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Review Article

A Review of Current Clinical Research on Herbal Monotherapy for Coronavirus Disease-19 (COVID-19)

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Objectives: The purpose of this study was to evaluate the effectiveness and safety of traditional herbal medicine as a stand-alone treatment group through major English databases due to the lack of RCTs in Korea, and to provide a review of the herbal interventions used.
Methods: Using four databases (Pubmed, EMBASE, OASIS, RISS), combination of words such as "Coronavirus" "RCT" "Herb" "Decoction" "TCM" were used. RCTs using herbal medicines to treat coronavirus were searched. Final 4 studies were selected by two authors according to inclusion and exclusion criteria.
Results: A total of 1,435 patients were studied. The Chinese herbs used in the treatment group were Shengmai Yin, JingYinGuBiao granules, Jinhua Qinggan granules, and Bufei Huoxue capsules. The intervention group showed greater attenuation of pneumonia lesions on CT. Also, improvement in 6-min walk distance (6MWD), and negative conversion rate in treatment group were reported. Furthermore, scores on the Fatigue Assessment Inventory (FAI) were lower in the herbal group than in the placebo group. The median time to recovery of COVID-19 related symptoms was shorter in TCM group compared to the control group. Reported adverse effects were diarrhea, liver dysfunction, and excessive menstruation, and two papers did not mention side effects in detail.
Conclusion: Herbal medicine alone can increase the conversion rate of viral negativity and relieve COVID-19 related symptoms without significant adverse effects.

Key Words : Coronavirus, RCT, Herb, Decoction, TCM

Introduction

Coronavirus diseases 2019 (COVID-19) first came to the attention of the medical community in December 2019 when China first notified the World Health Organization (WHO) of an outbreak of pneumonia of unknown origin[1]. The subsequent surge in COVID-19 infections worldwide led the WHO to declare it a public health emergency and declare a pandemic. The global effort to treat the coronavirus during the pandemic has resulted in the development of a COVID-19 vaccine that has significantly reduced mortality rates, but questions about the safety of the vaccine and inequities in vaccine distribution have made it difficult to achieve a level of herd immunity sufficient to prevent a pandemic[2,3]. In addition, elderly patients and those with chronic conditions such as obesity, diabetes, and cardiovascular disease are still more likely to develop severe illness or die after infection with COVID-19. The emergence of new variants of

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the virus, such as the highly contagious omicron virus, among other variants, continues to pose a threat to the global public health community. According to the WHO's September 27 announcement, COVID-19 has caused approximately 770 million confirmed cases and more than 6.9 million accumulated deaths worldwide, with 34,571,873 confirmed cases and 35,934 deaths reported in South Korea as of the end of September 2023[4].

The primary symptoms of COVID-19 infection are fever, dry cough, and weakness, and some patients report nasal congestion, runny nose, sore throat, muscle aches, headache, and diarrhea. In mild cases, fever is not high and only mild weakness occurs[5], but depending on the patient's immunity and health status, severe cases may develop pneumonia and other dysfunctions such as hypoxemia, respiratory distress syndrome, septic shock, metabolic acidosis, and multiple organ failure[6]. Therefore, it is important that mild COVID-19 patients receive treatment immediately to stop the progression to severe cases. Remdesivir, Molnupiravir, and Paxlovid are currently available as oral antiviral drugs for COVID-19. Remdesivir is only supplied to medical institutions, so it may be difficult to use if self-quarantine, and Paxlovid is prioritized for patients over 60 years old who have not been vaccinated, and it is limited to patients aged 40 to 59 years old with underlying medical conditions such as cardiovascular and renal diseases.

With limited options for antivirals, WHO's Traditional Chinese Medicine (TCM) evaluation team has reported that adding TCM to conventional treatment for mild to moderate COVID-19 can shorten the time to viral clearance, accelerate the disappearance of various clinical symptoms, and shorten the length of hospitalization for patients[7]. In China, the National Administration of TCM has approved TCM for use against COVID-19[8], and in Korea, the Association of Korean Medicine issued a guideline for the treatment of coronavirus, recommending Korean medicine, also opened a Korean medicine treatment center to treat patients by prescribing Korean medicine for their symptoms[9].

Both China and Korea have used herbal medicine to respond to the coronavirus. However, compared to China, there are no randomized controlled trials (RCTs) on the treatment of COVID-19 in Korea, only case reports. Therefore, this study analyzed data searched through international databases to evaluate the efficacy and safety of herbal treatments for COVID-19 and to provide a basis for promoting the use of herbal medicine in the treatment of COVID-19.

Materials and Methods

1. Data Sources and Search Strategy

We searched for clinical trials to investigate the effectiveness of Korean medicines and their ingredients in treating coronavirus infection. The databases used were Embase, Pubmed, OASIS and RISS, and the search period was from January 1, 2013 to September 18, 2023 for studies published in the last 10 years to get the latest trends. The keywords were 'coronavirus AND herb' OR 'coronavirus AND decoction' OR 'coronavirus and tcm' AND 'rct'.

2. Inclusion and exclusion criteria

Inclusion criteria included (1) studies that treated people with COVID-19, (2) studies that used orally administered Chinese herbs in the treatment group, (3) randomized controlled trials, and (4) studies that compared pure herbal medicine to a placebo to determine the effectiveness of herbal medicines.

The exclusion criteria were (1) studies on prevention or vaccines rather than treatment, (2) studies on treatment of coronavirus-derived diseases, (3) studies that did not use oral herbal medicines but were treated in other ways such as exercise or injections, (4) studies that did not specify the ingredients of the herbal medicines used and information about the study, (5) protocol studies or pilot studies, and studies that did not involve human subjects.

3. Data Collection and Extraction

Two researchers collected and screened the data independently. We initially established inclusion criteria, then reviewed the titles and abstracts of the articles to determine whether they were relevant to the topic. Reviewed the full text of the filtered articles and agreed on the final selection. If there was any disagreement among the researchers, a third researcher intervened to determine eligibility. We extracted the country, study participant information, treatment herbs, treatment duration, outcome measures and results, and reported adverse events from each article.

Introduction

1. Study selection

The combination of ‘coronavirus’, ‘herb’, ‘decoction’, ‘tcm’ and the word ‘rct’ to screen for clinical trials resulted in 113 articles, 31 in Pubmed, 54 in Embase, 2 in OASIS and 26 in RISS. After removal of 27 duplicates, 86 studies were included. A total of 68 studies were removed through title and abstract. The reasons for exclusion included 14 protocols and pilot studies, 28 studies that were not RCTs even though they were searched for by screening for RCTs, 7 studies that did not fit the topic of this study, 16 studies that did not use herbal medicines or used non-oral treatments, 1 study that was conducted on rats rather than humans, and 2 studies with unclear herbal names. Most of the Korean studies found in OASIS and RISS were removed because they were not RCT studies. After screening, the remaining 18 studies were reviewed for full text and another 14 studies were excluded for the following reasons: 2 studies with unclear experimental information, 11 studies for combination treatment with western medicine, and 1 study for comparison with western medicine alone. Finally, 4 studies were selected, and the flow chart of the selection process is provided in Figure 1.

2. Description of the selected studies

The four selected studies are shown in Table 1. Three studies were conducted in China and one in Pakistan. One was published in 2023 and three in 2022. Two were single-center and two were multi-center studies.

1) Characteristics of participants

Characteristic of participants data from the 4

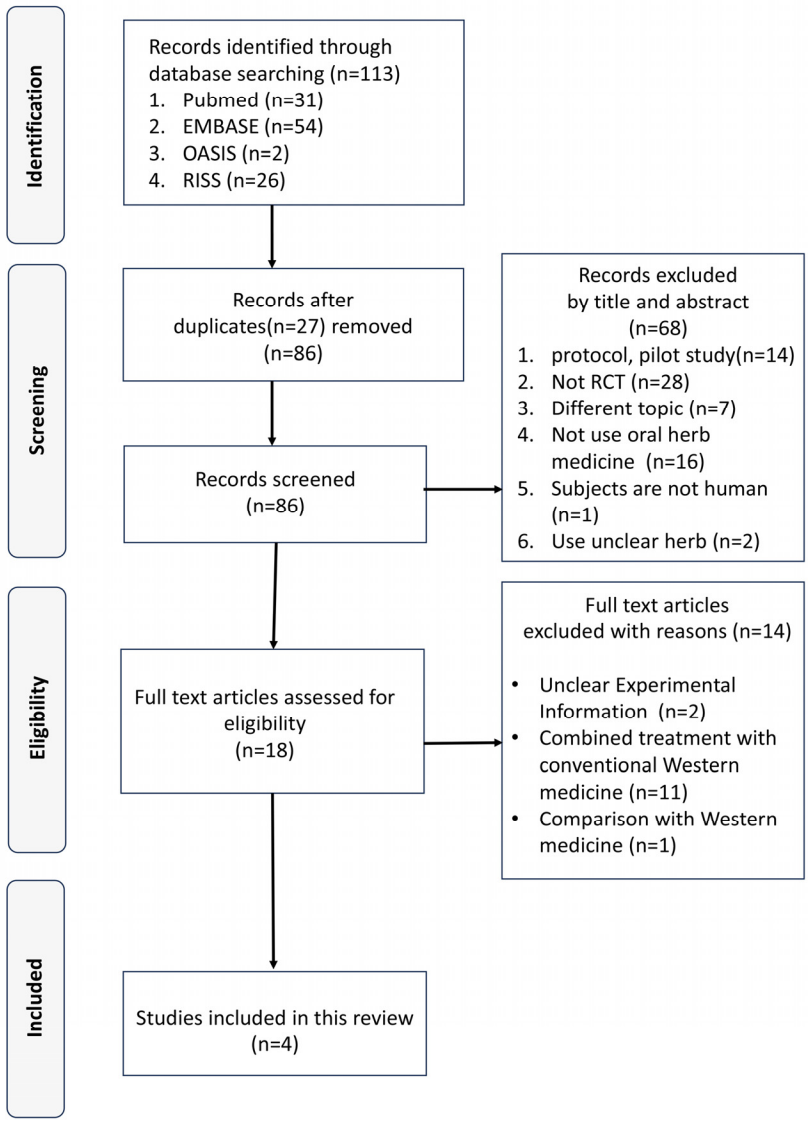

Fig. 1. Flow chart of literature selection

studies are summarized in Table 2. The total number of participants in the studies was 1,435, with the number of participants in each study range from 129[10] to 858[11]. The ratio of participants in the treatment and control groups was mostly 1:1, with a lower male gender ratio in the convalescent treatment studies. The average age ranged from 38.02 to 55 years, with a slightly higher average age in convalescent studies. Participants' COVID-19 severity ranged from asymptomatic infection, mild to moderate in two studies[11,12], and in the other two studies[10,13],

Table 1. List of Selected Studies

Author (year)	Title	Journal	Study type
An X.[13] (2023)	Effects of Shengmai Yin (生脉饮) on pulmonary and cardiac function in coronavirus disease 2019 convalescent patients with cardiopulmonary symptoms: a randomized, double blind, multicenter control trial	Journal of Traditional Chinese Medicine	Multicenter double blind randomized controlled trial
Chen B.[11] (2022)	Traditional Chinese Medicine JingYinGuBiao Formula Therapy Improves the Negative Conversion Rate of SARS-CoV2 in Patients with Mild COVID-19	International Journal of Biological Sciences	prospective, double blind randomized controlled trial
Muhammad R. S.[12] (2022)	Jinhua Qinggan granules for non-hospitalized COVID-19 patients: A double-blind, placebo-controlled, and randomized controlled trial	Frontiers in medicine	double blind randomized controlled trial
Chen Y.[10] (2022)	Efficacy and safety of Bufei Huoxue capsules in the management of convalescent patients with COVID-19 infection: A multicentre, double-blind, and randomised controlled trial	Journal of Ethnopharmacology	Multicenter double blind randomized controlled trial

Table 2. Characteristics of Study Patients

Author (year)	Sample size	Gender (Male, n%)	Average age	Severity of disease	Inclusion and exclusion criteria
An X.[13] (2023)	192	T: 98 (41, 41.83)	54	convalescent	I: 18-70yr, Conditions of recovery*: absence of fever for at least 72h, substantial improvement in both lungs in chest CT, clinical remission of respiratory symptoms, two throat-swab samples negative for SARS-CoV-2 RNA obtained at least 24h, With cardiopulmonary symptoms: with 2-3 symptoms or at least one symptom with a VAS score >4, discharged from hospital for 2-4weeks
		C: 94 (31, 32.97)	55		E: difficulty taking oral drugs /severe underlying diseases, Severe mental disorders, participating in other clinical trials, allergy, pregnancy, lactating.
Chen B.[11] (2022)	858	T: 490 (302, 61.63)	49.0	asymptomatic infections and mild	I: 18-80yr, Conditions of mild†: mild symptoms, no pneumonia on imaging.
		C: 368 (180, 48.91)	48.0		E: complicated by other active infections /severe underlying diseases (cardiovascular, metabolic disease), Severe mental disorders, allergy, pregnancy, lactating,
Muhammad R.S.[12] (2022)	256	T: 129 (91, 60.67)	38.89	mild-to-moderate	I: 18-75yr, confirmed COVID19 infection by RT-PCR, mild symptom cases with a score of <2: fever, sore throat, cough, headache, malaise, nausea, vomiting, diarrhea, myalgia, or loss of taste and smell symptoms
		C: 127 (98, 65.33)	38.02		E: previous infected COVID19, moderate or critical COVID19 infection, administered other western medicine within 3days prior to the visit /severe underlying diseases, participating in other clinical trials, allergy, pregnancy, lactating,
Chen Y.[10] (2022)	129	T: 64 (31, 48.44)	54.16	convalescent	I: >18yr, Conditions of recovery*, qi deficiency in the lung and spleen
		C: 65 (29, 44.62)	52.51		E: infections caused by other pathogen /severe underlying diseases (liver, kidney), participating in other clinical trials, allergy, pregnancy, lactating,

T: Trial group, C: Control group, I: Inclusion criteria, E: Exclusion criteria, *: Diagnosis and Treatment Guideline for COVID-19 (7th edition) for more information, †: Diagnosis and Treatment Guideline for COVID-19 (9th edition) for more information.

participants were in convalescent stage. To study patient severity and symptom improvement, we also presented criteria for selecting patient groups. The criteria for mild patients are mild symptoms (fever, sore throat, cough, headache, malaise, nausea, vomiting, diarrhea, myalgia, or loss of taste and smell symptoms), no pneumonia on imaging. The convalescent phase is characterized by decreasing fever, improvement on lung chest CT, remission of respiratory symptoms, and negative nucleic acid testing.

2) Characteristics of intervention

All of the herbal medicines were administered orally, 1 study[13] used decoction; Shengmai Yin, 2 studies[11,12] used granules processed by drying the decoction; JingYinGuBiao, Jinhua Qinggan granule, and 1 study[10] used capsule; Bufei Huoxue Capsule. Three were taken three times daily and one was taken twice daily. Treatment duration varied from 7 to 90 days, with convalescence studies generally lasting 14 to 90 days, longer than symptomatic treatment periods of 7 to 10 days. All control groups received a placebo drug, with the same dose, frequency, and duration as the treatment group. The treatment condition of the placebo group is the same as the treatment group in all four studies, but only Chen B[11]. and Chen Y[10]. describe the composition of the placebo. Chen B[11]. used 1 g each of Agastachis Herba (藿香) and Glycyrrhizae Radix et Rhizoma (甘草) to obtain a color and taste similar to JYGB. Chen Y[10]. used starch, caramel, and tartrazine to achieve the same smell, color, shape, and packaging as BFHX. Observation intervals ranged from daily to monthly. Selected studies are summarized in Table 3.

3) Endpoints and Outcomes

Endpoints consist of subjective measures such as visual analogue scales (VAS) or questionnaires for symptoms that involve patient opinion, and objective measures such as viral PCR, common blood tests, and chest imaging such as X-ray and CT. The study by An X.[13] used a VAS to assess five clinical symptoms; shortness of breath, hidrosis, chest distress, palpitations, and dry cough. The results showed that chest distress was significantly improved in the Shengmai Yin group compared to the placebo group. In Chen B.[11]'s study, the primary indicators of negative conversion rate and negative conversion time of SARS-CoV2 RNA were significantly different in the group taking JingYinGuBiao formula compared to the control group. The secondary indicators were length of hospitalization and symptom improvement, but only the length of hospitalization was significantly reduced in the treatment group. Muhammad R.S.[12]'s study used symptom improvement and a negative PCR as primary endpoints, but only clinical symptoms were significantly improved in the treatment group. In the secondary endpoints of recovery time, blood test changes, chest imaging, and Quality of life questionnaire, only recovery time and Quality of life questionnaire were significantly improved. In Chen Y.[10]'s study, the primary endpoints were improvement in chest CT and improvement in 6-minute walking distance(6MWD), both of which were significantly improved in the treatment group. Secondary endpoints included St. George's Respiratory Questionnaire (SGRQ) scores, Fatigue Assessment

Table 3. Summary of Selected Studies

Author (year)	Intervention method	Observation cycle	Efficacy endpoint	Result	Adverse Event
An X. [13] (2023)	T: Shengmai Yin 10ml, Tid for 2w C: placebo (No data)	0,1,2 weeks	VAS of clinical symptoms (shortness of breath, hidrosis, chest distress, palpitation, dry cough)	Remarkable therapeutic effects in chest distress	None
Chen B.[11] (2022)	T: JingYinGuBiao granule 15g, Bid for 7d C: placebo consists of 藿香(Agastachis Herba) 1g, 甘草(Glycyrrhizae Radix et Rhizoma) 1g	Everyday	1st negative conversion rate negative conversion time of SARS-CoV2 RNA 2nd hospitalized days symptom improvement	1st negative conversion rate 2,3,4,6 days (C<T) negative conversion time 5.0 vs 4.0 (C>T) 2nd hospitalized days 7.0 vs 6.0 (C>T)	Diarrhea (C:3, T:2)
Muhammad R.S.[12] (2022)	T: Jinhua Qinggan granule 5g, Tid for 10d C: placebo (No data)	Everyday telephone call, 0,10 day visit	1st symptom improvement negative on viral PCR 2nd time to recovery Change in blood test Change in radiographic findings Quality of life assessment	1st symptom improvement 10.74% vs 82.67% (C<T) 2nd time to recovery 11days vs 6days (C>T) QoL q. value improvement 0.44 vs 1.96 (C<T)	Mild to moderate (C:4, T:3)
Chen Y.[10] (2022)	T: Bufei Huoxue Capsule 1.4g(4cap.), Tid for 90d C: placebo consists of starch, caramel, tartrazine	Monthly follow up	1st improvement in 6MWD Improvement of chest CT 2nd FAI score SGRQ score Borg-Dyspnea Scale scores Chinese medicine syndrome scores	1st improvement of chest CT (C<T) Improvement in 6MWD (C<T) 2nd FAI score (C>T)	Abnormal liver function (C:2,T:4) Liver injury (C:0, T:1) Diarrhea (C:0, T:1) Excessive menstruation (C:1, T:0)

Bid: twice a day, Tid: 3 times a day, VAS: Visual analogue scale, w: week, d: day, C: control group, T: Treatment group, QoL q.: Quality of life questionnaire, 6MWD: 6-min walk distance, SGRQ score: St.George's Respiratory Questionnaire score, FAI score: Fatigue Assessment Inventory scores

Inventory (FAI) scores, Borg-Dyspnea Scale scores, and Chinese medicine syndrome scores, but only FAI scores were significantly reduced in the treatment group.

4) Ingredients of herbal medicine

The ingredients and medicinal characteristics of the decoction are summarized in Table 4. One prescription was used in each study. Shengmai Yin and Bufei Huoxue capsule used three herbs, while JingYinGuBiao granule (JYGB) and Jinhua Qinggan granule (JHQG) used 10 and 12 ingredients (11 botanicals and 1 mineral), respectively.

The herbs in the four prescriptions are summarized in Table 5 according to their herbal classification. A total of 25 herbs were used, with Lonicerae Flos, Astragali Radix, Glycyrrhizae Radix et Rhizoma being repeated twice. The most common category was the Cheongyeol-yak with nine herbs, especially the Cheongyeolhaedok, which included Lonicerae Flos, Forsythiae Fructus, Isatidis Radix. The second most common category was the Boik-yak, which included six herbs, many of which had Boqi properties among qi, blood, yang, and yin. The third most common category was Haepyo-yak with 5 herbs, followed by the three Hwadamjihaepyeongcheon-yak, two of which are Cheonghwayeoldam and one Jihaepyeongcheon. The remaining Banghyanghwaseup -yak and Soosap-yak are one each.

5) Adverse events

Adverse events were reported in three out of four studies. No severe adverse events occurred, and there was no significant difference in the

Table 4. Constituent of Herbal Medicine

Author (year)	Formula	Herbal medicine Ingredients			
An X.[13] (2023)	Shengmai Yin	紅蔘	Ginseng Radix		
		麥門冬	Liriopis Radix		
		五味子	Schisandrae Fructus		
Chen B.[11] (2022)	JingYinGuBiao granules	金銀花	Lonicerae Flos	板藍根	Isatidis Radix
		荊芥	Schizonepetae Spica	桔梗	Platycodonis Radix
		黃芪	Astragali Radix	蘆根	Phragmitis Rhizoma
		防風	Saposhnikoviae Radix	白朮	Atractylodis Rhizoma Alba
		藿香	Agastachis Herba	甘草	Glycyrrhizae Radix et Rhizoma
Muhammad R.S.[12] (2022)	Jinhua Qinggan granules	金銀花	Lonicerae Flos	知母	Anemarrhenae Rhizoma
		麻黃	Ephedrae Herba	牛蒡子	Arctii Fructus
		杏仁	Armeniacae Semen	青蒿	Artemisiae Annuae Herba
		黃芩	Scutellarie Radix	薄荷	Menthae Herba
		連翹	Forsythiae Fructus	甘草	Glycyrrhizae Radix et Rhizoma
		浙貝母	Fritillariae Thunbergii Bulbus	石膏	Gypsum Fibrosum
Chen Y.[10] (2022)	Bufei Huoxue capsule	補骨脂	Psoraleae Semen		
		黃芪	Astragali Radix		
		赤芍藥	Paeoniae Radix Rubra		

number of adverse events between the treatment and control groups. The studies by Chen B.[11] and Chen Y.[10] discuss adverse events in detail. Diarrhea was a common adverse event in both studies, and the most common adverse event was abnormal liver function.

Discussion

Historically, TCM has developed to treat many infectious and endemic diseases. The classical TCM book Shanghan Lun(傷寒論) categorized infectious diseases into six stages with characteristic symptoms and pulses that can be diagnosed and prescribed, which led to the development of a theory called Wenbing (溫病)[14]. Based on these theoretical systems, the combination of TCM and Western medicine in the treatment of severe acute respiratory syndrome (SARS) in 2002-2003 significantly reduced mortality by reducing the duration of fever in patients and reducing secondary infections[15,16]. This was possible because TCM prevented the virus from invading, replicating, and transcribing, as well as reducing the cytokine storm and dysregulated immunity that resulted

Table 5. Classification of Herbs for the Four Treatments.

Classifications	Herbal medicine			Number of Herbs
Cheongyeol-yak (清熱藥)	Cheongyeolsahwa (清熱瀉火)	知母	Anemarrhenae Rhizoma	9
		蘆根	Phragmitis Rhizoma	
	Cheongyeoljoseup (清熱燥濕)	黃芩	Scutellarie Radix	
	Cheongyeolyanghyeol (清熱凉血)	赤芍藥	Paeoniae Radix Rubra	
	Cheongyeolhaedok (清熱解毒):	金銀花	Lonicerae Flos	
		連翹	Forsythiae Fructus	
		板藍根	Isatidis Radix	
	Cheongheoyeol (清虛熱)	靑蒿	Artemisiae Annuae Herba	
Boik-yak (補益藥)	Boqi(補氣)	紅蔘	Ginseng Radix	6
		白朮	Atractylodis Rhizoma Alba	
		黃芪	Astragali Radix	
		甘草	Glycyrrhizae Radix et Rhizoma	
	Boyang(補陽)	補骨脂	Psoraleae Semen	
	Boeum(補陰)	麥門冬	Liriopis Radix	
Haepyo-yak (解表藥)	Balsanpunghan(發散風寒)	麻黃	Ephedrae Herba	5
		荊芥	Schizonepetae Spica	
		防風	Saposhnikoviae Radix	
	Balsanpungyeol(發散風熱)	薄荷	Menthae Herba	
		牛蒡子	Arctii Fructus	
Hwadamjihaepyeongcheon-yak (化痰止咳平喘藥)	Cheonghwayeoldam(淸化熱痰):	桔梗	Platycodonis Radix	3
		浙貝母	Fritillariae Thunbergii Bulbus	
	Jihaepyeongcheon(止咳平喘)	杏仁	Armeniacae Semen	
Banghyanghwaseup-yak (芳香化濕藥)		藿香	Agastachis Herba	1
Soosap-yak (收澁藥)	Sapjeongchooknyojidae(澁精縮尿止帶)	五味子	Schisandrae Fructus	1

from the infection[17]. In this background, the genetic information of the severe acute respiratory syndrome coronavirus (SARS-CoV) that caused SARS and the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that caused COVID-19 is about 80% similar[18,19], so the Chinese medicine that helped overcome SARS could be considered as one of the ways to treat COVID-19.

While many clinical studies and reviews have demonstrated better outcomes with combined Western medicine and TCM treatment for COVID-19 than with Western treatment alone[20], it was difficult to find studies that analyzed the effectiveness of TCM alone. Therefore, we analyzed the RCT studies that used only herbal medicines. Each of the four selected studies used a different herbal medicine as the treatment group: Shengmai Yin, JingYinGuBiao granules, Jinhua Qinggan granules, and Bufei Huoxue capsules. In accordance with the treatment period, mild cases took less than 10 days to treat, while the convalescent period took a relatively long 14-90 days. JYGB and JHQG, which were used in the shorter treatment period, can be used for patients in the acute phase of COVID-19, while SMY and BFHX can be used for the chronic phase of COVID-19 or the aftermath of what is called long COVID. Also, in terms of the stage of the disease, even if the current symptoms are mild, treatment at the beginning of the disease is more effective than treatment during the recovery period. Therefore, it is important to consider both the timing and duration of the treatment to ensure that the prescription is effective.

In all four studies, the indicators used to identify and assess patients' condition were different. Only An X.[13] used a VAS to measure subjective symptoms (shortness of breath, hydrosis, chest distress, palpitation, dry cough), while most of the studies used objective measures, with a primary and secondary indicator. In An X.[13]'s study, only chest tightness was significantly improved in the treatment group. Using objective measures, the treatment group had a higher conversion rate to virus negativity, shorter time to virus negativity, and shorter hospitalization[11]. In Muhammad.R.S.[12]'s study, there was no significant difference between the treatment and control groups in blood test results (WBC, ferritin, C-reactive protein (CRP), ALT, AST, TBIL, AKP, γ-GT, BUN and Cr), and only the reduction in recovery time of clinical symptoms (cough, sputum, sore throat, dyspnea, headache, nasal obstruction, fatigue and myalgia) in the treatment group was statistically significant. In the Muhammad study, the X-ray results did not show a significant difference between the placebo and treatment groups, but the CT results in the Chen Y.[10] study showed a significant improvement in the treatment group, which may be due to the difference in the length of the observation cycle between the Chen Y.[10] study, which had a monthly follow-up, and the Muhammad R.S.[12] study, which compared imaging after 10 days. In addition, the 6-minute walk distance increased more significantly in the treatment group than in the control group, and the improvement in fatigue and quality of life was also higher in the treatment group[10].

In all four studies, recovery from COVID-19 was faster in the treatment group than in the

control group. However, there are limitations to comparing these studies because the duration of treatment was not the same in all four studies, and the timing of testing was different in the case of imaging and blood tests. In order to compare the treatment and control groups of objective indicators in the future, it is necessary to conduct a comparative analysis with studies with similar test periods.

In addition, the number of herbs included in all four studies was different. An X.[13] and Chen Y.[10]'s study included 3 herb, Chen B.[11]'s study included 10 herbs, and Muhammad R.S.[12]'s study included 12 herbs. Of the four prescriptions, Cheongyeol-yak is the most common, followed by Boik-yak and Haepyo-yak. Notably, JingYinGuBiao granules (JYGB) and Jinhua Qinggan granules (JHQG) are a combination of two prescriptions. JYGB is a combination of Okbyeongpungsan and Eungyosan, and JHQG is a combination of Mahaenggamseoktang and Eungyosan. JYGB has been used in previous studies to treat upper respiratory tract infections, viral infections, and pneumonia, and has immunomodulatory properties that help patients recover faster from viral infections. As for JHQG, previous studies have shown that it is effective in treatment of symptoms of influenza, shortening recovery time, reducing fever time, and reducing antibiotic use. Mahaenggamseoktang[21] is mainly used clinically as an expectorant for bronchial asthma and septicemia by reducing lung heat, and Okbyeongpungsan[22] is used to prevent common colds and treat upper respiratory tract infections and chronic bronchitis as it prevents external pathogens from entering the body and enhances immunity. The common prescription in both herbal medicines are Eungyosan, which is mainly composed of Cheongyeol-yak such as Lonicerae Flos, Forsythiae Fructus, etc. Since ancient times, the cooling and detoxifying properties of Eungyosan have been used to reduce fevers and for respiratory infections such as urinary tract infections, bronchitis, and other inflammatory conditions[23].

In Korea, Yu.[24]'s study used Hyunggaeyungyo-tang and Saengmaek-san in convalescent patients, and used Saengmaek-san in common with An X.[12]'s study. In addition, Hyunggaeyungyo-tang used in combination with Cheongyeol-yak, Boik-yak, and Haepyo-yak, which are the frequent herbs in this study, are common. In Korea, the Clinical Practice Guideline of Korean Medicine for Coronavirus Disease-19 (2nd edition) provides recommended prescriptions based on the status and severity of COVID-19. Examining the entire recommended prescription composition, we compared the consistency of the prescription composition with the herbs in this study. The prescriptions composed of the herbs in this study were Mahaenggamseoktang (麻杏甘石湯), Shuanghuanglian (雙黃連), Mahaenggamseokhap Eungyosan (麻杏甘石合銀翹散), and Eungyosan (銀翹散), Sanggugeum (桑菊飮), Galgeunhaegitang (葛根解肌湯), Dalwoneum (達原飮), and Mahaenggamseokhapcheonggihwadamtang (麻杏甘石合淸氣化痰湯). Eungyosan, Sanggugeum, and Galgeunhaegitang are mainly used for mild cases, and Mahaenggamseoktang is mainly used for moderate to severe cases. In particular, Eungyosan and Galgeunhaegitang are insured herbal formulas and are recommended as accessible and

affordable prescriptions in the early stages of disease.

However, all four studies have the limitation that the number of herbs and formulations are not the same, making it difficult to identify the objectivity of the therapeutic mechanism, so it is necessary to standardize the herbs in the next study. After this study confirms the feasibility of utilizing herbal medicine as a treatment for COVID-19, it is necessary to design a systematic clinical study in Korea by compensating for the above disadvantages.

Conclusion

After reviewing four RCTs of herbal medicine alone in the treatment of COVID-19, we found the following findings.

1. Three of the four studies were RCTs conducted in China, and one was conducted in Pakistan.
2. The total number of samples was 1,435, and the ratio between treatment and control groups was mostly 1:1. In two of the studies, the patients were in mild to moderate condition, and in the other two, the patients were in convalescence.
3. The herbal medicines used in the treatment were one decoction, two granules, and one capsule: Shengmai Yin, JingYinGuBiao granules, Jinhua Qinggan granules, and Bufei Huoxue capsule. Among them, JingYinGuBiao granules and Jinhua Qinggan granules have Eungyosan in common. All control groups were given Placebo drugs.
4. The indicators were divided into subjective indicators such as clinical symptoms and objective indicators.
   1) Patients' clinical symptoms (shortness of breath, hydrosis, chest distress, palpitation, dry cough) were assessed by VAS. Recovery time from clinical symptoms (cough, sputum, sore throat, dyspnea, headache, nasal obstruction, fatigue and myalgia) and length of hospitalization were also used as indicators to assess improvement in clinical symptoms. In studies that evaluated clinical symptoms using only VAS, only chest distress was significantly reduced. Clinical symptom improvement and recovery time were more effective in the treatment group.
   2) The objective indicators were viral negative conversion rate, negative conversion time, imaging findings (X-ray, CT), laboratory findings (WBC, ferritin, C-reactive protein (CRP), ALT, AST, TBIL, AKP, γ-GT, BUN and Cr), 6-minute walking distance, quality of life questionnaire, SGRQ score, FAI score, Borg-Dyspnea Scale scores, and Chinese medicine syndrome scores. Of these, the rate of virus negative conversion and speed of time to negative conversion were significantly higher in the treatment group. Additionally, improvements in chest CT, 6MWD, and FAI scores were significant.
5. Three out of four studies reported adverse events of diarrhea, abnormal liver function, and menorrhagia, with no significant difference in the number of adverse events in the treatment and control groups.

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