Broad Anti-Viral Capacities of Lian-Hua-Qing-Wen Capsule and Jin-Hua-Qing-Gan Granule and Rational use Against COVID-19 Based on Literature Mining

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The novel coronavirus disease 2019 (COVID-19) has become a matter of international concern as the disease is spreading exponentially. Statistics showed that infected patients in China who received combined treatment of Traditional Chinese Medicine and modern medicine exhibited lower fatality rate and relatively better clinical outcomes. Both Lian-Hua-Qing-Wen Capsule (LHQWC) and Jin-Hua-Qing-Gan Granule (JHQGG) have been recommended by China Food and Drug Administration for the treatment of COVID-19 and have played a vital role in the prevention of a variety of viral infections. Here, we desired to analyze the broad-spectrum anti-viral capacities of LHQWC and JHQGG, and to compare their pharmacological functions for rational clinical applications. Based on literature mining, we found that both LHQWC and JHQGG were endowed with multiple antiviral activities by both targeting viral life cycle and regulating host immune responses and inflammation. In addition, from literature analyzed, JHQGG is more potent in modulating viral life cycle, whereas LHQWC exhibits better efficacies in regulating host anti-viral responses. When translating into clinical applications, oral administration of LHQWC could be more beneficial for patients with insufficient immune functions or for patients with alleviated symptoms after treatment with JHQGG.

Keywords: broad-spectrum antivirals, Lian-Hua-Qing-Wen capsule, Jin-Hua-Qing-Gan granule, medicinal plants, COVID-19, SARS-CoV-2, host-directed therapy

INTRODUCTION

Lian-Hua-Qing-Wen Capsule and Jin-Hua-Qing-Gan Granule are Both Recommended as Effective “Chinese Solution” Against COVID-19

The novel coronavirus disease 2019 (COVID-19) pandemics has reached almost every country in the world. Compared with the outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003 and the pandemic of Middle East Respiratory Syndrome (MERS) in 2012, COVID-19 caused by the novel coronavirus SARS-CoV-2 infection has relatively low fatality rate, whereas much more rapid and
higher human-to-human transmissibility (Meo et al., 2020). Typically, the existence of a large number of asymptomatic carriers of SARS-CoV-2 additionally exerts potential burden to the control and prevention of COVID-19.

SARS-CoV-2 can be easily transmitted through respiratory droplets or by aerosol, and infected people have a wide range of reported symptoms, from mild symptoms to severe illness. The most common manifestations of COVID-19 are fever or chill, dry cough and fatigue, which could be accompanied with a temporary loss of smell or taste, muscle or body aches. In critical cases, acute myocardial injury, liver or kidney dysfunction and blood-clotting complications may occur (Huang et al., 2020; Khider et al., 2020), consequently leading to septic shock and acute respiratory distress syndrome (ARDS) or death. The “Clinical Treatment for COVID-19” issued by the World Health Organization recommends that symptomatic treatments that relieve fever and pain, together with adequate nutritional supports are basically required for mild cases of COVID-19. For severe SARS-CoV-2 infections, oxygen therapy and fluid supply need to be reinforced. In spite of supportive measures above, potential anti-viral drugs which were used for diseases due to viral infections other than SARS-CoV-2 have been repurposed for COVID-19, such as remdesivir, ribavirin and hydroxychloroquine are however not addressed because of reported side-effects or lack of supporting evidence from large-scale randomized controlled trials (Izcvich et al., 2020; Trivedi et al., 2020; Qaseem et al., 2021). Likewise, vaccine development involves a difficult, complex and costly process, and the success of which is at a high risk of failure protecting against mutant viral variants (Biswas and Majumder, 2020; Penarrubia et al., 2020). Despite the development of vaccines, scientists are still tirelessly designing new drugs and repurposing existing drugs against SARS-CoV-2. Though tremendous strides have been made in the fight against coronaviruses, a lack of safe and effective anti-SARS-CoV-2 drugs is still a key factor restricting the prevention and control of COVID-19 pandemics.

The practice of Traditional Chinese Medicine (TCM) has accumulated a wealth of clinical experience in the treatment of infectious diseases since Qin-Han (about 221 BC to 220 AD) and developed into a theory in Ming-Qing period (about 1368–1777 AD). Infectious diseases in TCM have been described as “infections caused by toxic qi”, “warm pathogen first invades lung via nose and mouth”, and “disease spreads due to close contact”. These descriptions fit well with the epidemiological characteristics of modern acute infectious diseases. According to TCM theory, COVID-19 is the result of invasion by dampness-toxin pathogens, therefore COVID-19 is pathogenically characterized by dampness-toxin and host healthy-qi deficiency. Most patients first present mild sign of dampness, like fatigue, poor appetite and greasy thick tongue coating (Zheng, 2020). As disease progresses, dampness-toxin invades interiority and diffuses into triple energizer, leading to vital qi impairment and accumulation of toxin-qi in viscera. Excessive accumulation of dampness-toxin may easily lead to vital qi exhaustion and consequently loss of life. Hence, TCM formulae functioning to remove dampness-toxin are effective in preventing COVID-19 progress. Being the first country that was attacked by COVID-19, approximately 91.5% confirmed patients in China were treated with TCM formulae and the total effective rate has reached to 90%. In Wuhan Jiang-Xia Square Cabin Hospital, none of the 564 COVID-19 patients who received combined treatment of TCM and modern medicine developed into severe conditions, and TCM addition significantly reduced the course of hospitalization (Ren et al., 2020).

Both LHQWC and JHQGG belong to “Three Drugs, Three Prescriptions”, official prescriptions of TCM used in the fight against COVID-19 in China. LHQWC, composed of Forsythia suspensa (Thunb.) Vahl, Lonicera japonica Thunb., honey-fried Ephedra sinica Stapf, fried Prunus sibirica L., Gypsum Fibrosum, Isatis tinctoria L., Dryopteris crassirhizoma Nakai, Hawthornia cordata Thunb., Pogostemon cablin (Blanco) Benth., Rheum palmatum L., Rhodiola crenulata (Hook.f. and Thomson) H. Ohba, Mentha canadensis L. and Glycyrrhiza glabra L., is innovative Chinese Patent Medicine (CPM) approved during the SARS epidemics in 2003. JHQGG, the other CPM constituting Forsythia suspensa (Thunb.) Vahl, Lonicera japonica Thunb., Ephedra sinica Stapf, Prunus sibirica L., 1-Menthol, Glycyrhiza glabra L., Scutellaria baicalensis Georgi, Fritillaria thunbergii Miq., Anemarrhena asphodeloides Bunge, Arctium lappa L. and Artemisia annua L., has been approved to treat H1N1 influenza virus infection since 2009. Both LHQWC and JHQGG are developed based on Ma-Xing-Shi-Gan Decotion and Yin-Qiao Powder, classic TCM decoctions used for respiratory infections recorded in Treatize on Exogenous Febrile Disease (about 210 AD) and Systematic Differentiation of Warm Diseases (1798 AD), respectively. In clinical practices resolving respiratory infections, LHQWC is mainly used to clear away plague, remove toxins, ventilate lungs and discharge heat, whereas JHQGG is applied to dispel wind, clear heat and resolve toxicity. In the combat against COVID-19, National Health Commission of China approved both LHQWC and JHQGG as clinical therapies in China, and observational studies showed that both can effectively relieve fever, fatigue, cough and phlegm in the early stage of COVID-19, contributing to reductions in risks of rapid clinical deterioration. Supportively, in vitro studies have revealed that both formulae have anti-inflammatory effects, providing fundamental evidence for clinical application of both formulae in the fight against COVID-19 (Cheng, 2020; Duan, 2020; Hu et al., 2020; Runfeng et al., 2020; Zhang et al., 2020).

Holism Theory of TCM and Anti-viral Actions of Lian-Hua-Qing-Wen Capsule and Jin-Hua-Qing-Gan Granule, a Reflection of Host-Directed Therapy in Modern Medicine

Holism is the fundamental concept in TCM, which emphasizes the connections of the whole body and intends to treat the whole person rather than focusing on individual symptoms. Directed by holistic view, TCM practitioners adopt syndrome differentiation (Bian Zheng), a comprehensive analysis of a variety of clinical information, and herbal formulae to resolve single or complex uncomformability of patients. This holism theory of TCM
dovetails with the principle of host-directed therapy (HDT). HDT is a novel concept in the treatment for infectious diseases and was first used in *tuberculosis* in 2015 (Zumla et al., 2015). After then, HDT was gradually fulfilled as anti-viral strategies. Compared to conventional anti-viral therapies, which focus on inhibiting virus activity, HDT aims to maintain homeostasis of host by stimulating anti-viral responses and suppressing immune injuries. It has been shown that compared to single anti-pathogen treatment, HDT is able to reduce the risks of drug resistance induced by bacteria and viruses, endowing HDT a therapeutic potential of being broad-spectrum anti-viral tactics (Kaufmann et al., 2018). Clinical investigations proposed that viral infection-triggered cytokine storm was a vital factor mediating the rapid progress of COVID-19 (Wang T. et al., 2020). High levels of IL (Interleukin) -6 and IL-10, while low levels of CD4+ T and CD8+ T cells can be observed in COVID-19 patients (Guan et al., 2020; Wan et al., 2020). Moreover, plasma IL-2, IL-7, IL-10, GCSF (granulocyte colony-stimulating factor), IP-10 (interferon gamma-induced protein-10), MCP-1 (monocyte chemoattractant protein-1), MIP-1α (macrophage inflammatory protein-1 alpha) and TNF-α (tumor necrosis factor-alpha) are consistently higher in intensive care unit (ICU) patients compared to mild cases (Huang et al., 2020), suggesting that virus-induced exaggerated immune responses and the resulting immune injuries are involved in the progression of COVID-19. Accordingly, HDT-oriented treatments that inhibit IL-6 signaling by down-regulating IL-6 receptors have been suggested as a potential solution for COVID-19 patients (Zumla et al., 2020). Consistent with HDT, in the combat against COVID-19, TCM addresses that sufficient healthy-qi within the body is key to prevent pathogen invasion, so-called “strengthening host resistance to eliminate pathogenic factors”. Accordingly, inspiring vital qi is at the root of preventing infectious diseases in TCM. The functions of “healthy-qi” resemble “immunity” of host, and “pathogenic factors” stand for all substances that affect host homeostasis, such as viruses and bacteria. As emphasized in HDT that considering individuals as a whole rather than separating parts, “strengthening host resistance to eliminate pathogenic factors” in TCM addresses an overall reaction of host in response to invasive viruses, whereas the destiny of pathogen itself is not primarily important. Moreover, same as the HDT concept implicates, the ultimate goal of TCM treatment is to maintain host homeostasis via balancing interactions between host and pathogens, or by establishing equilibrium between stimulating anti-viral reactions and suppressing overactivated immune responses that subsequently cause tissue injuries.

Following the HDT principle and holism theory of TCM, this study primarily desired to gain more insight into the broad anti-viral features of LHQWC and JHQGG, both of which have been applied to treat a variety of viral infections. However, considering that the main herbal composition of LHQWC and JHQGG largely overlap, it therefore appears confusing in the selection of appropriate formula for individual clinical cases. In this scenario, it is of prime importance to also distinguish the similarities and differences between the two formulae in terms of pharmacological anti-viral functions. To implement these goals, we manually grouped the individual active components from either LHQWC or JHQGG or both into two categories, namely constituents that interfere with viral life cycle and components that regulate host immune responses and inflammation. Through comprehensive literature review, data mining and pharmacological target enrichment analysis, we investigated the strength of LHQWC and JHQGG in the above-mentioned virus or host arm to compare their anti-viral functionalities. The holism-directed analysis of LHQWC and JHQGG will provide more insightful information and comprehensive understanding for rational use of these two CPMs in the combat against COVID-19, as well as the emerging or re-emerging pandemics of infectious diseases.

**MATERIALS AND METHODS**

**Literature Collection and Inclusion**

In order to collect sufficient data on anti-viral effects of LHQWC and JHQGG, we employed Pubmed (https://pubmed.ncbi.nlm.nih.gov), Ovid (https://ovidsp.ovid.com/), CNKI (https://www.cnki.net), WANFANG (http://www.wanfangdata.com.cn/index.html) and WEIPU (http://www.cqvip.com/) database by searching either the full name of formulae, such as “Lianhua Qingwen Capsules”, “Jinhua Qinggan Granules”, or names of individual medicinal herbs, or active ingredients, together with “virus” as keywords. In addition, bioactive components that were proposed to be antivirals were included via network pharmacology-based prediction and analysis. A total of 1,110 articles were collected for next filtration. For the analysis of broad anti-viral activities, we then excluded studies reporting negative outcomes, clinical trials generally indicating viral infections without clarifying taxonomy of viruses, investigations using inactivated or attenuated viruses as vaccines, and articles with no access to full context due to age. A total of 812 articles were analyzed at this stage. For detailed comparisons of active anti-viral components and pharmacological functions of formulae, studies without indicating names of active components were further excluded. Notably, no information regarding Gypsum Fibrosum and fried *Prunus sibirica* L. in relevant to virus, and we did not find data by searching bioactive components directly isolated from JHQGG, hence we only took ingredients determined by predictive parsing of network pharmacology. Finally, 117 articles were included for comparison of pharmacological functions.

**Constructing “Formula–Herb–Virus–Baltimore Classification of Viruses” Network**

In order to describe broad-spectrum anti-viral activities of LHQWC and JHQGG, we grouped antiviral data collected as mentioned, and built a network in forms of “Formula-herb-virus-Baltimore classification of viruses”. To further interpret the common and distinctive anti-viral activities of LHQWC and JHQGG in terms of holism theory of TCM, we classified the anti-viral actions reported for LHQWC and JHQGG into being either associated with viral life cycle or responsible to host...
immune responses and inflammation. To gain more insightful understanding, we further categorized active components that disrupt virus life cycle into three levels, including direct virucidal activity, inhibition of viral entry, and suppression of viral replication and egress. Generally, inhibitors of virus entry act through deforming viral particles or blocking the attachment or
### TABLE 1 | Active anti-viral components from LHQWC and JHQGG, and their mechanisms of action regulating viral life cycle.

#### 1.1 Direct virucidal activity

| Virus                             | Active component | Herb References                                                                 |
|-----------------------------------|------------------|---------------------------------------------------------------------------------|
| Chikungunya Virus                 | Baicalin          | Scutellaria baicalensis Georgi (Huang Qin) Oo et al. (2018)                   |
| Coxackievirus A16                 | Glycyrrhizic acid| Glycyrrhiza glabra L. (Gan Cao) Wang et al. (2013)                            |
| Herpes simplex virus type1        | Chinonin/Asphoain| Anemarrhena asphodeloides Bunge (Zhi Mu) Jiang and Xiang (2004)               |
| Newcastle disease virus           | Baicalin          | Scutellaria baicalensis Georgi (Huang Qin) Jia et al. (2016)                  |
| Respiratory syncytial virus       | Lonicera japonica| Lonicera japonica Thunb. (Jin Yin Hua) Zhang et al. (2014)                    |

#### 1.2 Inhibit viral entry

| Virus                             | Active component | Mechanisms                                                                 | Herb References                                                                 |
|-----------------------------------|------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Coxackie virus B3                 | Artemisinin      | Inhibits viral absorption                                                 | Artemisia annua L. (Qing Hao) Ma (2004)                                         |
|                                   | Baicalin          | Reduces cellular lipid synthesis                                          | Scutellaria baicalensis Georgi (Huang Qin) Wang et al. (2020a)                 |
| Herpes simplex virus              | Houttuynia cordata| Blocks viral binding and penetration                                       | Houttuynia cordata Thunb. (Yu Xing Cao) Zhou (2017); Hung et al. (2015)        |
| Herpes simplex virus type1        | Isatis tinctoria L. extracts | Inhibits viral entry                                                       | Isatis tinctoria L. (Ban Lan Gen) Fang, 2005                                   |
| type2 and varicella zoster virus  | Houttuynoid A     | Blocks viral membrane fusion                                              | Houttuynia cordata Thunb. (Yu Xing Cao) Li et al. (2017a)                      |
| Herpes simplex virus type2        | Chinonin/Asphoain| Inhibits viral adsorption                                                  | Anemarrhena asphodeloides Bunge (Zhi Mu) Jiang et al. (2005)                   |
| Human cytomegalovirus             | Baicalin          | Blocks viral entry through inhibiting epidermal growth factor receptor tyrosine kinase activity and viral nuclear translocation | Scutellaria baicalensis Georgi (Huang Qin) Evers et al. (2005)                 |
| Human rotavirus                   | *Rheum palmatum* L. extracts | Inhibits viral entry                                                     | *Rheum palmatum* L. (Da Huang) He et al. (2013)                                |
| Influenza A Virus                 | Flavonoids-enriched extract from Scutellaria baicalensis root | Reduces hemagglutinin                                                    | Scutellaria baicalensis Georgi (Huang Qin) Zhi et al. (2019)                  |
|                                  | Rhein             | Inhibits viral absorption                                                | Rheum palmatum L. (Da Huang) Wang et al. (2018)                                |
| *Isatis tinctoria* L. extract     | Clemastanin B, epigotrin, phenylpropanoids portion and the mixture of phenylpropanoids, alkaloids and organic acid fractions | Blocks viral attachment                                               | *Isatis tinctoria* L. (Ban Lan Gen) Xiao et al. (2016)                        |
|                                  | Glycyrrhizin      | Reduces endocytotic activity and virus uptake                            | Glycyrrhiza glabra L. (Gan Cao) Wolkerstorfer et al. (2009)                   |
| *Isatis tinctoria* L. water extracts | Inhibits attachment of viruses to cells                              | *Isatis tinctoria* L. (Ban Lan Gen) Chen et al. (2006)                       |
| (+)-catechin                      | Inhibits acidification of endosomes and lysosomes                     | Ephedra sinica Stapf (Ma Huang) Mantani et al. (2001)                      |
| 5,7,4′- trihydroxy-8-methoxyflavone | Inhibits fusion of virus with endosome/lysosome membrane            | Scutellaria baicalensis Georgi (Huang Qin) Nagai et al. (1995a); Nagai et al. (1995b) |
| Influenza A virus, Coxsackievirus B3, Adenovirus | Patchouli alcohol | Inhibits infection at the earliest stages of the viral life cycle, including virus attachment and entry | Pogostemon cablin (Blanco) Benth. (Guang Hui Xiang) Wei et al. (2013)       |
| Porcine reproductive and respiratory syndrome virus | Flavaspidic acid AB | Inhibits viral endocytosis                                                | Oxypteris crassinervata Nakai (Mian Ma Guan Zhong) Yang et al. (2013)           |
| Respiratory syncytial virus       | Lonicera japonica Thunb. Extracts | Inhibits viral absorption                                                | Lonicera japonica Thunb. (Jin Yin Hua) Zhang et al. (2014)                   |
| Ephedra Sinica water extracts     | Inhibits viral absorption and penetration                            | Ephedra sinica Stapf (Ma Huang) Zhu and Li (2012)                          |
| Radix Glycyrrhizae water extracts | Inhibits viral attachment and penetration                            | Glycyrrhiza glabra L. (Gan Cao) Yeh et al. (2013)                          |
| SARS Coronavirus                  | Emodin            | Targets spike glycoprotein thus inhibits receptor binding                  | *Rheum palmatum* L. (Da Huang) Ho et al. (2007)                               |

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### TABLE 1 | (Continued) Active anti-viral components from LHQWC and JHQGG, and their mechanisms of action regulating viral life cycle.

#### 1.3 Inhibit viral replication and release

| Virus                                      | Active component                                           | Mechanisms                                           | Herb                                      | Ref                  |
|--------------------------------------------|------------------------------------------------------------|------------------------------------------------------|-------------------------------------------|----------------------|
| Bovine viral diarrhea virus, a surrogate in vitro model of hepatitis C virus | Novel artemisinin derivatives (AD)                         | AD1 and AD2 inhibit the release of Bovine virus diarrhea virus -RNA | Artemisia annua L. (Qing Hao)             | Blazquez et al. (2013) |
| Coxsackie virus B3                          | Emodin                                                     | Unknown                                               | Rheum palmatum L. (Da Huang)              | Cai and Luo (2014)   |
|                                            | Artemisinin                                                | Inhibits viral replication                           | Artemisia annua L. (Qing Hao)             | Ma (2004)            |
|                                            | Isatis tinctoria L. polysaccharides extracts                | Inhibits viral replication                           | Isatis tinctoria L. (Ban Lan Gen)         | Zhang et al. (2009)  |
| Coxsackievirus B5 and respiratory syncytial virus | Emodin                                                     | Inhibits Viral biological synthesis                  | Rheum palmatum L. (Da Huang)              | Liu et al. (2015)    |
| Dengue virus                               | Lonicerla japonica Thunb. aqueous extracts                 | The microRNA let-7a targets viral non-structural protein1 | Lonicerla japonica                        | Lee et al. (2017)    |
|                                            | 18β-glycoxythinic acid                                     | Binds to nucleoprotein                               | Glycyrrhiza glabra L. (Gan Cao)           | Fu et al. (2016)     |
| Enterovirus 71                             | Glycyrrhizic acid                                          | Inhibits viral replication                           | Glycyrrhiza glabra L. (Gan Cao)           | Wang et al. (2013)   |
|                                            | Rheum palatum L. extracts                                  | Reduces viral replication                            | Rheum palatum L. (Da Huang)               | Lin et al. (2009)    |
|                                            | Norwogonin, oroxylin A, mosloflavone                       | Inhibits expression of viral capsid proteins         | Scutellaria baikalensis                   | Choi et al. (2016)   |
|                                            | Baicalin                                                   | Interferes with 3D polymerase transcription and translation | Scutellaria baikalensis                   | Li et al. (2015)     |
|                                            | Honeysuckle-encoded microRNA2911                          | Targets viral envelope protein1 gene of Enterovirus 71 | Lonicerla japonica                        | Li et al. (2018)     |
|                                            | Emodin                                                     | Diminishes cell cycle arrest at S phase induced infection | Rheum palatum L. (Da Huang)               | Zhong et al. (2017)  |
| Epstein-Barr Virus                         | Baicalin                                                   | Represses Epstein-Barr nuclear antigen1 Q-promoter activity | Scutellaria baikalensis                   | Zhang et al. (2018)  |
|                                            | 5,7,2'-trihydroxy- and 5,7,2',3'-tetrahydroxyflavone     | Unknown                                               | Scutellaria baikalensis                   | Konoshima et al. (1992) |
|                                            | Arctium lappa L. extracts                                  | Suppresses viral replication and decreases viral antigen expression, including capsid antigen and early antigen | Arctium lappa L. (Niu Bang Z1)            | Chen and Huang (1994) |
| Hepatitis B virus                          | Novel artemisinin derivatives (AD)                         | AD1 and AD2 reduce the release of Hepatitis B virus -DNA | Artemisia annua L. (Qing Hao)             | Blazquez et al. (2013) |
| Hepatitis C virus                          | Pheophytin                                                 | Inhibits Hepatitis C virus -nonstructural3 protease | Lonicerla japonica                        | Wang et al. (2009a)  |
| Herpes simplex virus                       | Houttuynia cordata Thunb. Extracts                        | Suppresses viral replication via inhibiting NF-κB activation | Houttuynia cordata Thunb. (Yu Xing Cao) | Huyng et al. (2015)  |
| Herpes simplex virus type1                 | Isatis tinctoria L. extracts                               | Inhibits viral replication                           | Isatis tinctoria L. (Ban Lan Gen)         | Fang (2005)          |
|                                            | Arctium lappa L. hydroalcoholic extracts                   | Suppresses viral replication                         | Arctium lappa L. (Niu Bang Z1)            | Dias et al. (2017)   |
|                                            | Chinonin/Asphomin                                          | Inhibits viral replication                           | Anamartenha asphodeloides Bunge (Zhi Mu)  | Jiang and Xiang (2004) |
| Herpes simplex virus type2                 | Chinonin/Asphomin                                          | Inhibits viral replication                           | Anamartenha asphodeloides Bunge (Zhi Mu)  | Jiang et al. (2005)  |
| Human cytomegalovirus                      | Artemisinin-derived monomers artesunate (AS)              | Inhibits viral replication as hypophosphorylation (activity) of the retinoblastoma protein (pRb) | Artemisia annua L. (Qing Hao)             | Roy et al. (2015)    |
|                                            | Genistin                                                   | Blocks viral immediate-early protein functioning      | Scutellaria baikalensis                   | Evers et al. (2005)  |
| Human immunodeficiency virus type1         | Artemisia afra                                             | Unknown                                               | Artemisia annua L. (Qing Hao)             | Lubbe et al. (2012)  |
|                                            | Sennoside A                                               | Inhibits viral replication by targeting viral reverse transcription process including inhibiting HIV-1 Reverse Transcriptase-associated DNA Polymerase and Ribonuclease H activities | Rheum palatum L. (Da Huang)               | Esposito et al. (2016) |

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| Virus                                    | Active component                                                                 | Mechanisms                                                                 | Herb                                | Ref                          |
|-----------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------|-------------------------------------|------------------------------|
| Human rotavirus                          | *Rheum palmatum* L. extracts                                                    | Inhibits viral replication                                                  | *Rheum palmatum* L. (Da Huang)      | He et al. (2013)             |
| Influenza A Virus                       | *Isatis tinctoria* L. eruc acid                                                 | Reduces viral polymerase transcription activity                             | *Isatis tinctoria* L. (Ban Lan Gen) | Liang et al. (2020)          |
|                                        | *Aloe-emodin*                                                                   | Inhibits viral replication                                                  | *Aloe-emodin*                       |                              |
|                                        | *Baicalin* and biochinin A                                                      | Inhibits neuraminidase                                                       | *Aloe-emodin*                       |                              |
|                                        | *Chlorogenic acid*                                                              | Inhibits neuraminidase                                                       | *Aloe-emodin*                       |                              |
|                                        | *Flavonoids-enriched extract from Scutellaria baicalensis root*                 | Inhibits neuraminidase activities                                            | *Scutellaria baicalensis*           | Zhi et al. (2019)            |
|                                        | *Baicalin*                                                                       | Inhibits RNA polymerase activity                                             | *Scutellaria baicalensis*           | Guo et al. (2016)           |
|                                        | *Baicalin*                                                                       | Interacts with RNA binding domain of Non-structural protein1                 | *Scutellaria baicalensis*           | Nayak et al. (2014)         |
|                                        | *Glycyrrhizin*                                                                  | Inhibits influenza virus polymerase activity                                | *Scutellaria baicalensis*           | Moisy et al. (2012)         |
|                                        | *Aloe-emodin*                                                                   | Inhibits viral replication through galectin-3 up-regulation                 | *Aloe-emodin*                       |                              |
|                                        | *Baicalin*                                                                       | Inhibits viral replication                                                  | *Scutellaria baicalensis*           | Sithisarn et al. (2013)     |
|                                        | *Baicalin*                                                                       | Inhibits neuraminidase activity                                              | *Scutellaria baicalensis*           | Sithisarn et al. (2013)     |
|                                        | *Isatis tinctoria* L. extract Clemastanin B (GB), epigotrin, phenylpropanoids portion (PEP) and the mixture of phenylpropanoids, alkaloids and organic acid fractions | Inhibits viral replication                                                  | *Isatis tinctoria* L. (Ban Lan Gen) | Xiao et al. (2016)         |
|                                        | *Isatis tinctoria* L. extracts                                                  | Inhibits neuraminidase activity                                              | *Scutellaria baicalensis*           |                              |
|                                        | *Pogostemon cablin* (Blanco) Benth extracts                                     | Suppresses viral replication                                                | *Pogostemon cablin* (Blanco) Benth. (Guang Huo Xiang) | Yang (2010) |
|                                        | *Fritillaria thunbergii*                                                       | Unknown                                                                     | *Fritillaria thunbergii* Miq. (Zhe Bei Mu) | Kim et al. (2020)         |
|                                        | *Chlorogenic acid*                                                              | Inhibits neuraminidase                                                       | *Lonicera japonica* Thunb. (Jin Yin Hua) | Ding et al. (2017)         |
|                                        | *Honesuckle (HS)-encoded atypical microRNA-MIR2911*                             | Inhibits IAV-encoded PB2 and NS1 protein expression                          | *Lonicera japonica* Thunb. (Jin Yin Hua) | Zhou et al. (2015)        |
|                                        | *Forsythia suspensa* (Thunb.) Vahl fruit                                        | Reduces influenza viral M1 protein                                           | *Forsythia suspensa* (Thunb.) Vahl. (Lian Qiao) | Law et al. (2017)         |
|                                        | *Chalcones*                                                                     | Inhibits neuraminidase activity                                              | *Glycyrrhiza glabra L. (Zhe Bei Mu) | Dao et al. (2011)          |
|                                        | *Houttuynia cordata* Thunb. flavonoids extracts                                 | Inhibits neuraminidase activity                                              | *Houttuynia cordata* Thunb. (Yu Xing Cao) | Ling et al. (2020)        |
|                                        | *Isatis tinctoria* L. N-butanol extracts                                        | Inhibits viral replication                                                  | *Isatis tinctoria* L. (Bar Lan Gen) | Liu et al. (2012)          |
| Newcastle disease virus                 | *Baicalin*                                                                       | Inhibits apoptosis of virus-infected cells and suppresses viral spread         | *Scutellaria baicalensis*           | Jia et al. (2016)          |
|                                        | *Pogostemon cablin* (Blanco) Benth polyphenolic extracts                        | Inhibits neuraminidase activity                                              | *Pogostemon cablin* (Blanco) Benth. (Guang Huo Xiang) | Liu (2016)                |
| Porcine epidemic diarrhea virus         | *Pogostemon cablin* (Blanco) Benth poly saccharides extracts                    | Inhibits viral replication                                                  | *Pogostemon cablin* (Blanco) Benth. (Guang Huo Xiang) | Chen et al. (2020)       |
| Porcine reproductive and respiratory syndrome virus | *Isatis tinctoria* L. polysaccharides extracts                                 | Inhibits viral replication                                                  | *Isatis tinctoria* L. (Ban Lan Gen) | Wei et al. (2011)          |
|                                        | *Flavaspidic acid AB from Dryopteris crassirhizoma*                             | Inhibits viral replication                                                  | *Dryopteris crassirhizoma* Naikai (Mian Ma Guan Zhong) | Yang et al. (2013)       |

(Continued on following page)
binding of virions to host cells. The control of virus replication is mainly mediated by inhibiting replicator machineries encoded by viral systems, and prevention of virus egress is a process involves an interference with assembly and release of progeny viruses, which may initiate a secondary round infection. For the actions of regulating host immune responses and inflammation, it represents any virucidal effects due to an indirect response by modulating host immune system, such as increasing interferons (IFNs) expression, or decreasing self-targeted inflammatory injuries, or promoting repair process post virus infection without involving viral molecule-associated biological events. Based on literature mining and analysis, we next counted the frequencies of active components of LHQWC and JHQGG that have been sorted into each of the two categories, and accordingly a radar chart was drawn to visualize and compare the power of LHQWC and JHQGG against viral infection in terms of modulating viral life cycle and regulating host immune responses and inflammation.

**RESULTS**

The broad-Spectrum Anti-Viral Activities of Lian-Hua-Qing-Wen Capsule and Jin-Hua-Qing-Gan Granule

Multi-ingredients, multi-targets and multi-pathways are primary features of TCM formulae, suggesting that active ingredients of one medicinal herb may exert anti-viral functions via diverse pharmacological mechanisms. As shown in Figure 1, active components in both LHQWC and JHQGG have been shown to target 87 different types of viruses, covering all the seven classes according to the Baltimore classification. This wide range of anti-viral activities of LHQWC and JHQGG addresses that TCM formulae used in COVID-19 pandemics could be potentially applied for other virological infections, such as influenza A virus, Zika virus and herpesvirus.

**Similarities and Differences of Lian-Hua-Qing-Wen Capsule and Jin-Hua-Qing-Gan Granule as Antivirals**

Both LHQWC and JHQGG possess broad-spectrum anti-viral potentials through interfering with viral life cycle and modulating host immune responses, which are associated with a diversity of proposed pharmacological actions as detailed in Tables 1, 2, 3; Figure 2. When comparing LHQWC and JHQGG, no difference was found in the types of their targeted viruses (Table 1; Figure 1). In terms of active components that disrupt viral life cycle (Table 1; Figure 2), only few literatures reported a direct virucidal activity from components of LHQWC and JHQGG (Table 1-1.1; Figure 2), about 24% studies showed suppression of viral entry (Table 1-1.2; Figure 2), while 70% studies focused on inhibitory effects toward viral replication and release (Table 1-1.3; Figure 2) Among all data analyzed, constituents from *Scutellaria baicalensis* Georgi (Huang Qin) of JHQGG have been mostly reported to interfere with viral life cycle in all three phases analyzed. Besides, components from *Isatis tinctoria* L. (Ban Lan Gen) and *Rheum palmatum* L. (Da Huang) of LHQWC are shown highly effective in blocking viral entry, replication and release. JHQGG weights slightly higher than LHQWC in terms of viral replication and release, whereas little difference was obtained in the early phase of viral life cycle (Table 1; Figure 2). Regarding “host immune responses and inflammation”, it is interesting that constituents from *Scutellaria baicalensis* Georgi (Huang Qin) of JHQGG again exhibited the greatest potential, followed by components from *Isatis tinctoria* L (Ban Lan Gen) and *Rheum palmatum* L (Da Huang) in LHQWC. When comparing LHQWC and JHQGG, LHQWC weights slightly higher than JHQGG (Table 2; Figure 2). In addition, several studies have proposed other anti-viral mechanisms that could not be grouped into the above two categories, such as maintaining host redox homeostasis, or acting on microbiota, or gut-lung axis, or

| Virus                        | Active component                     | Mechanisms                                   | Herb                          | Ref            |
|------------------------------|--------------------------------------|----------------------------------------------|-------------------------------|----------------|
| Respiratory syncytial virus  | *Isatis tinctoria* L. polysaccharide extracts | Inhibits viral replication                   | *Isatis tinctoria* L. (Ban Lan Gen) | Lu (2016)      |
|                              | Artemisin                            | Inhibits viral replication                   | *Artemisia annua* L. (Qing Hao) | Lu (2016)      |
|                              | *Houttuynia cordata* root extract     | Inhibits viral NS1 and L proteins            | *Isatis tinctoria* L. (Ban Lan Gen) | Zhang (2017)  |
|                              |未知                                   | Inhibits viral biosynthesis                  | *Lonicera japonica* Thunb. | Li (2010)      |
| SARS coronavirus             | *Houttuynia cordata* Thunb. Extracts | Inhibits SARS-CoV 3C-like protease and RNA-dependent RNA polymerase | *Houttuynia cordata* Thunb. (Jin Yin Hua) | Liu et al. (2008) |
|                              | *Rheum palmatum* L. extracts         | Inhibits SARS coronavirus 3C-like protease   | *Rheum palmatum* L. (Da Huang) | Luo et al. (2009) |
### TABLE 2 | Active anti-viral components from LHQWC and JHQGG regulating host immune responses and inflammation.

| Virus | Active component | Mechanisms | Herb | References |
|-------|------------------|------------|------|------------|
| Bovine viral diarrhea virus | Forsythoside A | Promotes peripheral blood mononuclear cell proliferation and T cell activation, TRAF2-dependent CD28-4-1BB signaling; induces IFN-γ | Forsythia suspensa (Thunb.) Vahl (Lian Qiao) | Li et al. (2011) |
| Coxsackie virus B3 | Emodin | Reduces pro-inflammatory cytokines | Rheum palmatum L. (Da Huang) | Cai and Luo (2014) |
| | Emodin | Regulates IL-17/IL-23 axis | Rheum palmatum L. (Da Huang) | Jiang et al. (2014) |
| | Rhodiola | Unknown | Rhodiola crenulata (Hook.f. and Thomson) H.Ohba (Hong Jing Tian) | Liu et al. (2002) |
| Coxsackievirus BS and respiratory syncytial virus | Emodin | Decreases IFN-α, enhances TNF-γ | Rheum palmatum L. (Da Huang) | Liu et al. (2015) |
| Hepatitis B virus | Isatis tinctoria L polysaccharide extracts | Enhances IFN-α and antiviral proteins, including p-STAT-1, p-STAT-2, p-JAK1, p-TYK2, OAS1, and Mx, via activation of JAK/STAT signal pathway | Isatis tinctoria L. (Ban Lan Gen) | Wang et al. (2020b) |
| Hepatitis C virus | Artemisia annua polysaccharides | Promotes IFN-γ secretion | Artemisia annua L. (Qing Hao) | Bao et al. (2015) |
| | Essential oil of Mentha suaveolens | Reduces viral RNA-induced pro-inflammatory mediators through inactivation of NF-κB and p38 MAPK signaling pathway, Reduces CD8 (+) cytotoxic T lymphocyte recruitment | Mentha canadensis L. (Bohe) | Ovtelli et al. (2014) |
| Influenza A Virus | Isatis tinctoria L. erucic acid | Reduces viral RNA-induced pro-inflammatory mediators through inactivation of NF-κB and p38 MAPK signaling pathway, Reduce CD8 (+) cytotoxic T lymphocyte recruitment | Isatis tinctoria L. (Ban Lan Gen) | Liang et al. (2020) |
| | Oroxylin A | Increases IFN-β and IFN-γ | Scutellaria baicalensis Georgi (Huang Qin) | Jin et al. (2018) |
| | Flavonoids-enriched extract from Scutellaria baicalensis root | Reduces TNF-α, IL-6 and MCP-1, increases IFN-γ and IL-10 | Scutellaria baicalensis Georgi (Huang Qin) | Zhi et al. (2014) |
| | Baicalin | Modulates non-structural protein1-mediated cellular innate immune responses, IFN-induced antiviral signaling and a decrease in PI3K/Akt signaling | Scutellaria baicalensis Georgi (Huang Qin) | Nayak et al. (2014) |
| | Phyllyrin | Decreases IL-6 | Forsythia suspensa (Thunb.) Vahl (Lian Qiao) | Qu et al. (2016) |
| | Aloe-emodin | Restores NS1-inhibited STAT1-mediated antiviral responses | Rheum palmatum L. (Da Huang) | Li et al. (2014) |
| | Ephedra alkaloids: L-ephedrine and D-pseudo- ephedrine | Regulating TLRs and RIG-1 pathways | Ephedra sinica Stapf (Ma Huang) | Wei et al. (2019) |
| Radix Isatidis extract | Promotes T, B lymphocytes | Isatis tinctoria L. (Ban Lan Gen) | Jin (2007) |
| Radix Isatidis polysaccharides | Promotes IFN-γ secretion | Isatis tinctoria L. (Ban Lan Gen) | Zuo (2008) |
| | Scaldsrisde | Reduces IL-1β, IL-6, TNF-α and CRP, increases the number of CD4 (+) T cells | Radhola crenulata (Hook.f. and Thomson) H.Ohba (Hong Jing Tian) | Lin (2020) |
| | Baicalin | Balances host inflammatory response to limit immunopathologic injury; downregulated the key factors of the RLRs signaling pathway | Scutellaria baicalensis Georgi (Huang Qin) | Pang et al. (2018) |
| | Baicalin | Inhibits TLR7/MyD88 signaling pathway | Scutellaria baicalensis Georgi (Huang Qin) | Wan et al. (2014) |
| | Biochanin A | Reduces AKT, ERK 1/2 and NF-kB | Scutellaria baicalensis Georgi (Huang Qin) | Sithisam et al. (2013) |
| | Biochanin A | Reduces IL-6, IL-8 and IP-10 | Scutellaria baicalensis Georgi (Huang Qin) | Sithisam et al. (2013) |
| | Baicalin | Inhibits IL-6 and IL-8 | Scutellaria baicalensis Georgi (Huang Qin) | Sithisam et al. (2013) |
| | Radix Isatidis polysaccharides | Suppresses pro-inflammatory IL-6 and chemokines (IP-10, MIG, and CCL-5), inhibits host TLR3 Signaling | Isatis tinctoria L. (Ban Lan Gen) | Li et al. (2017b) |
| | Wogonin | Reduces inflammatory factors | Scutellaria baicalensis Georgi (Huang Qin) | Wu (2011) |
| | Epigoitrin | Reduces mitochondria mitofusin-2, which elevated mitochondria antiviral signaling and subsequently increased IFN-β and interferon inducible transmembrane 3 (IFITM3) | Isatis tinctoria L. (Ban Lan Gen) | Luo et al. (2019) |

(Continued on following page)
| Virus | Active component | Mechanisms | Herb | References |
|---|---|---|---|---|
| Rhein | Activates TLR4, Akt, p38, JNK MAPK, and NF-κB signal pathways | Rheum palmatum L. (Da Huang) | Wang et al. (2018) |
| Baicalin | Reduces TNF-α, IL-1 and 5-HT; increases IFN-γ, | Scutellaria baicalensis Georgi (Huang Qin) | Li (2019) |
| Isatis tinctoria L. extracts | Regulates immune response by enhancing proliferation and function of T and B cells | Isatis tinctoria L. (Ban Lan Gen) | Jin (2007) |
| Dryocarssin ABBA | Decreases bronchoalveolar lavage fluid pro-inflammatory cytokines, including IL-6, TNF-α, and IFN-γ, and increases anti-inflammatory cytokines, including IL-10 and MCP-1 | Dryopteris crassihizoma Nakai (Mian Ma Guan Zhong) | Ou et al. (2015) |
| Baicalin | Increases IFN-γ production | Scutellaria baicalensis Georgi (Huang Qin) | Chu et al. (2015) |
| Lonicera Japonica Thunb polysaccharide | Increases IFN-γ | Lonicera japonica Thunb. (Jin Yin Hua) | Jia (2018) |
| Lonicera Japonica water decoction | Increases IFN-γ | Lonicera japonica Thunb. (Jin Yin Hua) | Zhu (2016) |
| Lonicerae Japonicae Los and Forsythiae Fructus | Modulates MMP pathway and PRKCA pathway | Lonicera japonica Thunb. (Jin Yin Hua) | Li (2017) |
| Forsythoside A | Reduces TLR7, MyD88 and NF-κB secretion | Forsythia suspensa (Thunb.) Vahl (Lian Qiao) | Deng et al. (2016) |
| Ethanol extracts of Forsythia suspensa Vahl. (Oleaceae), Strobilanthes cusia (Ness.) O. Kurtze (Acanthaceae), Glycyrrhiza uralensis Fischer. (Leguminosae) | Suppresses RANTES secretion | Forsythia suspensa (Thunb.) Vahl (Lian Qiao) | Ko et al. (2006) |
| Houttuynia cordata Thunb. flavonoid extracts | Inhibits TLR signaling, increases IFN-β, decreases of TLR3/4/7 and NF-κB p65(p), MCP-1, IL-8, TNF-α and MDA | Houttuynia cordata Thunb. (Yu Xing Cao) | Ling et al. (2020) |
| | | | | |
| Influenza A Virus and Influenza B Virus | | | |
| Wogonin | Increases IFN | Scutellaria baicalensis Georgi (Huang Qin) | Seong et al. (2018) |
| Arctigenin | Anti-inflammatory | Arctium lappa L. (Ni Bang Zi) | Swarup et al. (2008) |
| | | | |
| Porcine reproductive and respiratory syndrome virus | | | |
| Flavaspidic acid AB | Induces IFN-α, IFN-β, and IL1-β expression in porcine alveolar macrophages | Dryopteris crassihizoma Nakai (Mian Ma Guan Zhong) | Yang et al. (2013) |
| | | | |
| Respiratory Syncytial Virus | | | |
| Baicalin | Increases IFN-1, decreases IL-6, IL-12 | Scutellaria baicalensis Georgi (Huang Qin) | Zhang (2018) |
| Rhein | Inhibits NLRP3 inflammasome activation through NF-κB pathway | Rheum palmatum L. (Da Huang) | Shen et al. (2020) |
| 4(Z)-Quinazolone | Inhibits IFN-β secretion | Isatis tinctoria L. (Ban Lan Gen) | He et al. (2017) |
| Total alkaloids, lignans and organic acids of Radix Isatidis extracts | Regulates IFN-γ, synergistic effects through RIG-I and MDAS signaling pathways | Isatis tinctoria L. (Ban Lan Gen) | Xu et al. (2019) |
| Baicalin joint resveratrol | Increase serum TNF-α, IL-2, IFN-γ and SlgA in bronchoalveolar lavage fluid | Scutellaria baicalensis Georgi (Huang Qin) | Cheng et al. (2014) |
| Radix Glycyrrhizae water extracts | Reduces TNF-α, IL-2, IFN-γ and IL-10; increases secretion of IL-2 and IL-10 by mouse splenic lymphocytes | Glycyrrhiza glabra L. (Gan Cao) | Yeh et al. (2013) |
| SARS coronavirus | Immunomodulatory effects: stimulating mouse splenic lymphocytes | Scutellaria baicalensis Georgi (Huang Qin) | Lau et al. (2008) |
| Houttuynia cordata Thunb. Extract | | | |
| Vesicular stomatitis virus | Inhibits IFN-alpha and IFN-γ, and stimulates TNF-α and IL (IL-12, IL-10) production | Scutellaria baicalensis Georgi (Huang Qin) | Blach-Olszewska et al. (2008) |
| Baicalin | Increases IFN-γ, reduces TNF-α and IL-10 production | Scutellaria baicalensis Georgi (Huang Qin) | Orzechowska et al. (2014) |

IFN, Interferon; IL, Interleukin; MCP-1 Monocyte chemoattractant protein-1; MDAS, Melanoma differentiation-associated protein 5; MRG, Monokine induced by gamma interferon; MMP, Matrix metalloproteinases; MYD88, Myeloid differentiation factor 88; NLRP3, NLR Family Pyrin Domain Containing 3; PRKCA, Protein Kinase C Alpha; RANTES, Regulated upon activation, normal T cell expressed and presumably secreted; RIG-I, Retinoic acid-inducible gene I; STAT, Signal transducer and activator of transcription; TLR, Toll-like receptor; TNF, Tumor Necrosis Factor; TRAF2, TNF Receptor-associated Factor 2; 5-HT, 5-hydroxytryptamine.
TABLE 3 | Active anti-viral components from LHQWC and JHQGG regulating host redox homeostasis and other molecular actions.

### 3.1 Regulate redox homeostasis

| Virus                               | Active component                                | Mechanisms                                                                 | Herb                           | References        |
|-------------------------------------|-------------------------------------------------|---------------------------------------------------------------------------|--------------------------------|-------------------|
| Herpes simplex virus type 1         | Piperitenone oxide                               | Interferes with redox-sensitive cellular pathways for viral replication   | Mentha canadensis L. (Bohe)    | Civitelli et al.  |
| Japanese encephalitis virus         | Arctigenin                                       | Promotes antioxidative effects                                             | Arctium lappa L. (Nu Bang Zi)  | Swarup et al.     |
| Influenza A virus                   | Oroxylin A                                       | Activates the nuclear factor erythroid 2-related factor 2 (Nrf2) transcription to increase antioxidant activities | Scutellaria baicalensis Georgi (Huang Qin) | J et al. (2015) |
| Rhein                               |                                                 | Reduces antioxidative stress                                              | Rheum palmatum L. (DaHuang)    | Wang et al.       |
| Coxsackie virus B3                  | Emodin                                           | Up-regulates anti-oxidant enzymes                                          | Rheum palmatum L. (DaHuang)    | Cai and Luo       |
| Honeysuckle                          |                                                 | Increases myocardial SOD activity and decreases MDA                       | Isatis tinctoria L. (Ban Lan Gen) | Wang et al. (2009b) |
| Porcine epidemic diarrhea virus     | Pogostemon cablin (Blanco) Benth polysaccharides extracts | Increases SOD and GSH-Px activity and decreases MDA                       | Pogostemon cablin (Blanco)      | Wang (2010)       |
| Hepatitis C virus                   | A glycyrrhizin-containing preparation            | Protects mitochondria against oxidative stress                            | Glycyrrhiza glabra L. (Gan Cao) | Korenaga et al. (2011) |

### 3.2 Other molecular actions

| Virus                               | Active component                                | Mechanisms                                                                 | Herb                           | References        |
|-------------------------------------|-------------------------------------------------|---------------------------------------------------------------------------|--------------------------------|-------------------|
| Enterovirus 71                      | Baicalin                                         | Inhibits virus-induced apoptosis through regulating the Fas/                | Scutellaria baicalensis Georgi (Huang Qin) | Li et al. (2015) |
|                                    |                                                 | FasL signaling pathways                                                  | Houttuynia cordata Thunb.      | Chen et al.       |
| Influenza A Virus                   | Houttuynia cordata Thunb. polysaccharides extracts | Acts on intestine and microbiota                                          | Houttuynia cordata Thunb. (Yu Xing Cao) | Zhu et al. (2018) |
|                                    |                                                  | Protects intestinal barrier and regulates mucosal immunity, which may be related to the regulation of gut-lung axis | Houttuynia cordata Thunb. (Yu Xing Cao) | Wang (2015)       |
|                                    |                                                  | Reduces endothelin (ET-1) and ET-1 receptor                               | Scutellaria baicalensis Georgi (Huang Qin) | Shu et al. (2020) |
|                                    | Houttuynia cordata Thunb.polysaccharides        | Regulates the balance of Th17/Treg cells in gut-lung axis                | Houttuynia cordata Thunb. (Yu Xing Cao) | Shu et al. (2020) |
| Influenza A Virus and influenza B Virus | Wogonin                                         | Suppresses AMPK phosphorynation                                           | Scutellaria baicalensis Georgi (Huang Qin) | Seong et al. (2018) |
| Human cytomegalovirus               | Baicalin                                         | Regulates vasoactive intestinal peptide                                   | Scutellaria baicalensis Georgi (Huang Qin) | Qiao et al. (2013) |
|                                    | Artemisin                                       | Modulates cell cycle through CDKs and hypophosphorylation (activity) of the retinoblastoma protein (pRb) | Artemisia annua L. (Qing Hao) | Roy et al. (2015) |
| Herpes simplex virus type 1         | Triterpene glycyrrhizic acid                    | Induces autophagy activator Beclin 1 to establish a resistance state to viral replication | Glycyrrhiza glabra L. (Gan Cao) | Lacom et al. (2014) |

GSH-Px: Glutathione peroxidase; MDA: Malondialdehyde; SOD: Superoxide dismutase.

AMPK: AMP-activated protein kinase; CDKs: Cyclin-dependent kinases; Th17/Treg: T helper 17 (Th17)/regulatory T cells (Tregs).

energy sensor AMPK, or autophagy (Table 3; Figure 2). Detailed information regarding the TCM features, pharmacological functions of individual herbs and components was outlined in Table 4.

In terms of COVID-19, the ACE-2 has been identified as the most important receptor for SARS-CoV-2 viral entry, which constitutes the initial step of infection (Walls et al., 2020). Through informatic analysis, the Rheum palmatum L (Da Huang) in LHQWC was found to be able to suppress viral infection by directly blocking interactions between the spike protein and ACE2. In addition, in the SARS-CoV, MERS-CoV and other coronaviruses, the 3CL (3C-like) protease is one of the crucial enzymes that mediates viral replication and has been recognized as a potential therapeutic target (Pillaiyar et al., 2016; Galasiti Kankanamalage et al., 2018). These predictive evaluations showed that Scutellaria baicalensis Georgi (Huang Qin), Anemarrhena asphodeloides Bunge (Zhi Mu) and Arctium lappa L (Niu Bang Zi) in JHQGG, as well as Rheum palmatum L (Da Huang) and Houttuynia cordata Thunb (Yu Xing Cao) in LHQWC can inhibit viral transcription and replication, especially that the Rheum palmatum L (Da Huang) in LHQWC was shown as a potential inhibitor of 3CL protease, suggesting underlying mechanisms of both LHQWC and JHQGG in the treatment of COVID-19.

Since LHQWC and JHQGG are both commonly used for the treatment of influenza in China, we additionally
analyzed their possible roles in the inhibition of influenza viral invasion. Hemagglutinin (HA) on the surface of influenza virus is a tri-polymer, which promotes virus binding and entering into host cells. In contrast to HA, the neuraminidase (NA) of influenza viruses involves detachment and release of mature viruses from host cells (Gamblin and Skehel, 2010; Gaymard et al., 2016). Components of *Scutellaria baicalensis* Georgi (Huang Qin) of JHQGG have been shown to inhibit the whole life cycle of influenza viruses, such as inhibiting HA and NA, and suppressing replicons. Meanwhile, *Isatis tinctoria* L. (Ban Lan Gen) and *Rheum palmatum* L. (Da Huang) of LHQWC have also been reported to reduce the internalization and replication of influenza viruses. The shared herbs, such as *Ephedra sinica* Stapf (Ma Huang), *Lonicera japonica* Thunb (Jin Yin Hua), *Forsythia suspensa* (Thunb.) Vahl (Lian Qiao) and *Glycyrrhiza glabra* L. (Gan Cao) in both LHQWC and JHQGG were experimentally proved as inhibitors of influenza virus life cycle (Table 1; Table 1).

**DISCUSSION**

In clinical practices of TCM, medicinal herbs are generally applied in the form of decoctions, which contain mixtures of a variety of herbs with different pharmacological functions. Instead of directly inactivating pathogens, therapeutic effects of TCM decoctions are achieved mainly through balancing host anti-viral responses and pathogenic factors. During COVID-19 epidemics, synergistic therapy of LHQWC with clinically approved repurposing antivirals, such as oseltamivir, umifenovir, ribavirin, lopinavir, peramivir, penciclovir or ganciclovir, has shown its advantages in improving associated symptoms and reducing the course of hospitalization and disease progression in several reported trials (Liu M. et al., 2020; Yu, 2020a; Yu, 2020b; Cheng, 2020; Hu et al., 2020; Li et al., 2020; Lv and Wang, 2020; Xiao et al., 2020; Chen, 2021; Liu et al., 2021). Similarly, combined anti-viral treatment with JHQGG in mild or moderate COVID-19 was beneficial in relieving clinical symptoms and reducing risks of severe COVID-19 (Liu Z. et al., 2020; Duan, 2020; Duan,
### 4.1 Specific medicinal herbs of LHQWC

| Components of medicinal herbs | TCM properties | Key characteristics | Active component | Virus | Pharmacological functions | References |
|-------------------------------|----------------|---------------------|------------------|-------|---------------------------|------------|
| Rheum palmatum L. (Da Huang)  | Bitter         | Purges clumped heat in the intestines | Emodin           | Coxackie virus B3 | Decreases overall mortality of virus-induced murine viral myocarditis model and potentially could act through inhibiting viral replication, reducing pro-inflammatory cytokines and up-regulation of anti-oxidant enzymes | Cai and Luo (2014) |
|                              | Cold           | Removes blood stasis |                 | IL-17/IL-23 axis | Reduces mice mortality rate and ameliorates myocardial damage by regulating the | Jang et al. (2014) |
|                              |                | Stops bleeding in its charred form |                 | Enterovirus 71  | Inhibits viral replication and diminishes cell cycle arrest at S phase induced by EV71 infection in MRC5 cells | Zhong et al. (2017) |
|                              |                |                    | Aloe-emodin      | Herpes simplex virus type 1 | Inhibits viral replication through galectin-3 up-regulation | Li et al. (2014) |
|                              |                |                    | Rhein            | Influenza A Virus | Suppresses lung inflammatory injury by reducing the release of pro-inflammatory cytokines, including IL-1β, IL-6, TNF-a, IL-18, and IL-33, in the serum and lung tissues of RSV-induced BALB/c mice through inhibiting NLRP3 inflammasome activation via NF-κB pathway | Shen et al. (2020) |
|                              |                |                    |                   |                   |                             |            |
| Houttuynia cordata Thunb. (Yu Xing Cao) | Acrid         | Disperses heat | Houttuynoid A | Influenza A virus | Inhibits viral absorption | Wang et al. (2018) |
|                              |                |                    |                   | Human immunodeficiency virus type 1 | Inhibits the HIV-1 replication by targeting the HIV-1 reverse transcription process including inhibiting HIV-1 | Esposito et al. (2018) |
|                              |                |                    |                   | SARS coronavirus | Inhibits SARS coronavirus 3C-like protease | Luo et al. (2009) |
|                              |                |                    |                   | Extracts | Inhibits viral entry and replication in MA-104 cells | He et al. (2013) |
|                              |                |                    |                   | Rotavirus |                         | Li et al. (2017a) |
|                              |                |                    |                   |                   |                         |            |
| Isatis tinctoria L. (Ban Lan Gen) | Bitter         | Drains heat | Erucic acid | Influenza A virus | Oral administration could ameliorate lung injury in virus-infected mice via directly regulating the balance of Th17/Treg cells in gut-lung axis | Shi et al. (2020) |
|                              |                |                    |                   |                   | Acts on intestine and microbiota | Chen et al. (2019) |
|                              |                |                    |                   | Influenza A virus | Significantly inhibit viral proliferation and suppress neuraminidase activity and TLR3, TLR4, and TLR7 agonist-stimulated cytokine secretion, NF-κB p65 phosphorylation, and nuclear translocation in vitro | Ling et al. (2020) |
|                              |                |                    |                   | Extracts | Protects intestinal barrier and regulates mucosal immunity, which may be related to the regulation of gut-lung axis | Zhu et al. (2018) |
|                              |                |                    |                   | Enterovirus 71  | Reduces plaque formation and neutralizes virus-induced cytopathic effects in Vero cells and could affect apoptotic processes in virus-infected Vero cells by inhibiting viral replication | Lin et al. (2009) |
|                              |                |                    |                   | SARS coronavirus | Exerts anti-viral effects, including inhibitory effects on SARS-CoV 3C-like protease and RNA-dependent RNA polymerase. Exhibits immunomodulatory effects, including stimulating the proliferation of mouse splenic lymphocytes and increasing the proportion of CD4 (+) and CD8 (+) T cells and the secretion of IL-2 and IL-10 by mouse splenic lymphocytes | Lau et al. (2008) |
|                              |                |                    |                   | Herpes simplex virus | Inhibits the infection of HSV-1, HSV-2, and acyclovir-resistant HSV-1 via blocking viral binding and penetration. Suppresses viral replication via inhibiting NF-κB activation | Hung et al. (2015) |

(Continued on following page)
### 4.1 Specific medicinal herbs of LHQWC

| Components of medicinal herbs | TCM properties | Key characteristics | Active component | Virus | Pharmacological functions | References |
|------------------------------|----------------|--------------------|------------------|-------|--------------------------|------------|
| Cold                         |                | Resolves fire toxicity | Epigoitrin        | Influenza A virus | Reduces mitochondria mitofusin-2, which elevated mitochondria antiviral signaling and subsequently increased IFN-β and interferon inducible transmembrane 3 | Luo et al. (2019) |
| Cools the blood              |                | Benefits the throat  | 4(3H)-Quinazolone | Respiratory Syncytial Virus | Inhibits IFN-β secretion | He et al. (2017) |
|                              |                |                     | Clemastatin B, epigoitrin, phenylpropanoids portion and the mixture of phenylpropanoids, alkaloids and organic acid fractions | Influenza A virus | Inhibits viral replication, entry and improves the viability of infected MDCK cells | Xiao et al. (2016) |
|                              |                | Poly saccharide extracts |               | Influenza A virus |                          |            |
|                              |                |                     |                  |                  |                           |            |
|                              |                |                     |                  |                  |                           |            |
|                              |                |                     |                  |                  |                           |            |
|                              |                |                     |                  |                  |                           |            |
| Pogostemon cablin (Blanco)   | Sweet          | Raises qi           | Salidroside      | Influenza A virus | Relieves lung inflammation in infected mice and reduce the level of inflammatory factors, including IL-1β, IL-6, TNF-α, and C-reactive protein in both serum and lung tissue. Increases the number of CD4^+ T cells | Lin (2020) |
| (Guang Huo Xiang)            |                |                    |                  |                  |                           |            |
| Thomson H.Ohiba (Hong Jing Tian) | Bitter          | Invigorates the blood | Salidroside      | Coxsackievirus B3 | Decreases LDH release of infected cardiomyocytes and increase myocardial SOD activity and decreases MDA concentration of CVB3-induced viral myocarditis mice | Wang et al. (2009b) |
|                              |                |                     |                  |                  |                           |            |
|                              |                | Neutral             | Rhodiola         | Coxsackievirus B3 | Decreases LDH release of CVB3-infected viral myocarditis mice | Li et al. (2012) |
|                              |                | Poly saccharides extract |                  | Coxsackievirus B3 |                           |            |
|                              |                |                     |                  |                  |                           |            |
| Rhodiola crenulata (Hook.f. and Thomson H.Ohiba (Hong Jing Tian)) | Acrid          | Transform turbidity with aroma | Patchouli alcohol | Influenza A virus | Inhibits viral replication and protect cardiomyocytes against virus-induced cell apoptosis | Chen et al. (2009) |
|                                | Slightly       | Check retching       |                  | Coxsackievirus B3 |                           | Wei et al. (2013) |
|                                | Warm           | Resolve summerheat   |                  | Adenovirus       |                           |            |
|                              |                | Poly phenolic extracts |                  | Influenza A virus |                           |            |

(Continued on following page)
| Components of medicinal herbs | TCM properties | Key characteristics | Active component | Virus | Pharmacological functions | References |
|-------------------------------|----------------|--------------------|------------------|------|--------------------------|------------|
| **Arctium lappa L. (Niu Bang Zi)** | Acid | Disperses heat in the exterior and clears internal heat toxin | Arctin | Influenza A virus | Arctigenin could inhibit viral replication and suppress the release of progeny viruses from the host cells. | Hayashi et al. (2010) |
| | Bitter | Benefits the throat | Arctigenin | | | |
| | Cold | | | | | |
| **Anemarrhena asphodeloides** | Bitter, Sweet | Clears fire and nourishes the Yin of the Lungs, Stomach, and Kidneys | Chinonin | Herpes simplex virus type 1 | Suppress viral replication | Swarup et al. (2008) |
| | Cold | | (—)-(R)-nyasol, (—)-(R)-4'-O-methylnyasol | Broussonin A | Respiratory syncytial virus | Suppresses viral replication more effective than ribavirin | Bai et al. (2007) |
| **Artemisia annua L. (Qing Hao)** | Bitter | Clears all types of yin level heat without injuring the qi, blood, or Yin | Artemisinin | Coxsackievirus B3 | Inhibits viral replication | Ma (2004) |
| | Cold | | | | | |
| **Scutellaria baicalensis Geor** | Bitter | Cools heat | Baicalein | Influenza A virus | Suppresses H5N1 replication with antioxidant N-acetylcySTEINE combination | Michalis et al. (2014) |
| | Cold | Dries dampness | | | | |
| | | Stops bleeding | | | | |
| | | Quits the fetus in pregnancy | | | | |
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| **Shi et al.** | | | | | | |
### TABLE 4 (Continued) Detailed information of TCM features and pharmacological functions of single medicinal herbs from LHQWC and JHQGG.

#### 4.2 Specific medicinal herbs of JHQGG

| Components of medicinal herbs | TCM properties | Key characteristics | Active component | Virus | Pharmacological functions | References |
|------------------------------|----------------|---------------------|------------------|-------|---------------------------|------------|
| Baicalin joint resveratrol   |                | Respiratory Syncytial Virus | Increases serum TNF-α, IL-2, IFN-γ and SigA in bronchoalveolar lavage fluid | Wogonin | Suppresses both influenza A and B virus replication in MDCK and A549 cells | Cheng et al. (2014) |
|                              |                |                      |                   | 5,7,4′-trihydroxy-8-methoxyflavone | Influenza A virus | Inhibits fusion of virus with endosome/lysosome membrane | Wu (2011) |
|                              |                |                      |                   | 5,7,2′-trihydroxy- and 5,7,2′,3′-tetrahydroxyflavone | Influenza A virus | Inhibits viral replication and release | Konoshima et al. (1992) |
|                              |                |                      |                   | Oroxylin A | Influenza A Virus | Inhibits neuraminidase | Jin et al. (2018) |
|                              |                |                      |                   | Norwogonin, Oroxylin A, mosloflavone | Enterovirus 71 | Inhibits expression of viral capsid proteins | Choi et al. (2016) |
|                              |                |                      |                   | Artemisinin derivatives | Hepatitis B virus | Reduces viral release | Blazquez et al. (2013) |
|                              |                |                      |                   | Extract containing baikalein and wogonin | Vesicular stomatitis virus | Inhibits IFN-α and IFN-β, and stimulates TNF-α and IL-12 production | Blach-Olszewska et al. (2008) |
|                              |                |                      |                   | Flavonoids-enriched extracts | Influenza A virus | Exhibits antiviral activity, including inhibiting viral replication in H1N1-infected MDCK cells, decreasing lung virus titers, reducing hemagglutinin titers and inhibiting neuraminidase activities in lungs of H1N1-infected mice | Zhi et al. (2019) |
|                              |                |                      |                   | Aqueous extracts | Human immunodeficiency virus type 1 | Inhibits HIV type-1 protease activities | Lam et al. (2000) |
| Fritillaria thunbergii Miq. (Zhe Bei Mu) | Bitter Cold |                      |                   | Extracts | Influenza A virus | Inhibits virus replication in embryonated eggs and reduces H1N1-infected mice mortality rate | Kim et al. (2021) |

(Continued on following page)
### Table 4 (Continued) Detailed information of TCM features and pharmacological functions of single medicinal herbs from LHQWC and JHQGG.

| Components of medicinal herbs | TCM properties | Key characteristics | Active component | Virus | Pharmacological functions | References |
|-------------------------------|----------------|---------------------|------------------|-------|---------------------------|------------|
| **Lonicera japonica Thunb. (Jin Yin Hua)** | Sweet | Disperses heat | Chlorogenic acid | Influenza A virus | Suppresses the nucleocapsid protein expression and the release of progeny viruses by inhibiting neuraminidase activity | Ding et al. (2017) |
| | Cold | Resolves toxicity | Pheophytin | Hepatitis C virus | Inhibits HCV viral proteins and RNA and exhibits synergistic anti-HCV activity with IFNa-2a | Wang et al. (2006b) |
| | Cools the blood | Honeycomb-encoded atypical microRNA2911 | Enterovirus 71 | Influenza A virus | Inhibits EV71 replication by targeting the VP1 gene | Li et al. (2018) |
| | Stops bleeding | Polysaccharides extracts | Influenza A virus | Respiratory | Inhibits virus attachment and replication in Hela cells | Li (2010) |
| | | Extracts | Respiratory | Syncytial Virus | Inhibits viral replication and release via the microRNA let-7a targeting viral non-structural protein 1 | Lee et al. (2017) |
| | | | Dengue virus | | Inhibits viral replication and release via the microRNA let-7a targeting viral non-structural protein 1 | Lou (2017) |
| | | | Coxackie virus B3 | | Increases serum SOD activity and decreases MDA concentration of CVB3-induced viral myocarditis mice | Zhou et al. (2015) |
| **Ephedra sinica Stapf (Ma Huang)** | Acrid | Induces sweating | (+)-catechin | Influenza A virus | Suppresses viral replication by inhibiting acidification of endosomes and lysosomes | Mantani et al. (2001) |
| | Slightly bitter | Calms wheezing | L-methylephedrin, L-ephedrine, D-pseudo- ephedrine | Influenza A virus | Increases IFN-γ and decreases TNF-α level by regulating TLRs and RIG-1 pathways | Wei et al. (2019) |
| | Warm | Promotes urination | Water Extract | Respiratory | Inhibits viral absorption and penetration | Zhu and Li (2012) |
| | Slightly acid | Resolves toxicity | Forsythoside A | Influenza A virus | Inhibits virus spread by reducing influenza viral M1 protein | Law et al. (2017) |
| | Slightly cold | Disperses clumps | Phlytin | Influenza A virus | Reduces TLR7, MyD88 and NF-kB p65 protein | Deng et al. (2016) |
| | | | | | Decreases IL-6 levels, and reduces the expression of hemagglutinin in mice infected with influenza A virus | Qu et al. (2016) |
| **Forsythia suspensa (Thunb.) Vahl (Lian Qiao)** | Bitter | Cools and vents heat, particularly in the Heart and upper burner | Forsythoside A | | | |
| | Slightly acid | Resolves toxicity | Forsythoside A | | | |
| | Slightly cold | Disperses clumps | Phlytin | Influenza A virus | Inhibits viral replication | Civitelli et al. (2014) |
| **Mentha canadensis L. (Bo He)** | Acrid | Facilitates the dispersal of upper burner wind-heat | Essential oil extract, piperitenone oxide | Herpes simplex virus type 1 | Inhibits viral replication | |
| | Aromatic | Cools the upper burner and clears the eyes and head | | | | |
| | Cooling | Soothers the throat | | | | |
| | | Facilitates the flow of Liver qi and expels turbid filth | | | | |
| **Glycyrrhiza glabra L. (Gan Cao)** | Sweet | Tonifies the Spleen qi | Glycyrrhizin | Influenza A virus | Reduces endocytosis activity and virus uptake | Wolkerstorfer et al. (2009) |
| | Neutral | Moistens the Lungs | Glycyrrhizinic acid | Enterovirus 71 | Inhibits influenza virus polymerase activity | Moisy et al. (2012) |
| | | Moderates urgency and toxicity | Chalcones | Influenza A virus | Inhibits viral replication | Wang et al. (2013) |
| | | Drains fire | Triterpene glycyrrhizinic acid | Herpes simplex virus type 1 | Inhibits neuraminidase activity | Dao et al. (2011) |
| | | | 18β-glycyrrhetinic acid | Ebola virus | Induces autophagy activator Beclin 1 to establish a resistance state to viral replication | Lacconi et al. (2014) |
| | | | A glycyrrhizin-containing preparation | Hepatitis C virus | Binds to nucleoprotein | Fu et al. (2016) |
| | | | Water extracts | Respiratory | Protects mitochondria against oxidative stress | Korenaga et al. (2011) |
| | | | Ethanol extracts | Syncytial virus | Induces IFN-γ secretion | Yen et al. (2013) |
| | | | | | Suppresses RANTES secretion | Ko et al. (2008) |
These studies provide clinical evidence that combined treatment with either LHQWC or JHQGG is superior to conventional monotherapy of antivirals.

The primary conclusion of our study is that both LHQWC and JHQGG are efficient for a large range of viral diseases has supported that TCM formulae can be potentially an alternative therapy for emerging viral diseases, especially when specific drugs and vaccines have not been fully developed and applied. However, when it comes to appropriate or precise clinical applications of LHQWC and JHQGG, differences of their associated pharmacological actions turn out to be an essential point to be addressed. When comparing the anti-viral targets of LHQWC and JHQGG, both CPMs have been documented effective in interfering with viral components, with Isatis tinctoria L. (Ban Lan Gen) and Rheum palmatum L. (Da Huang) in LHQWC being the predominate viral inhibitors, followed by Lonicera japonica Thunb (Jin Yin Hua) and Houttuynia cordata Thunb (Yu Xing Cao). While in JHQGG, the Scutellaria baicalensis Georgi (Huang Qin) and subsequently Lonicera japonica Thunb (Jin Yin Hua) are the most important virucidal herbs. Typically, Scutellaria baicalensis Georgi (Huang Qin) of JHQGG have been highly nominated among all analyzed herbs contributing to suppression of the whole viral life cycle. Intriguingly, a direct virucidal activity was observed mostly in components from Scutellaria baicalensis Georgi (Huang Qin) and Anemarrhena asphodeloides Bunge (Zhi Mu) of JHQGG, though shared herbs, Lonicera japonica Thunb (Jin Yin Hua) and Glycyrrhiza glabra L (Gan Cao) were also involved. This set of data indicate that from the angle of viral life cycle, JHQGG may overweight LHQWC due to Scutellaria baicalensis Georgi (Huang Qin), and will be appropriate for patients with high fever, sore throat and cough. On the other hand, owning to existence of Rhodiola crenulata (Hook.f. and Thomson) H. Ohba (Hong Jing Tian), LHQWC may have more essential roles in the balancing of host immunity, suggesting that LHQWC could be more suitable for patients with non-efficient anti-viral immune responses.

There are some possible limitations in this study. Firstly, based on five databases, we finally included relatively more articles associated with LHQWC compared with those of JHQGG; therefore, bias could be unintendedly introduced to conclusions supporting superiority of LHQWC. Secondly, a certain number of included studies focus on Scutellaria baicalensis Georgi (Huang Qin), Isatis tinctoria L (Ban Lan Gen) and Rheum palmatum L (Da Huang); therefore, this may lead to biases that only these herbs are important as antivirals. Thirdly, the quality of articles included in this study is variable, and the judgment for potential pharmacological actions may to some degree rely on the knowledge of authors.

COVID-19 initiates with mild or moderate symptoms in most cases, and the strategy to reduce risks in evolving into severe or critical COVID-19 is highly desired. Through literature mining, we provide general evidence that both LHQWC and JHQGG are effective for mild to moderate COVID-19 patients and potentially being able to prevent the progress of COVID-19 into severe or critical conditions. As discussed above, TCM therapy fits well with the principle of HDT, and anti-viral TCM formulae generally show a broad spectrum of anti-viral properties through balancing between viral activities and host immune reactions. This has gained TCM a key advantage over target-specific anti-viral medications. Since LHQWC and JHQGG are both CPMs with clear safety information, it is imperative that application of LHQWC and JHQGG can be contextualized to worldwide combat against the emerging or re-emerging of human pandemics.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

NL, RX and JL initiated and supervised this study, NL, RX, MS, BP, and AL performed data analysis and wrote this manuscript. PS assisted in organizing and analyzing data, and ZL contributed to editing.

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Shi et al. Anti-Viral Medicinal Plants

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