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Review

Chinese herbal medicine: Fighting SARS-CoV-2 infection on all fronts

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ABSTRACT

Ethnopharmacological relevance: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes coronavirus disease 2019 (COVID-19), a highly pathogenic virus that has spread rapidly across the entire world. There is a critical need to develop safe and effective drugs, especially broad-spectrum antiviral and organ protection agents in order to treat and prevent this dangerous disease. It is possible that Chinese herbal medicine may play an essential role in the treatment of patients with SARS-CoV-2 infection.

Aim of the review: We aim to review the use of Chinese herbal medicine in the treatment of COVID-19 both *in vitro* and in clinical practice. Our goal was to provide a better understanding of the potential therapeutic effects of Chinese herbal medicine and to establish a "Chinese protocol" for the treatment of COVID-19.

Materials and methods: We systematically reviewed published research relating to traditional Chinese herbal medicines and the treatment of SARS-CoV-2 from inception to the 6th January 2021 by screening a range of digital databases (Web of Science, bioRxiv, medRxiv, China National Knowledge Infrastructure, X-MOL, Wanfang Data, Google Scholar, PubMed, Elsevier, and other resources) and public platforms relating to the management of clinical trials. We included the active ingredients of Chinese herbal medicines, monomer preparations, crude extracts, and formulas for the treatment of COVID-19.

Results: In mainland China, a range of Chinese herbal medicines have been recognized as very promising anti-SARS-CoV-2 agents, including active ingredients (quercetagetin, osajin, tetrandrine, proscillaridin A, and dihydromyricetin), monomer preparations (xiyanping injection, matrine-sodium chloride injection, diammonium glycyrrhizinate enteric-coated capsules, and sodium aescinate injection), crude extracts (Scutellariae Radix extract and garlic essential oil), and formulas (Qingfei Paidu decoction, Lianhuaqingwen capsules, and Pudilan Xiaoyan oral liquid). All these agents have potential activity against SARS-CoV-2 and have attracted significant attention due to their activities both *in vitro* and in clinical practice.

Conclusions: As a key component of the COVID-19 treatment regimen, Chinese herbal medicines have played an irreplaceable role in the treatment of SARS-CoV-2 infection. The "Chinese protocol" has already demonstrated clear clinical importance. The use of Chinese herbal medicines that are capable of inhibiting SARS-Cov-2 infection may help to address this immediate unmet clinical need and may be attractive to other countries that are also seeking new options for effective COVID-19 treatment. Our analyses suggest that countries outside of China should also consider protocols involving Chinese herbal medicines combat this fast-spreading viral infection.

Abbreviations: ACE2, angiotensin-converting enzyme 2; andro, andrographolide; CHIKV, Chikungunya virus; 3CL^{pro}, 3C-Like protease; COVID-19, coronavirus disease 2019; EBOV, Ebola virus; EC_{50}, half maximal effective concentration; FCV, feline calicivirus; GA, glycyrrhizic acid; HBV, Hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; GRP78, glucose regulating protein 78; H1N1, influenza A; HSV-1, herpes simplex virus type 1; IC_{50}, half maximal inhibitory concentration; IL-10, interleukin-10; JHQG, Jinhua Qinggan granules; LHQW, Lianhuaqingwen capsules; MERS, Middle East respiratory syndrome coronavirus; MLAV, Mengla virus; M^{pro}, main protease; NHC PRC, National Health Commission of the People's Republic of China; nsp, nonstructural protein; PDL, Pudilan Xiaoyan oral liquid; PHEIC, public health emergency of international concern; PLpro, papain-like protease; RdRp, RNA-dependent RNA polymerase; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SI, selectivity index; TMPRSS2, transmembrane protease serine 2; TNF-α, tumor necrosis factor-α; WHO, World Health Organization; XYP, Xiyanping injection.

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1. Introduction

In late December 2019, a novel coronavirus disease (COVID-19) outbreak occurred in Wuhan, China (Jie et al., 2020). As the sixth public health emergency of international concern (PHEIC), this global pandemic still remains as a focus of concern due to the significant threat it poses to the lives of billions of individuals (WHO Emergency Committee, 2020). COVID-19 is causes by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and can cause multiple injuries to extrapulmonary organs and tissues, including the heart (Shi et al., 2020b), kidney (Puelles et al., 2020), liver (Zhang et al., 2020a), and brain (Rhea et al., 2020). However, the virus has also been shown to affect the ocular system (Wu et al., 2020), the gastrointestinal system (Redd et al., 2020), the musculoskeletal system (Cipollaro et al., 2020), the skin (Casas et al., 2020), and the cardiovascular system (Nishiga et al., 2020). There are numerous pathological mechanisms that are potentially involved in these forms of injury, including direct viral toxicity (Gupta et al., 2020), immune dysregulation (Acharya et al., 2020), endothelial derangement (Nizzoli et al., 2020), and an imbalance in the renin angiotensin aldosterone system (John et al., 2020). Given the complexity of the mechanisms involved, it is vital that we develop novel therapies against the SARS-CoV-2 virus that are novel, safe and effective.

Chinese herbal medicines are associated with a range of beneficial effects that had collectively led to this approach becoming an important option for fighting the epidemic in mainland China, including antiviral activity (Ma et al., 2020e), anti-inflammatory activity (Chen et al., 2019b), and anti-fibrotic activity (Yang et al., 2019b). On the 22nd January 2020, the National Health Commission of the People's Republic of China (NHC PRC) included traditional Chinese medicine as a recommended therapeutic option for the treatment of patients with COVID-19 The National Health Commission of the People's Republic of China (NHC PRC), 2020. As of the 23rd March 2020, a total of 74,187 patients infected with SARS-CoV-2 on the mainland of China (91.5% of the total number of confirmed cases at that time) were treated with traditional Chinese medicine; the overall efficacy of this approach exceeded 90% (Xinhua Net, 2020b; Yu, 2020b). As of the 6th January 2021, the COVID-19 epidemic has been well controlled in China; the current SARS-CoV-2 infection rate is 1279 cases (WHO, 2020). Chinese herbal medicine has played a critical role in the treatment of this novel viral infection by virtue of its proven activity against multiple SARS-CoV-2 pathways and targets (Huang et al., 2020). Globally, the epidemic is still ongoing, the World Health Organization (WHO) has reported that there are 84,780,171 confirmed cases across the world, including 23,707,908 cases of active SARS-CoV-2 infection (WHO, 2020). The rapid spread and highly infectious nature of this virus has created a health emergency on a global scale; none of the world's population is currently immune to this infection. It is vital that medical practitioners from across the world unite in a concerted effort to combat SARS-CoV-2 infection, including Chinese medicine practitioners.

The outstanding performance of Chinese herbal medicine, especially in mainland China, has led to the publication of several interesting reviews on COVID-19 from the perspectives of clinical experience (Lee et al., 2020; Shu et al., 2020; Zhuang et al., 2020), scientific foundation (Leung et al., 2020), efficacy and safety (Li et al., 2020f), pros and cons (Nugraha et al., 2020; López-Alcalde et al., 2020) and meta-analysis (Fan et al., 2020; Xiong et al., 2020b; Luo et al., 2020a). However, as yet, there has been no hierarchical (active ingredients, monomer preparations, crude extracts, and formulas) review covering the use of Chinese herbal medicine for the treatment of COVID-19 that covers both *in vitro* research and clinical practice.

The molecule (active ingredient) is responsible for the biological activity of Chinese herbal medicine. To better digest the potential therapeutic effects of Chinese herbal medicine, we attempted to focus on both representative and different categories of chemical components (involving high-quality anti-SARS-CoV-2 studies *in vitro*), rather than take a systematically driven approach. We also emphasize the unique advantages of Chinese herbal medicines in terms of organ protection and broad-spectrum activity against viruses.

This review presents a hierarchical overview of the current progress in potentially active anti-SARS-CoV-2 ingredients in Chinese herbal medicine, monomer preparations, crude extracts, and formulas. Our aim was to provide a 'Chinese protocol' for the treatment of COVID-19.

2. Promising active ingredients of Chinese herbal medicine that exhibit *in vitro* activity against SARS-Cov-2

The history of the modern pharmaceutical industry includes many anecdotes describing how traditional Chinese medicine inspired the discovery of several drugs; for example, artemisinin (Ma et al., 2020c) and arsenic trioxide (List et al., 2003). Chinese herbal medicine consists of a large group of secondary metabolites (e.g., flavonoids) that present wide structural diversity and includes a range of compounds (e.g., flavones, flavanols, flavanonols, and isoflavones) that mediate a wide range of valuable bioactivities, including anti-browning, anti-tuberculosis, anti-microbial, anti-cancer and anti-oxidant effects (Wang et al., 2013). As research continues, flavonoids have recently been recognized as promising antiviral agents against multiple viruses, including the influenza A (H1N1) virus (Roschek et al., 2009), Ebola virus (EBOV) (Fanunza et al., 2020), and severe acute respiratory syndrome coronavirus (SARS-CoV) (Jo et al., 2019).

Scutellarein, a flavone monomer, is an important natural product that can be isolated from the plant *Erigeron karvinskianus* and used as a traditional herbal medicine (Fig. 1A) (Miao et al., 2020). This agent has significant bioactivity against several diseases, including pulmonary fibrosis (Miao et al., 2020), but can also confer neuroprotective effects (Tang et al., 2014). Scutellarein has half maximal inhibitory concentration (IC_{50}) values of 0.86 μM and 2.50 μM against SARS-CoV (Yu et al., 2012) and HIV (Sansei et al., 1997), respectively. Quercetagetin is a natural flavonol that is extracted from *Tagetes erecta L.* (marigold), a traditional form of herbal medicine (Fig. 1B) (Kang et al., 2013). Extensive studies have demonstrated that quercetagetin exerts a range of pharmacological activities, as an anti-inflammatory agent (Kang et al., 2013) and as an anti-viral agent (Ahmed-Belkacem et al., 2014). Furthermore, quercetagetin exhibits broad-spectrum activities against viruses, including feline calicivirus (FCV) at an IC_{50} of 2.8 μM (Fumian et al., 2018), hepatitis C virus (HCV) at a half maximal effective concentration (EC_{50}) of 5.4 μM in Huh 7.5 cells, a stable HCV cell-line (Ahmed-Belkacem et al., 2014); and Chikungunya virus (CHIKV) at an IC_{50} of 43.52 μM (Lani et al., 2016). Dihydromyricetin, a flavanonol monomer, is a secondary metabolite isolated from the plant *Ampelopsis megalophylla* Dielset Gilg that has potential anti-oxidative effects (Fig. 1C) (Zhang et al., 2018a). Dihydromyricetin also been reported exert anti-inflammatory effects and was shown to reduce lung injury by inhibiting activation of the NLRP3 inflammasome in vascular endothelial cells (Wang et al., 2019).

The main protease (M^{pro}) of SARS-CoV-2, also referred to as the 3C-like protease ($3CL^{pro}$), plays an essential role in the maturation process of viral polyproteins and is therefore an attractive therapeutic target (Zhang et al., 2020f). Recent research by Liu et al. has shown that three natural flavonoids (scutellarein, quercetagetin, and dihydromyricetin) can effectively inhibit SARS-CoV-2 $3CL^{pro}$ activity *in vitro* and strongly inhibit the replication of SARS-CoV-2 in Vero cells at an IC_{50} of 5.80 μM, 1.27 μM, and 1.20 μM, respectively (Liu et al., 2020a).

Osajin, produced by the medicinal plant *Maclura pomifera*, is an antioxidative prenylated isoflavone (Fig. 1D) (Dilek et al., 2017). Osajin exhibits a range of significant pharmacological activities against prostate cancer, diabetes and bacterial infections (Dilek et al., 2017). Jeon et al. recently revealed that osajin could effectively inhibit the replication of SARS-CoV-2 *in vitro* with an EC_{50} at 3.87 μM with only mild levels of toxicity (selectivity index (SI) = 2.95) (Jeon et al., 2020). Based on molecular docking and binding stability, Kousar et al. further revealed that osajin could be considered as a potential inhibitor of the MTase

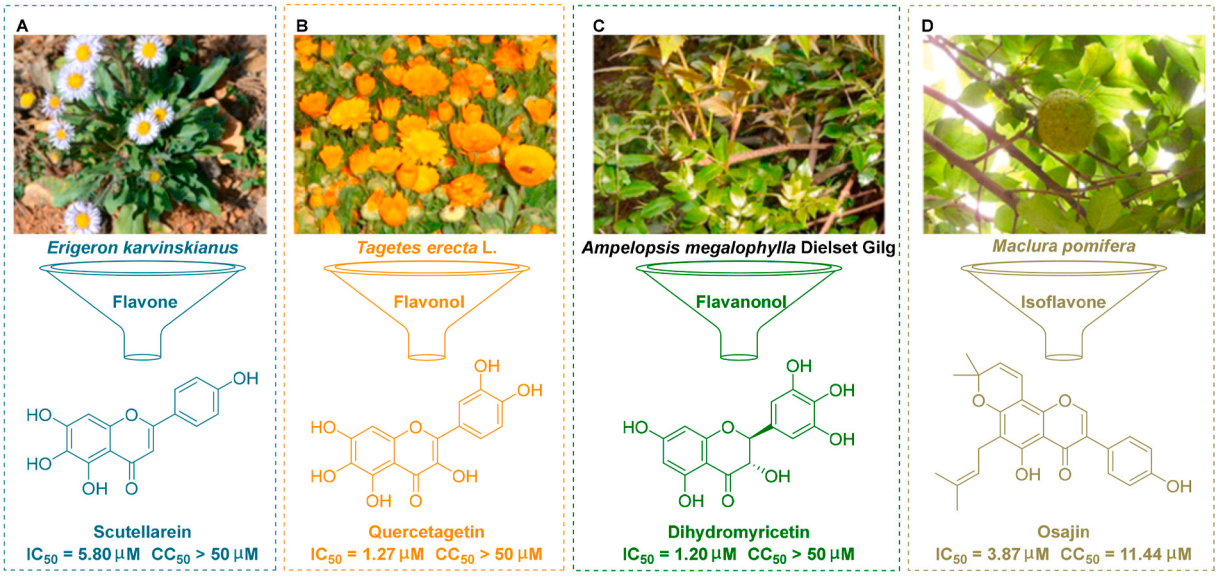

Fig. 1. Flavonoids that have been shown to exert activity against SARS-Cov-2 *in vitro*. (A) Scutellarein was isolated from the plant *Erigeron karvinskianus*. (B) Quercetagetin was isolated from the plant *Tagetes erecta L.* (C) Dihydromyricetin was isolated from the plant *Ampelopsis megalophylla* Dielset Gilg. (D) Osajin was isolated from the plant *Maclura pomifera.*

(−8.2 kcal/mol) and helicase (−8.2 kcal/mol) in SARS-CoV-2 (Kousar et al., 2020). Collectively, this evidence has highlighted a new potential role for natural flavonoids for the inhibition of SARS-CoV-2 replication *in vitro*. Further research is now needed to investigate whether these agents also exhibit anti-viral activities *in vivo*.

Bisbenzylisoquinoline alkaloids are structurally diverse natural products that contain approximately 500 compounds that are of medical importance (Weber and Opatz, 2019). Tetrandrine is a macrocyclic alkaloid and a natural product that can be extracted from the commonly used plant *Stephania tetrandra* S. Moore, a form of traditional Chinese medicine (Fig. 2A) (Han et al., 2007). As a herbal alkaloid, tetrandrine has been widely used for its pharmacological activity against lung injury (Han et al., 2007). Furthermore, tetrandrine has been recognized as a promising broad-spectrum antiviral drug that exhibits *in vitro* activity against a range of viruses, including human coronavirus (HCoV) OC43 at an EC_{50} of 0.296 μM (Kim et al., 2019), EBOV at an IC_{50} of 0.055 μM (Sakurai et al., 2015), and human immunodeficiency virus (HIV)/-Mengla virus (MLAV)-GP at an EC_{50} of 2.65 μM (Chen et al., 2019a). Very recently, Jeon et al. revealed that tetrandrine could effectively inhibit the replication of SARS-CoV-2 in Vero cells at an IC_{50} of 3.0 μM (Jeon et al., 2020), thus suggesting the clinical potential of tetrandrine for the treatment of SARS-CoV-2. Qian et al. also reported that tetrandrine could reduce the entry of SARS-CoV-2 by blocking the activity of the two-pore channel 2 which plays a critical role in endocytosis (Ou et al., 2020).

Berbamine, another typical bisbenzylisoquinoline alkaloid, can be extracted from *Berberis thunbergii* DC., a traditional form of Chinese medicine (Fig. 2B) (Zheng et al., 2017). Berbamine exhibits a range of promising pharmacological properties; for example, it can protect the heart from ischemia/reperfusion injury (Zheng et al., 2017) by maintaining cytosolic $Ca^{(2+)}$ homeostasis (Zhang et al., 2012). In addition, berbamine can exhibit efficacy for the treatment of influenza virus (Jin et al., 1986). Liu et al. recently revealed that berbamine can also effectively inhibit the replication of SARS-CoV-2 $3CL^{pro}$ in Vero cells at an IC_{50} of 7.87 μM with moderate levels of cytotoxicity (SI = 6.35) (Liu et al., 2020a).

Angiotensin-converting enzyme 2 (ACE2), a vital component of the angiotensin-regulating system, is a host cell entry receptor for SARS-CoV-2. Interaction between the glycosylated SARS-CoV-2 spike (S) protein and ACE2 is the first step of the SARS-CoV-2 infection (Clausen et al., 2020). SARS-CoV-2 can also bind to glucose regulating protein 78 (GRP78) (Elfiky, 2020) and transmembrane protease serine 2 (TMPRSS2) (Hoffmann et al., 2020). Balmeh et al. revealed that berbamine has high binding energy for ACE2 (−12.3kCal/mol), TMPRSS2 (−11.8kCal/mol) and GRP78 (−11kCal/mol) receptors; these are the most important receptors for SARS-Cov-2 (Balmeh et al., 2020).

Proscillaridin A, a Na^{+}/K^{+} pump inhibitor, is an active cardiac glycoside that can be isolated from the traditional Chinese medicine *Urginea maritima* L. Baker; this is commonly used to treat heart failure (Fig. 2C) (Maryam et al., 2018). Studies have shown that Proscillaridin A can exert therapeutic effects against heart failure (Costa et al., 2019), apoptosis in human fibroblasts (Winnicka et al., 2010), and non-small-cell lung cancer (Li et al., 2018). More recently, Liu et al. carried out an in-depth study of proscillaridin A to identify its effect against COVID-19. The authors revealed that proscillaridin A could effectively inhibit the replication of SARS-CoV-2 $3CL^{pro}$ in Vero cells at an IC_{50} of 2.04 μM (Liu et al., 2020a). Furthermore, proscillaridin A exhibited a low binding energy (−80.06 Kcal/mol) and well interactions (six interactions) with SARS-CoV-2 M^{pro}; in addition, this study provided additional evidence relating to the potential molecular mechanisms of action (Aishwarya et al., 2020).

Shikonin is a natural naphthoquinone derived from the traditional Chinese medicine *Arnebia euchroma* (Royle) Johnst (Fig. 2D). Shikonin has already demonstrated a broad spectrum of pharmacological properties that show significant potential for therapeutic development (Zhang et al., 2018b). Specifically, shikonin exhibits significant pharmacological activities both *in vitro* and *in vivo*, including anti-inflammatory, anti-fungal, and anti-HIV effects (Wang et al., 2020c). Jin et al. recently reported that shikonin can effectively inhibit the replication of SARS-CoV-2 M^{pro} r *in vitro* with an EC_{50} at 15.75 μM (Jin et al., 2020).

In order to support the precision design of a drug against SARS-Cov-2, Li et al. were the first to create a crystal structure of SARS-CoV-2 M^{pro} in complex with shikonin at 2.45 Å resolution (Fig. 3A and B) and generated various different views of the overall structure of SARS-CoV-2 M^{pro} in complex with shikonin (Fig. 3C) (Li et al., 2020a). Li et al. demonstrated that the catalytic dyad His41 and Cys145 residues undergo huge conformational changes, creating a striking difference with

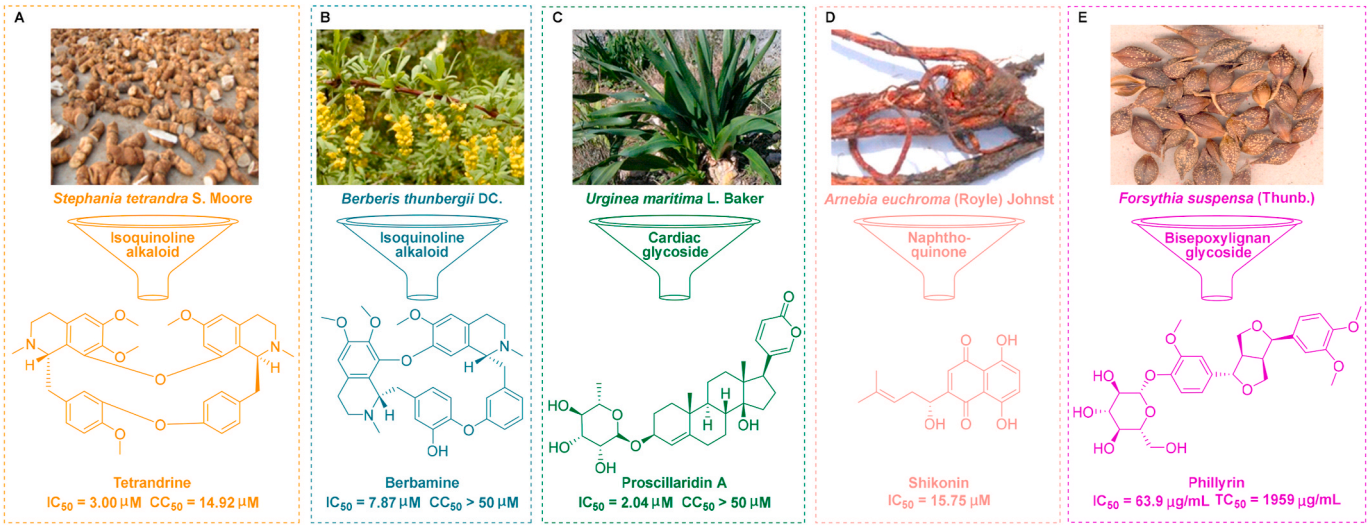

Fig. 2. Other traditional Chinese medicines that exhibit bioactivity against SARS-Cov-2 *in vitro*. (A) Tetrandrine was isolated from the plant *Stephania tetrandra* S. Moore. (B) Berbamine was isolated from the plant *Berberis thunbergii* DC. (C) Proscillaridin A was isolated from the plant *Urginea maritima* L. Baker. (D) Shikonin was isolated from the plant *Arnebia euchroma* (Royle) Johnst. (E) Phillyrin was isolated from the plant *Forsythia suspensa* (Thunb.).

other reported structures (Dai et al., 2020; Zhang et al., 2020e). Further analysis of the shikonin binding pocket revealed three novel interactions (π-π interactions with the His41 residue, hydrogen bond interactions with the Gln189 and Thr190 residues, and hydrogen bond interactions with the Met165, His164, and Cys145 residues) (Li et al., 2020a). This study demonstrated different binding patterns, thus suggesting significant diversity in terms of binding sites. However, Ma et al. recently revealed that shikonin might not be a target-specific SARS-CoV-2 M^{pro} inhibitor, due to the fact that its inhibitory ability is greatly reduced in the presence of 1,4-dithiothreitol (Ma et al., 2020a). Our growing understanding of different binding modes has offered an important strategy for designing and identifying effective anti-SARS-CoV-2 agents.

Phillyrin, a form of bisepoxylignan, can be extracted from the traditional Chinese medicine *Forsythia suspensa* (Thunb.) (Fig. 2E) (Xia et al., 2010). Literature shows that phillyrin exhibits promising pharmacological properties against lung inflammation (Zhong et al., 2013), traumatic brain injury (Jiang et al., 2020) and acute kidney injury (Zhang et al., 2020b). Yang et al. recently revealed that phillyrin could effectively inhibit the replication of SARS-CoV-2 in Vero E6 cells at an IC_{50} of 63.90 μg/mL with a low toxicity profile (SI = 30.66) by inhibiting activation of the nuclear factor kappa B (NF-κB) signaling pathway (Ma et al., 2020d). Furthermore, network pharmacology and molecular docking analysis further revealed that phillyrin could block the binding of SARS-CoV-2 S-protein and Gln325 in ACE2 (Yu et al., 2020a).

Our growing understanding of the processes that can be used to identify potential anti-SARS-CoV-2 molecules has led to the use of active ingredients from Chinese herbal medicines being recognized as a potential strategy for treating COVID-19. Besides the small molecules mentioned above, several other active ingredients from Chinese herbal medicines have also been shown to exhibit potent anti-SARS-CoV-2 activities *in vitro*. Table 1 summarizes a range of studies investigating the *in vitro* effects of such agents against SARS-CoV-2. In future, we hope that the active ingredients from Chinese herbal medicines will prove to be effective for treating SARS-CoV-2 infection in animal models and in humans.

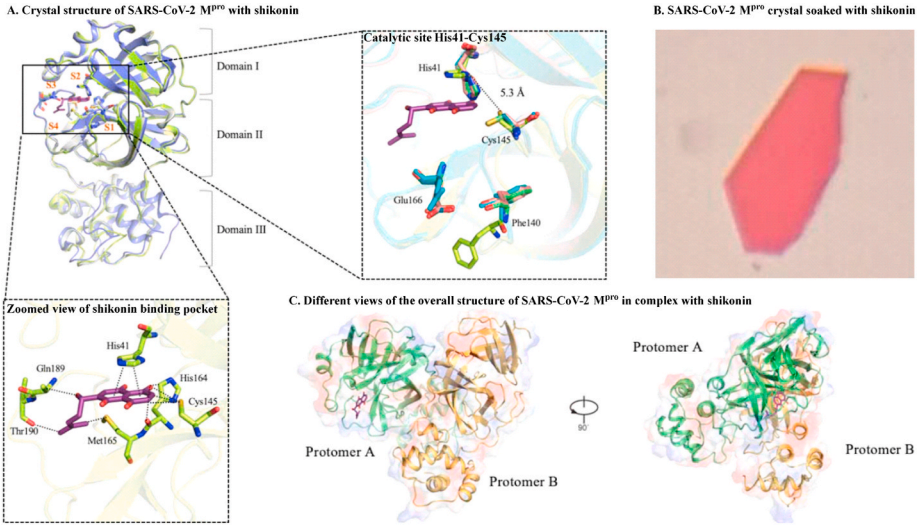

Fig. 3. The crystal structure of SARS-CoV-2 M^{pro} with shikonin. (A) Comparison of SARS-CoV-2 M^{pro} structures, conformational difference in catalytic site, and a zoomed view of shikonin binding pocket. (B) SARS-CoV-2 M^{pro} crystal soaked with shikonin. (C) Different views of the overall structure of SARS-CoV-2 M^{pro} in complex with shikonin (image reproduced with permission from Li et al., 2020a).

Table 1
Summary of the active ingredients from Chinese herbal medicines that have been shown to exert activity against SARS-Cov-2 *in vitro*.

No.	Compound	Plant	EC_{50} or IC_{50} (μM)	Reference
1	andrographolide	Herba andrographitis	0.034	Sa-ngiamsuntorn et al. (2020)
2	artemisinin	Artemisia annua	64.45	Cao et al. (2020)
3	baicalein	Scutellaria baicalensis	0.39	Liu et al. (2020a)
4	baicalin	Scutellaria baicalensis	6.41	Su et al. (2020)
5	berbamine	Berberis thunbergii	7.87	Liu et al. (2020a)
6	cannabidiol	Cannabis sativa	7.91	Raj et al. (2020)
7	cepharanthine	Stephania cephalantha	0.35	Ohashi et al. (2020)
8	chlorogenic acid	L. japonica	39.5	Su et al. (2020)
9	digitoxin	Digitalis purpurea	0.23	Jeon et al. (2020)
10	digoxin	Digitalis purpurea	0.19	Cho et al. (2020)
11	dihydromyricetin	Ampelopsis megalophylla	1.20	Liu et al. (2020a)
12	EGCG	Green tea	0.017	Jang et al. (2020)
13	emetine	Psychotria ipecacuanha	0.46	Choy et al. (2020)
14	forsythoside A	Forsythia suspensa	3.18	Su et al. (2020)
15	forsythoside B	Forsythia suspensa	2.88	Su et al. (2020)
16	glycyrrhizin	Glycyrrhiza uralensis	0.53	Sand et al. (2020)
17	homoharringtonine	Cephalotaxus harringtonii	2.25	Choy et al. (2020)
18	myricetin	Myrica rubra	0.22	Kuzikov et al. (2020)
19	osajin	Maclura pomifera	3.87	Jeon et al. (2020)
20	ouabain	Acocanthera ouabaio	0.024	Cho et al. (2020)
21	phillyrin	Forsythia suspensa	1.13	Ma et al. (2020d)
22	platycodin D	Platycodon grandiflorus	1.19	Kim et al. (2020)
23	proscillaridin A	Urginea maritima	2.04	Liu et al. (2020a)
24	pterostilbene	Pterocarpus santalinus	19	Ellen ter et al. (2020)
25	quercetagetin	Tagetes erecta	1.27	Liu et al. (2020a)
26	quercetin	Flos Sophorae Immaturus	4.48	Liu et al. (2020b)
27	resveratrol	Polygoni cuspidati rhizoma	66	Ellen ter et al. (2020)
28	scutellarein	Erigeron karvinskianus	5.80	Liu et al. (2020a)
29	shikonin	Arnebia euchroma	15.75	Jin et al. (2020)
30	Δ^9-tetrahydrocannabinol	Cannabis sativa	10.25	Raj et al. (2020)
31	tetrandrine	Stephania tetrandra	3.00	Jeon et al. (2020)
32	theaflavin	Black tea	0.015	Jang et al. (2020)

3. Promising Chinese herbal medicine monomer preparations for the treatment of SARS-CoV-2 infection in clinical practice

Herba andrographitis (Chinese name: Chuanxinlian), composed of the whole plant or leaves of *Andrographis paniculata* (Burm. F.) Nees, is a traditional herb that has been widely used over many centuries to treat a range of diseases in China (Fig. 4A) (Kumar et al., 2019). Recent studies have reported numerous pharmacological properties of *Herba andrographitis* extracts, both *in vitro* and *in vivo*, against HIV (EC_{50} value of 5.49 μg/mL) (Feng et al., 2012), complement (EC_{50} value of 23.1–638.3 μg/mL) (Wen et al., 2020), and excito-repellency (96.7% escape at 0.5–5.0% w/v concentration) (Sukkanon et al., 2019). This agent has also been used to treat osteoarthritis in the knee; a 300 mg/day dose was effective and safe when applied to reduce pain (Hancke et al., 2019). Andrographolide (andro) is a major component of *Herba andrographitis* and belongs to the diterpenoid family. Consistent with the reported function of *Herba andrographitis* extracts, andro has demonstrated a broad spectrum of bioactivities, including anti-inflammatory, anti--cancer, and anti-bacterial effects (Kumar et al., 2019). Andro also exhibits broad-spectrum activities against several different types of viruses, including influenza virus (Ding et al., 2017), herpes simplex virus type 1 (HSV-1) (Seubsasana et al., 2011), Chikungunya virus (Gupta et al., 2017), and Hepatitis B virus (HBV) (Chen et al., 2014).

Very recently, andro has been identified as a potential inhibitor of SARS-COV-2 M^{pro} with excellent pharmacodynamic properties, as demonstrated by *in silico* and computational studies (Enmozhi et al., 2020). The bioavailability of andro is increased when it is administered intravenously. Andro sulfonate is the major ingredient of Xiyanping injection (XYP), an agent that has been approved to treat respiratory infectious diseases in China (Huang et al., 2019). Nie et al. (Nie et al., 2012) reported the effect of XYP on acute lung injury in a rat model via bronchoalveolar lavage; XYP was shown to inhibit excessive anti-inflammatory responses and reduce the production of several proinflammatory cytokines (interleukin (IL)-1β, IL-6, and IL-8). Recent studies have also shown that XYP can play a vital role in the treatment of viral pneumonia and is more effective than ribavirin (Nie et al., 2012). XYP has also proven to be effective for the treatment of acute upper respiratory diseases (Qi et al., 2018). Given its broad-spectrum of activities, XYP has become a key component of COVID-19 treatment. To further investigate anti-SARS-Cov-2 activity, clinical studies have been registered to evaluate the effect of XYP for the treatment of COVID-19 (www.chictr.org/cn/, China Clinical Trial Registry number: ChiCTR2000032412, ChiCTR2000029756, ChiCTR2000030117, and ChiCTR2000030218).

Matrine, a clinical drug in China, is an active quinolizidine alkaloid that can be isolated from *Sophora flavescens* Aiton, a traditional Chinese medicine (Fig. 4B) (Zhou et al., 2014). Matrine is known to exhibit a therapeutic effect on asthma, skin inflammation, Alzheimer's syndrome, viral hepatitis, and cancer (Zhang et al., 2020c). More recently, matrine has been reported to play an important role in reducing organ injury (Xu et al., 2016a). Li et al. (Li et al., 2012) showed that matrine was able to significantly reduce acute myocardial injury by reducing the expression levels of dimethylarginine dimethylaminohydrolase-2 and by attenuating the serum levels of asymmetric dimethylarginine. During the treatment of silicosis, the combination of a matrine injection with tetrandrine tablets was able to reduce lung markings very effectively (Miao et al., 2012). Interestingly, Xu et al. reported that matrine significantly improved renal function in rats with nephropathy (Xu et al., 2016b). Furthermore, a clinical study showed that matrine was able to protect liver function in patients with primary hepatic carcinoma (Lao, 2005). In another study, Huang et al. found that matrine was able to inhibit allergic airway inflammation in asthmatic mice by reducing the production of eotaxin and Th2 cytokine (Huang et al., 2014). Matrine sodium chloride injection, which has been approved for clinical application to treat cancers and cancer-related pain in China (Guo et al., 2015). With regards to the treatment of COVID-19 treatment, Sun et al. reported that the injection of matrine sodium chloride has anti-COVID-19 activity (lung index inhibition rate was 86.86% at a dose of 36.67 mL/kg/d) in a mouse model combining disease with the syndrome (Sun et al., 2020). More importantly, an in-depth clinical trial of matrine sodium chloride injection was launched to identify its efficacy against COVID-19; the effective clinical rate was 100.0% in 40 cases (Yang et al., 2020a). As with ACE2 and M^{pro}, RNA-dependent RNA polymerase (RdRp) is another primary target associated with SARS-CoV-2 infection (Gao et al., 2020b). Based on molecular docking experiments,

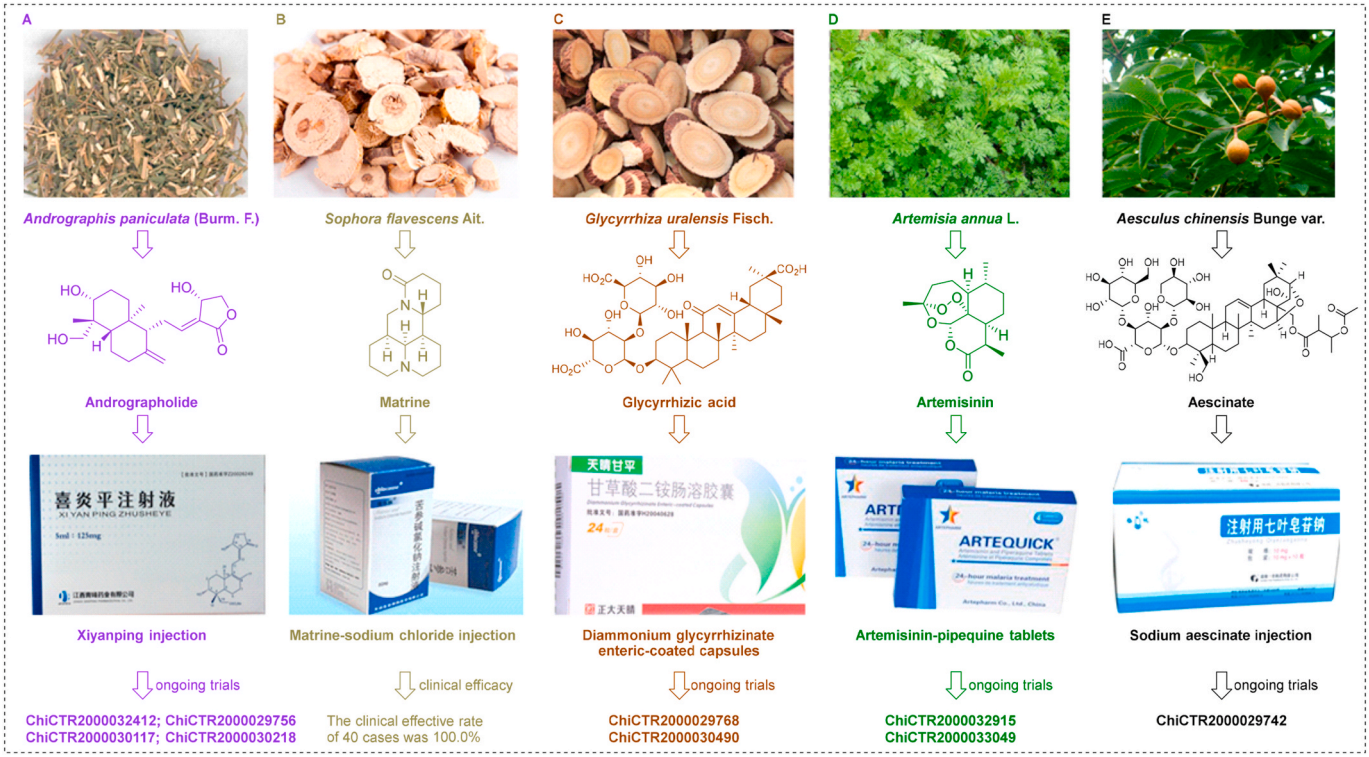

Fig. 4. Monomer preparations for the treatment of SARS-CoV-2 infection in clinical practice. (A) Andrographolide, the major ingredient of Xiyanping injection, was isolated from the plant *Herba andrographitis*. (B) Matrine, the major ingredient of matrine injection, was isolated from the plant *Sophora flavescens* Aiton. (C) Glycyrrhizic acid, the major ingredient of diammonium glycyrrhizinate enteric-coated capsules, was isolated from the plant *Glycyrrhizae uralensis* Fisch. (D) Artemisinin, the major ingredient of artemisinin-pipequine tablets, was isolated from the plant *Artemisia annua* L. (E) Aescinate, the major ingredient of sodium aescinate injection, was isolated from the plant *Aesculus chinensis* Bunge var.

Peng et al. revealed that matrine exhibits a high binding potential to RdRp (−6.3 kcal/mol), M^{pro} (−5.8 kcal/mol), and ACE2 (−6.1 kcal/mol) in SARS-CoV-2 (Peng et al., 2020). Furthermore, matrine could be used to treat COVID-19 by suppressing SARS-CoV-2 replication and by regulating inflammatory responses (Peng et al., 2020).

Glycyrrhizae Radix et Rhizoma (Chinese name: Gancao), the dried roots and rhizomes of *Glycyrrhiza uralensis* Fisch., is a traditional herb that is widely used to treat a variety of diseases, (Fig. 4C) (Gao et al., 2019). Glycyrrhizic acid (GA), an important active ingredient of Gancao, has therapeutic effects against cancer, bronchitis, and acquired immune deficiency syndrome (Sun et al., 2019). This triterpene glycoside has also played an important role not only in reducing myocardial injury (Yang et al., 2017), human coronary artery endothelial cell damage (Tang et al., 2020), lung injury (Yuan et al., 2020), and hepatotoxicity (Tian et al., 2020), but also in protecting the liver (Chen et al., 2016), and promoting neural repair (Cao et al., 2019). Furthermore, GA has been evaluated by many groups for its ability to inhibit infections to multiple viruses *in vitro* and in humans, including SARS-CoV (EC_{50} = 365 μM in Vero cells with an SI > 65) (Hoever et al., 2005), HIV (90% inhibition of HIV replication in 60% patients) (Sasaki et al., 2002), Epstein-Barr virus (Lin et al., 2008), and varicella-zoster virus (the 50% infectious dose was 710 μM with an SI = 30) (Baba et al., 1987). Multiple lines of evidence (Bailly et al., 2020; Sinha et al., 2020; Li et al., 2020d; Vardhan et al., 2020; Ray et al., 2020) now support the critical role of GA for the treatment of SARS-CoV-2 infection. Krawczyk et al. revealed that GA could effectively inhibit the replication of SARS-CoV-2 M^{pro} in Vero E6 cells at an EC_{50} of 0.44 mg/ml *in vitro* (Sand et al., 2020). GA is the major ingredient of diammonium glycyrrhizinate enteric-coated capsules; these are used as a hepatic protector in clinical practice in China. To further investigate anti-SARS-Cov-2 activity, clinical studies on diammonium glycyrrhizinate enteric-coated capsules for the treatment of COVID-19 have been carried out in open-label trials (www.chictr.org/cn/, China Clinical Trial Registry number: ChiCTR2000029768 and ChiCTR2000030490).

Artemisinin, a first-line antimalarial drug, is a sesquiterpene that was first isolated in 1972 from the traditional Chinese medicine *Artemisia annua* L. by Xia (Fig. 4D) (Xia et al., 2020a). Based on in-depth studies, accumulating evidence has shown that artemisinin also has therapeutic efficacy for respiratory diseases (Cheong et al., 2020), acute lung injury (Zhao et al., 2017), myocardial ischemia-reperfusion injury (Wang et al., 2020b), and acute kidney injury (Liu et al., 2019). Cao et al. (Cao et al., 2020) recently revealed that artemisinin was able to inhibit SARS-CoV-2 infection with an EC_{50} value of 64.45 μM *in vitro*. Molecular dynamics studies also confirmed that artemisinin exhibits potent binding to Lys353 and Lys31-binding hotspots in the SARS-CoV-2 S protein (Sehailia et al., 2020). Artemisinin is the major ingredient of artemisinin-pipequine tablets. Artemisinin is an approved drug with an excellent safety profile, highlighting a new potential role as an inhibitor of SARS-CoV-2 replication. To further investigate anti-SARS-Cov-2 activity, clinical studies have been registered to evaluate the effect of artemisinin-pipequine tablets against COVID-19 (www.chictr.org/cn/, China Clinical Trial Registry number: ChiCTR2000032915 and ChiCTR2000033049).

Sodium aescinate (SA), a prescription drug possessing organ-protective effects, is an important triterpene saponin product isolated from the traditional herbal medicine *Aesculus chinensis* Bunge var. (Fig. 4E), (Zhang et al., 2020e). SA exerts an important role in the neuroprotection of traumatic brain injury (*via* the nuclear factor erythroid 2-related factor 2/antioxidant-response element pathway) (Zhang et al., 2020d), protecting the liver (*via* decreasing aspartate aminotransferase and alanine aminotransferase activities) (Peng et al., 2016), promoting cardiopulmonary resuscitation (*via* increasing the expression of hypoxia-inducible factor-1α in the cerebral cortex) (Du et al., 2011), and protecting acute lung injury (*via* increasing

myeloperoxidase activity and nitric oxide level in the lung (Tian et al., 2011), and decreasing malondialdehyde and matrix metalloproteinase gelatinase B levels (Du et al., 2012)). Importantly, no observable cytotoxicity or adverse events both *in vivo* and *in vitro* with SA treatment have been reported to date. SA is the major ingredient of sodium aescinate injection. To further investigate anti-SARS-Cov-2 activity, clinical studies on SA injection for the treatment of this novel viral infection has been registered to evaluate the treatment outcomes in the an open-label trial (i.e., www.chictr.org/cn/, China Clinical Trial Registry number: ChiCTR2000029742).

4. Promising crude extracts from Chinese herbal medicines for the treatment of SARS-CoV-2 infection

Scutellariae Radix (Chinese name: Huangqin), the dried roots of *Scutellaria baicalensis* Georgi, is an essential Chinese herbal medicine widely used over for 2000 years in China to treat a range of diseases including lung and liver complaints (Zhao et al., 2019). Due to a successful clinical trial, it is now listed officially in the 2020 Chinese Pharmacopoeia, 2020 British Pharmacopoeia, and European Pharmacopoeia v10.0. Huangqin's major chemical constituents are flavonoids, which contribute to its therapeutic effects, including anti-viral (Lin et al., 2016), lung injury (Yang et al., 2019a), hepatoprotective (Yang et al., 2019a), and neuroprotective activities (Li et al., 2019). A total of 100 flavonoids (56 free flavonoids and 44 flavonoid glycosides) have been isolated from *Scutellaria baicalensis* (Wang et al., 2018), among which baicalein, baicalin, wogonin, and wogonoside (Fig. 5A) are the major components with broad-spectrum anti-viral effects active against H1N1 (Zhi et al., 2019), Dengue virus (Hassandarvish et al., 2016), HSV-1 (Luo et al., 2020b), and HBV (Guo et al., 2007).

A new therapeutic strategy is currently being expanded. Lai et al. recently revealed that the crude extract of *Scutellaria baicalensis* could effectively inhibit the replication of SARS-CoV-2 in Vero E6 cells at an EC_{50} of 0.74 μg/mL with minimal toxicity (SI > 675.7) (Liu et al., 2020a). Additionally, baicalein is highly effective at inhibiting SARS-CoV-2, 3C-like protease ($3CL^{pro}$) infection (IC_{50} = 0.39 μM) and has low toxicity (SI > 128.2), while wogonin only has 6.1% inhibition even at the concentration of 50 μM (Liu et al., 2020a). A molecular docking technique was used to better define the inhibitory activity of the flavones baicalein and wogonin. The docking model revealed that 6-OH in baicalein plays an essential role in inhibiting SARS-CoV-2 viral RNA replication (forming hydrogen bond interactions with the carbonyl group of L141), as shown in (Fig. 5B) (Liu et al., 2020a). Further study of the extract of *Scutellaria baicalensis* is needed to confirm its promising data. *Scutellaria baicalensis* is a widely used drug with a good safety profile, highlighting a new potential role for its extract in the inhibition of SARS-CoV-2 replication.

Very recently, organosulfur compounds have attracted significant attention due to their broad-spectrum anti-SARS-CoV-2 activities *in vitro*. For example, calpain inhibitor II could potently blocks SARS-Cov-2 M^{pro} infection at lower concentration (EC_{50} = 2.07 μM) with no observable cytotoxicity (SI > 48.3) (Ma et al., 2020b), S416 demonstrated significant inhibition of SARS-CoV-2 replication at an excellent EC_{50} of 17 nM with remarkable selectivity (SI > 5882) (Xiong et al., 2020a), auranofin could effectively inhibit the replication of SARS-Cov-2 in Huh7 cells at an EC_{50} of 1.40 μM (Rothan et al., 2020), and nelfinavir exhibits potent anti-COVID-19 activity (IC_{50} = 0.77 μM in VeroE6 cells) with a low toxicity profile (SI > 83.1) (Ohashi et al., 2020). As a valuable anti-virus source of organosulfur compounds, garlic has fueled significant attention and become a critical strategy in the treatment of SARS-Cov-2 infection.

Garlic (Chinese name: Dasuan), the highly enlarged bulbs of *Allium sativum L.*, is a well-known Chinese herbal medicine widely used for centuries in China to treat a range of ailments including arterial stiffness, asthma, common colds, leprosy, and influenza (Fig. 6A) (Rose et al., 2018). Garlic's major chemical constituents are organosulfur compounds, which contribute to its pharmacological effects such as liver injury (Murugavel et al., 2007), cytoprotective (Pari et al., 2007), anti-oxidant (Suo et al., 2019), and neuroinflammation (Chung et al., 2006).

Following extensive research of organosulfur compounds, multiple lines of evidence have implicated a critical role for garlic in viral infection. Thuy et al. (Thuy et al., 2020) showed that 99.4% (17/18) of the bioactive substances of garlic essential oil are organosulfur

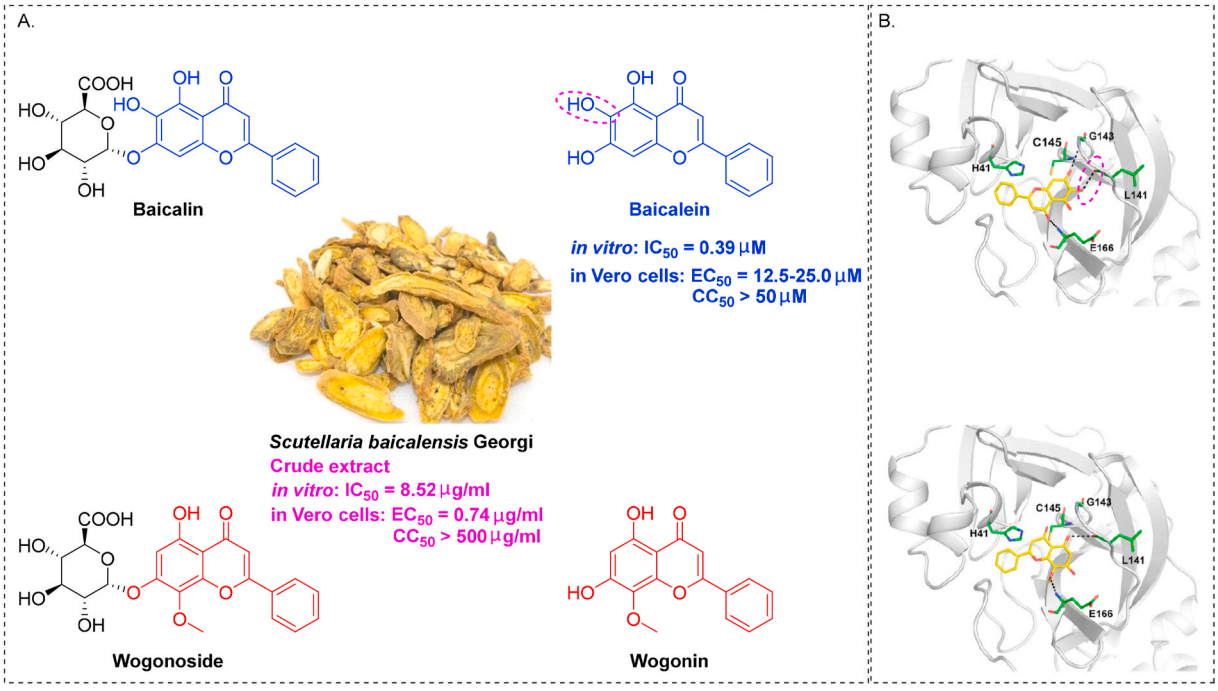

Fig. 5. *Scutellaria baicalensis* extracts for the treatment of SARS-CoV-2 infection. (A) Four major flavones derived from *Scutellaria baicalensis*. (B) Molecular docking patterns of baicalein and wogonin with SARS-CoV-2 $3CL^{pro}$ (image reproduced with permission from Liu et al., 2020a).

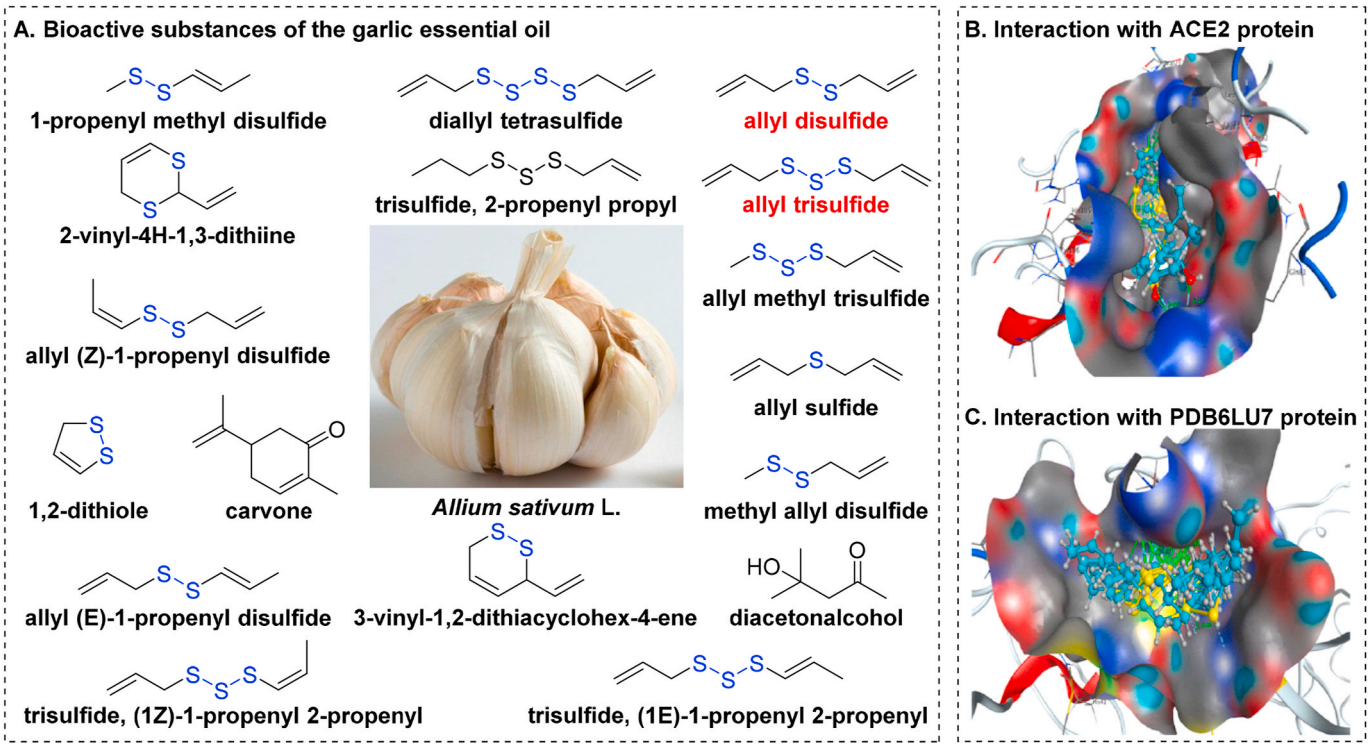

Fig. 6. Garlic Essential Oil for the treatment of SARS-CoV-2 infection. (A) Bioactive compounds in essential garlic oil. (B) Interactions of organosulfur compounds with the ACE2 protein of SARS-CoV-2. (C) Interactions of organosulfur compounds with the PDB6LU7 protein of SARS-CoV-2 (image reproduced with permission from Thuy et al., 2020; https://pubs.acs.org/doi/10.1021/acsomega.0c00772#; Copyright © 2021, American Chemical Society).

compounds (Fig. 6A)), which exhibit strong synergistic interactions with the ACE2 (host receptor for SARS-CoV-2, Fig. 6B) and the PDB6LU7 (main protease of SARS-CoV-2, Fig. 6C). The docking model revealed that allyl disulfide (docking score energy: −12.84 kcal mol^{-1} with the ACE2 Protein and −15.32 kcal mol^{-1} with the PDB6LU7 of SARS-CoV-2) and allyl trisulfide (docking score energy: −12.76 kcal mol^{-1} with the ACE2 protein and −15.02 kcal mol^{-1} with the PDB6LU7 protein of SARS-CoV-2) present the strongest anti-SARS-CoV-2 effects(Thuy et al., 2020). Numerous evidence has shown the potential usefulness of garlic essential oil as a treatment for viral infections, but further research is needed to explore whether it has anti-SARS-CoV-2 activity *in vivo*.

5. Promising Chinese herbal medicine formulas for the treatment of SARS-CoV-2 infection in clinical practice

Qingfei Paidu decoction (QFPD) consists of 21 materials derived from four traditional Chinese medicine prescriptions: Maxing Shigan decoction, Wuling powder, Xiaochaihu decoction, and Shegan Mahuang decoction (Fig. 7A) (Zhong et al., 2020). Maxing Shigan decoction, Wuling powder, and Xiaochaihu decoction were initially described in the *Treatise on Febrile Diseases* for the treatments of fever, influenza virus infections, asthma, and nephritic syndrome (Hsieh et al., 2012; Cheng et al., 2006; Yang et al., 2015). Shegan Mahuang decoction, derived from the *Synopsis of Golden Chamber,* was mainly used for the treatment of fever, asthma, inflammation and headache (Lin et al., 2020). QFPD has been widely used in treating SARS since 2002 in China (Chen et al., 2004a). Recently, QFPD has garnered considerable attention due to its ability to treat the mild, common, and severe types of COVID-19 (Wang et al., 2020a; Ren et al., 2020; Zhang et al., 2020h). Qingfeipaidu formula was shown to reach a total effective rate of 97.78% (n = 1202/1261) in COVID-19 patients without transfer from mild to severe cases (Xinhua Net, 2020a). According to the *Diagnosis and Treatment Protocol for Coronavirus (2019-nCoV) Pneumonia (Trial Version 7)*, QFPD is effective (cure rate > 90%) for patients with SARS-CoV-2 infection at all stages (NHC PRC, 2020a). Based on a retrospective multicenter cohort study, Shi et al. revealed that QFPD can yield favorable clinical outcomes, including faster recovery times and a shorter duration of hospital stay (Shi et al., 2020a).

The mechanism of action involved in the inhibition of SARS-CoV-2 infection by QFPD is incredibly challenging given the 21 herbs and hundreds of chemical constituents within this product. Yang et al. (Yang et al., 2020b) used liquid chromatography quadrupole-time of flight mass spectrometry analysis to identify 129 compounds in QFPD (45% flavonoids,15% glycosides, 10% carboxylic acids, and 5% saponins); the representative molecules of QFPD are shown in Fig. 7A. Additionally, Yang et al. (Yang et al., 2020) found that the anti-inflammatory activity of Maxing Shigan decoction played an integral role in the treatment of COVID-19, as determined by a computational molecular networking model and an experimental rat model of pneumonia. Extensive research on the immunological mechanisms involved indicate that QFPD induces a significant elevation of proinflammatory cytokines (IL-1β, IL-18, tumor necrosis factor-α (TNF-α), and IL-8) (Kageyama et al., 2020).

This novel virus can cause multiple extrapulmonary manifestations (Gupta et al., 2020). Chen et al. (Chen et al., 2020a) identified the protective effects of QFPD against COVID-19 injury mainly through antiviral, anti-inflammatory activity and metabolic programming. Following network topology analysis, the absorption, distribution, metabolism, elimination, and toxicity (ADMET) estimations, and drug-likeness test, Chen et al. (Chen et al., 2020a) showed that of the 8 chemical constituents of QFPD with the top molecular docking score, letrozole showed seven interactions with SARS-CoV-2-encoded nonstructural protein (nsp) 13 and five interactions with SARS-CoV-2 papain-like protease (PL^{pro}), leucocyanidol showed eleven interactions with nucleocapsid (N) protein NCB site and five interactions with nsp14. The molecular modelling of the compounds associated with COVID-19 proteins is shown in Fig. 7B. Chen et al. (Chen et al., 2020a) demonstrated that the mechanism for the efficacy of QFPD might be involve the harmonious treatment of SARS-CoV-2 pathways and multiple related

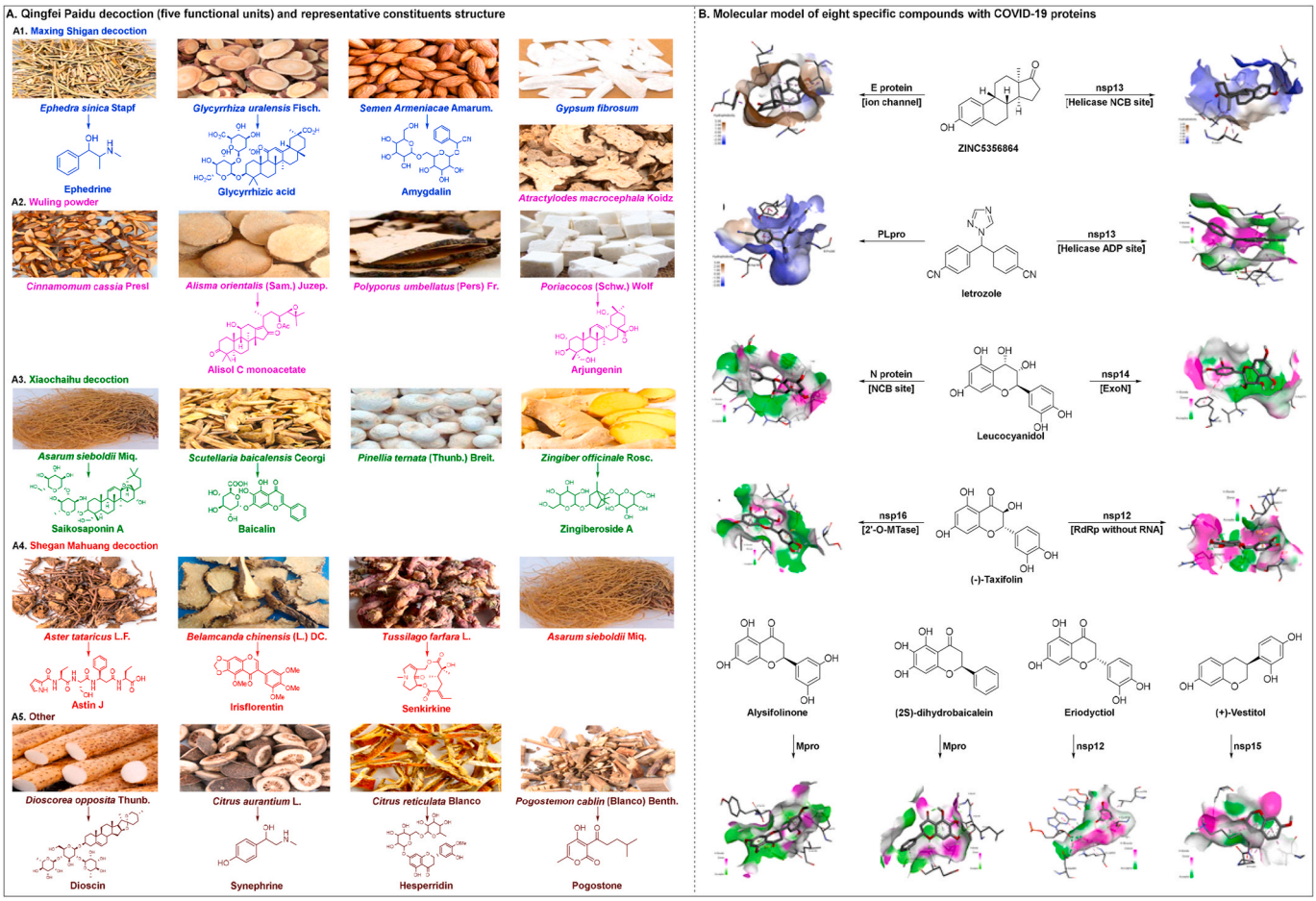

Fig. 7. Qingfei Paidu decoction for the treatment of SARS-CoV-2 infection. (A) Raw materials of QFPD and its potential active compounds. (B) molecular model of eight specific compounds with COVID-19 proteins (image reproduced with permission from Chen et al., 2020a).

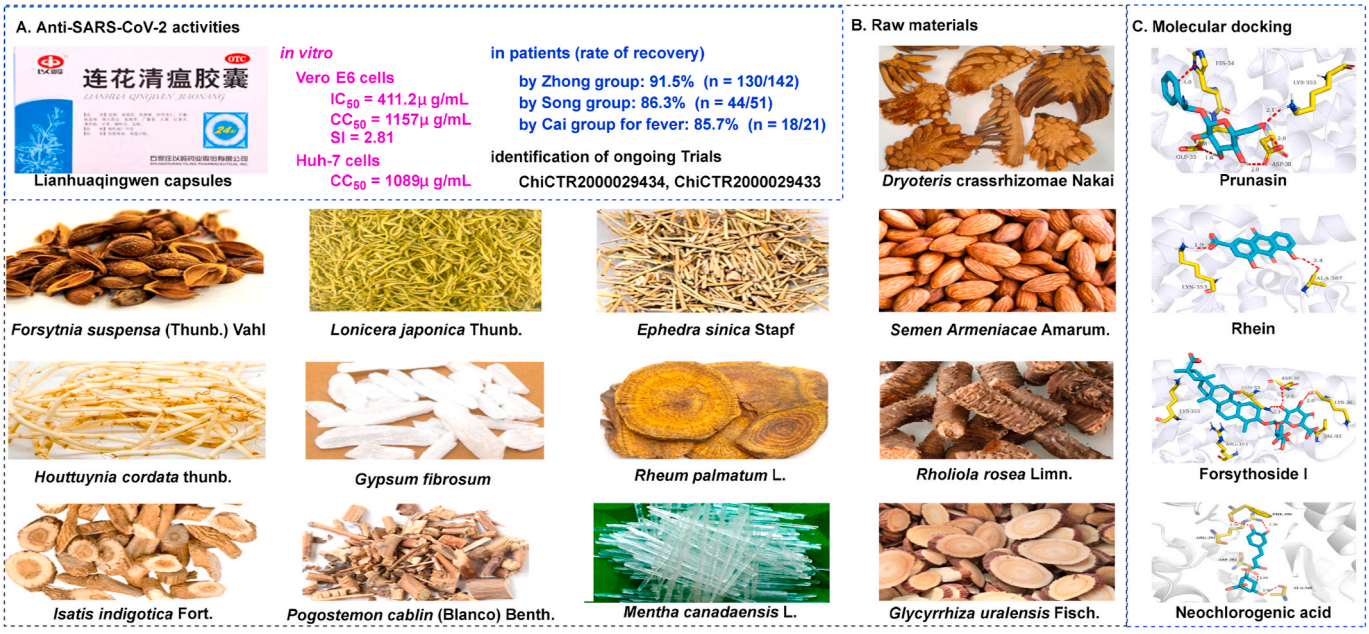

Fig. 8. Lianhuaqingwen capsules for the treatment of SARS-CoV-2 infection. (A) Lianhuaqingwen capsules. (B) Raw materials of Lianhuaqingwen capsules. (C) Molecular docking of representative components (prunasin, rhein, forsythoside I, and neochlorogenic acid) with ACE2 (image reproduced with permission from Chen et al., 2020c).

targets.

Lianhuaqingwen capsules (LHQW), a formulation developed by Shijiazhuang Yiling Pharmaceutical Co., Ltd, includes 13 types of traditional Chinese medicine that are derived from two classic prescriptions: Maxing Shigan decoction and Yinqiao powder (Fig. 8B) (Zhang et al., 2020i). As one of the most common prescriptions, LHQW has already been approved as an effective agent to treat influenza and pneumonia in China (Zhuang et al., 2020). As of the 4th December 2020, LHQW has been approved in 16 other countries, including Brazil, Indonesia, Romania, Singapore, Russia, Philippines, and Ukraine, for diseases related to influenza and pneumonia. In addition, LHQW has been launched for registration in more than 30 other countries in the Middle East, Africa, and Latin America, due to its efficacy against COVID-19. Furthermore, in September 2020, Kuwait approved LHQW to boost the survival of patients with COVID-19 (Forbes China, 2020).

Researchers have determined that LHQW demonstrates broad-spectrum activities against multiple viruses, including H1N1 (Gao et al., 2020a), H7N9 (NHFPC PRC, 2017), Middle East respiratory syndrome (MERS) coronavirus (NHFPC PRC, 2015), and SARS-CoV (CMA-CACM, 2004). Furthermore, LHQW has been shown to protect against acute lung injury in a rat model by downregulating the nuclear factor-kappa B (NF-κB) signaling pathway (Cui et al., 2016), thus reducing the infiltration of mononuclear macrophages (Li et al., 2020b). As a patented Chinese medicine, the potential of LHQW to treat SARS-CoV-2 has been documented *in vitro* and in a mouse model. Li et al. recently reported that LHQW could effectively inhibit the replication of SARS-CoV-2 in Vero E6 cells at an IC_{50} of 411.2 μg/mL and markedly reduce the mRNA expression of several proinflammatory cytokines (IL-6, TNF-α, and CCL-2/MCP-1) (Li et al., 2020c). Furthermore, Li et al. indicated that LHQW could alleviate lipopolysaccharide-induced endoplasmic reticulum stress and tumor necrosis factor-related apoptosis, thus inducing ligand expression in a co-culture model of inflammatory macrophages and alveolar epithelial cells and in a mouse model of acute lung injury (Li et al., 2020c). These data provided preliminary research evidence relating to the ability of LHQW to protect the lungs, implying its promising potential as a therapeutic for lung injury in patients with COVID-19.

Several clinical trials have attempted to evaluate the effects of LHQW on COVID-19. For example, Hu et al. conducted a clinical study (www.chictr.org/cn/, China Clinical Trial Registry number: ChiCTR2000029434) on 142 patients from 23 hospitals receiving LHQW therapy and reported that LHQW significantly improved the recovery rate (91.5%, n = 130/142), markedly shortened the recovery time (7 days), and improved the recovery of chest radiological abnormalities (83.8%), with no serious safety issues (Hu et al., 2020). Cheng et al. further showed that LHQW treatment led to a significant improvement in cardinal symptoms (86.3%, n = 44/51) (Cheng et al., 2020). Yao et al. also revealed that LHQW could significantly relieve cardinal symptoms, such as fever (85.7%, n = 18/21), cough (46.7%, n = 7/15), shortness of breath (77.8%, n = 7/9), and expectoration (64.3%, n = 9/14) (Yao et al., 2020). To explore appropriate treatments for patients with severe COVID-19, Li et al. conducted a clinical study (www.chictr.org/cn/, China Clinical Trial Registry number: ChiCTR2000030803) on the therapeutic effects of LHQW combined with other agents and determined that the combination of ribavirin, lopinavir/ritonavir, umifenovir, and LHQW, could exhibit a synergistic inhibitory effect in severe COVID-19 patients (improvement rate 84.9%, n = 28/33) (Li et al., 2020e). Other related clinical studies have also reported that LHQW can relieve the major symptoms of patients with COVID-19 (and suspected cases) with good levels of safety (Lv et al., 2020; Wang et al., 2020d; Cheng and Li, 2020).

From a mechanistic point-of-view, the combination of network pharmacology and molecular docking showed that the therapeutic effects of LHQW were closely associated with immune response, cell apoptosis, and virus infection (Xia et al., 2020b). In another study, Zhao et al. highlighted that Akt1 (a serine/threonine protein kinase) is a promising target for COVID-19 patients and could help to reduce lung injury and help eliminate viral infection (Zhao et al., 2020). Chen et al. further used a human exposure-based approach to identify the molecular mechanisms underlying the active components of LHQW. Results demonstrated that certain representative components exhibited high inhibitory effects on ACE2, including prunasin (affects the binding interface of ACE2 and S protein), rhein (the best binding interface of ACE2), forsythoside I (the binding interface of ACE2), and neochlorogenic acid (the binding interface of peptidase and S protein) (Fig. 8C) (Chen et al., 2020c). As a large formulation, LHQW may possess complex mechanisms of action; however, these are currently undefined and require additional research. Multiple lines of evidence have shown the value of LHQW as a treatment for SARS-CoV-2 infection, thus allowing this agent to be included in the *Diagnosis and Treatment Protocol for Coronavirus (2019-nCoV) Pneumonia (Trial Version 8)* (NHC PRC, 2020b).

Numerous traditional Chinese medicines have shown promising results and garnered considerable attention due to their ability to inhibit SARS-CoV-2 effectively. Pudilan Xiaoyan oral liquid (PDL), composed of four types of traditional Chinese medicine, has recently been recognized as a promising formulation with potent antiviral and antibacterial effects (Feng et al., 2018). Deng et al. (Deng et al., 2020) recently determined that PDL could effectively inhibit SARS-CoV-2 replication in Vero E6 cells *in vitro* at an EC_{50} of 1.078 mg/mL and with an excellent SI of 8.27. Furthermore, the effects of PDL were evaluated in SARS-CoV-2-infected hACE2 mice; results showed that PDL could relieve the symptoms of pneumonia, including asthma and chronic obstructive pulmonary disease (Deng et al., 2020). Liu et al. (Liu et al., 2020c) further showed that Jinhua Qinggan granules (JHQG) significantly reduced the recovery time by two days compared with a control group and was not associated with any adverse reactions. Kageyama et al. (Kageyama et al., 2020) showed that JHQG could down- and up-regulate the plasma levels of IL-6 and interferon-gamma (IFN-γ); these factors have been correlated with mortality in patients with SARS-CoV-2 infection (Blanco-Melo et al., 2020; Zhang et al., 2020g). Shuanghuanglian preparations, both oral liquid and injection, could effectively block SARS-CoV-2 replication in Vero E6 cells (Su et al., 2020). Chen et al. (Chen et al., 2020b) showed that 131 cases of COVID-19 patients were cured and discharged after receiving treatment with Ganlu Xiaodu decoction. Furthermore, Xuanfei Baidu decoction also improved the patient's clinical symptoms *via* its anti-inflammatory effect (Xiong et al., 2020c).

The safety profiles of traditional Chinese medicines have been evaluated in multiple clinical trials. Besides the above-mentioned prescriptions, several other clinical trial protocols have been registered to investigate the treatment outcomes of COVID-19 using traditional Chinese medicines (Table 2). It should be stressed that the small sample size of the control groups in these trials (often below 200 participants) is not large enough to detect statistically significant differences and support sufficiently scientific foundations for their clinical use in COVID-19 patients. Moreover, the majority of the registered Chinese herbal medicine formulas could not be completed due to the fact that the COVID-19 epidemic has been well controlled in China; this means that there were only small numbers of patients available for trials. However, as potential anti-SARS-CoV-2 agents, there is no doubt that Chinese herbal medicine formulas, including those have not yet completed clinical trials, could represent potential therapeutic options for the treatment of COVID-19.

6. Conclusion and future perspectives

At the time of writing, the COVID-19 epidemic has caused 1,853,525 deaths worldwide but continues to cause effect (WHO, 2020). Furthermore, mutation of the SARS-CoV-2 virus has strengthened increased the ability of this virus to infect and spread. In this scenario, safe and broad-spectrum anti-SARS-Cov-2 drugs are urgently needed. In mainland China, Chinese herbal medicines (active ingredients, monomer

Table 2
Registered clinical trials relating to traditional Chinese medicine prescriptions for the treatment of patients with COVID-19 (Chinese Clinical Trial Registry, www.chictr.org/cn/, 2020/01/30–2020/09/08).

Dosage form	Herbal formula	Ingredients (Latin name)	Registration number	Sample size of the control group
Pills	Liushen	Borneolum Syntheticum, Cinnabaris, Menthae Haplocalycis Herba, Bos taurus domesticus Gmelin, Moschus, Fel Ursi, Isatidis Radix, Realgar, Glycyrrhizae Radix et Rhizoma, Lonicerae Japonicae, Bufonis Venenum	ChiCTR2000030469	48
	Xiangsha Liujun pills	Aucklandiae Radix, Amomi Fructus, Codonopsis Radix, Atractylodes Macrocephala, Poria, Glycyrrhizae Radix et Rhizoma, Citri Reticulatae Pericarpium, Pinelliae Rhizoma, Zingiberis Rhizoma Recens, Jujubae Fructus	ChiCTR2000032237	100
	Gushen Dingchuan pills	Radix Rehmanniae praepar ata, Radix Aconiti lateralis Preparata, Moutan Cortex, Radix Achyranthis Bidentatae, Psoraleae Fructus, Amomi Fructus, Plantaginis Semen, Poria, Fructus Alpinae Oxyphyllae, Cinnamomi Cortex, Dioscoreae Rhizoma, Alismatis Rhizoma, Rosae Laevigatae Frucyus	ChiCTR2000030937	72
Powder	Danggui Shaoyao powder	Paeoniae Radix Alba, Angelicae Sinensis Radix, Chuanxiong Rhizoma, Atractylodes Macrocephala, Poria, Alismatis Rhizoma	ChiCTR2000032098	300
	Shengjiang powder	Bombyx Batryticatus, CicadaePeriostracum, Curcumae Longae Rhizoma, Rhei Radix et Rhizoma	ChiCTR2000030314	40
Decoction	Qingfei Paidu decoction	Ephedrae Herba, Glycyrrhizae Radix et Rhizoma, Semen Armeniacae Amarum, Gypsum Fibrosum, Ramulus Cinnamomi, Alismatis Rhizoma, Polyporus, Atractylodes Macrocephala, Poria, Bupleuri Radix, Scutellariae Radix, Pinelliae Rhizoma, Zingiberis Rhizoma Recens, Radix Asteris, Flos Farfarae, Belamcandae Rhizoma, Herba Asari, Dioscoreae Rhizoma, Fructus Aurantii Immaturus, Citri Reticulatae Pericarpium, Pogostemonis Herba	ChiCTR2000029433 ChiCTR2000030883 ChiCTR2000032767	120 100 782
	Maxing Shigan decoction	Ephedrae Herba, Semen Armeniacae Amarum, Gypsum Fibrosum, Glycyrrhizae Radix et Rhizoma	ChiCTR2000030522 ChiCTR2000030314	50 40
	Yiqi Huashi Jiedu decoction	Radix pseudostellariae, Astragali Radix, Atractylodes Macrocephala, Alismatis Rhizoma, Polyporus, Herba Ephedrae, Herba Artemisiae scoparia, Rosae Laevigatae Frucyus, Semen Euryales, Herba Leonuri, Pheretima, Cinnamomi Cortex, Glycyrrhizae Radix et Rhizoma	ChiCTR2000030479	50
	Xinguan I decoction	Scutellariae Radix, Saposhnikoviae Radix, Forsythiae Fructus, Lonicerae Japonicae, Radix Peucedani	ChiCTR2000029637	50
	Xinguan II decoction	Ephedrae Herba, Semen Armeniacae Amarum, Gypsum Fibrosum, Semen Coicis, Atractylodis Rhizoma, Rhizoma Polygoni Cuspidati, Verbenae Herba, Pogostemonis Herba, Descurainiae Semen, Phragmitis Rhizoma, Exocarpium Citri Rubrum, Glycyrrhizae Radix et Rhizoma	ChiCTR2000029628	50
	Xinguan III decoction	Astragali Radix, Radix Pseudostellariae, Radix Adenophorae, Poria, Atractylodes Macrocephala, Radix Ophiopogonis	ChiCTR2000030936	2130
	Xuanfei Baidu decoction	Herba Ephedrae, Semen Armeniacae Amarum, Gypsum Fibrosum, Semen Coicis, Rhizoma Atractylodis, Herba Pogostemonis, Herba Artemisiae Annuae, Herba Artemisiae Annuae, Verbenaceae, Rhizoma Phragmitis, Semen Lepidii, Exocarpium Citri Grandis, Radix Glycyrrhizae	ChiCTR2000034795	22
Syrup	Kesuting syrup	Eriobotryae Folium, Ephedrae Herba, Papaveris Pericarpium, Platycodonis Radix, Mori Cortex, Reineckia carnea (Andr.) Kunth, Aletris pauciflora var. khasiana (Hook. f.) Wang et Tang, Rhizoma Polygoni Cuspidati, Polygonati Rhizoma	ChiCTR2000029991	24
Capsules	Keqing capsules	Reineckia carnea (Andr.) Kunth, Papaveris Pericarpium, Physalis Calyx Seu Fructus, Rhizoma Polygoni Cuspidati, Eriobotryae Folium, Mori Cortex	ChiCTR2000029991	24
	Lianhuaqingwen capsules	Forsythiae Fructus, Lonicerae Japonicae, Ephedrae Herba, Semen Armeniacae Amarum, Gypsum Fibrosum, Isatidis Radix、Dryopteridis Crassirhizomatis Rhizoma, Herba Ephedrae, Pogostemonis Herba, Rhei Radix et Rhizoma, Rhodiola Rosae, menthol, Glycyrrhizae Radix et Rhizoma	ChiCTR2000029434	120
	Tanreqing capsules	Scutellariae Radix, Fel Ursi, Corne Caprae Hirci, Lonicerae Japonicae, Forsythiae Fructus	ChiCTR2000029813	36
	Bufei Huoxue capsules	Astragali Radix, Radix Padoniae Rubra, Psoraleae Fructus	ChiCTR2000032573	60
	Xiaoyao capsules	Bupleuri Radix, Angelicae Sinensis Radix, Paeoniae Radix Alba, Atractylodes Macrocephala, Poria, Glycyrrhizae Radix et Rhizoma, Menthae Haplocalycis Herba	ChiCTR2000032399	100
	Babaodan capsules	Bos taurus domesticus Gmelin, Agkistrodon Haly, Saiga tatarica Linnaeus, Margarita, Notoginseng Radix et Rhizoma, Moschus	ChiCTR2000029769	20
Injection	Xuebijing injection	Carthami Flos, Radix Padoniae Rubra, Chuanxiong Rhizoma, Salviae Miltiorrhizae Radix et Rhizoma, Angelicae Sinensis Radix	ChiCTR2000030388	30
	Tanreqing injection	Scutellariae Radix, Fel Ursi, Corne Caprae Hirci, Lonicerae Japonicae, Forsythiae Fructus	ChiCTR2000029432	72
	Shenfu injection	Ginseng Radix Rubra, Aconiti Lateralis Radix Praeparata	ChiCTR2000030043	150
	Shenqifuzheng injection	Codonopsis Radix, Astragali Radix	ChiCTR2000029780	80
Oral liquid	Kegan Liyan oral liquid	Lonicerae Japonicae, Scutellariae Radix, Schizonepetae Herba, Gardeniae Fructus, Forsythiae Fructus, Scrophulariae Radix, Bombyx Batryticatus, Rehmannia glutinosa, Belamcandae Rhizoma, Platycodonis Radix, Menthae Haplocalycis Herba, Cicadae Periostracum, Saposhnikoviae Radix, Glycyrrhizae Radix et Rhizoma	ChiCTR2000033720 ChiCTR2000033745 ChiCTR2000031982	240 240 240
	Shuanghuanglian oral liquid	Lonicerae Japonicae, Scutellariae Radix, Forsythiae Fructus	ChiCTR2000033133 ChiCTR2000029605	30 100
	Xiangxue antiviral oral liquid	Isatidis Radix, Gypsum Fibrosum, Phragmitis Rhizoma, Rehmannia glutinosa Libos, Curcumae Radix, Anemarrhenae Rhizoma, Acori Tatarinowii Rhizoma, Pogostemonis Herba, Forsythiae Fructus	ChiCTR2000030033	276
Granule	Sancai granule	Chebulae Fructus, Toosendan Fructus, Gardenia jasminoides Ellis	ChiCTR2000034794	30
	Huashi Baidu granule	Magnoliae Officinalis Cortex, Astragali Radix, Atractylodis Rhizoma, Pogostemonis Herba, Tsaoko Fructus, Glycyrrhizae Radix et Rhizoma, Pinelliae Rhizoma, Descurainiae Semen, Ephedrae Herba, Radix Padoniae Rubra, Semen Armeniacae Amarum, Rhei Radix et Rhizoma, Poria, Gypsum Fibrosum	ChiCTR2000030989	38
		Jiegeng Liujingao, Mori Cortex Liujingao, Emetine, Ephedrine Hydrochloride	ChiCTR2000030022	50

(*continued on next page*)

Table 2 (*continued*)

Dosage form	Herbal formula	Ingredients (Latin name)	Registration number	Sample size of the control group
	Xiaoer Huatan Zhike granule			
	Toujie Quwen granule	Forsythiae Fructus, Pseudobulbus Cremastrae seu Pleiones, Lonicerae Japonicae, Scutellariae Radix, Isatidis Folium, Bupleuri Radix, Herba Artemisiae Annuae, Cicadae Periostracum, Radix Peucedani, Bulbus Fritillariae Cirrhosae, Bulbus Fritillariae Thunbergii, Fructus Mume, Scrophulariae Radix, Astragali Radix, Poria, Radix Pseudostellariae	ChiCTR2000031888	150
	Jingyin granule	Schizonepetae Herba, Lonicerae Japonicae, Arctii Fructus, Isatidis Folium, Ilicis Chinensis Folium.	ChiCTR2000030255	200

preparations, crude extracts, and formulas) have been recognized as very promising anti-SARS-CoV-2 agents due to their broad-spectrum antiviral activities against SARS-CoV (Chen et al., 2004b) and MERS-CoV (Antonelli et al., 2020) and their unique role in organ protection as antiviral, anti-inflammatory, and anti-fibrotic agents both *in vitro* and in clinical practice. As a key component of the COVID-19 treatment regimen, Chinese herbal medicines have played an irreplaceable role in the treatment of SARS-CoV-2 infection since January 2020. Due to this effective treatment regimen, as of March 2020, the COVID-19 epidemic has been well controlled and has reached a plateau in China.

Nevertheless, cases of active SARS-CoV-2 infection have continuously advanced in other countries. It is clear that the "Chinese protocol" has shown important clinical value. Chinese herbal medicines that are capable of inhibiting SARS-Cov-2 infection may help to address this immediate unmet clinical need and may be attractive to other countries focusing on more effective COVID-19 treatment. Thus, countries outside China, should also pursue the use of Chinese herbal medicine protocols to combat this fast-spreading viral infection.

The safety and efficacy of traditional Chinese medicines, such as Lianhuaqingwen capsules, Xuanfei Baidu decoction, and Ganlu Xiaodu decoction, have been evaluated for patients with SARS-CoV-2 in several clinical trials. However, to respond effectively to concerns arising from the western medical community, it is crucial to investigate how Chinese herbal medicine exerts effect on SARS-Cov-2 infection (Cyranoski, 2020). The underlying molecular mechanisms involved remain elusive. To better understand the activity of Chinese herbal medicine, more validation studies, with high-quality evidence (both *in vitro* and *in vivo*), are now needed to systematically explore the underlying mechanisms. Furthermore, there is currently very little direct data associated with the protective effect of Chinese herbal medicines against extrapulmonary organ injuries during SARS-CoV-2 infection (Zhang et al., 2020d; He et al., 2020; Zhao et al., 2020). Nonetheless, Chinese herbal medicine has its own advantages. We sincerely hope that Chinese herbal medicine will prove to be a safe and effective therapy against SARS-Cov-2 worldwide.

Author contributions

Wang Zhong-lei and Yang Li-yan conceived the review. Wang Zhong-lei collected the literatures. Wang Zhong-lei and Yang Li-yan wrote and edited the manuscript.

Declarations of competing interest

The authors declare that they have no competing interests.

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