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Herbal medicine for treatment of children diagnosed with COVID-19: A review of guidelines

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ABSTRACT

This review aimed to summarize and analyze the pattern identification (PI), herbal formulae, and composition of herbs provided by recent guidelines for the treatment of pediatric COVID-19. Seven data sources were reviewed until March 25, 2020. We analyzed the herbal formulae included in the guidelines and performed a network analysis to identify the frequency of herbs recommended in the herbal formulae. All 3 guidelines were provincial guidelines from China. Our results showed that there were 4 stages, 12 PIs, and 13 herbal formulae recommended by the provincial guidelines. These herbal formulae included a total of 56 herbs. Based on our network analysis, Scutellariae Radix was paired with Artemisiae Annuae Herba in one cluster. In another cluster, Armeniacae Semen was paired with Coicis Semen and Ephedrae Herba was paired with Gypsum Fibrosum. This review serves as a reference for the use of traditional medicine in the treatment of pediatric COVID-19.

1. Introduction

As of March 2020, the outbreak of coronavirus disease (COVID-19) has been declared a pandemic, and at least 163 countries across all six continents sustained the transmission of the virus [1,2]. Although there is very limited information about the virus, current evidences show that people can be ill from COVID-19 regardless of their age, gender, ethnicity, and health status. While children are less likely to be infected by the virus as compared to the adults, they are not spared from the disease.

Recent epidemiological reports also showed that the cases reported among children are relatively few and less severe [3]. Mainland China, which has the highest number of cases worldwide has reported that the mean age of pediatric patients with COVID-19 infection was 7 years old. According to the Chinese Center for Disease Control and Prevention (China CDC), there are no fatalities found in children with age ranging from 1 to 9 years old [4]. Regardless of the number of cases reported, children remain vulnerable to COVID-19.

As there is no vaccine or antiviral treatment currently available for COVID-19, traditional medicine, which has been widely used in the past during epidemic outbreaks, is taken into consideration as one of the treatment modalities [5]. Although many countries have issued traditional medicine treatment guidelines on the prevention and treatment of COVID-19, only mainland China has issued the guidelines for children.

This review aimed to systematically summarize and analyze the herbal formulae recommended by all available Chinese guidelines in terms of the composition of herbs, pattern identification (PI) and disease stages in the treatment of pediatric COVID-19.

2. Methods

2.1. Data sources

Seven data sources were searched, until March 25, 2020, to identify available traditional medicine guidelines:

- Guidelines International Network (G-I-N) [6].

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lines. There were 13 herbal formulae recommended by the provincial COVID-19 were analyzed based on the disease stages and PI. Our results review were issued by the provincial government.

Although there were several versions of national diagnosis and treatment guidelines related to traditional medicine issued in mainland China that provide treatment measures for pediatric COVID-19. All herbal formulae recommended by the guidelines for treatment measures were included and those for preventive measures were excluded.

As herbal formulae provided by guidelines from the different provinces were formulated based on regional characteristics, regional folk medicines such as Tibetan medicine, Mongolian medicine, and Miao medicine were excluded. For provincial guidelines that integrate both folk medicine and conventional traditional medicine, only herbal formulae of the latter were included.

2.3. Data extraction and analyses

Data from the included guidelines were extracted based on a pre-defined data extraction table which included the stages of the disease, pattern identification, clinical symptoms, therapeutic principle, name and composition of herbal formulae, herb dosage, and the province of the provided guideline. The herbal formulae were analyzed based on pattern identification and disease stage. The frequency of herbs recommended in the herbal formulae were also identified by performing a network analysis using Netminer 4.0 (Cyram Inc, Seoul, Korea) which visualized the relationship between the herbs in clusters. In our network analysis, the nodes represented the herbs and their connections represented the relationship of the herbs with each other. The connections were stronger in herbs that were adjacent to each other. The herbs with closer connection as compared to the rest of the network belonged to the same cluster.

2.4. Terminology standardization

We standardized all the terminologies based on the WHO International Standard Terminologies on Traditional Medicine in Western Pacific Region [11]. Pattern identification terminology was standardized based on the clinical manifestation provided in the guidelines and Clinic Terminology of Traditional Chinese Medical Diagnosis and Treatment [12]. Unnamed herbal formulae were renamed using the Dictionary of Traditional Chinese Medicine Formula [13].

3. Results

We only found 3 traditional medicine guidelines from mainland China that provide treatment measures for pediatric COVID-19. Although there were several versions of national diagnosis and treatment guidelines related to traditional medicine issued in mainland China, contents on pediatric treatments were not provided in any of these guidelines. All 3 traditional medicine guidelines included in this review were issued by the provincial government.

The herbal formulae used for treating children diagnosed with COVID-19 were analyzed based on the disease stages and PI. Our results identified 4 stages and 12 PIs based on the provided provincial guidelines. There were 13 herbal formulae recommended by the provincial guidelines, of which 12 herbal formulae were oral decoction prescriptions and one of them was a decoction enema prescription (Table 1). The frequency of the herbs used in the herbal formulae was also calculated. These herbal formulae included a total of 56 herbs, of which 23 had a frequency of use of 3 or more times.

In the results of our network analysis, 11 herbs that appeared more than 3 times in the herbal formulae were able to be classified into two different clusters (Fig. 1), where 6 herbs (Angelicae Decursivae Radix, Belamcandae Rhizoma, Eriobotryae Folium, Trichosanthis Pericarpium, Scutellariae Radix, and Artemisiae Annuae Herba) belonged to one cluster and the other 5 (Armeniacae Semen, Lepidii seu Descurainiae Semen, Coicis Semen, Gypsum Fibrosum, and Ephedrae Herba) belonged to the second cluster. In the figure, Scutellariae Radix showed strong connections with Artemisiae Annuae Herba and Belamcandae Rhizoma in one cluster. The herb Armeniacae Semen and Coicis Semen, in addition to Ephedrae Herba and Gypsum Fibrosum, each had strong connections with one another in the other cluster.

4. Discussion

In this review, we systematically accessed the herbal treatment recommendations by the Chinese provincial guidelines for pediatric COVID-19. According to our results, only 3 provincial guidelines provided herbal treatment recommendations for pediatric COVID-19. A recent case series of 72,314 cases published by the Chinese Center for Disease Control and Prevention showed that children younger than 10 years old accounted for only 1% of cases and another 1% were patients whose age ranged from 10 to 19 years [4]. Besides, recent evaluation of the pediatric cases treated at the Wuhan Children’s Hospital, which is the only hospital in Wuhan, China that was assigned by the government for the treatment of pediatric COVID-19, also reported that most infected children presented with milder symptoms as compared to adults [3]. This may be the rationale behind the lack of guidelines issued for the treatment of pediatric COVID-19.

According to our network analysis, Scutellariae Radix, Artemisiae Annuae Herba, and Belamcandae Rhizoma were found to be correlated in one cluster. In the theory of traditional medicine, these three herbs have a heat-clearing effect and are frequently used together in herbal formulae. The herb Scutellariae Radix is approved by the China Food and Drug Administration for the treatment of viral diseases such as influenza, upper respiratory infection, and pneumonia [14]. Baicalin, which is the main bioactive compound derived from Scutellariae Radix, was also reported to have antiviral activity against SARS coronavirus [15]. Similarly, Artemisiae Annuae Herba was reported to have an antiviral compound and showed inhibitory effects on the SARS coronavirus strain [16]. Besides, Belamcandae Rhizoma has also been frequently used for the treatment of inflammation and throat disorder [17].

Additionally, our results also showed that Armeniacae Semen and Coicis Semen were correlated to one another in the second cluster. The herb Armeniacae Semen and Coicis Semen were often prescribed together for the treatment of upper respiratory infection as they both have the effect of nourishing the lungs in traditional medicine [18]. The herb Ephedrae Herba and Gypsum Fibrosum were also shown to have strong connections with one another. Both herbs are the major components of the herbal formula Ma Xin Shi Gan Tang, which is often used for the treatment of common cold. This herbal formula also claimed to antiviral effect that inhibits the entry of influenza virus and have potential in managing seasonal pandemics of influenza infection [19].

Notably, the herb Armeniacae Semen was one of the highest frequencies of use among the herbal formulae recommended for the treatment of pediatric COVID-19. In a nationwide population-based study conducted in Taiwan, Armeniacae Semen was the most frequently prescribed herb for the treatment of pediatric asthma [20]. Besides having antiasthmatic activity, Armeniacae Semen was also reported to inhibit Th2 cells, which are important for immune responses, reducing hyper-responsiveness in the airway [21]. This further validated...
the recommendation of Armeniacae Semen for the treatment of respiratory diseases in children.

In particular, the frequently used herbs in the recommended herbal formulae for the treatment of pediatric COVID-19 lack diversity compared to the adults [22]. In the recommendations on adult treatment for COVID-19, the herb Glycyrrhizae Radix et Rhizoma was the herb with the highest frequency of usage [22]. This might be due to the difference in the spectrum of diseases between the children and the adults. The course of diseases in adults was reported to be more severe than children; thus, the herb Glycyrrhiza Radix et Rhizoma, which has both antiviral and anti-inflammatory qualities were highly used. On the other hand, the herb Armeniacae Semen, which is widely used of respiratory diseases in children.

However, there are several limitations to this study. First, this review only summarized the herbal formulae and their herbal compositions recommended by the traditional medicine guidelines. There was no direct evidence on the efficacy of the herbal formulae for the treatment of pediatric COVID-19. Second, we only found 3 provincial traditional medicine guidelines that included pediatric treatments. This information is insufficient for us to provide any specific recommendations or guidance for the treatment of pediatric COVID-19. Third, this review only summarized information from the provincial traditional medicine guidelines available up to March 25, 2020. As guidelines issued on the pandemic COVID-19 are constantly updated, there may be updated information that we failed to retrieve in this review.

In conclusion, this review can only be used as a reference for the traditional medicine treatment of pediatric COVID-19. As the spectrum of disease in children differs from adults, there are many questions that remain unanswered. It is important to define the epidemiology of pediatric COVID-19 with more studies.

Author contributions

Conceptualization: MSL and HWL. Methodology: LA and AK. Data Curation: HWL and AK. Writing – Original Draft: LA and HWL. Writing – Review & Editing: JZ, AK, MSL and JAL. Supervision: MSL.

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Ethical statement

No ethics committee approval was required as no human or animal research was conducted.
Fig. 1. Network analysis of herbs with frequency of use of 3 or more times.

**Data availability**

Data will be made available upon request.

**Declaration of competing interest**

The authors declare no conflict of interest.

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None.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2020.101174.

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