Nutraceuticals and herbal extracts: A ray of hope for COVID-19 and related infections (Review)

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Abstract. The global pandemic caused by the novel coronavirus disease 2019 (COVID-19), for which there is no effective vaccine or treatment available yet, has led to a global health emergency. Despite a lack of clinical data, compelling evidence from the literature suggests that certain nutraceuticals (such as omega-3 fats, β-glucans, amino acids, probiotics, vitamins and minerals) and plant-based compounds derived from herbal extracts may potentially be used in the treatment of COVID-19. In the present review article, the benefits of such natural products in treating various respiratory complications are highlighted, and it is tentatively suggested that these benefits could be extrapolated to COVID-19. These natural compounds may not only modulate the immunity of a susceptible population, but may also pave the way towards the development of drugs which may be used to treat COVID-19. Although attention has recently focused on these compounds in this context, further clinical and experimental studies are required to validate their efficacy. It is thus suggested that the *in vitro* and *in vivo* evaluation of these compounds be carried out as soon as possible, in order to counteract the ongoing increase in the number of cases of COVID-19.

Contents

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1. Introduction

Coronavirus disease 2019 (COVID-19). Global health is threatened by an ongoing outbreak of COVID-19, a respiratory disease caused by the novel coronavirus, SARS-CoV-2, which was first identified in December, 2019 in Wuhan, China (1). As of August 28, 2020, >24.7 million individuals had been infected with the virus worldwide, and approximately 838,000 have succumbed to the disease (2). In total, seven types of coronaviruses, namely severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), OC43, NL63, 229E and HKU1, are known to infect humans. Of these, the first three can cause fatal infections, whereas the latter four typically cause mild common cold-associated symptoms, particularly in immunocompromised individuals (3). COVID-19 is highly contagious and infected patients exhibit symptoms of fever, pneumonia, thrombocytopenia, cough, dyspnea, myalgia and asthenia (4).

Prevention and treatment of COVID-19. As of August 5, 2020, no vaccine or successful treatment for COVID-19 has been reported and only supportive care, personal protection, early diagnosis and isolation are available to reduce the spread and severity of the infection (5). Huang *et al* (6) reported that patients with COVID-19 develop acute respiratory distress syndrome, followed by anemia, acute heart injuries and secondary infections. Empirical therapy with antibiotics (including cephalosporins, azithromycin, vancomycin, quinolones, tigecycline and carbapenems), antivirals (including lopinavir, ritonavir, remdesivir and oseltamivir) and corticosteroids (including dexamethasone and methylprednisolone) has thus been used for the treatment of patients with COVID-19 (7). The clinical efficacy of all of these treatments, however, warrants further confirmation.

Potential agents with which to combat COVID-19. Research proposals and clinical trials have suggested that some treatments, including supplements and phytochemicals, have the potential to help fight coronavirus infection. A recent study suggested that the risk of becoming infected could be reduced by vitamin D3 supplementation. Serum concentrations >40-60 ng/ml (100-150 nmol/l) were suggested to be

required in order to prevent infection, with even higher doses required to treat patients already infected (8). In addition, due to its antiviral and immunomodulatory properties, zinc supplementation may also be considered for use in the prevention or treatment of COVID-19 (9). Zhang *et al* (10) proposed that melatonin, which has antioxidant and anti-inflammatory properties, together with a good safety profile, and also potentially modulates the immune system, improves sleep quality, and reduces vessel permeability, anxiety and the use of sedatives, may lead to better clinical outcomes for patients with COVID-19. Ang *et al* (11) analyzed the potential of traditional herbal medicines, which contained a total of 56 herbs, for the treatment of patients with COVID-19. The detailed review by Islam *et al* (12) also reported that a wide range of herbal compounds, including tylophorine, lycorine, ouabain, silvestrol, homoharringtonine and 7-methoxycryptopleurine, broadly suppressed different coronaviruses, with IC_{50} values ranging from 12 to 143 nM. Yu *et al* (13) also demonstrated that the plant-derived flavonoids, myricetin and scutellarein, are inhibitors of SARS-CoV helicase. Collectively, the above-mentioned studies suggest that natural products and dietary supplements may help in the fight against COVID-19. A pictorial representation of the potential beneficial effects of nutraceuticals and herbal extracts against COVID-19 is depicted in Fig. 1.

SARS, SARS-CoV-2 and MERS are known as enveloped viruses (14), and several bioactive lipids, including omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been reported to inactivate these enveloped viruses and reduce their proliferation (15). Some metabolites of EPA and arachidonic acid, such as thromboxanes, leukotrienes and prostaglandins, induce inflammation (16), whereas other metabolites of EPA and DHA, such as maresins, protectins, resolvins and lipoxins, suppress inflammation, modulate the T-cell response, reduce microbial load, augment phagocytosis and enhance wound healing processes. These latter bioactive lipids can be used in the treatment of airway inflammation and common human lung diseases, such as chronic obstructive pulmonary disease (COPD) and asthma (17,18). A recent study revealed that both EPA and DHA, from fish oil, improved breathing for patients with asthma (19). The oral or intravenous administration of EPA or DHA could, therefore, potentially promote the recovery of patients with COVID-19 (20).

With regards to the recent increase in the number of published articles on COVID-19, including reports of infected cases, fatalities, disease severity and vulnerability (21), the purpose of the present review article is to draw the attention of medical and pharmacy professionals towards nutraceuticals and herbal extracts for the treatment of COVID-19. The present review focuses on reported facts and figures to highlight the potential of natural products to strengthen the immunity of the general population, and to pave the way for the identification of drugs which may be used in the treatment of patients with COVID-19. Mathematical models predict that reported numbers of cases of COVID-19 will continue to increase until a vaccine is made available to the global market (22). The present review article highlights the therapeutic significance of some promising natural products with activity against viruses in general, and COVID-19 in particular.

2. Therapeutic benefits of nutraceuticals for respiratory complications

Vitamins. A daily intake of 20-50 μg of vitamin D was recently recommended for obese individuals, healthcare workers and smokers in order to enhance their resistance to COVID-19 infection (23). Yalaki *et al* (24) reported that supplementation with vitamin D in patients suffering from acute bronchiolitis increased immunity and normalized pulmonary function. Other studies have also associated the administration of vitamin D with the reduced likelihood of developing respiratory infections (25,26). The administration of high-dose vitamin C (1,000-6,000 mg) has also been reported to decrease the time spent by critically ill patients on mechanical ventilation by 25%, and also reduced their length of stay in an intensive care unit (27). Of note, vitamin C has also been proven to be effective against asthma induced by the common cold (28,29).

Dietary minerals

Selenium. The importance of selenium for optimal immune function has been emphasized in the literature (30). Selenium provides resistance against viral infections through its redox homeostasis and antioxidant properties (31). Selenium deficiency has been associated with impaired immune function, likely due to increased oxidative stress in the host organism (32). This can lead to alterations in the viral genome, which may increase virulence and boost pathogenicity (33). Dietary selenium has been shown to improve immunity against the lethal H1N1 influenza virus infection (34-36) and can also be potentially used in the current battle against COVID-19 (37).

Zinc. Elderly individuals are often deficient in zinc, which is essential for immune function, and zinc deficiency is considered to be a potential risk factor for the development of pneumonia among the elderly (38,39). Barnett *et al* (40) found that older subjects with higher serum zinc concentrations (>70 μg/dl) were not only characterized by a lower incidence of pneumonia ($P<0.001$), but also with a lower duration of disease and less need for antibiotics than older patients with low serum zinc concentrations (<70 μg/dl). Other studies have demonstrated that zinc deficiency is associated with an up to 80% higher incidence of pneumonia in children (41,42) and zinc supplementation has also been reported to significantly decrease the development of respiratory diseases among children suffering from acute lower respiratory tract infections (43). A previous *in vitro* study also indicated that zinc salts inhibited the replication of respiratory syncytial virus (RSV) and prevent cell-to-cell spread in human epithelial type 2 (HEp-2) cells (44). Zinc is considered to be essential for the respiratory epithelium due to its anti-inflammatory and antioxidant activities, along with its ability to regulate tight junction proteins, including claudin-1 and Zonula occludens-1 (45,46). In a separate study, the length of cilia at the bronchial epithelium of zinc-deficient rats was shown to be improved by zinc supplementation (47). *In vitro* experiments in the study by Woodworth *et al* (48) highlighted the ability of zinc to boost mucociliary clearance by enhancing the beat frequency of cilia. Zinc ions have also been found to inhibit the RNA-dependent RNA polymerases of influenza virus, hepatitis C virus (HCV) and rhinoviruses, and to impair the

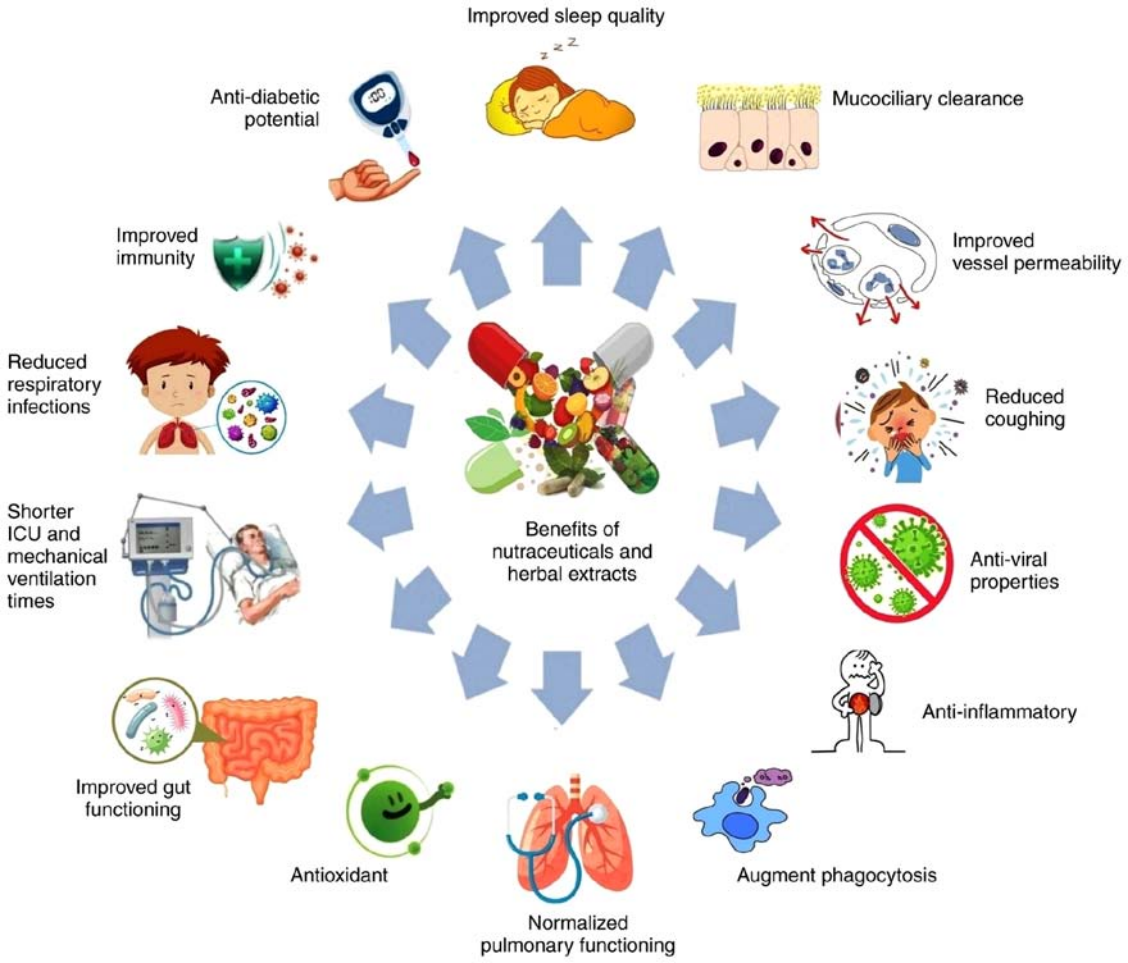

Figure 1. Schematic diagram illustrating the potential beneficial effects of nutraceuticals and herbal extracts in the management of COVID-19.

activity of the RNA-synthesizing machinery of nidoviruses, the order of viruses to which SARS-CoV-2 belongs (49,50).

Iron. Whereas excessively high serum concentrations of iron can cause oxidative stress and lead to viral mutations, iron deficiency can impair host immunity and increase susceptibility to infections (51). The dysregulated homeostasis of iron, which alters serum concentrations, has been associated with several respiratory diseases, including asthma, cystic fibrosis, COPD, idiopathic pulmonary fibrosis, acute respiratory tract infections and lung cancer (52,53). The strict regulation of serum iron concentration could thus provide favorable clinical outcomes for patients with COVID-19.

N-acetyl-cysteine (NAC). NAC, which is derived from the naturally occurring amino acid, cysteine, is most commonly prescribed to patients suffering from various respiratory complications, including respiratory tract infections, idiopathic pulmonary fibrosis and chronic bronchitis (54-56). The antioxidant and mucolytic effects of NAC have been reported to significantly improve the function of airways and to reduce COPD exacerbations (57). NAC treatment has also been reported to inhibit the RSV infection of human alveolar epithelial (A549) cells and to reduce mucin release (58). In a previous review article, Sadowska (59) concluded that NAC may be beneficial in the management of COPD, since it would promote clearance of mucus and alleviate oxidative stress and inflammation. Taken together, these results demonstrate the clear potential of NAC as an adjuvant supplement for COVID-19 patients (60,61).

Amino acids

Arginine. Arginine has been reported to act synergistically with virucidal conditions, such as high temperatures and acidic pH levels, and can thus potentially inactivate enveloped viruses (62,63). Tsujimoto *et al* (64) successfully inactivated herpes simplex virus type 2 (HSV-2) using a solution of arginine. Similarly, influenza A has been shown to be inactivated under similar conditions (65). Recently, Meingast and Heldt (63) suggested that arginine inactivates viruses through a variety of mechanisms, including pore formation and destabilization of the viral membrane, the inhibition of the function of non-structural proteins, the suppression of protein-protein interactions and aggregation. Ikeda *et al* (66) suggested that arginine associates with multiple sites on viral particles, thereby affecting glycoprotein-lipid interactions on the viral envelope. Due to the low cytotoxicity of arginine, a previous study demonstrated the possible use of an intranasal spray containing an aqueous solution of arginine to inhibit influenza A infection *in vivo* (67). In a NC/Nga mouse model of asthma, arginine was found to contribute to improved asthmatic symptoms by reducing airway inflammation in lung tissue and altering L-arginine metabolism (68).

Glutamine (GLN). GLN is one of the most abundant free amino acids within the human body, with a concentration of approximately 500-900 μmol/l (69). In a murine model of asthma, Lee *et al* (70) demonstrated that, at therapeutic doses, GLN suppressed inflammation by inhibiting the recruitment of neutrophils into the airways. In a ventilator-induced lung injury (VILI) mouse model, in which the lungs of mice are acutely injured by acid aspiration, the administration of GLN was reported to reduce the destruction of lung tissue, lung edema, cytokine production and neutrophil recruitment to the lung (71). Oliveira *et al* (72) proposed that exogenous GLN may be beneficial against asthma and acute respiratory distress syndrome (ARDS), and during the treatment of lung cancer. Thus, GLN may provide therapeutic benefits to COVID-19 patients (73).

Probiotics. Nutritional supplementation with probiotics has been reported to be beneficial for patients suffering from respiratory tract infections (74-76). Strasser *et al* (77) reported that various strains of probiotics, including *Lactococcus lactis* W58, *Lactobacillus brevis* W63, *Enterococcus faecium* W54, *Lactobacillus acidophilus* W22, *Bifidobacterium lactis* W51 and *Bifidobacterium bifidum* W23, helped to reduce the incidence of upper respiratory tract infections (URTIs) in trained athletes, without altering performance. Another probiotic strain, *Lactobacillus casei* Zhang, which exhibits immunomodulatory, anti-inflammatory and anti-oxidative effects, has been shown to alleviate the symptoms of URTI and restore gastrointestinal health in adults and elderly subjects (78). RSV infection has also been reported to be suppressed by various probiotic strains, including *Lactobacillus gasseri* SBT2055 and *Lactobacillus rhamnosus* CRL1505 (79,80). The results of the meta-analysis by Kang *et al* (81) revealed the efficacy of probiotics in the treatment of common cold infections. During the COVID-19 pandemic, the National Administration of Traditional Chinese Medicine and the Chinese National Health Commission recommended the use of probiotic therapy to control coronavirus infection (82); however, the effectiveness of probiotics in reducing the mortality rate of patients in intensive care units remains uncertain. Jayawardena *et al* (83) suggested the use of probiotics as a dietary supplement to prevent infection of susceptible populations with SARS-CoV-2. Since probiotics are readily available as dietary supplements and have negligible side-effects if administered at the correct doses, they may thus provide a useful intervention strategy against COVID-19 (84-86). A study to evaluate whether dietary supplementation with *Lactobacillus coryniformis* K8 can help to prevent healthcare workers from contracting COVID-19 was registered at ClinicalTrials.gov (NCT04366180) on April 28, 2020.

Omega-3 fatty acids. Fats, which can be classified as saturated or unsaturated, form an essential part of the human diet and play a vital role in nutrition and health (87,88). Fats serve as a main source of energy, participate in cell signaling and responses, and play a structural role as part of the cell membrane. Omega-3 polyunsaturated fatty acids have been reported to confer health benefits in patients suffering from respiratory complications, such as ARDS, COPD, impaired oxygenation and pulmonary fibrosis (89-92) and are attracting considerable attention due to their anticoagulant properties and ability to reduce inflammation (93). The consumption of omega-3 polyunsaturated fatty acids has been associated with a number of physiological alterations, including the production of lung surfactants, host-microbial interactions, alterations in blood rheology and the production of endogenous eicosanoids (94).

According to the study by Miyata and Arita (95), omega-3 fatty acids can alleviate the inflammatory complications resulting from allergic reactions and asthma. Omega-3 fatty acids have also been reported to suppress the synthesis of immunoglobulin E, leading to reduced airway inflammation and bronchoconstriction in patients with asthma (96). The lipid mediator, protectin D1, which is derived from omega-3 fatty acids, has been reported to suppress the replication of the highly pathogenic influenza H5N1 virus, and to improve the survival of H5N1-infected mice (97). Linday *et al* (98) found that the simultaneous administration of cod liver oil (which contains EPA and vitamin A) and a multivitamin-mineral supplement to children led to a statistically significant ($P<0.05$) decrease in the mean number of URTI-related medical consultations over time. Overall, omega-3 fatty acids confer significant health benefits to patients with URTI complications and shorten the length of stay of acutely ill patients in hospital (99-101). Since omega-3 fatty acids have proven to be effective in reducing airway inflammation and bronchoconstriction, have also exhibited efficacy against viral infections (102,103), their potential for use against COVID-19 warrants further investigation (104-106).

β-glucans. β-glucans, which are potent activators of immune cells, including neutrophils, natural killer cells and macrophages, exert a favorable effect on the host defense system (107). In addition to the immunomodulatory effects, the administration of β-glucans has been shown to reduce the susceptibility of healthy subjects to URTIs and to decrease the severity of URTIs in infected subjects (108-111). β-glucans have also been shown to exhibit antiviral activity against HSV-1 (112,113) and influenza virus (114,115). More recently, it was suggested that β-glucans can help to reduce morbidity and mortality associated with COVID-19 (116,117).

3. Therapeutic benefits of herbal extracts for respiratory complications

The use of phytochemicals and natural products for the treatment of various diseases is gaining worldwide attention (118,119). Prior to the discovery of antibiotics, herbal extracts played an important role in the treatment of diseases (120), and purified natural products and herbal extracts now provide a rich pool of compounds for the development of novel antiviral drugs (121). Lin *et al* (122) summarized the antiviral activity of various natural products and herbal medicines against some notable viral pathogens, including RSV, measles virus, dengue virus, influenza virus, human immunodeficiency virus (HIV), HSV, HCV, hepatitis B virus, enterovirus 71, coxsackievirus and coronavirus.

Cheng *et al* (123) examined the activity of naturally occurring triterpene glycosides (saikosaponins A, B, C and D), extracted from medicinal plants, such as *Bupleurum* spp., *Scrophularia scorodonia* and *Heteromorpha* spp., against coronaviruses. They found that the tested phytochemicals significantly inhibited the early stage of human coronavirus

229E infection by interfering with viral replication, absorption and penetration. In 2008, Lau *et al* (124) demonstrated that an aqueous extract of the medicinal herb, *Houttuynia cordata*, facilitated the clearance of SARS-CoV infection in mice, both by improving the immune response and by a direct antiviral effect. Firstly, it stimulated cell-mediated immunity and, secondly, it attenuated viral replication by inhibiting pivotal viral enzymes (RNA-dependent RNA polymerase and 3CL protease) involved in the replication process. Another traditional herb, *Pelargonium sidoides*, has been tested clinically as a treatment for human coronavirus, influenza A virus (H1N1 and H3N2), RSV, coxsackievirus, parainfluenza virus, coughs, URTIs and gastrointestinal conditions (125-128). Licorice extract, derived from the root of *Glycyrrhiza glabra*, has been shown to exhibit *in vitro* activity against vesicular stomatitis virus, vaccinia virus, SARS-CoV, RSV and HIV-1 (129,130). *Nigella sativa*, also known as black seed, has emerged as a 'miracle' herb, with potential antidiabetic, antioxidant, anticancer, anti-inflammatory, bronchodilatory, immunomodulatory and pulmonary-protective activities (131,132). In 2005, Li *et al* screened >200 Chinese medicinal herbs for activity against SARS-CoV and found that herbal extracts from four medicinal plants, namely *Lindera aggregata*, *Pyrrosia lingua*, *Lycoris radiata* and *Artemisia annua*, exhibited antiviral activity (133). Further fractionation and purification of the *L. radiata* extract identified lycorine as a potential candidate for the development of new anti-SARS-CoV drugs (133). Equally importantly, *Cordyceps* (medicinal mushrooms) have significant potential to strengthen the cardiovascular, respiratory and immune systems, and also have general antiviral and antioxidant properties (134-136). The medicinal and health-promoting attributes of therapeutic fungi have recently gained considerable attention in the field of COVID-19 research (137-139).

4. Conclusion

The present review attempted to highlight the potential of various nutraceuticals and herbal extracts as possible treatments for COVID-19. Although strong evidence for the potential of these compounds to combat the ongoing COVID-19 pandemic has already appeared in the literature, new evidence is gradually emerging (140). The reported clinical data are, however, still inconclusive and there are also inconsistencies within the data, since some clinical studies did not achieve the desired effects. These inconsistencies seem to be related to a number of factors, including the dose used, the heterogeneity of the target population, the plasma concentration, the beginning and duration of the treatment and the route of administration (141). Taking these factors into consideration, randomized and controlled trials are required to resolve these controversies and to clarify issues around the use of these compounds. In addition to an increase in the reported number of cases, some patients who have recovered from coronavirus are testing positive again (142). Clinical validation of compounds that could possibly help to combat the COVID-19 pandemic is thus urgently required.

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Competing interests

The authors declare that they have no competing interests.

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