



Mechanical Insights and Advances in Herbal Medicine Pharmacology for Covid-19 Treatment: Exploring Efficacy, Mechanisms, and Future Prospects

Amina Razzaq ¹, Huma Ameen ¹, Rida Aziz ²

Abstract

The global COVID-19 pandemic has necessitated the exploration of various therapeutic strategies, including the potential use of herbal medicine as an adjunctive treatment. This study, "Mechanical Insights and Advances in Herbal Medicine Pharmacology for COVID-19 Treatment: Exploring Efficacy, Mechanisms, and Future Prospects," aims to evaluate the efficacy and mechanisms of action of specific herbal compounds in combating SARS-CoV-2. Herbal medicines, with their rich historical usage and diverse bioactive constituents, offer a multifaceted approach to viral inhibition, immune modulation, and inflammation reduction. Compounds such as quercetin, curcumin, and resveratrol have shown promising antiviral activities by targeting key viral enzymes and modulating immune responses. Clinical trials of traditional Chinese medicine formulations like Lianhua Qingwen and Shufeng Jiedu have demonstrated potential benefits in symptom reduction and recovery enhancement. Moreover, herbal medicines are generally well-tolerated, affordable, and accessible, making them

viable for low-resource settings. This study highlights the need for rigorous scientific validation and standardization of herbal formulations to maximize their safety and efficacy. Future research should focus on integrating modern pharmacological techniques with traditional knowledge to discover new bioactive compounds and develop innovative therapeutic agents. The successful integration of herbal medicine into COVID-19 treatment protocols requires interdisciplinary collaboration and robust regulatory frameworks to ensure safety and efficacy.

Keywords: COVID-19, Herbal medicine, Antiviral mechanisms, Traditional Chinese medicine, Pharmacological efficacy

Introduction

The global COVID-19 pandemic has underscored the urgent need for effective therapeutic strategies to manage and mitigate the impact of SARS-CoV-2 (Huang et al., 2020). While vaccines and antiviral drugs have been at the forefront of this battle, there is a growing interest in exploring the potential of herbal medicine as an adjunctive treatment (Luo et al., 2020). The rich history of herbal medicine across various cultures provides a vast repository of compounds that could offer valuable therapeutic benefits (Ekor, 2014). "Mechanical Insights and Advances in Herbal Medicine Pharmacology for COVID-19 Treatment: Exploring Efficacy, Mechanisms, and Future Prospects" aims to investigate the efficacy of herbal medicines, elucidate their mechanisms of action, and

Significance | Exploring herbal medicine for COVID-19 treatment bridges traditional practices and modern science.

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consider their future role in COVID-19 treatment protocols.

One of the primary challenges in utilizing herbal medicine for COVID-19 treatment is the scientific validation of their efficacy (Chen et al., 2021). While anecdotal evidence and traditional use provide initial indications of potential benefits, rigorous scientific research is necessary to confirm these effects. Recent studies have begun to shed light on various herbs and their bioactive constituents that show promise against SARS-CoV-2 (Elfiky, 2020). For example, compounds such as quercetin, curcumin, and resveratrol have demonstrated antiviral activities in vitro (Jo et al., 2020). These compounds inhibit viral replication, interfere with virus-host cell interactions, and modulate the immune response, thereby offering a multi-faceted approach to combating the virus (Forni et al., 2021). Figure 1 shows the frequency of commonly used herbs in herbal formulas for treating patients with COVID-19 in the recovery stage.

The pharmacological mechanisms through which these herbal compounds exert their effects are complex and multifaceted (Lau et al., 2020). Quercetin, a flavonoid found in many fruits and vegetables, has been shown to inhibit key enzymes involved in the viral replication cycle, such as 3CLpro and PLpro (Derosa et al., 2020). Curcumin, derived from turmeric, exhibits broad-spectrum antiviral properties by modulating various signaling pathways, including NF- κ B and MAPK, which are critical in the inflammatory response (Mahmood et al., 2020). Resveratrol, a polyphenol found in grapes, exerts its antiviral effects by inhibiting viral protein synthesis and enhancing host immune responses (Wahedi et al., 2020). Understanding these mechanisms is crucial for optimizing the use of herbal medicines in COVID-19 treatment and for the development of more effective therapeutic strategies.

The efficacy of herbal medicine in the treatment of COVID-19 is also being evaluated in clinical settings (Luo et al., 2020). Several clinical trials have been conducted to assess the safety and effectiveness of various herbal formulations in COVID-19 patients. For instance, traditional Chinese medicine (TCM) formulations such as Lianhua Qingwen and Shufeng Jiedu have shown promising results in reducing symptoms and improving recovery times (Hu et al., 2020). These formulations contain a combination of herbs that work synergistically to enhance antiviral activity, reduce inflammation, and support the immune system. Clinical trials and observational studies have reported that these TCM formulations can improve clinical outcomes when used alongside conventional treatments (Ding et al., 2020).

In addition to their therapeutic potential, herbal medicines offer several advantages over conventional pharmaceuticals (Ekor, 2014). They are generally well-tolerated and have fewer side effects, making them suitable for long-term use and for patients with comorbidities. Furthermore, the accessibility and affordability of herbal medicines make them an attractive option for low-resource

settings where access to conventional treatments may be limited (Wachtel-Galor & Benzie, 2011). However, it is essential to standardize herbal formulations and ensure quality control to maximize their safety and efficacy.

The future prospects of herbal medicine in COVID-19 treatment are promising but require careful consideration and further research (Yang et al., 2020). There is a need for comprehensive clinical trials to validate the efficacy of herbal compounds and formulations in larger, diverse populations (Wu et al., 2020). Moreover, integrating modern pharmacological techniques with traditional knowledge can lead to the discovery of new bioactive compounds and the development of novel therapeutic agents (Yang et al., 2020). Advanced technologies such as high-throughput screening, molecular docking studies, and systems biology approaches can accelerate the identification of potential antiviral compounds from herbs and elucidate their mechanisms of action. Collaboration between traditional healers, ethnobotanists, pharmacologists, and clinicians is essential for the successful integration of herbal medicine into modern healthcare (Houghton et al., 2005). Such interdisciplinary efforts can bridge the gap between traditional practices and contemporary scientific research, ensuring that the benefits of herbal medicine are realized in a safe and effective manner. Regulatory frameworks should also be established to oversee the use of herbal medicines in clinical practice, ensuring that they meet rigorous safety and efficacy standards (Ekor, 2014).

The aim of this study is the exploration of herbal medicine for COVID-19 treatment, which presents a unique opportunity to harness the therapeutic potential of natural compounds. Investigating the efficacy and mechanisms of action, developing a deeper understanding of how these ancient remedies can contribute to modern healthcare. The integration of herbal medicine into COVID-19 treatment protocols holds promise not only for managing the current pandemic but also for preparing for future outbreaks. As research progresses, maintaining a balanced approach that combines traditional wisdom with scientific rigor will be crucial for developing innovative and effective therapeutic solutions for COVID-19 and beyond.

Herbal Plants and Their Active Constituents Against COVID-19

The use of allopathic antiviral agents often accompanies adverse events and toxicity issues. Conversely, herbal drugs have been widely explored for various disease conditions, with natural herbal remedies being utilized in both Ayurveda and Traditional Chinese Medicine (TCM) for respiratory ailments, showing significant therapeutic improvements. When COVID-19 emerged, herbal medicines were highly recommended in China to reduce case numbers and spread. TCM herbal plants, endorsed by regulatory bodies, were promptly used (Huang et al., 2020). Similarly, Ayurveda, the oldest medicinal system in India, was employed to

treat respiratory disorders, albeit mainly for prevention rather than cure. For example, the Chinese medicine Shuanghuanglian, a mixture of honeysuckle, Chinese skullcap, and forsythia, demonstrates antiviral and immunomodulatory actions. Ayurveda also recommends mixtures such as *Ocimum sanctum*, *Piper nigrum*, *Zingiber officinale*, *Cinnamomum verum*, and *Vitis vinifera* for boosting immunity in COVID-19 patients (Xu et al., 2020) as show in Table:1

***Lonicera japonica* (Japanese Honeysuckle)**

Lonicera japonica, part of the Caprifoliaceae family, contains important phytoconstituents such as hydroxycinnamic acid, isoflavone, and flavanones. These constituents inhibit SARS-CoV-2 by preventing the SARS-CoV-2-S protein/ACE2 binding and inhibiting Mpro activity (Zhang et al., 2023; Ye et al., 2023). Additionally, it reduces toll-like receptor 3 and tank-bound kinase 1 caused by respiratory syncytial viral infection (Chavda et al., 2022).

***Adhatoda vasica* (Vasaka)**

Adhatoda vasica, from the Acanthaceae family, contains vasicine, vascinone, vascinolone, and adhatodine, exhibiting strong anti-influenza virus activity. This activity includes inhibition of viral attachment and replication through various mechanisms, such as blocking viral HA protein and sialic acid receptors, preventing virus entry, and inhibiting replication or budding from infected cells. It also has antitussive and bronchodilatory actions, alleviating pneumonia-like symptoms seen in COVID-19 (Gheware et al., 2019).

***Tinospora cordifolia* (Guduchi)**

Guduchi, from the Menispermaceae family, contains compounds like berberine, palmatine, and tinocordiside, which target the main protease (Mpro) of SARS-CoV-2. These targets include virus receptor binding motifs and human ACE2 functional proteins, displaying immunomodulatory, anti-inflammatory, and antioxidant effects (Balkrishna et al., 2021; Jena et al., 2021).

***Swertia chirata* (Chirata)**

Swertia chirata, belonging to the Gentianaceae family, is used in traditional medicine for its antiviral properties against SARS-CoV-2 by targeting Mpro and RNA-dependent RNA polymerase (RdRp). It contains active compounds such as methyl swertianin and β -amyryn, which inhibit the spike protein and Mpro protein (Woo et al., 2019; Paul et al., 2023).

***Camellia sinensis* (Green Tea)**

Camellia sinensis, known for its polyphenols like epigallocatechin gallate (EGCG) and theaflavin, shows potential in inhibiting matrix metalloproteinases (MMPs) against SARS-CoV-2 main protease (Mpro) and ACE2 binding activity. EGCG exhibits significant inhibition of 3Clpro, a key protease in viral replication (Reyes et al., 2023; Mhatre et al., 2021; Wang et al., 2021).

***Zingiber officinale* (Sunthi)**

Ginger, from the Zingiberaceae family, contains compounds like 6-gingerol, which inhibit Plpro and bind to the SARS-CoV-2 spike protein, interfering with ACE2 interaction. It also stimulates interferon secretion, inhibiting viral replication in the respiratory tract (Sheikh et al., 2023; Jafarzadeh et al., 2021; Chang et al., 2013).

***Withania somnifera* (Ashwagandha)**

Withania somnifera, from the Solanaceae family, acts as an immunomodulatory, antiviral, and anti-inflammatory agent. Its active compounds, such as withaferin A and withanolide D, inhibit RNA polymerase and exhibit antipyretic effects by suppressing COX-2 and prostaglandins (Saggam et al., 2021; Shree et al., 2022; Manish et al., 2021).

***Allium sativum* (Garlic)**

Garlic, known for its sulphur-containing components like allicin and ajoenes, reduces pro-inflammatory cytokines and exhibits antiviral potential against SARS-CoV by inhibiting thiol enzymes. It also enhances immune parameters, making it useful for improving immune processes in COVID-19 (Khubber et al., 2020; Hashemifesharaki et al., 2020; Hsieh et al., 2019).

***Azadirachta indica* (Neem)**

Neem leaves, from the Meliaceae family, have antimicrobial properties and fever-reducing effects. Compounds like nimbolin and cycloartenol bind to SARS-CoV-2 proteins, showing inhibitory roles against the virus (Borkotoky et al., 2021).

***Curcuma longa* (Turmeric)**

Turmeric contains curcumin, which exhibits immunomodulatory and antiviral actions by inhibiting 3Clpro and pro-inflammatory mediators like IL-6 and TNF- α . Curcumin activates natural killer cells and cytokine production, making it a potential inhibitory agent against SARS-CoV-2 (Chavda et al., 2022; Nugraha et al., 2020).

***Piper nigrum* (Black Pepper)**

Black pepper, containing piperine, inhibits viral RNA packaging and exhibits anti-inflammatory effects by inhibiting cytokines like IL-6 and TNF- α . It also shows potential against SARS-CoV-2 by targeting main protease (Mpro) and ACE2 receptors (Tripathi et al., 2022; Bui et al., 2020; Bilginer et al., 2022).

Potential mechanism of herbal medicines in COVID-19 treatment:

Disturb SARS-CoV-2 Replication and Proliferation

Drug targets to intervene based on key molecules or events at each stage of the virus life cycle is a strategy for many drug developments. In the life cycle of SARS-CoV-2, the S protein is the main protein for the virus to invade the host. It is also a key factor in determining the host tropism and tissue phagocytosis of the coronavirus. Previous studies have found that mutations in the SARS-CoV S protein, such as N479L and T487S, can significantly increase the affinity of the virus to human ACE2, while mutations in the MERS-CoV S protein may contribute to the virus zoonotic sexual transfer

(De et al, 2018), which shows that S protein and host are very important for the establishment of coronavirus infection in humans. The ORF1ab protein occupies two-thirds of the viral genome and can be cleaved into at least 16 predicted nsps (Fehr et al, 2015).

Among them, PLpro protein protease and phosphatase activities participate in regulating the virus replication process and have the function of antagonizing IFN antagonism (Báez-Santos et al, 2015), and 3CLpro and RdRp regulate RNA replication (Morse et al, 2020). Therefore, S protein and ORF1ab protein have become the main targets of anti-SARS-CoV-2 drugs. Conversely, the inhibition of virus entry into cells, replication, and translation is also one of the possible mechanisms for many drugs to treat COVID-19. QFPD decoction is reported to directly inhibit viral invasion and replication in the treatment of COVID-19 (Wu et al, 2020).

For the study of anti-SARS-CoV-2 drug mechanisms, the structure-based screening of chemical or phytochemical databases can provide clues to large numbers of crystal targets (Meng et al, 2017). A prediction based on molecular simulation showed that the ingredients in Chinese medicine prescriptions such as quercetin (Nguyen et al, 2012), andrographolide (Enmozhi et al, 2020), glycyrrhizic acid (Cinatl et al, 2013), baicalin (Su et al, 2020), patchouli alcohol (Yu et al, 2019), and luteolin (Ryu et al, 2010) had binding sites against SARS-CoV-2 protein, 3CLpro, ACE2, S protein, RdRp, and PLpro.

In addition, their potential role in the interference of viral life cycles has been previously reported, indicating that these components may inhibit virus infection by binding to SARS-CoV-2 protein, inhibiting virus entry into cells, inhibiting the activation of virus-induced cellular pathways, and inhibiting virus replication and proliferation in the body. An analysis of the protein-protein interaction core network using the TCM Systems Pharmacology Database and Analysis Platform suggested that there are many COVID-19-related genes acted on by the active Chinese herbal medicine ingredients such as 9,10-dimethoxypterocarpan-3-O- β -D-glucoside (Yu et al, 2020).

Ye et al. speculated that rutin, forsythoside E, and hyperoside components in LHQW may directly target the main protease of SARS-CoV-2 and exert antiviral effects (Ling et al, 2020). Chen et al (2020) showed that baicalin, scutellarin, hesperetin, glycyrrhizin, and nicotianamine could interact with ACE2, and Chinese herbs containing these compounds may have a potential role in antiviral invasion and infection. The molecular interaction analysis of QFPD components shows that QFPD may directly inhibit virus invasion and replication.

Among them, Pogostemonis Herba, Bupleuri Radix, Polyporus, Asteris Radix et Rhizoma, and 23-acetic acid alisol B can directly target the SARS-CoV-2 3CLpro protein to prevent virus proliferation. Alcohol, Farfarae Flos, ergosterol, asaramine,

Ephedrae Herba, and Asteris Radix et Rhizoma in QFPD have ACE2 binding sites; it may block SARS-CoV-2 from binding to host ACE2 and affect virus invasion of the epithelial cell (Tao et al 2020). Sun et al. found that baicalein and licorice phenol in HSBD formula may target Mpro and ACE2 proteins (Jimilihan et al, 2020). The active ingredients of JHQG granules kaempferol, quercetin, luteolin, baicalein, oroxylin A, licochalcone B, and glyasperin C have the potential to target ACE2 and may regulate PTGS2, BCL2, CASP3, and related pathways, thereby affecting virus replication (Shahrajabian et al, 2021). Herbal medicines also function as suppressors of stress and anxiety and improve mental health in the context of COVID-19 (Hajaj et al, 2020)

Affecting Host Immune/Inflammatory Response

Studies based on imaging and pathology have shown that COVID-19 is not just a lung infection, but also has the manifestations of thrombotic inflammation. With the progress of the disease, SARS-CoV-2 infection initially affects the lungs and perfuses organs through the whole body (Yang et al, 2020). It is worth noting that many factors affect the progression of the disease, besides the viral load, such as poor interferon response (Mehta et al, 2020). It is currently believed that the inflammatory factor storm caused by the body's excessive inflammatory response to SARS-CoV-2 infection is the main cause of severe disease and death in COVID-19 patients (Zhang et al, 2020). The high levels of circulating cytokines and lymphocytes in the lungs, heart, spleen, lymph nodes, and kidneys and a large number of mononuclear cell infiltrations may be closely related to the severity of COVID-19 disease (Li et al, 2020).

A study of KEGG enrichment analysis of a series of 26 herbal components predicted to have binding sites on viral proteins showed that the pathways of these herbal actions were related to the regulation of viral infections, immune/inflammatory responses, and hypoxia responses, suggesting the potential regulatory pathways of these herbs in viral respiratory infections (Zhao et al, 2020). In vitro cell experiments and virological experiments showed that LHQW, which is widely used to treat COVID-19, not only significantly inhibited the replication of SARS-CoV-2 in Vero E6 cells, but also reduced the expression of pro-inflammatory cytokines (TNF- α , IL-6, CCL-2/MCP-1, and CXCL-10/IP-10) (Chen et al, 2020). Moreover, chemical components of LHQW may inhibit inflammation-related pathways such as JAK-STAT, PI3K-AKT, MAPK, and NF- κ B (Huang et al, 2020).

QFPD is another Chinese medicine formula widely used in COVID-19 treatment (Liu et al, 2020). QFPD has more than 300 active ingredients and can act on more than 790 targets (Ren et al, 2020). Emerging evidence has revealed that QFPD may inhibit the invasion and replication of SARS-CoV-2 by directly targeting the virus 3C protein and host ACE2 (Cao et al, 2020), whose main target organ is the lung, followed by the spleen. By regulating a series of proteins co-expressed with ACE2 and a series of signal transduction

pathways closely related to the occurrence and development of diseases, QFPD plays a role in balancing immunity and eliminating inflammation, inhibiting the translation of viral mRNA, and inhibiting a group of proteins that interact with viral proteins by targeting ribosomal proteins (ribosomal proteins necessary for virus replication) (Ren et al, 2020).

GO enrichment and KEGG pathway annotation analysis suggest that IL6, IL10, MAPK, CXCL8, CCL2, IL1B, and PTGS2 genes are potential targets of compounds in Qingfei Jiedu granules (Shen et al, 2020). Ren reported that the frequently used Chinese formulas for COVID-19, including HXZQ capsules, JHQG granules, LHQW capsules, and QFPD decoction, play a protective role against SARS-CoV-2 by regulating cytokine levels through the arachidonic acid metabolic pathway (Zhang et al, 2020). For SFJD, several studies suggest its active ingredients might be involved in anti-inflammation. These ingredients (quercetin, β -sitosterol, luteolin, acacetin, wogonin, kaempferol, licochalcone A, and isorhamnetin, 5,7,4'-trihydroxy-8-methoxyflavone) might target inflammatory cytokines (IL6, IL1B, CCL2, MAPK8, MAPK1, MAPK14, CASP3, FOS, ALB, CALM1, NOS2, PTGS2, DPP4, and PTGS2) and signaling pathways (Xiong et al, 2020).

Yang et al. analyzed the transcriptomic profile of ILP-induced pneumonia and found that the Toll-like signaling pathway might be one of the most important pathways for Qingfei Paidu Decoction to mediate its anti-SARS-CoV-2 effect, and inhibition of Toll-like signaling pathway agonist and IL-6 production in macrophages involved in the antiviral mechanism of MXSG (Zhang et al, 2021). Notably, Chinese medicine targets diversity, and some Chinese medicines have been found to inhibit virus replication and inflammation. For example, Liu Shen capsules inhibit SARS-CoV-2 replication in Vero E6 cells and prevent and inhibit the mRNA levels of TNF- α , IL-6, IL-1 β , IL-8, CCL-2/MCP-1, and CXCL-10/IP-10 (Cui et al, 2021).

A pilot randomized clinical trial revealed that Xuanfei Baidu decoction can not only increase white blood cells and lymphocytes but also reduce C-reactive protein and erythrocyte sedimentation rate (De et al, 2021). Tanreqing Capsule is a TCM. A retrospective cohort study showed that the use of Tanreqing Capsule as a conventional drug supplement can benefit patients with mild and moderate COVID-19 and increase the level of immune CD3+ T cells in patients (Yang et al, 2020). The herbal formulation Divya-Swasari-Vati contains a mixture of different plant compounds, such as gallic acid, ellagic acid, cinnamic acid, eugenol, 6-gingerol, piperine, and glycyrrhizin, which can reduce spike protein-induced inflammation in a humanized zebrafish model (Xiong et al, 2020). Herbal medicine also has therapeutic effects on COVID-19-related complications. A study found that *Arenaria kansuensis* significantly alleviated pulmonary fibrosis caused by COVID-19. The possible pathway involves the activation of Nrf2 and inhibition of the NF-

kB/TGF- β 1/Smad2/3 pathway (Zhao et al, 2020). Additionally, the analysis of the drug network topology suggests that TCMs used for rehabilitation can inhibit fibrosis-related signal pathways such as VEGF, MAPK, and TGF- β 1 (Cao et al, 2020).

Effect and potential mechanism of herbal Medicines in COVID-19 treatment:

Effect of herbal medicines on COVID-19 Treatment

Through computational and biological processing, a series of small molecules, including those from natural compounds, have been screened and confirmed to directly inhibit important proteins in SARS or MERS coronaviruses (Wen et al, 2017). The gene sequence of SARS-CoV-2 suggests high similarities with viruses previously identified in SARS-CoV or MERS-CoV (Zhou et al, 2020). Consequently, previously reported anti-SARS-CoV or anti-MERS-CoV natural compounds may be a valuable guide to finding anti-SARS-CoV-2 herbal plants among the traditional Chinese herbs used to treat viral pneumonia. Chinese herb formulas used to treat SARS-CoV infection include Yin Qiao San (Ding et al, 2017), Yu Ping Feng San (Gao et al, 2019), Sang Ju Yin, LHQW Capsule (Gao et al, 2019), Shuanghuanglian (Su et al, 2020), Ma Xin Gan Shi Tang et al (2020).

These drugs have antiviral activity, anti-inflammatory, and immune regulation functions and can improve the function of the upper respiratory mucosal immune system after administration. These drugs, originally used for the treatment of SARS-CoV, continue to be used for the treatment of COVID-19 this time. Among them, LHQW is recommended by the new guidelines for patients in the medical observation period. Clinical evidence suggests that LHQW capsules have a certain effect on obviously alleviating the symptoms of cough, fever, and fatigue in patients with COVID-19, reducing the proportion of severe cases, shortening fever time, and inhibiting virus replication (Cheng et al, 2020). There is also evidence that Shuanghuanglian, a Chinese herbal product made of honeysuckle and forsythia, can inhibit the activity of SARS-CoV-2 (Li et al, 2020).

LHQW, composed of 13 herbs and 733–3084 chemical ingredients, also shows antiviral activity and is capable of inhibiting the replication of SARS-CoV-2. Further research shows that it may be related to regulating the human immune response and reducing the cytokine storm (Runfeng et al, 2020). Chinese medicine QFPD, recommended for COVID-19 treatment in China, has a potential role in inhibiting entry and replication of SARS-CoV-2 by targeting the 3Clpro protein and host ACE2 (Hu et al, 2020). SFJD, consisting of eight medicinal herbs, is widely used for COVID-19 for its antiviral, antibacterial, antitumor effects, and anti-inflammatory activities (Liu et al, 2021). A clinical real-world pragmatic study has shown that compared with standard treatment, the number of days of fatigue and coughing symptoms in patients with combined use of SFJD has been significantly reduced. Providing SFJD be used as

Table 1.Herbal plants and their active constituents potential against COVID-19

Herbal Plant	Active Constituents	Mechanism
<i>Azadirachta indica</i> (Neem)	Azadirachtin, Nimbin	Antiviral, Anti-inflammatory, Immunomodulatory
<i>Nigella sativa</i> (Black Cumin)	Thymoquinone, Nigellidine	Antiviral, Anti-inflammatory, Immunomodulatory
<i>Glycyrrhiza glabra</i> (Licorice)	Glycyrrhizin	Inhibits SARS-CoV-2 replication, Immunomodulatory
<i>Salvia officinalis</i> (Sage)	Safficinolide, α -Pinene, β -Myrcene	Antiviral, Immunomodulatory
<i>Perilla frutescens</i>	Rosmarinic acid, Luteolin	Inhibits SARS-CoV-2 replication
<i>Eurycoma longifolia</i> (Tongkat Ali)	Eurycomanone, Quassinoids	Antiviral, Anti-inflammatory, Immunomodulatory
<i>Toona sinensis</i> (Chinese Mahogany)	Toosendanin	Inhibits SARS-CoV replication
<i>Lycoris radiata</i> (Red Spider Lily)	Lycorine	Inhibits SARS-CoV replication
<i>Ocimum basilicum</i> (Basil)	Apigenin, Ursolic acid	Antiviral, Immunomodulatory
<i>Scutellaria baicalensis</i> (Baikal Skullcap)	Baicalein, Wogonin	Inhibits SARS-CoV-2 replication, Anti-inflammatory
<i>Rheum palmatum</i> (Chinese Rhubarb)	Emodin	Inhibits binding of SARS-CoV S protein to ACE2

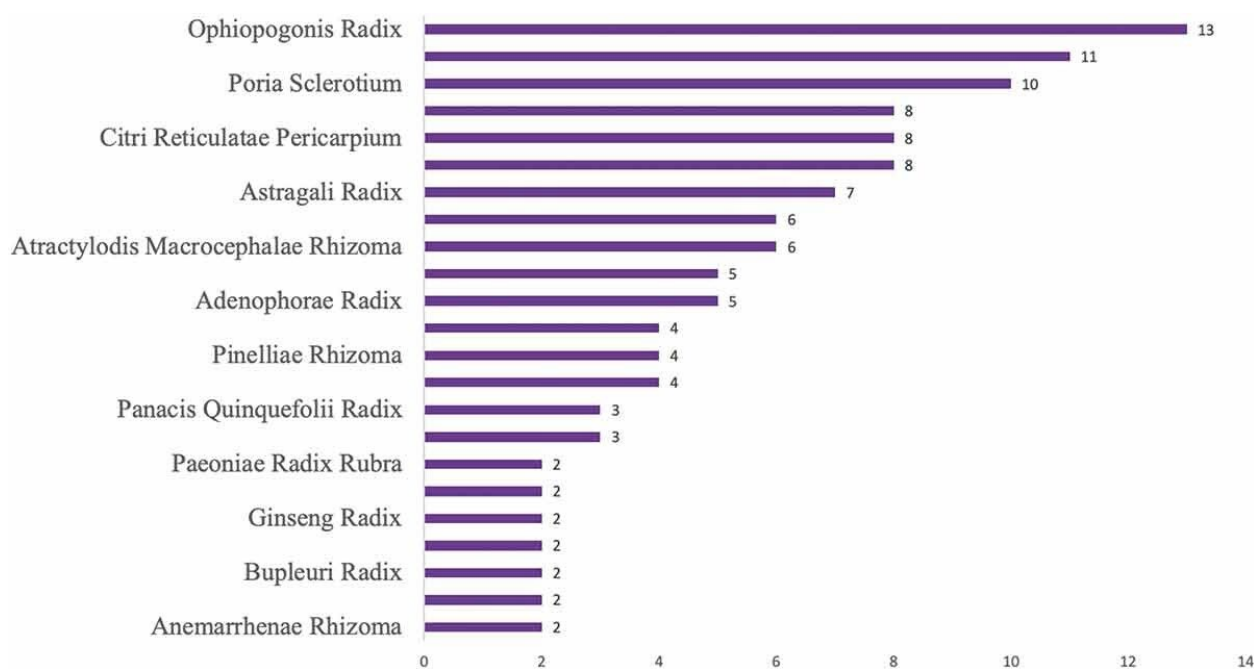


Figure 1. Frequency of commonly use herbs in herbal formulas for treating patients with COVID-19 in recovery stage.



Figure 2. Countries were reported using herbal medicine for treating COVID-19 patients.

early as possible in the first 8 days once the onset of symptoms, the benefits of patients shall be more obvious (Lu et al, 2021). Yin'an Jie Du Granules (YDJDG) is a Chinese herbal formula newly applied by Beijing Ditan Hospital. Compared with lopinavir-ritonavir treatment, YDJDG can shorten the average duration of fever and lung exudative lesions to speed up (Liu et al, 2021). Shenhuang Granule (SHG), composed of ginseng, palm rhubarb stem, sea cucumber, dandelion, aconite, and *Whitmania pigra* Whitman, has a significant effect on shortening the hospital stay of severely ill patients (Feng et al, 2021). Recently, Brian et al. Reported an oral liquid of traditional medicine, respiratory Detox Shot, which contains mostly herbal ingredients against traditional lung diseases, can directly inactivate the infectivity of SARS-CoV-2 virus particles and inhibit the infection of lentivirus-based lenti-SARS-CoV, lenti-SARS-CoV-2 (Hetrick et al, 2021). In summary, clinical trials and in vitro evidence have suggested that Chinese medicine granules as a whole play a role in reducing mortality and reducing fever (Wang et al 2020).

However, these clinics are not standard randomized clinical trials, and further large-scale randomized, double-blind, placebo-controlled clinical trials are needed to provide more confident evidence. *Nigella sativa* is a famous edible spice with antiviral and immunomodulatory activities, which was used in an open-label randomized controlled clinical trial of Saudi Arabia to reduce symptoms and shorten the recovery time of symptomatic patients with mild COVID-19 (Koshak et al, 2021). Another open-label randomized controlled clinical trial from India showed that *Kabasura Kudineer* reduces the SARS-CoV-2 viral load of asymptomatic COVID-19 patients and did not record any adverse reactions (Natarajan et al, 2021).

Herbs in combination with conventional therapy in COVID-19 treatment

In addition, superiority was displayed in the treatment of COVID-19 through a combination of the *Huashi baigu* (HSBD) Formula. Compared with treatment with western medicine alone, TCM combined with western medicine can benefit patients more by reducing the rate of exacerbation of the disease. At the same time, there is no increase in the incidence of adverse events (Liang et al, 2021). Liu et al (2021) Observed that Arbidol combined with LHQW treatment shortened the time for the negative result of the SARS-CoV-2 nucleic acid detection and had a better effect on the resolution of lung inflammation than LHQW alone Another clinical trial showed that LHQW combined with conventional treatment can shorten fever, fatigue, and cough and recovery time than conventional treatment, with better effects on improving chest CT performance and clinical cure rate (Hu et al, 2021).

To Chinese herbal formulas, traditional Chinese medicine injections also have immunosuppressive function. Wang et al. Reported that Shen Fu Injection, Shenmai Injection, and Re Du

Ning Injection could inhibit the levels of inflammatory factors such as IL-1 β , IL-6, TNF α , and other factors, thereby reducing the function of lung inflammation (Han et al, 2021). Xiyanping injection can significantly improve the symptom relief and virus clearance time of patients with mild to moderate COVID-19 (Zhang et al, 2021). Therefore, it can be speculated that the mechanism of traditional Chinese medicine injections in the treatment of COVID-19 may be related to the reduction of tissue inflammation levels. Future experiments on cell and animal levels will provide more detailed information.

Limitations

Although Chinese medicine is used for antiviral purposes, particularly in the treatment of COVID-19, there is insufficient evidence to conclusively demonstrate its efficacy in alleviating patients' symptoms. Concerns arise regarding the difficulty in determining whether the antiviral activity of Chinese herbal medicine (CHM) is due to a single and precise action mechanism or a synergistic therapeutic effect. Another challenge faced in implementing Chinese medicine worldwide for COVID-19 treatment is the inability to provide a high supply. Additionally, a significant limitation is the lack of rigorous randomized controlled trials (RCTs), raising concerns about safety. Therefore, future prospective cohort studies, RCTs, or registry studies, as well as bioinformatics-based target analysis, are necessary to evaluate the effectiveness of herbal medicine formulas in preventing COVID-19 and treating related conditions. These efforts aim to provide stronger evidence for the application of herbal medicines in preventing COVID-19 and treating re-emergent conditions, maximizing benefits for patients with indications (Yang et al, 2020).

Conclusion

In conclusion, due to the incomplete understanding of COVID's pathology and the complexity of its pathological mechanisms, the limitations of single-target drug development become evident. Traditional medicine prescriptions comprise various components that may target multiple therapeutic targets and host cell cytokine signaling, potentially playing a unique role in COVID-19 treatment. Herbal medicine has been widely used against COVID-19 in China, East Asia, Saudi Arabia, Bangladesh, Morocco, India, Africa, and America. This review has summarized the application of herbal medicine in the prevention and treatment of coronaviruses, highlighted the antiviral activity of herbal medicine ingredients, and discussed progress in understanding the molecular mechanisms of herbal medicine. Specifically, we outlined the application of herbal medicine in combating COVID-19 in China. Additionally, we suggest that Kurarinone, Anupana containing epicatechin and hesperidin, curcumin, and piperine offer protection against epithelial damage caused by virus infection and

possess anti-coronavirus anti-infective activity. Current herbal medicines mainly improve or treat COVID-19 by inhibiting virus entry, replication, or enhancing the host's immune defense level.

Author contributions

A.R., H.A., and R.A. contributed equally to this work. A.R. conceived the study and designed the experiment. H.A. conducted the data analysis and interpretation. R.A. provided critical revisions to the manuscript and assisted with data collection. All authors reviewed and approved the final version of the manuscript.

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