused by P. aeruginosa and MRSA. No adverse haematological or histological changes were seen in these animals [22].

Importance of the pulmonary route

Because allicin rapidly passes through cell membranes and reacts with circulating glutathione (GSH), there is some debate concerning its ability to develop sufficient concentrations in tissue to exert the desired clinical effect.[2]This conclusion was based in part on the results of clinical research which suggested that although clinical trials on the effect of consuming garlic or garlic oil capsules on cystic fibrosis patients were encouraging, the treatment did not produce statistically significant results significant improvements [23]. However, laboratory studies, including one involving the use of a lung model, showed allicin to be effective in the vapour phase against a range of clinical isolates of different strains of bacteria including. Multi-drug resistant strains (MDRs) of Streptococcus pneumoniae were equally susceptible to allicin as the non- MDR strains.

It is therefore theoretically possible to deliver allicin to the entire inner surface of the lung using an aqueous solution in a nebuliser, with obvious implications for the treatment of Covid-19 and other serious pulmonary infections. Using nebulised allicin in conjunction with oral antibiotics could provide an effective treatment option for pulmonary disease, as synergistic effects between garlic extracts and beta-lactams (cefazolin, oxacillin, and cefoperazone) and the antifungals amphotericin-B and polymixin-B has already been demonstrated. The possible toxicity of allicin administered via the pulmonary route has been considered previously [2]. Although cytotoxic to lung cells in vitro, toxicity is largely eliminated in the presence of glutathione, known to be present in large quantities in alveolar fluid.

Conclusion

Allicin has a good safety profile as about 30m tons of garlic are consumed annually. It has proven broad- spectrum antibacterial, antiviral, and antifungal activity and is also active against biofilms which can render some species of bacteria immune to conventional antimicrobial therapy resulting in intractable infections throughout the body, particularly the lungs of vulnerable patients such as those who have been infected with Covid-19. Current research using molecular modelling techniques suggests that allicin may potentially combat Covid-19 infections by interacting with key proteases such as those at the virus/cell membrane interface, which enable the virus particle to first enter the cell, and others involved in the replication of viral particles and their subsequent release.

Administration of allicin by nebuliser would ensure it reaches the target areas, potentially preventing viral ingress and combatting secondary microbial infections resistant to conventional treatments. Administration of allicin by nebuliser is not a novel concept as it has formed the subject of anecdotal reports in the literature. However, the evidence suggests it is an idea worth revisiting in the present pandemic because of the wealth of scientific data now available. Allicin liquid appears to be safe, relatively cheap and is freely available. At least two liquid preparations are available in the UK, Allimed Liquid (Allicin International) and Allitech (Dulwich Health).

A formal clinical trial is clearly required to prove the value of nebulised allicin, but for existing patients with serious pulmonary infections associated with SARS-CoV-2 (Covid 19), and for whom no clearly defined effective form of therapy is available, the administration of a short course of nebulised allicin as an adjunctive treatment must be worthy of serious consideration.

Acknowledgement

Mr Peter Philips, Director of SMTL for reading early versions of the manuscript and providing critical constructive advice.

Conflict of interest

None.

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