



Possible Prophylactic and Therapeutic Foods for Prevention and Management of COVID-19- An Updated Review

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Abstract

Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has resulted in an outbreak that is spreading globally. In the absence of a vaccine or effective treatment, improving the body's immune response to combat the virus, or, at least alleviate its health complications, becomes imperative. Potential prophylactic and therapeutic food interventions using black seed, garlic, honey, wasabi and high vit C foods have been proposed in various studies on previous coronaviruses, SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Due to the high similarity in the three dimensional structure between SARS-CoV-2 and SARS-CoV, studies that reported antiviral action of certain foods against various viruses including SARS-CoV and MERS-CoV have been discussed in this short review.



Article History

Received: 14 May 2020
Accepted: 26 September 2020

Keywords

Antiviral;
Coronavirus;
COVID-19";
SARS-Cov-2

Introduction


Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel single-stranded positive-sense RNA β -coronavirus. It is associated with a recent outbreak of coronavirus disease 2019 (COVID-19), which was discovered to be highly contagious, and rapidly spreading, hence forcing the world health organization to declare a global health emergency.^{1,2} There are no registered medications or vaccines for COVID-19 so far. This raises the demand to seek alternative natural and safe solutions to prevent COVID-19 spread, or at least help to manage active cases.

A recent review has suggested that optimal host nutritional status plays a vital role in the immune system function, and is essential in limiting the impact of emerging viral infections,³ indicating that this acquired through maintaining a balanced diet in addition to supplementations of vitamins and minerals. In particular, this review highlighted the importance of vitamins C and D, zinc and omega-3 fatty acids in enhancing the immune defense.³ Suboptimal status of micronutrients can impair the innate immune system through the impairment of phagocytosis, microbial killing and altering cytokines production.⁴ It also can affect the adaptive

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Doi: 10.12944/CRNFSJ.8.3.02

immune system through decreasing the number of lymphocytes and reducing antibody responses.⁴

During the past 20 years, two other coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle-East respiratory syndrome coronavirus (MERS-CoV) have caused deadly types of pneumonia.^{5,6} Some previous *in-vivo*, *in-vitro* and laboratory mechanistic studies discovered some foods that have pharmaceutical components which were found to be affective against these as well as other viruses. These foods might be proposed as prophylactic (which has an effect if administered before the disease onset) and therapeutic (which has an effect if administered after the disease onset) nutrients against Covid-19 as there is a high similarity in the three dimensional genetic structure between SARS-CoV-2 and SARS-CoV.⁷ In this short review, we will summarize the most important previous findings regarding possible prophylactic and therapeutic nutrient options for the prevention and management of COVID-19, in particular black seed, garlic, honey, wasabi, and vitamin C rich foods.

Black Seed *Nigella sativa*

Black seed (*Nigella sativa*) has been used for decades for medical purposes. Its pharmacological effects are attributed to high content of quinines.⁸ Quinine is widely known as an anti-malarial, anti-inflammatory agent⁹ and as a potent antioxidant.¹⁰ In animal studies, black seed oil has been shown to provide protective action against murine cytomegalovirus infection in mice through increasing number and activity of macrophages, and interferon (IFN)-gamma production.¹¹ Black seed oil also showed complete inhibition of virus titers in spleen and liver of mice on the third day of infection, while the titers remained unchanged in the control mice.¹¹ Furthermore, In a study on poultry birds, namely turkeys infected with influenza virus (H9N2), it was noted that feeding with black seeds has enhanced the immune response by increasing the production of IFN-gamma and hemagglutinin-inhibition (HI) titers, which significantly suppressed the pathogenicity and clinical signs of H9N2.¹² Moreover, in laboratory studies, black seed at concentration of 35µM has shown good antiviral effects in Chicken Embryo Rough Cells (CER) infected with Laryngotrachietis Virus (ILTV).¹³

Human studies provided further evidence to the efficacy of black seed against viral infections. Results from a clinical trial indicated that the administration of 450mg of black seed three times daily for 3 months decreased viral load and oxidative stress in patients infected with Hepatitis C virus (HCV), and that the dose was tolerable and safe.¹⁴ In addition, a case study on an HIV-positive patient reported that daily administration of 10mls two times daily of black seed concoction for 6 months resulted in both the disappearance of symptoms associated with HIV as measured by absolute count of CD4 cells, and viral load as measured in (HIV-RNA) copies per ml in blood in a gradual, and duration dependent manner, thus resulting in the patient becoming sero-negative for HIV.¹⁴

Studies indicated that thymoquinone, found at a concentration of 3.5-8.7 mg/g in fixed oil, is one of the most active constituents in black seed oil.^{8,16} Very recent studies suggested that the modified forms of quinines, chloroquine, and hydroxychloroquine, a derivative of thymoquinone, were potent inhibitors of SARS coronavirus infection at clinically admissible concentrations through interfering with angiotensin-converting enzyme 2 (ACE2) receptor which is one of cell surface binding sites for S protein of SARS-CoV that the virus uses for entry into human cells as revealed by docking simulation technique.^{17,18} This interference was proposed to result in the elevation of vesicular pH, which in turn, inhibits the viral spreading of SARS-CoV to uninfected cells.¹⁷ Therefore, black seed might be a possible prophylactic and therapeutic option for COVID-19. However, its efficacy still needs to be confirmed by well-designed and controlled clinical trials.

Garlic

Garlic (*Allium sativum* L.) has been widely used in traditional alternative medicine prescriptions. Various healing, and health enhancing effects of garlic have also been reported in more recent reviews of *in-vitro*, *in-vivo* and clinical studies. Reported effects included: antioxidant, anti-bacterial, -microbial and -viral, as well as anti-carcinogenic activities that were associated with improvement in respiration and digestion processes during infections, treatment of infectious diseases, and decrease of symptoms of non-communicable diseases.^{19,20}

Many of the biological effects of garlic are attributed to its organosulfur constituents, with the strength of its biological activities depending on the number of sulfur atoms.²¹⁻²⁴ Allyl disulfide and allyl trisulfide account for more than 50% in content of garlic essential oil.²⁰

Garlic is considered one of the richest vegetable sources of total phenolic compounds that contribute to its antioxidant action.^{25,26} Previous reviews reported different antioxidant activities of garlic including radicals trapping, scavenging of hydroxyl radicals, interaction with thiol containing proteins, inhibition of superoxide and nitric oxide production and modification of SH-dependent activities.²⁵⁻²⁹ This strong antioxidant action has been suggested to attribute to the therapeutic properties of garlic including antimicrobial, anti-carcinogenic and anti-aging properties.³⁰ Sulfur-containing compounds which are present in essential oil extracts of garlic have been reported to exert marked antimicrobial activities against wide range of bacteria and fungi which led to the suggestion of the use of garlic as natural antimicrobial additive in food products.^{26,31} Garlic's mechanism of antimicrobial action is suggested to be the ability to inhibit thiol-containing enzymes and other bacterial enzymes such as those involved in the acetyl-CoA-forming system which cause severe damage in the microorganism tissues.³¹

In-vitro laboratory studies reported that garlic showed antiviral activities against influenza A and B,³² cytomegalovirus,^{33,34} rhinovirus,³⁵ HIV,³⁵ herpes simplex virus 1³⁵ and 2,²⁴ viral pneumonia, and rotavirus,^{35,36} and were suggested to be strong potent inhibitors of SARS-CoV-2 coronavirus.²² The anticoronavirus suggested mechanism was through the inhibition of ACE2 protein receptor, which leads to loss of the host receptor of the virus, in addition to attacking the PDB6LU7 protein, which is a main protease of SARS-CoV-2 at the same time.²² These findings suggest that garlic has potential preventive and therapeutic properties against COVID-19, but this needs to be addressed further by clinical trials to obtain conclusive evidence.

Honey

For centuries, honey has been used in traditional medicine to treat many diseases. Its type varies

depending on the bees species and the plants on which the bees feed on, which in turn influence its therapeutic value.³⁷ Honey has been reported to possess anti-microbial and healing activities due to its phenolic and flavonoid constituents.³⁸ Furthermore, honey's effective wound healing activities were attributed to its antibacterial, anti-inflammatory and cell growth-stimulating properties, as well as immunomodulatory properties and immune-boosting capabilities.³⁹ In an *in-vitro* study on monocytic cell line, MonoMac-6 (MM6), honey was found to stimulate the immune system through inducing the maximal release of monocyte cytokines.⁴⁰ Some types of honey exhibit a very high antimicrobial activity and so far, bacteria has not been able to develop resistance to the antibacterial components in these types of honey.⁴¹ For example, tualang (*Koompassia excelsa*) honey possess strong antimicrobial properties against many different microorganisms that are stronger than manuka (*L. scoparium*) honey in some cases.⁴¹

In addition, anti-viral properties of honey in cell culture studies were reported against Rubella, Varicella Zoster and influenza viruses, as the incubation of low concentrations of honey with infected cell lines resulted in viral plaque reduction and decreased viability of infected cells.⁴²⁻⁴⁴ Different types of honey including manuka, soba (*F. esculentum*; buckwheat), kanro (honeydew), acacia (*R. pseudoacacia*) and renga (*A. sinicus*) honey were reported to have antiviral activity against influenza virus in a dose dependent manner, with manuka honey showing the most potent viral-inhibitory activity.⁴⁴ Indeed, Manuka honey also was reported to have a potential medicinal value in treating influenza due to its effective virucidal action against the virus at the pre-infection stage, as well as during and after infection by inhibiting viral replication and growth.⁴⁴ Due to these antiviral mechanisms, honey may be proposed as a potential therapeutic agent against viral infections and their complications, including those caused by COVID-19. Indeed, the National Institute for Health and Care Excellence (NICE) guidelines suggest that honey can be used as a treatment for acute cough caused by upper respiratory tract infection which is currently a core symptom in COVID-19 disease.⁴⁵ In the light of this, a current ongoing clinical trial has been established to investigate the efficacy of natural honey in treatment

of patients infected with COVID-19 compared with current standard care.⁴⁶

Wasabi

Japanese wasabi (*Wasabia japonica*) is a unique traditional cruciferous Brassicaceae crop, that is close to the nasturtiums botanically and that grows on the wet banks of cool mountain streams and springs in Japan.⁴⁷ Wasabi plant is rich in glucosinolates which become metabolized into isothiocyanates by the action of the myrosinase enzyme which is expressed in the cells of Brassicaceae plants.⁴⁸ Several bioactive compounds were isolated from the wasabi roots including lignan glycosides, wasabisides and phenolic compounds.⁴⁹

Its extract have powerful pharmacological properties due to its isothiocyanate and sinigrin constitutes.⁵⁰ Phenethyl isothiocyanate has been shown to have immunomodulatory effects on both the innate and

specific immune systems of mice.⁵¹ Japanese wasabi was reported to have potent anti-influenza activity as its ethanol extracts highly inhibited virus production of H1N1, H3N2 and B-Shamine influenza viral strains by more than 98%, regardless of the hemagglutinin antigen type in cell cultures.⁵² The same study reported that wasabi ethanol extract did not exhibit inhibitory effect on intracellular influenza virus synthesis or on the release of the virus from the cell surface as measured by the cytopathic effect of replicating infected cells. However, it suggested that the Japanese wasabi extract inhibited viral adsorption and entrance into cells which possibly occurs in the early phase of infection as measured by influenza virus titer and replication inhibition rate.⁵² These antiviral effects of wasabi suggests that it could be an alternative preventive, or therapeutic option for COVID-19. However, further controlled studies are needed to confirm its therapeutic value.

Table 1: The top 5 foods highest in vitamin C

Food	Vitamin C (mg/cup)	Number of cups to obtain 200 mg of vitamin C	Number of cups to obtain 1g of vitamin C
Guavas	377	0.5	2.7
Bell peppers	190	1.1	5.3
Kiwi fruit	167	1.2	6.0
Strawberries	98	2.0	10.2
Oranges	96	2.1	10.4

Source⁶⁴

Vitamin C Containing Food

Respiratory viruses including influenza, rhino and corona are usually the main cause of common cold which usually results in respiratory symptoms.⁵³⁻⁵⁵ Various reviews reported that vitamin C deficiency increased the risk of severe respiratory infections such as pneumonia.^{56,57} A recent meta-analysis reported that administration of vitamin C lead to a significant reduction in the risk of pneumonia in individuals with low dietary intakes and that vitamin C reduced disease severity and risk of death in older patients with pneumonia especially in individuals with low plasma vitamin C level.⁵⁸ A recent review concluded that vitamin C level is reduced in leukocytes and urine secretion during common

cold episodes and that the administration of high doses of vitamin C during cold episodes reversed this reduction, suggesting that administration of high doses of vitamin C might accelerate the recovery process.⁵⁶ Furthermore, various clinical trials reported that administration of high doses of vitamin C introduced orally or intravenously in hospitalized patients with acute respiratory infections resulted in returning of plasma vitamin C levels to normal, as well as decreased severity of the respiratory symptoms, and rapid clearance of chest in x-rays.⁵⁹⁻⁶¹ Moreover, supplementation of Vitamin C has been shown to have both prophylactic and therapeutic values in reducing the duration and severity of upper respiratory tract infections.^{57,62}

The prophylactic effect of vitamin C was reported to be more effective in people under enhanced physical stress.⁶² In addition, a clinical trial reported that vitamin C supplementation resulted in a greater reduction in “total days indoor” in individuals with low vitamin C dietary intake compared with higher intake suggesting that the therapeutic effect of vitamin C is more profound in individuals with low intake of vitamin C.⁶³ A recent review recommended that healthy individuals need to increase their daily intake of vitamin C to 200mg during outbreaks such as COVID-19 to protect themselves from the disease, and that sick individuals need 1–2 g/day to restore normal blood levels.³ These levels are above the Recommended Dietary Allowances (RDA) but still within the US tolerable upper limit for adults.³ According to FoodData Central system of the United States Department of Agriculture, the top 5 foods highest in vitamin C are guavas, bell peppers, kiwi fruits, strawberries and oranges (Table 1).⁶⁴

Since common cold is caused by viruses such as corona virus and vitamin C supplementation has been shown to decrease the duration and severity of common cold, it is worth investigating the prophylactic and therapeutic effects of vitamin C supplementation in the current Covid-19 outbreak.

The discussed prophylactic and therapeutic food intervention for COVID-19 was in accordance to studies on the previous coronaviruses, SARS-CoV and MERS-CoV, and studies that reported antiviral action of these food types. This approach was adopted partly due to the high similarity in the three dimensional structure between SARS-CoV-2 and SARS-CoV.⁷ The available evidence from previous studies that some components of the discussed

food types may interfere with the binding sites of SARS-CoV-2 suggests that the consumption of these foods might protect from getting infected. However, more *in-vitro* studies that address the influence of discussed foods on all aspects of viral-host interaction, accompanied by longitudinal studies that evaluate the incidence rate of COVID-19 according to the consumption of these food are needed to confirm their prophylactic effect. Clinical studies that investigate the effect on rate of recovery, severity and duration of the disease, duration of lung inflammation and mortality rate in COVID-19 patients are also needed to confirm the therapeutic value of these food types.

Conclusion

Black seed, garlic, wasabi, honey, and vitamin C rich foods contain pharmacologically active components that make them possible prophylactic and therapeutic food interventions for COVID-19 in the absence of clearly indicated medications, and vaccines for this disease. More laboratory, longitudinal and clinical studies are required to confirm these medicinal values.

Acknowledgements

Acknowledgement to Prof. Suhad Bahijri for her help in reviewing the work.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

The author declares no conflict of interest.

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