Review Article

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

Lin Ang a,b,1, Hye Won Lee c,1, Anna Kim d, Myeong Soo Lee a,b,∗

a Clinical Medicine Division, Korea Institute of Oriental Medicine, Daejeon, Republic of Korea
b Korean Convergence Medicine, University of Science and Technology, Daejeon, Republic of Korea
c Herbal Medicine Research Division, Korea Institute of Oriental Medicine, Daejeon, Republic of Korea
d Future Medicine Division, Korea Institute of Oriental Medicine, Daejeon, Republic of Korea

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 Glycerichizae 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.

© 2020 Korea Institute of Oriental Medicine. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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.7,8

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.9,10 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.

https://doi.org/10.1016/j.imr.2020.100465
2213-4220© 2020 Korea Institute of Oriental Medicine. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
| 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 (Sheng Chuan Pu) 12 g, Agastachis Herba (Huo Xiang) 12 g, Crateae Fructus (Shan Zao) 5 g, Citri Reticulatae Pericarpium (Chen Pi) 6 g, Peucedani Radix (Qian Hu) 12 g, Bupleuri Radix (Chai Hu) 8 g, Peucedani Radix (Qian Hu) 8 g, Atractylodis Rhizoma (Cang Zhu) 10 g, Zingiberis Recens (Sheng Jiang) 2 g, Glycyrrhizae Radix et Rhizoma (Gan Cao) 10 g |
| Fatigue + fever + chills| Notopterygi Rhizoma seu Radix (Qiang Hua) 12 g, Atractylodis Rhizoma (Cang Zhu) 10 g, Perillae Foenum (Su Ye) 10 g, Magnoliae Flos (Jin Yin Hua) 10 g, Atractylodis Radix (Jin Qiao) 12 g, Zingiberis Recens (Sheng Jiang) 10 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, Sapochnikoviae Radix (Fang Feng) 10 g, Ephedrae Herba (Mu Huang) 10 g, Scutellariae Radix (Huang Qin) 10 g, Magnoiae Officinalis Cortex (Hou Po) 10 g, Bupleuri Radix (Chai Hu) 8 g, Phenylleucone (Qing Feng) 10 g, Angelicae Dahuricae Radix (Bai Zhi) 10 g, Citri Reticulatae Pericarpium (Chen Pi) 10 g |
| Fatigue + fever + dry cough + chills + gastrointestinal symptoms | Bupleuri Radix (Chai Hu) 12 g, Peucedani Radix (Qian Hu) 10 g, Angelicae Dahuricae Radix (Bai Zhi) 10 g, Phenylleucone (Qing Feng) 10 g, Bupleuri Radix (Huo Xiang) 10 g, Phenylleucone (Qing Feng) 10 g, Zingiberis Recens (Sheng Jiang) 10 g, Glycyrrhizae Radix et Rhizoma (Gan Cao) 3 g |
| Fatigue + gastrointestinal symptoms | Astragali Radix (Huang Qin) 3 g, Atractylodis Rhizoma (Cang Zhu) 15 g, Scutellariae Radix (Huang Qin) 15 g, Scutellariae Radix (Huang Qin) 15 g, Bupleuri Radix (Chai Hu) 15 g, Peucedani Radix (Jin Qiao) 12 g, Zingiberis Recens (Sheng Jiang) 10 g, Glycyrrhizae Radix et Rhizoma (Gan Cao) 3 g |
| Fatigue + gastrointestinal symptoms + heavy limbs | Bupleuri Radix (Chai Hu) 15 g, Scutellariae Radix (Huang Qin) 9 g, Perillae Foenum (Su Ye) 9 g, Codonopsis Radix (Dang Shen) 12 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 Fructus (Zao Cao) 6 g, Zingiberis Recens (Sheng Jiang) 2 g, Zingiberis Recens (Sheng Jiang) 2 g |
| Fever + upper respiratory tract infection symptoms + myalgia | Scrophulariae Spica (Jing Jie) 15 g, Saposchnikoviae Radix (Fang Feng) 15 g, Ephedrae Herba (Mu Huang) 10 g, Angelicae Dahuricae Radix (Bai Zhi) 10 g, Notopterygi Rhizoma seu Radix (Qiang Hua) 15 g, Bupleuri Radix (Huo Xiang) 10 g, Peucedani Radix (Jin Qiao) 10 g, Huanxiong Rhizoma (Chuan Xiong) 15 g, Zingiberis Recens (Sheng Jiang) 10 g, Glycyrrhizae Radix et Rhizoma (Gan Cao) 10 g |
| No clear symptoms      | Bulbus (Bai He) 30 g, Dendrobii Herba (Shi Hu) 10 g, Lonicerae Flos (Jin Yin Hua) 15 g, Forsythiae Fructus (Lian Qiao) 15 g, Imperatae Rhizoma (Bai Mao Gen) 10 g, Platycodonis Radix (Jie Geng) 10 g, Notopterygi Rhizoma seu Radix (Qiang Hua) 15 g, Atractylodis Rhizoma (Cang Zhu) 15 g, Zingiberis Recens (Sheng Jiang) 10 g, Zingiberis Recens (Sheng Jiang) 10 g |
| Korea                  |                                                          |
| No clear symptoms      | Forsythiae Fructus (Lian Qiao) 8 g, Lonicerae Flos (Jin Yin Hua) 8 g, Schizonepetae Spica (Jing Jie) 8 g, Saposchnikoviae Radix (Fang Feng) 8 g, Notopterygi Rhizoma seu Radix (Qiang Hua) 8 g, Atractylodis Rhizoma (Cang Zhu) 8 g, Zingiberis Recens (Sheng Jiang) 10 g, Zingiberis Recens (Sheng Jiang) 10 g, Zingiberis Recens (Sheng Jiang) 10 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)
3.2. 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.

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 decocction 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 Glycyrrhiza 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.

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 Glycyrrhiza Radix et Rhizoma has the strongest correlations among herbs. Both herbs are often prescribed together in herbal formulae. In the theory of traditional medicine, Citri Reticulatae Pericarpium regulates the Qi, nourishes the spleen, and dry dampness to resolve phlegm whereas Glycyrrhiza Radix et Rhizoma tonifies the Qi and enhances the function of Citri Reticulatae Pericarpium in resolving phlegm and reducing cough. Additionally, a prior study on the distribution patterns of herbs used for respiratory disease treatment using data mining methods also reported that Glycyrrhiza Radix et Rhizoma was often grouped with Citri Reticulatae Pericarpium. 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.

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. Glycyrrhizae Radix et Rhizoma possesses beneficial effects in respiratory diseases by nourishing Qi, resolving phlegm, and reducing cough. Based on the currently available evidence, this herb has also been proposed as a novel immunomodulatory drug for COVID-19. 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.

Funding

This study is supported by the Korea Institute of Oriental Medicine (KSN2013210).

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.

References

1. Lai KKR, Wu J, Harris R, McCann A, Collins K, Watkins D, et al. Coronavirus map: tracking the spread of the outbreak. <https://www.nytimes.com/interactive/2020/world/coronavirus-maps.html?action=click&module=RelatedLinks&pgtype=Article>. Accessed April 19, 2020.

2. World Health Organization (WHO). WHO Director-General’s opening remarks at the media briefing on COVID-19 - 11 March 2020. <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19-11-march-2020>. Accessed April 19, 2020.

3. Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P, et al. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe 2020;27:325–8.

4. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. The Lancet 2020;395:470–3.

5. World Health Organization (WHO). Coronavirus disease 2019 (COVID-19) situation report – 73. <https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200402-sitrep-73-covid-19.pdf>; Published 2020. Accessed April 28, 2020.

6. Tindale L, Coombe M, Stockdale JE, Garlock E, Lau WWY, Saraswat M, et al. Transmission interval estimates suggest pre-symptomatic spread of COVID-19. medRxiv 2020;2020.03.03.20029983.

7. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med 2020;172:577–82.

8. Xie M, Chen Q. Insight into 2019 novel coronavirus — an updated intram review and lessons from SARS-CoV and MERS-CoV. Int J Infect Dis 2020;94:119–24.

9. Ang L, Lee HW, Choi JY, Zhang J, Soo Lee M. Herbal medicine and pattern identification for treating COVID-19: a rapid review of guidelines. Integ Med Res 2020;9:100407.

10. Luo H, Tang QL, Shang YX, Liang SB, Yang M, Robinson N, et al. 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;26:243–50.

11. Chan KW, Wong VT, Tang SCW. COVID-19: an update on the epidemiological, clinical, preventive and therapeutics evidence and guidelines of integrative Chinese-Western medicine for the management of 2019 novel coronavirus disease. Am J Chin Med 2020;48:737–62.

12. Wu YQ, Zou L, Yu X, Sun D, Li SB, Tang L, et al. Effects of integrated traditional Chinese and western medicine on COVID-19: a systematic review. Shanghai J Tradit Chin Med 2020;54:29–36.

13. Yang Y, Islam MS, Wang J, Li Y, Chen X. Traditional Chinese medicine in the treatment of patients infected with 2019-novel coronavirus (SARS-CoV-2): a review and perspective. Int J Biol Sci 2020;16:1708–17.

14. National Health Commission of the People’s Republic of China. New coronavirus infected pneumonia prevention and control protocol. <http://www.nhc.gov.cn/jkj/s7923/202001/470b128513fe46f086d79667db9f76a5.shtml>. Published 2020.

15. Chen Y, Fan J, Meng XC. Analysis of the medication rule of Glycyrrhiza uralensis-containing antitussive prescriptions based on 2015 edition of Chinese pharmacopoeia (part I). Zhongyi Yaofang 2020;31:281–6.

16. Xi SY, Gong YW. Essentials of Chinese materia medica and medical formulas: new century traditional Chinese medicine. 1st ed. Academic Press; 2017.

17. Fu X-j, Song X-x, Wei L-b, Wang Z-g. 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;19:621–8.

18. Shi Q, Liu Z, Yang Y, Geng P, Zhu Y-y, Zhang Q, et al. Identification of anti-asthmatic compounds in Pericarpium citri reticulatae and evaluation of their synergistic effects. Acta Pharmacol Sin 2009;30:567–75.

19. Yu X, Sun S, Guo Y, Liu Y, Zhang D, Li G, et al. Citri Reticulatae Pericarpium (Chen Pi) (Chenpi): botany, ethnopharmacology, phytochemistry, and pharmacology of a frequently used traditional Chinese medicine. J Ethnopharmacol 2018;220:265–82.

20. Xing XL, Liu D, Bian K, Zhang DD. Study on in vitro anti-inflammatory activity of total flavonoids from Glycyrrhiza Radix et Rhizoma (Gan Cao) and its ingredients. Zhongguo Zhong Yao Za Zhi 2013;38:99–104.

21. Chen F, Chan KH, Jiang Y, Kao YTT, Lu HT, Fan KW, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol 2004;31:69–75.

22. Li T, Peng T. Traditional Chinese herbal medicine as a source of molecules with antiviral activity. Antiviral Res 2013;97:1–9.

23. Yang R, Wang L-q, Yuan B-c, Liu Y. The pharmacological activities of licorice. Planta Med 2015;81:1654–69.

24. Luo L, Jiang J, Wang C, Fitzgerald M, Hu W, Zhou Y, et al. Analysis on herbal medicines utilized for treatment of COVID-19. Acta Pharm Sinica B 2020, http://dx.doi.org/10.1016/j.apsb.2020.05.007. In press.