Review

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COVID-19 and Phytotherapy

COVID-19 ve Fitoterapi

Melike Nur AKBAŞ[1], Adem AKÇAKAYA[2]

[1]Bezmialem Vakıf University, Phytopharmacy, İstanbul, Turkey

[2]Bezmialem Vakıf University Faculty of Medicine, Department of General Surgery, İstanbul, Turkey

ABSTRACT

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), emerging in Wuhan city, China, causing COVID-19 disease, has been described as a pandemic by WHO (World Health Organization), leading to outbreaks of pneumonia. The COVID-19 pandemic continues to affect millions of people worldwide. SARS-COV-2 enters the cell via ACE-2 (Angiotensin-converting enzyme 2) receptor. These receptors are predominantly found in lung, small intestine, and vascular endothelial cells. Since ACE 2 is found more frequently in these tissues, common clinical symptoms include fever, cough, sore throat, fatigue, dyspnea, and diarrhea. Currently, although symptomatic treatments are applied for COVID-19, there is no specific treatment yet. It takes a long time before targeted therapies can be found. For this reason, it is necessary to develop emergency treatment or methods that can quickly control the disease. Phytotherapeutic compositions offer a potentially valuable resource for this purpose. Many countries, especially China, aimed to reduce morbidity and mortality by using phytotherapy throughout COVID-19 patients. Phytotherapeutic products are known to be safe and tolerable with their background knowledge. In this regard, the use of phytotherapy as a complementary treatment in COVID-19 patients is very important. In this review, phytotherapeutic approaches related to symptoms that may occur in the clinical course of COVID-19 disease will be discussed.

Keywords: COVID-19, coronavirus, phytotherapy, comlementary therapy

ÖZ

Çin'in Wuhan şehrinde ortaya çıkan ve COVID-19 hastalığına sebep olan SARS-CoV-2 (Şiddetli Akut Solunum Sendromu Korona Virüsü 2), pnömoni salgınlarına yol açarak DSÖ (Dünya Sağlık Örgütü) tarafından pandemi olarak nitelendirilmiştir. COVID-19 pandemisi dünya genelinde milyonlarca kişiyi etkilemeye devam etmektedir. SARS-COV-2, ACE-2 (Anjiyotensin dönüştürücü enzim 2) reseptörünü kullanarak hücre içine giriş yapmaktadır. Bu reseptörler ağırlıklı olarak akciğer, ince barsak ve vasküler endotel hücrelerinde bulunmaktadır. ACE 2'nin bu dokularda daha sık bulunması sebebiyle, yaygın görülen klinik semptomlar arasında ateş, öksürük, boğaz ağrısı, yorgunluk, dispne ve ishal yer almaktadır. Şu anda, COVID-19 için semptomatik tedaviler uygulansa da henüz spesifik bir tedavisi bulunmamaktadır. Hedefe yönelik tedavilerin bulunabilmesi için çok uzun bir zaman geçmesi gerekmektedir. Bu sebeple acil tedavi veya hızlı bir şekilde hastalığı kontrol altına alabilecek yöntemler geliştirilmesi gerekmektedir. Fitoterapötik bileşimler, bu amaçla potansiyel olarak değerli bir kaynak sunmaktadır. Başta Çin olmak üzere pek çok ülke COVID-19 hastalarında, tedavi seyri boyunca fitoterapiyi uygulayarak morbiditeyi ve mortaliteyi azaltabilmeyi amaçlamıştır. Fitoterapötik ürünler geçmişten gelen bilgi birikimi ile birlikte güvenli ve tolere edilebilir olduğu bilinmektedir. COVID-19 hastalığında tamamlayıcı tedavi olarak kullanımı bu açıdan çok önemlidir. Bu derlemede COVID-19 hastalığının klinik seyrinde ortaya çıkabilecek semptomlara ilişkin fitoterapötik yaklaşımlardan bahsedilecektir.

Anahtar Sözcükler: COVID-19, koronovirüs, fitoterapi, tamamlayıcı tedavi

Address for Correspondence: Adem AKÇAKAYA, Bezmialem Vakıf University Faculty of Medicine, Department of General Surgery, İstanbul, Turkey
E-mail: aakcakaya@bezmialem.edu.tr **ORCID ID:** orcid.org/0000-0003-3116-7033

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Introduction

Coronaviruses are enveloped RNA viruses that threaten human health by causing diseases usually in the respiratory tract, digestive system and central nervous system of humans and animals. Six coronavirus species are known to cause illness in humans. Four of these (229E, OC43, NL63 and HKU1) are common and they also cause typical cold symptoms in the individuals with strong immune system. The other two strains which are severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are zoonotic and wile some bodies can survive with mild symptoms, sometimes they can be fatal. SARS-CoV is the virus that caused severe acute respiratory syndrome outbreaks in Guangdong province of China in 2002 and 2003. MERS-CoV is the pathogen responsible for severe respiratory disease outbreaks that occurred in the Middle East in 2012 (1).

In December 2019, as a result of studies conducted on a group of patients with pneumonia of unknown cause, it was determined that the factor causing pneumonia was a previously undiscovered betacoronavirus. This virus, which is different from MERS-CoV and SARS-CoV, was named 2019-nCoV and registered as the 7th member of the coronavirus family (1). The name 2019-nCoV was later changed to SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus 2) by the International Virus Taxonomy Committee (ICTV) (2). The disease caused by the SARS-COV-2 virus was called COVID-19, which means 2019 coronavirus disease by the World Health Organization (WHO) (3). Early reports of COVID-19 point to a similar incubation period with SARS-CoV and MERS-CoV. Clinical features are also very similar among these viruses: fever, cough, chest pain, dyspnea, and respiratory distress (4). This similarity between symptoms of SARS-CoV and COVID-19 is due to the fact that they both use the ACE-2 (angiotensin converting enzyme 2) receptor (4).

Since the first reports of COVID-19, it has been stated that the infection has affected more than 12 million people worldwide. There are approximately 3 million confirmed cases in the USA, where COVID-19 is most effective. Countries with the highest number of cases after the USA were reported as Brazil, India, Russia, Peru, Chile, Mexico, England, Spain, and Iran, respectively. The number of people who died due to the virus has reached to 559.047 (5).

COVID-19 was declared an international public health emergency by WHO on January 30, 2020 (6) and later labeled as a pandemic. Although existing chemical drugs or combinations have been tried against COVID-19 disease, which appears to cause serious morbidity, mortality and economic losses, there is no specific treatment or vaccine yet. Phytotherapeutic prophylaxis is very important at this point. The correct use of phytotherapy with scientific data can reduce the progressive course of the disease and the possibility of side effects, and can benefit the country in terms of cost. Therefore, many countries, especially China, aimed to reduce morbidity and mortality by applying phytotherapy throughout the treatment course in COVID-19 patients (7). In recent years, phytotherapy has gained an increasing usage area in our country as well as in the world. In this review, phytotherapeutic approaches which are used in COVID-19 disease or having potential efficacy against symptoms such as URTI (upper respiratory tract infection), bronchitis etc., that may occur in the course of the disease will be mentioned.

COVID-19 and Clinical Findings

ACE-2 receptor is the intracellular entry receptor for SARS-COV-2 and some types of coronavirus (SARS-CoV, HCoV-NL63). ACE-2 plays an important role in the renin-angiotensin-aldosterone system (RAAS) regulating blood pressure and body-fluid balance. ACE-2 also has functions such as protecting organs from inflammatory damage and regulating intestinal functions. The outer membrane of SARS-CoV-2 contains S (spike) glycoprotein, which binds with high affinity to the ACE-2 receptor in the host cell. Although 79% of the current SARS-CoV-2 genome is similar to SARS-CoV, it has been reported that due to mutations in the S glycoproteins, the ability of SARS-CoV-2 to bind to ACE-2 receptors has increased, and hence the contagiousness of SARS-CoV-2 has risen (8). When glycoprotein S is cut by proteases such as TMPRSS2 in the host cell, it becomes possible to bind to ACE-2 receptors and initiates the infection. ACE-2 receptor and TMPRSS2 are co-expressed in human respiratory and intestinal tract cells. Therefore, these tissues will be the main target of the virus (9).

Like many respiratory diseases, COVID-19 is spread through droplets. Researchers have reported that SARS-CoV-2 can remain infectious in airborne droplets for at least 3 hours (4). Since these droplets will also land on the surface, it has been stated that the virus can remain alive on that surface for a certain time depending on the type of surface (4). The virus can be transmitted by droplets emitted from sick individuals through coughing, sneezing, or by contact with surfaces contaminated by patients (mouth, nose and eye mucosa).

While COVID-19 may be clinically asymptomatic, it may cause clinical pictures ranging from ARDS (acute respiratory distress syndrome) and multiorgan failure. SARS-COV-2, which enters through the mucous membranes, binds to epithelial cells and starts replication. Although the virus can be detected by the RT-PCR method in the asymptomatic phase, there are no clinical symptoms or pathological pulmonary imaging findings (10).

As the virus travels through the airways, a stronger natural immune response is triggered. In individuals with a strong immune system, symptoms and clinical course may be milder due to the natural immune response. This is the case in approximately 80% of infected patients and the disease is mostly limited to the upper airways (10). This group of patients has symptoms such as fever, dry cough, sore throat, nasal congestion / rhinorrhea, fatigue, headache or myalgia. Since ACE-2 receptors, which are the entry receptors of the virus, are present in large numbers in the gastrointestinal system, complaints such as diarrhea, nausea, vomiting and abdominal pain may occur. It has been stated that gastrointestinal symptoms can sometimes occur alone (11).

Unfortunately, in about 20% of infected patients, the disease progresses and pulmonary infiltrates develop, and in some of them the disease progresses very severely (10). In a study, it was reported that 17% of COVID-19 patients developed Acute Respiratory Distress Syndrome (ARDS) and 65% of them died due to multiple organ failure (12).

Presence of pre-existing medical conditions such as asthma, hypertension, diabetes, and old age are important parameters affecting the treatment course of COVID-19 disease (4). In addition to the damage caused by COVID-19 in the lung, failure of various organs may occur. Mild, temporary, or severe liver damage can be seen in the clinical course of COVID-19 patients with abnormal liver function tests. Current evidence suggests that liver damage may result from the direct pathogenic effect of the virus, systemic inflammation, or the toxicity of drugs commonly used in these patients (13). Although the exact pathogenesis of kidney involvement in COVID-19 infection is unclear, it has been reported that acute kidney injury caused by acute tubular necrosis in COVID-19 can occur with multiorgan failure and shock. In addition, since ACE-2 in kidney cells is the direct target of SARS-COV-2, it is possible that it may cause direct damage due to virus (11).

Use of Phytotherapeutic Agents in the Treatment of COVID-19

Phytotherapy is a supportive and complementary treatment method in which medicinally effective parts, extracts of plants and different pharmaceutical forms prepared from these are used as an adjunct to treatment or for preventing diseases. The use of medicinal plants for these purposes is as old as human history. The use of medicinal herbs in Traditional Chinese Medicine and subcontinent of India in Ayurvedic Medicine has a long history and traditionally continues (14).

There are about 20 families of viruses that can infect humans, and some of them can also infect animals. If viruses enter the living organism and cannot be prevented by the immune system, it is almost impossible to prevent their spread. They need to use the host cell's metabolic pathways to enable them to reproduce. Today, there are synthetic drugs that can prevent virus replication by various mechanisms. However, there are adverse conditions such as resistance to these drugs, cytotoxicity and low efficiency. Another antiviral treatment is vaccination, but it is a method that needs to be developed more because it cannot provide sufficient protection (15).

As mentioned above, although specific vaccines and antiviral agents are the most effective methods to prevent and treat viral infection, a treatment protocol that fully targets COVID-19 has not yet been found. It may take months or years to achieve targeted treatments. For this reason, emergency treatment or methods that can control them quickly should be developed. Phytotherapeutic compositions offer a potentially valuable resource for this purpose. Approximately 40% of currently available drugs are direct or indirect components of plants. Plants are the main source of alkaloids, anthocyanins, carotenoids, flavonoids, isoflavones, lignans, monoterpenes, organosulfides, saponins and many more phytochemicals. These phytochemicals have been shown to be responsible for the antimicrobial, antihypertensive, antidiabetic, antioxidant, hepatoprotective, cardioprotective etc. effects (15).

Phytotherapy is often preferred in Traditional Chinese Medicine. The effectiveness of Traditional Chinese Medicine in infectious diseases was also demonstrated during the SARS epidemic in 2003 (16). During the treatment period of COVID-19, more than 3100 healthcare professionals with competence of Traditional Chinese Medicine practice were transferred to Hubei province and the protocol implemented by this team was included in the "Diagnosis and Treatment Guide of COVID-19" in China (17) .

In a study conducted in 102 patients with mild symptoms treated with Traditional Chinese Medicine, the patients were regularly given a mixture of about 30 different herbs, called qingfei paidu decoction, that included cinnamon, licorice root, dried tangerine peel and fresh ginger. According to this study it was reported that: the time to disappear clinical symptoms is shortened by 2 days; the recovery time of body temperature was shortened by 1.7 days; the average hospital stay was shortened by 2.2 days; the rate of improvement in CT (Computed tomography) image increased by 22%; clinical cure rate increased 33 the severity rate of the cases decreased by 27.4% and the lymphocyte count increased by 70% (17).

In addition to these, it has been reported that in traditional Chinese medicine treatment applied to seriously ill patients, the average hospital stay and PCR negativity time are shortened by more than 2 days (17).

In another study in 701 cases where this mixture was applied, it was reported that 130 cases were treated and discharged, clinical symptoms disappeared in 51 of them, clinical symptoms improved in 268 of them and 212 cases remained stable without worsening symptoms. It has been stated that the cure rate is over 90% with the Qingfei paidu decoction (17).

In addition to this, there is a case in which western and Chinese medicine was applied integratively. Oral oseltamivir, intravenous ganciclovir infusion, aerosol etc. treatments have been applied to this patient who had recurrent cough and fever but whose respiratory rales are not apparent at the time of admission to the hospital. Although the RT-PCR result was negative, his BT was considered to be compatible with COVID. Because of the increase in body temperature and sweating, the patient was given a decoction of qingfei paidu with herbal mixture, that is, Traditional Chinese Medicine. It was reported that body temperature dropped to 36.2 °C at the night of the application and then tended to normalize. It was reported that after 6 days of treatment, chest CT was better than before and inflammation regressed. After discharge, he continued to take 7 more doses of this herbal mixture, and his clinical symptoms were reported to have significantly improved (17).

In COVID 19, it has been stated that the application of Traditional Chinese Medicine in the early period reduces the duration of the disease, decreases the mortality and delays the progression of the disease (17).

The Relationship Between Plants and Cytokin Storm

Concerns have been raised that some herbs that act on the immune system may deleteriously increase the cytokine response during acute respiratory viral infections. The excessive immune response that occurs in the post-infection period has been defined as "cytokine storm" and is associated with excessive levels of pro-inflammatory cytokines and extensive tissue damage (18).

It has been suggested that our response to a respiratory virus occurs in three stages: stage I, an asymptomatic incubation period during which the virus can or cannot be detected; stage II, a symptomatic period not severe in the presence of the virus; stage III, symptomatic stage with severe respiratory distress with high viral load. During the incubation or non-severe stages, a specific adaptive immune response is required to eradicate the virus and prevent the disease from progressing to the severe stage. This is a dynamic, innate event involving the local release of cytokines known as signaling agents. Therefore, strategies that increase immune responses in the early stages are considered important at this stage (19).

When the protective immune response is impaired, the virus is expected to spread faster and cause more damage to the tissues affected. In COVID-19 disease, damaged host cells induce inflammatory response in the lungs as a response. It is largely mediated by proinflammatory macrophages and granulocytes and a cytokine storm occurs (19). In other words, cytokine storm is a late clinical finding in viral diseases and occurs when the immune system fails to keep the virus under control.

Plants That May Be Used As a Support Treatment in COVID-19 Infection

Coronaviruses are just one of the viral agents that can cause infection in the upper respiratory tract. The infection is indistinguishable from seasonal flu in many ways and is often not severe.

The main approach in the treatment of bronchitis or pneumonia includes the use of expectorants, mucolytics, and immunosupporting supplements. Antibiotics are especially beneficial in pneumonia. In this section, phytotherapeutic treatments that may benefit the COVID-19 clinic will be discussed. Table 1 summarizes the plants that can be used in the treatment of COVID-19.

• Licorice (Glycyrrhiza glabra)

Licorice (Glycyrrhiza glabra) is an herb that has been used in Egyptian, Indian and Chinese medicine for centuries. The medicinal part of the plant is its root. Licorice root is well known for its antiviral properties. During the SARS epidemic, researchers were attracted to this point because some family members who consumed Traditional Chinese Medicine herbal mixtures containing licorice did not experience infection (20). Since then, there have been many published research articles demonstrating the efficacy of the various phytochemicals found in licorice against the SARS virus. Unfortunately, most of these researches started in the post-SARS period and its interest areas decreased after 2012.

Table 1. Plants that can be used as an adjunct to COVID-19 treatment and their effects in this treatment

Turkish name of the plant	Latin name of the plant	Major Effective Compound	Effect
Licorice	*Glycyrrhiza glabra*	Glycyrrhizin, Flavonoids (liquiritin and liquiritigenin)	Antiviral Anti-inflammatory, Immunomodulator, Mucoprotective Antitussive
South African Geranium	*Pelargonium sidoides*	Coumarins (eg Umckalin) and polyphenolic compounds	Immunstimulant, Antimicrobial, Antimicobacterial, Antiviral Expectorant
Common Ivy	*Hedera helix*	Alpha-hederine, hederacoside C	Mucolytics, Spasmolytic, Bronchodilator Antibacterial Expectorant
Absinth	*Artemisia annua*	Artemisinin	Antimalarial Immunomodulator
Elderberry	*Sambucus nigra*	Kempferol, Quercetin, Isoramnetin	Antiviral Immunomodulator
Echinacea	*Echinacea purpurea*	Alkylamides, caffeic acid derivatives and polysaccharides	Immunomodulator
Galangal	*Alpinia officinarum*	Diarylheptanoids	Anti-inflammatory Immunomodulator
Thistle	*Silybum marianum*	Silymarin mixture (silibin A, silibin B, isosilibin, silicristin, silidianin)	Hepatoprotective Anti-inflammatory

In an in vitro study by Fiore et al. (21), It was reported that licorice root exerted antiviral effects on various viruses, including SARS-associated coronavirus, HIV-1 and RSV. In a review conducted by Asl and Hosseinzadeh in 2007 with licorice root, it was concluded that it was effective against SARS, HIV, varicella zoster, hepatitis A, B, C, CMV, HSV type 1 viruses (22). In another review in 2014, it was concluded that this plant shows activity against H1N1, H5N1, Influenza A virus (IAV), Hepatitis C virus, Rotavirus, HIV and SARS virus (23).

Glycyrrhiza glabra is a plant approved by Comission E in upper respiratory tract diseases and cough (24). In addition to its expectorant and antitussive effects, it also has anti-inflammatory, immunomodulatory and mucoprotective effects. For this reason, it has traditionally been used in respiratory tract infections (25). The expectorant effect of licorice is related to the stimulation of tracheal mucus secretion. In this way, it helps to remove mucus from the respiratory tract (26). Its antitussive effect has also been shown in animal studies (27). This effect is based on the active ingredients of liquiritine and liquiritigenin contained in licorice root.

In in vitro studies, it has been reported that some compounds obtained from licorice root inhibit the growth of gram positive bacteria and yeast and show strong antibacterial activity against streptococcus mutans. Tanaka Uosuo et al. found that compounds derived from licorice root show activity against upper respiratory tract bacteria (Streptococcus pyogenes, Haemophilus influenzae and Moraxella catarrhalis) (28).

In a randomized, double-blind, controlled study by Yanagawa et al., the effect of glycyrrhizin on URIs was evaluated. The patients were divided into 2 groups and only 500 ml of ringer's lactate was given to one group, while the other group was administered iv 40 ml of glycyrrhizin (0.2%) and ringer's lactate. Glycyrrhizin treatment has been found to be associated with a shorter hospital stay, lower fever and lower treatment costs compared to the control group (25). Considering all these results, it can be predicted that licorice root preparations can be applied as a support to existing treatments in severe cases of COVID-19 with mild symptoms or pneumonia.

• South African Geranium (Pelargonium sidoides)

EPs 7630 (Umcka®), an alcohol extract obtained from rhizomes and tubers of Pelargonium Sidoides, is an approved herbal medicine in Germany for acute bronchitis. Primary active ingredients include highly oxygenated coumarins (eg Umckalin) and polyphenolic compounds. Umcka is used for a three-pronged approach in acute bronchitis: 1- enhances immune function; 2- antimicrobial - antimicobacterial and antiviral and prevents bacteria and viruses from adhering to the mucous membranes of the respiratory tract; and 3- acts as an expectorant. EP 7630 at a dose of 100 mcg / mL prevents the reproduction of seasonal influenza A virus strains (H1N1, H3N2), respiratory syncytial virus (RSV), human coronavirus, parainfluenza virus and coxsackievirus. However, it has been reported to have no effect on highly pathogenic avian influenza virus (H5N1), adenovirus or rhinovirus. EPs 7630 causes a decrease in the Bronchitis Severity Score (BSS) due to improvement in cough, sputum production, chest pain, and shortness of breath after 7 days of treatment (29, 30). In many clinical studies, the efficacy of EPs 7630, a preparation of Pelargonium sidoides, in reducing symptoms caused by infection of the airways, from common cold to acute bronchitis, has been widely demonstrated in the adult population. It has also been noted that the use of the EPs 7630 preparation during the initial period of respiratory tract infection symptoms reduces the severity of symptoms and the duration of the disease. It has been reported that EPs 7630 is well tolerated and can be used in children older than 1 year (30). In addition, it should be considered to be a good complementary therapy in COVID-19 infection in order to reduce the need for NSAII (Non-steroidal anti-inflammatory drug) and antibiotics, and provide preventive effect against clinical deterioration or complications.

• Common Ivy (Hedera Helix)

Extracts obtained from ivy leaves are used for cough and asthma. More than 80% of herbal expectorants prescribed in Germany are preparations containing ivy extract. Ivy leaves contain saponins with expectorant, mucolytic, spasmolytic, bronchodilator and antibacterial effects. The mucolytic expectorant effect is based on the indirect beta-2 adrenergic effect as a result of the saponins alpha-heder and the hederacoside C. Ivy is generally a herb that shows good safety, tolerability, and efficacy in acute and chronic bronchitis. It is usually included in preparations alone. It has been reported that the combination of ivy and thyme (Thymus vulgaris) for acute bronchitis causes earlier throat softening and reduced cough compared to placebo (29).

• Absinth (Artemisia Annua)

Chloroquine (CQ) and hydroxychloroquine (HCQ) are anti-malarial drugs synthesized from the henna henna (Cinchona pubescens) plant and tested for COVID-19, which are also used against autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE). Although HCQ exhibits a safer toxicity profile than CQ, it has significant side effects. The most important side effect is cardiac toxicity. Therefore, HCQ treatment is alarming, especially in patients with COVID-19 who have cardiovascular problems (31). Artemisinins are sesquiterpene lactones with a peroxide part isolated from the Artemisia annua plant. Although the antimalarial mode of action of artemisinin is different from CQ or HCQ, its immunomodulatory effects are similar. It is traditionally used in the treatment of high fever. Since high fever is observed in the vast majority of COVID-19 patients, it is thought to be useful in the treatment of this disease (31). Considering the ability of artemisinin to reduce key mediators such as TNF-α and IL-6, this herb can be seen to be a promising therapeutic agent in the ARDS picture that worsens the condition of COVID-19 patients.

Artemisinin has been reported to exhibit a safe toxicity profile. Thus, high doses can be reached with less worry. It is thought that artemisinin can be used as adjunctive therapy to reduce the

dose required for CQ or HCQ and thus reduce side effects and at the same time suppress cytokine storm (31).

• Echinacea (Echinacea Purpurea)

It is known that echinacea has an activity on the immune system as well as its antimicrobial activity. Alkylamides, caffeic acid derivatives and polysaccharides are important components of the plant. In addition, many in vitro and in vivo studies have shown that alkylamides have a role in the immunomodulatory activity of echinacea extracts (32).

Cytokine antibody arrays are used to investigate changes in proinflammatory cytokines released from human bronchial epithelial cells after rhinovirus exposure. It is stated that the majority of cytokines released by virus infection decrease with the application of E. purpurea extract. By their very nature, in vitro studies have a narrow perspective for clinical prediction due to potentially included bioavailability, dosage issues, etc. problems. Probably the most significant in vitro studies for echinacea are studies involving alkylamides, as the bioavailability of these compounds has been demonstrated in several studies (33).

It has been shown that a lipophilic extract of E. purpurea stimulates TNF-α mRNA (transcription) synthesis in peripheral monocytes, but has no effect on its translation, ie TNF-α protein itself. As is known, for a protein synthesis, first transcription must be followed by translation. In other words, TNF-α protein formation from mRNA is prevented. TNF-α protein production is significantly increased when monocytes are treated with LPS (lipopolysaccharide or endotoxin: a powerful stimulator of the immune system). However, it has been shown that incubation of monocytes with LPS and Echinacea extract strongly inhibits this effect of LPS. In studies conducted for a long time, it has been shown that echinacea extracts interact with CB2 (cannabinoid receptor type 2) receptors, modulating and prolonging TNF-α production if present in an immune stimulation environment. These studies suggest that E. purpurea acts as a modulator or facilitator of the immune response rather than an immune stimulant (33). According to the researches here, it can be concluded that lipophilic echinacea extract rich in alkylamide can increase the immune response before virus exposure due to its immunomodulatory activity and with the retention of the virus, the immune response continues to be maintained in a reduced manner.

Elderberry (Sambucus nigra)

Elderberry (Sambucus nigra) is a plant commonly used in many parts of the world, often referred to as the tree of life. Both its fruits and flowers are rich in flavonols (e.g. Kempferol, quercetin, isoramnetine and derivatives), proanthocyanidins and phenolic acids (e.g. chlorogenic, neuro-chlorogenic or crypto-chlorogenic acid) (34) Initial studies on the use of elderberry are related to the antiviral property of the plant. However, subsequent research is on the immune response and especially its effectiveness in increasing cytokine production (35). According to the results of a meta-analysis conducted in 2019, standardized elderberry extract supplementation has been shown to be significantly effective in reducing the overall duration and severity of upper respiratory tract symptoms compared to a placebo group (36).

473 patients with early flu symptoms (<48 h) were included in a randomized double-blind study. Patients received oseltamivir for 5 days and placebo or a combination of elderberry and Echinacea for the other 5 days. It has been reported that the herbal medicine combination is as effective as the antiviral drug oseltamivir (37).

In another study, 312 passengers traveling from Australia to an overseas country were asked to take elderberry extract or placebo 10 days before the flight and up to five days after arrival at the travel destination. Although the common cold was less common in the elder group, this value was not statistically significant. However, it was reported that the duration of cold symptoms was shorter in the group taking elderberry (38).

There is preclinical evidence showing that elderberry is different from COVID-19 but inhibits the replication and viral binding of Human coronavirus NL63 (HCoV-NL63), which is a member of the coronavirus family (39).

There is no study stating that Sambucus nigra will cause a cytokine storm in coronavirus infections. In a study, it was reported that Sambucus nigra could be more effective in the prophylaxis of corona virus infections or in the early stage of the disease (40). Remarkably, Sambucus has also been reported to significantly increase inflammatory cytokines, including IL-B1 (41). For this reason, it is considered to be discontinued as a result of positive test or when the symptoms become evident. According to an evidence-based systematic review conducted by the Natural Standard Research association, elderberry contains B-level evidence to support its use for influenza (42). Although this result does not support its use in COVID-19 prophylaxis and treatment, more studies are needed on this subject.

• Galangal, (Alpinia Officinarum)

Alpinia officinarum and Zingiber officinale Roscoe (ginger) are aromatic plants belonging to the Zingiberaceae family, both of whose rhizomes are used as spices. Galangal, is a plant rich in bioactive components, mostly used in Far Eastern countries in many diseases such as common cold, bronchitis, stomach pain, diabetes, ulcer, abdominal distension, diarrhea, vertigo, neuropathy, rheumatoid arthritis and inflammatory bowel diseases (43).

There are studies showing that some diarylheptanoids isolated from Alpinia officinarum show antioxidant activity, inhibit iNOS (inducible nitric oxide synthase) expression and biosynthesis of prostaglandin and leukotrienes (44). In *in vitro* studies, it is stated that besides all plant and rhizome extracts, galangin and caemferid content also show activity against some pathogenic bacteria (44-47). In mice, it has been reported that the methanol extract of the rhizomes shows inhibitory activity against the malaria parasite Plasmodium berghei (48). It has also been reported that Alpinia officinarum extract shows anti-influenza activity following oral administration in mice (44).

There are also studies showing that Alpinia officinarum rhizome extracts have anti-inflammatory and immunomodulatory effects. In a study on this subject, the activity of CAME (p-Coumaryl alcohol-γ-O-methyl ether) substance isolated from Alpinia officinarum was evaluated. In this study, it has been shown that CAME inhibits the formation of IFNγ, which is a proinflammatory cytokine, by suppressing T-bet expression. According to this study, it was concluded that CAME may be useful in modulating inflammatory immune disorders mediated by excessive IFNy production (49). In another study, it is stated that the immunomodulatory effect of Alpinia officinarum is due to its antioxidant fraction (especially quersetin), since free radicals are effective in T cell activation (50).

SARS-CoV-2 papain-like protease (PLpro) is required for the survival and replication of the virus and is one of the drug targets to be developed against SARS-CoV-2 (51). According to a study by Goswami D et al., it was concluded that eight compounds found in Alpinia officinarum and ginger rhizomes are potential inhibitors against SARS-CoV-2 PLpro (51).

Other Phytotherapeutic Supplements

There have been many studies showing that curcumin, the essential component of turmeric (Curcuma longa), may be beneficial in the prophylaxis or treatment of diseases from cancer to viral infections (52). In a study conducted on rats in 2015, it was stated that curcumin provides cardiovascular protection by increasing ACE-2 expression and improves myocardial fibrosis (53). Since the ACE-2 receptor is the entry mechanism of the virus, the use of curcumin during COVID-19 infection is currently under discussion. Because it is feared that curcumin will increase the ACE-2 receptor, making the infection worse. At first, ACE-2 is seen as the main target in the fight against coronovirus, but this information is questioned with new studies. As an example, it has been reported that increased ACE-2 protects against viral lung damage by increasing the production of angiotensin 1-7 (54). In another animal study that supports this, it has been shown that SARS-COV reduces ACE-2 receptor expression and ACE-2 is protective against ARDS (55). A double-blind, randomized controlled Phase II clinical trial of the oral spray formulation containing curcumin and artemisinin is currently underway (CT number: NCT04382040) (56). Although preclinical data shed light on clinical data, the efficacy of curcumin in COVID-19 infection needs to be proven by further clinical studies.

Thistle (Silybum marianum) is the best researched herb in the treatment of liver disease. The active complex of thistle is a mixture of silymarin obtained with a lipophilic extract from plant seeds (57). Liver damage associated with COVID-19 is defined as liver damage that can occur during the course of COVID-19 treatment, with or without pre-existing liver disease. According to a study conducted with COVID-19 patients, it was reported that abnormalities in liver function tests were found in one third of patients (58). Recently, it has been suggested that liver failure seen in COVID-19 patients may also be drug-related (59). The effect of silymarin on liver regeneration can be explained by stimulating protein synthesis, increasing cellular glutathione level and suppressing lipid peroxidation (60). Silymarin also reduces liver function tests (61). In order to accelerate liver regeneration and improve liver function tests, its use should be considered as complementary therapy for liver protection in COVID-19 disease. In addition, because silymarin inhibits the p38 MAPK pathway and reduces inflammation and autophagy, a Phase III, randomized, double-blind controlled clinical trial is currently being conducted to test the efficacy of silymarin on COVID-19 pneumonia (CT number: NCT04394208) (62).

Since the clinical course of COVID-19 is not always severe, it is important to use phytotherapeutic products in mild URTI symptoms such as sore throat. In this regard, sage (Salvia triloba), which grows naturally in our country, is frequently preferred in throat infections with its anti-inflammatory properties. According to the results of a randomized, double-blind, clinical study, it was stated that the spray formulation containing echinacea-sage ethanolic extracts provided similar benefits to chlorhexidine / lidocaine spray in reducing symptoms in the patient group diagnosed with acute pharyngitis and tonsillitis (63). Pomegranate (Punica granatum) plant can also alleviate sore throat by reducing the effectiveness of pathogens that cause throat infections due to the polyphenolic components in its shell (64).

Conclusion

In the COVID-19 pandemic, which causes serious morbidity and mortality and economic losses, there is no specific treatment other than supportive treatment. Traditional Chinese Medicine and conventional medicine have been used together at certain stages by the Chinese health system since the first reports of COVID-19. Although most of the plants here are not found in our country, the use of similar plants in terms of their content can both contribute economically and provide an additional benefit to the treatment by using plants that are safe and tolerable. In the last 20 years, coronoviruses have emerged as epidemics and it is possible that the same epidemics will continue for the next years due to reasons such as increased human-animal interactions and frequent mutations of viruses. Since targeted therapies require a long time to be implemented in each new epidemic, phytotherapeutic approaches that can be implemented quickly are very important. For example, using standardized preparations of plants such as licorice and ivy for antitussive and expectorant purposes or using plants with immunomodulatory effects for treatment purposes at the beginning of COVID-19 prophylaxis or disease may shorten the treatment period and increase the quality of life of the person. As the disease progresses, this virus is not limited to the lungs, but may also cause failure in other organs. The use of silymarin at this point is very important. Because it is a plant-based compound that has been studied for a long time and its hepatoprotective activity has been supported by many preclinical and clinical studies. Silymarin should be considered an important supportive therapy in cases of deterioration or failure of liver function that may be seen with COVID-19 disease. Since COVID-19 is not always severe, it can be diagnosed with typical cold symptoms and treated at home. In this case, it may be recommended to use infused teas

or lozenge forms of herbs such as sage, chamomile, pomegranate peel with anti-inflammatory properties. There are many factors that can assist treatment in the field of phytotherapy. However, evidence-based prospective studies are unfortunately inadequate. For this reason, it will be possible to add supportive treatment or prophylaxis protocols if more clinical studies are conducted for plants used for many years.

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