Potential Health Survey of Traditional Spices & Herbs in Prevention and Treatment of COVID-19: A Review

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Abstract
The coronavirus (COVID-19) is a global public health pandemic disease emerged from the novel strain of the coronavirus 2 (SARS-CoV-2) that caused severe acute respiratory syndrome. It is the most significant respiratory illness that has affected the world since World War II. Currently, there is no globally approved drug for the treatment of pandemic COVID-19 except for some recently approved vaccines. Instead, various non-specific treatment options are being utilized by different countries. While some of these are effective, there is a lack of well-documented studies on the impact of traditional medicines on the management of SARS-CoV-2 in vitro and in silico. For thousands of years, traditional healers have been using various herbs and spices products and dietary plants to treat various diseases. This review aims to provide information on the use of traditional spices & herbs in COVID-19 protection and treatment and present the main characteristics of these products and their potential antiviral actions. Various databases were searched for articles related to the use of various herbs for the treatment of viral infections. Many of these studies show that various plant compounds can be utilized for the treatment of viral infections. This study aims to summarize the common used of herbal products and dietary supplements with potent bioactive compounds in treatment or prevent of COVID-19.
Keywords: Herbal plants, natural products, infection, COVID-19, Phytopharmaceuticals, Traditional Chinese medicine, survey

1. Introduction

Coronaviruses are single-stranded positive-sense RNA viruses that spread between humans and animals [1]. The first severe acquired respiratory syndrome coronavirus (SARS-CoV) was observed in 2002 In China spread worldwide across Canada and Vietnam. The World Health Organization (WHO) designated the coronavirus infection of March 2019 (COVID-19) to be a worldwide pandemic outbreak caused by the SARS-CoV-2 virus. It was first detected in China's Wuhan city as greatest global health crisis caused more than 6.000.000 deaths in the world according to the Institute for Health Metrics and Evaluation (IHME) analysis [2].

Pathogenesis and immune response

SARS-CoV-2 is a novel coronavirus strain of spherical enveloped beta-coronavirus and nonsegmented positive-sense eRNA virus. It has four structural proteins, which include a spike glycoprotein, a membrane glycoprotin (Figure 1), CoV-2 enters the host through a nasopharyngeal route and infects lung cells by targeting the angiotensin-converting enzyme 2 (ACE2) receptor protein on the outer surface. The initial infection of a potential host cell involves the interaction of the SARS-CoV-2 spike proteins with the cell. The S1 and S2 subunites of the virus are designed to specifically bind to the host cell's angiotensin-Converting enzyme .The SARS-CoV-2 virus can enter the cytoplasm through the activation of the functional S2 protein. It then produces viral RNA to be expressed in the host cell [3].

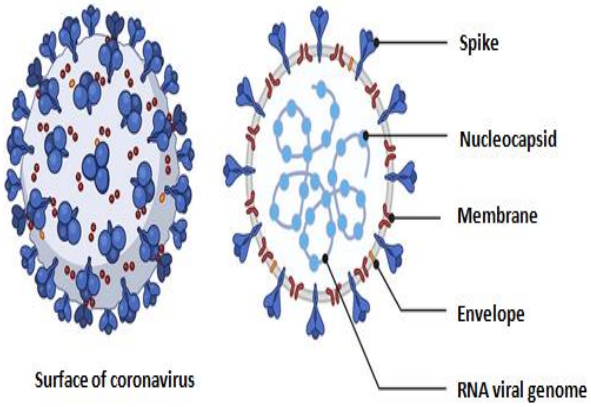

Figure 1: Structure of SARS-CoV-2 virus

The coronavirus goes through a cyclic process known as nucleogenesis, which involves hydrolyzing the viral polyproteins to generate functional proteins. After infection, the virus can then infect other cells.The pattern recognition region on the membrane of the host cell triggers the activation of the innate immune system. During an infection, the

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coronavirus can trigger the production of IL-6 and IL-1, which can affect the alveoli and bronchi. The uncontrolled inflammatory response caused by COVID-19 can lead to the development of severe respiratory failure. It is also known to affect other organs such as the kidney and the heart [4].

After the respiratory system has been infected by COVID-19, the virus disperses to other organs and tissues. This process triggers a variety of changes in the organs' pathways and symptoms. Understanding the pathogenesis and the various mechanisms involved in the development of COVID-19 can help develop effective treatments and protective food [3].

While most countries affected by the COVID-19 pandemic rely on orthodox medicine, some regions, such as China, have adequate evidence of successful management through the use of traditional Chinese medicines. Literature has revealed that China and other Asian countries follow a traditional medicine system that is heavily integrated with Western medicine. This was the reason why the SARS-CoV epidemic was successfully contained in Guangdong in 2002 [5].

During the time of the pandemic, many Chinese herbal recipes and formulations were used as adjuvant for western medicines. Some of these include the San Ren Tang, the Qing Ying Tang, and the Ma Xing Shi Gan Tang. Scutellaria baicalensis and Brassicaceae were among the plants used as adjuvant for the treatment of COVID-19. Following the successful use of these medicines, the outbreak of SARS-CoV2 in China was immediately approved as an integral part of the traditional Chinese-Western medicines [6].

In China, traditional Chinese medicines were also used as adjuvant for western drugs. The use of phytomedicines, which are also known as herbal medicines, is well-established in primary healthcare. The extensive use of traditional medicines, which are mainly plant-derived, has been associated with the country's socio-cultural endowments. This prompted the WHO to step up its efforts to integrate traditional and alternative medicines into the health system of countries.

Due to the outbreak of the COVID-19 pandemic and the lack of authorized medicines, the use of phytomedicines has increased in countries. According to the CDC, the continent was the last to be hit by the SARS-CoV pandemic. It had a mortality rate of less than 2% until July 2020 [7].Despite the continent's vulnerability, only 5% of the global cases of COVID-19 were reported where malaria is a common illness, many traditional medicines are used as home remedies. They are also being used as co-administers with orthodox drugs.

Diagnosis and preventive measures

According to the official report of US's, an increase in SARSCoV- 2 cases stated that the need of in-vitro analysis of ailments like SARSCoV- 2. And the infected patients suffering from vague symptoms that cannot be diagnosed The COVID-19 infectious patients show vague symptoms that cannot be utilized, around 44% and 89% of 1099 Chinese patients had a fever when they admitted to hospital or already being hospitalized respectively [8].. Additionally, it was noted that nearly 19% of patients experienced dyspnea, 34% of cases produced sputum, 38% of patients showed signs of exhaustion, and almost 68% of cases had a cough. Nucleic acid analysis and computed tomography (and nucleic acid analysis are appropriate employed methods for detection and precise diagnosis of SARSCoV- 2 virus infection. The molecular methods based on detection the pathogen's genetic constitution alteration before and after causing disease [9].

The most practical method of preventing infectious diseases is the availability of potential vaccines that can effectively combat bacteria that infect humans. This strategy, in particular, primarily focuses on the production of an adaptive immune response by limitation the spread of several human life-threatening viruses. Several novel preventive effective vaccines, like mRNA BNT162b2, mRNA-1273, ad26.COV2.5, AZD1222, Gram-COVID-Vac, Corona Vac, WIBP/BBIBp-CorV COVID-19 platforms of anti-SARS-CoV-2 vaccines have been approved for clinical use.

Alshammari et al. [10] investigated the role of dietary Supplements (DS) like vitamins/ multivitamins during COVID-19 pandemic disease, the participants in this study reported that C plays a vital role in cold preventing cold. El Alami et al., (2020) the authors were identified and using medicinal plants species and used during COVID-19 pandemic in Moracco, [11]

Other studies on using 23 herbal and medicinal plant species were belonging to 11 botanical families for preventing the COVID-19 pandemic disease; the most important families were that of the Zingiberaceae, Cupressaceae and Lamiaceae. While the used plants were Allium sativum, Pimpinella anisum, Thymus satureioide, Eucalyptus globulus, Curcuma xanthorrhiza, cepa Foeniculum Olea europaea, Zingiber officinale, Allium vulgare, Thymus maroccanus, , Phoenix dactylifera, Rosmarinus officinalis, and Mentha pulegium [12]. A survey study reported that over one-fifth of (n=5258) from Saudi respondents utilized by herbal products in during the COVID-19 pandemic prevention and relieving disease symptoms as, breathing difficulties, loss of smell and fatigue included recitation of Quran or meditation; acupuncture, massage, Hijama (cupping therapy) and specific nutrition or herbs like garlic, olives, black cumin seeds, chamomile, honey, figs, peaches and dates [13, 14]

2. Therapeutic Strategies

Drug Repurposing

Since COVID-19 spread from Wuhan, China, the demand for vaccines and medications has increased due to the unexpectedly rapid evolution of new virus varieties. During the early stages of the COVID-19 pandemic, our knowledge of COVID-19 and its potential treatment options was incredibly

restricted. This increased the necessity of using novel medicines and possibly drug repurposing to treat the new viral illness. After that, the researchers' collectively intense efforts achieved significant progress that led to a better knowledge of COVID-19 and its control. This has accelerated the development of revolutionary vaccinations and creative medicinal treatments in a remarkable way [15]. Several drug groups were investigated against COVID-19 like Chloroquine, remdesivir, lopinavir, ritonavir, and others fall within this category. These are well-known medications used to treat SARS-CoV, MERS-CoV, and other [16].

Phytopharmaceuticals

Chinese medicine has been known to reduce the severity and incidence of various chronic diseases, such as respiratory and kidney disease. It can also help decrease the duration of the disease and improve the quality of life for those suffering from it. In addition, it can help treat COVID-19, which is a type of bacterial skin disease. COVID-19 infection can be categorized into three main categories: wet, heat, and congestion in the respiratory system. According to Chinese medicine, the first affected organ is the lung. The wet factor can lead to various health conditions, such as damage to the body's organs and prolong the disease's severity [17].

The concept of hot, dry, and rising turbidness refers to the factors that can trigger the development of a viral condition. Another contributing factor is congestion, which can affect the blood circulation and cause pain. One of the most effective ways to prevent respiratory disease is by using a Chinese medicine known as Yupingfeng San [3].

In China, there are three types of plants that are commonly used as herbal medicines: astragalus, atractylodes, and Fangfeng. These three plants can help improve the function of the lungs and the digestion. Studies have also shown that the use of Yupingfeng San can help regulate the immune system.In addition to being used by the medical establishments; home preparations can also be used to treat COVID-19 in Ethiopia. Some of the ingredients used in these preparations include garlic, ginger, chili, lemon, and hot water [18].

Individuals infected with mild COVID-19 disease usually experience a fever, sweating, a sore throat, a red tongue tip, and a floating pulse. Based on the symptoms, it is considered less severe than a severe case. Traditional Chinese medicine also suggests treating the lung using two types of prescriptions. One of these is "clearing lung heat and dampness.

Traditional Chinese medicines can help lower the severity of COVID-19's symptoms and overall mortality. They can also relieve chronic lung disease and improve the efficacy of various respiratory conditions. Like in India traditional Chinese medicines are also used to treat COVID-19. Symptoms of the infection include fever, body aches, and respiratory distress. The term “wet” refers to the factor that has high or sticky turbidness that can damage the body's ability to function. The other factors that can contribute to the virus' severity are hot and dry [19].

Because of the nature of the virus and the properties of the plants used, China has a unique approach to treating respiratory conditions. It uses a combination of traditional Chinese herbs known as Yupingfeng San. Studies have shown that certain herbs such as the Sichuan pepper can help boost the body's immune function. Some of these include the use of various medicinal products such as hot water and ginger [3].

The treatment of COVID-19 mild infections is provided by using a combination of traditional Chinese medicines. Most people with COVID-19 experience a variety of symptoms such as fever, headaches, sweating, and coughing. They can also feel irritable and sluggish [3]. Traditional Chinese medicine practitioners usually use two different types of prescriptions for treating COVID-19.In China, both the Yinqiao San and the Sangju yin are commonly used as part of a clinical management approach. These two herbs help clear the respiratory tract and improve the patient's breathing. A study revealed that incorporating various herbs such as black seed, ginger, and vitamin C can help improve the effectiveness of COVID-19's treatment [20].

If the infection can't be controlled, then it should be considered a serious infection. Most of the time, patients with this illness exhibit the following symptoms: fever, dry cough, abdominal pain, nausea, and vomiting. Some of the herbs commonly used to treat COVID-19 are known to boost the body's immune system.

In China, two types of herbal medicines known as Yinqiao san and Sangju yin are commonly used for clinical management. The main purpose of these two medicines is to relieve cough and clear lung heat. They are used for treating patients with a high fever and a severe cough.A study conducted on various herbal supplements revealed that certain components, such as ginger, orange, honey, black seed, and vitamin C, can help improve the management of COVID-19. If the infection can't be controlled, multiple organ failure, respiratory failure, and death can occur during the early stages of COVID-19 management. Most of the time, serious infection is considered when these conditions worsen. Some of the other symptoms of COVID-19 include high-grade fever, dry cough, fatigue, sweating, nausea, bloating, and red or dark-colored tongue [12, 21].

Some of the other natural therapies that can help improve the management of COVID-19 include the use of various plant components, such as G. glabra, Thymus vulgaris, Althea officinalis, and Allium sativum. Currently, there is only one approved medication for treating COVID-19. Antibiotics can't cure COVID-19. Researchers are currently testing various treatments [22].

The Food and Drug Administration has approved remedesivir for treating COVID-19 in adults and children who are older than 12 years old and are in

the hospital. It can also be given to people with a higher risk of serious illness, such as those who require supplemental oxygen. The FDA has approved a drug known as Paxlovid, which includes the antiviral medication nirmatrelvir and the drug ritonavir. These two drugs are used to treat people with mild to moderate COVID-19. They can be taken by mouth as pills [23].

Another drug known as molnupiravir has been approved by the FDA to treat COVID-19 in adults who are at high risk of serious illness. It can be taken as a pill. The agency has also approved the drug baricitinib for treating COVID-19 in patients with rheumatoid arthritis. It works by reducing inflammation and bringing about antiviral activity. Baricitinib can be used in people who are in the hospital and require supplemental oxygen.

Currently, there are various types of monoclonal antibodies that can be used to treat COVID-19. Some of these are known as sotrovimab and bebtelovimab. However, these drugs aren't effective at treating the disease caused by the omicron variant. These drugs are commonly used to treat COVID-19 in people who are at high risk of developing serious illness. They can be given intravenously, which is done in an outpatient setting. The most effective way to use these drugs is to give them to patients' right after their COVID-19 symptoms start [24].

The NIH has also suggested that patients with severe COVID-19 who require mechanical ventilation or supplemental oxygen should be given dexamethasone. Other steroids, such as hydrocortisone, methylprednisolone, hydrocortisone, or prednisone, can also be given if dexamethasone is unavailable. In some cases, the drugs remedesivir, tocilizumab, or baricitinib can be given to patients in the hospital who require supplemental oxygen or mechanical ventilation [25].

The FDA has also approved the use of convalescent plasma therapy, which is blood that's been donated by people who have recovered from the illness. This type of therapy can be used to treat patients who are already sick with COVID-19 and have weak immune systems. Although people with COVID-19 may have mild symptoms, they can still be treated with supportive care. This type of care aims to help them manage their condition. Nonsteroidal anti-inflammatory drugs, such as ibuprofen and naproxen, are not considered to be harmful for people with COVID-19 [26].

Some of the herbs used to treat COVID-19

Although single plant species have many therapeutic properties, studies on the pharmacologic value of plants are still challenging due to the wide variety of biochemicals present in them. On the other hand, some of the herbs used for COVID-19 treatment may also have anti-inflammatory properties. This could explain the increasing number of inflammatory indicators in the body. Table 1 summarizes the common used herbal plant in treatment of COVID-19 [27].

Azadirachta indica

The main goal of treating COVID-19 is to reduce the fever. In addition, the leaves of neem (*Azadirachta indica*) (Figure2) are known to have anti-inflammatory properties. [28] A study revealed that their various constituents, such as flavonoids and phenolics, can counteract the effects of different viruses. Studies related to SARS-CoV-2 have revealed that certain compounds found in the neem can bind to the virus' envelope and its various glycoproteins. These properties could help boost the body's immune response.

Table 1: The common used herbal plant in COVID-19 treatment

Scientific name	Family name	Constituents	Mechanism/outcome
Malva sylvestrisL.	Malvaceae	Polysaccharides	Tetrastigma hemsleyanum Diels & Gilg/Vitaceae
			Tetrastigma hemsleyanum Diels & Gilg/Vitaceae
			Emollient/potent antitussive activity
Aloe barbadensis Mill.	Asphodelaceae	(polysaccharide)	Emollient/potent antitussive activity
Salvia officinalisL.	Lamiaceae	Polysaccharide	Emollient/potent antitussive activity
Cynara scolymusL.	Compositae	Cynaroside	ACE inhibition/IC50 = 49.7%
Erigeron abajoensis Cronquist	Compositae	Flavone (Scutellari	ACE inhibition
Hibiscus sabdariffaL.	Malvaceae	Anthocyanins	ACE inhibition/decrease serum angiotensin-converting enzyme, decrease plasma aldosterone
Hancornia speciosa Gomes	Apocynaceae	Chlorogenic acid	ACE inhibition
Isatis indigotica	Brassicaceae	Phenol (indigo, sinigrin, aloe emodin, hesperetin, Sinigrin), 2,2-Di (3-indolyl)- 3-indolone, Phaitanthrin D	SARS-3CLpro inhibition/IC50 = 53.8 ± 4.2 μg/mL
Alnus japonica (Thunb.) Steud.	Betulaceae	Diarylheptanoid (Hirsutenone)	PLpro inhibition/IC50 = 4.1 μM
Paulownia tomentosa Steud.	Paulowniaceae	Geranylated flavonoids	PLpro inhibition/IC50 = 5.0–14.4 μM
Torreya Nucifera (L.) Siebold & Zucc.	Taxaceae	Biflavone [Amentoflavone (9)], Authentic flavones (Apigenin)	SARS-3CLpro inhibition/62% at 100 μg/mL

In mice, treating them with neem seed extract produced a higher level of IFN- post-vaccination. This effect was observed in animal studies. According to various studies, the traditional use of neem leaves for medicinal purposes depends on the consumption of the leaves [29]. A clinical trial should be carried out to ensure the safety of the leaves and the formulation used. Although neem leaves have been used for a long time, their toxicity is not well-documented. They have also been known to cause renal injury and acidosis in the body [25].

Figure 2: Neem extraction that used in COVID-19 treatment

Nigella Sativa

We evaluated the various properties of black cumin (Nigella Sativa) seed extract (Figure3) and concluded that it has anti-viral properties. Its ethanolic extract was able to reduce the viral load and improve liver function parameters in hepatitis C patients. In a study [30], black cumin seed extract was shown to reduce cytomegalovirus' viral load by increasing the CD3 and CD4 counts. It also boosted the release of interferon-gamma. Studies on mice revealed that the ethanolic extract of the Nigella Sativa seeds prevented the replication of the MHVA59 virus by down regulating the expression of certain genes.
It has been used traditionally for its anti-inflammatory and antioxidant properties. Its positive effects on the respiratory system have been documented in various review papers. Follow-up studies indicated that the consumption of 3 g/day of N. Sativa seeds did not have significant effects on the liver and kidney functions. However, it should be noted that high doses of over 2 g/kg can cause liver enzymes to malfunction [31].

Figure 3: Black cumin extraction that is used in treatment of COVID-1

Eurycoma longifolia

Eurycoma longifolia (Figure 4) is a well-known plant used for improving men's health. Although it doesn't have direct antiviral effects, its standardized extract can induce a level of CD4+ cell proliferation in older individuals with low molecular mutagenicity Preclinical evidence of the plant's anti-inflammatory properties is already available. The compounds extracted from this plant have potent NF-B inhibitory effects.

Various phenolic components were obtained from the roots of the plant to decrease the expression of the IL-6 in the gut. The safety profile of the extract has been established based on the Organization for Economic Cooperation and Development's guidelines [32].Studies on the safety and anti-inflammatory effects of *Eurycoma longifolia* have been successfully carried out [33]. Its use as a potential treatment for COVID-19 is also supported by the various studies.

Figure 4: Eurycoma longifolia extraction that is used in treatment of COVID-19

Allium sativum

Traditionally, garlic (*Allium sativum*) and onion (*Allium cepa*) have been used as home remedies for different diseases. The use of these two vegetables has been acknowledged as a way to cure various conditions. According to researchers, onions can be used as a potential treatment for COVID-19 patients due to its numerous anti-viral and immunological properties.

Active compounds of garlic can be divided into two groups: those that contain allicin and alliin, and those that do not contain sulfur. Its ability to inhibit the SARS-CoV-2 protease has been widely studied. When taken daily, garlic can increase the number of T helper cells and cytotoxic T cells in the body. It cans also down regulate the levels of various inflammatory and protein-related genes.Due to its anti-viral and immunological properties, onions are considered as potential treatment options for COVID-19 [34].

Potentially used Plants bioactive compounds

Various plant preparations and phytoconstituents have a history of being used for the prevention of SARS transmission. Currently, COVID-19 patients are being treated with standard anti-viral drugs and ventilator. Although COVID-19 is a complex illness, traditional Chinese medicine has focused on the treatment of its various symptoms. The use of herbs and plant compounds is considered as a way to improve a patient's health.

Various studies have been successfully carried out on the use of various herbal plants for the management of COVID-19. The findings of these studies have shown that these plants could help in the prevention of the disease. Due to the low toxicity of many natural products, some of which contain active compounds that can target COVID-19, screening plants for potential use could be a strategy to minimize the spread of the disease [35].

We analyzed the various herbs commonly used to treat COVID-19. The formulators include various herbs such as the Radix astragali praeparata, the Glycyrrhizae, and the Lonicera japonica. They also use various plant derivatives. A previous study screened over 96,606 classical prescriptions for the use of various high-frequency herbal plants for the prevention of pestilence. The results of the study revealed that out of the 574 identified plants, 52 contained active compounds that can target COVID-19.

Two of the studies analyzed involved the use of high-frequency herbal plants [36]. These include the Glycyrrhizae Radix Et Rhizoma and the Atractylodes lancea. Most of the commonly used herbs are dietetic plants. Various vegetables and herbal plants were also tested for their ability to inhibit the replication of COVID-19 in vitro. The results of these experiments revealed that the use of these plants led to a reduction in the number of cells infected with the SARS-CoV strain [37].

A capsule made by the Lianhua Qingwen group has been proven to be effective against various influenza strains. It was also selected as a general treatment for COVID-19.Due to the limited availability of COVID-19; many of the studies were conducted using virtual simulation techniques to predict the potential effects of various natural products and their action mechanisms [38].

A total of 167 herbal prescriptions containing various plant compounds were analyzed for their potential use against COVID-19.A study analyzed the effects of various chemicals from high-frequency medicinal plants on the SARS-CoV-2 target. The results of the study showed that some of the compounds exhibited molecular docking with the target.

Some of the plants that were studied include the Scutellaria baicalensis, the Glycyrrhizae, and the Bupleurum falcatum L. Glycyrrhizae Radix et Rhizoma, for instance, exhibited the strongest binding activity to the ACE site 1. Other compounds, such as glyasperin and Isorhamnetin, exhibited high levels of binding ability to the target [39].

A substance known as emodin can inhibit the binding of SARS-CoV S protein to ACE2.Flavonoids are known to stimulate the production of inflammatory cytokines in the body. The high levels of these chemicals are known to contribute to the development of respiratory distress syndrome caused by SARS coronaviruses. Various flavonoids have also been shown to interfere with the NLRP3 inflammatory signalling pathway. They have been able to relieve the inflammatory response caused by SARS-CoV infection. The compounds found in these studies could be used as dietary supplements and could be taken at a daily dose of 100 to 500 mg. One of them is resveratrol, which can inhibit the growth of COVID-19 and prevent its infection.

The main constituent of the Nigella sativa plant, thymoquinone, exhibited antioxidant, antimicrobial, and anti-tumor properties. Its extract has been shown to be effective against various strains of the avian influenza virus and the cytomegalovirus. For coronavirus infection, the use of Nigella sativa extract can reduce the replication of the virus in cells. It has also been shown that this substance can decrease the virus' load.

Thymoquinone has also been shown to have anti-sepsis and immunomodulatory properties. It can also prevent the development of multiple organ dysfunction syndrome.It can also protect the body from the effects of collagen and lung fibrosis by regulating the Nrf-2 signalling pathway [40].

Table 2 shows some herbal plants leaves and or aerial parts can be used in COVID-19 treatment. In table 3 a list of plants that its root is used in treatment of COVID-19. Other plants seeds can be used for

fighting COVID-19 (Table 4). On the other hand, some fruits and flowers of herbal plants can be used in treatment of COVID-19 (Table 5).

Several conventional and Orthodox medicine treatments are undergoing various phases of clinical trials. One of these is Remdesivir, which was granted an emergency use authorization by the FDA on May 1, 2020. This drug has been the furthest along in the clinical trials of any of these drugs. Some of the commonly used medications for treating psoriasis include Dexamethasone, Tocilizumab, Azithromycin, Hydroxychloroquine, and Chloroquine. Others include Oseltamivir, Lopinavir/Ritonavir, Abidol, and Convalescent Plasma [41].

Table 2: Herbal plants that its leaves used in treatment of COVID-19

Family	Genera	Commo n name
Saxifragaceae	Saxifraga spinulosa	Spider plant
Acanthaceae	Strobilanthes cusia	Assam Indigo
Acanthaceae	Strobilanthes callosa	Karvi
Loranthaceae	Taxillus chinensis	Chinese Mistletoe
Taxaceae	Torreya nucifera	Japanese nutmeg

Table 3:Herbal plants that its roots used in treatment of COVID-19

Family	Genera	Common name
Fabaceae	Astragalus membranaceus	Mongolian
Fabaceae	Glycyrrhiza glabra)	Liquorice
Apiaceae	Saposhnikovia divaricate	fang feng Siler
Asteraceae	Atractylodes lancea	Cang Zhu.
Lauraceae	Lindera aggregate	Spicewood
Polypodiaceae	Pynosia lingua	Tongue Fern
Menispermaceae	Stephania tetrandra	Fen Fang Ji

Table 4:Herbal plants that its seeds used in treatment of COVID-19

Family	Genera	Common name
Solanaceae	Capsicum annuum	Sweet Pepper , Cayenne Pepper,Chili Pepper
Ranunculaceae	Nigella Sativa	Black cumin, Blackseed, Black caraway
Leguminosae	Cassia tora,	Sickle Senna, Sicklepod

Table 5: Herbal plants that its fruits and flowers used in treatment of COVID-19

Family	Genera	Common name
Forsythia suspensa	Forsythia suspensa	Golden Bell
Paulowniaceae	Paulownia tomentosa	Paulownia, empresstree or Princess tree
Asteraceae	Anthemis	Chamomile
Dioscoreaceae	Dioscorea batata,	Chinese Yam

Thousands of COVID-19 clinical trials are currently taking place all around the world. The updated list of these trials can be found at the World Health Organization's website, ClinicalTrials.gov. The use of traditional medicine dates back to around 4,000 to 5,000 BC. The WHO has acknowledged the importance of this practice and has launched a series of initiatives aimed at supporting the implementation of policies and programs that will improve the health of the population. In response to a resolution passed by the World Health Assembly in 2013, the organization has also established a strategy that aims to help member states develop effective policies and implement action plans.

People from various parts of the world have been

using various medicinal plants to treat and prevent infectious diseases since the prehistoric era. For instance, Indian herbs can be used to treat respiratory viral infections. Traditional Chinese medicine has also been instrumental in treating various epidemics in China.According to a 2004 study by Bodeker and Willcox, over 80% of individuals use some form of herbal medicine. The WHO states that the global market for medicinal plants is expected to reach over 60 billion dollars annually [42].

The various advantages of COVID-19 over orthodox medicine have been cited by Stoofora in 1993. These include its low toxicity and affordability.Some of the compounds found in medicinal plants can also prevent the entry of viral cells into the host cells. These compounds have been shown to be effective in treating various viral infections.

There are many similarities between the two variants of SARS, namely SARS-CoV-2 and SARS-CoV. These two are both related to the same beta family and have the same genetic material. In addition, they both attach to the same cell through the ACE2 receptor. In 2003, it was reported that the plant metabolites used in the treatment of SARS-CoV could be considered as potential drug candidates for COVID-19.During the early stages of the SARS-CoV-2 pandemic in China, the use of traditional Chinese medicine (TCM) was widely used as a treatment option. According to a study conducted by Yang et al., over 85% of the infected individuals were receiving treatment. This practice has shown that the use of this type of medicine can be effective in the treatment of the disease. The effects of COVID-19 have been shown to improve the cure rate and reduce the incidence of delayed disease progression. These are also evidenced by the reduction in mortality rates [23].

3. Role of herbal plant in fighting COVID-19 infection

Pre- infection

One of the most important steps that people can take to prevent COVID-19 is by taking preventive measures. This strategy can be considered as a first-line intervention against this disease. In the first phase of COVID-19, anti-SARS-CoV-2 vaccine efficacy and effectiveness may have decreased in aged and immune-compromised patients; therefore current evidence suggests that the use of nutrients as immunomodulatory agents can modulate their innate and adaptive immune responses to vaccination against SARS-CoV-2

. This can be done through the use of herbal and nutritional supplements. One of the most important factors that people can consider when it comes to preventing the virus from entering their bodies is the prevention of replication.

Natural compounds can help boost the immune response in the pre-exposure stage. They can also help improve the gut microbiome, which is composed of beneficial bacteria that help maintain the health of the body's immune system. One of the most important factors that people can consider when it comes to preventing the spread of COVID-19 is hand hygiene. This includes regular hand washing with soap and alcohol-based hand rub. It is a part of the CDC's response to the spread of the disease [43, 34].

In addition to regular hand hygiene, the use of essential oils and plant-based hand sanitizers can also help prevent the spread of bacteria and viruses. Tea tree oil is a complex mixture of terpenes and hydrocarbons, has been used in various hand wash formulations for years. Previous studies have shown that the antiviral properties of tea tree oil can be effective against influenza. At a concentration of less than two percent, this natural substance inhibited the replication and entry of the virus into the host cell.

The antiviral properties of the natural substance known as aloin and aloe-emodin can be found in the gel of the Andrographis paniculata (Burm.f.) Nees plant. These compounds can help eliminate various types of viruses, such as SARS-CoV-1, influenza, and HIV. They can also destruct the lipid envelope of the virus. This leaves the plant an attractive choice for non-alcoholic hand sanitizers [34].

Post-exposure

The interaction between the viral spike and the cellular angiotensin converting enzyme 2 (ACE2) leads to the activation of various host cell-associated proteins, these factors contribute to the virus' entry into the host cells. One of the most important strategies that researchers can consider when it comes to developing new drugs against COVID-19 is to find compounds that can prevent these viral entry and binding mechanisms [30].The coronaviruses have various common proteins, such as nucleocapsid, protuberances, and the membrane. They also have a special type of protein known as hemagglutinin. The coronavirus infection begins when the spike protein-S binds to the receptor of a cell known as ACE2. The expression of this receptor could determine the severity of the disease [44].

A study on the essential oil the Desf. ammoides verticillata revealed that isothymol, which is a component of the oil, exhibited good results when it came to inhibiting the activation of the ACE2 receptor. This compound is also a component of the Ajowan essential oil, which has antimicrobial and antiviral properties.A combination of factors such as the docking, metabolism, distribution, elimination, and toxicity

of compounds can be used to determine their potential to block the activation of ACE2. For instance, the components of propolis, which are a resinous substance produced by bees, have been shown to have inhibitory effects on the activity of ACE2.

In silico studies have shown that glycyrrhizin, which is the bioactive constituent of the Glycyrrhiza glabra L. root, could be an effective inhibitor of ACE2 due to its safety and affordability. Another plant flavonol known as quercetin is present in various food products such as black tea, grapefruit, apples, and black salt. It is also proposed that this compound could be an effective disruptor of the viral binding process.It should be noted that isothymol is not very effective in treating oral conditions due to biotransformation. It is therefore suggested to use it as a nasal or throat spray.

The serine protease known as TMPRSS2 is located on the surface of the cell and interacts with SARS-CoV-2 to induce invasion. It is known to be involved in the replication and in the development of cancer and influenza. In one study, the flavonoids baeinical and baicalin were shown to be effective at inhibiting the expression of TMPRSS-2 in in vitro and in vivo studies.A study on the natural substance known as Withania somnifera, which is produced by the Ashwagandha plant, revealed that it can block the entry of SARS-CoV-2 into the host cells by inhibiting the TPMRSS2.

The lysosomal enzyme known as CatL is a component of the endosome that contributes to various pathological and physiological processes. It is also involved in the degradation of the extracellular matrix, which is a major factor that contributes to the binding of SARS-CoV-2 to the spike protein. Various phytochemicals and plants with potential CatL-inhibiting properties could be considered as potential therapeutic targets for treating COVID-19 patients.

A study conducted by an international team of researchers revealed that there are nine natural products that could potentially block the activity of the CatL receptor. These include Ararobinol, which is produced by the Senna occidentalis Link plant; oxoturkiyenine, which is produced by the Hypecoum pendulum L.; Rugosanine B, which is produced by the Ziziphus rugosa Lam plant; Tectol, which is produced by the Clerodendrum trichotomum Thunb.; Silymonin, which is produced by the Silybum marianum Gaertn plant; Picrasidine, which is produced by the D.Don plant; and 3, 17-cinchophylline, which is produced by the Cinchona calisaya Wedd [45].

Mechanism of action of herbal plants against COVID-19

The medicinal plants and SARS-CoV-2Edible direct target have unique anti-viral capabilities. They can inhibit the virus' proliferation and promote the secretion of IFN. Since the ACE2 surface receptor is the critical component of SARS-CoV-2 invasion, the use of soluble forms of this protein could be a strategy to treat COVID 19.

Isorhamnetin, which is a soluble form of the ACE2 site protein, has a strong binding ability to the protein. The two viral proteases, 3CLpro and PLpro, are also known to be key targets of SARS-CoV-2 infection.A study involved the high-throughput docking of over 12,000 compounds with the 3CLpro and ACE2. They discovered that isorhamnetin and quercetin exhibited remarkable binding ability with the protease .

Ginger has been known to have strong affinity to pLpro, which is a key component of SARS-CoV-2 replication. Another protease that could be a potential target is TMPRSS2.A database containing over 30,000 natural compounds was used to identify potential candidates for further docking with TMPRSS2. After initial analysis, 2,140 compounds were identified as potential candidates [24].

Among the compounds that exhibited high docking scores against TMPRSS2, geniposide was the most notable. It is known that the increased levels of pro-inflammatory cytokines, such as IFN-, are significantly increased in COVID-19 patients. Since the pathogenesis of COVID-19 is influenced by the release of many cytokines; agents that can reduce the levels of these molecules could help prevent the progression of the disease.

Numerous studies have shown that various herbs, vegetables, fruits, and spices have anti-inflammatory properties. They can trigger the production of optimal immune responses.The activation of the NF-B pathway is also known to contribute to the pathogenesis of lung inflammatory diseases caused by respiratory viruses. In a study, older macaques exhibited stronger host responses than those with younger ones.

Due to their anti-inflammatory properties, many edible and medicinal plants commonly used in COVID-19 have been found to have the ability to reduce inflammation. Some of the major compounds known to inhibit SARS-CoV-2 infection are acetoside, isorhamnetin, and gingerol.Isorhamnetin is a constituent of the medicinal plant Hippophae rhamnoides L., which has been shown to have anti-inflammatory properties. It can also improve the management of chronic inflammatory conditions.

Acetoside can relieve acute lung injury caused by LPS by suppressing the activation of the NF-B pathway and the proinflammatory cytokines. It has also exhibited a positive effect on the regulation of osteoarthritic rats.Quercetin is a

phenolic in many fruits and vegetables and has anti-inflammatory properties. It can inhibit the activation of the NF-B pathway in animal models. Kaempferol is another flavonoid aglycone that can produce similar effects in the body [12].

Kaempferol can reduce the inflammatory response of LPS-treated macrophages by suppressing the activation of the Src, Syk, and IRAK4 genes.Kaempferol and its glycosides can decrease the release of TNF- and NO in LPS-treated cells. Baicalein, a bioflavone component, has anti-inflammatory properties [44].

Baiicalein can also decrease the generation of inflammatory cytokines and inhibit the activation of the ERK1/2 or NF-B pathway in mice with lethal endotoxemia. These effects can be prevented through the use of plant sterols.It has been demonstrated that the effects of -Sitosterol on human endothelial cells can be mediated by the activation of several transcription factors. Stigmasterol is a plant chemical that can inhibit the pro-inflammatory mediators involved in the degradation of human cartilage.

Geniposide is a common component of ginger that can reduce the expression of TMPRSS2, which is a key component of the NF-B pathway. It also exerts anti-inflammatory effects through the regulation of the expression of TLR4. Another component of ginger that can reduce the production of inflammatory cytokines is gingerol. These compounds can also target anti-viral pathways that are involved in the pathogenesis of SARS-CoV-2. An ingredient of Ephedra polysaccharide can also reduce the generation of several inflammatory factors in the lungs [34].

Bupleurum can protect the lungs from injury by suppressing the recruitment of neutrophils through the P-selectin-mediated recruitment. In addition, polysaccharides can be used to treat colitis by suppressing the NLRP3 inflammasome activation and the NF-B signalling. The excessive inflammatory response following viral infection can lead to tissue injury. In cases of SARS-CoV-2 infection, the host's immune response is also impaired.

The development of vaccines or drugs against COVID-19 could be initiated if the infections have altered the body's innate immunity system.In severe cases of COVID-19, a decrease in the number of circulating CD4+ T cells, CD8+ T cells, and B cells has been observed. A study conducted on 452 patients with severe COVID-19 revealed that the number of cytotoxic T cells and T helper cells had also decreased significantly .

The presence of lymphopenia is associated with the severity of the disease and mortality. It has been hypothesized that the injured organs' ability to generate ACE2 receptors could affect the body's response to the infection. In mice, the effects of herbal formulations on the mucosal immune response were enhanced by increasing the CD4+ and CD8+ T cell population.

Gingerol can also improve the function of the intestine's barrier by increasing the number of CD4+ T cells. It can also prevent colitis caused by dextran sulfate sodium exposure. Also, the use of red-ginseng-derived compounds such as ginsenoside Rg3 can improve the efficacy of inhaled anti-pulmonology drugs by suppressing the migration of neutrophils.

One of the major activators of the JAK/STAT signalling pathway is the IL-6 protein. In addition, increasing the amount of IL-6 can trigger the downstream activation of the JAK/STAT signalling. Several drugs that target the JAK/STAT signalling pathway have been studied in various clinical trials for COVID-19. The results of these assessments have shown that the use of these compounds can help improve the effectiveness of the treatment

Kaempferol, on the other hand, decreased the release of TNF-, IL-6, VCAM-1, and STAT signalling molecules in inflamed colon microvascular endothelial cells. This study highlights the potential role of this drug in suppressing the inflammatory response of colitis.In contrast, the use of quercetin, a flavonoid, inhibited the JAK/STAT pathway in human cholangiocarcinoma cells. The reduction in the up-regulated STAT1 and STAT3 proteins was also observed.

In numerous laboratory studies, the use of compounds that can regulate the activity of the JAK-STAT signalling pathway has been shown. For instance, baicalein decreased the expression of STAT3/4 in a colitis model. Sitosterol can reduce the inflammatory effects of macrophages by suppressing the STAT1 and NF-B signalling pathways. Acetoside can also improve the survival rate of osteoarthritic rats by suppressing the inflammatory response of the animals.

In addition, the use of isorhamnetin can maintain the level of glucose in the myotubes by stimulating the JAK/STAT pathway. Geniposide can also induce the cell division in exocrine cells through the activation of the JAK/STAT3 pathway. The use of resveratrol can also suppress the inflammatory response caused by LPS [41].

The S1P protein can also regulate the movement of various types of immune cells within the body. It can also reduce the cytokines produced by an immunological response caused by an infection. The use of -sitosterol can also reduce the inflammatory effects of macrophages by suppressing the activation of the S1P and NF-B signalling pathways. This finding supports the possibility that COVID-19 could be a potential target for treating pulmonary fibrosis [45].

In colitis-induced mice, the use of baicalein significantly decreased the levels of mediators and suppressed the expression of S1P-STAT3 signalling. Geniposide can also suppress the expression of S1P and SphK1 signal transduction. It can also enhance the antimicrobial defense of human skin by producing a cathelicidin antimicrobial peptide [12, 28,].

These compounds might also help the body's defense against COVID-19 by suppressing the S1P-STAT3 signalling pathway. In addition, their use could prevent the development of COVID-19-related diseases. The level of circulating IL-6 can also be a risk factor for COVID-19's cardiovascular events. Also, the destruction of lung tissue can allow COVID-19 to infiltrate other organs through the ACE2 receptor.

For instance, the use of angiotensin II receptor type 1 can increase the production of IL-6 by the JAK/STAT pathway. This activates the signalling pathway and leads to the onset of vascular inflammation. Various studies have shown that the properties of certain herbs, such as their anti-inflammatory and anti-apoptosis properties, can contribute to the protection of various organs. They can also inhibit the SARS-CoV-2 protein and activate other signalling pathways.

Another type of herbal formula can also act on the ACE2 and IL-6 signalling pathways. It can prevent the development of COVID-19-related diseases by suppressing the inflammatory response.

Virus-Directed Therapies

Studies suggest that using herbal preparations as a treatment for patients infected with the beta-coronavirus 57 can help decrease the severity of the infections. More studies are needed to confirm the results of the various studies that have been conducted on the use of various natural compounds against COVID-19. These include in vitro and animal studies. It is also important to identify the effective agents for treating COVID-19 in clinical trials .

The various components of the virus' replication process are known to be targets of anti-viral compounds. One of the most important factors that can be considered when it comes to identifying effective agents against SARS-CoV is the presence of a certain type of enzyme known as the 3-chymotrypsin-like (3CLpro). Other non-structural proteins such as the helicase, nsp13, and RdRp can also be utilized as drug targets. A pervious study conducted on the Tinospora cordifolia shows that its components, which include berberine, can suppress the function of 3CLpro, which is a protein that helps prevent the replication of the virus. Other compounds, such as polyphenols, can also help control the infection [12]

The role of the N protein in the virus' replication process is also known to be a contributing factor to the development of mature virions. A study revealed that the Asparagus racemosus Willd inhibited the activity of this protein. Various viruses, such as SARS-CoV, require the addition of cyclophilin to their replication process. Research has shown that inhibiting the activity of this protein can help prevent the virus from replicating.

Although there is currently no proof supporting the use of cyclophilin inhibition by herbal compounds, some studies have been conducted on the effects of glycyrrhizin on the replication of SARS-CoV in plants. This compound, which is a bioactive component of the root of the liquorice tree, has antiviral properties. Other compounds such as N sativa, Citrus sinensis, and Anthemis hyalina have also been known to have antiviral properties. A hyalina DC is considered to be the most potent of these.

Host-Directed Therapies

The first phase of COVID-19 is characterized by the respiratory tract infection. This is followed by the involvement of other organs. In many cases, the infection is accompanied by inflammation in other organs, Among the common symptoms of the disease are myalgia and gastrointestinal symptoms. The neurotropism of SARS-CoV-2 can lead to inflammation, axonal damage, and edema, which can result in more severe neurological complications such as encephalitis and Guillain-Barré syndrome.

In addition to the respiratory tract infection, other organs such as the heart and lungs are also affected by the virus. These include systemic inflammation and acute cardiac injury. In addition to reducing the viral load, certain drug targets can also help improve the symptoms of the infection.

SARS-CoV-2 has been known to have affinity for the ACE2 receptors, which are widely distributed in various tissues and organs, including the heart and nervous system. The main route for the virus to enter neurons is through the activation of this receptor. In the lungs, the spike-like projections produced by the SARS-CoV-2 antigen have been observed in the epithelium of the bronchiolar.

ACE2 is a receptor that can be targeted by various drug compounds. In the previous sections, we talked about the use of herbs that can block this receptor.The presence of SARS-CoV-2 in the airways can trigger an innate immune response. Within a week after the respiratory tract infection, the levels of IgM and IgG are usually seen in patients. COVID-19 can also trigger cell-mediated responses [27].

The development of an immune response to COVID-19 can be influenced by the actions of certain cells. These include the CD4 and B cells,

which are known to produce neutralizing antibodies. In patients with COVID-19, the number of these cells has decreased, and their exhaustion and functionality can worsen the conditions. The presence of a certain type of immune cell known as a cytotoxic CD8 T-cell is known to play a role in clearing the virus from the body. However, the inability to prevent the replication of the virus and the removal of infected cells can lead to an increased response [23].

Some of the known proinflammatory cytokines that can stimulate the response include IL-6, IFN-gamma, IL-1 and IL-2. On the other hand, other factors such as monocytes/macrophages, cytotoxic and helper T cells, and regulatory T cells have also been identified. In addition to being beneficial for the development of an innate immune response, certain herbs can also help improve the functioning of the host's immune system [23]. Ginsenoside Rg1, a component of the Panax ginseng C.A.Mey, can stimulate the activity of CD4 T cells. A recent study revealed that fermented ginseng extract can improve the survival rates and protection against influenza in patients with conditions that are lacking in the adaptive immune components.

A substance known as Lophatherum gracilenicum, which is commonly used for treating respiratory syncytial virus infection, has antiviral properties. In rats, the proposed mechanism involved the enhancement of the CD4 and /CD8 cell ratios and the inhibition of certain cytokines.In addition to being beneficial for the development of an innate immune response, certain herbs can also help improve the functioning of the host's immune system. For instance, the Viscum album L. can stimulate the activity of human peripheral T lymphocytes by altering their migratory behavior. It can also increase the time it takes for these cells to move through collagen lattices.

Various herbs have been found to help decrease the severity of the cytokine storm by inhibiting the production of certain proinflammatory cytokines. For instance, Scutellearia baicalensis can help decrease the levels of these cytokines by inhibiting their expression.Although studies on the effects of various herbal compounds on the development of an innate immune response are still limited, they can still provide some protection against the effects of severe influenza. One example is parthenolide, which is a component of Tanacetum parthenium Sch.Bip.

Parthenolide is a sesquiterpene that has been shown to significantly reduce the levels of certain proinflammatory cytokines. These include IL-1 and IL-2. Due to the significant contribution of IL-6 to the development of adverse clinical outcomes, it could be a potential candidate for evaluation in clinical trials. The overexpression of the PAK1 protein in response to the SARS-CoV-2 infection in the lung can be a critical mediator of the development of a cytokine storm. Propolis-derived compounds can decrease the activity of various proinflammatory cytokines and improve the function of the host's immune system [11].

Anti-Complement Agents

The excessive release of cytokines by the immune system can cause a decline in the activity of the complement system and contribute to the development of COVID-19 patients' ARDS. Some of the compounds that have been shown to help decrease the activity of the cytokine storm are derived from the blossoms of a certain plant.In addition to being beneficial for the development of an innate immune response, certain herbs can also help improve the functioning of the host's immune system. For instance, they can help decrease the severity of pulmonary edema and improve the oxidant-antioxidant imbalance. Due to the presence of COVID-19 in the environment, it has been reported that various dermatological disorders such as urticaria, maculopapular rashes, petechiae, and purpura can develop.

4. Future perspective

The large numbers of current studies, could help answer various questions by suggesting a beneficial role of the use of herbs and spices products and food supplements as a complementary treatment, prevention or therapeutic agents during the COVID-19-related by suppressing its SARS-CoV-2 infection. They can also reduce fever and cough by boosting the anti-inflammatory effects of certain plant biochemicals.

Some of the herbal products that can be used for COVID-19 infection include the following: amygdalinum, amygdalinum, elkirachta indica, and Eurycoma longifolia. On the other hand, various drugs such as ginseng can also help boost the immune system. A strategy to prevent COVID-19 might involve providing promising and convincing protective components to the body.

Various compounds found in plants have anti-inflammatory and anti-viral properties. They can also protect the organs by working together through various pathways. A review of the studies on these compounds' effects on the immune system and anti-inflammatory properties revealed that some of the compounds could potentially target COVID-19.A study conducted on the compounds' properties revealed that many of them could be easily incorporated into the development of functional food supplements and dietary products designed to prevent COVID-19.

Medicinal herbs and natural resources can play an important role in the discovery of new drug candidates for COVID-19. Similar to the processes involved in the production of synthetic and semisynthetic medicines, a rational strategy should be followed in developing effective vaccines and drugs.

The goal of this review was to explore the various aspects of the development of herbal drugs for the treatment and prevention of COVID-19. Some of these include the role of hand hygiene and boosting the immune response before and after exposure.

There are various therapeutic options available for the treatment of COVID-19. These include the use of 3C-like and virus-directed agents, as well as host-directed and ACE2 inhibitors. Researchers can use these strategies in the challenging conditions of discovering new drugs against COVID-19. Numerous studies have been conducted on the use of natural products in the treatment and management of the pandemic. Although some of these studies are in silico, further studies are needed to confirm their safety and efficacy. Plant phytochemicals may therefore be the most effective alternative medicine for COVID-19 infection.

References

Pandit K, Gupta S, Sharma AG. (2020). Clinico-pathogenesis of nCOVID-19 in children. Indian Journal of Biochemistry & Biophysics. ; 57: 264–269.

Hayder M. Al-kuraishy, Omnia Momtaz Al-Fakhrany, Engy Elekhnawy. (2022). Traditional herbs against COVID-19: back to old weapons to combat the new pandemic, European Journal of Medical Research 27:186 ://doi.org/10.1186/s40001-022-00818-5

P. M. Kapepula et al., "Artemisia Spp. (2020). derivatives for COVID-19 Treatment: Anecdotal use, political hype, treatment potential, challenges, and road map to randomized clinical trials," American Journal of Tropical Medicine and Hygiene, vol. 103, no. 3. doi:10.4269/ajtmh.20-0820.

H. Korkmaz, (2021). "Could Sumac Be Effective on COVID-19 Treatment?" Journal of Medicinal Food, vol. 24, no. 6. doi: 10.1089/jmf.2020.0104.

L. Ang, H. W. Lee, A. Kim, J. Y. Choi, and M. S. Lee, (2021). "Network analysis of herbs recommended for the treatment of covid-19," Infect Drug Resist, vol. 14, doi:10.2147/IDR.S305176.

K. Kuchta, S. Cameron, M. Lee, S. Q. Cai, and Y. Shoyama, (2022). "Which East Asian herbal medicines can decrease viral infections?" Phytochemistry Reviews, vol. 21, no. 1.. doi: 10.1007/s11101-021-09756-2.

P. Musoke et al., (2021). "Fear of COVID-19 and the media influence on herbal medication use in uganda: A cross-sectional study," Risk Manag Healthc Policy, vol. 14, doi: 10.2147/RMHP.S332325

Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, Li P, Zhou Y, Lin YF, Duan Q and Luo G. (2020). Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. J. Infect., 80(6): 656-665.

20Verma N, Patel D and Pandya A. (2020). Emerging diagnostic tools for detection of COVID-19 and perspective. Biomed microdevices. 22(4): 1-18.

Alshammari SA, Alwakeel LS, Alghtani JA, Alsabbagh LM. (2021). Effect of COVID-19 on awareness and consumption of dietary supplements in Saudi Arabia, .J Nat Sci Med;4(2):190

El Alami A, Fattah A, Chait A. Medicinal plants used for the preventionpurposes during the COVID-19 pandemic in Morocco. J Anal SciAppl Biotechnol 2020; 2(1):2-11.

Nugraha RV, Ridwansyah H, Ghozali M, Khairani AF, Atik N. (2020). Traditionalherbal medicine candidates as complementary treatments for COVID-19: Areview of their mechanisms, pros and cons. (https://www.hindawi.com/journals/ecam/2560645/) Evid BasedComplement Alternat Med. doi: 10.1155/2020/2560645.

pAlyami HS, Orabi MA, Aldhabbah FM, Alturki HN, Aburas WI, Alfayez AI, etal. (2020). Knowledge about COVID-19 and beliefs about and use of herbalproducts during the COVID-19 pandemic: A cross-sectional study in SaudiArabia. (https://www.sciencedirect.com/science/article/pii/S1319016420302036? via%3Dihub) Saudi Pharm J;28(11):1326-32.

Maideen NM. (2020). Prophetic medicine-Nigella sativa (Black cumin seeds)-potential herb for COVID-19? (https://www.journal-jop.org/journal/view.html?doi=10.3831/KPI.23.010) J Pharmacopunct 2020; 23(2):62.

Cascella M. et al. (2022). Features, evaluation, and treatment of coronavirus (COVID-19). Statpearls [internet]. Accessed 1 june 2022

Mani, D.; Wadhwani, A.; Krishnamurthy, P.T. (2019). Drug Repurposing in Antiviral Research: A Current Scenario. J. Young Pharm, 11, 117–121. [CrossRef]

K. Aprilio and G. Wilar, (2021). "Emergence of ethnomedical covid-19 treatment: A literature review," Infection and Drug Resistance, vol. 14. doi: 10.2147/IDR.S327986.

L. Ang, H. W. Lee, J. Y. Choi, J. Zhang, and M. Soo Lee, (2020). "Herbal medicine and pattern identification for treating COVID-19: a rapid review of guidelines," Integrative Medicine Research, vol. 9, no. 2. 2020. doi: 10.1016/j.imr.100407.

A. Jalali, F. Dabaghian, H. Akbrialiabad, F. Foroughinia, and M. M. Zarshenas, (2021. "A pharmacology-based comprehensive review on medicinal plants and phytoactive constituents possibly effective in the management of COVID-19," Phytotherapy Research, vol. 35, no. 4. doi: 10.1002/ptr.6936

Z. Shu et al., (2020). "Clinical features and the

traditional Chinese medicine therapeutic characteristics of 293 COVID-19 inpatient cases," Front Med, vol. 14, no. 6, doi: 10.1007/s11684-020-0803-8.
Y. Li et al., (2020). "Traditional Chinese herbal medicine for treating novel coronavirus (COVID-19) pneumonia: Protocol for a systematic review and meta-Analysis," Syst Rev, vol. 9, no. 1, doi: 10.1186/s13643-020-01343-4.
P. Sun, (2020). "The treatment of covid-19 with Chinese herbal medicine," Journal of Chinese Medicine, vol. no. 123, 2020.
57M. de los Angeles et al.,(2020). "Herbal medicine as prevention and treatment against covid-19," Archivos Venezolanos de Farmacologia y Terapeutica, vol. 39, no. 8, doi:10.5281/zenodo.4543573.
S. Yuvejwattana, (2020). "Thailand Clears Use of Herbal Medicine for Covid-19 Treatment," Prgnosis, Bloomberg.
L. Ang, H. W. Lee, A. Kim, and M. S. Lee, (2020). "Herbal medicine for the management of COVID-19 during the medical observation period: A review of guidelines," Integrative Medicine Research, vol. 9, no. 3. 2020. doi: 10.1016/j.imr.100465
M. E. Gondokesumo, K. Budipramana, and S. Q. Aini, (2021). "Study of Jamu as Indonesian Herbal Medicine for Covid-19 Treatment,"
K. Dzobo, H. Chiririwa, C. Dandara, and W. Dzobo, (2021). "Coronavirus Disease-2019 Treatment Strategies Targeting Interleukin-6 Signaling and Herbal Medicine," OMICS, vol. 25, no. 1, doi: 10.1089/omi.2020.0122.
M. A. DiPietro and C. Mondie, (2021). "Toxicity of herbal medications suggested as treatment for COVID-19: A narrative review," J Am Coll Emerg Physicians Open, vol. 2, no. 2, doi: 10.1002/emp2.12411
D. Y. W. Lee, Q. Y. Li, J. Liu, and T. Efferth, (2021). "Traditional Chinese herbal medicine at the forefront battle against COVID-19: Clinical experience and scientific basis," Phytomedicine, vol. 80, doi: 10.1016/j.phymed.2020.153337
69S. H. Nile and G. Kai, (2021). "Recent Clinical Trials on Natural Products and Traditional Chinese Medicine Combating the COVID-19," Indian Journal of Microbiology, vol. 61, no. 1. doi: 10.1007/s12088-020-00919-x.
E. Kim, J. Choi, S. Y. Min, J. H. Kim, and A. Jeong, (2021). "Efficacy of traditional herbal medicine for psychological sequelae in COVID-19 survivors A protocol for systematic review and meta-analysis," Medicine (United States), vol. 100, no. 20. doi: 10.1097/MD.0000000000025609
Y. Gao et al., (2021). "COVID-19 rehabilitation with herbal medicine and cardiorespiratory exercise: Protocol for a clinical study," JMIR Res Protoc, vol. 10, no. 5, doi:10.2196/25556
Z. K. Shinwari, M. Qaiser, M. Q. Nasar, and A. Ali, (2020). "Indigenous knowledge based herbal medicine for corona (COVID-19) treatment," Pak J Bot, vol. 52, no. 4, doi:10.30848/PJB-4(13)
S. Jang, D. Kim, E. Yi, G. Choi, M. Song, and E. K. Lee, (2021. "Telemedicine and the use of Korean medicine for patients with COVID-19 in South Korea: Observational study," JMIR Public Health Surveill, vol. 7, no. 1, doi: 10.2196/20236.
J. A. Yanez et al., (2021). "Prescription, over the counter (OTC), herbal, and other treatments and preventive uses for COVID-19," in Environmental and Health Management of Novel Coronavirus Disease (COVID-19), doi: 10.1016/B978-0-323-85780-2.00001-9.
X. Du, L. Shi, W. Cao, B. Zuo, and A. Zhou, (2021). "Add-on effect of Chinese herbal medicine in the treatment of mild to moderate COVID-19: A systematic review and meta-analysis," PLoS ONE, vol. 16, no. 8 August. doi: 10.1371/journal.pone.0256429
A. Mirzaie, M. Halaji, F. S. Dehkordi, R. Ranjbar, and H. Noorbazargan, (2020). "A narrative literature review on traditional medicine options for treatment of corona virus disease 2019 (COVID-19)," Complementary Therapies in Clinical Practice, vol. 40. doi:10.1016/j.ctcp.2020.101214.
89U. K. Caliskan and M. M. Karakus,(2021). "Evaluation of botanicals as potential COVID-19 symptoms terminator," World Journal of Gastroenterology, vol. 27, no. 39. doi:10.3748/wjg.v27.i39.6551.
D. Silveira et al., "COVID-19: (2020). Is There Evidence for the Use of Herbal Medicines as Adjuvant Symptomatic Therapy?" Frontiers in Pharmacology, vol. 11. doi:10.3389/fphar.2020.581840.
T. He et al., (2020). "Potential mechanisms of Chinese Herbal Medicine that implicated in the treatment of COVID-19 related renal injury," Saudi Pharmaceutical Journal, vol. 28, no. 9, doi: 10.1016/j.jsps.2020.08.002.
S. Kwon et al., (2020). "Could herbal medicine (Soshihotang) be a new treatment option for COVID-19?: a narrative review," Integrative Medicine Research, vol. 9, no. 3. doi: 10.1016/j.imr.2020.100480.
105Wang, X. et al. (2020) A systematic review and meta-analysis of the efficacy and safety of western medicine routine treatment combined with Chinese herbal medicine in the treatment of COVID-19. Medicine, 99(32), [Online] Available from: doi.org/10.1097/MD.0000000000021616
Y. Gao et al., (2021). "COVID-19 rehabilitation with herbal medicine and cardiorespiratory exercise: Protocol for a clinical study," JMIR Res Protoc, vol. 10, no. 5, doi: 10.2196/25556.
D. Liana and A. Phanumartwiwath, (2022). "Leveraging knowledge of Asian herbal

medicine and its active compounds as COVID-19 treatment and prevention," Journal of Natural Medicines, vol. 76, no. 1. doi: 10.1007/s11418-021-01575-1.

N. Chaachouay, A. Douira, and L. Zidane, (2021). "COVID-19, prevention and treatment with herbal medicine in the herbal markets of Sale Prefecture, North-Western Morocco," Eur J Integr Med, vol. 42, 2021, doi: 10.1016/j.eujim.2021.101285.