

Herbal Medicine for Coronavirus Disease 2019 (COVID-19) in Children: a Literature Review

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Abstract

Herbal Medicine for Coronavirus Disease 2019 (COVID-19) in Children: a Literature Review

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Objectives

Few studies to date reviewed herbal medicines prescribed to pediatric patients with coronavirus disease 2019 (COVID-19). We aimed to summarize and analyze these herbal medicines.

Methods

Nine databases were searched for studies published up until November 24, 2020. Nine case reports and one case series involving 17 pediatric patients were included in the study. The clinical symptoms, interventions, outcomes, pattern identification, composition, and frequency of herbal medicine administration were analyzed.

Results

The symptoms of pediatric patients with COVID-19 treated with herbal medicines were mild or moderate. Herbal medicines have been used to alleviate symptoms, such as fever and cough. No adverse events were reported. All of the patients who received herbal medicines were discharged from the hospital after symptomatic relief. Pattern identification revealed that the lungs were the most affected organs. Epidemic toxins, wind, dampness, and heat were the primary etiological factors. More pediatric patients with COVID-19 were prescribed a combination of herbal and Western medicines than herbal medicines alone. The frequently used herbs include *Glycyrrhizae Radix et Rhizoma*, *Lonicerae Flos*, *Scutellariae Radix*, *Armeniacae Semen*, *Citri Reticulatae Pericarpium*, and *Astragal Radix*.

Conclusions

Our review can serve as a reference for the treatment of COVID-19 in children.

Key words: Coronavirus disease 2019, COVID-19, children, herbal medicine; Korean medicine, review

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I. Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)^{1,2}. Currently, COVID-19 is spreading rapidly worldwide, posing a serious threat to public health. As of February 1, 2021, more than 100 million confirmed cases of COVID-19 and 2 million COVID-19-attributed deaths worldwide³. It has been reported that children and adolescents accounted for approximately 13% of all COVID-19 cases⁴.

Pediatric COVID-19 patients are asymptomatic or have common symptoms, such as fever and cough. These symptoms may be accompanied by gastrointestinal symptoms, such as diarrhea^{5,6}. Children infected with COVID-19 are less likely to develop serious illnesses than adults^{7,8}. However, recent studies have shown that the hospitalization rates among children with COVID-19 are not low. Approximately one in three children in the United States is admitted to the intensive care unit due to COVID-19. This rate is similar to that reported for adults^{9,10}. In Spain, 60% of pediatric COVID-19 patients require hospitalization, and approximately 10% are admitted to the intensive care unit¹¹.

No drugs have been officially approved by the United States Food and Drug Administration for the treatment of COVID-19 in children. This has led healthcare workers to use several drugs¹². Concerns have also been raised about the high rates of antibiotic prescriptions in a state of uncertainty about specific treatment options⁵.

Traditionally, herbal medicines are used to prevent and treat viral infections. They have been shown to be effective for the treatment of respiratory infections¹³. Many clinicians have suggested that herbal medicine is effective in preventing the spread of COVID-19^{13,14}. Guidelines have been published regarding the use of herbal medicines in the diagnosis and treatment of patients with mild-to-critical COVID-19¹⁵. However, there are limited studies or reviews on the diagnosis and treatment of pediatric patients with COVID-19 using herbal medicine. Owing to dissimilarities in pharmacokinetics and pharmacodynamics between children and adults, the use of herbal medicines requires caution. In general, children have decreased ab-

sorption, metabolism, and excretion of drugs compared with adults¹⁶. Therefore, it is necessary to analyze herbal medicine treatments for pediatric patients with COVID-19 to provide additional accurate information. By reviewing articles on the treatment of COVID-19 pediatric patients with herbal medicine, we aimed to summarize and analyze oral herbal medicines for COVID-19 in children. We analyzed these medicines in terms of single or combination therapy with Western medicine, herbal composition, pattern identification, and treatment progress.

II. Materials and Methods

A. Search Strategy

Two authors performed a literature search of the electronic databases from inception to November 24, 2020. There were no language restrictions English databases included: PubMed, Cochrane Library, Embase (via Elsevier), Allied and Complementary Medicine Database (AMED) (via EBSCO), and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The Chinese databases included the Chinese National Knowledge Infrastructure Database (CNKI) and Wanfang Database. Korean databases include the Oriental Medicine Advanced Searching Integrated System (OASIS) and the Korean Association of Medical Journal database (KoreaMed).

The searches were conducted in English, Chinese, and Korean. The following search terms were used in PubMed: (coronavirus disease 2019 OR COVID-2019 OR COVID-19 OR Coronavirus OR Coronavirus Infection* OR 2019 novel coronavirus OR 2019-nCoV OR novel coronavirus pneumonia OR NCP OR severe acute respiratory syndrome coronavirus 2 OR SARS-CoV-2 OR novel coronavirus OR new coronavirus OR Wuhan seafood market pneumonia virus OR Wuhan coronavirus) AND (herbal medicine OR traditional medicine OR East Asian traditional medicine OR oriental medicine OR Chinese medicine OR Chinese herbal medicine OR Korean medicine OR herbal formula OR herb).

B. Inclusion and Exclusion Criteria

1. Types of Studies

Case reports or case series that used herbal medicine with or without Western medicine for COVID-19 were eligible.

2. Participants

Children and adolescents aged ≤ 18 years who were diagnosed with COVID-19 were included regardless of sex, race, nationality, or severity. If data on children could be extracted from a case study involving both adult and pediatric patients, the study was included in the review. However, if data on pediatric patients could not be extracted from a case study because patient information concerning adult and pediatric subjects was integrated, the study was excluded from the analysis.

3. Intervention

Any type of oral herbal medicine treatment, with or without Western medicine for COVID-19, was included. Oral herbal medicines include traditional herbal decoctions, powders, pills, ointments, and patent Chinese medicine.

4. Outcome

The primary outcomes included the following: clinical outcomes (discharge or death), conversion time to obtain negative test results for SARS-CoV-2 nucleic acids, and time to clinical recovery (abatement time of fever and duration of cough or rhinorrhea). The secondary outcomes included the following: (1) length of hospital stay, (2) total clinical effective rate = (number of cured cases + number of effective cases)/total number of cases $\times 100$ (%), (3) pulmonary function and imaging, (4) duration of mechanical ventilation, (5) quality of life, and (6) incidence of adverse events.

C. Study Selection, Data Extraction, and Data Analyses

Two independent authors searched the databases, screened the titles and abstracts of the articles, and determined the studies that met the predefined criteria. Data from

the literature were extracted independently by the authors using a standardized data extraction form. The extracted information included country name, number of trials included, clinical data on participants, interventions, and treatment outcomes. The composition of the herbal decoction prescription for each case was analyzed, and the frequency of each herbal decoction was calculated using Microsoft Office Excel 2016 (Microsoft Corporation, Redmond, WA, USA). Disagreements were discussed until consensus was reached.

D. Methodological Quality

Both authors read the papers and independently assessed their quality according to the tool for evaluating the methodological quality of case reports and case series suggested by Murad et al.¹⁷⁾. The tool comprises four domains: selection, ascertainment, causality, and reporting. These domains were evaluated using eight questions. However, questions 4 (“Were other alternative causes that may explain the observation ruled out?”), 5 (“Was there a challenge/rechallenge phenomenon?”), and 6 (“Was there a dose-response effect?”) were judged to be unrelated to our study question as they were more relevant to adverse drug events. Therefore, these three questions were excluded from the analysis. The case studies were evaluated using the remaining five questions. If all the domains were satisfied, the study was judged to be of “good quality”. If more than three domains were satisfied, the study was judged to be of “fair quality”. If one or two domains were satisfied, the study was judged to be of “poor quality”.

III. Results

A. Literature Search and Study Characteristics

The literature search identified 10,102 studies. A total of 165 studies were included by screening the titles and abstracts of 8,780 studies after removing duplicates. Finally, 10 case studies met the predefined inclusion criteria after a review of full-text articles (Figure 1)¹⁸⁻²⁷⁾. The characteristics of the included studies are summarized in

Table 1. Nine case reports and one case series were identified. Nine studies¹⁹⁻²⁷⁾ were published in China and one study was published¹⁸⁾ in Japan. Seven studies²¹⁻²⁷⁾ were published in Chinese and three studies¹⁸⁻²⁰⁾ were published in English. Among the ten studies, 17 cases with children met the inclusion criteria. Eleven children were boys and six were girls. Further, the age of 11 of the children was <10 years, and that of six of the children was 10 - 18 years. Eight children were prescribed herbal medicines alone and nine children were prescribed both herbal and Western medicines.

B. Clinical Symptoms

Thirteen pediatric patients had COVID-19 symptoms, such as fever and cough¹⁸⁻²⁵⁾ and four patients were asymptomatic^{26,27)}. The main symptoms were fever (n = 6) and cough (n = 6)^{19,21,22,25,27)}. Other respiratory symptoms include runny nose, nasal congestion, shortness of breath, and sore throat. Taste disorders were observed in two patients¹⁸⁾. Two patients had digestive symptoms, such as diarrhea²⁰⁾ and nausea²¹⁾. The details of pediatric patients in the included studies are shown in Table 2.

C. Radiologic Tests

Of the 17 included pediatric patients, 15 underwent radiologic testing¹⁹⁻²⁷⁾; 13 underwent chest CT and two patients underwent chest radiography^{21,25)}. However, the results were not reported for 4 patients who underwent chest computed tomography (CT)²⁷⁾. Therefore, 11 radiological test results were confirmed. Normal findings were

reported in three patients^{22,24)}. Imaging findings revealed lung marking thickening in three patients, small nodules and bronchovascular bundle thickening in one patient¹⁹⁾, and ground-glass opacities in one patient²⁷⁾. Furthermore, in three patients^{20,21,23)}, the findings were suggestive of pneumonia.

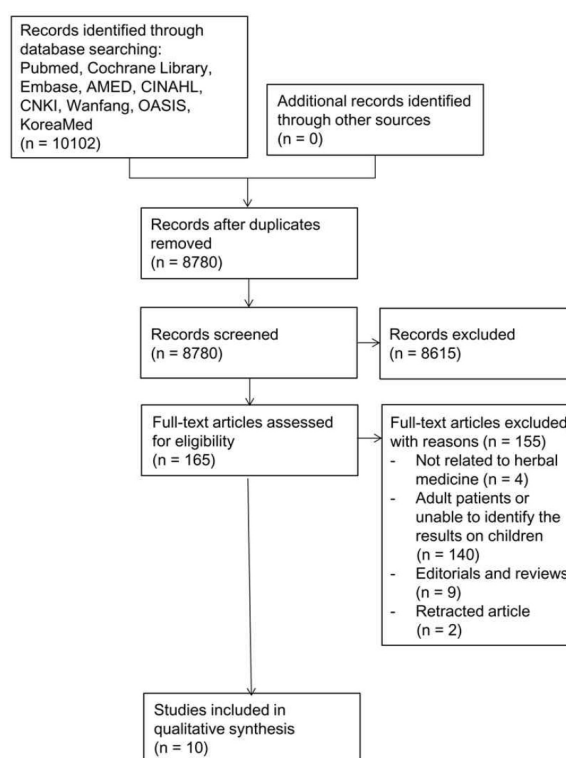


Figure 1. Flowchart of the literature search and study selection

AMED, Allied and Complementary Medicine Database; CINAHL, Cumulative Index to Nursing and Allied Health Literature; CNKI, Chinese National Knowledge Infrastructure Database; OASIS, Oriental Medicine Advanced Searching Integrated System

Table 1. Summary of the Included Studies

1 st author	Publication date	Study design	Country	Language	No. of pediatric patients who meet criteria/total cases	Age	Sex	Intervention
Irie ¹⁸⁾	September 19, 2020	Case report	Japan	English	2/3	12 and 16 years	1 M, 1 F	HM
Li et al ¹⁹⁾	May 12, 2020	Case report	China	English	1/1	3 months	M	HM + WM
Liu ²⁰⁾	June 25, 2020	Case report	China	English	1/1	23 months	M	HM
Zhu ²¹⁾	February 2020	Case report	China	Chinese	2/2	5 and 7 years	1 M, 1 F	HM
Luo ²²⁾	April 2020	Case report	China	Chinese	2/3	6 and 8 years	2 F	HM
Li ²³⁾	June 2020	Case report	China	Chinese	1/2	17 years	F	HM + WM
Li ²⁴⁾	May 2020	Case report	China	Chinese	1/2	10 years	M	HM + WM
Shang ²⁵⁾	May 2020	Case report	China	Chinese	1/1	7 years	M	HM + WM
Chen ²⁶⁾	July 2020	Case report	China	Chinese	1/1	7 years	M	HM
Hu ²⁷⁾	NA, 2020	Case series	China	Chinese	5/9	6, 8, 12, 13 years	4 M, 1 F	HM + WM

M, male; F, female; HM, herbal medicine; WM, Western medicine; NA, not available

D. Pattern Identification

The pattern identification used in the included studies was described according to the World Health Organization International Standard Terminology for Traditional Medicine²⁸. Pattern identification was used in five of the 17 patients (Table 3)^{20,21,23,25}. Pattern identification applied in the early stage of COVID-19 was “Lung qi failing to diffuse due to wind-damp”^{21,25} and “Depressed heat damaging fluid”^{22,24}. For the middle stage, “Damp-heat inner blocking and epidemic toxin blocking the lung”^{21,25} and “Damp-heat blocking upper and middle energizer, dual deficiency of qi and yin, lung and spleen qi deficiency”^{21,25} were used. In the recovery stage, “lung and spleen qi deficiencies were applied to two patients”^{21,25}. One patient, whose stage was not specified, was diagnosed with “Epidemic toxin blocking the lung”²³.

E. Intervention

1. Herbal Medicine Treatment

Herbal decoctions were prescribed to eight patients^{20-22,24,27}, patent medicine was prescribed to four patients^{18,19,25}, and both types of herbal medicines were prescribed to five patients^{23,26,27} (Table 2). In total, one – seven herbal medicines were prescribed to one patient. The names and composition of the herbal decoctions are listed in Table 3.

2. Frequency of Herbs Prescribed in Herbal Decoctions

When analyzing the herbal medicines used in each case, the most frequently prescribed herb was *Glycyrrhizae Radix et Rhizoma* (甘草, n = 13), followed by *Lonicerae Flos* (金銀花, n = 9), *Scutellariae Radix* (黃芩, n = 9), and *Armeniaca Semen* (杏仁, n = 8) (Table 4, Figure 2). The therapeutic effects, properties, flavor, and channel tropism of each herb are shown in Figure 2.

3. Western Medicine Treatment

Of the 17 included patients, eleven patients were given a combination of Western and herbal medicines. Western medicines prescribed with herbal medicines include recombinant human interferon-α2b (spray or injection)^{22,24-27},

oral antivirals (such as lopinavir/ritonavir and ribavirin tablets)^{24,26,27}, antibiotics (e.g., cefixime and azithromycin tablets)²⁶, antitussive expectorants (such as ambroxol hydrochloride oral solution)¹⁹, vitamin C tablets²⁵, and probiotics²⁵ (Table 2).

F. Outcomes

1. Primary Outcomes

All patients with COVID-19 (n = 17) in the included studies were discharged from the hospital after their symptoms had improved. No deaths were reported¹⁸⁻²⁷. The time of conversion to negative test results for SARS-CoV-2 nucleic acids after the intervention in symptomatic children (n = 12) ranged from five days to 1 month¹⁸⁻²⁶. One case series²⁷ did not report the timeframe. The duration of the symptoms after the intervention ranged from 2 to 19 days^{18,21,23-27}.

2. Secondary Outcomes

The length of hospital stay in the 13 patients ranged from 6 to 24 days^{18,19,21-25,27}. The time to improvement in chest imaging findings after the interventions in four patients ranged from 6 days to 4 weeks^{19,20,23,25}. In three patients reporting data on routine blood and biochemical tests, the test results were recorded as normal at 6 – 12 days^{19,20,23,25,26}. No adverse events related to the herbal medicines were reported in any of the included studies. In the case of Western medicine, one patient experienced nausea and vomiting during oral antiviral therapy (lopinavir/ritonavir). Hence, the therapy was discontinued²⁴. None of the studies reported outcomes, such as the total clinical effective rate, duration of mechanical ventilation, or quality of life.

G. Methodological Quality of case studies

The quality assessment of each study is presented in Table 5. Of the 10 studies, eight studies^{18-21,23-26} were evaluated as having fair quality, as they fulfilled three domains, and two studies^{22,27} were classified as having poor quality, as they fulfilled two domains. None of the studies met any of the four domains. Except for one study²⁷, the selection domain of nine studies was not fulfilled owing to lack of clarity.

Table 2. Cases of Children with COVID-19 Who Were Prescribed Herbal Medicine

Patient No. (Ref.)	Age	Sex	Symptoms	Radiologic			Herbal medicines		Results		
				Test	Findings	Western medicines	(The dose, frequency, and duration of administration of the herbal medicine are listed when available.)	Primary outcome		Secondary outcome	
								(1) Clinical outcome	(2) Time of conversion to be negative for the novel coronavirus nucleic acids after the intervention	(1) Secondary outcomes excluding adverse events	(2) Adverse events
1 ⁽¹⁸⁾	16y	F	Nasal congestion; taste disorder; no fever	NA	NA	None	Saikatsugekito (extracts of kakkonto 2.5 g; extracts of shosaiiko-kakikyosekko 2.5 g) bid for 7 days	(1) Discharged (2) 12 days (3) 12 days	(1) DH: 16 days (2) NR		
2 ⁽¹⁸⁾	12y	M	Nasal congestion; taste disorder; no fever	NA	NA	None	Saikatsugekito (extracts of kakkonto 2.5 g; extracts of shosaiiko-kakikyosekko 2.5 g) bid for 7 days	(1) Discharged (2) 12 days (3) 7 days	(1) DH: 16 days (2) NR		
3 ⁽¹⁹⁾	3mo	M	Cough; rhinorrhea; lab test: elevated ALT and AST, abnormal CK-MB, myoglobin, and troponin T; hypersensitivity	Chest CT	Small nodules in the upper and lower lobe; bronchovascular bundles thickening	Ambroxol hydrochloride oral solution (2 mL, bid), fructose sodium diphosphate oral solution (3 mL, tid) for 3 weeks	Ganxile granules (1.33 g) tid for 3 weeks	(1) Discharged (2) 1 month (3) NR	(1) Great improvement on CT images: 4 weeks; incubation: 16 days (2) NR		
4 ⁽²⁰⁾	25mo	M	Diarrhea, on the 6th day after hospitalization, elevated ALT and AST	Chest CT	suggesting pneumonia	None	Traditional Chinese medicine prescription	(1) Discharged (2) 17 days* (3) Not applicable	(1) DH: 20 days*; normal liver function upon laboratory evaluation: 12 days*; no new pulmonary lesions on chest CT: 18 days* (2) NR		
5 ⁽²¹⁾	7y	F	Cough, fever (MBT: 37.5 °C), runny nose, sore throat	Chest radiograph	Imaging showed bilateral lung markings thickening	None	(1) Modified Yin Qiao San + Liu Wei Tang (A) for 3 days (2) Modified Yin Qiao San + Liu Wei Tang (B) for 3 days	(1) Discharged (2) 6 days (3) 1 day after taking medicine, fever subsided and cough decreased; on the 6th day after admission, all the symptoms disappeared	(1) NR (2) NR		
6 ⁽²¹⁾	5y	M	Cough, fever (MBT: 38.5 °C), shortness of breath, headache, dizziness, nausea	Chest CT	Suggesting pneumonia	None	(1) Modified Ma Xing Shi Gan Tang + Gan Lu Xiao Du Dan (A) for 3 days (2) Modified Ma Xing Shi Gan Tang + Gan Lu Xiao Du Dan (B) for 5 days (3) Modified Liu Jun Zi Tang + San Ren Tang for 5 days	(1) Discharged (2) 13 days (3) 2 days after taking the medicine, the fever subsided; 8 days after admission, clinical symptoms disappeared except sputum, a little cough, and lack vigor	(1) DH: 13 days (2) NR		

Patient No. (Ref.)	Age	Sex	Symptoms	Radiologic			Results		
				Test	Findings	Western medicines	Herbal medicines (The dose, frequency, and duration of administration of the herbal medicine are listed when available.)	Primary outcome	Secondary outcome
7 ²²⁾	6y	F	Fever (MBT: 38.6°C)	Chest CT	Normal	Rehydration, supportive care, recombinant human interferon- α 2b spray bid	Oral Chinese traditional medicine	(1) Discharged (2) 5 days (3) NR	(1) DH: 6 days (2) NR
8 ²³⁾	8y	F	Fever (MBT: 37.4°C)	Chest CT	Normal	Rehydration, supportive care, recombinant human interferon- α 2b spray bid	Oral Chinese traditional medicine	(1) Discharged (2) 5 days (3) NR	(1) DH: 6 days (2) NR
9 ²³⁾	17y	F	Headache, dizziness, shortness of breath	Chest CT	Mild inflammation of the left lung	None	(1) Lianhua Qingke granules (6 g) tid for 3 days (2) Xinguan Yihaofang bid for 6 days	(1) Discharged (2) 8 days (3) 10 days	(1) DH: 10 days; normal image on chest CT: 8 days (2) NR
10 ²⁴⁾	10y	M	Sore throat	Chest CT	Normal	Nebulization (interferon), oral antiviral therapy (lopinavir/ritonavir)	(1) Qiao He Tang + Sheng Jiang San (A), tid for 4 days (2) Qiao He Tang + Sheng Jiang San (B), tid for 5 days	(1) Discharged (2) 5 days (3) NR	(1) DH: 6 days (2) HM: NR; WM (antiviral therapy): stopped taking the medicine due to nausea and vomiting
11 ²⁵⁾	7y	M	Fever (MBT: 38.3°C), cough, runny nose;	Chest radiograph	Imaging showed bilateral lung markings thickening	Recombinant human interferon- α 2b injection bid, vitamin C tablet bid; live combined Bifidobacterium, Lactobacillus, and Enterococcus capsules bid	(1) Xiao'er Chaigui Tuike granules (7.5 g) tid for 6 days; Puddilan Xiaoyan oral liquid 10 mL tid for 12 days (2) Huangqing Qingre Lishi Heji (10 mL) bid for 11 days; Xingpi Yang'er granules (6 g) for 11 days; Huangqi granules (4 g) bid for 5 days; Xiao'er Jinbai Heji (10 mL), bid for 5 days (3) Huaqihuang granules (10 g) bid for 6 days	(1) Discharged (2) Testing with nasal and throat swabs was negative: 12 days; feces sample remained positive until the 18th day after admission (3) 19 days	(1) Normal blood routine test, biochemical analysis, and chest radiograph: 6 days (2) NR
12 ²⁶⁾	7y	M	Asymptomatic	Chest CT	Imaging showed bilateral lung markings thickening	Recombinant human interferon- α 2b injection bid, antiviral therapy (ribavirin tablet, 0.075 g) tid, antibiotics (cefixime (75 mg, bid) and azithromycin tablet (0.25 g, qd))	(1) Zhengyang decoction (2) Modified Qingfei Paidu decoction 100 mL bid (3) Toujie Quwen granules 0.5 pack bid	(1) Discharged (2) 22 days (3) asymptomatic	(1) Normal blood routine test: 11 days (2) NR

Patient No. (Ref.)	Age	Sex	Symptoms	Test	Findings	Western medicines	Herbal medicines (The dose, frequency, and duration of administration of the herbal medicine are listed when available.)	Results	
								Primary outcome	Secondary outcome
13 ⁽²⁷⁾	12y	M	Asymptomatic	Chest CT	NA	α-interferon aerosol inhalation, lopinavir/ritonavir	Xinguan Yufang Erhaofang bid for 13 days	(1) Discharged (2) NR (3) Asymptomatic	(1) DH: 13 days (2) NR
14 ⁽²⁷⁾	8y	M	Cough; no fever, headache, or dizziness	Chest CT	Imaging showed ground-glass opacities in the right lung	α-interferon aerosol inhalation	Xinguan Yufang Erhaofang bid for 3 days	(1) Discharged (2) NR (3) Cough subsided: 3 days	(1) DH: 3 days (2) NR
15 ⁽²⁷⁾	13y	M	Asymptomatic	Chest CT	NA	α-interferon aerosol inhalation	Lianhua Qingke capsules + Xinguan Yufang Erhaofang for 17 days	(1) Discharged (2) NR (3) Asymptomatic	(1) DH: 17 days (2) NR
16 ⁽²⁷⁾	6y	M	Asymptomatic	Chest CT	NA	α-interferon aerosol inhalation	Lianhua Qingke capsules + Xinguan Yufang Erhaofang for 9 days	(1) Discharged (2) NR (3) Asymptomatic	(1) DH: 9 days (2) NR
17 ⁽²⁷⁾	8y	F	Fever, cough	Chest CT	NA	α-interferon aerosol inhalation, lopinavir/ritonavir	Lianhua Qingke capsules + Xinguan Yufang Erhaofang for 24 days	(1) Discharged (2) NR (3) Fever and cough subsided: 2 days	(1) DH: 24 days (2) NR

y, year; mo, months; F, female; M, male; NA, not available; DH, duration of hospitalization; NR, not reported; bid, 2 times a day; tid, 3 times a day; qd, once a day; CT, computed tomography; ALT, alanine aminotransferase; AST, aspartate transaminase; CK-MB, creatine kinase myocardial band; MBT, maximum body temperature; *The date of hospitalization was calculated on the first day of hospitalization as day 0.

Table 3. Herbal Medicines and Pattern Identifications for Treating Pediatric Patients with COVID-19

Herbal formula	Composition of herbal formula (Latin name) (for 1 day)	Pattern Identification (stage of disease)	Patient NO. (Reference)
Saikatsugokito (柴葛解肌湯)*	<i>Puerariae Radix</i> (葛根), <i>Ephedrae Herba</i> (麻黃), <i>Cinnamomi Cortex Spissus</i> (肉桂), <i>Paeoniae Radix Alba</i> (白芍藥), <i>Zingiberis Rhizoma Recens</i> (生薑), <i>Glycyrrhizae Radix et Rhizoma</i> (甘草), <i>Bupleuri Radix</i> (柴胡), <i>Scutellariae Radix</i> (黃芩), <i>Pinellia Rhizoma</i> (半夏), <i>Ginseng Radix</i> (人參), <i>Gypsum Fibrosum</i> (石膏)	NR	1, 2 ¹⁸⁾
Ganxile (肝鬱) granulé*	<i>Schizandrae Fructus</i> (五味子), <i>Acanthopanaxis Senticosii Radix et Caulis</i> (刺五加)	NR	3 ¹⁹⁾
Chinese traditional medicine (prescription name: NR)	<i>Puerariae Radix</i> (葛根) 9 g, <i>Lophatheri Herba</i> (淡竹葉) 6 g, <i>Poria Sclerotium</i> (茯苓) 6 g, <i>Forsythiae Fructus</i> (連翹) 6 g, <i>Craegi Fructus</i> (山楂) 6 g, <i>Massa Medicata Fermentata</i> (神麴) 6 g, <i>Hordei Fructus Germinatus</i> (麥芽) 6 g, <i>Armeniacae Semen</i> (杏仁) 4 g, <i>Amomi Fructus</i> (砂仁) 4 g	NR	4 ²⁰⁾
Modified Yin Qiao San + Liu Wei Tang (銀翹散合六味湯加減) (A)	<i>Lonicerae Flos</i> (金銀花) 6 g, <i>Forsythiae Fructus</i> (連翹) 6 g, <i>Platycodonis Radix</i> (桔梗) 6 g, <i>Glycyrrhizae Radix et Rhizoma</i> (甘草) 6 g, <i>Schizonepetae spica</i> (荊芥) 6 g, <i>Siposhnikovia Radix</i> (防風) 3 g, <i>Cicadae Periostracum</i> (蝉蛻) 6 g, <i>Bombyx Batryticatus Herba</i> (蠶香) 3 g, <i>Agastachis Herba</i> (藿香) 6 g	Lung Qi failing to diffuse due to wind-damp (the early stage)	5 ²¹⁾
Modified Yin Qiao San + Liu Wei Tang (B)	<i>Forsythiae Fructus</i> (連翹) 6 g, <i>Platycodonis Radix</i> (桔梗) 6 g, <i>Glycyrrhizae Radix et Rhizoma</i> (甘草) 6 g, <i>Schizonepetae spica</i> (荊芥) 6 g, <i>Siposhnikovia Radix</i> (防風) 3 g, <i>Cicadae Periostracum</i> (蝉蛻) 6 g, <i>Bombyx Batryticatus Herba</i> (蠶香) 3 g, <i>Agastachis Herba</i> (藿香) 6 g		
Modified Ma Xing Shi Gan Tang + Gan Lu Xiao Du Dan (麻杏石甘湯合甘露消毒湯加減) (A)	<i>Ephedrae Herba</i> (麻黃) 3 g, <i>Armeniacae Semen</i> (杏仁) 3 g, <i>Gypsum Fibrosum</i> (石膏) 15 g, <i>Scutellariae Radix</i> (黃芩) 6 g, <i>Acori graminei Rhizoma</i> (石菖蒲) 6 g, <i>Fritillariae Bulbus</i> (貝母) 6 g, <i>Agastachis Herba</i> (藿香) 6 g, <i>Agastachis Herba</i> (藿香) 6 g, <i>Belamcandae Rhizoma</i> damp-heat inner blocking, epidemic toxin blocking	the lung (the middle stage)	6 ²¹⁾
Modified Ma Xing Shi Gan Tang + Gan Lu Xiao Du Dan (B)	<i>Armeniacae Semen</i> (杏仁) 3 g, <i>Scutellariae Radix</i> (黃芩) 6 g, <i>Acori graminei Rhizoma</i> (石菖蒲) 6 g, <i>Fritillariae Bulbus</i> (貝母) 6 g, <i>Agastachis Herba</i> (藿香) 6 g, <i>Amomi Fructus</i> (砂仁) 6 g, <i>Platycodonis Radix</i> (桔梗) 6 g, <i>Aurantii Fructus Pericarpium</i> (枳殼) 6 g, <i>Massa Medicata Fermentata</i> (神麴) 6 g, <i>Hordei Fructus Germinatus</i> (麥芽) 9 g		
Modified Liu Jun Zi Tang + San Ren Tang (六君子湯合三仁湯加減)	<i>Pseudostellariae Radix</i> (太子參) 6 g, <i>Atractylodes Rhizoma Alba</i> (白朮) 6 g, <i>Poria Sclerotium</i> (茯苓) 10 g, <i>Glycyrrhizae Radix et Rhizoma</i> (甘草) 3 g, <i>Citri Reticulatae Pericarpium</i> (陳皮) 3 g, <i>Pinelliae Praeparatum cum Zingiberis</i> (薑半夏) 3 g, <i>Amomi Fructus</i> (杏仁) 6 g, <i>Coicis Semen</i> (薏苡仁) 9 g, <i>Lophatheri Herba</i> (淡竹葉) 6 g	Lung and spleen Qi deficiency (the recovery stage)	6 ²¹⁾
Oral Chinese traditional medicine (prescription name: NR)*	<i>Ephedrae Herba</i> (麻黃), <i>Armeniacae Semen</i> (杏仁), <i>Gypsum Fibrosum</i> (石膏), <i>Glycyrrhizae Radix et Rhizoma</i> (甘草), <i>Cinnamomi Ramulus</i> (桂枝), etc.+	NR	7, 8 ²²⁾
Xinguan Yihoufang (新冠1號方)	<i>Lonicerae Flos</i> (金銀花) 10 g, <i>Forsythiae Fructus</i> (連翹) 10 g, <i>Imperatae Rhizoma</i> (白茅根) 30 g, <i>Armeniacae Semen</i> (杏仁) 10 g, <i>Scutellariae Radix</i> (黃芩) 10 g, <i>Fritillariae Bulbus</i> (貝母) 10 g	epidemic toxin blocking the lung (stage: NR)	9 ²³⁾
Qiao He Tang and Sheng Jiang San (A) (麴荷湯合升降散)	<i>Lonicerae Flos</i> (金銀花) 5 g, <i>Menthae Herba</i> (薄荷) 1 g, <i>Scrophulariae Radix</i> (玄參) 6 g, <i>Cicadae Periostracum</i> (蝉蛻) 3 g, <i>Bombyx Batryticatus</i> (白僵蠶) 3 g, <i>Hordei Fructus Germinatus</i> (麥芽) 6 g, <i>Platycodonis Radix</i> (桔梗) 2 g, <i>Isatidis Radix</i> (板藍根) 5 g, <i>Ophiopogonis Radix</i> (麥門冬) 5 g	depressed heat damaging fluid (the early stage)	10 ²⁴⁾
Qiao He Tang and Sheng Jiang San (B) (麴荷湯合三仁湯加減)	<i>Forsythiae Fructus</i> (連翹) 5 g, <i>Menthae Herba</i> (薄荷) 1 g, <i>Scrophulariae Radix</i> (玄參) 6 g, <i>Cicadae Periostracum</i> (蝉蛻) 3 g, <i>Bombyx Batryticatus</i> (白僵蠶) 3 g, <i>Hordei Fructus Germinatus</i> (麥芽) 6 g, <i>Isatidis Radix</i> (板藍根) 5 g, <i>Ophiopogonis Radix</i> (麥門冬) 5 g, <i>Fritillariae Bulbus</i> (貝母) 6 g, <i>Rhei Rhizoma</i> (大黃) 3 g, <i>Curcumae Longae Rhizoma</i> (薑黃) 2 g		

Herbal formula	Composition of herbal formula (Latin name) (for 1 day)	Pattern Identification (stage of disease)	Patient NO. (Reference)
Xiao'er Chaigui Tuire (小兒柴胡退熱) granule*	<i>Bupleuri Radix</i> (柴胡), <i>Cinnamomi Ramulus</i> (桂枝), <i>Puerariae Radix</i> (葛根), <i>Spirodelae Herba</i> (浮萍), <i>Scutellariae Radix</i> (黃芩), <i>Paeoniae Radix Alba</i> (白芍藥), <i>Cicadae Periostracum</i> (蟬蛻)		
Pudilan Xiaoyan (浦地藍消炎) oral liquid*	<i>Isatidis Radix</i> (板藍根), <i>Corydalis Bungeanae Herba</i> (苦地丁), <i>Taraxci Herba</i> (蒲公英), <i>Scutellariae Radix</i> (黃芩)		
Huangqin Qingre Lishi Heji (黃芩清熱利濕合劑)	<i>Artemisiae Capillaris Herba</i> (茵陳蒿) 25 g, <i>Poria Sclerotium</i> (茯苓) 15 g, <i>Alismatis Rhizoma</i> (澤瀉) 15 g, <i>Polyporus</i> (豬苓) 15 g, <i>Chrysanthemi Flos</i> (甘菊) 15 g, <i>Taraxci Herba</i> (蒲公英) 15 g, <i>Viola Herba</i> (地丁) 15 g, <i>Lonicerae Flos</i> (金銀花) 15 g, <i>Begonia Fimbristipula Hance</i> (紫背天葵) 15 g, <i>Atractylodis Rhizoma Alba</i> (白朮) 6 g, <i>Cinnamomi Ramulus</i> (桂枝) 1 g	NR	11 ²⁵⁾
Xingpi Yang'er (醒脾養兒) granules (咖啡香)	<i>Emilia sonchifolia</i> (一點鐘), <i>Gerbera piloselloides</i> (毛大丁草), <i>Pitosporum illicitoides Makino</i> (山柰茶), <i>Valeriana jatamansi</i> (佛手香)		
Huangqi (黃芪) granules*	<i>Astragali Radix</i> (黃芪)		
Xiao'er Jinbai Heji (小兒金百合劑)	<i>Fagopyri Cymosi Radix et Rhizoma</i> (開金鎖) 12 g, <i>Scutellariae Radix</i> (黃芩) 9 g, <i>Mori Radicis Cortex</i> (桑白皮) 9 g, <i>Stemona Radix</i> (百部根) 9 g, <i>Asteris Radix</i> (紫菀) 9 g, <i>Peucedani Radix</i> (前胡) 9 g, <i>Armeniacae Semen</i> (杏仁) 9 g, <i>Eriobotryae Folium</i> (枇杷葉) 9 g		
Huajiqi Huang (槐杞黃) granules*	<i>Trametes robiniophila Murr</i> (槐耳), <i>Lycii Fructus</i> (枸杞子), <i>Polygonati Rhizoma</i> (黃精)		
Zhengyang decoction (正陽湯煎)	<i>Astragali Radix</i> (黃芪) 10 g, <i>Mori Radicis Cortex</i> (桑白皮) 10 g, <i>Atractylodis Rhizoma Alba</i> (白朮) 6 g, <i>Rhizoma Zingiberis Preparata</i> (炮乾薑) 4 g, <i>Pseudostellariae Radix</i> (太子參) 10 g, <i>Paeoniae Radix Alba</i> (白芍藥) 6 g, <i>Belamcandae Rhizoma</i> (射干) 3 g, <i>Glycyrrhizae Radix et Rhizoma</i> (甘草) 3 g, <i>Scrophulariae Radix</i> (玄參) 6 g, <i>Lonicerae Flos</i> (金銀花) 6 g		
Modified Qingfei Paidu decoction (清肺解毒湯加減)	<i>Glycyrrhizae Radix et Rhizoma</i> (甘草) 6 g, <i>Armeniacae Semen</i> (杏仁) 9 g, <i>Gypsum Fibrosum</i> (石膏) 15 - 30 g, <i>Alismatis Rhizoma</i> (澤瀉) 9 g, <i>Polyporus</i> (豬苓) 9 g, <i>Atractylodis Rhizoma Alba</i> (白朮) 9 g, <i>Poria Sclerotium</i> (茯苓) 15 g, <i>Scutellariae Radix</i> (黃芩) 6 g, <i>Pinelliae Praeparatum cum Zingiberis</i> (薑半夏) 9 g, <i>Zingiberis Rhizoma Recens</i> (生薑) 9 g, <i>Asteris Radix</i> (紫菀) 9 g, <i>Farfarae Flos</i> (款冬花) 9 g, <i>Belamcandae Rhizoma</i> (射干) 9 g, <i>Dioscoreae Rhizoma</i> (山藥) 12 g, <i>Citri Reticulatae Pericarpium</i> (陳皮) 6 g, <i>Agastachis Herba</i> (藿香) 9 g	NR	12 ²⁶⁾
Xinguan Yufang Erhaofang (新冠藥方號方)	<i>Astragali Radix</i> (黃芪) 30 g, <i>Lonicerae Flos</i> (金銀花) 15 g, <i>Citri Reticulatae Pericarpium</i> (陳皮) 9 g, <i>Jujubae Fructus</i> (大棗) 10 g, <i>Glycyrrhizae Radix et Rhizoma</i> (甘草) 7 g	NR	13-17 ²⁷⁾

*No description of the medication dose; NR, not reported; +etc., in the reference literature, all the herbs were not described, and were indicated as "etc. (et cetera)"; † A modified Qingfei Paidu decoction excluded Ephedrae Herba (麻黃), *Cinnamomi Ramulus* (桂枝), *Bupleuri Radix* (柴胡), *Asari Radix et Rhizoma* (細辛), and *Aurantii Fructus Immaturus* (枳實) from the original decoction.

Table 4. Frequency of Herbs Used in the Herbal Decoction for the COVID-19 in Children

Herb	Frequency	Therapeutic Effect	Property	Flavor	Channel Tropism
Glycyrrhizae Radix et Rhizoma	13	Qi-tonifying	natured	sweet	heart, lung
Lonicerae Flos	9	Heat-clearing	cold	sweet	lung, stomach
Scutellariae Radix	9	Heat-clearing	cold	bitter	lung, stomach, large intestine
Armeniacae Semen	8	Expectorant & cough-suppressing	(slightly) warm	bitter	lung, large intestine
Citri Reticulatae Pericarpium	7	Qi-regulating	warm	bitter, pungent	lung, spleen
Astragali Radix	7	Qi-tonifying	warm	sweet	lung, spleen
Forsythiae Fructus	6	Heat-clearing	(slightly) cold	bitter	lung, heart
Gypsum Fibrosum	6	Heat-clearing	cold	pungent	lung, stomach
Jujubae Fructus	5	Qi-tonifying	warm	sweet	spleen, stomach
Agastachis Herba	5	Dampness-resolving	(slightly) warm	pungent	spleen, stomach
Puerariae Radix	5	Exterior-relieving	(slightly) cold	pungent, sweet	spleen, stomach
Ephedrae Herba	5	Exterior-relieving	warm	pungent	lung, bladder
Cicadae Periostracum	5	Exterior-relieving	cold	sweet	lung, liver

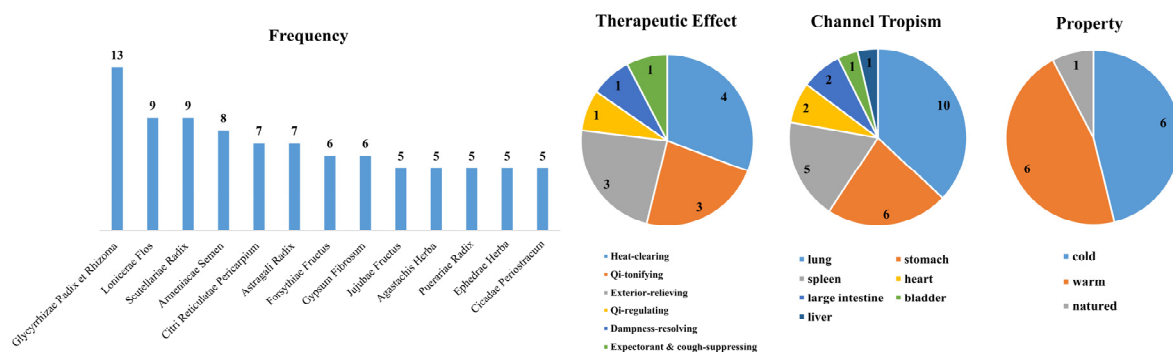


Figure 2. Frequency of herbs used in the herbal decoction for the management of pediatric COVID-19

Table 5. Evaluation Results Based on the Tool for Assessing the Methodological Quality of Case Reports and Case Series

1 st author	Selection ¹	Ascertainment ²	Ascertainment ³	Causality ⁴	Reporting ⁵	Judgement
Irie ¹⁸⁾	0	1	1	1	1	Fair
Li ¹⁹⁾	0	1	1	1	1	Fair
Liu ²⁰⁾	0	1	1	1	1	Fair
Zhu ²¹⁾	0	1	1	1	1	Fair
Luo ²²⁾	0	1	1	1	0	Poor
Li ²³⁾	0	1	1	1	1	Fair
Li ²⁴⁾	0	1	1	1	1	Fair
Shang ²⁵⁾	0	1	1	1	1	Fair
Chen ²⁶⁾	0	1	1	1	1	Fair
Hu ²⁷⁾	1	1	0	0	0	Poor

¹Do the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentations may not have been reported?; ²Was the exposure adequately ascertained?; ³Was the outcome adequately ascertained?; ⁴Was the follow-up long enough for outcomes to occur?; ⁵Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners to make inferences related to their own practice?; 0 = No; 1 = Yes

IV. Discussion

The severity of COVID-19 clinical manifestations was divided into four categories: mild, moderate, severe, and critical²⁹. In the included studies, the severity of symptoms in children who received herbal medicine for COVID-19 was primarily mild or moderate. There were no cases of tachypnea, shock, or respiratory failure that required mechanical ventilation. It is known that clinical symptoms in pediatric COVID-19 patients are less severe than those in adults due to reduced expression of angiotensin-converting enzyme 2 (ACE2) receptors, an infectious pathway of SARS-CoV-2^{5,30}. Most mild or moderate disease stages in pediatric COVID-19 patients who received herbal treatment may originate from these general clinical features. However, as only a few studies were included in this review, it may be difficult to generalize the indications for herbal treatment in pediatric COVID-19 patients to mild or moderate stages. According to randomized controlled trial studies in adults, it has been reported that the range of subjects treated with herbal medicines range between mild and critical cases³¹. In epidemiological studies on COVID-19 in children in China, 2.7%-5.8% of cases were severe or critical³²⁻³⁴. Therefore, additional studies are required to examine the severe and critical stages in pediatric COVID-19 patients treated with herbal medicine.

In the included cases, eight out of 11 patients showed abnormal imaging findings, such as thickening of lung tissue and bronchovascular bundles, similar to the previously reported chest X-ray features³⁵. A European multicenter study of 82 medical institutions found that 47% of pediatric COVID-19 patients had radiographic findings suggestive of pneumonia and 25% had symptoms of lower respiratory tract infection³⁶. These cases often require intensive care unit admission. Hence, when treating pediatric COVID-19 patients with herbs, chest imaging with X-rays and CT is required in addition to diagnostic tests for SARS-CoV-2.

Lung dysfunction is a major consequence of COVID-19 infection. However, it is necessary to carefully observe not only respiratory symptoms, but also abnormalities in oth-

er organ systems. Among pediatric COVID-19 patients treated with herbal medicine, although respiratory symptoms were mild, cases of liver and myocardial damage were observed via blood tests^{19,20}. Abnormal liver enzymes are common in children with COVID-19. They also serve as prognostic factors for assessing COVID-19^{37,38}. Cardiovascular disease is emerging as one of the most important and life-threatening complications of adult COVID-19 patients³⁹. The overall severity of heart disease associated with COVID-19 infection appears to be much lower in children than in adults. However, multi-system inflammatory syndrome (MIS-C), which may occur in children during COVID-19, is associated with cardiac complications. Therefore, caution should be exercised^{40,41}.

All pediatric patients with COVID-19 in the included studies were discharged from the hospital after their symptoms improved. Pediatric patients with COVID-19 have a favorable prognosis and regain their health within 1 - 2 weeks of disease onset⁸. None of the studies reported any adverse effects of herbal medicine treatments with or without Western medicine in children with COVID-19. It has been reported that mild pediatric COVID-19 patients recover 1 - 2 weeks after onset⁶. Herbal medicine has been reported to reduce the duration of fever and hospitalization. However, there is insufficient evidence on its effect on the recovery period of pediatric COVID-19 patients³¹.

The COVID-19 treatment guidelines recommend that infectious diseases be treated according to the stage of the disease and via pattern identification during herbal medicine treatment^{29,42}. Of the 17 patients, 5 who were treated using pattern identification were prescribed various herbal medicines according to the changes in their symptoms or based on the findings of tongue examinations^{21,23-25}. The lungs were the most affected organs. Epidemic toxins, wind, dampness, and heat were the main etiologies, and the pattern identification used in the studies had some similarities with those used in the article in the guideline review⁴². For example, "epidemic toxins blocking the lungs, lung, and spleen qi deficiency" were mentioned in the guideline review^{21,42}. In the guideline review of COVID-19 treatment, pattern identification and prescriptions were divided according to disease⁴². However,

according to our study, pattern identification belonging to the stage was not fixed. For example, “lung and spleen qi deficiency” is a pattern identification used mainly in the recovery stage. However, it can also be used in the middle stage. It was reported that “Lung and spleen qi deficiency” could occur by inducing “Dual deficiency of qi and yin” due to “damp-heat” in the middle stage^{21,25}).

Thirteen herbs were used more than 5 times. Except *Jujubae Fructus*, these herbs have been frequently used to treat COVID-19^{31,42-45}. In particular, *Lonicerae Flos*, *Scutellariae Radix*, *Forsythiae Fructus*, *Gypsum Fibrosum*, *Ephedrae Herba*, and *Cicadae Periostracum* mainly have lung channel tropism, heat-clearing, and exterior-relieving effects, which have been associated with the classification of COVID-19 as a lung-afflicting damp-heat epidemic and the frequent use of antipyretic herbs for treatment^{44,46}.

The use of qi-tonifying and spleen/stomach channel tropism formed another characteristic of the prescribed herbal medicine. Therapeutic strategies for qi-tonifying and invigorating the spleen/stomach were concerned with not only treating the disease but also helping with recovery. In particular, invigorating the spleen/stomach can remove damp^{47,48}. *Astragali Radix* (7 times) and *Jujubae Fructus* (5 times) were warm-natured and had spleen channel tropism. *Astragali Radix* has been shown to tonify qi, remove sputum, and treat COVID-19-related renal damage^{49,50}. *Astragali Radix* is rarely used in other stages. However, it is often used in the recovery stage of COVID-19 patients⁴². There have been no reports of pattern identification or disease stage in patients prescribed *Astragali Radix*. However, the efficacy of these herbs allowed us to speculate that these pediatric COVID-19 patients were in a deficiency syndrome or stage of recovery^{26,27}. The frequent use of *Jujubae Fructus* for the treatment of pediatric COVID-19 patients was a distinct feature. *Jujubae Fructus* is traditionally used to tonify qi, treat blood deficiency, and improve the overall nutritional status^{51,52}. *Jujubae Fructus* was prescribed together with *Astragali Radix*; therefore, it could be speculated that this combination was used to tonify qi and ameliorate the deficiency syndrome in pediatric COVID-19 patients.

Glycyrrhizae Radix et Rhizoma, which was used a total of 13 times, was the most commonly used herb. This is

consistent with a previous study that *Glycyrrhizae Radix et Rhizoma* was the most frequently used herbal medicine for all stages, including mild, moderate, severe, and recovery⁴². This is most likely because *Glycyrrhizae Radix et Rhizoma* has antiviral effects and is used as an adjuvant treatment in most herbal prescriptions⁴³. *Lonicerae Flos* (nine times) has been used to prevent respiratory viral diseases since ancient times and has been found to be efficacious in the treatment of patients with H1N1 influenza virus and adenovirus infections^{53,54}. Additionally, a study using in silico screening showed that *Lonicerae Flos* binds to ACE2 to exhibit an anti-COVID-19 effect⁵⁵. Furthermore, the combination of *Lonicerae Flos* and *Forsythiae Fructus* (six times) has been reported as a key herbal combination for treating COVID-19⁵⁵. *Forsythiae Fructus* is one of the five most frequently used herbs for treating COVID-19^{31,43,44}. *Forsythiae Fructus* has been reported to be effective against viral bronchitis. Hence, its efficacy in the treatment of COVID-19 may be related to this effect⁴⁴.

Scutellariae Radix (nine times) had a heat-clearing effect and could inhibit the infection of viruses and bacteria; thus, it could be used to treat upper respiratory tract infection of COVID-19^{31,45}. In particular, the combination of *Scutellariae Radix* and *Glycyrrhizae Radix et Rhizoma* (13 times) has been reported to act on immune disease targets⁴⁵. *Armeniacae Semen* (eight times) is an herb used for pediatric asthma, and one guideline review reported it to be the most used herb in patients with pediatric COVID-19⁵⁶. Amygdalin, the active ingredient of *Armeniacae Semen*, has a strong affinity for ACE2. Therefore, it is speculated that it can block the spread of SARS-CoV-2⁵⁷. The combination of *Armeniacae Semen* and *Ephedrae Herba* (five times) was the most frequently used couplet medicines for the treatment of COVID-19⁵⁸.

According to a review of COVID-19 guidelines, *Citri Reticulatae Pericarpium* (seven times) is the most frequently used herb to treat COVID-19⁴³. *Citri Reticulatae Pericarpium* has antipyretic properties and is effective in removing phlegm^{59,60}. In addition, *Citri Reticulatae Pericarpium* is often paired with *Glycyrrhizae Radix et Rhizoma* (13 times) to treat respiratory problems. A combination of these two herbs has been used to treat the symptoms of fatigue and fever^{43,61}. *Gypsum Fibrosum* is

mainly used for moderate and severe stages, and in particular, when high fever is confirmed, it is additionally used^{31,42}. *Agastachis Herba* was used five times, and another study reported it to be the most commonly used drug for the treatment of COVID-19⁴³. *Agastachis Herba* has been reported to be used in the mild and moderate stages of COVID-19⁴². *Puerariae Radix* has an exterior-relieving effect and is often used to treat COVID-19, and the combination of *Puerariae Radix* and *Glycyrrhizae Radix et Rhizoma* is often prescribed for the treatment of COVID-19⁴⁵. *Cicadae Periostracum* has also been frequently used to treat COVID-19 and has been reported to be used specifically for the mild stage^{45,62}.

More pediatric patients with COVID-19 were prescribed a combination of herbal medicines and Western medicine than herbal medicines alone (Table 2). Recombinant human interferon- α 2b, antibiotics, and antivirals are primarily used in Western medicine. Compared with Western medicine alone, herbal medicine combined with Western medicine has been reported to reduce the duration of clinical symptoms, fever, and cough; improve radiological and nucleic acid tests; and increase the recovery rate. No significant difference in adverse events were observed⁶³. Considering this aspect and the ethical issue that a placebo cannot be administered to a control group, it is necessary to proceed with a trial comparing the effects of a combination of herbal medicine and Western medicine with those of Western medicine alone in future clinical trials with children.

We analyzed case reports and a case series of herbal medicine treatment for pediatric COVID-19 patients. Several case studies have applied the proposed tool to methodological quality assessment⁶⁴⁻⁶⁶. When evaluating the methodological quality of the case studies included in our study, most studies demonstrated fair quality^{18-21, 23-26}. In the selection domain, most of the studies included in our study were judged to be unsatisfactory. There was no information on how the cases were selected and there was a possibility of selection bias¹⁷. In addition, it was determined that the reporting domain was not satisfied in two of the included case studies^{22,27}. There is insufficient information regarding treatment and clinical processes that other researchers or clinicians can fully uti-

lize in clinical practice.

Knowledge of the pathogenesis and treatment of pediatric COVID-19 is incomplete⁵. Our review could be used as a reference for herbal medicine treatment of COVID-19 in children. However, this study had several limitations. The number of patients was small and the studies were retrospective. This makes it difficult to draw conclusions regarding the therapeutic effects and safety of herbal medicine treatment for children with COVID-19. In future studies, it is important to accumulate more cases of pediatric patients treated with herbal medicine.

V. References

1. Bourgonje AR, Abdulle AE, Timens W, Hillebrands JL, Navis GJ, Gordijn SJ, Bolling MC, Dijkstra G, Voors AA, Osterhaus AD, van der Voort PH, Mulder DJ, van Goor H. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). *J Pathol.* 2020;251(3):228-48.
2. Dong M, Zhang J, Ma X, Tan J, Chen L, Liu S, Xin Y, Zhuang L. ACE2, TMPRSS2 distribution and extrapulmonary organ injury in patients with COVID-19. *Biomed Pharmacother.* 2020;131:110678.
3. Wang C, Wang Z, Wang G, Lau JY, Zhang K, Li W. COVID-19 in early 2021: current status and looking forward. *Signal Transduct Target Ther.* 2021;6(1):114.
4. Parcha V, Booker KS, Kalra R, Kuranz S, Berra L, Arora G, Arora P. A retrospective cohort study of 12,306 pediatric COVID-19 patients in the United States. *Sci Rep.* 2021;11(1):10231.
5. Borrelli M, Corcione A, Castellano F, Fiori Nastro F, Santamaria F. Coronavirus disease 2019 in children. *Front Pediatr.* 2021;9:668484.
6. Alsohime F, Temsah MH, Al-Nemri AM, Somily AM, Al-Subaie S. COVID-19 infection prevalence in pediatric population: etiology, clinical presentation, and outcome. *J Infect Public Health.* 2020;13(12):1791-6.
7. Society of Pediatrics, Chinese Medical Association; Editorial Board, Chinese Journal of Pediatrics. Recom-

- mendations for the diagnosis, prevention and control of the 2019 novel coronavirus infection in children (first interim edition). *Zhonghua Er Ke Za Zhi*. 2020; 58(3):169-74.
8. Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, Rovida F, Baldanti F, Marseglia GL. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. *JAMA Pediatr*. 2020;174(9):882-9.
 9. Kim L, Garg S, O'Halloran A, Whitaker M, Pham H, Anderson EJ, Armistead I, Bennett NM, Billing L, Como-Sabetti K, Hill M, Kim S, Monroe ML, Muse A, Reingold AL, Schaffner W, Sutton M, Talbot HK, Torres SM, Yousey-Hindes K, Holstein R, Cummings C, Brammer L, Hall AJ, Fry AM, Langley GE. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the U.S. coronavirus disease 2019 (COVID-19)-associated hospitalization surveillance network (COVID-NET). *Clin Infect Dis*. 2020;72(9):e206-14.
 10. Kim L, Whitaker M, O'Halloran A, Kambhampati A, Chai SJ, Reingold A, Armistead I, Kawasaki B, Meek J, Yousey-Hindes K, Anderson EJ, Openo KP, Weigel A, Ryan P, Monroe ML, Fox K, Kim S, Lynfield R, Bye E, Shrum Davis S, Smelser C, Barney G, Spina NL, Bennett NM, Felsen CB, Billing LM, Shiltz J, Sutton M, West N, Talbot HK, Schaffner W, Risk I, Price A, Brammer L, Fry AM, Hall AJ, Langley GE, Garg S; COVID-NET Surveillance Team. Hospitalization rates and characteristics of children aged <18 years hospitalized with laboratory-confirmed COVID-19 - COVID-NET, 14 states, March 1 - July 25, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(32):1081-8.
 11. Tagarro A, Epalza C, Santos M, Sanz-Santaefemia FJ, Otheo E, Moraleda C, Calvo C. Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid, Spain. *JAMA Pediatr*. 2021;175(3):316-7.
 12. Ferorelli D, Spagnolo L, Marrone M, Corradi S, Silvestre M, Misceo F, Bianchi FP, Stefanizzi P, Solarino B, Dell'Erba A, Tafuri S. Off-label use of COVID-19 vaccines from ethical issues to medico-legal aspects: an Italian perspective. *Vaccines (Basel)*. 2021;9(5):423.
 13. Nugraha RV, Ridwansyah H, Ghozali M, Khairani AF, Atik N. Traditional herbal medicine candidates as complementary treatments for COVID-19: a review of their mechanisms, pros and cons. *Evid Based Complement Alternat Med*. 2020;2020:2560645.
 14. Panyod S, Ho CT, Sheen LY. Dietary therapy and herbal medicine for COVID-19 prevention: a review and perspective. *J Tradit Complement Med*. 2020;10(4):420-7.
 15. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, Fang C, Huang D, Huang LQ, Huang Q, Han Y, Hu B, Hu F, Li BH, Li YR, Liang K, Lin LK, Luo LS, Ma J, Ma LL, Peng ZY, Pan YB, Pan ZY, Ren XQ, Sun HM, Wang Y, Wang YY, Weng H, Wei CJ, Wu DF, Xia J, Xiong Y, Xu HB, Yao XM, Yuan YF, Ye TS, Zhang XC, Zhang YW, Zhang YG, Zhang HM, Zhao Y, Zhao MJ, Zi H, Zeng XT, Wang YY, Wang XH. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res*. 2020;7(1):4.
 16. Fernandez E, Perez R, Hernandez A, Tejada P, Arteta M, Ramos JT. Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. *Pharmaceutics*. 2011;3(1):53-72.
 17. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med*. 2018;23(2):60-3.
 18. Irie Y, Nakae H, Fukui S. Three mild cases of coronavirus disease 2019 treated with saikatsugekito, a Japanese herbal medicine. *Traditional & Kampo Medicine*. 2020; 8(1):111-4.
 19. Li C, Luo F, Wu B. A 3-month-old child with COVID-19: a case report. *Medicine (Baltimore)*. 2020;99(23):e20661.
 20. Liu Q, Zhang Y, Long Y. A child infected with severe acute respiratory syndrome coronavirus 2 presenting with diarrhea without fever and cough: A case report. *Medicine (Baltimore)*. 2020;99(33):e21427.
 21. Zhu YL, Yang BB, Wu F. Understanding of COVID-19 in children from different perspectives of traditional Chinese medicine and western medicine. *Chin Tradit Herb Drugs*. 2020;51(4):883-7.
 22. Luo S, Zhou C, Zhang Y, Huang H, Yang H, Cheng

- Y, Zhen X, Zhang Y. Three child cases of COVID-19 in Henan province: a clinical analysis. *Chin J Clin Infect Dis.* 2020;2(13):109-12.
23. Li X, Li L, Zhang J, Yang H, Wang X, Gou C. Two cases of common coronavirus disease 2019 treated by syndrome differentiation of traditional Chinese medicine. *J Tradit Chin Med.* 2020;61(11):935-7.
24. Li B, Ge ZX, Xu T, Yang XY, Liu H. Two cases of mild new type of coronavirus pneumonia treated with Chinese medicine alone. *J Guizhou University Tradit Chin Med.* 2020;42(03):9-12.
25. Shang FN, Huang YD, Lu JM, Zhu YQ, Zhu L, Li ZP. Clinical pharmaceutical care and interpretation of children with COVID-19. *Chin Pharm J.* 2020;55(10):773-6.
26. Chen SJ, Wei YF, Jiao YJ, Li MY. A case report of diagnosis and treatment of asymptomatic children with new coronavirus infection. *China's Naturopathy.* 2020;28(14):1-3.
27. Hu GH, Yu ZL, Liu F, Yi XY, Ji Q, Chu Z. Clinical characteristics of SARS-CoV-2 infection in children in Zhuzhou city. *J Hunan Normal Univ. (Med Sci).* 2020;4(17):42-5.
28. World Health Organization, Regional Office for the Western Pacific. WHO international standard terminologies on traditional medicine in the western pacific region. Manila: WHO Regional Office for the Western Pacific. 2007:23-238.
29. National Health Commission & National Administration of Traditional Chinese Medicine. Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7). *Chin Med J.* 2020;133(9):1087-95.
30. Balasubramanian S, Rao NM, Goenka A, Roderick M, Ramanan AV. Coronavirus disease 2019 (COVID-19) in children - what we know so far and what we do not. *Indian Pediatr.* 2020;57(5):435-42.
31. Xiong X, Wang P, Su K, Cho WC, Xing Y. Chinese herbal medicine for coronavirus disease 2019: A systematic review and meta-analysis. *Pharmacol Res.* 2020;160:105056.
32. Peng H, Gao P, Xu Q, Liu M, Peng J, Wang Y, Xu H. Coronavirus disease 2019 in children: Characteristics, antimicrobial treatment, and outcomes. *J Clin Virol.* 2020;128:104425.
33. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong S. Epidemiology of COVID-19 among children in China. *Pediatrics.* 2020;145(6):e20200702.
34. Cruz AT, Zeichner SL. COVID-19 in children: initial characterization of the pediatric disease. *Pediatrics.* 2020;145(6):e20200834.
35. Caro-Dominguez P, Shelmerdine SC, Toso S, Secinaro A, Toma P, Damasio MB, Navallas M, Riaza-Martin L, Gomez-Pastrana D, Ghadimi Mahani M, Desoky SM, Ugas Charcape CF, Almanza-Aranda J, Ucar ME, Lovrenski J, Gorkem SB, Alexopoulou E, Ciet P, van Schuppen J, Ducou le Pointe H, Goo HW, Kellenberger CJ, Raissaki M, Owens CM, Hirsch FW, van Rijn RR. Thoracic imaging of coronavirus disease 2019 (COVID-19) in children: a series of 91 cases. *Pediatr Radiol.* 2020;50(10):1354-68.
36. Götzinger F, Santiago-García B, Noguera-Julían A, Lanasa M, Lancella L, Calò Carducci FI, Gabrovská N, Velizarova S, Prunk P, Osterman V, Krivec U, Lo Vecchio A, Shingadia D, Soriano-Arandes A, Melendo S, Lanari M, Pierantoni L, Wagner N, L'Huillier AG, Heininger U, Ritz N, Bandi S, Krajcar N, Roglić S, Santos M, Christiaens C, Creuven M, Buonsenso D, Welch SB, Bogyi M, Brinkmann F, Tebruegge M. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health.* 2020;4(9):653-61.
37. Zhou YH, Zheng KI, Targher G, Byrne CD, Zheng MH. Abnormal liver enzymes in children and infants with COVID-19: A narrative review of case-series studies. *Pediatr Obes.* 2020;15(12):e12723.
38. Abdulla S, Hussain A, Azim D, Abdullah EH, Elawamy H, Nasim S, Kumar S, Naveed H. COVID-19-induced hepatic injury: a systematic review and meta-analysis. *Cureus.* 2020;12(10):e10923.
39. Rodriguez-Gonzalez M, Castellano-Martinez A, Cascales-Poyatos HM, Perez-Reviriego AA. Cardiovascular impact of COVID-19 with a focus on children: A systematic review. *World J Clin Cases.* 2020;8(21):5250-83.
40. Minocha PK, Phoon CKL, Verma S, Singh RK. Cardiac Findings in pediatric patients with multisystem inflammatory syndrome in children associated with

- COVID-19. Clin Pediatr (Phila). 2021;60(2):119-26.
41. Abi Nassif T, Fakhri G, Younis NK, Zareef R, Al Amin F, Bitar F, Arabi M. Cardiac manifestations in COVID-19 patients: a focus on the pediatric population. Can J Infect Dis Med Microbiol. 2021;2021:5518979.
 42. Ang L, Lee HW, Choi JY, Zhang J, Lee MS. Herbal medicine and pattern identification for treating COVID-19: a rapid review of guidelines. Integr Med Res. 2020;9(2):100407.
 43. Ang L, Lee HW, Kim A, Lee MS. Herbal medicine for the management of COVID-19 during the medical observation period: a review of guidelines. Integr Med Res. 2020;9(3):100465.
 44. Luo L, Jiang J, Wang C, Fitzgerald M, Hu W, Zhou Y, Zhang H, Chen S. Analysis on herbal medicines utilized for treatment of COVID-19. Acta Pharm Sin B. 2020;10(7):1192-204.
 45. Ren X, Shao XX, Li XX, Jia XH, Song T, Zhou WY, Wang P, Li Y, Wang XL, Cui QH, Qiu PJ, Zhao YG, Li XB, Zhang FC, Li ZY, Zhong Y, Wang ZG, Fu XJ. Identifying potential treatments of COVID-19 from traditional Chinese medicine (TCM) by using a data-driven approach. J Ethnopharmacol. 2020;258:112932.
 46. Li Z, Chen H, Zhang H, Li Y, Wang C, Bai L, Zhang W, Jiang Z. Similarity and specificity of traditional Chinese medicine formulas for management of coronavirus disease 2019 and rheumatoid arthritis. ACS Omega. 2020;5(47):30519-30.
 47. He Y, Zheng X, Sit C, Loo WT, Wang Z, Xie T, Jia B, Ye Q, Tsui K, Chow LW, Chen J. Using association rules mining to explore pattern of Chinese medicinal formulae (prescription) in treating and preventing breast cancer recurrence and metastasis. J Transl Med. 2012;10 Suppl 1(Suppl 1):S12.
 48. Yin L, Gao Y, Li Z, Wang M, Chen K. Analysis of Chinese herbal formulae recommended for COVID-19 in different schemes in China: a data mining approach. Comb Chem High Throughput Screen. 2021;24(7):957-67.
 49. Xu J, Zhang Y. Traditional Chinese medicine treatment of COVID-19. Complement Ther Clin Pract. 2020;39:101165.
 50. He T, Qu R, Qin C, Wang Z, Zhang Y, Shao X, Lu T. Potential mechanisms of Chinese herbal medicine that implicated in the treatment of COVID-19 related renal injury. Saudi Pharm J. 2020;28(9):1138-48.
 51. Chen J, Tsim KWK. A review of edible jujube, the *Ziziphus jujuba* fruit: a health food supplement for anemia prevalence. Front Pharmacol. 2020;11:593655.
 52. Liu SJ, Lv Y, Tang ZS, Zhang Y, Xu HB, Zhang DB, Cui CL, Liu H, Sun HH, Song Z, Wei S. *Ziziphus jujuba* Mill. a plant used as medicinal food: a review of its phytochemistry, pharmacology, quality control and future research. Phytochem Rev. 2021;20(3):507-41.
 53. Luo H, Tang QL, Shang YX, Liang SB, Yang M, Robinson N, Liu JP. Can Chinese medicine be used for prevention of corona virus disease 2019 (COVID-19)? a review of historical classics, research evidence and current prevention programs. Chin J Integr Med. 2020;26(4):243-50.
 54. Wu HY, Li J, Mao YZ, Yuan ZY, Li F, Li L, Huang HY. Network pharmacology approach to investigate the preventive mechanism of Hunan expert group recommended Chinese medicine prevention No. 2 prescription against COVID-19. Digit Chinese Med. 2020;3(2):116-32.
 55. Gao LQ, Xu J, Chen SD. In silico Screening of potential Chinese herbal medicine against COVID-19 by targeting SARS-CoV-2 3CLpro and angiotensin converting enzyme II using molecular docking. Chin J Integr Med. 2020;26(7):527-32.
 56. Ang L, Lee HW, Kim A, Lee JA, Zhang J, Lee MS. Herbal medicine for treatment of children diagnosed with COVID-19: A review of guidelines. Complement Ther Clin Pract. 2020;39:101174.
 57. Wang Y, Gu W, Kui F, Gao F, Niu Y, Li W, Zhang Y, Guo Z, Du G. The mechanism and active compounds of *semen armeniacae amarum* treating coronavirus disease 2019 based on network pharmacology and molecular docking. Food Nutr Res. 2021;65.
 58. Gao K, Song YP, Song A. Exploring active ingredients and function mechanisms of Ephedra-bitter almond for prevention and treatment of Corona virus disease 2019 (COVID-19) based on network pharmacology. BioData Min. 2020;13(1):19.

59. Shi Q, Liu Z, Yang Y, Geng P, Zhu YY, Zhang Q, Bai F, Bai G. Identification of anti-asthmatic compounds in *Pericarpium citri reticulatae* and evaluation of their synergistic effects. *Acta Pharmacol Sin.* 2009;30(5):567-75.
60. Gao Z, Li FS, Upur H. A study of the law of herbal administration in treating lung-distension by TCM physicians through history using cluster analysis. *J Tradit Chin Med.* 2011;31(4):303-7.
61. Fu XJ, Song XX, Wei LB, Wang ZG. Study of the distribution patterns of the constituent herbs in classical Chinese medicine prescriptions treating respiratory disease by data mining methods. *Chin J Integr Med.* 2013;19(8):621-8.
62. Ang L, Lee HW, Kim A, Choi JY, Lee MS. Network analysis of herbs recommended for the treatment of COVID-19. *Infect Drug Resist.* 2021;14:1833-44.
63. Liang SB, Zhang YY, Shen C, Liang CH, Lai BY, Dai N, Li YQ, Tian ZY, Zhang XW, Jiang Y, Xiong M, Zhang YP, Zhang Y, Robinson N, Liu JP. Chinese herbal medicine used with or without conventional western therapy for COVID-19: an evidence review of clinical studies. *Front Pharmacol.* 2021;11:2321.
64. Della Gatta AN, Rizzo R, Pilu G, Simonazzi G. Coronavirus disease 2019 during pregnancy: a systematic review of reported cases. *Am J Obstet Gynecol.* 2020;223(1):36-41.
65. Borges do Nascimento IJ, Cacic N, Abdulazeem HM, von Groote TC, Jayarajah U, Weerasekara I, Esfahani MA, Civile VT, Marusic A, Jeroncic A, Carvas Junior N, Pericic TP, Zakarija-Grkovic I, Meirelles Guimarães SM, Luigi Bragazzi N, Bjorklund M, Sofi-Mahmudi A, Altujjar M, Tian M, Arcani DMC, O'Mathúna DP, Marcolino MS. Novel coronavirus infection (COVID-19) in humans: a scoping review and meta-analysis. *J Clin Med.* 2020;9(4):941.
66. Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: a systematic review of 108 pregnancies. *Acta Obstet Gynecol Scand.* 2020;99(7):823-9.