

Koronavirüs Hastalığının Önlenmesi ve Tedavisi İçin Şifalı Bitkiler

Medicinal Plants for Prevention and Treatment of Coronavirus Disease

Önder OTLU¹, Ceyhun BERKETOĞLU², Tuğba Raika KIRAN¹, Aysun BAY KARABULUT³
1 Malatya Turgut Ozal University School of Medicine Department of Biochemistry Malatya, Turkey

onder.otlu@ozal.edu.tr, raika.kiran@ozal.edu.tr

2 İskenderun Technical University, Faculty of Engineering and Natural Sciences, Hatay, Turkey
ceyhun.berketoglu@iste.edu.tr

3 Ankara Yıldırım Beyazıt University School of Medicine Department of Biochemistry, Ankara, Turkey
aysunbay@hotmail.com

Özetçe—2019-nCoV (yeni Korona Virüsü) salgını Uluslararası Acil Halk Sağlığı Kuruluşu olan Dünya Sağlık Örgütü (WHO) tarafından 30 Ocak 2020'de ilan edildi ve DSÖ 12 Şubat'ta, 2019-nCoV patojenini SARS-CoV-2 ve Corona virüs Hastalığı 2019 (COVID-2019) olarak adlandırdı. COVID-19 11 Mart 2020'de resmi olarak WHO tarafından Pandemi olarak kabul edildi. Bitkiler tüm dünyada, viral hastalıklar da dahil olmak üzere birçok kronik enfeksiyonu tedavi etmek için yüzyıllardır geleneksel ilaç olarak kullanılmaktadır. Son yıllarda, bilim adamları fonksiyonel ve nutrasötik gıdalar üzerinde yaptıkları araştırmalarla fonksiyonel bileşiklerin insan sağlığını koruma ve hastalıkları iyileştirme potansiyelini doğrulamaya çalışmaktadırlar. Geleneksel tıbbi bitkiler, sağlıklı yaşamın sürdürülmesi, günlük hayatta alınan toksinler, hastalıklarla mücadele ve önleme, uzun ömür gibi birçok araştırma ile desteklenmiş uzun bir geçmişe sahiptir. Etnomedikal bitkiler ve doğal fitokimyasalların antiviral, antiinflamatuvar ve antioksidan özellikleri üzerine yapılan araştırmalar, Covid-19 tedavisinin yanı sıra çeşitli rahatsızlıklara karşı büyük bir potansiyel ilaç kaynağı olarak kabul edilebilir. Bu çalışmadan yola çıkarak bitki özütlerinin Covid-19 gibi ölümcül sonuçlara yol açabilen viral enfeksiyonlarda beyaz kan hücrelerinin ve lenfositlerin sayısındaki yükselişle bağışıklığa arttırma, proinflamatuvar sitokinlerin üretimini ve salınımını düzenleme, C-reaktif protein ve eritrosit sedimentasyon oranındaki düşüşle anti-inflamatuar bir etki gösterme, virüsün gelişimine müdahale etme gibi olumlu etki ve potansiyel antiviral ajan aktivitesi sergilediği görülmektedir. Bu çalışmada COVID-19 enfeksiyonu ile ilişkili fitokimyasallar ve etkileri derlenmiştir.

Anahtar Kelimeler—COVID-19; şifalı bitkiler; bitkisel ilaçlar.

Abstract—The 2019-nCoV (new Corona Virus) outbreak was announced by the World Health Organization (WHO), the International Emergency Public Health Organization, on January 30, 2020, and WHO reported the 2019-nCoV pathogen to SARS-CoV-2 and Corona virus Disease 2019 on 12 February. (COVID-2019). COVID-19 was officially recognized as a Pandemic by WHO on March 11, 2020. Plants have been used all over the world

as traditional medicine for centuries to treat many chronic infections, including viral diseases. In recent years, scientists have been trying to verify the potential of functional compounds to protect human health and cure diseases with their research on functional and nutraceutical foods. Traditional medicinal plants have a long history supported by many researches such as maintaining a healthy life, toxins taken in daily life, fighting and preventing diseases, and longevity. Studies on the antiviral, anti-inflammatory and antioxidant properties of ethnomedical plants and natural phytochemicals can be considered as a great potential drug source against various ailments as well as Covid-19 treatment. Based on this study, plant extracts increase immunity with the increase in the number of white blood cells and lymphocytes in viral infections such as Covid-19, which can lead to fatal consequences, regulating the production and release of proinflammatory cytokines, showing an anti-inflammatory effect with a decrease in the C-reactive protein and erythrocyte sedimentation rate. It appears to have a positive effect such as interfering with the development and potential antiviral agent activity. In this study, phytochemicals and effects associated with COVID-19 infection were reviewed.

Keywords—COVID-19; medicinal plants; herbal drugs.

I. INTRODUCTION

COVID-19 Pandemic

COVID-19 left its mark on the 21st century as the most important health problem affecting all countries of the world in terms of both economic and health. Covid -19 was detected in Wuhan, the capital of China's Hubei province, in late 2019 and later, it was found that the infection was mostly transmitted from China to other countries. With the rapid spread of COVID-19 to more than 210 countries (Europe, Asia and Africa and across the world), costly health threats have emerged [1]. Most of the cases were reported to originate from the Huanan Seafood Market in Wuhan, where a wide variety of livestock species such as fish and pangolin, poultry, rats, and bats were traded [2].

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International Emergency Public Health Organization, on 30 January 2020, WHO named the 2019-nCoV pathogen as SARS-CoV-2 and Corona virus Disease 2019 (COVID-2019) on February 12. COVID-19 was officially recognized as a Pandemic by WHO on March 11, 2020 [3]. All countries of the world are taking precautions to restrict the spread of the virus. COVID-19 is the third coronavirus epidemic in the world and caught the 3rd highest mortality rate in the history of the pandemic [4]. Due to Corona virus 19 (COVID-19), which shook health systems around the world, even the world's largest economies have had difficulty controlling the virus. Government and research institutes are screening a certain part of the population on a daily basis due to limited resources, new initiatives are also made to establish more comprehensive diagnostic centers, institutions are working with superior performance to increase their screening capacity. Medical professionals, researchers, and government leaders continue to work on potential treatment methods, vaccines, and treatments [5].

Corona viruses, alpha, beta, gamma and delta, including 4 genus Letovirina and Orthocoronavirina named a member of the family consisting of two sub-Coronaviridae family. Corona viruses are RNA viruses with a single positive strand with a diameter of 80 - 140 nm enveloped. In the electron microscope, the outer periphery of the virus is surrounded by unique crown-like spikes, which is why it is referred to as Corona, which means crown in Latin [6]. Viral parent proteins include spike (S) protein, matrix protein (M), small envelope protein (E) protein, and nucleocapsid protein

(N). The location of viral attachment to the host cell is by the S protein. S protein can bind to angiotensin converting enzyme 2 (ACE2), transmembrane protease serine 2 (TMPRSS2) and glucose regulatory protein 78 to enter the cell. [7]. In addition, there are other corona viruses such as OC43, NL63, HKU1 and 229-E, which are known to cause mild respiratory infections in the human circulation. It is predicted that the receptor binding sites of SARS-CoV and SARS-CoV-2 are structurally similar despite variation of amino acids in their key sites [8] and that ACE2 is used by the new virus to enter the host cells [9].

The incubation period of Covid-19 is generally limited to 4-8 days. The most common symptoms of COVID-19 disease are fever, cough, dyspnea, sore throat and headache [10]. It has been reported that individuals with diabetes, asthma, liver and kidney diseases in all age groups are at higher risk of infection and tend to have severe disease [11]. Studies have shown that patients with COVID-19 infection develop secondary clinical complications caused by hyperinflammatory response and cytokine storm due to respiratory failure, the picture is in a vicious circle, and as a result, multiple organ failure and death occur [12].

In the pandemic that affected the whole world, all personnel working in hospitals and clinics had difficulties in both working overtime and in obtaining the materials they used. While the patient density in hospitals left clinicians in a difficult position in terms of implementing treatment protocols, at the same time, deciding which of the patients to give priority put pressure on clinicians psychologically. In such a large pandemic, the inadequacy of pharmacological treatment methods and the lack of appropriate and definitive treatment caused the disease to increase. Supportive methods with specific effects such as mechanical ventilation were used in addition to various drug treatments [13]. Remdesivir [14], Remdesivir and chloroquine combination [15], Chloroquine [16], Arbidol [17,18], Lopinavir / Ritonavir, Neuraminidase inhibitors and peptide EK1 nucleoside analogues [19] can be used as antivirals in the treatment of COVID 19 patients. Dexamethasone has also been reported to be beneficial in critically ill patients [20]. According to the World Health Organization, there are currently more than 50 new corona virus vaccine candidates all over the world, and only a few of them have passed the pre-clinical research stage and reached the clinical trial stage.

Herbal Prescriptions for Covid 19 Treatment and Prevention

Considering the increasing number of deaths and cases in pandemics that deeply shake the world, medicinal herbs with immunomodulator, antioxidant, antiviral and antipyretic properties should be included in our daily life routine and included in the medical system with new strategies to increase immunity and prevent diseases [21]. The human coronavirus and several picornaviruses are responsible for widespread epidemic epidemics around the

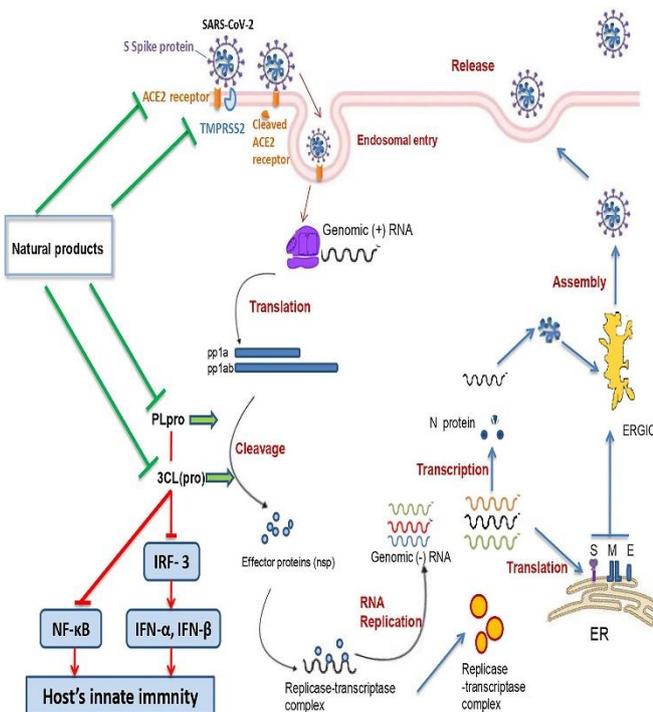


Figure I: Possible anti-SARS-CoV 2 actions of natural products

world, placing heavy burdens on hosts and therefore on the healthcare system.

Plants have been used all over the world as traditional medicine for centuries to treat many chronic infections, including viral diseases. In recent years, scientists have been trying to verify the potential of functional compounds to protect human health and to cure various diseases with their research on functional and nutraceutical foods [22, 23]. In addition, it is known that approximately 80% of the world population uses herbal treatment during the prevention and treatment phase of diseases. In addition, herbal compounds reduce the symptoms of viral diseases by strengthening or treating the immune system, thus allowing individuals to overcome infections much more comfortably [24,25]. Immunomodulators are defined as substances of biological or synthetic origin that have the ability to stimulate, suppress or modulate any component in the immune system [26]. Phytotherapeutics are known to have a wide range of potential effects, both curative and preventative. The purpose of this review is to present a document on biologically active functional food plants in the epidemic of Covid-19, to protect against infectious agents by increasing the immune system, to overcome the symptoms of the disease and to treat it more comfortably. Figure 1 summarizes the possible anti-SARS-CoV 2 actions of natural products [27].

In the study examining approximately 1033 medicinal herbal compounds related to ACE2, TMPRSS2, GRP78 and AT1R receptors, which are the receptors used by the coronavirus to enter the cell, it was determined that the most effective and suitable compounds to prevent COVID-19 infection are berbamine, hypericin and hesperidin. It has been stated that clinical evaluation of these compounds for the prevention, control and treatment of COVID-19 infection can have striking and effective results. [28].

In one study, the antiviral effect of mulberry tree (*Morus* spp.) leaves and stem bark was examined on enveloped and non-enveloped viral pathogens such as human coronavirus (HCoV 229E) and different members of the Picornaviridae family - human poliovirus 1, human parecovirus 1 and 3, human ecovirus 11. It has been determined that the extracts reduce the viral titer and cytopathogenic effects, while water-alcohol extracts of mulberry leaves exhibit maximum antiviral activity on human coronavirus. In addition, water and water-alcohol extracts of stem bark and leaves have been reported to be more effective on picornaviruses [29]. Zhang et al reported that 26 of 125 herbs used in traditional Chinese medicine to treat viral respiratory infections regulate immune / inflammation reactions and hypoxia response, and 13 of these natural compounds may have potential anti-2019-nCoV activity [30].

Roselle (*Hibiscus sabdariffa* L.) powder calyces have high Niacin (B3) content, rich in pyridoxine, folic acid, riboflavin, and pantothenic acid and B vitamins, high in mineral composition of Ca, K, Mg as well as Fe, Na, Zn, Cu, and Mn were detected. It has been reported that *Hibiscus*

sabdariffa L. may have the power to be considered as an effective drug with its richness in bioactive components such as polyphenols and flavonoids, especially anthocyanins [31].

Alam et al. reported that the use of *Tiryag-e-Wabai* will be effective in outbreaks such as Covid 19 [32]. In another study, it was stated that *Joshandah Sual*, which is a poly herbal formulation, could be effective in the treatment of Covid 19. The contents of both herbal formulations are given in Table 1 [33].

Withanone, the natural phytochemical obtained from *Withania somnifera*, has different effects on the viral receptor binding domain (RBD) and host ACE2 receptor complex, the AEC2-RBD complex is very well coupled to the binding interface and moves slightly to the interface center in the simulation. It has been stated that interruption of electrostatic interactions between RBD and ACE2 in this way will prevent the entry of COVID-19 into the host or weaken its contagiousness [34].

They reported that *Tinocordiside* is very well interlocked in the center of the interface of the ACE2-RBD complex and stabilized well in molecular dynamics simulation, the free binding energies of the ACE2-RBD complex reduce the electrostatic component and the increase in the spherical elasticity of the complex will weaken the SARS-CoV-2 entry and its subsequent contamination. They reported that *Tinocordiside*, which is a natural phytochemical, will show positive effects in controlling the transmission of SARS-CoV-2 and its entry into host cells [35].

Tulsi (*Ocimum sanctum*) extract is known to be rich source of flavones and flavonoids. *Scutellarein* which found in *Tulsi* is a natural flavone. The medicinal properties of *Ocimum sanctum* have been studied in in vitro, animal and human experiments with scientific studies and it has been reported to have a unique content. It has been reported in many studies that *tulsi* has anti-asthma, anti-tussive, adaptogenic, anti-stress anti-pyretic antimicrobial, antibacterial, antimalarial, anthelmintic, antiviral, antifungal, antiprotozoal, anti-diarrhea, anti-oxidant, anti-inflammatory, hepatoprotective, neuroprotective, cardioprotective, anti-diabetic, analgesic and anti-allergic activities [36-40]. Flavones are known to have an increased antiviral effect on herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) in cell culture with the simultaneous application of apigenin and acyclovir [41]. It has been reported that *myricetin* and *scutellarein* inhibit SARS-CoV helicase, and this effect is mediated by the inhibition of ATPase activity [42].

Balkrishna et al. Investigated the effect of herbal drug, *Divya-Swasari-Vati* (Table 1), zebrafish injected with the recombinant spike protein of SARS-CoV-2. They reported that cytokine profile and immune cell infiltration, morphological and cytological changes were completely reversed by *Divya-Swasari-Vati* drug within 7 days of

treatment. Divya-Swasari-Vati has also been reported to suppress proinflammatory cytokines, IL 6 and TNF- α levels in a dose-dependent manner in vivo and in vitro. In Divya-Swasari-Vati medical formulation, phyto compounds determined by HPLC were Gallic acid, Protocatechuic acid, Methyl gallate, Ellagic acid, Coumarin, Cinnamic acid, Glycyrrhizin, Eugenol, 6-Gingerol, Piperine, Glabridin [43]. It has been evaluated that the formulation consisting of Sibr (Aloe barbadensis), Murr (Commiphora myrrh) and Zafran (Crocus sativus) may have a prophylactic effect against COVID-19 [44].

It has been reported that glycyrrhizin and glycyrrhetic acid, an active ingredient of licorice roots, had a direct effect to reduce the spread of Covid-19. ACE2 is part of the broad renin-angiotensin-aldosterone system. Compounds that upregulate plasma aldosterone and aldosterone receptor (MR) activation may inhibit classical ACE. MR activation can therefore protect organs from binding to COVID-19 by reducing ACE2 expression. Glycyrrhetic acid inhibits 11beta hydroxysteroid dehydrogenase (11betaHSD2) and activates the plasma aldosterone and aldosterone receptor in organs expressing this enzyme, including the lung. It has been stated that glycyrrhizin can reduce the severity of COVID-19 infection in two different ways. The first is to reduce the number of intracellular entry points and the second is to provide an anti-inflammatory mechanism independent of ACE2 [45]. Glycyrrhiza glabra and Andrographis paniculata, which can support immunity in the treatment of Covid-19, also have antiviral properties [46]. It has been reported that Withania somnifera (Indian ginseng), which is known for its antiviral, immunomodulatory, anti-inflammatory, therapeutic and powerful antioxidant properties, can be used as an antiviral agent in the treatment of COVID 19 [47].

Local name of the formulation	Ingredients	Reference
Tiryaq-e-Wabai	2 g of Aloe barbedensis L. extract, 1 g of Crocus sativus L. stamini and 1 g of Commiphora myrrha gum	[32]
Joshandah Sual	Glycyrrhiza glabra L. root, Tinospora cordifolia willd stem, Oscimum sanctum L. leaves, Nigella sativa L. seed, Zingiber officinale Roscoe rhizome, Piper longum L. fruit, Ziziphus jujube Mill fruit, Rosa damascena Mill flower, Viola odorata L. flower, the whole plant of Swertia chirata L. and Fumaria officinalis L.	[33]
Divya-Swasari-Vati	64 mg of Mulethi (Glycyrrhiza glabra), 63 mg of Kakadasingi (Pistacia integerrima), 63 mg of Rudanti (Cressa cretica), 42 mg of Sounth (Zingiber	[43]

	officinale), 42 mg of Chhoti Pipal (Piper longum), 42 mg of Marich (Piper nigrum), 32 mg of Dalchini (Cinnamomum zylanluspyscium), 32 mg of Akarkara ((Anacyclus pyrethrum), 32 mf og Lavang (Syzygium aromaticum), 12.6 mg of Mukta-Shukti Bhasma, 12.6 mg of Abhrak bhasma, 12.6 mg of Kapardak Bhasma, 12.6 mg of Godanti Bhasma, 12.6 mg of Sphatika Bhasma, 12.6 mg of Praval Pishti, 12.6 mg of Tankan Bhasma	
Liu Shen Herbal Capsule	0.12 % gamabufotalin, 0.10 % arenobufagin, 0.26 % telocinobufagin, 0.21 % desacetylcinobufotalin, 0.25 % bufotalin, 0.41 % cinobufotalin, 0.27 % bufalin, 0.70 % resibufogenin, 0.68 % cinobufagin, 1.81 % cholic acid, 0.27 % anserine deoxycholic acid and 0.23 % deoxycholic acid	[69]
Japanese Mix (no spesific name)	Bupleurum chinense, Ramulus Cinnamomi, Scutellaria baicalensis, Glycyrrhiza, Atractylodes macrocephala, Rhizoma Zingiberis, Agastache rugosa, Stephania tetrandra root, Polygonum cuspidate, Rheum palmatum, tangerine peel, Semen Armeniphacae Amaricum	[73]
Natural Herbal Medicine (no spesific name)	15 g of Lonicera japonica Thunb, 15 g of Lablab purpureus, 15 g of Wolfiporia Ryv, 15 g of Rehmannia glutinosa, 12 g of Scutellaria baicalensis, 10 g of Bubalusbubalis Linnaeus, 10 g of Eriobotrya japonica Thunb, 9 g of Scrophularia ningpoensis Hemsl, 9 g of Forsy suspensa	[75]
Lian Hua Qing Wen	Forsythiae Fructus, Lonicerae Japonicae Flos, Ephedrae Herba, Armeniacae Semen Amarum, Gypsum Fibrosum, Isatidis Radix, Dryopteridis Crassirhizomatis, Rhizoma, Houttuyniae Herba, Pogostemonis Herba, Rhei Radrenix etizixoma, Rhoi Radrenix etizixoma,	[78]

	Glycyrrhizae Radix et Rhizoma	
Mahuang Liu Jun Tang	Fuling (<i>Poria cocos</i>), Huangqi (<i>Astragalus membranaceus</i>), Huoxiang (<i>Pogostemon cablin</i>), Kuxingren (<i>Prunus armeniaca L.</i>), Baizhu (<i>Atractylodes macrocephala</i>), Banxia (<i>Pinellia ternata</i>), Gancao (<i>Glycyrrhiza</i>), It includes Houpo (<i>Magnolia officinalis</i>), Mahuang (<i>Ephedra sinica</i>), Guizhi (<i>Cinnamomum cassia</i>), Huangqin (<i>Scutellaria baicalensis</i>), Sharen (<i>Amomum villosum</i>), Jiegeng (<i>Platycodon grandiflorum</i>), Peilan (<i>Eupatorium fortunei</i>), and Dangshenglos	[81]
Xuanfei Baidu	Ephedrae Herba, Armeniaca Semen Amarum, Gypsum Fibrosum, Atractylodis Rhizoma, Semen Coicis, Agastachis Herba, Polygoni Cuspidati Rhizoma et Radix, Lepidii seu Descurainiae Semen, Verbenae Herba, Phragmitis Rhizoma, Artemisiae Annuae Herba, Citri Grandis Rubrum Exocarpium, Glycyrrhizae Radix et Rhizoma	[82]

Table I: Ingredients of some herbal formulations

Many nutritional plants such as Aloe vera, *Angelica gigas* (Korean angelica), *Astragalus membranaceus* (Mongolian milkvetch), *Ganoderma lucidum* (lingzhi mushroom), *Panax ginseng* (ginseng) and *Scutellaria baicalensis* (Chinese skullcap) are known to exhibit antiviral and immunomodulatory activities. Herbs with such antiviral and immunomodulatory activity could be used in diet or as complementary therapy to prevent infection and strengthen immunity [48]. Sinha et al reported that glisperin A, a phytocomponent of the *Glycyrrhiza glabra L.* from the family Fabaceae, inhibits viral replication after entering the host, unlike glycyrrhizin. [49].

Phytochemical compounds of *Tinospora cardifolia* (Guduchi) from the Menispermaceae family, such as tinosponone, xanosporic acid, cardiopholioside B, tembetarine, and berberine, have been identified as possible main molecules to combat SARS-CoV-2 [50]. It has been reported that quinine, which is the major antiviral compound of Cinchona tree (Quina) from the Rubiaceae family, is suitable for use in obtaining an effective synthetic drug chloroquine to fight Covid-19 due to its DNA interlayer feature [51]. Apigenin, the active component of *Petselinum crispum* from the Apiaceae family, has been reported to

show strong binding affinity for Covid-19 spike protein and have strong antiviral activity [52]. It has been reported that *Camellia sinensis* (Green Tea), a member of the Theaceae family, may have a strong therapeutic property due to its ability to inhibit the main protease required for the replication of the new Corona virus due to the presence of polyphenols such as Epicatechingallate, epigallocatechin gallate and galliccatechin-3 gallate [53].

Parida et al systematically investigated 1916 of phytochemicals from 55 different Indian medicinal plants with anti-viral properties with rational screening to develop prophylactic treatment against Covid-19. Steroidal lactones (37%) from *Withaniasomnifera* and triterpenoids (19%) from *Azadirachtaindica* were determined from the highest scored phytochemicals that scanned [54].

Since the course of Covid-19 disease in adults is reported to be more severe than in children, the Glycyrrhizae Radix et Rhizoma plant, which has both antiviral and anti-inflammatory properties, is used more frequently. However, it has been reported that Armeniaca Semen plant, which is widely used in respiratory tract diseases, has been used in children because of the milder disease [55]. Xu and Zhang recommended the use of *Astragalus membranaceus*, *Atractylodis Rhizoma*, *Eupatorii Herba*, *Agastache rugosa*, *Ophiopogon japonicas*, *Scrophularia ningpoensis*, *Rhizoma phragmitis*, *Adeinophora stricta* Miq, and *Dendrobium nobile* Lindl. medicinal plants for Covid-19 treatment and infection prevention. [56]. On the other hand, Luo et al reported that *Astragalus membranaceus*, *Glycyrrhizae uralensis*, *Saposhnikoviae divaricata*, *Rhizoma Atractylodis Macrocephalae*, *Lonicerae Japonicae Flos*, *Fructus Forsythiae*, *Atractylodis Rhizoma*, *Radixycodonis* could be effective in the infection of the Covid-19 [57]. It has been reported that glycyrrhetic acid, baicalein, amygdalin, fihlorogenic acid, forsythiaside, ephedrine, pachymic, acid, patchouli, alcohol platycodin D active ingredients respectively from Glycyrrhizae Radix et Rhizome, *Scutellariae Radix*, *Armeniaca Semen Amarum*, *Lonicerae Japonicae Flos*, *Forsythiae Fructus*, *Ephedrae Herba*, *Poria*, *Pogostemon Cablin*, *Citri Reticulatae Pericarpium*, *Platycodonis Radix* plants may be effective in chronic inflammatory disorders caused by viral infection such as Covid-19 [58]. Hensel et al reported that extracts prepared with *Echinacea* species (Asteraceae), which are thought to be anti-infectious plants, have an important role on the immune system due to the alkyl amides that interact with the cannabinoid receptor, among other factors [59].

In another study, it was reported that *Althaea officinalis*, *Commiphora molmol*, *Glycyrrhiza glabra*, *Hedera helix* and *Sambucus nigra* had sufficient levels of evidence to deserve their potential clinical use as adjuvant in the treatment of Covid-19 early / mild cases [60]. Enmozhi et al showed that the andrographolide compound obtained from *Andrographis paniculata* could be a potential inhibitor of the main protease (Mpro) of SARS-COV-2, with in-silico studies such as molecular docking, target analysis, toxicity

prediction and ADME prediction. They also reported that andrographolide had good solubility, pharmacodynamics and target accuracy [61]. It was reported that the active compounds of baicalin (*Scutellaria baicalensis* Georgi), Scutellarin (*Erigeron breviscapus*), Hesperetin (citrus aurantium), Nicotianamine (soybean), and glycyrrhizin (*Glycyrrhiza radix*) have potential anti-2019-nCoV effects and has the potential to bind to ACE2 and prevent 2019-nCoV entry [62]. Also *Rhizoma Polygonati* can eliminate the immune response and cytokine storm of COVID-19 during the treatment of pneumonia [63].

With a structure-based molecular insertion study, eight compounds found in the natural product of galangal (*Alpinia officinarum*) rhizomes and ginger (*Zingiber officinale* Roscoe) were identified as potential inhibitors of SARS-CoV-2 Papain-like protease [64]. According to research on alkaloids and terpenoids originating from African plants, Gyebi et al reported that 10-Hydroxysambarensine, Cryptoquinoline, 6-Oxoisoquaguerin and 22-Hydroxyhopan-3-one is a potent drug and may be potent inhibitors which effect against 3-chymotrypsin-like protease (3CLpro) that controls virus replication in SARS-CoV-2 [65]. Abd El-Aziz et al investigated the potential of eight natural polyphenols, such as quercetin, naringenin, caffeine, oleuropein, ellagic acid, benzoic acid, resveratrol, and gallic acid as inhibitors of SARS-CoV-2 RNA-dependent RNA polymerase (RdRp). According to the results obtained, it has been shown that gallic acid and quercetin exhibit high binding affinity to RdRp [66]. Cepharanthine, an alkaloid tetrandrin isolated from *Stephania tetrandra* S. Moore, has antioxidant and anti-inflammatory activity. Cepharanthine has been reported to have therapeutic potential, as it can bind to SARS-CoV-2, NSP12-NSP8 active interface pockets [67]. It has also been observed that quercetin, kaempferol, luteolin, isorhamnetin, baicalein, naringenin, and wogonin compounds target ACE2 and 3CL protein, inhibit inflammatory mediators, regulate immunity and have the potential to eliminate free radicals, and it has been reported that these compounds may be included in the treatment of COVID-19 [68]. According to the results of in vitro studies conducted with Liu Shen capsule (Table 1), it has been reported that this capsule regulates the activity of the NF- κ B / MAPK signaling pathway induced by inflammatory cytokines, decreases the expression of the virus and therefore has an anti-SARS-CoV-2 effect. It has been reported that Liu Shen capsules can be an effective anti-inflammatory agent and can be used to treat inflammation caused by SARS-CoV-2 [69]. As a result of their study, Ang et al reported that *Citri Reticulatae* Pericarpium and *Glycyrrhizae Radix et Rhizoma* have the strongest correlations between plants in terms of COVID-19 [70].

Lianhuaqingwen (LH), an herbal medicine administered in conjunction with traditional treatment, has been reported to be more effective in mild or ordinary COVID-19 patients [71]. Based on the available evidence, it is believed that the herbal medicine Soshihotang (SSHT) consisting of *Bupleuri*

Radix, *Scutellariae Radix*, *Pinelliae Tuber*, *Ginseng Radix*, *Zingiberis Rhizoma Recens*, *Zizyphi Fructus*, and *Glycyrrhizae Radix et Rhizoma* plants may be a new therapeutic option for COVID-19 [72]. Another study reported that Traditional Chinese herbal formula (Table 1) containing herbs with fever-reducing, expectorant, antitussive and anti-virus activity may be effective on COVID-19 [73]. Nugraha et al. reported that *Echinacea*, *Cinchona*, *Curcuma longa* and *Curcuma xanthorrhiza* herbal medicines in the treatment of COVID-19 may have the ability to regulate the production and release of proinflammatory cytokines, interfere with the development of the virus in the host cell, and alter certain molecular pathways related to the renin-angiotensin-aldosterone system [74].

In a clinical study involving 22 COVID-19 positive patients, the effectiveness of herbal therapy combined with drug therapy was investigated. The natural herbal medicine (NHM) content used in the study is given in Table 1. As a result of the study, the duration of febrile days, hospital stay and recovery time of chest CT of the patients in the NHM group along with drug therapy were shorter compared to the group that received only the drug. They reported that the results showed that NHM could improve the clinical symptoms of COVID-19 patients and be effective in the treatment of COVID-19 [75]. In silico work has been done that the essential properties of *Nyctanthes arbor-tristis*, *Tinospora cordifolia*, *Aloe barbadensis miller*, *Curcuma longa*, *Azadirachta indica*, *Withania somnifera*, *Zingiber officinale*, *Allium cepa*, *Ocimum sanctum*, *Cannabis sativa*, *Piper nigrum* against eye protection against COVID-19. They reported that the inhibition potential of *Nyctanthes arbor-tristis*, *Tinospora cordifolia*, *Aloe barbadensis miller* is of particular interest, and that other potential inhibitors of COVID-19 protease include turmeric, neem, ashwagandha and ginger. They also reported that the inhibition potential of these plant extracts was greater than those of chloroquine and hydroxychloroquine [76]. Many Chinese herbs such as Baical Skullcap root (*Huangqin*, *Radix Scutellariae Baicalensis*), Forsythia Fruit (*Lianqiao*, *Fructus Forsythiae Suspensae*), Liquoric root (*Gancao*, *Radix Glycyrrhizae*) have certain anti-oxidation, anti-bacterial, antiviral effects. It has been reported that it can be used in the treatment of acute respiratory infections [77]. It has been reported that treatment with Lian Hua Qing Wen formula (Table 1) can modulate the inflammatory process, exert antiviral effects, repair lung damage, alleviate the 'cytokine storm', and improve symptoms caused by ACE2 expression dysfunction [78]. The antiviral and anti-inflammatory effects of Shufeng Jiedu capsules on lung index, viral load in the lung, cytokine release and T and B lymphocytes were analyzed in the HCoV-229E mouse model. As a result of the study, it was found that capsules significantly reduced the viral load in the lung, inhibited inflammatory factors, improved clinical recovery time and reduced fatigue and cough [79].

The effectiveness of Chinese herbal medicines in pharmacological and non-pharmacological kidney damage

caused by Covid 19 infection has been investigated. Bioactive compounds such as quercetin, formononetin, kaempferol, etc. have been reported that protect the kidney through antioxidation, inhibition of inflammation and apoptosis pathways by modulating targets such as PTGS2 (COX2), PTGS1 (COX1), IL6, CASP3, NOS2 and TNF [80]. In a cohort study of 312 patients, the risk of death was reported to be 82.2 % lower in groups that received the Chinese herbal medicine, Mahuang Liu Jun Tang (Table 1), compared to those who did not use the drug [81]. In a clinical trial involving 42 patients, the efficacy of the drug Xuanfei Baidu (Table 1) with commercial therapy was studied. At the end of the experiment, it was found that clinical symptoms such as fever, cough, fatigue and loss of appetite decreased significantly, the number of white blood cells and lymphocytes increased significantly and all returned to normal levels, C-reactive protein and erythrocyte sedimentation rate decreased significantly in individuals using Xuanfei Baidu [82].

Result of molecular insertion analysis by Erlina et al they identified six potential compounds as Hesperidin, Kaempferol-3,4-di-O-methyl ether (Ermanin), Myricetin-3-glucoside, Peonidine 3- (4'-arabinosylglucoside); Quercetin 3- (2G ramosylrutinoside); and Ramnetin 3-mannosyl- (1-2) -aloside as inhibitors of SARS-CoV-2 major proteases. They reported that bioactive compounds obtained from various plants may have antiviral potential for SARS-CoV-2, and Psidium guajava may be effective in preventing Covid 19 infection [83]. Zong et al have found that the affinity of core compounds such as quercetin, kaempferol, and baicalin are similar to the drugs recommended in the treatment of COVID-19. He reported that the active compounds in Da-Yuan-Yin can regulate multiple signaling pathways by binding angiotensin converting enzyme II (ACE2) and may be effective in COVID-19 inhibition by acting on targets such as PTGS2, HSP90AA1, and ESR1 [84]. It has been stated that anti-cytokine therapy can be beneficial to reduce serious mortality as a result of cytokine storm seen in patients with diabetes mellitus and cardiovascular diseases with Covid 19 infection. It has been reported that Parthenolide, the active ingredient of *Tanacetum parthenium*, is effective in reducing IL-1, IL-2, IL-6, IL-8, and TNF- α production pathways and can therefore be used in anti-cytokine treatment [85]. Shahrajabian et al reported that the combination of the influenza season and the second wave of COVID-19 could cause more confusion and put much more pressure on public health systems. They reported that may be the most important antiviral herbs for cold and flu include thyme leaf (*Thymus vulgaris*), honeysuckle flowers (*Lonicera japonica*), andrographis (*Andrographis paniculata*), green chireta (*Andrographis paniculata*), peppermint leaf and oil (*Mentha piperita*) and *Calendula* (*Calendula officinalis*) In the category of expectorant herbs, tulsi (*Ocimum sanctum*), snake root (*Polygala senega*), licorice root (*Glycyrrhiza glabra*), clove (*Syzygium aromaticum*), slippery elm, marshmallow osha root (*Ligusticum porteri*) and sage leaf (*Salvia officinalis*) [86].

In another study, TCM (Traditional Chinese medicine) herbal prescriptions containing 290 different herbs were used in addition to antiviral / antibiotics and standard supportive treatments for 273 of COVID-19 patients who were diagnosed with a total of 293 diagnoses, 207 of which were moderate and 86 severe. COVID-19 cases include elderly patients with advanced age (average 57 years) and high comorbidity rates (61%). It has been reported that TCM herbal prescriptions used in the treatment of COVID-19 infections mainly consist of *Pericarpium Citri Reticulatae*, *Radix Scutellariae*, *Rhizoma Pinellia* and their combinations. It was found that subjects who received TCM treatment had lower mortality rates than those who did not receive TCM treatment [87]. It has been determined that the most commonly used plants in the COVID-19 outbreak are *Allium Sativum*, *Olea europaea*, *Allium cepa*, *Zingiber officinale*, *Thymus maroccanus*, *Eucalyptus globules*, *Foeniculum vulgare*, *Curcuma xanthorrhiza*, *Phoenix dactylifera*, *Rosmarinus officinalis*, *Thymus sature pulegides*, *Thymus pulegioides*. In addition to the positive effects of the second metabolites in these plants on respiratory system functions, it has been emphasized that some plants among them may contain toxic components that may cause overdose poisoning [88]. Yan et al found that the use of herbal medicines (*Jinhaoartemisia* antipyretic granules and *Huoxiangzhengqi* oral fluids) in patients during the COVID 19 outbreak reduced the risk of cold by 89.6% in the whole population and 94.0% in those aged 16 to 59 [89]. *Tribulus terrestris* against papain-like protease (PLpro), which is the proteolytic enzyme in pathogenic viruses and bacteria, *Withania somnifera* and *Curcuma longa* against 3C-like main protease (3CLpro), *Ocimum sanctum*'s main Protease and Papain-like against Protease and *Phyllanthus emblica* has been reported to be effective against COVID-19 by showing high affinity for Helicase protein and Spike Protein [90]. According to the structure of the corona virus (SARS-CoV-2), treatment with *Momordica charantia* (bitter melon), *Lagenaria breviflorus* (wild colocynth), *Citrullus colocynthis* (bitter melon), *Annona muricata* (soursop) and *Citrus aurantium bergamia* (bergamot orange) may be useful in COVID-19 infection [91].

According to the molecular placement study results; it has been reported that the bioactive compound of *Atractylodes lancea* (Thunb.) Dc., *Atractylenolide III*, has a strong binding affinity with ACE2, also has anti-inflammatory and antiviral effects and has a high distribution to the lungs in in vivo study. [92]. It has been reported that many Chinese plants are included in *Berberis integerrima* Bunge, *Crataegus laevigata* (Poir.), *Onopordum acanthium* and *Quercus infectoria*, *B. integerrima*, *C. microphylla*, *O. Acanthium*, *Polygonaceae*, *Labiatae*, *Oleaceae*, *Magnoliaceae*, *Lauraceae* and *Nelumbonaceae* families that designated as ACE2 blockers [93]. It has been reported that the therapeutic efficacy against COVID 19 is associated with rapid immunomodulatory activity due to the decrease in plasma IL-6 rapid level and increase in IFN-in volunteers treated with *Jinhua Qinggan* granule [94]. It has

been reported that the consumption of herbal medicines such as *Allium sativum*, *Camellia sinensis*, *Zingiber officinale*, *Nigella sativa*, *Echinacea* spp, *Hypericum perforatum* and *Glycyrrhiza glabra*, *Scutellaria baicalensis* may have positive effects on the immune response. It has also been reported that plant terpenoids may be effective in inhibiting viral replication, and some alkaloid bioactive components such as homoharringtonine, lycorine and emetin have strong anti-coronavirus effects. It has been reported that natural products can inhibit different coronavirus targets and viral enzyme replication, such as S protein (emodin, baicalin) 3CLpro (Igueterin), PLpro (Cryptotanshinone), helicase (Silvestrol), and RdRp (Sotetsuflavone) [95]. The ginseng plant is rich in saponin and steroid compounds. Steroid compounds known to have immunostimulating properties are effective in cytokine production (IL-2, IL6, TNF- α and IFN- γ), macrophage activation and lymphocyte activity, while saponins are effective in COVID 19 infection due to their ability to stimulate the immune response of cells and increase antibody production [96]. It has been reported that hesperidin, an antioxidant and anti-inflammatory agent and herbal medicine, may be promising in the treatment of COVID-19 by preventing its entry into host cells through ACE2 receptors, enhancing its anti-viral activity and host cellular immunity against infection, helping to control its anti-inflammatory activity and cytokine storm. [97].

CONCLUSION

Traditional medicinal plants have a long history supported by many researches such as maintaining a healthy life, combating toxins taken in daily life, treating and preventing diseases, and longevity. These plants are rich in sugar, vitamins, minerals, fatty acids, amino acids, enzymes, etc. They also contain a wide variety of bioactive compounds, including essential oils, flavonoids, organosulfur compounds, glycosides, secoiridoid, tannin, mucus, lignans, coumarins, alkaloids, aromatic compounds, phenolic lipids, carotenoids, steroids, and many other compounds. It has been determined by several researches that the bioactive components of these types of plants have many biological effects such as anti-inflammatory, antifungal, antiviral, antibacterial, antioxidant, antiseptic, antitumor, anticancer, antiallergic antiatherogenic and analgesic activities. Studies on the antiviral, anti-inflammatory and antioxidant properties of ethnomedicinal plants and natural phytochemicals can be considered as a great potential drug source against various ailments as well as Covid-19 treatment.

Based on this study, it has been observed that plant extracts have the effects of increasing immunity, regulating the production and release of proinflammatory cytokines with the increase in the number of white blood cells and lymphocytes in viral infections such as Covid-19, which can lead to fatal consequences. It is seen that some plants exhibit an anti-inflammatory effect with a decrease in the C-reactive protein and erythrocyte sedimentation rate, and a positive

effect such as interfering with the development of the virus, as well as potential antiviral agent activity. It should be kept in mind that the use of herbal supplements for the prevention of COVID-19 or improvement of clinical symptoms is better to use under the supervision of a clinician rather than advice. In addition, pre-clinical and clinical study evaluations of these herbal agents, which are considered to be effective in the treatment of COVID-19, are required. It may be possible to discover potential new anti-viral plants with advanced studies.

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