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Herbal medicines in the treatment of coronavirus disease 2019 (COVID-19)

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ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by a novel coronavirus, started in livestock within the markets of Wuhan, China and was consequently spread around the world. The virus has been rapidly spread worldwide due to the outbreak. COVID-19 is the third serious coronavirus outbreak in less than 20 years after Severe Acute Respiratory Syndrome (SARS) in 2003 and Middle East Respiratory Syndrome (MERS) in 2012. The novel virus has a nucleotide identity closer to that of the SARS coronavirus than that of the MERS coronavirus. Since there is still no vaccine, the main ways to improve personal immunity against this disease are prophylactic care and self-resistance including an increased personal hygiene, a healthy lifestyle, an adequate nutritional intake, a sufficient rest, and wearing medical masks and increasing time spent in well ventilated areas. There is a need for novel antivirals that are highly efficient and economical for the management and control of viral infections when vaccines and standard therapies are absent. Herbal medicines and purified natural products have the potential to offer some measure of resistance as the development of novel antiviral drugs continues. In this review, we evaluated 41 articles related to herbal products which seemed to be effective in the prevention or treatment of COVID-19.

Implication for health policy/practice/research/medical education:

Some herbal products seemed to be effective in the prevention or treatment of COVID-19.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by a novel coronavirus, started in livestock within the markets of Wuhan, China and was consequently spread around the world in December 2019. It can be transmitted from one person to another through sneezing or physical contact. COVID-19 mainly affects the respiratory system with symptoms such as cough, fever and shortness of breath. In most cases, the disease is mild; however, it may lead to respiratory failure in some patients, particularly in the elderly and those with co-morbidities, such as diabetes or obesity (3). When it progresses to respiratory failure

or acute respiratory distress syndrome (ARDS), it often comes with multi-organ dysfunction and a disturbed immune system; in addition, it often comes with lower levels of lymphocytes, especially natural killer (NK) cells and extremely high inflammatory parameters, including C-reactive protein (CRP) and pro-inflammatory cytokines (IL-6, TNF α and IL-8) (1-3).

COVID-19 is the third serious coronavirus outbreak in less than 20 years. The first two were Severe Acute Respiratory Syndrome (SARS) in 2003 and Middle East Respiratory Syndrome (MERS) in 2012. Nucleotide identity of COVID-19 to the SARS coronavirus is almost

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80% as compared to 52% with MERS coronavirus, that is COVID-19 is much closer in construct to the SARS coronavirus than to MERS coronavirus. Angiotensin-converting enzyme 2 (ACE2) acts as a functional receptor on the surface of cells for the entry of SARS coronavirus and COVID-19 into the body (3). At present, it is important to control the source of infection, to cut off the transmission route, and to administer effective drugs that can control the progress of the disease proactively. Currently, the drug therapy for COVID-19 is mainly comprised of four antiviral drugs, traditional medicines, immune-enhancement therapy and viral-specific plasma globulin.

Antivirals, respiratory supportive therapies and sometimes anti-inflammatory drugs have been the main treatments of severe cases of COVID-19. Promising ongoing clinical trials for COVID-19 include interferon, lopinavir/ritonavir, ribavirin, Arbidol, remdesivir, tocilizumab, glucocorticoids, IL-6 antagonist, JAK inhibitors and chloroquine/hydroxychloroquine, pseudoephedrine, rographolide, abacavir, oseltamivir and thalidomide, though none of them have shown to be universally effective (1-6). Hence, there is a vital need to discover the novel antivirals that are highly efficient and economical for the control and management of viral infections when vaccines and standard therapies are not available. Herbal medicines and purified natural products seem to play role in developing the new antiviral drugs. In this review, we evaluated herbal products that have been effective in preventing or treating COVID-19.

Materials and Methods

To collect data, a variety of sources were scrutinized such as, PubMed, Scopus, Embase, Google Scholar and Web of Science. To this end, the following keywords and their equivalents were searched through the aforementioned sources: COVID-19, herbal medicines, flavonoids, coronavirus disease 2019 and angiotensin-converting enzyme 2.

Treatment of COVID 19 based on antiviral herbal medicine treatment

Herbal medicine is purely originated from nature, so it tends to induce fewer side effects (6). Many substances derived from plants, such as flavonoids, alkaloids, and terpenoids, have biological effects *in vitro* and *in vivo*. Along with the biological activities of the natural products derived from plants, the anti-inflammatory, antiviral, antiplatelet, antitumor, anti-allergic and antioxidant activities should also be considered. However, most of the reports have assessed the effects of these compounds in experimental models, and clinical trials are rare on this subject.

To shed some lights on this issue, there is an essential need to investigate the influence of herbal medicines on coronavirus.; In addition, the magnitude of this essence is

highlighted because of rapid expansion and epidemics of COVID-19 infection, increased public concern about the transmission of the disease, lack of knowledge concerning the definitive treatment and the need for safe treatment at home. Although the review of some research articles such as one by Santana et al emphasizes the beneficial and fruitful effects of various natural products on pulmonary diseases in both experimental cases or human cases, there is not any unanimous consensus over this issue (7).

Prevention

Currently, the only way to prevent the spread of COVID-19 is infection control through hand washing, cleaning, disinfecting, sterilizing, and wearing masks. Therefore, prophylactic care or self-resistance is the main way to maintain personal immunity to the disease. Patients with underlying diseases such as hypertension, diabetes, heart disease and cancer are at higher risk due to respiratory system problems and their weak immune system responses because of their specific drug consumptions. Thus, self-resistance in these patients who constitute the most vulnerable population is of utmost importance.

Prevention of infectious diseases by traditional medicine has been recorded for many decades in Chinese history. Similarly, previous studies on the prevention of SARS have been conducted by traditional Chinese medicine. Five of the most commonly used plants in traditional medicines include; astragalus, liquorice, fangfeng, baizhu and honeysuckle. In addition, other studies have shown that vitamin C, vitamin D and vitamin E supplementation, may increase resistance against coronavirus (8). Moreover, these traditional medicines are cost-effective approaches to prevent the spread of COVID 19.

Targeting ACE2 has been considered to be an alternative for preventing and inhibiting COVID-19 infection (3). Inhibiting the ACE2 receptor through using Chinese herbal medicine due to the low toxicity and high availability could be to be an alternative for treating COVID-19 (8). Molecular docking was used by Chen et al to find natural compounds for targeting the ACE2 receptor. They proposed five components with anti-virus activity including scutellarin, baicalin, hesperetin, nicotianamine and glycyrrhizin that could prevent COVID- 19 infection (9).

Among the large number of Chinese herbal components, Emodin (6-methyl-1,3,8-trihydroxyanthraquinone) was identified as an effective ingredient of polygonaceae to prevent the interaction of the SARS coronavirus protein with the ACE2 receptor and to reduce the severity of the infection. It is suggested that viral ion channels may be a good target for the development of antiviral agents. However, the pathway for the reach of the virus into its target cells is not completely blocked, and the virus may enter through other receptors, , as a result, further investigations are needed to be conducted on other cellular entry modes (10,11).

An alternative approach to the prevention of COVID-19 in high-risk populations may be based on previous evidence about viral treatments which has been proposed by traditional Chinese medicine. *Huangdi's Internal Classic*, an ancient Chinese book about medicine, reported about preventive effects of herbal medicine on infectious disease epidemics. In their book, Huangdi and his physician talk about the balancing of wind, heat, and dampness, which are the main principles of using Chinese medicine (12). Herbs with these historical origins used for the prevention of COVID-19 are *Rhizoma Atractylodis Macrocephalae* (Baizhu), *Radix glycyrrhizae* (Gancao), *Radix saphoshnikoviae* (Fang Feng), *Radix astragali* (Huangqi), *Lonicerae Japonicae Flos* (Jinyinhua), and *Fructus Forsythia* (Lianqiao) (13).

Lau et al investigated a herbal formula (Yupingfeng Powder plus Sangju Decoction) for prevention of SARS with 16437 hospital care workers, 1063 of whom took the herbal formula (herbal group) while 15374 of whom did not (non-herbal group). None of the participants in the herbal group developed SARS disease, while 0.4% of the participants in the non-herbal group developed SARS (14). In two hospitals in Beijing, China, Xu et al (15) and Zhang et al (16) conducted studies in which a formula of Yupingfeng powder mixed with some heat-clearing and detoxifying herbs. In one hospital, 163 subjects used the powder for 6 days, and in the other hospital, 3561 subjects took it for 12- 25 days. The outcomes of these two studies revealed that none of these subjects developed SARS disease.

Treatment of cough, breathless and asthma

Traditional medicine often recommends a combination of three different strategies including lifestyle modification, herbal remedies and manual procedures for the treatment of diseases. The guidelines recommend herbal medicines alone or often in a combination. For example, a combination of *Plantago major* seed with its antioxidant and anti-inflammatory has effect on lungs, as well as, a combination of Almond gum with its anti-ulcerogenic has influence on the gastrointestinal epithelium, both of which were well-tolerated and deemed potentially useful for patients of 28 participants with refractory asthma in trial (17).

A murine model study assessed the effects of the Chinese herbal formula, PM014 (contains *Schizandra chinensis*, *Stemona sessilifolia*, *Asparagus cochinchinensis*, *Rehmannia glutinosa*, *Scutellaria baicalensis*, *Prunus armeniaca*, and *Paeonia suffruticosa*), on lipopolysaccharide induced, chronic obstructive pulmonary disease. It was confirmed that PM014 improved the lung inflammation markers and decreased accumulation of immune cells and levels of TNF- α and IL-6 in bronchoalveolar lavage fluid (18).

A study on 76 discharged patients in China, showed that the average time of hospitalization decreased in 59 cases after treatment with Qingfei Paidu decoction. In addition,

the thoracic computed tomography scan (CAT scan) indicated the improvement of inflammatory lesions by Qingfei Paidu decoction (19). Another study revealed the treatment efficacy of Jinxin Oral Liquid (JOL), modified from Ma Xing Shi Gan decoction from traditional Chinese medicines for pneumonia and asthma (20).

Moreover, *Nigella sativa* was also shown to possess antiviral activity against hepatitis-C infection in patients with type-2 diabetes. In a single-arm pilot study conducted on type-2 diabetic patients, the administration of *Nigella sativa*, instead of interferon/ribavirin therapy, significantly reduced the viral load and improved oxidative stress and glycemic control (21). Another study showed the possible effects of *Nigella sativa* on immune-response and pathogenesis of influenza virus subtype H9N2 (H9N2) on 130 non-vaccinated mixed-sex turkey poult. Supplementation of *Nigella sativa* was found to reduce the pathogenicity of influenza viruses and increased immune responses (22). Similarly, Sinupret[®], another naturopathic mucolytic, has a wide range of antiviral activity in vitro against respiratory viruses (23), and Lamiaceae is one of the most important and well-known herbal families because of numerous biological and medicinal effects that could help prevent and treat some viral diseases (24).

Anti-SARS herbal compounds

Patients with SARS treated with traditional Chinese medicines have been proven to take benefit from shorter hospitalizations, fewer steroid-related side effects, and improvement of symptoms. In this field, a study by Zhang et al provided methods to identify several Chinese medicinal plants categorized as antiviral/pneumonia-effective that might directly prevent the COVID-19 infection (25). They highlighted the prospect of computer-aided and structure-based traditional Chinese medicinal drugs for the novel coronavirus pneumonia. These methods assisted in the combination and categorization of compounds into a subclass, in a short amount of time with finite resources, for the future clinical use of traditional Chinese medicinal formulas (26).

Using the molecular docking modelling, Khaerunnisa et al identified potential bioactive compounds against COVID-19 via blocking protease in some medicinal plants. The study showed nelfinavir, lopinavir, kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, and epicatechin-gallate acted as the best potential for COVID-19 main protease inhibitors (27).

It has also been suggested that many Indian medicinal plants with antiviral, anti-inflammatory and antioxidant properties could be favorable for the treatment of COVID 19. However, standard clinical trials are needed to prove the efficacy of these herbs to manage the immune system. *Glycyrrhiza glabra*, *Allium sativum*, *Clerodendrum inerme* Gaertn, and *Strobilanthes cusia* seem to be alternative candidates against COVID-19 by targeting the viral

replication of SARS coronavirus, inactivating the viral ribosome, blocking the viral RNA genome synthesis and inducing protease activity (28). Keyaerts et al evaluated a special collection of 33 plant lectins with different specificities. Herbal lectins presented a selective and potent anti-coronavirus activity by interfering in the viral replication cycle (29).

In their review, Lin et al found that several natural and herbal medicines had antiviral effects on COVID-19. These herbs included: *Artemisia annua*, *Lycoris radiata*, *Pyrrosia lingua*, and *Lindera aggregata*, *Isatis indigotica*, *Torreya nucifera*, myricetin, scutellarin and *Houttuynia cordata* (30). Another study showed that viral loads and replication of SARS coronavirus were decreased after treatment with *Anthemis hyalina*, *Nigella sativa* and peels of *Citrus sinensis* extracts. *Anthemis hyalina* extract is the best candidate and could be used in highly effective drugs against coronavirus and other viruses. In addition, a mixture of *Nigella sativa* and honey has the ability to improve respiratory tract infections (31).

The development of anti-SARS coronavirus agents is essential to combat the pandemic of COVID-19. Using a cell-based assay on Vero E6 cells measuring SARS coronavirus induced cytopathogenic effect in vitro, Wen et al tested over 200 Chinese medicinal extracts. Six herbal extracts, one from *Gentianae radix*, *Dioscoreae rhizoma*, *Cassiae semen* and *Loranthi ramus* and two from *Rhizoma Cibotii*, were found to be potent inhibitors of SARS-coronavirus (32). Several important herbal resources against SARS coronavirus are summarized in Table 1.

Herbals with beneficial effects on inflammatory markers like *Allium sativum* and *Ocimum basilicum* may be effective in the treatment of inflammatory phase of COVID-19 (42).

Conclusion

Currently, there are no specific vaccines or antiviral

treatments for COVID-19 and no vaccine is expected to be ready for months. A discovery of novel antivirals which are highly efficient and economical for the supervision and control of viral infections are absolutely essential in the absence of vaccines and standard therapies. Therefore prophylactic care and self-resistance are the main ways to preserve personal protection and immunity. Furthermore, the development of anti-SARS coronavirus herbal agents seems to be inevitable in protecting against the COVID-19 pandemic disease because of the structural similarity of these two viruses.

Authors' contribution

AA and MA prepared the primary draft. MK, HRH, RT and AT completed and extended the manuscript. AB and ZM edited the paper. AA finalized the paper. All authors read and signed the final manuscript.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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Table 1. Some important herbal resource against SARS coronavirus

Plant	Component	Reference
Cinnamomi Cortex	Procyanidins and butanol	(33)
<i>Isatis indigotica</i> root extrac	Two phenolic compounds aloe emodin and hesperetin	(34)
Tylophorine compounds	Naturally and synthetic phenanthroindolizidines and phenanthroquinolizidines	(35)
<i>Houttuynia cordata</i> Thunb. (Saururaceae) (HC)		(36)
<i>Echinacea</i> and <i>Lycoris radiata</i>		(37)
<i>Indometachin</i>		(38)
<i>Toona sinensis</i> Roem,		(39)
<i>A. annua</i> , <i>L. radiata</i> , <i>P. lingua</i> , and <i>L. aggregata</i>	lycorine	(40)
<i>Cimicifuga rhizoma</i> , <i>Meliae cortex</i> , <i>Coptidis rhizoma</i> , and <i>Phellodendron cortex</i>		(41)
Six herbal extracts, one each from <i>Gentianae Radix</i> , <i>Dioscoreae Rhizoma</i> , <i>Cassiae Semen</i> and <i>Loranthi Ramus</i> and two from <i>Rhizoma Cibotii</i>		(32)
Viral ion channels of emodin		(10)
<i>Anthemis hyalina</i> (Ah), <i>Nigella sativa</i> (Ns) and peels of <i>Citrus sinensis</i> (Cs) extracts		(31)

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