

Could Allicin Inhalation Bring Covid- 19 Pandemic Under Control: New delivery of ancient medicine garlic

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Article information

Received: 30 April 2021

Revised: 30 April 2021

Accepted: 27 June 2021

Key words

COVID-19
SARS-CoV-2
Pandemic
Garlic
Allicin
Inhalation

Abstract

Urgent researches are needed to test potential therapeutic agents against COVID-19 pandemic. Several studies are evaluating the beneficial and harmful effects of different pharmacological interventions such as antimalarial drugs, antiviral drugs, biologics, and interferon. To the best of our knowledge there was no trial for inhalation of raw freshly crushed garlic as a COVID-19 therapeutic although of many beneficial effects with minimal side effects. When the bulbs of garlic are cutted or crushed alliin is transformed into the Allicin by the enzyme alliinase. Allicin has anti-viral, anti-IL-6, anti-platelets and immunomodulatory effect; properties that could help to alleviate SARS-CoV-2 rapid spread, infection and subsequent complications.

Allicin may be one of our best choices in the current Covid-19 pandemic because of its direct and indirect anti-viral activities with minimal side effects. Virucidal activity can reduce infection load, prevent infection and or may be of a value for significant treatment.

Introduction

Coronavirus disease-2019 (COVID-19) is a term used to describe severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1].

The COVID-19 pandemic is a global human health problem. Worldwide trials to face the rapid infectivity spread of this virus by using different measures. These measures create destructive social, economic and political problems. SARS-CoV-2 is one of zoonotic origin coronavirus. Human Coronaviruses usually result in mild upper respiratory tract diseases; however SARS-CoV-2 is a new coronavirus that has not been experienced in humans before [2]. As of 23 June 2020, there have been at least 473,650 confirmed deaths and more than 9,154,232 confirmed cases in the COVID-19 pandemic [3]. Lack of specific or effective antiviral medications and vaccines may lead to recurrence of this pandemic [2]. The most common medications used for trying to treat COVID-19 patients include antiviral agents (remdesivir, hydroxychloroquine, chloroquine, lopinavir, umifenovir, favipiravir, and oseltamivir), and supporting agents (Ascorbic acid, Azithromycin, Corticosteroids, Nitric oxide, IL-6 antagonists), and others. However, there are no proven effective medications against this virus [4].

Leaves and cloves of garlic have been used worldwide in traditional medicine for a long time [5]. The characteristic flavor of garlic has attracted scientists' attention [6]. Fresh crushed garlic release allicin which is the main components responsible for many biological activities of garlic [7].

Allicin is bactericidal in its gas phase and was successfully used to treat patients with tuberculosis by breathing crushed garlic [8].

SARS-CoV-2 encodes spike S protein which binds to the human angiotensin-converting enzyme-2 (ACE2) [9]. If the ACE2 protein is blocked, corona virus infection can be prevented [10].

It was reported that garlic different components, have strong interactions with the amino acids forming ACE2 protein and the main protease PDB6LU7 of SARS-CoV2 [11]. These findings suggest that the garlic can prevent the invasion of coronavirus into the human body

Garlic exerts its antiviral activity through two mechanisms; the first is the direct toxic effect on viruses the second through enhancement NK-cell (Natural killer-cell) activity that destroys virus-infected cells [12].

Interleukin-6 (IL-6) one of major pathological mediators that may result in cytokine release syndrome which is one of the major leading cause to death in COVID-19 patients. If pathway of IL-6 is inhibited, this may alleviate the complications suffered by severe COVID-19 patients. [13]. Allicin treatment significantly reduces the production of IL-6 [14].

The aim of the present study is to explore the promising effects of allicin inhalation due to its biological properties that may put COVID-19 pandemic under control.

Traditional uses of garlic in medical history (*Allium sativum*)

The ancient Egyptians used garlic to treat diarrheal diseases and described its potential medical applications on papyrus dating to 1500 BC. The Greek physicians Hippocrates used it to treat many diseases; ancient Japanese and Chinese used it to treat headaches, flu, sore throat, and fever. In Africa, it is used to

treat respiratory tract infections [15, 16]. Garlic was used to treat common colds in Europe and India [17].

Garlic is nicknamed as Russian penicillin. It was used topically or systemically as antibiotic and improve healing power [17].

Leaves and cloves of garlic have been used in traditional medicine worldwide for a long time [5]. Allicin is bactericidal via the gas phase and was used to successfully treat patients with tuberculosis from inhalation of freshly crushed raw garlic [8].

Formation mechanism and degree of stability of Allicin

Volatile components of raw garlic cloves are a total of 85 sulfur containing compounds and 40 non-sulfur-containing have been reported in many researches [18].

Intact garlic bulbs contain glutamyl L-cysteine which is the primary precursor. glutamyl L-cysteine is hydrolysed and oxidized to alliin (S-allylcysteine sulphoxide). Its concentration increases in bulbs during storage and exposure to coldness. Cutting or crushing of the bulbs converts alliin to Allicin by alliinase enzyme [19].

Alliin and alliinase enzyme are located away from each other within garlic clove. By cutting or crushing the clove, alliin and alliinase are brought into contact to produce allicin [20].

Allicin (diallylthiosulfinate) is a sulfur-containing natural compound with a broad range of biological activities [19].

Allicin gives crushed garlic its characteristic smell. Being a volatile compound makes it potentially useful for treating different respiratory tract infections [21].

About 4–5mg of Allicin is found in each gram of fresh raw garlic and its presence can be easily detected through its characteristic odor [22].

Once it is formed, allicin is immediately converted into many other secondary compounds depending on the temperature and pH of the formulation [20]. Allicin decomposes to sulphide compounds, including ajoenes, diallyl sulphide (DAS), diallyl disulphide (DADS), diallyl trisulphide (DATS), dipropyl disulphide (DPDS) [18].

Allicin is not present in intact garlic or in garlic products and destroyed by cooking. Once it is formed it is converted into other thiosulphinates but is stable at room temperature [23].

Allicin can rapidly penetrate cell membranes easily due to its hydrophobic nature, reaching intracellular compartments where reacts rapidly with free thiol groups [20] therefore, it rapidly disappears from circulation within a few minutes after infusion.

Allicin could be detected after 1h exposure by diffusion through the gas phase. This aspect is of great interest for allicin application as vapor inhalation in the treatment of lung diseases; especially tuberculosis [21].

High allicin oral doses consumption (30-59mg) may cause gastric irritation, especially when subject are fast. The most

remarkable adverse effect is the characteristic breath smell produced by allicin [24].

Allicin and its secondary compounds are responsible for most of the pharmacological activity of crushed raw garlic clove including antibacterial, antiviral, antifungal, antiinflammatory and anti-oxidative effects.

Biological properties of Allicin that have an impact on different respiratory tract infection including COVID -19 PANDEMIC

Antiviral effects

The antiviral effects of Allicin may have an impact on COVID-19 through two mechanisms indirect and direct one.

The indirect one is through Angiotensin-converting enzyme-2 (ACE2) protein inhibition as SARS-CoV-2 encodes spike S protein containing receptor binding domain (RBD) that binds to the human angiotensin-converting enzyme-2 (ACE2), and promotes membrane fusion and uptakes of the virus into human cells such as the lung by endocytosis [9]. Angiotensin-converting enzyme-2 (ACE2) is an integral membrane glycoprotein that is known for the highest expression in most tissues such as kidneys, endothelium, lungs, and heart [25]. The ACE2 protein is the functional host-cell receptor of SARS-CoV-2 [26].

If the ACE2 protein is inhibited, it may be the key for coronavirus prevention and or treatment [10].

By using the molecular docking technique [11] investigate the interactions of ligands in the garlic essential oil with the ACE2 and PDB6LU7 proteins reported that the organosulfur compounds of garlic have strong interactions with the amino acids of the ACE2 protein and the main protease PDB6LU7 of SARS-CoV2. The strongest anti-coronavirus activity is expressed in Allicin secondary products; allyl disulfide and allyl trisulfide.

Lipid bilayers do not constitute a barrier for allicin penetration and its diffusion through the lipid bilayer does not cause membrane leakage, fusion or aggregation [27]. As Allicin vapors naturally from the crushed garlic into surrounding air. Allicin vapors inhaled into lungs' alveoli pass alveoli membranes and exert its biological activities intracellularly. Allicin affects the processing of DNA, RNA synthesis, signal transduction and apoptosis [28].

The inhibitory effect of garlic extract on Infectious bronchitis virus (IBV) which is a coronavirus in the chicken's embryo was reported by [29]. This research adds to expected anti-coronavirus activity of allicin.

The antiviral effect of garlic is explained by in part to direct antiviral effects and in part to immune system stimulation as it enhanced NK-cell (Natural killer-cell) activity that destroys virus-infected cells [12].

Also it was reported that garlic extract showed *in vitro* activity against influenza A and B [30], cytomegalovirus [31, 32], rhinovirus, HIV, herpes simplex virus 1 [33], herpes simplex virus 2 [34], viral pneumonia, and rotavirus. Allicin and its secondary products; diallyl trisulfide and ajoene all have been

shown to have biological activities [34, 35], Allicin is thought to be the major compounds responsible for the antimicrobial effect of garlic as it inhibits RNA polymerase which is necessary for viral replication [7]. Ajoene, one of the secondary compounds of Allicin, has a direct antiviral activity [34]. Allicin can kill bacteria [8]. This adds to the benefits of Allicin to prevent secondary bacterial infection associated with COVID-19 patients.

These findings suggest that Allicin and its secondary products may be a valuable natural antiviral source, which prevent viral invasion into the human cells and its intracellular multiplication.

Anti-platelet effects

One of the core pathologic processes that lead to multi-organ failure and death in COVID-19 patients is hyper-coagulability. The hyperstimulated immune system damages the endothelium and activates blood clotting, causing the formation of micro and macro blood clots. These blood clots impair blood flow [36]. Short-term treatment with garlic may improve the endothelial function and may affect hs-CRP levels [37]. Sulfur-containing compounds have been shown to have prophylactic effects on thrombosis [38]. Following consumption of garlic, there was a significant increase in partial thromboplastin time and bleeding time. The effect being more obvious after just 24 hours [39].

Garlic has antithrombotic, fibrinolytic and anti-platelet effects [40, 41]. Ajoene, which is the second product of allicin metabolism [42], has potent anti-platelet effects.

Anti-inflammatory antioxidant effects:

Hyper-inflammation (Cytokine storm) is defined as dysregulated immune systems whose cells infiltrate and damage multiple organs, such as the lungs, kidneys, and heart. It is now widely accepted that SARS-CoV-2 causes aberrant T lymphocyte and macrophage activation resulting in a "cytokine storm" [43]. Allicin exerts negative effects on human T-cell migration through fibronectin by downregulating actin reorganization [44].

Interleukin-6 (IL-6) plays an important role in cytokine release syndrome. If it is possible to block the signal transduction pathway of IL-6, it is expected to become a new method for the treatment of severe COVID-19 patients. [13].

Allicin treatment significantly alleviates the inflammation through reducing the production of TNF- α and IL-6 [14]. The anti-inflammatory effects of allicin may be explained by modulation of the cytokines that control infection.

Allicin inhibits the migration of neutrophilic granulocytes into epithelia, which is a crucial process during inflammation [45].

Allicin reacts with thiol-containing enzymes to work as an efficient antioxidant. Indeed, Allicin antioxidant properties can be explained in terms of hydroxyl and superoxide radical's inhibition. Allicin plays a crucial role as nitric oxide (NO) formation inhibitor [46]. Allicin has a high amount of selenium and sulfur, with antioxidant effect by reacting with intracellular thiol compounds [47]. The high efficacy and low adverse effects

of natural products make them efficient and promising therapeutic agents [48].

Immune effects

Garlic and its components, such as organosulfur compounds, have been reported to exert positive effects in the immune system acting through several mechanisms, and have been so far investigated in a number of *in vitro* or *in vivo* experimental models [49]. For instance, [50] reported that allicin significantly inhibited IL-1 β , IL-8, IP-10, and MIG secretion, induced by TNF- α in a dose-dependent manner. IL-1 β , an important cytokine released during pyroptosis, is elevated during SARS infection [51].

Immunomodulation is one of the main targets for synthetic drugs and chemicals. However, its high cost, anticipated toxicity, and adverse effects render it undesirable for the patients [52]. On the other hand, the high efficacy and low adverse effects of natural products make them efficient and promising therapeutic agents [53].

Garlic has been suggested as a promising candidate for maintaining the homeostasis of the immune system. Several studies have been carried out in animal models to examine immune modulatory effects of different garlic components and formulations [52].

Allicin was reported to prevent an increase in the expression of proinflammatory genes IL-6, MCP-1, and Egr-1 and in the protein levels of

IL-6 and MCP-1. Interestingly, the phosphorylation of ERK1/2, which is involved in LPS-induced inflammation in adipocytes [52].

Diallyl sulfide (DAS), and other Allicin secondary compounds can inhibit transcription factor NF- κ B, a master regulator, inhibiting the transcription of several cytokine genes involved in proinflammatory responses, such as TNF- α , interleukin-1 β (IL-1 β), IL-6, MCP-1, and IL-12 [54].

Environmental disinfection

Active air sampling which measures the airborne bacterial count in cfu/m³ of air was utilized to validate the efficiency of herbal fumigation in improving microbiological air quality. The airborne bacterial count was reduced from 75.66 \pm 4.93 cfu/m³ to 21.55 \pm 3.34 when garlic peel was used. In addition, garlic peel is effective in disinfecting surfaces of drug-resistant MRSA bacteria which is one of the main bacteria responsible for nosocomial infections. It can be used as an alternative to harmful and toxic conventional chemical fumigation for healthcare environmental disinfection [55]. Based on this study, garlic vapors may also reduce the viral count of air and subsequent viral load and spread.

How to have these benefits?

The first step to have these benefits is to use raw garlic as previous researchers found that raw garlic acts as antibacterial and antiviral agent better than cooked one and boosts the immune system. As cooking garlic destroys the allicin. This may explain why Italian and Spanish populations who are great

garlic consumers are affected seriously by corona virus as they use the cooked one.

The second step is crushing or slicing the garlic glove as when fresh garlic is crushed, alliinase can convert alliin to Allicin that represents the characteristic odor of crushed fresh garlic. Garlic cloves is Peeled and disinfected with a 1% chlorine solution for 5 min, and then the garlic is crushed.

The third step is the direct inhalation of Allicin vapors that potentially offers an immediate route for the treatment of lung pathogens. Allicin, is volatile, as tested by the odor. It evaporates into the air by crushing or cutting garlic cloves. Due to its relatively large size and high polarity, its vapour pressure is not high. Indeed, there is a historical precedent with high success rate for treating tuberculosis in patients by inhaling the vapour from crushed garlic pulp held in a specially designed inhaler [56].

Inhalation can offer significant benefits, including direct delivery to the disease target site, rapid onset of action, high and long-term pulmonary efficacy, and reduced risk of systemic side effects [57].

Chewing fresh garlic cloves and then Swallowed, is highly ineffective method of enjoying allicin benefits. Since it takes several hours from allicin creation in the mouth until it reaches the small intestine where it can enter the blood stream, by then, most of the allicin already transformed into other compound not effective as allicin-especially in the stomach, it is attacked by acids and enzymes. Thus Swallowing allicin is poor way to put allicin into action.

Also Allicin is unstable compound having life span of about an hour in room temperature. Also when fresh garlic cloves are chewed they produce very hot taste that many humans cannot tolerate, however inhaling fresh garlic scent is much less irritating thus it is possible for healthy and ill people to inhale garlic scent many times a day which is necessary in preventing and treating infection. It may help as Allicin vapors naturally flow from the crushed garlic into surrounding air. Allicin vapors inhaled into lungs' alveoli pass alveoli membranes and enter into the blood stream within seconds after allicin is produced. Allicin carried by blood stream reach all body organs within seconds ready to destroy microbes. This is done by generating allicin from its origin Substances: allin and enzyme alliinase and inhaling this allicin vapors.

Conclusion and Recommendation:

Allicin could be a choice in the current Covid-19 pandemic because of its documented direct and indirect antiviral activities. Virucidal activity can be used as a prophylactic strategy before viral infection and may also be successful as a treatment after infection, thereby avoiding virus dissemination. Also Allicin is virucidal agent with anti-IL-6, anti-platelet and immunomodulatory effect, properties that help to alleviate infection and subsequent complications.

Furthermore, inhalation of this volatile compound as the majority of cases is pulmonary in origin. Accordingly, therapies that target early lung infections may decrease infection, also it may act as a chemical mask reducing microbial infection and subsequent viral load.

A proper population based use of this natural compound may reduce the overall air born infection.

A population based study on the effect of inhaled freshly crushed garlic is recommended.

Inhalation methodology

Two inhalers were designated and suggested by the author (Assistant professor Dr/ Samah Mohammed Mahmoud Abozaid) to help patients in hospitals or self-isolated cases

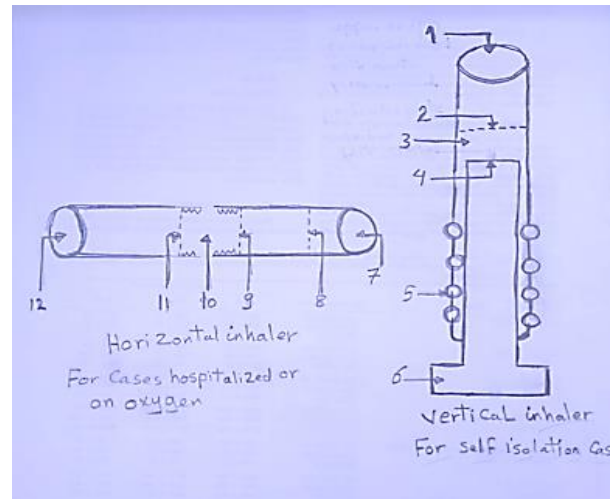


Fig. 1 showing the author suggestion of two inhalers allowing fresh garlic crushing within them, reusable after disinfecting them and can be connected with mouth piece or nasal prongs. The horizontal one can be connected with O2 supply and have additional perforated plate to prevent any garlic material entering nose or mouth. The vertical one is easy to use for self-isolated cases.

Using an air-flow rate of 10-11 L/min for a 20 min flow time of 2 raw freshly crushed gloves is recommended. Cases inhale 4-6 times per day if possible it is desirable for patients to hold their breath for 10-20 seconds. Complete formation of allicin takes place in 0.5 minute after garlic glove crushing.

A single garlic clove has about 5 mg to 18 mg of allicin. In research, doses between 300 mg and 1,500 mg of garlic have been studied. No standard dose for inhaled allicin is determined. Some studied recommend 10 mg/kg day.

Possible expected benefits:

- It may shorten time to clinical improvement
- It may shorten time to clearance of virus
- It may reduce complications

If It has a population acceptance and compliance for this line of treatment, it may reduce the virus spread and control the pandemic

- Possible expected adverse effects:
- Eye irritation (mild to moderate)
- Nasal discharge
- Bad smell. Cases can get rid of it by drinking lemon juice, eating apple, herb leaves or chew spearmint gum.

Acknowledgments

Many Thanks to Allah for help and guidance. I hope that this research help human mankind.

Conflict of interests

The author declares no conflict of interest.

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