ORIGINAL ARTICLE

Traditional Chinese medicine practices used in COVID-19 (Sars-cov 2/Coronavirus-19) treatment in clinic and their effects on the cardiovascular system

COVID-19 (Sars-cov 2/Koronavirüs-19) tedavisinde klinikte kullanılan geleneksel Çin tıbbı bitkileri ve kardiyovasküler sisteme etkileri

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ABSTRACT

Objective: The aim of this study was to evaluate the effectiveness of plants used in the formulations of traditional Chinese medicine (TCM), which were also used in clinical trials to treat patients with the novel coronavirus COVID-19, and to assess their effects on the cardiovascular system.

Methods: A literature review of PubMed, ResearchGate, ScienceDirect, the Cochrane Library, and TCM monographs was conducted and the effects of the plants on the cardiovascular system and the mechanisms of action in COVID-19 treatment were evaluated.

Results: The mechanism of action, cardiovascular effects, and possible toxicity of 10 plants frequently found in TCM formulations that were used in the clinical treatment of COVID-19 were examined.

Conclusion: TCM formulations that had been originally developed for earlier viral diseases have been used in COVID-19 treatment. Despite the effectiveness seen in laboratory and animal studies with the most commonly used plants in these formulations, the clinical studies are currently insufficient according to standard operating procedures. More clinical studies are needed to understand the safe clinical use of traditional plants.

ÖZET

Amaç: Koronavirüs (COVID-19) tedavisi için Çin'de yapılan klinik çalışmalarda kullanılan geleneksel Çin tıbbı (GÇT) formülasyonlarında yer alan bitkileri ve kardiyovasküler sistem üzerine etkilerini değerlendirmek.

Yöntemler: Bu araştırmada PubMed, Researchgate, Sciencedirect, Cochrane adlı arama motorları ve GÇT Monografları kullanılarak literatür taraması yapılmış ve belirlenen bitkilerin COVID-19 tedavisinde etki mekanizmaları üzerinden yeri ile kardiyovasküler sistem üzerindeki etkileri değerlendirilmiştir.

Bulgular: Yapılan literatür taramaları sonucunda, klinikte hastalara verilen GÇT formülasyonları belirlenmiştir. Bu karışımlarda sıklıkla bulunan 10 bitkinin, COVID-19 tedavisi için önerilen etki mekanizmaları, kardiyovasküler etkileri ve olası toksisiteleri açıklanmıştır.

Sonuç: Geleneksel Çin Tıbbında farklı viral hastalıklarda kullanılan formülasyonların COVID-19 tedavisi için de denendiği görülmüştür. Formülasyonlarda en çok yer alan bitkilerin laboratuvar ve hayvan çalışmalarında etkinlikleri görülmesine rağmen klinik çalışma verileri yetersizdir. Bitkilerin klinik düzeyde güvenli olarak kullanabilmeleri için daha fazla klinik çalışmaya ihtiyaç duyulmaktadır.

More than 100 clinical studies, some complete and some ongoing, have been initiated to study treatments for the current coronavirus pandemic, which has infected more than 80,000 and killed more than 3,000 in China. Studies of potential approaches to this virus, COVID-19, have primarily evaluated the

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effects of standard and new antiviral medications on this novel coronavirus, in both single and combination drug therapies. A number of protocols are being tested by doctors with the aim of treating symptoms of the disease in addition to antiviral medications. The types of treatments that have been tested in China to treat COVID-19 are provided in Figure 1.[1] Among the treatments used in these clinical trials are remedies from traditional Chinese medicine (TCM), most of which are plant-based formulations. Approximately 20% of COVID-19 patient-oriented clinical trials have examined TCM treatments.

The fight against COVID-19 can be summarized in 2 strategies: prevention and treatment. The search for a vaccine is at the forefront of prevention, and work is progressing in earnest to this end. Aside from isolation, contact avoidance, and disinfection, another hotly debated approach to disease prevention is fortification of the immune system and preventing the entry of the virus into the body using various plant-based blends, supplement products and vitamins, or other methods. The appropriateness of strengthening the immune system, a very complex system, as a treatment for a viral infection that is still not fully understood is open to discussion. A considerable number of those infected with the virus show no symptoms and there are unpredictable risks associated with using immunity-strengthening products on such individuals. The antiviral activity of some aromatic compounds has been proven in a laboratory setting. However, there remains insufficient proof of their safety in clinical usage. We must take into consideration any potential harmful effects, such as irritation, especially of the lungs, resulting from improper use of aromatherapeutic treatment. In theory, while administration in drop form seems feasible, protective usefulness against the virus has not been clinically proven.[2]

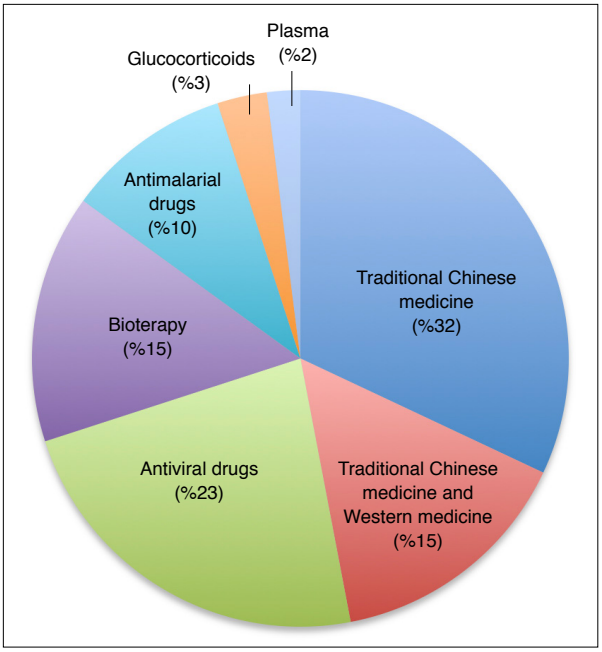

Figure 1. Classification of treatments used in China for Covid-19.

Abbreviations:

COX-2	*Cyclooxygenase 2*
eNOS	*Endothelial nitric oxide synthase*
H1N1	*Influenza A virus subtype H1N1*
HAdV-3	*Human adenovirus type 3*
HMPC	*Committee on Herbal Medicinal Products*
IL	*Interleukin*
IFN-γ	*Interferon gamma*
JAK	*Janus kinase 2*
NF-κB	*Nuclear factor kappa B*
NO	*Nitric oxide*
STAT	*Signal transducer and activator of transcription*
Tan	*Tanshinone*
TNF-α	*Tumor necrosis factor alpha*
TCM	*Traditional Chinese medicine*
WHO	*World Health Organization*

The presence of source plants in pharmacopoeias and monographs does not necessarily indicate the safe clinical use of these plant products or dietary supplements. The word "pharmacopoeia" is derived from the Ancient Greek words for the practice of making healing medicines. Today, pharmacopoeias have been defined as "documents containing the physiochemical properties of all active ingredients and inactive ingredients used in the production of medicines, along with methods for their qualitative and quantitative analysis, and including national and international rules that must be adhered to, both legally and scientifically."[3] Monographs have been defined as "the portion of a pharmacopoeia that describes chemically/biologically active and inactive ingredients, plant-based drugs and botanical preparations, along with the description, contents, properties (such as appearance, solubility, melting and boiling points), identification analyses, dosage, handling and storage conditions, and impurities of the finished products. The quality control analyses of the products contained in the monographs primarily include analytic methods conforming to the necessary standards, microbiological purity, dissolution, stability and similar test protocols."[4]

Regardless of how many sections are devoted to therapeutic information, such as the description and identification parameters of plant products alongside traditional or scientifically verified usage in pharmacodynamic and pharmacokinetic studies, the limits

of preclinical and clinical safety, toxicity, contraindications, special warnings and precautions, unwanted side-effects, dosage effect, and dose-drug interactions, inclusion in extended monographs of international institutions and countries does not necessarily translate to safety in clinical use.[3,5]

The European Pharmacopoeia, which is Turkey's official pharmacopoeia, contains the contributions of 37 countries, including Turkey.[3] The pharmacopoeia and its printed supplements have only the necessary sections covering the protocols necessary for standardization, such as identification, description, and analytic procedures. In Turkey, monographs with the specific aim of standardizing medicinal plant use are being prepared for plants widely used in the country.[5]

Founded in 2004, the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency shares data on herbal substances with European Union member countries as well as observer countries, such as Turkey. Thus far, the HMPC has approved 84 of 169 Turkish monographs. However, because the majority of the usages they describe are traditional methods, it emphasizes the need for clinical investigation.[4]

Traditional Chinese medicine (TCM)

TCM is a system with a history spanning more than 2500 years and with foundations in the Chinese civilization's first schools of philosophy: Taoism, Confucianism and Buddhism. TCM adheres to the principle of restoring balance in the body as a whole during treatment and applies a number of different methods according to a differentiation of syndromes. TCM emphasizes a holistic approach to diagnosis and treatment. Alongside medicines made from plant, animal, and mineral materials, TCM utilizes a number of different physical techniques, including oil massage, tui na massage, scraping massage, acupuncture, heat therapy, and qi gong and related forms of massage therapy.[6]

The classic TCM diagnostic procedures of looking, listening/smelling, asking, and touching are still used by today's practitioners of TCM alongside modern procedures.[7]

More than 32,000 plants are found growing naturally in China. According to the most recent data, 11,200 species of plants are used there medicinally. Plants make up 87% of the sources of medicines used in TCM.[8]

The Chinese Pharmacopoeia is reviewed every 5 years; the 10th edition, printed in 2015, is in use today. This most recent pharmacopoeia consists of 4 volumes. The first contains information on plants and drugs, plant oils and extracts, mixture preparations in the form of formula recipes and single-plant preparations, and features 2165 monographs. The second volume contains monographs related to chemicals, antibiotics, biochemical medications, and radioactive drugs. The third volume is dedicated to biological products, and the fourth consists of monographs with topics such as general principles on the preparation of medicine, test procedures, guides, reference materials and relevant test solutions, reagent guidelines, and pharmaceutical additives. The Chinese Pharmacopoeia is available in both Chinese and English in digital and print form.

The aim of this study was to evaluate plants found in mixtures used in TCM treatments in the context of evidence-based medicine and to analyze the effects of these plants on the cardiovascular system.

METHODS

A search of PubMed, ResearchGate, ScienceDirect, the Cochrane Library, and TCM monographs was conducted to retrieve studies related to plants used in mixtures used in TCM formulations published between 1990 and 2020. The 10 plants used most often in the examined TCM mixtures were selected for this study based on the effective role in the mixture and the mechanism of action. The information provided in the various literature sources about these 10 plants was compiled and organized for this study, and includes the scientific name, the Turkish name (omitted in cases where the plant does not have a Turkish name), the English name, the Chinese name, the parts used, active substances, potential pharmacologic mechanism of action against COVID-19, the pharmacologic mechanism of action with respect to effects on the cardiovascular system, interactions with cardiovascular medications, and toxicity. The compounds listed as responsible for effects are shown in bold.

RESULTS

Clinical studies

There are relatively few detailed reports of TCM treatments and/or studies conducted in line with the

criteria of good clinical practices. In summary, TCM methods are generally used in the form of plant products given as supplements alongside conventional Western treatments.

In data released by the National Administration of Traditional Chinese Medicine, 214 COVID-19 patients in 4 provincial hospitals were given an additional treatment of the Qingfei Paidu Decoction for 3 days. In all, 60% of the patients showed a significant improvement, and 30% saw a reduction of symptoms. This prescription was recommended for patients in mild, serious, and even critical condition.[9]

Another report published by the same administration stated that the Qingfei Paidu Decoction was in wide use in 28 cities with good results. A total of 1262 patients, 57 of whom were on the verge of being seriously ill, were treated with the Qingfei Paidu Decoction in 66 of China's major cities. Cure rates reached 99.28% and 1253 patients were discharged from the hospital. Not a single patient experienced an increase in severity from mild/normal to critical condition. The results suggest that the preparation may prevent the illness from reaching a critical stage.[10]

In a study conducted by Wang et al.,[11] the Qingfei Paidu Decoction was used to treat 98 newly diagnosed COVID-19 patients in China's Sichuan Province and the lab test indicators were compared with the pretreatment results after 3, 6, and 9 days of treatment. After the third day of treatment, lymphocyte percentages, aspartate aminotransferase, and alanine aminotransferase, and D-dimer lab indices had returned to normal in more than 70% of the patients ($p<0.01$). After 6 days, C-reactive protein and erythrocyte sedimentation rate laboratory indices had normalized in more than 80% of the patients ($p<0.01$). Following 9 days of treatment, lab indices had returned to normal in more than 90% of the patients. CT results showed normalization in 79 patients after six days of treatment.

Of 101 COVID-19 patients with pneumonia at the Wuhan Iron and Steel Corporation General Hospital, which is affiliated with the Wuhan Science and Technology Medical College, 63 were given Lianhua Qingwen granules orally in addition to standard treatments (nutritional supportive therapy, symptomatic therapy, antiviral and antibiotic drug therapy) and defined as the treatment group, while 38 patients in a control group were treated only with conventional procedures. The duration of primary symptoms (fever, cough, fatigue, shortness of breath) and rates of symptom loss were compared between the 2 groups after 10 days. The treatment group demonstrated symptom reduction rates of 86.7%, 55.6%, and 82.5% for fever, cough, and fatigue, respectively. These rates were significantly higher than those of the control group (respectively, 67.7%, 30.6%, 58.6%; $p<0.05$) The Lianhua Qingwen treatment group also saw fever reduction after 6 days, while the controls had a fever reduction period of 7 days. There was a 68.2% reduction in labored breathing in the Lianhua Qingwen group, which was a significant increase compared with that of the control group (20%; $p<0.05$). The condition of 4 patients (6.4%) in the treatment group and 6 patients (15.8%) in the control group worsened. No serious side effects were observed in the Lianhua Qingwen group. As a result, it was found that a combination therapy of Western medicine and Lianhua Qingwen granules may significantly reduce fever, cough, fatigue, shortness of breath and other symptoms in cases where pneumonia is suspected.[12]

In another study analyzing the clinical effectiveness of conventional treatment versus conventional treatment combined with Lianhua Qingwen granules, Cheng et al.[13] analyzed 2 groups of 51 patients in a Lianhua Qingwen treatment group and a control group and compared the duration and rate of symptom reduction for primary symptoms (fever, fatigue, cough), as well as other symptoms, such as the presence of phlegm, shortness of breath, chest tightness and loss of appetite, as well as BT results of each group after 7 days of treatment. The rate of reduction of the primary symptoms of fever, fatigue, and cough in the treatment group was 83.7%, 61.3%, and 62.2%, respectively, while it was 61%, 34.3%, and 35.9% in the control group. The differences between the groups were statistically significant ($p<0.05$). The rate of the symptoms of phlegm, shortness of breath, chest tightness, and loss of appetite was 55%, 61.5%, 54.6%, and 34.8% in the treatment group, while it was 15.8%, 14.3%, 15.8%, and 7.7% in the control group, respectively. The condition of 4 patients (7.8%) in the treatment group and 11 (21.6%) in the control declined from moderate to severe. The BT results of 28 patients (54.9%) from the treatment group and 23 (45.1%) in the control group returned to normal. The results offer evidence of Lianhua Qingwen granules as a potential treatment option in the treatment of COVID-19.[13]

In a retrospective clinical study that included 42 patients in the city of Wuhan diagnosed with COVID-19, a combined treatment using Lianhua Qingwen was demonstrated to significantly reduce clinical symptoms such as fever, cough, phlegm, and shortness of breath. The duration of symptoms was reduced by 1.5 days on average, and it had a positive effect on fatigue, muscle aches, nasal congestion, and headache.[14]

In addition, another study evaluated traditional Chinese medicine data based on treatment plans published by the State and Provincial Health Committee and the National Administration of Traditional Chinese Medicine from the outbreak of COVID-19 in Wuhan through February 19, 2020. The study found that 84 plant mixtures and 230 plant-based drugs had been used and analyzed the frequency of use (Table 1).[15–20]

Plants used

Given the vast number of plants found in the research evaluated in this study, and in accordance with TCM principles that some may not be directly responsible for the mixture's effect, it was decided that this review would be limited to 10 plants and exclude auxiliary plants considered not responsible for the primary effect. Criteria regarding the usage frequency of the mixtures and plants, the results in COVID-19 treatment, effects on the cardiovascular system, and the known mechanism of action were also included. The most commonly used plants were Glycyrrhiza uralensis (216), Scutellaria baicalensis (188), Forsythia suspensa (153), Lonicera japonica (134), Pogostemon cablin (115), and Atractylodes macrocephala (88). Astragalus membranaceus, Bupleurum chinense, Isatis tinctoria, and Salvia miltiorrhiza were also included in the study due to the fulfillment of other criteria; however, the rate of use was not analyzed. Of the more than 300 scientific sources evaluated, those that contained information other than chemical contents; known antiviral, immunomodulator, anti-inflammatory, and cardiovascular effects; and side effects and toxicity were excluded from the study. This study provides the scientific name, the Chinese name, the English name, and the Turkish name of the plants examined; however, many of the species do not have a Turkish name. Only "çivitotu" (Isatis tinctoria) grows naturally in Turkey.

Lonicera japonica, **Japon hanımeli,** Japanese honeysuckle (Jin yin hua)

Drug name: Lonicera japonicae flos

Chemical compounds: The main compounds are the organic acids (**chlorogenic acid**, **caffeic acid**, cinnamic acid, ferulic acid), flavonoids (sinarozit, luteolin, lonicerin, chrysin, apigenin, rutin, quercetin, astragalin, hyperozit), iridoids (loganin, loganic acid, 8-epiloganic acid, secologanin, **secoxiloganin**, **dimetiksecologanosit**, centaurosit, sverosit), saponins (a-hederein, lonicerocid A-E hederagenin), oleanolic acid, and ursolic acid.[21]

Pharmacological action mechanisms

Anti-inflammatory effect: In an *in vitro* study, extract containing chlorogenic and caffeic acids showed an effect against inflammation and oxidation caused by free radicals. It inhibited nitric oxide (NO) production, tumor necrosis factor alpha (TNF-α), and secretion of interleukin (IL) IL-1B, IL-6, IL-8, and increased IL-10 secretion.[21]

Antiviral effect: *In vitro*, a compound of secoxiloganin has been reported to have antiviral effects against the H1N1 (Influenza A) virus and inhibit H1N1 replication.[22] *In vivo*, the fruit extract of the plant demonstrated an inhibitory effect against HIV, adenovirus, herpes simplex type 1, and herpes simplex type 2.[23]

Effect on the cardiovascular system: The results of the application of an extract of pure polysaccharides obtained from the flowers of the plant to streptozosin-induced rats for 42 days were analyzed. Total cholesterol, triglyceride, very low-density lipoprotein, and low-density lipoprotein levels decreased, while high-density lipoprotein levels increased.[24]

Drug interaction: Not reported.

Toxicology: With use as an injection, hypersensitivity reactions may suddenly appear.

Although hypothermia was observed after an injection in animal studies, the injection was generally recorded as safe.[21]

Forsythia suspense, Weeping forsythia, (Lian qiao)

Drug name: Forsythiae fructus

Chemical compounds: **Phenylethanoid glycosides**, lignans (pinoresinol, phillygenin, **phillyrin [forsythin], phorsytiasid**), flavonoids, terpenoids,

alkaloids, chlorogenic acid, and caffeic acid are main compounds.[25]

Pharmacological action mechanisms

Antiviral effect: In an *in vivo* study, it was determined that when the compound of **phillyrin (forsythin)**, which is obtained from the fruit of the plant, was applied to H1N1-infected mice, tissue damage and lung damage were reduced and survival was prolonged. Furthermore, the IL-6 level, virus load, and influenza hemagglutinin level decreased.[26]

Effect on the cardiovascular system: When fractions obtained from the fruit of the plant were applied to mice with streptozosin-induced diabetes for 4 weeks, an ethyl acetate fraction was more inhibited in the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase fractions compared with n-butanol and chloroform fractions. Serum total cholesterol, hepatic total cholesterol, and total triglyceride levels decreased.[27]

Drug interaction: Not reported.

Toxicity: Thus far, no toxicity has been reported. Water and ethanol extracts obtained from the leaves of the plant did not cause acute toxicity in studies with mice.[28]

***Glycyrrhiza uralensis*, Çin meyankökü,** Chinese licorice (Gan cao)

Drug name: Liquiritiae radix

Chemical compounds: It contains triterpenic saponins (**glycyrrhizin**, glycyrrhic acid, glyciric acid, glycyrrhetinic acid) and flavonoids (liquritin, liquiritigenin, isoliquiritigenin, licoricidin).[29]

Pharmacological action mechanisms

Anti-inflammatory effect: It has been demonstrated that glycyrrhizin suppresses proinflammatory cyclooxygenase 2 (COX-2), inducible NO synthase, and TNF-α, and it was found to inhibit the phosphorylation and secretion of protein kinase C and HMGP 1 in an *in vivo* study.[30]

Antiviral effect: It was noted that glycyrrhizin reduced the production of chemokine ligand 10, IL-6 and chemokine ligand 5, and suppressed Avian influenza H5N1-induced apoptosis.[31] It has been observed that 18p-glycyrrhetinic acid effectively inhibits HIV-1 and virus antigen p24 accumulation, and protects cells from the cytopathogenic effect of the virus.[32]

Immunomodulatory effect: In an *in vivo* study on mice, glycyrrhizin was found to prevent airway resistance and increases in the number of eosinophils, improve IL-4, IL-5, and IL-13 levels in the bronchoalveolar lavage fluid and increase the level of interferon gamma (IFN-γ).[33]

Effect on cardiovascular system: In an *in vivo* study, isoliquiritigenin reduced the severity of reperfusion-induced arrhythmias and myocardial infarction by improving the activation of the Janus kinase 2-signal transducer and activator of transcription 3 (JAK-STAT3) pathway.[34] In another study, positive effects were reported regarding protection against heart disease such as ischemic damage due to the strong inhibition of K+ channels.[35]

Drug interaction: It can reduce the effectiveness of antihypertensive drugs. When taken with the thiazide group diuretics, it may pose a risk of hypokalemia and interact with digitalis glycosides.[36]

Toxicity: Severe hypertension and hypokalemic metabolic alkalosis can be observed with long-term use of the root of the plant.[37]

***Isatis tinctoria (sin. Isatis indigotica),* Çivitotu,** Indigo woad, (Song lan)

Drug name: Isatidis radix

Chemical compounds: The root extract contains **alkaloids** (isatindigoside A, isatindigoside B, isatindigobisindoloside A, isatindigobisindoloside B), **polysaccharides**, terpenic compounds, aldehydes (furfural), nitriles (2-Pentenenitrile) and isothiocyanates (3-Butyl).[38]

Pharmacological action mechanisms

Anti-inflammatory effect: According to an *in vitro* study, the alkaloids in the root extract had a COX inhibitory effect and reduced the release of proinflammatory cytokines.[38]

Antiviral effect: An *in vitro* study indicated that polysaccharides in the root extract of the plant inhibited viral duplication and adsorption of the virus to cell surfaces.[38]

Effect on the cardiovascular system: Not reported

Drug interaction: Not reported.

Toxicity: Not reported.

***Pogostemon cablin,* Paçuli (Tefârik),** Patchouli (Guang huo xiang)

Drug name: Pogostemonis herba

Chemical compounds: It includes **essential oils** (pogostemon, trans-caryophyllene), **phenylethanoids** (isoacteoside, acteoside and krenatoside) flavonoids (apigenin), phytosterols (daucosterol, β-sitosterol, stigmasterol), glycosides, terpenic compounds and organic acids (succinic acid).[39]

Pharmacological action mechanisms

Antiviral effect: In an *in vitro* study, phenylethanoids (neurosinidase) showed a neuraminidase inhibitory effect and reduced the replication and infectiousness of the influenza virus.[40]

Anti-inflammatory effect: According to the results of an *in vitro* study, pogostone, eugenol, and rosmarinic acid substances in the essential oil decreased the release of proinflammatory cytokines by inhibiting the nuclear factor kappa B (NF-κB) pathway.[41]

Effect on the cardiovascular system: In an *in vivo* study, it was stated that the alpha-bulnesene substance in its content may increase platelet aggregation time as a result of an inhibitory effect on the platelet activating factor.[42]

Drug interaction: Theoretically, it can increase the coagulation time by increasing the effectiveness of anticoagulant and antiaggregant drugs.[42]

Toxicity: Not reported.

Atractylodes macrocephala, Large head (Bai zhu)

Drug name: Atractylodis macrocephalae rhizoma

Chemical compounds: Its rhizome extracts include **polysaccharides**, steroids (β-sitosterol, stigmasterol), flavonoids, flavonoid glycosides, benzoquinones, phenylpropanoids (caffeic acid, ferulic acid, 2-hydroxiferulic acid), sesquiterpenoids (**atractilenolide**, biatractilenolide, biepiasterolid), polyacetylenes, and coumarins.[43]

Pharmacological action mechanisms

Anti-inflammatory effect: In an *in vitro* study, the terpenic atractilenolide substance in the plant content decreased the release of proinflammatory cytokines (TNF-a, IL-1β and IL-6) by inhibiting the NF-κB pathway.[44]

Immunomodulatory effect: An *in vivo* study of mice indicated that polysaccharides increased T lymphocyte activity and IFN-γ release.[45]

Effect on the cardiovascular system: According to an *in vivo* study, the lactones in the extract can prolong bleeding time by inhibiting ADP-dependent platelet aggregation.[46]

Drug interaction: Theoretically, it could increase coagulation time by increasing the effectiveness of anticoagulant and antiaggregant drugs.[46]

Toxicity: It has been stated that an aqueous extract given to mice at doses of 20 and 100 mg/kg in the form of an intraperitoneal injection did not cause toxicity.[43]

***Scutellaria baicalensis,* Baykal kasidesi,** Baical skullcap (Huang qin)

Drug name: Scutellariae radix

Chemical compounds: **Flavonoids** (**baicalin, baicalein,** wogonoside, wogonin), diterpenoids, polysaccharides, β-carotene, and β-sitosterols are the main compounds.[47]

Pharmacological action mechanisms

Antiviral effect: Baicalin has demonstrated an antiviral effect through HIV-1 inhibition. Baicalin acts by binding to selected chemokines and interfering with the capacity of cellular receptors. For HIV-1 infection, these 2 mechanisms have co-receptor effects on essential elements. Baicalin causes HIV-1 reverse transcriptase inhibition by binding near the active site of the enzyme to which the viral RNA will bind.[48] In cell studies, the wogonin compound, which belongs to the flavonoid group of the plant, has an inhibitory effect on influenza A and B viruses via type 1 IFN and the adenosine monophosphate activated protein kinase pathway.[49]

Effect on cardiovascular system: It has been noted that after the spontaneous application of the active ingredient of baicalin, found in the flavone structure obtained from the plant, to hypertensive rats for 14 days, there was a decrease in systolic blood pressure and vascular tension of the aorta. When the mechanism of the active substance of baical for an antihypertensive effect was examined, the activation of ATP-dependent K+ channels and intracellular Ca^{+2} channels in vascular smooth muscles had a vasorelaxant effect.[50]

Drug interaction: Theoretically may interact with warfarin.[51]

Toxicity: The plant has been used safely in TCM for centuries. However, some studies have shown that it can also have toxic effects. Despite the absence of a pronounced allergic reaction in oral preparations, some patients have had stomach discomfort and diarrhea. Hypothermia, muscle pain, and leukopenia were noted when high-dose injectable preparations were administered to humans. Nonetheless, it is widely used in clinical practice due to its low toxicity.[47] There have been cases of hepatotoxicity in which the related mechanisms cannot be explained. It was observed that jaundice and other symptoms appeared in patients within 6–24 weeks and that enzyme cases typically affect the hepatocellular level. After cessation of plant use, recovery was rapid. Case series with acute liver injuries that began with jaundice 1–3 months after the use of the plant were recorded.[52]

Astragalus membranaceus, **Çin geveni,** Milkvetch, (Huang qi)

Drug name: Astragali radix

Chemical compounds: It contains triterpene saponins (**astragalosides I-VII** and acetyl derivatives, agroastragalosides I-VI, astramembranins), isoflavones (formononetin and calycosin), polysaccharides (astragaloglucans).[29]

Pharmacological action mechanisms

Anti-inflammatory effect: In an *in vitro* study, astragaloside IV significantly inhibited the production of NO, proinflammatory cytokines IL-1β, and TNF-α, depending on the dose.[53] Astragaloside IV lowered the serum levels of monocyte chemoattractant protein-1 and TNF-α in mouse lungs and also significantly suppressed mRNA levels of MCR-1, TNF-α, IL-6, and TLR4. It has been observed to reduce neutrophil infiltration and activation.[54]

Immunomodulatory effect: Astrogaloside II increased T and B lymphocyte proliferation *in vitro*. It also significantly increased CD25 and CD69 expression.[55] Astragaloside I, II, III, and IV showed marked IL-2 inducing activity.[56]

Antiviral effect: Published studies have reported that astragaloside IV has anti-human adenovirus type 3 (HAdV-3) capacity, and the underlying mechanisms are inhibition of HAdV-3 replication and HAdV-3-induced apoptosis.[57] It also reduced eosinophil and lymphocyte infiltration. It was observed that it modulates Th1/2 immune balance and activates peroxisome proliferator-activated receptors.[58]

Effect on cardiovascular system: In rats with isoprenaline-induced myocardial ischemia, it has been noted that astragaloside IV showed a calcium antagonistic effect, inhibiting calcium overload due to ischemia and hypoxia.[59]

In an *in vivo* study, astragaloside IV induced phosphorylation of JAK and STAT3, increasing the activity of the vascular endothelial growth factor regulated by STAT3. Therefore, it has been shown to promote angiogenesis and alleviate heart failure.[60]

Drug interaction: Not reported.

Toxicity: Not reported.

Bupleurum chinense, **Çin şeytanayağı,** Chinese thorowax (Bei chai hu)

Drug name: Bupleuri radix

Chemical compounds: The plant contains triterpene saponins (**saikosaponins**, saikogenins), polysaccharides (bupleurans) and phytosterols.

Pharmacological action mechanisms

Anti-inflammatory effect: In an *in vitro* study, saikosaponins in the extract were shown to have anti-inflammatory effects by reducing COX-2, NO synthase, TNF-α, IL-1β, IL-6, NF-κB, and mitogen-activated protein kinase levels and increasing the IL-10 level.[61]

Antiviral effect: Saikosaponins exhibited antiviral activity by reducing the replication of influenza A virus strains, NF-κB, and caspase-3-dependent virus ribonucleoprotein nuclear transport, and proinflammatory cytokine production.[62]

Immunomodulatory effect: An *in vivo* study revealed that saikosaponins had increased the proliferation of T lymphocytes, IL-4, and IL-10 levels, as well as decrease IFN-γ and TNF-α levels.[63]

Effect on the cardiovascular system: Not reported.

Drug interaction: Not reported.

Toxicity: Acute or accumulative chronic hepatotoxicity and other digestive system diseases have been reported due to the use of Radix Bupleuri ex-

tract and TCM formulas containing this plant extract at high doses.[64]

***Salvia miltiorrhiza,* Çin Adaçayı,** Danshen/Chinese sage, (Dan shen)

Drug name: Radix Salviae miltiorrhizae

Chemical compounds: Diterpenoids (**tanshinone [Tan] IIA** and Tan IIB, cryptotansinone), phenolic acids (**salvianolic acid**, caffeic acid, isoferulic acid), fatty acids, salvianen, luteolin, and glycosides are the main compounds.[29]

Pharmacological action mechanisms

Anti-inflammatory effect: Salvianolic acid B and the plant's aqueous ethanol extract inhibited TNF-α-induced NF-κB activation in human aortic endothelial cells.[65]

Antiviral effect: In an *in vitro* study, *Salvia miltiorrhiza* root extract inhibited viral entry and RNA synthesis, and lightened the apoptotic process in cells infected with enterovirus.[66]

Immunomodulatory effect: In a study on mice, the plant extract reduced serum immunoglobulin E production at different doses and increased cell-mediated immunity. It inhibited the production of oxygen radicals in the liver and spleen and NO production in the liver. It also increased the host resistance to *Listeria monocytogenes* by increasing the number of peripheral monocyte and natural killer cells and reduced IL-1β production.[67]

Effect on cardiovascular system: In an *in vivo* study, a Tan IIA compound was found to decrease the mean arterial pressure, have a vasodilator effect, and increase the amount of periarteriolar NO. Tan IIA prevented the reduction of endothelial nitric oxide synthase (eNOS) due to hypertension and increased eNOS expression.[68]

Drug interactions: It has been noted that Chinese sage increased bleeding time and decreased thromboxane formation and platelet aggregation when used with warfarin.[69]

Toxicity: It has been observed that the injection given to patients in China may have caused some negative results, such as headache, flushing, dizziness, skin itching, thrombocytopenia, and abnormal liver function.[70]

Table 1. High frequency preparations and the plant content

Preparations	Plants
Lian Hua Qing Wen[17]	*Lonicera japonica Thunb.* *Ephedra sinica Stapf* *Prunus armeniaca L.* *Gypsum Fibrosum* *Isatis tinctoria L. / Isatis indigotica Fortune* *Dryopteris crassirhizoma* *Houttuynia cordata Thunb.* *Pogostemon cablin (Blanco) Benth.* *Rheum palmatum L.* *Rhodiola rosea L.* *Mentha haplocalyx* *Glycyrrhiza uralensis Fisch.*
Tan Re Qing[18]	*Scutellaria baicalensis Georgi* *Ursus arctos Linnaeus* *Capra hircus Linnaeus* *Lonicera japonica Thunb.* *Forsythia suspensa (Thunb.) Vahl*
Shuang Huang Lian[17]	*Lonicera japonica Thunb.* *Scutellaria baicalensis Georgi* *Forsythia suspensa (Thunb.) Vahl*
Qing Fei Jie Du Tang[19]	*Ephedra sinica Stapf* *Glycyrrhiza uralensis Fisch.* *Prunus armeniaca L.* *Gypsum Fibrosum* *Cinnamomum cassia (L.) J.Presl* *Alisma plantago-aquatica subsp. orientale* *Polyporus umbellatus* *Atractylodes macrocephala Koidz.* *Wolfiporia extensa (Beck) Ginns* *Bupleurum chinense DC.* *Scutellaria barbata D.Don* *Zingiber officinale Roscoe* *Aster tataricus L.f.* *Tussilago farfara L.* *Belamcanda chinensis (L.) DC.* *Dioscorea batatas Decne.* *Citrus × aurantium L.* *Citrus reticulata Blanco* *Agastache rugosa (Fisch. & C.A.Mey.) Kuntze*
Xue Bi Jing[20]	*Carthamus tinctorius L.* *Paeonia veitchii Lynch* *Ligusticum striatum DC.* *Salvia miltiorrhiza Bunge* *Angelica sinensis (Oliv.) Diels*

DISCUSSION

The extract mixtures chosen for this study are derived from plants trialed in their respective traditional medicine, generally to prevent and improve symptoms of other respiratory tract diseases (such as H1N1 and severe acute respiratory syndrome). In other words, these are not novel formulas for the treatment of COVID-19.[1]

The plant ingredients found in the mixtures investigated have been generally shown to exhibit immunomodulator, antiviral, and anti-inflammatory activity in *in vitro* and *in vivo* clinical studies. Each plant mixture has been provided with a dedicated formula and name and is administered via oral or parenteral routes.

Generally, the plants are in use because they demonstrate multiple actions. There are anti-inflammatory and antiviral effects (*Lonicera japonica, Isatis tinctoria, Pogostemon cablin*), anti-inflammatory and immunomodulatory effects (*Atractylodes macrocephala*), or only antiviral effects (*Forsythia suspensa, Scutellaria baicalensis*), just as there are species demonstrating 3 of the mentioned properties (*Glycyrrhiza uralensis, Astragalus membranaceus, Bupleurum chinense, Salvia miltiorrhiza*). Table 2 lists the plants used in the treatment of COVID-19 categorized according to their activity and the mechanism of action.

Taking into account the most recent data on the effect of the virus on the function of the epithelial tissue of blood vessels, we also studied the effect of the plants on the cardiovascular system.

Of these plants, 8 (*Forsythia suspensa, Glycyrrhiza uralensis, Scutellaria baicalensis, Astragalus membranaceus, Lonicera japonica, Pogostemon cablin, Atractylodes macrocephala, Salvia miltiorrhiza*) were chosen because of the various effects they are shown to have on the cardiovascular system. The cardiovascular effects are provided in Table 3. Damage to the endothelial tissues on the inside of blood vessels is one of the effects of COVID-19 infection. Some phy-

Table 2. Classification of plants used in the treatment of COVID-19 according to their effect and mechanisms of action

Effect	Mechanism of action	Plants
Antiviral effect	Inhibition of viral replication and adsorption of the virus to cell surfaces.[22,38,40,48,57,62,66]	*Forsythia suspensa* *Lonicera japonica* *Scutellaria baicalensis* *Glycyrrhiza uralensis* *Astragalus membranaceus* *Bupleurum chinense* *Isatis tinctoria* *Pogostemon cablin* *Salvia miltiorrhiza*
Anti-inflammatory effect	Cyclooxygenase-inhibitory effect, reduction of tumor necrosis factor and proinflammatory cytokine release, inhibition of the Nuclear factor kappa B pathway,[30,38,41,44,61] inhibition of nitric oxide production,[21,53] inhibition of neutrophil infiltration and activation.[54]	*Lonicera japonica* *Glycyrrhiza uralensis* *Astragalus membranaceus* *Atractylodes macrocephala* *Bupleurum chinense* *Isatis tinctoria* *Pogostemon cablin* *Salvia miltiorrhiza*
Immunomodulatory effect	Increased phagocytic activity and interferon-γ release of T lymphocytes.[45,55] Increased cell-mediated immunity[67] and interleukin 2-inducing activity.[56]	*Astragalus membranaceus* *Atractylodes macrocephala* *Bupleurum chinense* *Salvia miltiorrhiza*

tochemicals have demonstrated a reparative action on damaged endothelial function in a laboratory setting. Of compounds from the plants used in TCM treatments in our study, the phenolic acids and Tan II found in *Salvia miltiorrhiza*, polysaccharides found in *Astragalus membranaceus* and baicalein found in *Scutellaria baicalensis*, in particular are thought to have a positive effect on endothelial dysfunction through their anti-inflammatory and antioxidant activities.[29,71,72]

Aside from the demonstrated positive effect of their mechanisms of action on the cardiovascular or hemostatic systems, potential drug interactions may lead to undesirable side effects associated with the use of some plants. St. John's wort (*Hypericum perforatum* L.), ginseng (*Panax ginseng* C.A. Mey), ginkgo (*Ginkgo biloba* L.), garlic (*Allium sativum* L.), grapefruit (*Citrus paradisi Macfad*), and licorice root (*Glycyrrhiza glabra* L.) are the plants with the most common instances of such interactions. Interactions may be observed between plants used in the treatment of COVID-19 and some cardiovascular drugs.

Especially, *Glycyrrhiza uralensis* may interact with antihypertensive drugs, thiazide diuretics and digitalis glycosides.[36] *Salvia miltiorrhiza, Atractylodes macrocephala, Pogostemon cablin* and *Scutellaria baicalensis* may interact with anticoagulant drugs and warfarin.[42,46,69]

Among the plants in use, the species Scutellaria baicalensis and Bupleurum chinense must be considered carefully due to their potential for liver toxicity. Possible side effects of the species *Lonicera japonica* and *Scutellaria baicalensis* in preparations used for injection should be evaluated, as well as hypertension and hypokalemia linked with the use of *Glycyrrhiza uralensis*.

Although there may not be work specific to the effects on COVID-19, the plants in some TCM formulations have been tested in clinical studies for other viral infections and some have had positive results. However, debate is ongoing whether these applications are in line with evidence-based medical principles.

The World Health Organization (WHO) has stated concerns about clinical studies performed on traditional Chinese plant extracts, including difficulty in accepting their results due to a lack of a sufficient number of subjects and appropriate protocol, and the need for future clinical studies to be updated and developed in line with the appropriate standards.[16] Sackett,[73] a major contributor to the development of the concept of the clinical study around 50 years ago,

Table 3. Effects of plants used in the treatment of COVID-19 on the cardiovascular system

Effect	Mechanism of action	Plants
Anticholesterol effect	Lowering total cholesterol, LDL and VLDL, increasing HDL.(24) HMG-CoA reductase inhibition, decrease in serum and hepatic total triglyceride levels.[27]	*Lonicera japonica* *Forsythia suspensa*
Antiplatelet effect	Inhibition of platelet activating factor.[42,46,69]	*Pogostemon cablin* *Atractylodes macrocephala* *Salvia miltiorrhiza*
Vasodilator effect Antihypertensive effect	Activation of intracellular Ca^{+2} channels in vascular smooth muscles, reduction of systolic blood pressure and vascular tension in the aorta.[50] eNOS expression, reducing arterial pressure, increasing nitric oxide production.[68]	*Scutellaria baicalensis* *Salvia miltiorrhiza*
Calcium antagonistic effect	Inhibition of calcium overload due to ischemia and hypoxia, improving the activity of myocardial calcium pumps.[59]	*Astragalus membranaceus*
Antiarrhythmic effect	Activation of JAK-STAT3 pathway, inhibition of K^+ channels.[34,35]	*Glycyrrhiza uralensis*

said that evidence-based medicine was not restricted to randomized trials and meta-analysis. We cannot act on randomized trials and meta analyses alone in the midst of the current pandemic, because there is not enough time for many extensive studies while there are thousands of patients in need of urgent treatment. This means that a greater number of safety studies and clinical studies meeting good clinical practice guidelines are needed in order for these plants to reach the level of evidence necessary to be used for treatment. As a case in point, after reports were published putting forward artemisin, derived from the plant *Artemisia annua*, as a compound possessing preventive and curative properties for COVID-19, the WHO released a statement saying that while it supports traditional remedies, there was insufficient evidence to support claims to prevent or treat COVID-19.[74]

Besides the need for more clinical studies in accordance with good clinical practice standards, the biggest problems seen with such treatment recommendations are generally a lack or abandonment of treatment using standard methods, and interruption in the course of treatment. As specified in the studies from China, the tests were given supplementary to normal treatment. Another critical point that must be taken into account is interactions with other medications. The mechanisms of action of the plants and/or mixtures administered must be well understood in order to elucidate these issues. Another important problem is the safety of the administered product. Just as interaction problems may result from substances found in the plant used, they may also result from the methods of preparation and administration. For this reason, we have provided the side effects associated with a portion of the aforementioned plants.

Plant products may interact with drugs used for cardiovascular diseases, such as warfarin, digitalis, aspirin, alpha blockers, calcium channel blockers, diuretics, statins, antihypertensives, steroids, cardiac glycosides, and anticoagulants. Among the most common unwanted side effects of these plants, most notably bleeding and arrhythmia, are effects with other serious implications, such as hypokalemia, rising or falling blood pressure, and increased heart rate.[75]

It is impossible to say how the many botanical products used during the COVID-19 pandemic will affect a virus whose mechanism of infection is not fully known. These products can create a false sense of confidence among those who use them and have a negative effect on the spread of the pandemic. People who use these products or methods may feel like they cannot get infected or fall ill, which may lead them to act recklessly in terms protecting themselves and others from infection.

As a result, although the plants found in these formulations have been observed to have effects in laboratory or animal studies, the existing clinical studies in accordance with standard procedures are insufficient. More clinical studies are necessary in order to be able to use these plants safely at a clinical level.

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