Coronavirus disease 2019 and the natural agents: Is there a role for the primary care?

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a newly discovered RNA virus that belongs to corona virus group. It leads to an infectious state manifested as fever, loss of smell and taste sensations, cough, myalgia, fatigue and headache. The condition may become more serious as difficulty in breathing, chest pain and even death. Until successful vaccine is developed, complimentary and herbal medicine can be used as alternative prevention measure against COVID-19 in high-risk populations. This is because the none of the traditional agents used in the treatment protocols had proven effective results. In addition, recent studies reported that dietary supplements and herbal agents may have effective antioxidant and anti-inflammatory properties that may contribute efficiently to amelioration of the effects of COVID-19. This review sheds light on the possible role of the natural agents in the management of COVID-19 with reference to the role of the primary care in this issue.

Keywords: Coronavirus disease 2019, dietary supplements, herbs, natural agents, primary care

Introduction

COVID-19 disease is caused by RNA coronavirus and is associated with severe acute respiratory syndrome.[1] The severity of COVID-19 infection is highly variable from one patient to another. The clinical picture ranges from cases with apparently no symptoms to cases with severe acute respiratory distress syndrome with septicaemia.[2] The most common general symptoms frequently encountered with COVID-19 include dry cough, fever, muscle pain, anorexia, dyspnea, fatigue, and loss of taste and smell sensations. These symptoms may progress to cytokine storm syndrome, insomnia, and even respiratory failure.[3]

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Access this article online	
Quick Response Code:	**Website:** www.jfmpc.com
	DOI: 10.4103/jfmpc.jfmpc_2195_20

Analysis of the immune profile of COVID-19 patients showed significant reduction in regulatory T-cells, cytotoxic and T-helper cells, monocyte/macrophages ratio, and the natural killer cells.[4] Also, there is an elevation of the levels of the pro-inflammatory cytokines such as interleukin-6, interleukin-15, tumor necrosis factor alpha, and interferon-gamma as well as leptin.[5]

A number of well-known antiviral drugs such as oseltamivir, favipiravir, remdesivir, lopinavir/ritonavir and darunavir/umifenovir are widely used for management of COVID-19 together with other drugs that had proven a great efficiency in such cases such as tocilizumab, hydroxychloroquine, chloroquine, azithromycin, interferon-β, and dexamethasone.[1] However, none of these medications was proven to show high efficacy against COVID-19.[6] Many preclinical and clinical trials are carried out to search for an effective line for treatment of COVID-19.

A vast number of these trials used the medicinal plants and their secondary metabolites as possible remedies for treatment of COVID-19.[7] This was attributed to the antioxidant and the anti-inflammatory properties of these agents together with their ability to inhibit the key enzymes involved in COVID-19 replication and propagation.[8] Our aim was to shed light on the possible role of the natural agents in the current COVID-19 pandemic with reference to the role of the primary care in this issue. This study was approved by the Research Ethics Committee, College of Pharmacy, Taif University on 29 March 2020.

Garlic (Allium Sativum)

For many years, the beneficial impact of Garlic (Allium sativum) on health was clearly verified. Garlic contains various constitutes that can affect immunity.[9] Due to the fact that the progression of many diseases is associated with dysfunction in the immune system, garlic may help greatly in treatment and prevention of diseases such as gastric ulcer, obesity, cardiovascular diseases, and even cancer.[10] Compared to chemotherapy, aged garlic extract may be used as herbal therapy with fewer side effects in treating cancer produced by toxic substances such as aflatoxin B1.[9] Allicin is the primary organosulfur compound in garlic which decreases the expression of the pro-inflammatory cytokines such as interleukin 6 and tumor necrosis factor alpha.[11]

T-cells have an essential role in regulation of the immune responses in the biological systems.[4] The main two types of T-cells are cytotoxic T- cells (CD8 + T- cells) and T-helper cells (CD4 + T-cells). Cytotoxic T-cells kill the pathogens while T-helper cells help other cells originating from the immune system. Natural killer cells are cytotoxic cells that kill the tumor and virus-infected cells.[12] Garlic supplements were noted to cause significant elevation in T-helper and cytotoxic T-cells. Moreover, it stimulates natural killer cells and reduces leptin levels, which is responsible for appetite loss in COVID-19 patients.[13]

Allicin, which is considered as the main biological component of garlic, was proven to have potent antimicrobial effects.[11] Recent reports found that allicin may exhibit activity against tumor growth, cytomegalovirus, and malaria. In addition, allicin was effective for treatment of mice infected with malaria, possibly through affection of macrophages, dendritic cells, and CD4 + T cells.[14] Administration of protein fragments purified from garlic inside the tumors resulted in significant elevation in CD8 + T cells, increased infiltration of CD8 + T cells into the tumor tissues, tumor size reduction, and inhibition of tumor growth. Consequently, garlic and its constituents were considered as effective preventive measures to ameliorate the harmful effects of COVID-19.[15]

Nigella Sativa (Black Cumin Seeds)

Nigella Sativa is a member of the Ranunculaceae family that was used for centuries in the alternative medicine to treat a variety of diseases, including common cold, nasal congestion, bronchial asthma, headaches, warts, and rheumatic diseases.[16,17] Also, it may be used for treatment of respiratory tract infections, diabetes mellitus, hypertension, and gastrointestinal disorders.[16] This wide variety of uses may be attributed to the fact that black seeds possess potent immunomodulatory, antiviral, anti-inflammatory, bronchodilator, antitussive, antipyretic, antioxidant, anticoagulant, and analgesic properties.[18]

The active ingredients of nigella sativa include α-hederin and nigellidine which were clearly proven as possible inhibitors of SARS CoV-2.[19] Several clinical trials had shown the effectiveness of nigella sativa in treating disease states having viral aetiology such as human immunodeficiency virus and hepatitis C virus (HCV) infections.[20] Nigella sativa was reported to significantly decrease the viral load and improve the CD4 count in AIDS patients compared to the control.[18] Also, administration of a combination of natural agents (Nigella sativa, vitamin D, and linolenic acid) in addition to chloroquine to HCV-infected patients was reported to yield HCV-RNA negative in 42% of the participants within 6 months, reaching up to 64.3% of the participants in 18 months of treatment.[20]

COVID-19 pathogenesis was associated with stimulation of the macrophages and neutrophils leading to overproduction of the reactive oxygen species (ROS) with significant inhibition of the antioxidant enzyme systems.[3] This fact supports the promising role of nigella sativa in treatment of COVID-19 infection, owing to the potent antioxidant properties of nigella sativa and its constituents.[21]

Recent reports had proven the effectiveness of nigella sativa as an anti-inflammatory agent, which affects the different stages of the inflammatory cascade and may be effective in reduction of the cytokine storm which is noted in a wide range of hospitalized COVID-19 patients and may even lead to multiple organ failure.[22] Patients with bronchial asthma who were treated with nigella sativa showed significant improvement in the respiratory function tests with significant reduction in the fractional exhaled nitric oxide.[23] These beneficial respiratory effects of nigella sativa may improve the respiratory signs and symptoms related to COVID-19 infection.[22] Also, the adjunctive anti-diabetic, an anti-hypertensive, and antineoplastic effects of nigella sativa may make it an ideal agent for COVID-19 patients with comorbid conditions.[21]

Green Tea

Green tea is a form of tea that was originated in China, then had spread to other countries all over the world.[24,25] Recent reports found that methylxanthines and other extracts of green tea may efficiently contribute to management of the respiratory diseases caused by viral infections.[26] The green tea primarily contains polyphenols, methylxanthines, and other phytochemicals. In the last years, massive experimental studies had proven that methylxanthines may play a key role in prevention and treatment of various diseases.[24]

Recent reports stated that methylxanthines have protective effects on the respiratory system and are beneficial in airway diseases with growing prevalence in children, especially asthma and cough.[27] In addition, theobromine was reported to have positive inotropic effect on the heart and produce vasodilatation of the blood vessels, thereby decreasing the blood pressure.[28] Theophylline, which is one of the constituents of the green tea, has been used for years in treating asthma and is still among the most prescribed medications due to its bronchodilator and anti-inflammatory properties.[29] Several studies had shown that both black and green teas and their isolated components contribute to the preventive and therapeutic measures against HIV infection.[26] Also, the antioxidant properties of green tea could efficiently inactivate the influenza virus and shorten the course of the disease.[30]

Caffeine, composed of methylxanthine, theophylline, theobromine, and the polyphenols, seem to have curative properties for a wide range of bacterial and viral infections, including those affecting the respiratory and cardiovascular system.[31] Accumulating data had proven that methylxanthine and theobromine may have a strong inhibitory effect on viral replication and assembly, thus limiting viral infectivity.[26] Also, it has been found that the crude tea extract has a beneficial effect against bovine coronavirus. So, in the current COVID-19 pandemic, it is essential to carry out careful studies to see whether green tea's biochemical compounds can be used to combat COVID-19 pandemic somehow.[32]

Curcumin

Curcumin is a bright yellow substance produced by Curcuma longa plants that is commonly used as a cosmetics ingredient, herbal supplement, food flavoring, and food coloring agent.[33,34] Recent studies suggested that curcumin should be added to the protocols of treatment of SRAS-CoV-2 infection. These studies relied on the well-documented antioxidant, anti-inflammatory, and anti-infective properties of curcumin.[35]

In SARS-CoV-2, angiotensin-converting enzyme 2 is the key receptor for subunit S1 of viral spike protein. Curcumin was found to interact with and decrease the expression of the S1 subunit of SARS-CoV-2 which prevents the entry of the virus into the body cells.[36] Moreover, curcumin was found to block the interaction between ACE2 and the viral spike protein which augments the efficacy of curcumin for treatment of COVID-19 infection.[35] Also, curcumin was found to inhibit the basigin which is an alternative route for the entry of SRAS-CoV-2 to the target cells.[37] In addition, curcumin can directly and irreversibly inhibit aminopeptidase N/CD13 receptors which play a role in viral invasion of the infected cells.[38] Therefore, curcumin shows the ability to target three different receptors of SARS-CoV-2 which increases the possibility of prevention of the cellular entry of the virus.[35]

RNA-dependent RNA polymerases and proteases are two groups of enzymes involved in replication of SARS-CoV-2.[39] Curcumin was able to interact with these enzymes, thus hindering viral replication.[40] Also, curcumin was found to decrease the expression of angiotensin AT1 receptor leading to significant reduction in the possibility of development of acute respiratory distress syndrome, a major manifestation of COVID-19 infection.[41]

Elevations in cytokine levels, also called cytokine storm, had been designated as the principal cause of deterioration and multiple organ failure frequently encountered in end-stage COVID-19 patients.[35] Curcumin was proven to suppress influenza-A virus-induced production of the proinflammatory cytokines in the host cells.[42] This supports the hypothesis that curcumin has the ability to delay the onset of cytokine storm. Also, the ability of curcumin to induce fibrinolysis and anticoagulation may help to prevent the development of cardiovascular complications frequently encountered in cases with COVID-19 infection.[40] Moreover, curcumin was found to alleviate renal fibrosis that may occur in advanced cases of COVID-19 infection through affection of the Akt signaling pathway.[43]

The Primary Care, COVID-19, and The Natural Agents

There is no doubt that the primary care centers and the family physicians have a key role in COVID-19 pandemic.[44] The primary care centers took the major responsibility for early detection of cases of COVID-19 infection and participated efficiently in provision of the primary care services that largely contributed to reduction of the morbidity and mortality rates of this pandemic in various areas of the world.[45] In addition, the family physicians participated efficiently in health education of the patients and their caregivers regarding the possible preventive measures of COVID-19 infection and the possible ways of dealing with active cases of the disease.[46] Moreover, they participated efficiently in application of the instructions of the healthcare authorities that significantly reduced the rate of transmission of this disease.[44] The primary care centers may contribute largely to application of the natural compounds and dietary supplements as adjuvant agents for prevention and treatment of COVID-19 infection, possibly through health education programs.[47]

Conclusion

Naturally occurring phytochemicals may provide a valuable resource of chemical compounds that have potent antiviral properties towards COVID-19. The most used natural agents for amelioration of the manifestations of COVID-19 include garlic, nigella sativa, green tea, and curcumin. *In vitro* and *in vivo* studies are needed to determine the potential safety and the effective therapeutic levels for each agent before clinical application of these compounds in humans. The primary care physicians may have a key role in early detection of cases with COVID-19 infection and the potential application of the natural agents as adjuvant therapy in these cases.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

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