Garlic: a potential spice with multifunctional pharmacological properties can prevent COVID-19 disease

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ABSTRACT

Novel coronavirus disease (COVID-19) is the major health crisis in the world. World Health Organisation has declared COVID-19 as a global pandemic. There are no effective drugs to treat COVID-19 infection. Till date include remdesivir, umifenovir, favipiravir, lopinavir/ritonavir, ribavirin, hydroxychloroquine, etc. are used to treat this disease. There is an urgent need for public health measures, not only to limit the spread of the virus, but also to implement preventive approaches to control severe COVID-19 disease. Most drugs on the market have shown unwanted symptoms and toxic effects related to these drugs. In this situation people are searching for safe herbal extracts and pharmacologically active molecules having numerous therapeutic properties. Garlic (Allium sativum L.; Family: Amaryllidaceae) is an aromatic herbaceous annual spice with numerous therapeutic properties. Garlic is one of the most efficient natural antibiotics against the wide spectrum of viruses and bacteria. Organosulfur (e.g. allicin and alliin) and flavonoid (e.g. quercetin) compounds are responsible for immunomodulatory effects of this healthy spice. The viral replication process is accelerated with the main structural protease of severe acute respiratory syndrome corona virus-2 (SARS-CoV-2). The formation of hydrogen bonds between this serine-type protease and garlic bioactivities in the active site regions inhibits the COVID-19 outbreak. Intake of garlic and its derived-products in regular diet as an adjuvant therapy may minimise side effects and toxicity of the main therapeutic drugs of COVID-19 infection.

Keywords: COVID-19, SARS-CoV-2, Garlic, Allicin, Quercetin, Antiviral

INTRODUCTION

The coronavirus disease 2019 (COVID-19) epidemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily induces pro-inflammatory cytokines e.g. interleukins (IL-1 and IL-6) and lung inflammation. This virus can also damage vital organs of the host body through the expression of the angiotensin-converting enzyme 2 (ACE2) receptor. Besides, the imbalance between the renin-angiotensin system and ACE2/angiotensin-(1–7)/MAS axis after the SARS-CoV-2 infection enhances comorbidities and multi-organ injuries.¹ There is no effective drugs to treat COVID-19 disease have been reported so far. Till date the drug treatments of COVID-19 include remdesivir, umifenovir, favipiravir, lopinavir/ritonavir, ribavirin, hydroxychloroquine, etc. In this situation dietary therapy and herbal medicine as an adjuvant therapy may be one of the efficient strategies to fight against COVID-19. Bioactive compounds involved in immunomodulatory, antioxidant, and antimicrobial activities in certain foods and herbs may be able to increase the activity and number of cytokine suppressors, lymphocytes, natural killer cells, and macrophages. So herbal products decrease the adverse impacts of antivirals by reducing the used dose and synergically improves the remedy and outcomes by decreasing the inflammation and respiratory symptoms.²

Sulfur-containing phytochemicals present in garlic (Allium sativum L.) provides substantial immunomodulatory, anti-
inflammatory, anticancer, antitumor, anti-diabetic, anti-atherosclerotic, and cardioprotective properties. Important sulfur containing phytochemicals (~82%) of garlic are thiosulfonates (alliin), S-allyl cysteine sulfoxide (alliin), ajoenes (E- and Z-ajoene), vinylidithins (2-vinyl-(4H) -1,3-dithiin, 3-vinyl-(4H)-1,2-dithiin), and diallyl (di and tri) sulfide. In garlic there are some allin-derived organosulfur compounds (OSC) such as S-allyl-cysteine, S-allyl-mercaptocysteine, and N-acetylcysteine. The antiviral effect of garlic against a number of viruses like influenza B, human-immunodeficiency virus (HIV) (type 1), vesicular stomatitis virus, herpes simplex virus (types 1 and 2), coxsackievirus species, and gamma retrovirus has been reported. Recently, researchers have realized the structure of the main protease of SARS-CoV-2, a serine-type Mpro (chymotrypsin-like protease (3CLpro)) protease with the kind of amino acids (such as Thr24, Thr26, and Asn19) present in the active site regions (e.g. 6LU7 and 2GTB). Mpro has a considerable structural similarity (~96.0%) between types 1 and 2 of SARS-CoV. As this protease is responsible for the viral replication and the production of functional protein as a result of the proteolytic maturation of SARS-CoV-2, the rate of infection may be substantially reduced by hindering the cleavage of the viral polyprotein. In an in silico approach on the inhibitory effect of garlic against SARS-CoV-2, seven OSCs of alliiin, S-(allyl/methyl/ethyl/propyl)-cysteine, S-propyl L-cysteine, and S-allyl-mercapto-cysteine were considered as possible constituents to inhibit the Mpro of SARS-CoV-2 through H-bonds with this protease. Molecular docking analysis showed that alliiin among other OSCs has higher anti-viral potential to prevent COVID-19. This bioactive component alone or in combination with the main therapeutic drug would be an efficient therapy to eradicate SARS-CoV-2 with the lowest side effects and toxicity. The quercetin could also inhibit protease present in SARS-CoV-2 during the multiplication in host cells via blocking the viral attachment stage.

Organosulfur (e.g. alliiin) and flavonoid (e.g. quercetin) compounds in aqueous extracts and essential oils of garlic and their interaction with the Mpro protease decrease the rate of COVID-19 infection. The encapsulation of these bioactive substances at the micro- and nano-size drug particles maintains their oxidative stability and bio-functionality and provides their controlled release and delivery to the targeted sites. Finally, the consumption of functional foods prepared by encapsulated/free bioactive compounds of garlic may have a key role in the incidence reduction of COVID-19 in different communities.

PHARMACOLOGICAL PROPERTIES OF GARLIC

Garlic is a spice with multifunctional pharmacological properties. Garlic is very much used in our daily diet as an aromatic spice. It is rich in bioactive components. Organosulfur (e.g. alliiin and alliiin) and flavonoid (e.g. quercetin) compounds are responsible for immunomodulatory effects of this potent spice. Important sulfur containing phytochemicals (~82%) of garlic are thiosulfonates (alliin), S-allyl cysteine sulfoxide (alliin), ajoenes (E- and Z-ajoene), vinylidithins (2-vinyl-(4H) -1,3-dithiin, 3-vinyl-(4H)-1,2-dithiin), and diallyl (di and tri) sulfide.

Anti-cardiovascular disease activity

Garlic and its phytochemicals are well known for prevention and treatment of cardiovascular diseases (CVD). Garlic intake has significant effects on lowering blood pressure, prevention of atherosclerosis, reduction of serum cholesterol and triglyceride, inhibition of platelet aggregation, and increasing fibrinolytic activity. Both experimental and clinical studies on different garlic preparations demonstrate these favourable cardiovascular effects. Garlic shows antihypertensive activity by decreasing peripheral vascular resistance. It has been reported that garlic significantly reduced serum cholesterol, triglyceride, and low-density lipoproteins (LDL), but there was very little effect on serum high density lipoproteins (HDL). Allicin and S-allyl cysteine, two phytochemicals present in garlic extract and diallyl disulfide, present in garlic oil have been found to show anti-atherosclerotic effect. Furthermore garlic can prevent thrombosis by inhibiting platelet aggregation.

Anti hyperglycemic effect

Garlic and its phytochemical derivatives have anti hyperglycemic effect. Various studies showed that garlic can reduce blood glucose level in diabetic animals. It has been found that garlic can reduce blood glucose level in streptozotocin- and alloxan-induced diabetes mellitus in rats and mice. The beneficial effect of garlic on diabetes mellitus is mainly attributed to the presence of volatile sulfur compounds, such as alliiin, allicin, diallyl disulfide, diallyl trisulfide, diallyl sulfide, S-allyl cysteine, ajoene, and allyl mercaptan. Garlic extracts have been reported to be effective in reducing insulin resistance.

Antioxidant activity

Frequent garlic intake promotes antioxidant activities and reduces oxidative adverse effects either by increasing the endogenous antioxidant synthesis or reducing the production of oxidizers such as oxygen-free radical species (ORS). Alliiin isolated from garlic, showing wide-spectrum antioxidant activities by controlling ROS generation and preventing mitogen-activated protein kinase (MAPK). Moreover, it was reported to prevent ROS production by inhibiting NADPH oxidase 1, and thus, inhibiting the osteoclast fusion caused by receptor activator of nuclear factor-kappa B ligand (RANKL). Allicin also isolated from garlic showed an antioxidant effect in lower doses at the physiological level.

Anti-inflammatory activity

Garlic its bioactive phytochemicals have been reported to possess anti-inflammatory activity. It has been observed
that the anti-inflammatory activity of garlic is caused by inhibiting the emigration of neutrophilic granulocytes into epithelia.\textsuperscript{17} It has been investigated that the anti-inflammatory effect of garlic may be due to the direct suppression of toll-like receptor 4 (TLR4) signalling cascade activation in macrophages, reducing nuclear NF-kB level and improving the NF-kB and IxkB cytosolic levels in LPS-activated RAW264.7 cells.\textsuperscript{18} Furthermore it has been observed that garlic extract may act by inhibiting the iNOS and COX-2 expression, and so, prevented the NO, interleukin-6 (IL-6) and TNF-α formation of in LPS-activated RAW264.7 cells and TPA-mediated dermatitis in mice. Allicin showed a defensive mechanism against pathogens by enhancing the activity of immune cells and influence signalling pathways associated with these immune cells. Moreover, allicin works on T-cell lymphocytes by inhibiting the SDF1α chemokine which is related with the weakness of the dynamic structure of the actin cytoskeleton and it leads to inhibit the transendothelial migration of neutrophils.\textsuperscript{19}

**Anti-cancer effect**

Numerous studies have shown cancer-preventive effects of garlic. Garlic has been found to contain various potent bioactive compounds with anticancer properties, mainly allylsulfide derivatives. Various garlic derivatives have been shown to modulate an increasing number of molecular mechanisms in carcinogenesis, such as deoxyribonucleic acid (DNA) adduct formation, mutagenesis, scavenging of free radicals, cell proliferation and differentiation as well as angiogenesis. The growth rate of cancer cells is reduced by garlic, with cell cycle blockade that occurs in the G2/M phase.\textsuperscript{20} Garlic has a variety of anti-tumor effects, including tumor cell growth inhibition and chemopreventive effects. Diallyl trisulfide (DATS), an organosulfur compound isolated from garlic, has potent anticancer activity. It has potent anti-cancer activity against PC-3 cancer cells.\textsuperscript{21} Furthermore it has also been found to reduce tumor mass and number of mitotic cells within tumors. DATS reduced mitosis in tumors by decreasing histone deacetylase activity and increasing acetylation of H3 and H4. It has also been found to inhibit cell cycle progression and decrease pro-tumor markers (survivin, Bcl-2, c-Myc, mTOR, EGFR, VEGF).\textsuperscript{22}

**Anti-hepatotoxic activity**

Several studies showed that garlic can protect the liver cells from some toxic agents. Acetaminophen is a leading analgesic and antipyretic drug used in many countries.\textsuperscript{23} It is demonstrated that garlic protects against acetaminophen-induced hepatotoxicity. Gentamycin also induces hepatic damage as revealed by elevation of liver damage marker enzymes (aspartate transaminase and alanine aminotransferase) and reduction in plasma albumin level. Dietary inclusion of garlic powder protects rats against gentamycin-induced hepatotoxicity, improves antioxidant status, and modulates oxidative stress.\textsuperscript{24} Garlic extract may reduce lipid peroxidation and enhance antioxidant defence system.\textsuperscript{25}

**Anti-Alzheimer’s disease activity**

Alzheimer’s disease (AD) is the main cause of dementia in the elderly with neurodegenerative and cerebrovascular disorders. Acetylcholinesterase (AChE) is the main enzyme that break down the acetylcholine (ACh) in the nervous system into acetate and choline.\textsuperscript{26} Acetylcholine depletion in the central nervous system is the important pathophysiology found in AD.\textsuperscript{27} For this reason donepezil (AChE inhibitor) was effectively used in the management and prevention of AD. It has been observed that oil from garlic bulbs suppressed AChE activity of cerebral cortex synaptosome. Garlic oil exhibits antioxidant properties and due to this anti-oxidant property it inhibits AChE activity in vitro\textsuperscript{28}. Thus garlic can be used to prevent AD.

**Anti-obesity activity**

Obesity is the severe lifestyle disorder in recent times. It can cause diseases like hypertension, dyslipidemia, cardiovascular disorders. Garlic extracts have been shown to reduce body weight, adipose tissue mass.\textsuperscript{29} Furthermore garlic extracts have also been shown to improve plasma lipid profiles in mice with high-fat diet-induced obesity. These effects might be attributed due to the downregulation of multiple gene expression that is included in adipogenesis along with upregulation of the mitochondrial inner membrane proteins expression.\textsuperscript{29}

**Antimicrobial activity**

The antimicrobial activity of garlic is due to allicin. Allicin present in garlic acts toward a wide variety of microorganisms including antibiotic-resistant, gram-positive and gram-negative bacteria such as Shigella, Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus mutans, S. faecalis, S. pyogenes, Salmonella enterica, Klebsiella aerogenes, Vibrio, Mycobacteria, Proteus vulgaris, and Enterococcus faecalis.\textsuperscript{30-33} Furthermore garlic has also been found as a treatment for multi-drug resistant tuberculosis.\textsuperscript{34}

**Anti-protozoal activity**

Numerous studies reported the anti-protozoal activity of garlic extracts. Allicin has been found to prevent the parasite’s RNA, DNA and protein synthesis. Moreover allicin and DATS showed antiparasitic activity against Entamoeba histolytica, Plasmodium falciaparum, Babesia, Theileria, Trypanosoma brucei, and Giardia lamblia.\textsuperscript{35} Ajoene, another phytochemical isolated from garlic, has also been found to exhibit antiparasitic activity by inhibiting the human glutathione reductase and T. cruzi trypansomione reductase.\textsuperscript{36} Furthermore, garlic oil has been reported to show its activity against broad-spectrum microorganisms such are Cochlospernum.
Garlic extracts showed a broad-spectrum fungicidal effect against a wide range of fungi including Candida, Torulopsis, Trichophyton, Cryptococcus, Aspergillus, Trichosporon, and Rhodotorula species. Aliicin and garlic oil have been found to show potent antifungal effects against Candida albicans, Ascosphaera apisin, and A. niger. These two phytochemicals act by penetrating the cellular membrane as well as organelles membranes like the mitochondria and leading to organelles destruction and cell death. Furthermore, DADS and DATS isolated from garlic essential oil have been found to show antifungal activity against a number of fungi (C. albicans, C. tropicalis, and Blastoschizomyces capitatus). It has also been found that garlic exhibited antifungal effects on two species, the air-borne pathogen Botrytis cinerea and Trichoderma harzianum. Moreover, it has also been found that garlic is more effective than nystatin in patients with denture stomatitis.

Antiviral activity

There are very few information regarding the antiviral activity of garlic. Antiviral activity of garlic extracts has been shown against influenza A and B, rhinovirus, HIV, herpes simplex virus 1, human cytomegalovirus (HCMV), herpes simplex type 1 and 2 herpes simplex virus 2, parainfluenza virus type 3, viral pneumonia, rotavirus, vaccinia virus, and vesicular stomatitis virus. The antiviral activity of garlic is mainly due to allicin, organosulfur compound present in garlic. Allicin shows antiviral activity by preventing several thiol enzymes. Diallyl trisulfide and ajoene have also been shown to be active. Ajoene acts by inhibiting the integrin dependent processes in HIV infection. Allyl alcohol and diallyl disulfide have also been shown to be effective against HIV infection. In the context of recent COVID-19 pandemic scientists over the globe is searching for safe antiviral drug which might prevent us from this fatal disease. A very recent study attempted to explore the potential of effective natural compounds from garlic against the main protease of COVID-19 in comparison to proposed drug hydroxychloroquine. In another study garlic clove extract showed a potent in vivo inhibitory effect against SARS-CoV-1 multiplication, probably due to the formation blocking of structural proteins and genetic materials. Recently, researchers have realized the structure of the main protease of SARS-CoV-2, a serine-type MPRO (chymotrypsin-like protease (3CLpro)) protease with the kind of amino acids (such as Thr24, Thr26, and Asn119) present in the active site regions (e.g. 6 LU7 and 2 GTB). MPRO has a considerable structural similarity (~96.0%) between types 1 and 2 of SARS-CoV. Since this protease is responsible for the viral replication and the production of functional protein as a result of the proteolytic maturation of SARS-CoV-2, the infection rate may be substantially reduced by hindering the cleavage of the viral polyprotein. It has been observed that allin showed the best binding efficacy against COVID-19 main proteases. Further study is needed to examine its potential in pre-clinical and clinical studies.

CONCLUSION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects pulmonary epithelial cells. In severe cases, COVID-19 is accompanied by excessive activation of the innate immune system with progressive inflammation and a cytokine storm from activated cells, particularly in the airways, leading to the acute respiratory distress syndrome (ARDS). WHO has declared COVID-19 as a global pandemic.

Older peoples are more prone to have COVID-19 disease than younger people. The reason for this might be due to their less immune power and age related comorbidity like cardiovascular disease and diabetes mellitus. Modification of nutritional pattern can control COVID-19 disease. Till date there is no effective drug to control COVID-19 infection. Garlic is a spice with numerous therapeutic properties. Sulfur-containing phytochemicals present in garlic provides substantial immunomodulatory, anti-inflammatory, anti-diabetic, anti-atherosclerotic, and cardioprotective properties. Furthermore garlic is one of the most efficient natural antibiotics against the wide spectrum of viruses and bacteria. Organosulfur (e.g. allicin and allin) and flavonoid (e.g. quercetin) compounds are responsible for immunomodulatory effects of this healthy spice. Allin present in garlic showed anti-COVID-19 activity. Further study is needed to examine its potential in pre-clinical and clinical studies. Intake of garlic and its derived-products in regular diet as an adjuvant therapy may minimise side effects and toxicity of the main therapeutic drugs of COVID-19 infection.

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