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Hot Topic

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*

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ABSTRACT **Objective:** Since December 2019, an outbreak of corona virus disease 2019 (COVID-19) occurred in Wuhan, and rapidly spread to almost all parts of China. This was followed by prevention programs recommending Chinese medicine (CM) for the prevention. In order to provide evidence for CM recommendations, we reviewed ancient classics and human studies. **Methods:** Historical records on prevention and treatment of infections in CM classics, clinical evidence of CM on the prevention of severe acute respiratory syndrome (SARS) and H1N1 influenza, and CM prevention programs issued by health authorities in China since the COVID-19 outbreak were retrieved from different databases and websites till 12 February, 2020. Research evidence included data from clinical trials, cohort or other population studies using CM for preventing contagious respiratory virus diseases. **Results:** The use of CM to prevent epidemics of infectious diseases was traced back to ancient Chinese practice cited in *Huangdi's Internal Classic* (Huang Di Nei Jing) where preventive effects were recorded. There were 3 studies using CM for prevention of SARS and 4 studies for H1N1 influenza. None of the participants who took CM contracted SARS in the 3 studies. The infection rate of H1N1 influenza in the CM group was significantly lower than the non-CM group (relative risk 0.36, 95% confidence interval 0.24–0.52; *n*=4). For prevention of COVID-19, 23 provinces in China issued CM programs. The main principles of CM use were to tonify qi to protect from external pathogens, disperse wind and discharge heat, and resolve dampness. The most frequently used herbs included *Radix astragali* (Huangqi), *Radix glycyrrhizae* (Gancao), *Radix saposhnikoviae* (Fangfeng), *Rhizoma Atractylodis Macrocephalae* (Baizhu), *Lonicerae Japonicae Flos* (Jinyinhua), and *Fructus forsythia* (Lianqiao). **Conclusions:** Based on historical records and human evidence of SARS and H1N1 influenza prevention, Chinese herbal formula could be an alternative approach for prevention of COVID-19 in high-risk population. Prospective, rigorous population studies are warranted to confirm the potential preventive effect of CM.

KEYWORDS Chinese medicine, corona virus disease 2019 (COVID-19), prevention program, clinical evidence, review

In December 2019, a pneumonia associated with the corona virus disease 2019 (COVID-19) emerged in Wuhan, Hubei Province, China.[1] It is highly contagious and has quickly spread to many other parts of China and some other countries within 1 month since the first report emerged. As of February 11, 2020, 44,653 cases of confirmed infections and 1,113 deaths have been reported in Chinese mainland.[2] Outside of China, there had been 395 confirmed cases and 1 death from 24 countries were reported as of February 11, 2020.[3] The outbreak of COVID-19 raised intense attention not only within China but internationally.[4] On 20 January 2020, the Chinese government added it to the Notifiable Communicable Disease List and gave the highest priority to its prevention and treatment.[5] On 30 January 2020, the World Health Organization

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(WHO) declared a public health emergency of international concern for China's COVID-19.

Although the WHO said: "To date, there is no specific medicine recommended to prevent or treat the novel coronavirus",[6] in China, historically, when the outbreak started, Chinese medicine (CM) approaches including oral administration of preventive herbal formulae, wearing CM sachets, indoor herbal medicine fumigation, etc. were recommended for prevention and treatment.[7,8] For example, in 2003, CM approaches were used to prevent and treat severe acute respiratory syndrome (SARS),[9,10] which was the most serious infectious disease outbreak in China prior to the COVID-19. In 2009, during the pandemic of H1N1 influenza around the world, the National Administration of Traditional Chinese Medicine of China issued a CM prevention program, which included 4 Chinese herbal medicine (CHM) formulae for adults of different CM body constitutions and one for children.[11] The current outbreak of COVID-19 resulted in many provinces in China issuing CM prevention and control programs, among which the prevention programs are mainly oral CHM formulae. This study has reviewed the historical and human research evidence on CM in preventing and control of infections in order to provide guidance for the prevention of COVID-19.

METHODS

Data Sources

Three types of data were searched, including historical classics records, human research evidence and current prevention programs. (Ⅰ) Historical classics records: records on the prevention of epidemic diseases in ancient CM books were searched, including history, treatment principles, medicines and application of CM to prevent epidemic disease. (Ⅱ) Human research studies: studies to evaluate the preventive effects of CM on contagious respiratory virus diseases were included. The inclusion criteria were as follows. (1) Study design: clinical trials, cohort studies, and other population studies without control. (2) Population: high-risk populations exposed to SARS or H1N1 influenza. (3) Intervention: oral CHM formulae, including decoction, granules, or patent medicine. (4) Control: placebo, blank or without control group. (5) Outcome: infection rate defined as laboratory-confirmed incidence of disease. (Ⅲ) Current prevention programs: CM prevention programs for COVID-19 issued by the state or provincial health authorities in China. Considering that some provinces had regularly updated the programs according to the local prevalence and clinical practice, the most recent versions of the programs were included for analyses in this study.

Literature Search

Retrieval strategy differed among the above three types of data. The first type of data was based on mainly manual retrieval of ancient books of CM on epidemic diseases, supplemented by electronic database retrieval. The list of literature retrieved was determined by discussion among all authors. Secondly, 6 databases were searched including PubMed, Google Scholar, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Data, and CQVIP database, with the key words of "severe acute respiratory syndrome" (or "SARS"), "influenza", "H1N1", "prevent*" and "Chinese medicine" (pinyin: zhongyi or zhongyao). Thirdly, government websites or official media websites were searched for prevention programs on COVID-19. Two authors (Luo H and Tang QL) conducted the literature search independently. The search date was up to February 10, 2020.

Data Extraction and Analysis

The following data were extracted and analyzed: source of evidence, time of publication or release, author, setting, basis for formulation of CM prevention strategy, composition of CM prescription, target disease, course of prevention, effect, and adverse reaction. The data was qualitatively described and presented, and if possible, quantitative or descriptive statistics were conducted. When the data were available for pooling, meta-analysis would be conducted by RevMan 5.3 software (https://community.cochrane.org/help/tools-and-software/revman-5/revman-5-download).

RESULTS

CHM Formula for Preventing "Pestilence" in Ancient CM Classics

The theory of prevention and treatment of "pestilence" (refers to fatal epidemic disease, pinyin: wenyi) in CM originated from *Huangdi's Internal Classic* (Huang Di Nei Jing), which was written about 2000 years ago.[12] It suggested two aspects which should be employed to prevent the spread of epidemics. One was to maintain and improve the

healthy qi in the body by taking preventive medicine [Xiaojin Dan (小金丹) in *Huangdi's Internal Classic*, the first recommended formula of CM to prevent pestilence], healthy diet care, exercise and so on, so as to resist the invasion of external pathogen, and the other was to avoid the source of infection.[13] These two principles of epidemic disease prevention have been followed by CM practitioners till now.[12,14]

Since *Huangdi's Internal Classic*, a large number of formulae for preventing epidemic diseases have been recorded in other ancient CM classics, such as, the *Handbook of Prescriptions for Emergencies* (Zhou Hou Bei Ji Fang), *Essential Prescriptions Worth a Thousand Gold for Emergencies* (Bei Ji Qian Jin Yao Fang), *Medical Secrets of an Official* (Wai Tai Mi Yao), *Compendium of Materia Medica* (Ben Cao Gang Mu), etc.[15] The famous doctor SUN Si-miao (541–682 AD) expounded the basis of medicines to prevent "pestilence" in his book *Essential Prescriptions Worth a Thousand Gold for Emergencies*: "pestilence comes from nature, so to prevent it, we need to find medicinal herbs that also come from nature. People would not be infected if they know and take preventive medicine."[16] A literature study compared the characteristics of medicinal formulae for preventing pestilence in different periods of ancient China, found that during the Jin and Tang Dynasties (3rd–10th century AD), medicinal formulae were mainly used to eliminate the pathogenic factors, while Ming and Qing dynasties (14–20th century AD) focused on fortifying Spleen (Pi), resolving dampness, clearing heat, and detoxifying.[17]

Although many formulae for pestilence prevention were recorded in ancient CM books, the case description of prevention was relatively rare. Through limited literature searches, we found an interesting case report: SU Shi (1037-1101 AD), a famous poet in the Northern Song Dynasty, accidentally found a formula for preventing pestilence named Sheng San Zi (圣散子), a powder consisting of 22 herbs.[18] Later, when he was demoted to Huangzhou, Hubei Province, the pestilence had been outbreak for several years. He disclosed the prescription to the local people. After taking this formula, the number of patients with the disease was significantly reduced, and many lives were saved. This story was recorded by SU Shi himself, when he wrote a preface to his doctor friend PANG An-shi's book *General Treatise on Febrile Diseases* (Shang Han Zong Bing Lun).[18]

Evidence of CHM Formula for Preventing SARS

Three studies were identified including 1 controlled study[19] and 2 single cohort studies[20,21] conducted during the epidemic of SARS.

Lau, et al[19] designed a controlled study to evaluate a herbal formula for prevention of SARS (no herbal intervention in the control group) and conducted it in Hong Kong SAR, China. The sample size was 16,437 (1,063 in the herbal group and 15,374 in the non-herbal group), and all participants were hospital care workers including doctors, nurses, and other staff. The result showed that none of the participants who took modified formula of Yupingfeng Powder (玉屏风散) plus Sangju Decoction (桑菊饮) contracted SARS, while 64 out of 15,347 (0.4%) in the non-herbal group were infected with SARS (P=0.035). Nineteen cases (1.8%) appeared minor adverse effects after 14 days taking herbal medicine, including diarrhea, sore throat, dizziness, and nausea.

Both single cohort studies were conducted in Beijing, China with sample sizes of 3,561[21] and 163, respectively. All participants were medical staff from two hospitals, where SARS patients were recruited and treated during the study period. Among them, Xu, et al's study[20] only included first-line medical staff in treating SARS. The courses of taking herbal formulae for prevention were 6 days[20] and 12–25 days,[21] respectively. The formulae used in these studies were both classical formula Yupingfeng Powder plus some heat-clearing and detoxifying herbs. The results showed that none of the participants who took the preventive herbal medicine had contracted SARS in the two studies. Information on the safety of the herbal medicines was not reported.

The details of the preventive herbal formulae of the three studies are presented in Table 1.

Evidence of CHM Formula for Preventing H1N1 Influenza

Four studies were identified, including 3[22-24] randomized controlled trials (RCTs) and 1[25] non-randomized controlled clinical study. All the studies were conducted during the prevalence of H1N1 influenza in Chinese mainland and published in Chinese. In

Table 1. Ingredients of Herbal Formulae for Preventing SARS

Study	Latin name	Pinyin	Chinese name
Lau JT 2005[19]	*Folium mori*	Sangye	桑叶
	Flos chrysanthemi	Juhua	菊花
	Semen armeniacae amarum	Xingren	杏仁
	Fructus forsythia	Lianqiao	连翘
	Herba menthae	Bohe	薄荷
	Radix platycodonis	Jiegeng	桔梗
	Radix glycyrrhizae	Gancao	甘草
	Rhizoma phragmitis	Lugen	芦根
	Radix astragali	Huangqi	黄芪
	Radix saposhnikoviae	Fangfeng	防风
	Folium isatidis	Banlangen	板蓝根
	Radix scutellariae	Huangqin	黄芩
Xu JY 2006[20]	*Lonicerae Japonicae Flos*	Jinyinhua	金银花
	Radix astragali	Huangqi	黄芪
	Rhizoma Atractylodis Macrocephalae	Baizhu	白术
	Radix saposhnikoviae	Fangfeng	防风
	Glehniae Radix	Shashen	沙参
	Crystal sugar	Bingtang	冰糖
Zhang L 2005[21]	*Radix astragali*	Huangqi	黄芪
	Rhizoma Atractylodis Macrocephalae	Baizhu	白术
	Radix saposhnikoviae	Fangfeng	防风
	Cyrtomium fortune J. Sm.	Guanzhong	贯众
	Isatidis Folium	Daqingye	大青叶
	Radix Scutellariae	Huangqin	黄芩
	Talcum	Huashi	滑石
	Radix glycyrrhizae	Gancao	甘草

these studies, participants were exposed to high-risk environments, such as hospitals and schools where H1N1 influenza occurred. The total sample size was 25,636 with the largest one of 25,329.[25] The tested herbal interventions included self-made herbal formulae and Chinese patent medicines [Qingjie Fanggan Granule (清解防感颗粒), Kangbingdu Oral Liquid (抗病毒口服液); Ganmao Qingre Granule (感冒清热胶囊)]; while in the control group, 1 study used placebo and 3 used blank control. The course of herbal formulae ranged from 3 to 7 days, while the follow-up ranged from 5 to 30 days. The outcome measure was infection rate of H1N1 influenza tested by laboratory serological diagnosis. One study reported that no adverse events occurred,[22] while the others did not report. The details of the characteristics of included trials are presented in Table 2.

The data on infection rate of H1N1 influenza from 4 studies were pooled in meta-analysis. The results showed that the infection rate in the herbal formulae group was significantly lower than that in the control group [relative risk (RR) 0.36, 95% confidence Interval (CI) 0.24–0.52, $P<0.01$]. A sensitivity analysis was conducted to exclude non-RCT and the results showed similar effect (RR 0.36, 95% CI 0.21–0.62, $P<0.01$, Figure 1).

Summary of Officially Issued CM Prevention Recommendations for COVID-19

Up to February 12, 2020, the National Health Commission of China has issued 5 versions of diagnosis and treatment programs for COVID-19, but none have included any content on CM prevention and control, but on treatment since the 3rd versions.[26]

Table 2. Characteristics of Included Trials of Herbal Formulae for H1N1 Influenza

Study	Design type	Population	Average age (Year)	Sample size (Case, P/C)	Herbal intervention	Control	Course (d)	Follow up (d)	Outcome
Song YP 2019[22]	RCT	Population in close contact with H1N1 influenza patients; high-risk population	P: 25.6±14.2 C: 27.1±14.5	200 (100/100)	Qingjie Fanggan Granule	Placebo	3	30	Infection rate; adverse event
Liu L 2013[23]	RCT	Medical staff	P: 30.5±5.3 C: 31.4±4.7	3 (28/25)	Decoction of self-made formula[*1]	Blank	7	10	Infection rate
Xia BL 2010[24]	RCT	Population in close contact with H1N1 influenza patients	23.5 (18–26)	54 (27/27)	Kangbingdu Oral Liquid; Ganmao Qingre Granule	Blank	3	14	Infection rate
Liu BL 2010[25]	CCT	Student	Not report	25329 (23947/1382)	Decoction of self-made formula[*2]	Blank	5	5	Infection rate

Notes: RCT: randomized controlled trial; CCT: controlled clinical trial; C: control group; P: prevention group. Ingredients of formulae: [*1] *Arnebiae Radix* (Zicao), *Herba Menthae* (Bohe), and *Radix Glycyrrhizae* (Gancao). [*2] *Cyrtomium Fortune* J. Sm (Guanzhong), *Lonicerae Japonicae Flos* (Jinyinhua), *Fructus Forsythiae* (Lianqiao), *Folium Isatidis* (Banlangen), *Fructus Arctii* (Niubangzi), *Herba Agastaches* (Huoxiang), *Lophatheri Herba* (Zhuye), *Radix Glycyrrhizae* (Gancao), and *Isatidis Folium* (Daqingye).

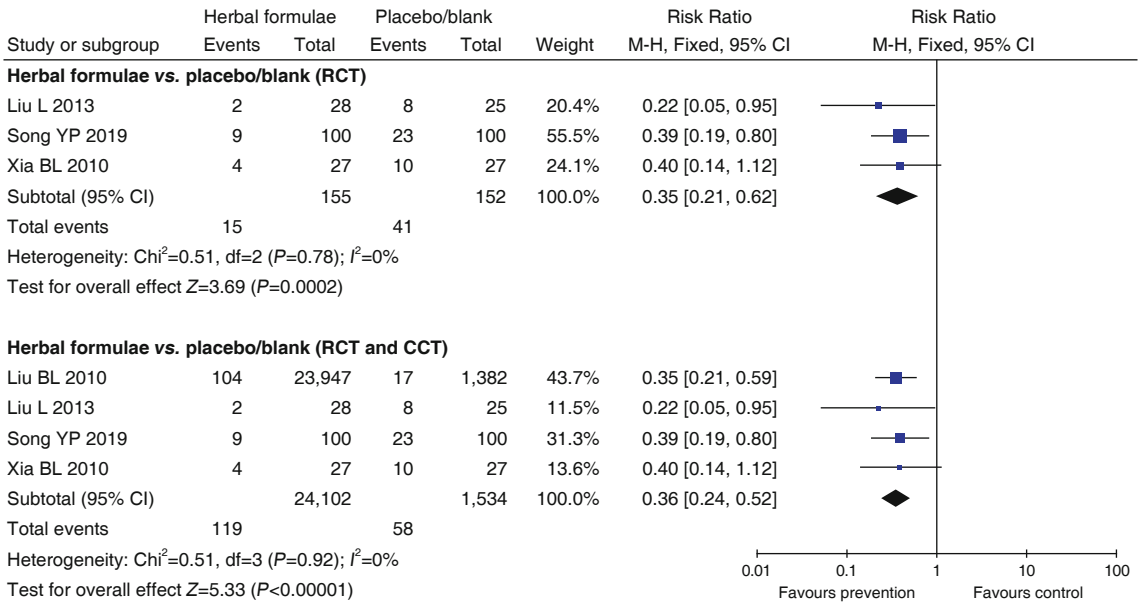

Figure 1. Meta-Analysis of Comparison between Chinese Medicine Prevention and Control (Blank or Placebo) on Infection Rate of H1N1 Influenza

Of the 31 provinces (including autonomous regions, and municipalities) in Chinese mainland, health authorities in 23 provinces had officially issued programs recommending herbal formulae to preventing COVID-19. These 23 provinces cover 7 regions of mainland: Northeast, North, Central (including Wuhan, Hubei Province, the original outbreak of COVID-19), South, East, Northwest, and Southwest China. All programs were formulated by clinical experts organized by local health authorities according to local geographic and climate characteristics and COVID-19 prevalent conditions. The earliest program recommending CM for prevention was issued by Sichuan Province on January 21, 2019. Ten provinces have updated their programs since the first announcement, 7 of them have issued the 2nd edition and 3 issued the third edition. The applicable population of preventive programs included general and special population (such as the elderly, children, pregnant women, patients with chronic comorbidity diseases). Different groups of populations had specified preventive CM formulae. The programs issued by the 23 provinces included CM formulae ranging from 1 up to 10, with an average of 3.4 per program. With regard to the course of CM formulae for prevention, 11 provinces recommended from 3 to 14 days, while 12 provinces did not mention. In addition, Tibet Autonomous Region recommended Tibetan medicine and Guizhou province recommended Miao medicine formulae (one of the minority folk medicines). The basic characteristics of 23 provincial programs are shown in Appendix 1.

We counted the frequency of the herbs used in CM formulae for prevention of general population issued by the 23 provinces. The results showed that these formulae contained 54 different herbs, of which 19 herbs with a frequency of use for 3 or more times in preventive formulae for general population (Figure 2). The top two were *Radix astragali* (Huangqi) and *Glycyrrhizae Radix Et Rhizoma* (Gancao).

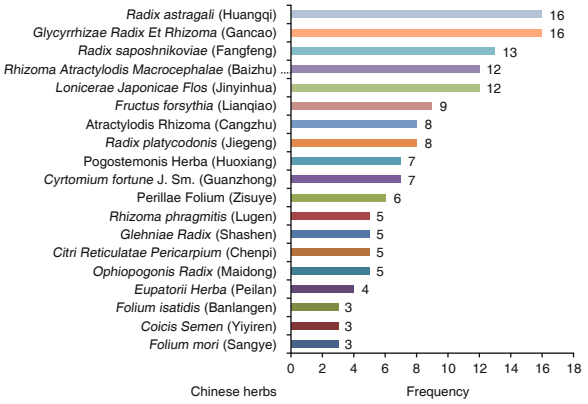

Figure 2. Frequency of Commonly Used Herbs in Preventive Formulae for COVID-19

DISCUSSION

As a new emerging acute respiratory infectious disease, COVID-19 lacks effective methods to control and treat the infection. It is urgent and reasonable to explore effective intervention strategies from traditional

medicine for its prevention. This study examines the historical records for infection prevention in CM, as well as previous clinical evidence on CM prevention for similar public health emergencies such as SARS and H1N1 influenza. Recorded literature showed that the use of CM to prevent epidemics of infectious diseases can be traced back to ancient CM practice over thousands of years, and its successful effects were preliminarily substantiated by modern human clinical researches when applied to SARS and H1N1 influenza epidemics suggesting that historical CM experience is a worthwhile approach.

Based on the comprehensive analyses of the prevention programs issued by 23 provinces since the COVID-19 outbreak, we found that the main CM principles in preventing COVID-19 were to tonify qi to protect and provide defense from external pathogens, disperse wind and discharge heat, and resolve dampness with aroma. It was also similar to the characteristics of CHM formulae for preventing "pestilence" in ancient times and SARS in 2003.[17,19] The 6 most commonly used herbs were *Astragali Radix* (Huangqi), *Glycyrrhizae Radix Et Rhizoma* (Gancao), *Saposhnikoviae Radix* (Fangfeng), *Atractylodis Macrocephalae Rhizoma* (Baizhu), *Lonicerae Japonicae Flos* (Jinyinhua), and *Forsythiae Fructus* (Lianqiao). *Astragali Radix* (Huangqi), *Saposhnikoviae Radix* (Fangfeng), and *Atractylodis Macrocephalae Rhizoma* (Baizhu) are all ingredients of a classical herbal formula Yupingfeng Powder, for tonifying qi to protect from external pathogens. In Lao, et al's controlled study[19] of CM formula for preventing SARS, Yupingfeng Powder was also the main ingredients. Some studies have confirmed that Yupingfeng Powder has antiviral, anti-inflammatory and immunoregulatory effects.[27,28] *Japonicae Flos* (Jinyinhua) and *Forsythiae Fructus* (Lianqiao) are the core components of Yinqiao Powder, which is a classical formula used to prevent and treat respiratory infectious diseases in ancient.[29] An experimental study found that the effect of Yinqiao Powder (银翘散) in preventing and treating upper respiratory tract infection could be explained by its antibacterial and antiviral properties and improvement of the function of upper respiratory mucosal immune system.[30] A multicenter, large-scale, randomized trial found that Yinqiao Powder plus another heat-clearing formula could reduce time to fever resolution in patients with the H1N1 influenza virus infection.[29]

At present, the National Health Commission of China has not issued a CM prevention program for COVID-19. The reasons may be, first, according to the CM theory of three-factors concerned treatment (Sanyin Zhiyi, 三因制宜), due to the differences of individual, regional, and seasonal factors in the occurrence and distribution of diseases, these factors should be considered in prevention and treatment,[31,32] and second, lack of solid evidence of CM formula for COVID-19. By comparing and analyzing the prevention programs issued by provincial levels, we also found that there was slight regional difference in the recommended herbal formulae and prescription principles. For example, due to the dry climate in northern China, there are additional one or two herbs for nourishing yin in the formula, like *Glehniae Radix* (Shashen) and *Ophiopogonis Radix* (Maidong), while in the south, due to the humid climate, aromatic herbs with the function of resolving dampness and turbidity are used in the formulae, like *Pogostemonis Herba* (Huoxiang) and *Eupatorii Herba* (Peilan).

Individual difference was also considered in the prevention programs in some provinces. There were two or more formulae recommended in 18 provinces' programs, which were applicable for different populations, such as the elderly, children, pregnant women, or patients with chronic comorbidity diseases, population in close contact with COVID-19 patients, etc. In addition, 7 provinces or province-level municipality (Beijing, Tianjin, Shanxi, Henan, Hunan, Shandong, Yunnan) recommended formulae according to the types of CM body constitutions of the population. This tailored prevention strategy might help to improve the preventive effect.

We suggest that the safety should also be paid attention to when taking CHM formula to prevent COVID-19, especially when they are used for long period. The public should choose the prescriptions under the guidance of CM doctors according to the program issued by provincial health authorities, and avoid taking the prescriptions or herbs with unknown origin and without officially approval. It should also be noted that the prevention advice for taking decoction were not reported in the 12 provinces' program. According to the programs of other provinces, it is appropriate to take the decoction for 1 week.

Based on the consideration of health economics

and balance of risks and benefits, we do not recommend that all people should take CHM to prevent COVID-19. Due to the highly contagion,[33,34] high-risk populations exposed to COVID-19 patients, including medical personnel, family members, and other people who are in close contact with COVID-19 patients, as well as residents living in COVID-19 outbreak areas, would probably benefit from taking CHM formulae for prevention. These formulae recommended in the prevention programs are easily available in pharmacies and hospitals across the country.

There are some limitations within this study. Firstly, historical records of using CM for "pestilence" prevention were examined in the review, however, the term "pestilence" might be a broad concept in ancient CM books, including infectious diseases transmitted through respiratory tract, digestive tract and other ways, so it might not be completely representative of the respiratory viral diseases especially the COVID-19. Secondly, as there is no direct clinical evidence for the prevention of the new emerging COVID-19, currently reported researches were from previous literature on the prevention of SARS and H1N1 influenza by CM which can only be considered as indirect evidence to refer to the current outbreak. Thirdly, the prevention programs for preventing COVID-19 were issued shortly after the outbreak, which were formulated by CM experts based on their previous experience in the prevention and treatment of similar diseases and their initial understanding of the disease; therefore, the actual effect of these programs needs to be verified in clinical application, and updated and improved according to the evidence of new researches on COVID-19.

For future studies, we recommend prospective cohort studies, RCTs or registry studies to evaluate the effect of CHM formulae in prevention of COVID-19. At present, as the COVID-19 has not yet been controlled, we expect that a series of prospective population studies with rigorous design and large sample should commence with protocol registration, ethical approval, and implementation in a timely manner, to produce reliable evidence for CM prevention of COVID-19 or similar emerging respiratory infectious diseases in the future.

In conclusion, based on historical records and clinical evidence of SARS and H1N1 influenza prevention, CHM formula could be an alternative approach for the prevention of COVID-19 in high-risk population while waiting for the development of a successful vaccine. Prospective well design population studies are needed to evaluate the preventive effect of CM.

Conflicts of Interest

The authors declare that they have no competing interest.

Author Contributions

Luo H, Tang QL, and Liu JP conceived of the design and carried out the study. Tang QL undertook the literature review of historical evidence and assisted in writing the manuscript. Shang YX and Liang SB translated and assisted in analyzing Chinese data. Yang M provided suggestions for the design of study. Luo H undertook the literature review of prevention programs and wrote the manuscript. Liu JP supervised the study and revised the manuscript. Robinson N revised the manuscript and provided important perspectives. All authors read and approved the final manuscript. Luo H and Tang QL contributed equally to this work.

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