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Review Article

Could herbal medicine (Soshihotang) be a new treatment option for COVID-19?: a narrative review

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ABSTRACT

Background: While the world struggles under the coronavirus disease 2019 (COVID-19) pandemic, a variety of antiviral agents and symptomatic treatments are being administered to patients and urgent clinical trials are underway. Under these circumstances, it is important to explore various possibilities for the treatment of COVID-19 including herbal medicines. Among various herbal medicines, Soshihotang (SSHT, *Xiao Chai Hu Tang* in Chinese) has been prescribed to treat various viral diseases and is used in combination with other herbal medicines depending on the patient's symptoms.
Methods: For conducting the present review, we searched electronic databases focusing on the antiviral effect of SSHT in experimental and clinical study until April 2020. The search keywords included SSHT, constituents of SSHT, and antiviral effect. We also searched for materials related to topic directly from websites and published books. Based on these search results, we summarized the results of the included materials in the form of a narrative review.
Results: In a number of recent clinical studies, treatment with SSHT improved the infection status of the respiratory and hepatobiliary systems, and experimental studies demonstrated the antiviral effect of SSHT and its components. Furthermore, SSHT are being used in China—where COVID-19 outbreak first took place—and offer a new option to treat COVID-19.
Conclusion: Based on the present evidences, it is believed that SSHT is likely to be a new therapeutic option for COVID-19. Conducting further studies might provide improved understanding regarding the use of SSHT in treating COVID-19.

Introduction

On March 11, 2020, the World Health Organization declared that the outbreak of coronavirus disease 2019 (COVID-19) is a global pandemic. The decision came as a result of 120,000 COVID-19 infections and 4300 deaths worldwide. Currently, there are no established treatments other than supportive therapies that treat the symptoms of COVID-19. However, as COVID-19 is a viral infectious disease caused by SARS-CoV-2,[1] some antiviral agents have been used for treatment. Antiviral agents such as lopinavir–ritonavir, chloroquine (including hydroxychloroquine), remdesivir, umifenovir, and ribavirin are being used, and clinical trials are ongoing.[2] However, clinical trials of lopinavir–ritonavir (a combination of the HIV protease inhibitors) in patients admitted with severe COVID-19 did not show a significant effect.[3] In addition, ribavirin is known to have specific adverse effects such as psychiatric problems,[4] making it unsuitable as a first-choice medication. Clinical trials involving remdesivir and chloroquine are still in progress. In addition to treatment with antiviral agents, interferons, steroids, intravenous immunoglobulin, antibiotics, and convalescent blood plasma are used depending on the patient's condition.[2] There is no conclusive evidence that these antiviral agents and other treatments are effective against COVID-19.[2] Consequently, there is a need to search for candidate drugs other than conventional therapies.

In this situation, China, the first country to experience COVID-19, has used traditional Chinese herbal medicine (TCHM) for the

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prevention and treatment of COVID-19 based on the experience of using TCHMs during the past epidemic of Severe Acute Respiratory Syndrome (SARS).[5,6] In the Chinese Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-Induced Pneumonia (7th Edition),[7] Qingfei Paidu Tang (QPT) has been suggested as a herbal medicine that can be used regardless of the stage of the disease, along with prescriptions for herbal medicines that are stage-specific. Based on this guideline, herbal medicine treatment has been used in more than 50% of confirmed patients with COVID-19 in a region.[8] In a recent study aimed at evaluation of the combined effect of herbal medicine and conventional treatments, the rate of symptom loss at discharge, the rate of chest computed tomography (CT) image improvement, and the rate of clinical cure were significantly improved and the rate of disease exacerbation was significantly decreased compared with those after conventional treatments only.[9] In addition, clinical trials of various oral medications and injections based on herbal medicine are underway in China.[10]

In this short narrative review, we will discuss the current clinical use and antiviral effects of Soshihotang (SSHT, *Xiao Chai Hu Tang* in Chinese, *Shosaikoto* in Japanese), which has been used in the past mainly for infectious diseases with chronic progression. In addition, we suggest the possibility of utilizing SSHT as a new therapeutic option for COVID-19.

Methods

For conducting the present review, we searched electronic databases (PubMed, Scopus, Citation Information by NII (CiNii), J-STAGE, and Korean Traditional Knowledge Portal (KTKP)) focusing on the antiviral effect of SSHT in experimental and clinical study until April 2020. The search keywords included Soshihotang (or Xiao Chai Hu Tang, Shosaikoto), Bupleuri Radix, Scutellariae Radix, Pinelliae Tuber, Ginseng Radix, Zingiberis Rhizoma Recens, Zizyphi Fructus, Glycyrrhizae Radix et Rhizoma, and antiviral effect. There was no language restriction in the searching process. In addition to searching for electronic databases, we also searched for materials related to topic directly from websites and published books.

Based on the search results, we summarized the following items in the form of a narrative review; i) indications of SSHT in classical medicine and in symptoms of COVID-19, ii) utilization status and clinical evidence of SSHT in infectious diseases, especially viral diseases, iii) antiviral effect of SSHT in experimental studies, iv) potential role of SSHT in repurposing the treatment of COVID-19, v) SSHT variants that can be used according to various clinical symptoms, and vi) cautions when using SSHT.

Results

Through the electronic databases search, we found articles evaluating the clinical usefulness of SSHT for infectious diseases, especially viral diseases (n = 11),[11–21] and experimental studies (n = 21)[22–42] for antiviral effects of SSHT and its constituents. In addition to these, we wrote this review using articles found through direct searches on websites and published books.

Indications of SSHT in classical medicine and in symptoms of COVID-19

SSHT is a traditional herbal medicine prescription that consists of a total of seven herbs (Bupleuri Radix, Scutellariae Radix, Pinelliae Tuber, Ginseng Radix, Zingiberis Rhizoma Recens, Zizyphi Fructus, and Glycyrrhizae Radix et Rhizoma) (Table 1[43]). SSHT appeared first in Shanghan Zabing Lun, a classic of traditional East Asian medicine that is thought to have been published before AD 220.[44] One part of Shanghan Zabing Lun is Shanghan Lun, translated as "Treatise on Cold-induced Diseases"—a medical classic that contains traditional medical treatments for infectious diseases with fever. In Shanghan Lun infectious diseases are categorized as "greater yang," "lesser yang," "yang brightness," "greater yin," "lesser yin," or "reverting yin" according to the stage of disease progression, and the text describes the indications and the prescriptions that could be used at each stage.[45]

Table 1
Components of Soshihotang and guidelines by the Korean Ministry of Food and Drug Safety Permit.[43]

Item	Contents
Constituents	Bupleuri Radix, Scutellariae Radix, Pinelliae Tuber, Ginseng Radix, Zingiberis Rhizoma Recens, Zizyphi Fructus, and Glycyrrhizae Radix et Rhizoma
Indications	Nausea, anorexia, gastritis, gastrointestinal weakness, fatigue, and symptoms of delayed common cold
Contraindicated in	1) Patients receiving interferons 2) Patients with liver cirrhosis and liver cancer (interstitial pneumonia can occur, which can lead to serious consequences such as death) 3) Patients with platelet counts less than 100,000/mm^3 because of liver dysfunction

SSHT has been classified as a representative prescription of "lesser yang," but it is suggested as a prescription that can be used at almost any stage of the disease. SSHT appears in several verses of Shanghan Lun, and the representative indications are as follows:

- After suffering from zhong feng syndrome with cold damage for five or six days, there is alternating chills and fever, discomfort and fullness in the chest and hypochondriac region, taciturnity with no desire to eat, a sick and discomforting feeling in the stomach and easily vomiting with any of the following possible symptoms and signs; vexation in the chest and absence of vomiting, thirst, abdominal pain, fullness and hardening below the hypochondriac region, palpitation in the epigastrium and abnormal urination, absence of thirst and slight fever on the body or cough. SSHT should be prescribed.[14]
- In yang brightness disease, when there is tidal fever, loose stool, normal urination, and fullness in the chest and costal/hypochondriac region that has not abated, SSHT might be prescribed.[46]
- In zhong feng syndrome of yang brightness disease, there are wiry, floating and big pulses, shortness of breath, fullness in the abdomen, pain in the epigastric region and costal/hypochondriac region, a sense of qi blockage under prolonged pressure, a dry nose, the absence of sweating somnolence, yellow coloration all over the body and the eyes, difficult urination, tidal fever, hiccup at times, and swelling in front of and behind the ears. The condition is slightly better after needling, but the exterior syndrome remains unchanged. If the disease has lasted for more than ten days and the pulse is still floating, SSHT might be prescribed.[46]

Considering the indications above,[46] SSHT should be prescribed when there are symptoms in fever and chest discomfort along with the symptoms of digestive tract (loss of appetite, nausea, vomiting, diarrhea, or constipation, etc.) after initial onset or within 7 days of the occurrence of infectious diseases. Based on the indications and recommendations in the Shanghan Lun, SSHT has been used for various infectious diseases, especially respiratory, gastrointestinal, and liver diseases with or without fever.

The typical clinical symptoms of COVID-19 are lower respiratory symptoms (including dry cough), high fever, and difficulty breathing. In a Chinese study of 72,314 diagnosed COVID-19 cases,[47]

approximately 14% revealed severe dyspnea (oxygen saturation of 93% or less, lung infiltration 24%), and 5% showed fatal symptoms such as respiratory failure, organ failure, dysfunction, and septic shock. There have also been reports of accompanying gastrointestinal symptoms such as nausea, vomiting, and abdominal discomfort (although the frequency is low) after the initial respiratory symptoms.[48] In another investigation in Wuhan, Hubei, the most commonly reported clinical manifestations were fever (91.7%), cough (75.0%), fatigue (75.0%), and gastrointestinal symptoms (39.6%).[49] In addition, there have been some cases that have shown only gastrointestinal symptoms from the onset. The first COVID-19 case in the United States is the representative example.[50] This patient was hospitalized with nausea and vomiting on the second day of onset and was confirmed as a COVID-19 case after the symptom of loose stool was observed on the second day of hospitalization.

The clinical appearance of COVID-19, which is accompanied by fever, respiratory and gastrointestinal symptoms at a relatively early stage, is similar to the indications of SSHT described in the medical classic, Shanghan Lun.

Utilization status and clinical evidence of SSHT in infectious diseases, especially viral diseases

SSHT has been used to treat infectious diseases caused by various bacteria and, particularly, viruses. With respiratory system infections, in particular, there have been reports of SSHT used to treat viral infections such as influenza or the common cold. In a study comparing the effects of oseltamivir in patients with influenza A,[11] SSHT treatment had an antipyretic effect equivalent to that of oseltamivir. The time required for the antipyretic effect was evaluated according to the treatment: oseltamivir (n = 8 participants), Mahwangtang (MHT, *Ma Huang Tang* in Chinese, *Maoto* in Japanese; n = 6), or SSHT (n = 6). The oseltamivir group required 2.0 ± 0.6 days for antipyretic effect, and both the MHT and SSHT groups showed antipyretic effect after 2.3 ± 1.0 days, with no significant difference between the two groups. SSHT has also been reported to be a treatment for the common cold with more than five days progress.[12] SSHT (n = 131) or placebo (n = 119) was administered to patients (25–75 years old) with colds more than 5 days after the onset of illness, accompanied by oral discomfort, anorexia, and tiredness. Within one week (7 days) after treatment, SSHT group showed better results than placebo in the overall improvement (total effective rate: 64.1% vs 43.7%, SSHT vs placebo). The SSHT group showed significant improvement in the symptoms of sore throat and tiredness in 3–4 days compared with the placebo group. After the final SSHT administration, appetite, arthralgia, and muscle pain were significantly improved compared with placebo administration. This result suggests that SSHT might be an effective treatment of the common cold with delayed progress.

In a report of a non-viral infection, pulmonary tuberculosis,[13] three treatment groups were assessed: chemotherapy alone (A group, n = 40), chemotherapy + Bojungikgitang (BJIGT, *Buzhong Yiqi Tang* in Chinese, *Hochuekkito* in Japanese) (B group, n = 31), and chemotherapy + BJIGT + SSHT (C group, n = 30). After treatment, all three groups showed increase in peripheral blood lymphocyte count. After 3 months, only group C showed a significant increase in the weight gain compared with group A, and after 5 months, group C and B showed a significant increase compared with group A (A: 3.2 kg vs B: 4.7 kg vs C: 5.3 kg). These results suggest the possibility of SSHT as an adjuvant therapy in pulmonary tuberculosis chemotherapy.

SSHT has also been used in the treatment of idiopathic interstitial pneumonia. Tanaka et al.[14] divided idiopathic interstitial pneumonia patients into a control group (n = 20) without additional medication administration and a treatment group (n = 9) administered SSHT and compared the treatment results after more than 10 months. Improvement was shown in 11.1% (1/9) of the patients in the treatment group and slight improvement (33.3%, 3 of 9 patients) was shown in the n treatment group.

SSHT has attracted much more attention for its antiviral effect in chronic hepatitis B and C. Although the Shanghan Lun did not intend for SSHT to be used in liver disease, SSHT has been used for this purpose based on indicative phrases in the text such as “yellow coloration all over the body and the eyes” and “discomfort and fullness in the chest and hypochondriac region”. In cases of hepatitis C, it was confirmed that fever, alopecia, and leukocyte levels were significantly improved following the combination therapy of SSHT and interferon compared with those following interferon monotherapy.[15] Improvements in the levels of aspartate transaminase (AST), alanine transferase (ALT), and Knodell’s histology activity index, in 38% (9/24 patients) were evident when patients were administered SSHT for 12 months.[16] In another study, SSHT was administered for three years, and fibrosis markers were regularly followed (n = 93). As a result, ALT levels were reduced in both chronic active hepatitis and chronic persistent hepatitis (CPH) patients. In addition, in CPH, procollagen III peptide (PIIIP) was normalized in 69% of cases and 7S collagen in 92% of cases, which suggests a liver fibrosis suppressive effect of SSHT in chronic hepatitis C.[17] There are an increasing number of reports of the use of SSHT in the treatment of chronic hepatitis B. In most of these studies, patients are given combination therapy of SSHT with interferon-based chemotherapy. Although there was a slight difference in the results of each study, the adjunctive or single administration treatment using SSHT showed a tendency to improve liver function, partial HBeAg negative, and reduced viral load in patients with hepatitis B compared with chemotherapy alone or placebo.[18–21] These results suggest that SSHT has an antiviral effect against the chronic hepatitis virus.

Antiviral effect of SSHT in experimental studies

As described above, SSHT has been applied to the treatment of viral diseases of the respiratory system and hepatobiliary system. The clinical results of SSHT treatment can be explained by the antiviral effects of SSHT itself and the effects of each constituent herb.

SSHT has been shown to inhibit coxsackievirus B1 infection by inducing the expression of type I interferons[22,23] and has been reported to inhibit antigen production through chemical promoters against Epstein-Barr virus.[24] It has also been reported that SSHT could prevent hepatitis C virus (HCV) disease progression by promoting interleukin-10 and -12 production.[25]

Experimental research has shown that each constituent herb in SSHT has antiviral effects. In particular, saikosaponin, a major component of Bupleuri Radix, has been reported to have antiviral activity against HCoV-22E9, a coronavirus similar to COVID-19.[22] In addition, saikosaponin A inhibits influenza A replication.[26] It has been found that ginsenoside Rb1, a major component of ginseng, can remove cytoprotective macrophages found in human immunodeficiency virus type 1 (HIV-1) infection by inhibiting the AKT pathway.[27] The most extensively studied antiviral herb is Scutellariae Radix. The major component of Scutellariae Radix, baicalin, is known to have antiviral activity against influenza A,[28,29] HIV-1,[30,31] respiratory syncytial virus (RSV),[32] dengue,[33] chikungunya,[34] duck hepatitis virus (DHV),[35,36] enterovirus,[37] and HBV.[38] Another component of Scutellariae Radix, wogonin, also has an antiviral effect against the influenza virus[39] and HBV.[40] Lastly, Glycyrrhizae Radix et Rhizoma and its components have been reported to have antiviral activity against HCV, coxsackievirus B3, DHV, influenza, rotavirus, RSV, and herpes simplex virus[41,42] (Table 2[21–42,51]).

Table 2
Antiviral effect of Soshihotang as observed in experimental studies.[21–42]

Components	Antiviral effects	References
Soshihotang	Group II: Epstein-Barr virus; Hepatitis C virus	24,25
	Group IV: Coxsackievirus	22,23
Bupleuri Radix (Saikosaponin)	Group IV: Coronavirus (HCoV-22E9)	22
	Group V: Influenza A	26
Scutellariae Radix (Baicalin)	Group IV: Chikungunya virus; Dengue; Duck hepatitis virus (DHV); Enterovirus	33–37
	Group V: Influenza A, Respiratory syncytial virus (RSV)	28,29,32
	Group VI: Human immunodeficiency virus type 1 (HIV-1)	30,31
	Group VII: Hepatitis B virus	38
Scutellariae Radix (Wogonin)	Group V: Influenza	39
	Group VII: Hepatitis B virus	40
Ginseng Radix (Ginsenoside Rb1)	Group VI: HIV-1	27
Glycyrrhizae Radix	Group I: Herpes simplex virus	42
	Group II: Hepatitis C virus	41,42
	Group III: Rotavirus	42
	Group IV: Coxsackievirus B3; DHV	42
	Group V: Influenza; RSV	42

Group of virus are determined based on Baltimore Classification.[51]
Group I: viruses possessing double-stranded DNA.
Group II: viruses possessing single-stranded DNA.
Group III: viruses possessing double-stranded RNA genomes.
Group IV: viruses possessing positive-sense single-stranded RNA genomes.
Group V: viruses possessing negative-sense single-stranded RNA genomes.
Group VI: single-stranded RNA viruses that replicate through a DNA intermediate.
Group VII: viruses possessing double-stranded DNA genomes and replicating using reverse transcriptase.

As such, SSHT has antiviral action against various RNA and DNA viruses, including coronaviruses. The pharmacological actions of SSHT are thought to support the use of SSHT to treat infectious diseases with fever since the time of Shanghan Lun, and this pharmacology gives SSHT value as a new treatment option for COVID-19.

Potential role of SSHT in repurposing the treatment of COVID-19

In China, which saw the first manifestation of COVID-19 and experienced local epidemics, treatment for the disease included TCHMs in combination with conventional therapies.[5,6] In the Chinese Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-Induced Pneumonia (7th Edition),[7] QPT has been suggested as a general treatment regimen for diagnosed patients. QPT is a new type of herbal medicine prescription that consists of a total of 21 herbs (Ephedrae Herba, Glycyrrhizae Radix et Rhizoma, Armeniacae Semen, Gypsum Fibrosum, Cinnamomi Ramulus, Alismatis Rhizoma, Polyporus, Atractylodis Rhizoma Alba, Poria Sclerotium, Bupleuri Radix, Scutellariae Radix, Pinelliae Tuber, Zingiberis Rhizoma Recens, Asteris Radix et Rhizoma, Farfarae Flos, Belamcandae Rhizoma, Asiasari Radix et Rhizoma, Dioscoreae Rhizoma, Ponciri Fructus Immaturus, Citri Unshius Pericarpium, and Agastachis Herba) It has been proposed as a prescription that can be widely used in mild to severe cases, and results of actual clinical use are now frequently being reported. In Sichuan, China, a total of 98 patients with COVID-19 were administered QPT with conventional therapies for 9 days.[52] Three days after QPT treatment, mean lymphocyte percentage, AST, ALT, and D-dimer levels were significantly normalized, and all laboratory indices were normalized in 70% of patients. Six days after treatment, mean C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were significantly normalized, and all laboratory indices were normalized in 80% of patients. After 9 days, all laboratory indices were normalized in 90% of patients. CT findings were normalized in 79 patients (80.6%). However, since this study was a single group, non-controlled study, it is difficult to interpret it as showing the definitive effect of QPT on COVID-19.

QPT is a combination of SSHT, Mahaenggamseoktang (MHGST, *Ma Xing Gan Shi Tang* in Chinese *Makyokansekito* in Japanese), Saganmahwangtang (SGMHT, *She Gan Ma Huang Tang* in Chinese, *Shagamaoto* in Japanese), and Oryeongsan (ORS, *Wulingsang* in Chinese, *Goreisan* in Japanese), and most of them have been known to have antiviral effects. Notably, SSHT is included in QPT. Although MHGST and ORS are also prescriptions with antiviral effects—MHGST inhibits RNA and protein synthesis in cases of influenza A virus[53] and ORS shows effectiveness in a clinical setting for treating infectious diarrhea caused by norovirus[54]—it is SSHT that presents the most evidence of antiviral effect. As mentioned earlier, SSHT has been used in the treatment of various infectious diseases, including respiratory and hepatobiliary diseases.[11–21] Furthermore, the antiviral action of SSHT and its constituent herbs has been verified through various experimental studies.[22–42] Based on these results, it can be assumed that the therapeutic effect of QPT on COVID-19 is derived mainly from the antiviral effects of SSHT and that the synergistic effect of symptomatic treatment with the antiviral effects of other prescriptions contributes to the total effect of SSHT.

Zhou Zhongying, a traditional Chinese medicine expert for infectious disease, and his research team are also paying attention to SSHT. Zhou Zhongying is a scholar who has been studying traditional Chinese herbal medicine treatment for various epidemic diseases (including SARS) for about 70 years.[55] Recently, Zhou Zhongying and his research team prepared a summary report, Traditional Chinese Medicine Differentiation and Treatment of New Coronavirus Pneumonia in Jiangsu Province (Version 3) based on the clinical data obtained after the epidemic of COVID-19.[56] This report had been verified by relevant experts in Jiangsu Province, China. The report gives guidelines on prescribing treatments based on the disease stage, and all of the prescriptions that were recommended for the early to middle stages of COVID-19 are based on SSHT (Early stage: SSHT + Gwakbakharyeongtang (GBHRT, *Huo Pu Xia Ling Tang* in Chinese, *Katsubokukaryoto* in Japanese), Middle stage with pattern of heat toxin and stagnant lung: SSHT + GBHRT + MHGST).

The results of a network pharmacology analysis of the effect of SSHT on COVID-19 also suggested that SSHT may be effective for early COVID-19 prevention and treatment.[57] The authors investigated 12 components of SSHT that show anti-SARS-CoV-2 activity (baicalein, beta-carotene, coptisine, formononetin, glycyrrhizic acid, kaempferol, moupinamide, quercetin, saikosaponin A, saikosaponin B2, saikosaponin D, and **7**-methoxy-2-methyl isoflavone) could be effective for pneumonia treatment and immunoregulation by acting on a total of 95 key targets (IL-6, NOS2, ESR1, etc.). Based on these results, it was assumed that SSHT could have effects such as inhibition of SARS-CoV2 activity, blocking of SARS-CoV2-invasion pathway, and suppression of cytokine storm expression. This phenomenon demonstrates multi-target and multi-directional activity, which is an advantage of herbal medicine composed of various herbs (Table 3).

Furthermore, it is necessary to pay special attention to the immunomodulatory effect of SSHT. In an experimental study using a cyclophosphamide-induced immunosuppression animal model,[58] SSHT was shown to exert an immunomodulatory effect that increases lymphocytes only in the immunosuppressive model (and is invalid in the normal animal model). In an observational study of 21 patients with COVID-19,[59] early lymphocyte degradation was observed to be a characteristic observation in the patients, suggesting that early lymphocyte degradation would have diagnostic value. Considering these serologic abnormalities associated with early COVID-19 and the immunomodulatory effect of SSHT, it

Table 3
The potential of Soshihotang as a treatment option for COVID-19.

Effects of Soshihotang	Contents	Expected effects in COVID-19
Anti-SARS-CoV-2 activity[57]	Components of soshihotang show Anti-SARS-CoV-2 activity (baicalein, beta-carotene, coptisine, formononetin, glycyrrhizic acid, kaempferol, moupinamide, quercetin, saikosaponin A, saikosaponin B2, saikosaponin D, and 7-methoxy-2-methyl isoflavone)	Inhibition of SARS-CoV-2 activity
Immunomod-ulatory effect[58]	Soshihotang increases lymphocytes only in the immunosuppressive model (invalid in the normal animal model)	Correction of early lymphocyte degradation in patients with COVID-19
Hepato-protective effects[15–21,25]	Soshihotang has been utilized in patients with HBV or HCV infection and has shown significant antiviral and hepato-protective effects	Management of liver injury in patients with COVID-19

COVID-19; coronavirus disease 2019.
HBV; Hepatitis B virus.
HCV; Hepatitis C virus.

is possible that the use of SSHT in the early to mid-term stages of the disease could be helpful (Table 3).

Finally, SSHT could also have a role in the management of liver damage in patients with COVID-19. Recently, Wang et al. emphasized more intensive or customized treatment of liver injury in patients with COVID-19 based on the recent finding that liver dysfunction occurs in 16.1–53.1% of patients with COVID-19.[60] Although liver damage in patients with COVID-19 might be caused by drug hepatotoxicity, cytokines storm, or pneumonia-associated hypoxia, considering that the results of pathological studies in patients with SARS or MERS, liver injury in patients with COVID-19 is likely to be directly affected by viral infection of liver cells.[60] Most minor liver injuries will recover without special treatment, but severe liver injuries will result in significant disease burden. As mentioned earlier, SSHT has been utilized in patients with HBV or HCV infection and has shown significant antiviral and hepato-protective effects.[15–21,25] These clinical and pharmacological evidences of SSHT will be expected to play a role in the management of liver injury in patients with COVID-19 (Table 3).

SSHT variants that can be used according to various clinical symptoms

Traditionally, SSHT has been used in combination with various prescriptions depending on the symptoms accompanying various infectious diseases. An example is given in Table 4.

As we discussed earlier, SSHT (as part of QPT) has been utilized in the COVID-19 epidemic as a basic prescription that can be used at various stages.[7,56] This history of SSHT use suggests that each prescription for each patient can be modified according to symptoms and that the antiviral action of SSHT can also form the basis of prescription.

Cautions when using SSHT

SSHT should be used with caution. The Korean Ministry of Food and Drug Safety permits the use of SSHT, except in the following contraindications (Table 1)[43]: patients receiving interferon; patients with liver cirrhosis and liver cancer (use of SSHT can lead to interstitial pneumonia, which can further cause serious consequences such as death); patients with platelet counts of less than 100,000/mm^3 owing to liver dysfunction.

Table 4
Soshihotang variant prescriptions in Traditional East Asian Medicine.

Prescription name (Chinese, Japanese)	Constituents	Indications[a]
Shihogyejitang (Chai Hu Gui Zhi Tang, Saikokeishito)	SSHT + Gyejitang (SSHT + Cinnamomi Ramulus, Paeoniae Radix)	Gastroenteritis accompanied by abdominal pain; common cold with mild fever, chilling, headache, nausea; and symptoms of delayed common cold
Shiryeongtang (Chai Ling Tang, Saireito)	SSHT + Oryeongsan (SSHT + Poria Sclerotium, Polyporus, Alismatis Rhizoma, Cinnamomi Ramulus, Atractylodis Rhizoma)	Watery diarrhea; gastroenteritis; heatstroke; and edema. These conditions accompanied by nausea, loss of appetite (anorexia), thirst and decreased urine output
Shihamtang (Chai Xian Tang, Saikanto)	SSHT + Sohamhyungtang (SSHT + Coptidis Rhizoma, Trichosanthis Semen)	Cough, chest pain originating from coughing
Shibaktang (Chai Pu Tang, Saibokuto)	SSHT + Banhahubaktang (SSHT + Poria Sclerotium, Magnoliae Cortex, Perillae Folium)	Pediatric asthma; bronchial asthma; bronchitis; cough; and anxiety. These conditions accompanied by foreign body sensation in the esophagus and throat, palpitations, dizziness, and nausea, etc.
Soshihotang ga Gilgyeong Seokgo (Xiao Chai Hu Tang jia Jiegeng Shigao, Shosaikoto ka Kikyo Sekko)	SSHT + Platycodonis Radix, Gypsum Fibrosum	Tonsillitis and peritonsillitis. These conditions accompanied by sore throat:

SSHT; Soshihotang.
[a] The indications are based on drug approvals from Korea and Japan.

It is known that administering SSHT in the above situations may cause interstitial pneumonia; therefore, use of SSHT in these situations should be avoided. In particular, because of the risk of interstitial pneumonia, using SSHT requires caution with combination with interferon. According to the COVID-19 treatment guideline of Korean Association of Internal Medicine, use of type I interferon as monotherapy is not recommended, but use of combined therapy is recommended.[61] Therefore, when considering the use of SSHT in clinical practice, it is necessary to confirm whether interferon is used or not. Moreover, there have also been case reports of pulmonary edema occurring after SSHT was used for liver dysfunction of unknown etiology.[62,63] Therefore, it is necessary to pay attention to the use of SSHT when there is a liver dysfunction of unknown cause.

Conclusions

SSHT has been used for infectious diseases for perhaps the last 1900 years, and its efficacy in infectious diseases has been scientifically established.[11–21] In particular, SSHT has been used in various viral diseases based on its antiviral effect and—if contraindications are dully considered—it can be regarded as a relatively safe medication given its long history of use. In addition, considering the indications of SSHT, and the scope of its previous usage, we think that SSHT could be prescribed for COVID-19 patients with persis-

tent fever, respiratory symptoms such as cough or sputum, and liver injury caused by conventional therapies.

Based on the evidence so far, it is believed that SSHT is likely to be a repurposing medication for COVID-19. Conducting further studies might provide improved understanding regarding the use of SSHT in treating COVID-19.

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Author contribution

Conceptualization: SK. Methodology: SK, WL, IJ. Investigation: SK, CJ, WL, and WSJ. Writing - Original Draft: SK and CJ. Writing - Review & Editing: SKM and CKH. Supervision: SK.

Conflicts of interest

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Ethical statement

Not applicable.

Data availability

Data will be made available upon request. All data used for this study are from previous studies which are included in References.

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