Mini-Review

DOI: 10.5582/bst.2022.01534

Herbal medicines exhibit a high affinity for ACE2 in treating COVID-19

Bo Zhang[1], Fanghua Qi[2,*]

[1] Department of Traditional Chinese Medicine Orthopedics, Neck-Shoulder and Lumbocrural Pain Hospital affiliated to Shandong First Medical University, Ji'nan, China;
[2] Traditional Chinese Medicine, Shandong Provincial Hospital affiliated to Shandong First Medical University, Ji'nan, China.

SUMMARY Coronavirus Disease 2019 (COVID-19) has been an unprecedented disaster for people around the world. A point particularly worth noting is that herbal medicines have made great contributions to the prevention and treatment of COVID-19 in China. Angiotensin converting enzyme 2 (ACE2) has been identified as the critical functional receptor for SARS-CoV-2. It can bind to the receptor-binding domain (RBD) of the spike protein (S protein), which is responsible for the entry of the coronavirus into host cells. Therefore, ACE2 can be regarded as an important intervention target for COVID-19. Recently, many herbal medicines have exhibited a high affinity for ACE2 in treating COVID-19. The current work summarized these herbal medicines including formulas (such as Lianhua Qingwen capsules, Xuebijing injection, Qingfei Paidu Decoction, Huashi Baidu formula, Shufeng Jiedu capsules, and Maxing Shigan decoction), single herbs including *Ephedra sinica Stapf* (Mahuang), *Scutellariae radix* (Huangqin), *Lonicera japonica* (Jinyinhua), and *Houttuynia cordata* (Yuxingcao), and active ingredients (such as ursodeoxycholic acid, glycyrrhizic acid, glycyrrhizin, salvianolic acid, quercetin, and andrographidine C), which have exhibited a high affinity for ACE2 in treating COVID-19. We hope this work may provide meaningful and useful information on further research to investigate the mechanisms of herbal medicines against SARS-CoV-2 and follow-up drug discovery.

Keywords COVID-19, SARS-CoV-2, herbal medicines, ACE2, S protein

1. Introduction

Coronavirus Disease 2019 (COVID-19) has been an unprecedented disaster for people around the world. A point particularly worth noting is that herbal medicines have made great contributions to the prevention and treatment of COVID-19, and they have been used in over 90% of treatments across China. Many herbal medicines are reported to have antiviral, anti-inflammatory, and immunoregulatory action and to protect target organs during the treatment of COVID-19 by multiple components acting on multiple targets in multiple pathways (*1*).

Angiotensin converting enzyme 2 (ACE2) has been identified as the critical functional receptor for SARS-CoV-2. It can bind to the receptor-binding domain (RBD) of the spike protein (S protein), which is responsible for the entry of the coronavirus into host cells (*2*). After entry, the SARS-CoV-2 RNA genome is released into the cytosol, where it highjacks host replication machinery for viral replication, assemblage, as well as the release of new viral particles. Therefore, ACE2 should be a target to screen drugs inhibiting the replication and proliferation of SARS-COV-2.

Recently, many herbal medicines have exhibited a high affinity for ACE2 in treating COVID-19 (*3*). These herbal medicines can target ACE2 to prevent SARS-CoV-2 from entering into host cells. The current work has summarized these herbal medicines including formulas, single herbs, and active ingredients, which have exhibited a high affinity for ACE2 in treating COVID-19 (Figure 1). This work may provide meaningful and useful information on further research to investigate the mechanisms of herbal medicines against SARS-CoV-2.

2. Herbal formulas

COVID-19 is categorized as a pestilence according to traditional Chinese medicine (TCM) theory. Herbal medicines have been used to treat and prevent viral infections for thousands of years, and herbalists have

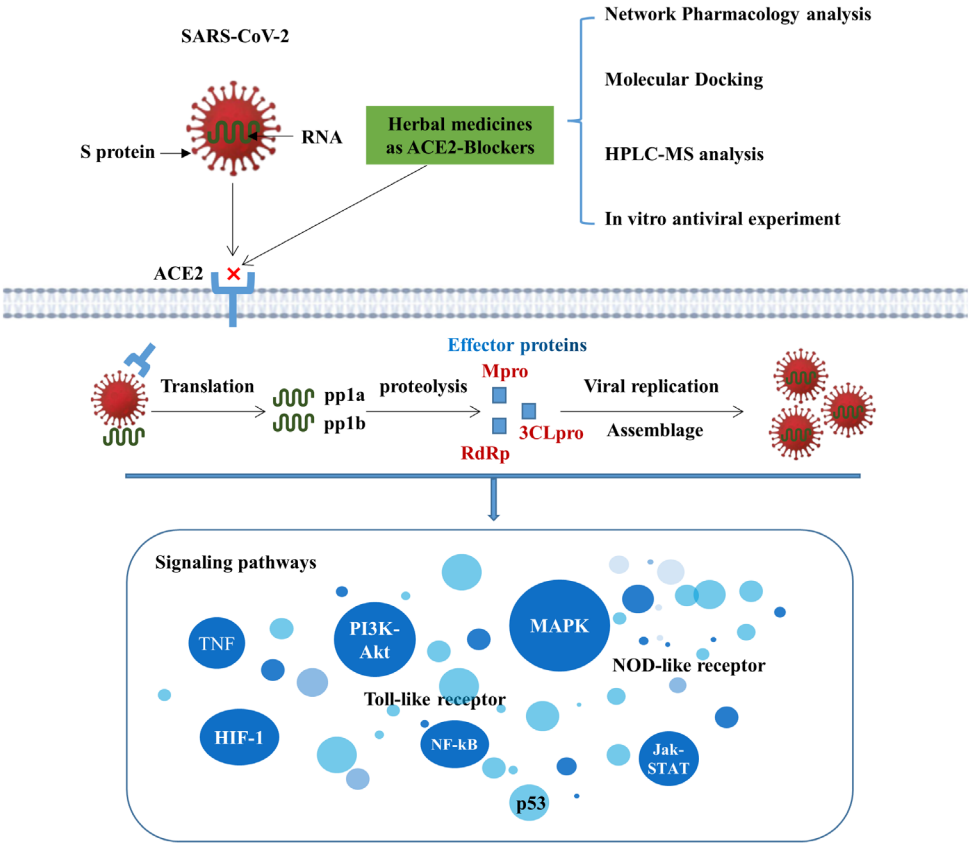

Figure 1. Overview of the probable anti-COVID-19 activities of herbal medicines. Herbal medicines might be ACE2-blockers against COVID-19.

accumulated a large amount of clinical experience and they have developed effective prescriptions (*4*). In guidelines on fighting COVID-19, the National Health Commission (NHC) of China has recommended some herbal formulas, and particularly "three Chinese patent medicines and three TCM prescriptions", which have proven to be efficacious in treating COVID-19 (*5*). Recently, numerous studies have indicated that the potential mechanisms of these herbal formulas in the treatment of COVID-19 might involve down-regulating ACE2 (Table 1).

Lianhua Qingwen capsules/granules have been officially repurposed by the China Food and Drug Administration (CFDA) for patients with mild COVID-19 since April 2020. Several components of Lianhua Qingwen capsules (rhein, forsythoside A, forsythoside I, neochlorogenic acid, and its isomers) not only showed a high affinity for ACE2 but also inhibited SARS-CoV-2 by affecting binding between ACE2 and the S protein (*6*). Xuebijing injection is the only Chinese patent medicine approved in China for the treatment of sepsis with efficacy in severe and critical COVID-19 cases. Based on a bioinformatic analysis, Xuebijing injection alleviated COVID-19-induced cardiac dysfunction by inhibiting oxidative stress, preventing atherosclerotic plaque formation, and limiting inflammation and apoptosis by targeting ACE2 and 7 hub genes (CCL2, CXCL8, FOS, IFNB1, IL-1A, IL-1B, and SERPINE1) (*7*). In addition, molecular docking results revealed that most of the active compounds in Xuebijing injection had a good binding activity with ACE2, 3CLpro, and the S protein; the three compounds with the highest affinity were anhydrosafflor yellow B, salvianolic acid B, and rutin (*8*).

Qingfei Paidu Decoction is recommended for all stages of COVID-19 according to the “Diagnosis and Treatment Program for COVID-19” issued by the NHC of China. Supported by network pharmacology, Qingfei Paidu Decoction and its major herbs including *Ephedra sinica*, Bupleurum chinense, Pogostemon cablin, Cinnamomum cassia, and Scutellariae Radix displayed anti-oxidative, immuno-modulatory, and antiviral action by preventing a cytokine storm and regulating ACE2 receptor binding (*9*). Three active components (oroxylin A, hesperetin and scutellarin) of Qingfei Paidu Decoction significantly inhibited the release of IL-6, IL-1β, and CXCL-10 from THP-1 macrophages challenged with the SARS-CoV-2 S protein, which suggested that the anti-inflammatory effects of Qingfei Paidu Decoction might be attributed to the effects of these active components (*10*). Oroxylin A inhibits the entry of SARS-CoV-2 pseudovirus into target cells and prevents SARS-CoV-2 S protein-mediated cell-cell fusion by binding with the ACE2 receptor.

Table 1. Some herbal formulas exhibiting a high affinity for ACE2 in treating COVID-19

Herbal formulas	Composition	Screened ingredients	Effects	Experimental method	*Ref.*
Lianhua Qingwen capsules	13 herbs: Lianqiao, Jinyinhua, Mahuang, Kuxingren, Shigao, Banlangen, Guanzhong, Yuxingcao, Huoxiang, Dahuang, Hongjingtian, Bohe, and Gancao	Rhein, forsythoside A, forsythoside I, neochlorogenic acid, and its isomers	(*i*) Exhibit a high affinity for ACE2, (*ii*) Inhibit SARS-CoV-2 by affecting the binding between ACE2 and S protein.	Biochromatography screening, molecular docking bioinformatics, and molecular docking technology	*6*
Xuebijing injection	5 herbs: Honghua, Chishao, Chuanxiong, Danshen, and Danggui	Quercetin	Target ACE2 and 7 hub genes (CCL2, CXCL8, FOS, IFNB1, IL-1A, IL-1B, SERPINE1).	Network pharmacology and RNA-sequencing	*7*
		Anhydrosafflor yellow B, salvianolic acid B and rutin	Bind with ACE2, 3CLpro, and S protein.	Network pharmacology and molecular docking	*8*
Qingfei Paidu Decoction	21 herbs: Mahuang, Gancao, Kuxingren, Shigao, Guizhi, Zexie, Zhuling, Baizhu, Fuling, Chaihu, Huangqin, Banxia, Shengjiang, Ziyuan, Kuandonghua, Shegan, Xixin, Shanyao, Zhishi, Chenpi, and Huoxiang	Oroxylin A, hesperetin and scutellarin	Inhibit the IL-6, IL-1β and CXCL-10 release and bind with ACE2.	Bioinformatics methods, network pharmacology, and molecular docking	*10*
Huashi Baidu formula	14 herbs: Mahuang, Huoxiang, Shigao, Kuxingren, Banxia, Houpu, Cangzhu, Caoguo, Fuling, Huangqi, Chisao, Tinglizi, Dahuang, and Gancao	Baicalein and quercetin	Bind with ACE2.	Network pharmacology and molecular docking	*11*
		Isotrifoliol and ellagic acid	Bind with ACE2, ADAM17, and 3CLpro.	Network pharmacology and molecular docking	*12*
Shufeng Jiedu capsule	8 herbs: Huzhang, Lianqiao, Banlangen, Chaihu, Baijiangcao, Mabiancao, Lugen, and Gancao	Kaempferol, Wogonin, and Baicalein	Exhibit a strong potential affinity for ACE2 and Mpro.	Network pharmacology and molecular docking	*13*
		β-sitosterol, luteolin, kaempferol, quercetin, and stigmasterol	Bind well with three typical target proteins including ACE2, 2OFZ, and 1SSK.	Network pharmacology and molecular docking	*14*
Maxing Shigan decoction	4 herbs: Mahuan, Kuxingren, Shigao, and Gancao	Amygdalin, euchrenone, glycyrrhizin, and glycyrol	Exhibit a strong potential affinity for ACE2, Mpro and RdRp.	Network pharmacology, molecular docking, and *in vitro* experimental verification	*15*

As one of the "three Chinese patent medicines and three TCM prescriptions", Huashi Baidu formula is usually recommended as an auxiliary medicine for the treatment of patients with severe COVID-19. A network analysis indicated that Huashi Baidu formula affected SARS-CoV-2 mainly by regulating multiple signaling pathways (TNF, PI3K-Akt, NOD-like receptor, MAPK, and HIF-1) through ACE2 (*11*). Baicalein and quercetin, the two leading compounds in Huashi Baidu formula, have a high affinity for ACE2, which indicated that they might play an important role in the treatment of COVID-19. Another network analysis indicated that the active ingredients in Huashi Baidu formula, such as isotrifoliol and ellagic acid, had an excellent binding ability with crucial proteins directly related to COVID-19, including ACE2, ADAM17, and 3CLpro, and that they were directly efficacious (*12*).

Shufeng Jiedu capsules are a Chinese patent medicine that is recommended as a basic prescription and used widely in the clinical treatment of COVID-19. According to a network analysis, the active components in Shufeng Jiedu capsules (such as kaempferol, wogonin, and baicalein) had good binding activity with both SARS-CoV-2-Mpro and ACE2 and acted on multiple signaling pathways (such as PI3K-Akt, TNF, HIF-1, p53, and Toll-like receptor), thus affecting novel coronaviruses (*13*). Another network analysis identified 5 key compounds (β-sitosterol, luteolin, kaempferol, quercetin, and stigmasterol) in Shufeng Jiedu capsules and 10 hub target genes (TP53, AKT1, NCOA1, EGFR, PRKCA, ANXA1, CTNNB1, NCOA2, RELA, and FOS) (*14*). The hub target genes were mainly enriched in pathways including the MAPK, PI3K-Akt, and cAMP signaling pathways, which could be the underlying pharmacological mechanisms of Shufeng Jiedu capsules for treating COVID-19. Moreover, the above key compounds had a high binding activity with three typical target proteins including ACE2, 2OFZ, and 1SSK.

Maxing Shigan decoction is a classic herbal formula that was first recorded in the famous book "Shanghan Zabing Lu" written by Zhang Zhongjing during the Eastern Han Dynasty (25-220 A.D.). The "three Chinese patent medicines and three TCM prescriptions", excluding the Xuebijing injection, contain Maxing Shigan Decoction. Maxing Shigan Decoction might play an antiviral, anti-inflammatory, and immunoregulatory role through the JAK-STAT and PI3K/AKT signaling pathways mainly *via Glycyrrhiza uralensis* (Gancao) and *Semen armeniacae amarum* (Kuxingren) (*15*). Moreover, the components with a strong potential affinity (the top 10) for ACE2, Mpro, and RdRp are mainly from Gancao and Kuxingren. Amygdalin was selected as the optimal candidate component to bind to all three key targets, and euchrenone, glycyrrhizin, and glycyrol also exhibited superior affinity for ACE2, Mpro, and RdRp, respectively.

3. Single herbs

Some single herbs have been widely used in Asia to treat lung diseases, such as a cold, cough, and asthma for thousands of years and they are the major constituent herbs of some famous formulas to treat COVID-19. These single herbs such as *Ephedra sinica* Stapf (Mahuang), *Scutellariae radix* (Huangqin), *Lonicera japonica* (Jinyinhua), and *Houttuynia cordata* (Yuxingcao) have displayed efficacy against pneumonia caused by SARS-CoV-2, and the potential mechanism might be related to ACE2 (Table 2).

Mahuang, as one of the major constituent herbs of a multi-component herbal formula, has been widely used to treat COVID-19 in China. Lv et al. found that three compounds (ephedrine, pseudoephedrine, and methylephedrine) screened out from Mahuang with ACE2-binding features acted as blockers, inhibiting the SARS-CoV-2 spike pseudovirus from entering ACE2h (HEK293T cells over-expressing ACE2) (*16*). Another similar study indicated that quinoline-2-carboxylic acids identified as novel active constituents of Mahuang could be considered as potential therapeutic agents for COVID-19 (*17*). They inhibited both the binding of SARS-CoV-2 RBD to ACE2 and the infectivity of SARS-CoV-2 S protein pseudoviruses in 293T-ACE2 and Calu-3 cells. The herb pair Mahuang-Kuxingren was used to prevent and treat COVID-19 by directly inhibiting the virus, regulating immune responses, and promoting body repair. Some key components of Mahuang-Kuxingren, such as β-sitosterol, estrone, and stigmasterol, had a high binding activity to 3CLpro and ACE2 according to a molecular docking simulation (*18*). In addition, the active compounds, and especially licorice glycoside E and xambioona, from the herb pair Mahuang-Gancao, bound well to COVID-19 related targets, including 3CLpro, the S protein, and ACE2 (*19*).

Huangqin is considered to be an "herbal antibiotic" that can fight against COVID-19. Based on a network analysis, Huangqin primarily regulated the MAPK and NF-κB signaling pathways *via* active components such as baicalein and scutellarin and blocked SARS-CoV-2 spike binding to human ACE2 receptors (*20*). In addition, *in vitro* bioassays showed that Baicalein inhibited SARS-CoV-2 from entering into Vero E6 cells. It was the most effective component in Huangqin, with both anti-inflammatory and antiviral action.

Based on its effect on heat-clearing and detoxification, Jinyinhua has been used as a dietary supplement, tea, or beverage for millennia. A Jinyinhua water extract demonstrated an interrupting effect on SARS-CoV-2-S protein/ACE2 binding, and chlorogenic acids were found to dominate the anti-inflammatory effects of Jinyinhua by inhibiting oxidative stress (*21*). Yuxingcao is a time-honored herb widely used in Asian countries to treat pneumonia, and it potentially exhibits antiviral activity against enveloped viruses. Some key

Table 2. Some single herbs and herb pairs exhibiting a high affinity for ACE2 in treating COVID-19

Chinese name	Scientific name	Screened ingredients	Effects	Experimental method	*Ref.*
Mahuang	*Ephedra sinica* Stapf	Ephedrine, pseudoephedrine, and methylephedrine	(*i*) Three active ingredients with ACE2-binding activity; (*ii*) Bind to SARS-CoV-2 RBD and prevent SARS-CoV-2 from entering $ACE2^h$ cells.	ACE2/CMC-HPLC-IT-TOF-MS approach, molecular docking, SPR assays, and *in vitro* antiviral experiment	*16*
	Ephedra sinica Stapf	Quinoline-2-carboxylic acids	Disrupt the interaction between ACE2 and SARS-CoV-2 RBD.	Competition inhibition assays, SPR assays, molecular docking, and *in vitro* antiviral experiment	*17*
Mahuang-Kuxingren	*Ephedra sinica* Stapf and *Semen armeniacae amarum*	β-sitosterol, estrone, and stigmasterol	Have a high binding activity for 3CLpro and ACE2.	Network pharmacology and molecular docking	*18*
Mahuang-Gancao	*Ephedra sinica* Stapf and *Glycyrrhiza uralensis*	Licorice glycoside E and xambioona	Bind well to COVID-19 related targets, including 3CLpro, S protein, and ACE2	Network pharmacology, molecular docking, and molecular dynamics	*19*
Huangqin	*Scutellariae radix*	Baicalein and scutellarin	Regulates the MAPK and NF-κB signaling pathways and blocks SARS-CoV-2 spike binding to ACE2.	Network pharmacology, HPLC-MS based plant metabolomics, and *in vitro* bioassays	*20*
Jinyinhua	*Lonicera japonica*	Chlorogenic acid, neochlorogenic acid, cryptochlorogenic acid and cynaroside	Inhibits SARS-CoV-2-S protein/ACE2 binding.	*In vitro* bioassays, bioassay-coupled HPLC approach, and MRM-MS/MS approach	*21*
Yuxingcao	*Houttuynia cordata*	Afzelin, apigenin, kaempferol, and quercetin	Binds with ACE2 and 3CLpro.	Network pharmacology and molecular docking	*22*

Note: Abbreviations: cell membrane chromatography (CMC); surface plasmon resonance (SPR); ACE2 over-expressed HEK293T cells ($ACE2^h$ cells); surface plasmon resonance (SPR); high-performance liquid chromatography (HPLC); multiple reaction monitoring tandem mass spectrometry (MRM-MS/MS).

components of Yuxingcao, such as afzelin, apigenin, kaempferol, and quercetin, have been reported to bind with ACE2 and 3CLpro of SARS-CoV-2 in four signaling pathways, including PI3K-Akt, Jak-STAT, MAPK, and NF-kB (*22*).

4. Active ingredients

Herbal medicine has a wide array of active ingredients with potential health benefits, including antiviral activity, that may be explored as an alternative treatment for COVID-19. Interestingly, some of these active ingredients might prevent SARS-CoV-2 from infecting human cells by blocking the ACE-2 protein (Table 3).

Ursodeoxycholic acid is a major active ingredient of the Chinese herb bear gall powder. A recent study indicated that ursodeoxycholic acid down-regulated ACE2 expression and reduced the susceptibility to SARS-CoV-2 infection *in vitro*, *in vivo*, and in human lungs and livers perfused *ex situ* (*23*). Moreover, ursodeoxycholic acid reduced ACE2 expression in the nasal epithelium in humans. Glycyrrhizic acid derived from the Chinese herb Gancao has been found to be a broad-spectrum anti-coronavirus candidate with low toxicity. Its antiviral mechanism might be due to disrupting viral uptake into host cells and impairing interaction between the RBD of SARS-COV2 and ACE2 (*24*). Glycyrrhizin, a main active ingredient of Gancao, prevents SARS-CoV-2 from entering cells and replicating by reducing the expression of ACE2 and inhibiting interaction between the S protein RBD and ACE2 (*25*).

Salvianolic acids (salvianolic acid A, salvianolic acid B, and salvianolic acid C), as major active ingredients of the Chinese herb *Salvia miltiorrhiza* (Danshen), inhibit the entry of the SARS-CoV-2 spike pseudovirus into HEK293T cells highly expressing ACE2 by binding to both the RBD of the SARS-CoV-2 S protein and receptor ACE2 (*26*). Salvianolic acid B displayed the greatest binding affinity and anti-SARS-CoV-2 pseudoviral action among these three compounds. Quercetin as a naturally abundant flavonoid that is widely found in various herbal medicines, such as *Forsythia suspensa* (Lianqiao) and *Lonicera japonica* (Jinyinhua). It might be a potential treatment for COVID-19-induced acute kidney injury (*27*). It might serve as a SARS-CoV-2 inhibitor by binding with the active sites of SARS-CoV-2 main protease 3CLpro and ACE2, therefore suppressing the functions of the proteins and interrupting the viral life cycle. In addition, andrographidine C, a major active ingredient of the Chinese herb *Andrographis paniculata* (Chuanxinlian), formed a stable complex with the key target ACE2, so it can be considered as a potential drug to treat COVID-19 (*28*).

5. Conclusion

The combination of the SARS-CoV-2 S protein with

Table 3. Some active ingredients exhibiting a high affinity for ACE2 in treating COVID-19

Ingredients	Chemical class	Source	Effects	Screening method	*Ref.*
Ursodeoxycholic acid	Steroids	Bear gall powder	(*i*) Downregulates ACE2 expression and reduces SARS-CoV-2 infection; (*ii*) Reduces ACE2 levels in the nasal epithelium of healthy individuals.	*In vitro*, *in vivo*, and *ex vivo* antiviral experiment	*23*
Glycyrrhizic acid	Terpenoids	Glycyrrhiza uralensis	Disrupts viral uptake into the host cells and impairs the interaction between RBD of SARS-COV2 and ACE2.	Computer-aided drug design and biological verification	*24*
Glycyrrhizin	Terpenoids	Glycyrrhiza uralensis	Reduces the expression of ACE2 and inhibits the interaction between the S protein RBD and ACE2.	Molecular docking and *in vitro* antiviral experiment	*25*
Salvianolic acid A, B and C	Phenols	Salvia miltiorrhiza	Binds to both RBD of SARS-CoV-2 S protein and receptor ACE2.	Molecular docking and *in vitro* antiviral experiment	*26*
Quercetin	Flavonoids	Various herbal medicines, such as Forsythia suspensa and Lonicera japonica	Binds with the active sites of SARS-CoV-2 main protease 3CL and ACE2.	Network pharmacology and molecular docking study	*27*
Andrographidine C	Flavonoids	Andrographis paniculata	Forms a stable complex with the key target ACE2	Network pharmacology, molecular docking, and molecular dynamics	*28*

Note: Abbreviations: angiotensin-converting enzyme 2 (ACE2); receptor-binding domain (RBD); spike protein (S protein).

ACE2 of the host cell to promote membrane fusion is an initial critical step for SARS-CoV-2 infection. Therefore, screening herbal medicines that inhibit the binding of the SARS-CoV-2 S protein and ACE2 might provide a feasible strategy for the treatment of COVID-19. This work has summarized some herbal medicines including formulas, single herbs, and active ingredients, that have exhibited a high affinity for ACE2 in treating COVID-19. We hope this work may provide meaningful and useful information on further research to investigate the mechanisms of herbal medicines against SARS-CoV-2 and follow-up drug discovery. However, most of the current research is based on network pharmacology, molecular docking, and *in vitro* bioassays, there is still a lot of work to be done in the real sense of drug design and development.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received November 30, 2022; Revised December 26, 2022; Accepted December 29, 2022.

*Address correspondence to:
Fanghua Qi, Traditional Chinese Medicine, Shandong Provincial Hospital affiliated to Shandong First Medical University, No. 324 Jingwuweiqi Road, Ji'nan, Shandong, China.
E-mail: qifanghua2006@126.com

Released online in J-STAGE as advance publication January 2, 2023.