



# Data-mining-based of ancient traditional Chinese medicine records from 475 BC to 1949 to potentially treat COVID-19

Yaxue Han<sup>1</sup>  | Zi Yang<sup>2</sup>  | Shan Fang<sup>3</sup> | Mengqing Zhang<sup>1</sup> | Zhijun Xie<sup>3</sup> | Yongsheng Fan<sup>3</sup> | Ting Zhao<sup>3</sup>

<sup>1</sup>The First School of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China

<sup>2</sup>The Third School of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China

<sup>3</sup>School of Basic Medical Sciences, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China

## Correspondence

Yongsheng Fan and Ting Zhao, School of Basic Medical Sciences, Zhejiang Chinese Medical University, No. 548 Binwen road, Binjiang district, Hangzhou, China.  
 Email: fyszjtc@163.com and ztjztc@163.com

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## Abstract

Traditional Chinese Medicine (TCM) plays a role in preventing and treating COVID-19 in China. Based on the manifestations and symptoms of COVID-19, our study used the data mining method to summarize related therapeutic experience left by predecessors who used TCM to treat epidemics in their eras. Initially, we collected abundant medical records with similar manifestations of COVID-19 in Chinese ancient times. The key words including *wen* (瘟), *yi* (疫), *li* (痢), and *zhang* (瘴) were searched in *ZhongyiZhiku* (<https://www.zk120.com/>) from Warring States Period (475 BC–221 BC) to the Republic of China era (1912–1949) to locate ancient medical records according to inclusion criteria and exclusion criteria. Moreover, COVID-19-related manifestations and corresponding medications in those records were categorized. Eventually, Traditional Chinese Medicine Inheritance Support System version 2.5 was used to build a medical record database of TCM treating COVID-19. Our study collected 263 epidemic medical records comprising COVID-19 related manifestations and found that Chinese Materia Medica (CMM) combinations excavated from ancient medical records included *Ren Shen Bai Du San*, *Wu Ling San*, *Xiao Chai Hu Tang*, *Da Cheng Qi Tang*, *Da Chai Hu Tang*, *Ling Gui Zhu Gan Tang*, and *Qing Wen Bai Du Yin*. The recurrent CMMs with a high frequency for treating COVID-19 manifestations were *Scutellariae Radix* (*Huang Qin*), *Paeoniae Alba Radix* (*Bai Shao*), *Poria* (*Fu Ling*), and *Bupleuri Radix* (*Chai Hu*). Our study suggests that TCM might offer new therapeutic strategies for COVID-19.

## KEYWORDS

Chinese Materia Medica, COVID-19, traditional Chinese medicine, treatment based on syndrome differentiation

## Chinese Abstract

中医药在预防和治疗新型冠状病毒肺炎中发挥重要作用。为了应对该病并探索中医药治疗的方法，本项研究基于其临床表现，采用数据挖掘的方法，总结前人留下的宝贵的治疗经验。首先收集大量古代与该病症状相似的医案，根据纳入标准和排除标准，在中医智库(<https://www.zk120.com/>)中查找从战

Yaxue Han and Zi Yang contributed equally to this study.

国(公元前475-公元前221年)至中华民国(1912–1949)时期包含关键词瘟、疫、疠、瘴的医案。随后，用EXCEL分类医案中与该病相关的症状及其所使用的方药。最后，利用中医传承发展平台(TCMISS) 2.5版创建了中医治疗的医案数据库。研究结果共收集263份包含该病相关症状的医案，并根据挖掘出的药物组合锁定人参败毒散、五苓散、小柴胡汤、大承气汤、大柴胡汤、苓桂术甘汤及清瘟败毒饮，同时发现治疗该病的高频次药物包括黄芩、白芍、茯苓及柴胡。研究表明，中医药为新型冠状病毒肺炎的治疗提供了有价值的策略。

## 1 | INTRODUCTION

The 2019 coronavirus disease (COVID-19) is a disease caused by coronavirus-2 (SARS-CoV-2), which induces severe acute respiratory syndrome (Stasi et al., 2020). The pandemic is widespread and rapidly infectious (Liu & Liu, 2020). On January 30, 2020, WHO declared COVID-19 as a pandemic, with almost 100 million confirmed cases and more than 2.7 million deaths by March 22, 2021 around the world. These numbers are still increasing (<https://www.worldometers.info/coronavirus/>). When severely and critically ill, COVID-19 patients have dyspnea and decreased saturation of blood oxygen level, they need respiratory support, even invasive mechanical ventilation, and mechanical circulatory support. In the meantime (Liu et al., 2021), Traditional Chinese Medicine (TCM) interventions like Shengmai Injection and Shenfu Injection could be complementary to conventional medicine for preventing the disease progression. Specifically, the early intervention of TCM may promote immune function, reduce pulmonary inflammation, and reduce systemic inflammatory responses (Zhang et al., 2020). In addition, TCM appears to improve mild COVID-19 cases, including improving the main symptoms such as fever, fatigue, and cough, as well as shortening the course of the disease (Ouyang et al., 2021).

TCM has experienced a long process of development through accumulation of practical experiences and the theory of TCM is constantly improving (Liu et al., 2021). Knowledge of TCM's utility for epidemic diseases also has a long history. The presence of *yi bing* (疫病), a name that is still used for pandemics so far, was recorded 2,000 years ago in the *Zhou Dynasty Compilation of Changes* (Zhou Yi; Gu et al., 2020). *Shuo Wen Jie Zi*, the origin of Chinese characters, explained *yi* (疫) as epidemic diseases among civilians (Ma, Ma, et al., 2020). The manifestations of *yi* included dry throat and myalgia and were first recorded in *The Yellow Emperor's Inner Classic* (*Huang Di Nei Jing*), which is the foundation of TCM. Aside from *yi*, many other words refer to epidemic diseases as well. *Shi xing zhi qi* (时行之气), described as

similar manifestations among adults and children, was first brought into view by *Zhang Zhongjing* in *Treatise on Cold Damage* (*Shang Han Lun*). *Zhou Hou Bei Ji Fang* (Emergency Formulae to Keep Up One's Sleeve) pointed out that *li qi* (疠气) is one of the related pathogenic factors of contagious diseases. *Guai li zhi qi* (乖戾之气) first appeared in the *Zhu Bing Yuan Hou Lun* (Treatise on the Origins and Manifestations of Various Diseases). This was developed into the *li qi* theory (戾气论) written in the *Wen Yi Lun* (Treatise on Warm-Heat Pestilence), which emphasized that *Li Qi* could spread from person to person through the mouth and nose as the pathogen of *Yi Bing*.

TCM has accumulated 1,000 of years of experience in the treatment of epidemic diseases. An estimate is that more than 100 TCM formulae were invented for combating ancient epidemic infections throughout China's history (Lee et al., 2021). Recently, during the SARS epidemic in 2003, TCM was used as an auxiliary therapy to Western Medicine which was applied for the treatment of SARS, with 3,104 of 5,327 clinically confirmed patients (58%) in China received TCM treatment had a therapeutic beneficial effect (Chen et al., 2007). According to the official reports (Chen et al., 2007), the mortality rate in China was about 7%, which was lower than the global mortality (about 10%). For example, among 112 SARS inpatients in Guangdong Province TCM Hospital, under the treatment of TCM, the symptoms of 105 patients were improved (Xiao & Zhang, 2014). The treatment effect of TCM (Ding et al., 2017; Liu et al., 2017; Zhou et al., 2011) also happened in treating patients infected with H1N1, H7N9 (H7N9 avian influenza), and EVD (Ebola Virus Disease). In addition to TCM formulae, Chinese herbal tea, acupuncture (Zhu et al., 2021), moxibustion, Qigong (Da et al., 2021), and other TCM therapeutics also play a part in the treatment of these pandemics.

Today, data mining is widely used in TCM for analyzing medical records (Hsieh et al., 2020; You et al., 2019). Some studies recognized the contribution of TCM in fighting pestilence through data mining and analyzed

the related formulae (Ren et al., 2020). However, due to the diversity of pandemics, precise identification of the symptoms of COVID-19 patients among ancient epidemics is difficult. The Chinese Materia Medica (CMMs) and formulae applied to the similar manifestations as COVID-19 patients in ancient times might provide valuable information for combating the COVID-19 pandemic. Therefore, our study used known manifestations of COVID-19 to look back in ancient times in China during epidemics, using more than 1,800 ancient medical books containing effective formulae and CMM combinations during ancient epidemics. We used data mining methods to summarize therapeutic experience, using ancient TCM left by predecessors that may provide suggestions for clinical application of TCM to treat patients with COVID-19.

## 2 | METHODS

### 2.1 | Data collection

ZhongyiZhiku (<https://www.zk120.com/>) is the largest online library of ancient Chinese medicine books, supervised by the expert group of China Academy of Chinese Medical Sciences, which archives more than 1,800 classical TCM books and over 40,000 medical cases from Warring States Period (475 BC–221 BC) to the Republic of China era (1912–1949). Epidemic medical cases were retrieved by searching each key word, respectively, including *wen* (瘟), *yi* (疫), *li* (痢), and *zhang* (瘴).

#### 2.1.1 | Inclusion criteria and exclusion criteria

Medical records from Warring States Period (475 BC–221 BC) to the Republic of China era (1912–1949) comprising complete symptoms and medication were included. Medical records referring to epidemic diseases with incomplete symptoms and medication were not included. Follow-up visits with similar prescriptions were excluded.

### 2.2 | Data processing

By analyzing ancient epidemic medical cases, we extracted the known COVID-19 manifestations according to several literary sources (Du et al., 2020; Inomata et al., 2020; Jin et al., 2020). Other clinical manifestations and corresponding medications were also acquired from the cases. Later, the data of COVID-19 related manifestations and corresponding medications in each ancient epidemic medical case was input into a database (Excel). Then, the

clinical manifestations were standardized by *Standard Terminology for Common Symptoms in Chinese Medicine Clinical Practice* (Li & Ma, 2015) and CMMs were unified according to the *Chinese Pharmacopoeia* and *Chinese Materia Medica* (National Pharmacopoeia Commission, 2015; Zhong, 2016). After removing duplicate cases, at least two of our team (Y.X.H., F.S., and M.Q.Z.) confirmed accuracy of the data processing. Finally, Traditional Chinese Medicine Inheritance Support System (TCMISS) version 2.5 was used to build a medical records database of ancient TCM to potentially treat COVID-19.

### 2.3 | Data analysis

TCMISS version 2.5, recommended by the Academy of Chinese Medical Sciences, was used. This system is specialized in the analysis of TCM data by integrating the association rules algorithm and complex-system entropy method. Among them, the frequency of manifestations and CMMs were analyzed by the association rules algorithm of the statistical analysis, which was assessed by the support degree and confidence coefficient (Tang et al., 2019). The formula of the support degree is as below:

$$\text{Support}(A \rightarrow B) = P(A \cup B) = \frac{\text{sum}(A \& B)}{\text{sum}} \times 100\%$$

where A represents one of the manifestations or CMM and B represents the other manifestation or CMM. P (AUB) represents that the probability of A and B occurrence at the same time in the transaction set.

The support degree settings were changed according to the frequency of the specific manifestations. The confidence coefficient was 1 for this study. The networks were visualized and analyzed by Cytoscape 3.7.1 (Shannon et al., 2003). The complex system entropy method, an unsupervised learning algorithm, was applied for mining composition patterns with the maximum amount of information by setting the variables of correlation degree and penalty degree. The correlation degree implies the relevance between one CMM with the other ones, while a penalty degree is set for shielding interfering information (Wang, 2020). The settings of correlation degree = 8 and penalty degree = 2 are recommended by TCMISS.

## 3 | RESULTS

### 3.1 | Descriptive analysis

We found 263 ancient epidemic medical records, including with COVID-19 manifestations (Data S1). The

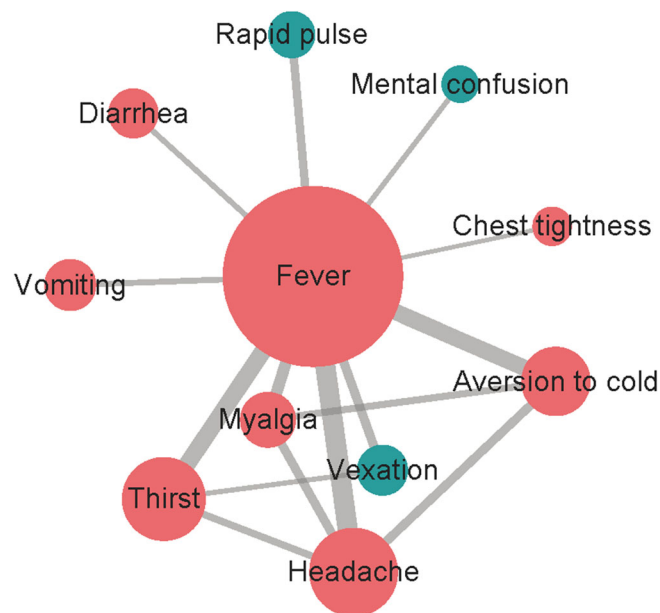
distribution details of the ancient epidemic medical records and COVID-19 manifestations are presented in Figure 1. The manifestations with occurrence more than 15 times were considered as the core manifestations and subjected for the following study. The top 10 COVID-19 manifestations in the ancient TCM records were fever, headache, thirst, aversion to cold, myalgia, vomiting, diarrhea, chest tightness, cough, and fatigue, as shown in Figure 2. The top 10 non-COVID-19 manifestations were vexation, rapid pulse, mental confusion, delirious speech, constipation, a surging pulse, a thready pulse or a wiry pulse, a yellow tongue coating, and poor appetite.

Two hundred and thirty-two CMMs were identified from the collected ancient medical records (Data S2). The 10 most frequently used CMMs were Glycyrrhizae Radix Et Rhizoma (*Gan Cao*, frequency = 158), Scutellariae Radix (*Huang Qin*, frequency = 87), Paeoniae Alba Radix (*Bai Shao*, frequency = 66), Bupleuri Radix (*Chai Hu*, frequency = 61), Ginseng Radix Et Rhizoma (*Ren Shen*, frequency = 58), Poria (*Fu Ling*, frequency = 57), Citri Reticulatae Pericarpium (*Chen Pi*, frequency = 52), Rhei Radix Et Rhizoma (*Da Huang*, frequency = 51), Platycodonis Radix (*JieGeng*, frequency = 47), and Rehmanniae Radix Recens (*Sheng Di Huang*, frequency = 47). Since Glycyrrhizae Rhizoma is mostly used as an envoy herb for harmonizing the actions of all other CMMs in a formula, we excluded Glycyrrhizae Rhizoma in the following study for analyzing the primary CMMs. As illustrated in Figure 3, the frequency of the CMMs channel entry into the Lung, Spleen, Stomach, and Heart channels surpassed 65%, among which the frequency of the Lung channel was the highest (20%). The CMMs were classified into 24 categories and the frequencies in each category are listed in Table 1. The details are provided in Data S3. Heat-clearing CMMs were the most commonly used in

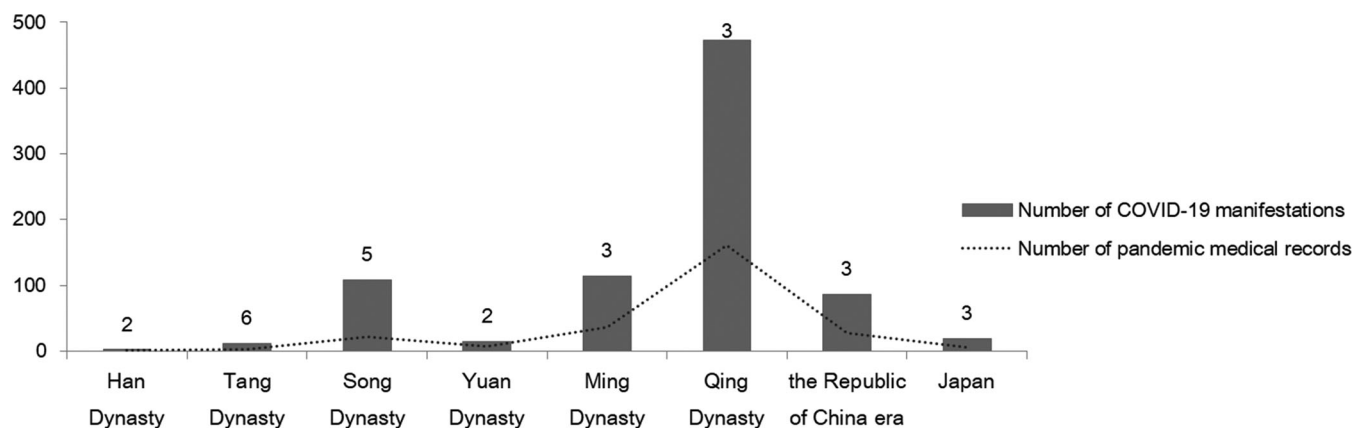
ancient epidemic medical records. The total frequency of heat-clearing CMMs, exterior-releasing CMMs, and qi-tonifying CMMs exceeded 50%.

### 3.2 | Association rule analysis

The analysis of the association rule was applied to study the collected manifestations in general. Figure 2 suggests



**FIGURE 2** The network of the common manifestations in medical records. The red circles represent the manifestations of COVID-19, while the green circles represent the non-COVID-19 manifestations. The size of the circles represent the frequency of the manifestation. The width of the lines represents the co-occurrence frequency of the two connected manifestations. The support was degree  $\geq 10\%$



**FIGURE 1** The distribution of pandemic medical records and COVID-19 manifestations. The numbers above represent the mean number of COVID-19 manifestations in each medical record of the specific period

### Frequency of CMMs channel entry

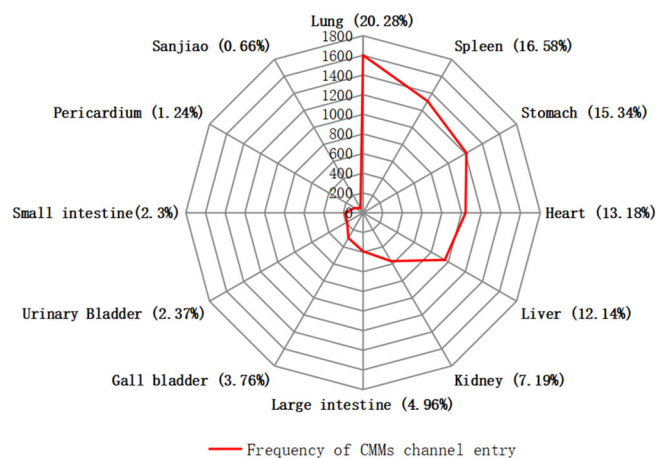


FIGURE 3 Frequency of CMMs channel entry

a close relationship between fever, headache, aversion to cold, thirst, myalgia, and vexation.

Next, the association rule of CMMs was analyzed for each manifestation listed in Table 2. Twenty-eight association rules corresponding to eight COVID-19 manifestations and four non-COVID-19 manifestations are shown in Table 3.

### 3.3 | Network analysis of manifestations and CMMs

To further understand the associations between the core manifestations and the high-frequency CMMs (frequency  $\geq 20$ ), the network of manifestations and CMMs was constructed, as illustrated in Figure 4. A node is defined as a hub when the degree of the node is more

TABLE 1 Frequency of CMMs categories

No.	CMMs category (quantity)	Frequency	Rate (%)	Cumulative frequency (%)
1	Heat-clearing CMMs (37)	606	22.82	22.82
2	Exterior-releasing CMMs (26)	451	16.99	39.81
3	Qi-tonifying CMMs (12)	317	11.94	51.75
4	Phlegm-resolving, cough-suppressing, and panting-relieving CMMs (25)	184	6.93	58.68
5	Qi-regulating CMMs (12)	164	6.18	64.86
6	Dampness-draining diuretic CMMs (13)	150	5.65	70.51
7	Blood-tonifying CMMs (6)	129	4.86	75.37
8	Dampness-resolving CMMs (8)	119	4.48	79.85
9	Purgation-promoting CMMs (8)	85	3.20	83.05
10	Blood-activating and stasis-resolving CMMs (12)	70	2.64	85.69
11	Yin-tonifying CMMs (7)	67	2.52	88.21
12	Liver-calming and wind-extinguishing CMMs (11)	57	2.15	90.36
13	Interior-warming CMMs (9)	49	1.85	92.20
14	Orifices opening CMMs (5)	40	1.51	93.71
15	Mind-calming CMMs (5)	33	1.24	94.95
16	Astringent CMMs (8)	33	1.24	96.20
17	Wind-dispelling and dampness-resolving CMMs (8)	28	1.05	97.25
18	Digestion-promoting CMMs (4)	27	1.02	98.27
19	CMMs for resolving toxin, killing worms, and relieving itching (4)	14	0.53	98.79
20	Worm-expelling CMMs (1)	13	0.49	99.28
21	Yang-tonifying CMMs (7)	9	0.34	99.62
22	Hemostatic CMMs (3)	5	0.19	99.81
23	CMMs for drawing out toxin, suppuration, and promoting granulation (1)	4	0.15	99.96
24	Vomiting-inducing CMMs(1)	1	0.04	100.00

**TABLE 2** The frequency of COVID-19 manifestations and non-COVID-19 manifestations in the pandemic medical records (frequency  $\geq 15$ )

COVID-19 manifestations	Frequency	Non-COVID-19 manifestations	Frequency
Fever	186	Vexation	52
Headache	91	Rapid pulse	48
Thirst	86	Mental confusion	38
Aversion to cold	71	Delirious speech	27
Myalgia	57	Constipation	20
Vomiting	53	Surging pulse	20
Diarrhea	51	Thready pulse	19
Chest tightness	40	Wiry pulse	18
Cough	33	Yellow coating	18
Fatigue	31	Poor appetite	18
Abdominal pain	29	Cold limbs	16
Sore throat	27		
Shortness of breath	22		
Expectoration	16		
Conjunctivitis	15		

than twofold of the median degree of all nodes in the same network (Li et al., 2007). Four CMMs, including *Scutellariae Radix*, *Paeoniae Radix*, *Alba Poria*, and *Bupleuri Radix* are classified as hub nodes in this network.

### 3.4 | Formulae associated with *Yi Bing* manifestations

According to *Formulae of Traditional Chinese Medicine* (Li, 2006), seven classical formulae were acquired from the collected CMMs, as listed in Table 4. These formulae are *Ren Shen Bai Du San*, *Wu Ling San*, *Xiao Chai Hu Tang*, *Da Cheng Qi Tang*, *Da Chai Hu Tang*, *Ling Gul Zhu Gan Tang*, and *Qing Wen Bai Du Yin*.

## 4 | DISCUSSION

TCM has guided prevention and treatment of pandemics, such as SARS, H7N9, and EVD (Du et al., 2020). Several reports point out TCM contributions to alleviating clinical manifestations of and promoting pharmacological investigations for COVID-19 (Luo, Jiang, et al., 2020; Luo, Ni, et al., 2020; Zhang et al., 2020; Zhou et al., 2020). In ancient times, TCM used empirical treatment, which may lead to useful potential applications to COVID-19 cases. One of the characteristics of *Yi Bing* is the similar manifestations among patients with COVID-19. Thus, the summary and

analysis of ancient TCM treatments may be particularly important for today's pandemic (Chen et al., 2020).

The selected prescriptions are mainly distributed in the Song, Ming, and Qing dynasties as well as the Republic of China era. Ancient medical records in the Song dynasty show similar manifestations of COVID-19. By collecting medical records associated with ancient epidemics, our study found that some manifestations might be ignored in COVID-19 clinical diagnoses, such as vexation, constipation, cold limbs, pulse manifestation, and tongue appearance. The level of vexation (anxiety) is higher in COVID-19 patients compared to healthy people (Qin et al., 2020). Constipation may occur in patients with COVID-19 (Chow et al., 2020). A symptom such as cold extremities mostly appears in shock cases of COVID-19 (Li et al., 2020). A clinical study of COVID-19 reported that a yellow tongue coating is associated with severe cases (Pang et al., 2020). Most manifestations in our study are found in the COVID-19 literature, which suggests that the retrospective analysis of ancient medical records might be meaningful for mining potential therapies.

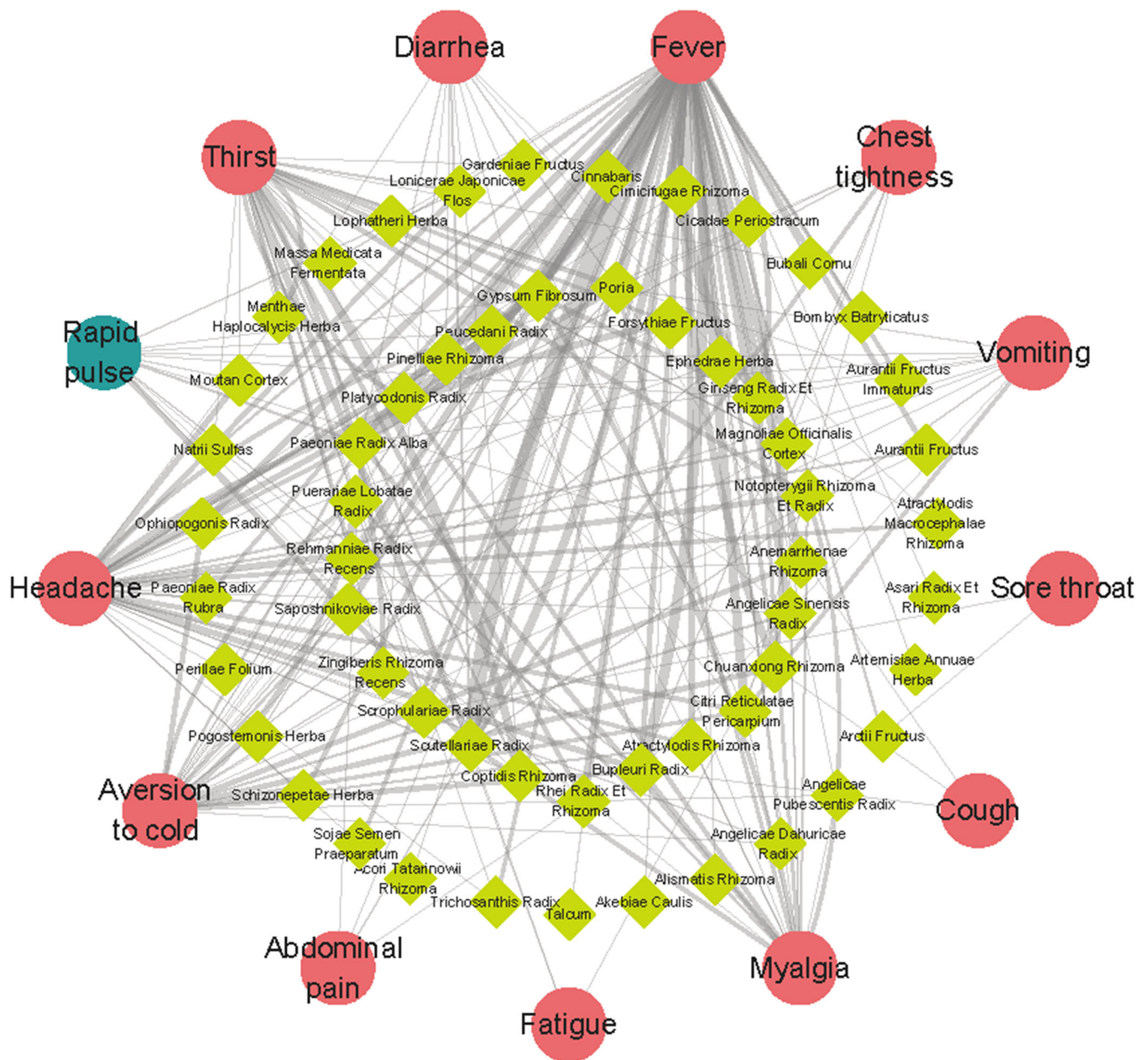
While COVID-19 primarily presents as a respiratory illness, one-third of the confirmed cases may also have gastrointestinal symptoms and neurological manifestations (Ahmadirad & Ghasemi, 2020; Rajan et al., 2020). Our study shows that the frequencies of CMMs channel entry into the Lung, Spleen, Stomach, and Heart channels rank as the top four in the channel list, which is surprisingly consistent with the COVID-19 analysis (Gu

TABLE 3 Association rule analysis of common manifestations in *yi bing* medical records

Category	Manifestation	Association rule of CMMs	Confidence (%)	Support (%)
COVID-19	Aversion to cold	Ginseng Radix Et Rhizoma, Notopterygii Rhizoma Et Radix → Platycodonis Radix	1	12
		Notopterygii Rhizoma Et Radix, Bupleuri Radix ≥ Platycodonis Radix	1	12
	Myalgia	Aurantii Fructus → Poria	1	14
		Chuanxiong Rhizoma, Bupleuri Radix → Platycodonis Radix	1	14
		Chuanxiong Rhizoma, Bupleuri Radix → Notopterygii Rhizoma Et Radix	1	14
		Chuanxiong Rhizoma, Bupleuri Radix and Platycodonis Radix → Notopterygii Rhizoma Et Radix	1	14
		Chuanxiong Rhizoma, Notopterygii Rhizoma Et Radix, Bupleuri Radix → Platycodonis Radix	1	14
		Chuanxiong Rhizoma, Bupleuri Radix → Notopterygii Rhizoma Et Radix, Platycodonis Radix	1	14
		Diarrhea	Alismatis Rhizoma → Poria	1
		Ginseng Radix Et Rhizoma, Bupleuri Radix → Scutellariae Radix	1	10
		Scutellariae Radix, Ginseng Radix Et Rhizoma → Bupleuri Radix	1	10
	Chest tightness	Gypsum Fibrosum → Scutellariae Radix	1	10
		Alismatis Rhizoma → Poria	1	10
		Zingiberis Rhizoma Recens, Scutellariae Radix → Pinelliae Rhizoma	1	10
	Cough	Notopterygii Rhizoma Et Radix → Chuanxiong Rhizoma	1	15
	Fatigue	Rhei Radix Et Rhizoma → Scutellariae Radix	1	13
		Aurantii Fructus Immaturus → Scutellariae Radix	1	13
	Abdominal pain	Natrii Sulfas → Rhei Radix Et Rhizoma	1	18
		Magnoliae Officinalis Cortex → Rhei Radix Et Rhizoma	1	18
	Sore throat	Rehmanniae Radix Recens, Scrophulariae Radix → Lonicerae Japonicae Flos	1	15
Lonicerae Japonicae Flos, Scrophulariae Radix → Rehmanniae Radix Recens		1	15	
Lonicerae Japonicae Flos, Rehmanniae Radix Recens → Scrophulariae Radix		1	15	
Non-COVID-19	Vexation	Pinelliae Rhizoma → Scutellariae Radix	1	10
	Delirious speech	Natrii Sulfas → Rhei Radix Et Rhizoma	1	15
		Magnoliae Officinalis Cortex → Rhei Radix Et Rhizoma	1	15
	Constipation	Aurantii Fructus Immaturus → Rhei Radix Et Rhizoma	1	30
	Poor appetite	Zingiberis Rhizoma Recens → Scutellariae Radix	1	20
		Pinelliae Rhizoma → Scutellariae Radix	1	20

et al., 2020). The CMMs with the functions of clearing heat, releasing the exterior, and tonifying qi belong to most of the components in the ancient epidemic formulae. Heat-clearing and exterior-releasing CMMs were

almost evenly used in the early stage of COVID-19. Heat-clearing CMMs were mostly used in the severe stage whereas tonifying CMMs were frequently applied to the recovery stage (Gu et al., 2020). Furthermore, several



**FIGURE 4** The network of the core manifestations and the high-frequency CMMs. The red circles represent the manifestations of COVID-19, while the blue–green circles represent the non-COVID-19 manifestations. The yellow–green diamonds represent CMMs. The width of the lines represents the co-occurrence frequency of the two connected manifestations

studies demonstrated that clearing heat is the primary treatment of COVID-19 (Fan et al., 2020; Yuan et al., 2020).

Our study found several CMM combinations (Table 3) for the specific manifestations in the collected ancient medical records. Interestingly, almost all the combinations are included in ancient formulae, as shown in Table 4. *Ren Shen Bai Du San*, a popular formula used for the treatment of *Yi Bing*, has the function of boosting healthy *qi*, expelling wind, removing dampness, and resolving toxins, especially for treating the inward

invasion of exterior pathogens. It is reported that *Ren Shen Bai Du San* is helpful for the treatment of mild cases of COVID-19 (Wang, Kong, & Wang, 2020), apparently because the mild cases mostly pertain to the combination of the exterior syndrome and interior syndrome. *Wu Ling San* and *Xiao Chai Hu Tang* were included in the formula *Qing Fei Pai Du Tang*, which may prevent progression and shorten duration of symptoms of COVID-19 (Zhong et al., 2020). *Wu Ling San* could unblock *yang qi* and promote urination, relieving symptoms such as nausea, vomiting and heavy limbs. *Xiao*



TABLE 4 Formulas associated with *yi bing* manifestations

Formula	CMMs	Book	Author
<i>Ren Shen Bai Du San</i>	Bupleuri Radix Peucedani Radix Chuanxiong Rhizoma Aurantii Fructus Immaturus Notopterygii Rhizoma Et Radix Angelicae Pubescentis Radix Poria Platycodonis Radix Ginseng Radix Et Rhizoma Glycyrrhizae Radix Et Rhizoma	<i>Tai Ping Hui Min He Ji Ju Fang</i>	Imperial Medical Bureau, revised by Chen Shi-wen
<i>Wu Ling San</i>	Polyporus Poria Atractylodis Macrocephalae Rhizoma Alismatis Rhizoma Cinnamomi Ramulus	<i>Shang Han Za Bing Lun</i>	Zhang Zhong-Jing
<i>Xiao Chai Hu Tang</i>	Bupleuri Radix Pinelliae Rhizoma Ginseng Radix Et Rhizoma Glycyrrhizae Radix Et Rhizoma Scutellariae Radix Zingiberis Rhizoma Recens Jujubae Fructus		
<i>Da Cheng Qi Tang</i>	Rhei Radix Et Rhizoma Magnoliae Officinalis Cortex Aurantii Fructus Immaturus Natrii Sulfas		
<i>Da Chai Hu Tang</i>	Bupleur Radix Scutellariae Radix Rhei Radix Et Rhizoma Aurantii Fructus Immaturus Pinelliae Rhizoma Paeoniae Alba Radix Jujubae Fructus Zingiberis Rhizoma Recens		
<i>Ling Gui Zhu Gan Tang</i>	Poria Cinnamomi Ramulus Atractylodis Macrocephalae Rhizoma Glycyrrhizae Radix Et Rhizoma		
<i>Qing Wen Bai Du Yin</i>	Gypsum Fibrosum Rehmanniae Recens Radix Bubali Cornu Coptidis Rhizoma Gardeniae Fructus Platycodonis Radix Scutellariae Radix Anemarrhenae Rhizoma Paeoniae Rubra Radix Scrophulariae Radix Forsythiae Fructus Glycyrrhizae Radix Et Rhizoma Moutan Cortex Lophatheri Herba	<i>Yi Zhen Yi De</i>	Yu Lin

*Chai Hu Tang*, the representative formula for treating *shaoyang* syndrome, including alternating chills, fever, and chest tightness. Additionally, several studies found

that *Xiao Chai Hu Tang* may exert an anti-infection effect against SARS-CoV-2 (Kwon et al., 2020; Wang, Ming, et al., 2020). *Da Chai Hu Tang*, a representative formula

for *yang ming* and bowel excess syndrome, may improve symptoms such as constipation and abdominal distention in severe cases of COVID-19 (Chen et al., 2020), which could be explained by the interior–exterior relationship between Lung and Large Intestine.

Similarly, *Da Cheng Qi Tang* is recommended by official TCM guidelines to inhibit inflammation by promoting bowel movement (Tang et al., 2020). With the function of activating *qi* and promoting purgation, *Da Cheng Qi Tang* may remove heat accumulation and regulate *qi* flow in the bowel. The enema treatment of *Da Cheng Qi Tang* is applied in severe cases of COVID-19 for relieving symptoms like constipation and abdominal distention (Shanghai Association of Integrated Chinese and Western Medicine respiratory Diseases Professional Committee, 2020). *Qing Wen Bai Du Yin* has an anti-inflammatory effect and is widely used in pandemics, such as H1N1 influenza and epidemic hemorrhagic fever (Zheng et al., 2020). *Qing Wen Bai Du Yin* is primarily given to patients with dual severe *qi* and blood syndrome, which is manifested as thirst, headache, and delirious speech. Another suggestion is that *Qing Wen Bai Du Yin* may alleviate the inflammatory reaction in COVID-19 patients and may have a protective effect on organ damage caused by inflammation (Wen et al., 2020). Moreover, *Lonicerae Japonicae Flos (Jin Yin Hua)*, a prominent CMM in *Qing Wen Bai Du Yin*, is frequently used in combination with *Qing Wen Bai Du Yin* to treat pneumonia (Nie et al., 2010). Water retention in the lung could worsen pulmonary edema and phlegm, which could be alleviated by *Ling Gui Zhu Gan Tang* with the function of warming *yang qi* and dissolving fluid retention. The application of *Ling Gui Zhu Gan Tang* in treating COVID-19 patients with *yang qi* deficiency and water retention syndrome is a unique TCM strategy (Dai et al., 2020).

As for the four hub nodes in the network analysis, *Scutellariae Radix* is reported as one of the most frequently used CMMs for COVID-19 (Luo, Jiang, et al., 2020; Luo, Ni, et al., 2020). The major chemical constituents of *Scutellariae Radix* have anti-inflammatory, antibacterial, antiviral, neuroprotective effects, and enhance body immunity (Wang et al., 2018). Thirty compounds isolated from *Scutellariae Radix* have anti-H1N1 activities (Ji et al., 2015). *Paeoniae Alba Radix* is recommended to prevent inflammation as well as to enhance the body's immunity to inhibit a SARS-CoV-2 infection (Shanghai Association of Integrated Chinese and Western Medicine respiratory Diseases Professional Committee, 2020). *Paeoniflorin*, which is the most abundant compound in *Paeoniae Alba Radix*, is also an ingredient of Xuebijing injection, which reduces lung injury in patients with severe COVID-19 infection (Ma, Qiu,

et al., 2020). Furthermore, *Poria* is a popular CMM for treatment of severe COVID-19 patients (Wang, Ming, et al., 2020). *Poriacocos polysaccharides* has a variety of pharmacological activities such as regulating immunity, and has anti-inflammatory, antioxidation, antitumor, and liver protection (Cheng et al., 2020). *Bupleuri Radix* has the functions of antipyretic, anti-inflammatory, enhancing immunity, and analgesia (Su et al., 2021). One study shows that the extracts of *Bupleuri Radix* have an effect on H1N1 (Su et al., 2011). The three-fourth of the hub nodes, that is, *Scutellariae Radix*, *Poria*, and *Bupleuri Radix* in our study are also included in the formula *Qing Fei Pai Du Tang*. This formula is associated with better prognosis for COVID-19 patients (Zhong et al., 2020). Again, our findings support the results of other studies that indicate that *Scutellariae Radix* and *Bupleuri Radix* contain numerous potential compounds to potentially treat COVID-19 (Fang et al., 2020; Ren et al., 2020).

However, there are some limitations to our current study. Although our results found that TCM has a role in preventing and treating COVID-19. TCM and western medicine have their own advantages, the combination of them may be more effective. Moreover, because the current COVID-19 pandemic persists, we will continue to focus on this pandemic for further study. In the future, further experimental researches are expected to validate the results of this study.

## 5 | SUMMARY

In summary, the overlapped data of epidemic diseases in ancient medical records and the manifestations of COVID-19 patients today were analyzed in our study. CMM combinations from ancient medical records are found in classical TCM formulae. The effective CMMs corresponding to the COVID-19 symptoms with high frequency may provide new insights and opportunities to treat the COVID-19 pandemic.

## AUTHOR CONTRIBUTIONS

**yaxue Han:** Data curation (equal); investigation (equal); methodology (equal); software (equal). **ZI YANG:** Investigation (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **shan Fang:** Investigation (equal); methodology (equal); resources (equal). **mengqing Zhang:** Conceptualization (equal); data curation (equal); investigation (equal). **zhijun Xie:** Supervision (equal); validation (equal).

## ORCID

Yaxue Han  <https://orcid.org/0000-0002-2935-1774>

Zi Yang  <https://orcid.org/0000-0002-0329-3254>

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## SUPPORTING INFORMATION

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