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Review Article

Herbal medicine for the management of COVID-19 during the medical observation period: A review of guidelines

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ABSTRACT

Background: Medical observation period is a period of 14 days after any exposure to coronavirus disease 2019 (COVID-19) occurred. This review aimed to summarize and analyze the herbs and herbal formulae recommended by available guidelines.
Methods: A total of 14 sources were searched for potential guidelines that provide herbal medicine treatment for the medical observation period of COVID-19. We summarized and analyzed the recommended herbal formulae and performed a network analysis to identify the relationship between herbs.
Results: We found 9 guidelines that provide herbal formula for medical observation based on clinical manifestation. There are 12 herbal formulae with a total of 53 herbs recommended by the guidelines. The result of our network analysis showed that the herb Citri Reticulatae Pericarpium (*Chen Pi*) strongly paired with the herb Glycyrrhizae Radix et Rhizoma (*Gan Cao*).
Conclusion: This review briefly summarized the usage of herbal medicine for the medical observation period of COVID-19 and may serve as a reference for future studies. More research is needed in the future to provide evidence on the usage of herbal medicine in various phases of COVID-10.

1. Introduction

The recent emergence of a novel coronavirus has caused a pandemic and sickened more than 2.5 million people in at least 177 countries.[1,2] This novel strain of coronavirus which caused coronavirus disease 2019 (COVID-19) also belonged to the same family of viruses that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) in the past.[3] The infection of COVID-19 can result in acute respiratory illness and present common symptoms such as fever, cough, and fatigue.[4] According to reports from World Health Organizations, evidence has shown that there are three routes for the transmission of COVID-19: symptomatic transmission, pre-symptomatic transmission, and asymptomatic transmission.[5] A recent publication also showed that the actual intervals of transmission are shorter than the incubation period which suggests that pre-symptomatic transmission is more substantial than expected.[6] Hence, it is hard to predict or estimate the potential spread of COVID-19. As the understanding of COVID-19 remains limited, active monitoring, surveillance, and control of the disease are crucial for public health.[7]

Medical observation period is defined as a period of 14 days after any exposure of COVID-19 occurred and is set based on the incubation time from virus exposure to illness onset.[7,8] Individuals who are put under medical observation are usually those who required monitoring and restriction of movements (i.e., home quarantine and quarantine stations). They are required to complete the 14 days of medical observation before they are given medical clearance.

To date, many guidelines related to herbal medicine have been issued for the prevention and treatment of COVID-19.[9,10] Recent clinical evidence also showed the therapeutic effectiveness of traditional medicine in treating different stages of COVID-19.[11–13] In this review, we aimed to summarize and analyze the herbal formulae recommended for use during the medical observation period of COVID-19.

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Table 1
Herbal medicines recommendation for medical observation period of COVID-19.

Clinical Manifestation	Recommended Herbal Formula Composition (Latin Name, *Pinyin*)
China	
Fatigue + fever	Cinnamomi Ramulus (*Gui Zhi*) 12 g, Atractylodis Rhizoma (*Cang Zhu*) 12 g, Acori Tatarinowii Rhizoma (*Shi Chang Pu*) 12 g, Agastachis Herba (*Huo Xiang*) 12 g, Crataegi Fructus (*Shan Zha*) 15 g, Citri Reticulatae Pericarpium (*Chen Pi*) 9 g, Pinelliae Rhizoma (*Ban Xia*) 9 g, Poria Sclerotium (*Fu Ling*) 12 g, Puerariae Radix (*Ge Gen*) 12 g, Scutellariae Radix (*Huang Qin*) 12 g, Lonicerae Flos (*Jin Yin Hua*) 9 g, Zingiberis Rhizoma Recens (*Sheng Jiang*) 30 g, Glycyrrhizae Radix et Rhizoma (*Gan Cao*) 5 g Astragali Radix (*Huang Qi*) 20 g, Codonopsis Radix (*Dang Shen*) 15 g, Atractylodis Macrocephalae Rhizoma (*Bai Zhu*) 15 g, Poria Sclerotium (*Fu Ling*) 15 g, Citri Reticulatae Pericarpium (*Chen Pi*) 10 g, Bupleuri Radix (*Chai Hu*) 10 g, Lonicerae Flos (*Jin Yin Hua*) 15 g, Saposhnikoviae Radix (*Fang Feng*) 10 g, Angelicae Sinensis Radix (*Dang Gui*) 15 g, Paeoniae Radix (*Chi Shao*) 15 g, Chuanxiong Rhizoma (*Chuan Xiong*) 10 g, Armeniacae Semen Amarum (*Ku Xing Ren*) 10 g, Ophiopogonis Radix (*Mai Dong*) 15 g, Glycyrrhizae Radix et Rhizoma (*Gan Cao*) 10 g
Fatigue + fever + chills	Notopterygii Rhizoma seu Radix (*Qiang Huo*) 10 g, Atractylodis Rhizoma (*Cang Zhu*) 10 g, Perillae Folium (*Su Ye*) 10 g, Armeniacae Semen Amarum (*Ku Xing Ren*) 10 g, Eupatorii Herba (*Pei Lan*) 10 g, Agastachis Herba (*Huo Xiang*) 10 g, Citri Reticulatae Pericarpium (*Chen Pi*) 6 g, Peucedani Radix (*Qian Hu*) 10 g, Bupleuri Radix (*Chai Hu*) 10 g, Menthae Herba (*Bo He*) 6 g, Platycodonis Radix (*Jie Geng*) 6 g, Glycyrrhizae Radix et Rhizoma (*Gan Cao*) 3 g
Fatigue + fever + upper respiratory tract infection symptoms	Lonicerae Flos (*Jin Yin Hua*) 10 g, Forsythiae Fructus (*Lian Qiao*) 10 g, Saposhnikoviae Radix (*Fang Feng*) 10 g, Ephedrae Herba (*Ma Huang*) 10 g, Scutellariae Radix (*Huang Qin*) 10 g, Armeniacae Semen Amarum (*Ku Xing Ren*) 10 g, Platycodonis Radix (*Jie Geng*) 10 g, Adenophorae Radix (*Sha Shen*) 15 g, Agastachis Herba (*Huo Xiang*) 10 g, Magnoliae Officinalis Cortex (*Hou Po*) 10 g
Fatigue + fever + dry cough + chills + gastrointestinal symptoms	Agastachis Herba (*Huo Xiang*) 10 g, Angelicae Dahuricae Radix (*Bai Zhi*) 10 g, Citri Reticulatae Pericarpium (*Chen Pi*) 10 g, Pinelliae Rhizoma (*Ban Xia*) 10 g, Magnoliae Officinalis Cortex (*Hou Po*) 10 g, Atractylodis Rhizoma (*Cang Zhu*) 10 g, Poria Sclerotium (*Fu Ling*) 15 g, Perillae Folium (*Su Ye*) 10 g, Arecae Pericarpium (*Da Fu Pi*) 10 g, Massa Medicata Fermentata (*Shen Qu*) 15 g
Fatigue + gastrointestinal symptoms	Astragali Radix (*Huang Qi*) 30 g, Atractylodis Macrocephalae Rhizoma (*Bai Zhu*) 15 g, Poria Sclerotium (*Fu Ling*) 15 g, Saposhnikoviae Radix (*Fang Feng*) 10 g, Perillae Folium (*Su Ye*) 9 g, Citri Reticulatae Pericarpium (*Chen Pi*) 10 g, Agastachis Herba (*Huo Xiang*) 10 g, Eupatorii Herba (*Pei Lan*) 10 g, Massa Medicata Fermentata (*Shen Qu*) 10 g, Glycyrrhizae Radix et Rhizoma (*Gan Cao*) 6 g Atractylodis Rhizoma (*Cang Zhu*) 12 g, Perillae Folium (*Su Ye*) 12 g, Agastachis Herba (*Huo Xiang*) 12 g, Citri Reticulatae Pericarpium (*Chen Pi*) 12 g, Puerariae Radix (*Ge Gen*) 12 g, Lonicerae Flos (*Jin Yin Hua*) 9 g, Zingiberis Rhizoma Recens (*Sheng Jiang*) 20 g
Fatigue + gastrointestinal symptoms + heavy limbs	Bupleuri Radix (*Chai Hu*) 15 g, Scutellariae Radix (*Huang Qin*) 9 g, Pinelliae Rhizoma (*Ban Xia*) 9 g, Codonopsis Radix (*Dang Shen*) 9 g, Atractylodis Rhizoma (*Cang Zhu*) 12 g, Citri Reticulatae Pericarpium (*Chen Pi*) 9 g, Magnoliae Officinalis Cortex (*Hou Po*) 9 g, Forsythiae Fructus (*Lian Qiao*) 12 g, Amomi Tsao-ko Fructus (*Cao Guo*) 6 g, Agastachis Herba (*Huo Xiang*) 9 g, Zingiberis Rhizoma Recens (*Sheng Jiang*) 6 g, Zizyphi Fructus (*Da Zao*) 6 g, Glycyrrhizae Radix et Rhizoma (*Gan Cao*) 9 g
Fever + upper respiratory tract infection symptoms + myalgia	Schizonepetae Spica (*Jing Jie*) 15 g, Saposhnikoviae Radix (*Fang Feng*) 15 g, Ephedrae Herba (*Ma Huang*) 10 g, Angelicae Dahuricae Radix (*Bai Zhi*) 10 g, Notopterygii Rhizoma seu Radix (*Qiang Huo*) 15 g, Bupleuri Radix (*Chai Hu*) 15 g, Peucedani Radix (*Qian Hu*) 10 g, Platycodonis Radix (*Jie Geng*) 10 g, Aurantii Fructus (*Zhi Qiao*) 10 g, Chuanxiong Rhizoma (*Chuan Xiong*) 15 g, Agastachis Herba (*Huo Xiang*) 10 g, Atractylodis Rhizoma (*Cang Zhu*) 15 g, Zingiberis Rhizoma Recens (*Sheng Jiang*) 10 g Astragali Radix (*Huang Qi*) 15 g, Atractylodis Macrocephalae Rhizoma (*Bai Zhu*) 10 g, Saposhnikoviae Radix (*Fang Feng*) 6 g, Lilii
No clear symptoms	Bulbus (*Bai He*) 30 g, Dendrobii Herba (*Shi Hu*) 10 g, Lonicerae Flos (*Jin Yin Hua*) 10 g, Forsythiae Fructus (*Lian Qiao*) 30 g, Imperatae Rhizoma (*Bai Mao Gen*) 30 g, Platycodonis Radix (*Jie Geng*)10 g, Phragmitis Rhizoma (*Lu Gen*) 30 g, Glycyrrhizae Radix et Rhizoma (*Gan Cao*) 6 g Bupleuri Radix (*Chai Hu*) 9 g, Scutellariae Radix (*Huang Qin*) 9 g, Pinelliae Rhizoma (*Ban Xia*) 9 g, Crassirhizomae Rhizoma (*Guan Zhong*) 9 g, Lonicerae Flos (*Jin Yin Hua*) 15 g, Forsythiae Fructus (*Lian Qiao*) 15 g, Pseudostellariae Radix (*Tai Zi Shen*) 10 g, Astragali Radix (*Huang Qi*) 15 g, Saposhnikoviae Radix (*Fang Feng*) 9 g, Atractylodis Macrocephalae Rhizoma (*Bai Zhu*) 9 g, Glycyrrhizae Radix et Rhizoma (*Gan Cao*) 6 g Astragali Radix (*Huang Qi*) 9 g, Glehniae Radix (*Bei Sha Shen*) 9 g, Anemarrhenae Rhizoma (*Zhi Mu*) 9 g, Tropaeoli Herba (*Han Jin Lian*) 5 g, Forsythiae Fructus (*Lian Qiao*) 9 g, Atractylodis Rhizoma (*Cang Zhu*) 9 g, Platycodonis Radix (*Jie Geng*) 6 g
Korea	
No clear symptoms	Forsythiae Fructus (*Lian Qiao*) 8 g, Lonicerae Flos (*Jin Yin Hua*) 8 g, Schizonepetae Spica (*Jing Jie*) 8 g, Saposhnikoviae Radix (*Fang Feng*) 8 g, Notopterygii Rhizoma seu Radix (*Qiang Huo*) 8 g, Araliae Continentalis Radix (*Du Huo*) 8 g, Bupleuri Radix (*Chai Hu*) 8 g, Peucedani Radix (*Qian Hu*) 8 g, Cnidii Rhizoma (*Chuan Xiong*) 8 g, Aurantii Fructus (*Zhi Qiao*) 8 g, Platycodonis Radix (*Jie Geng*) 8 g, Poria Sclerotium (*Fu Ling*) 8 g, Glycyrrhizae Radix et Rhizoma (*Gan Cao*) 16 g, Menthae Herba (*Bo He*) 2 g, Zingiberis Rhizoma Recens (*Sheng Jiang*) 28 g, Atractylodis Rhizoma (*Cang Zhu*) 16 g, Magnoliae Cortex (*Hou Po*) 8 g, Citri Unshius Pericarpium (*Chen Pi*) 8 g, Agastachis Herba (*Huo Xiang*) 8 g, Pinelliae Rhizoma (*Ban Xia*) 8 g, Zizyphi Fructus (*Da Zao*) 15 g Astragali Radix (*Huang Qi*) 12 g, Ginseng Radix (*Ren Shen*) 8 g, Atractylodis Rhizoma Alba (*Bai Zhu*) 8 g, Glycyrrhizae Radix et Rhizoma (*Gan Cao*) 16 g, Angelicae Gigantis Radix (*Dang Gui*) 4 g, Citri Unshius Pericarpium (*Chen Pi*) 4 g, Cimicifugae Rhizoma (*Sheng Ma*) 3 g, Bupleuri Radix (*Chai Hu*) 11 g, Forsythiae Fructus (*Lian Qiao*) 8 g, Lonicerae Flos (*Jin Yin Hua*) 8 g, Schizonepetae Spica (*Jing Jie*) 8 g, Saposhnikoviae Radix (*Fang Feng*) 8 g, Notopterygii Rhizoma seu Radix (*Qiang Huo*) 8 g, Araliae Continentalis Radix (*Du Huo*) 8 g, Peucedani Radix (*Qian Hu*) 8 g, Cnidii Rhizoma (*Chuan Xiong*) 8 g, Aurantii Fructus (*Zhi Qiao*) 8 g, Platycodonis Radix (*Jie Geng*) 8 g, Poria Sclerotium (*Fu Ling*) 8 g, Menthae Herba (*Bo He*) 2 g, Zingiberis Rhizoma Recens (*Sheng Jiang*) 14 g

2. Methods

2.1. Data sources

The following data sources were searched up to June 2, 2020 for eligible guidelines:

- English sources: World Health Organizations (WHO), National Institutes of Health of United States (NIH), European Centre for Disease Prevention and Control of the European Union (ECDC), Guidelines International Network (G-I-N), and Evidence Aid's "Chinese guidelines on Novel Coronavirus" resources
- Chinese sources: Institute of Medical Information (IMI) and Library of the Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), National Health Commission of the People's Republic of China, administration office of all 31 provinces in People's Republic of China (including municipal and autonomous regions), and Centre for Health Protection of the Hong Kong Special Administrative Region
- Other sources: Association of Korean Medicine, Korean Pulmonary Association of Traditional Medicine, Japanese Association for Infectious Diseases, Japanese Respiratory Society (JRS), and Ministry of Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homoeopathy (AYUSH)

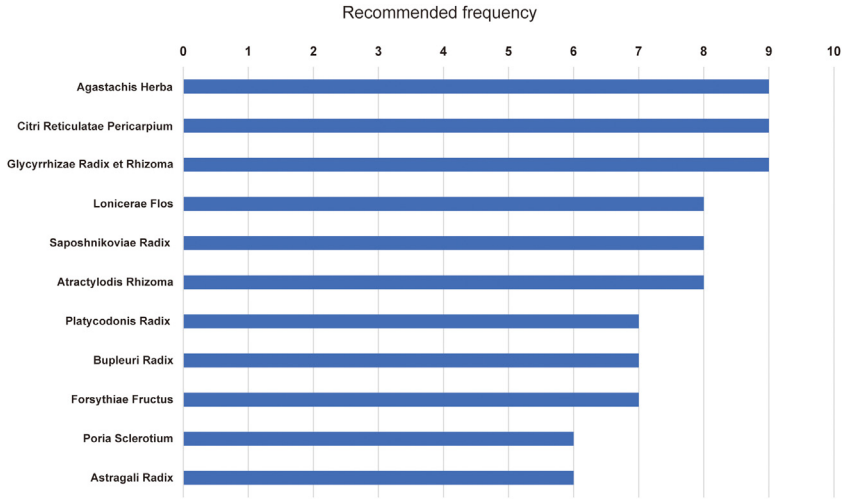

Fig. 1. Frequency of commonly used herbs in the herbal formulae the management of COVID-19 during the medical observation period.

2.2. Inclusion and exclusion criteria

This review only focused on the treatment of modalities for COVID-19 during the medical observation period. All guidelines that provide treatment measures related to herbal medicine in the form of oral ingested herbal formula or single herbs were included. Herbal medicines in the form of patent medicine, herbal injections, herbal patches, and herbal fumigation were excluded. Guidelines that only provide preventive measures or treatment measures for confirmed cases of COVID-19 were also excluded.

2.3. Data extraction and analyses

Data from each included guideline were extracted using a predefined data extraction table. The content of the data extraction tables comprised of the place of issue, clinical manifestations, type of herbal medicine used, therapeutic principle, name of herbal formulae, herbal compositions, treatment frequency, and treatment duration. The herbal formulae were analyzed according to clinical manifestations. The types of herbs included in the herbal formulae for each clinical manifestation were also computed and analyzed. To have a better understanding of the inter-relations between herbs, network analysis was also performed and visualized.

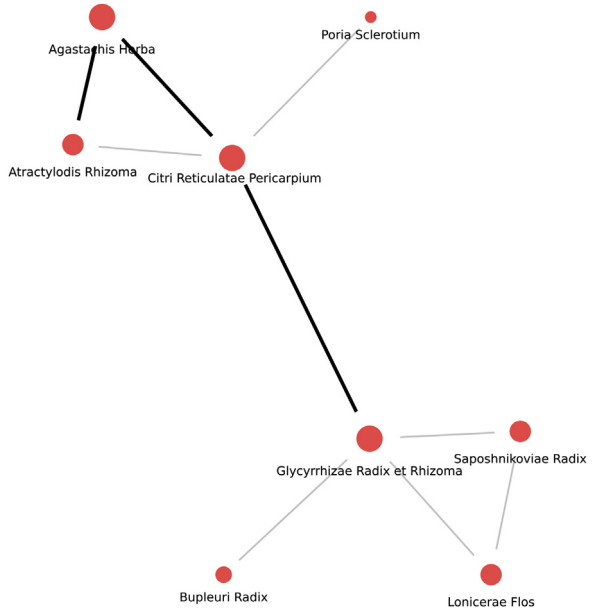

Fig. 2. Network analysis of herbs with frequency of use of paring 6 or more times.

3. Results

We found 9 guidelines that provide herbal formulae recommendations for the medical observation period of COVID-19; 8 were Chinese guidelines issued by the provincial government and 1 was Korean guideline issued by the Korean Pulmonary Association of Traditional Medicine. Herbal formulae recommended by these guidelines were mostly formulated based on the clinical manifestations. After clustering the clinical manifestation and their relative herbal formula, there are 8 groups of clinical manifestations with 12 recommended herbal formulae for the Chinese guidelines. For the Korean guideline, 2 herbal formulae were recommended without specifying the clinical manifestations. All 14 were oral decoction prescriptions (Table 1).

In the analysis of all 14 herbal formulae, a total of 53 herbs were recommended by the guidelines. Of the 53 herbs, 11 herbs had a frequency of use for 6 or more times. The herb with the highest frequency of use was Agastachis Herba (*Huo Xiang*), Citri Reticulatae Pericarpium (*Chen Pi*), and Glycyrrhizae Radix et Rhizoma (*Gan Cao*) as shown in Fig. 1. These herbs were commonly recommended in clinical manifestation groups consisting of fatigue, fever, chills, heavy limbs, and gastrointestinal symptoms. Looking at the dosage of the high-frequency herbs, the dosage of Agastachis Herba used in the recommended herbal formulae ranged from 8 to 12 g whereas the recommended dosage of Citri Reticulatae Pericarpium in the herbal formulae ranged from 4 to 12 g. Notably, the dosage of Glycyrrhizae Radix et Rhizoma varied the most in each herbal formula, ranging from 3 to 60 g.

In the network formation of herbs with a high frequency of usage, the 8 herbs that were recommended for 6 or more times were classified into 2 clusters. The herb Agastachis Herba, Citri Reticulatae Pericarpium, Atractylodis Rhizoma (*Cang Zhu*), and Poria Sclerotium (*Fu Ling*) were grouped in one cluster and the herb Glycyrrhizae Radix et Rhizoma, Saposhnikoviae Radix (*Fang Feng*), Lonicerae Flos (*Jin Yin Hua*), Atractylodis Rhizoma, and Bupleuri Radix (*Chai Hu*) were grouped in another (Fig. 2). Looking at the visualization of the weighted network, the weight represents the number of times the two herbs were paired together, and the thickness of the edge shows the weight of the relationship. Citri Reticulatae Pericarpium was strongly paired with Glycyrrhizae

Radix et Rhizoma, whereas Agastachis Herba was highly correlated with both Citri Reticulatae Pericarpium and Atractylodis Rhizoma.

According to the centrality analysis, the degree centrality was shown to be the highest for the herb Citri Reticulatae Pericarpium and the herb Glycyrrhizae Radix et Rhizoma. The pairing of Citri Reticulatae Pericarpium and Glycyrrhizae Radix et Rhizoma were most frequently recommended in clinical manifestation groups which include fatigue, fever, chills, heavy limbs, and gastrointestinal symptoms.

4. Discussion

In this review, we systematically summarized and analyzed the herbal formulae recommended for use during the medical observation period of COVID-19. Medical observation period of 14 days not only includes individuals that are exposed to the virus but also those that recovered from the diseases, where both circumstances required active monitoring. However, the individuals that required to be under medical observation period might slightly differ from country to country according to their severity distributions.

Based on our findings, only mainland China and South Korea provide treatment measures for medical observation period of COVID-19. In mainland China, individuals that required to be put under medical observation period include those who have close contact with COVID-19 infected people within 14 days prior to the onset of disease without appropriate protection, have symptoms of respiratory illness but tested negative for COVID-19, or recently recovered from the disease. During medical observation period, people who have an outbreak will be referred for nucleic acid testing for possible infection of COVID-19 and proceed to isolation.[14]

In South Korea, individuals that required for medication observation period not only include those who have close contacts with the virus and recent recoveries, but also those who were tested positive for COVID-19 with no signs of acute respiratory infection. Such difference may be due to the inter-country variation in risk perception where they come to a different conclusion as to the cost-benefit in minimizing the risk to an acceptable level.

Despite the differences in the inclusion standard, herbal formulae were recommended for all individuals who are put under medical observation period based on the symptoms they showed instead of pattern identification. None of the guidelines provided additional information on the pattern identification for each group of individuals even though pattern identification is one of the most important aspects of herbal formula prescription. Without pattern identification, the herbal formulae and composition recommendations may be less ideal. Additionally, the included guidelines did not clearly define the therapeutic principle for those individuals who have no clear symptoms. These individuals could be symptomatic or non-symptomatic and relevant information was insufficient in the guidelines.

On the other hand, we have performed a network analysis in order to identify the relations among all the herbs recommended for medical observation period. Our analysis results have shown that Citri Reticulatae Pericarpium and Glycyrrhizae Radix et Rhizoma has the strongest correlations among herbs. Both herbs are often prescribed together in herbal formulae.[15] In the theory of traditional medicine, Citri Reticulatae Pericarpium regulates the Qi, nourishes the spleen, and dry dampness to resolve phlegm whereas Glycyrrhizae Radix et Rhizoma tonifies the Qi and enhances the function of Citri Reticulatae Pericarpium in resolving phlegm and reducing cough.[16] Additionally, a prior study on the distribution patterns of herbs used for respiratory disease treatment using data mining methods also reported that Glycyrrhizae Radix et Rhizoma was often grouped with Citri Reticulatae Pericarpium.[17] Studies also showed that the herb Citri Reticulatae Pericarpium has anti-inflammatory and anti-asthmatic properties which may relieve fever, soothe cough and dyspnea, stimulate appetite, as well as enhance the immune system.[18,19]

Particularly, the recommended dosage range for the herb Glycyrrhizae Radix et Rhizoma ranged from 3 to 60 g, which may be related to the nature of the herb itself. The herb Glycyrrhizae Radix et Rhizoma has been the most commonly used adjuvant in most herbal medicine formulae in assisting herbal interactions. Studies have reported that the herb itself contains antiviral and anti-inflammatory qualities.[20–22] Glycyrrhizae Radix et Rhizoma possesses beneficial effects in respiratory diseases by nourishing Qi, resolving phlegm, and reducing cough.[23] Based on the currently available evidence, this herb has also been proposed as a novel immunomodulatory drug for COVID-19.[24] Hence, the recommended dosage of the Glycyrrhizae Radix et Rhizoma highly depends on the role of herbs play in each herbal formula.

There are several limitations to this study. This review only focused on oral ingested herbal formulae and their herbal compositions as provided by the available guidelines. Other forms of herbal medicine such as patent medicine or herbal injections are not taken into consideration for the analysis of this study as we intended to identify the relationships between herbs using network analysis. As the clinical symptoms presented during the medical observation period are mainly mild, patent medicines such as over-the-counter herbal medicines are often prescribed. Another limitation of this study is the lack of information. Additional information is not available in the relevant guidelines even though the medical observation period includes different groups of individuals (i.e. exposed to the virus, recovered from the disease, confirmed without signs of acute respiratory infection, symptomatic, or non-symptomatic) that may require different therapeutic principles. Besides, current researches on COVID-19 primarily focused on the potential treatment measures in various disease stages. There are very few studies that mention the medication used during medical observation period in general. Hence, we are unable to obtain much information or evidence to conduct a more comprehensive review.

In conclusion, this review provided an insight into the potential role of herbal medicine in regulating COVID-19 during the medical observation period. Although we are unable to provide a firm recommendation, this study serves as a reference for future studies. It is necessary to define the usage of herbal medicine in various phases of COVID-19, including before and aftercare.

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.

Conflict of interest

The authors declare no conflict of interest.

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Ethical statement

No ethics committee approval was required as no human or animal research was conducted.

Data availability

Data will be made available upon request.

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