ORIGINAL RESEARCH

Network Analysis of Herbs Recommended for the Treatment of COVID-19

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Purpose: In this study, we aimed to identify the pattern and combination of herbs used in the formulae recommended for treating different stages of COVID-19 using a network analysis approach.

Methods: The herbal formulae recommended by official guidelines for the treatment of COVID-19 are included in the present analysis. To describe the tendency of herbs to form a "herb pair", we computed the mutual information (MI) value and distance-based mutual information model (DMIM) score. We also performed modularity, degree, betweenness, and closeness centrality analysis. Network analyses were performed and visualized for each disease stage.

Results: A total of 142 herbal formulae comprising 416 herbs were analyzed. All possible herbal pairs were examined, and the top frequently used herbal pairs were identified for each disease stage. The herb *Glycyrrhizae radix et rhizoma* is only identified in one herb pair, even though this herb is identified as one of the herbs with high frequency of use for every disease stage. This suggests that the DMIM score could be used to identify the optimal combination rule of herbal formulae by achieving a balance among the herbs' frequency and relative distance in herbal formulae.

Conclusion: Our results presented the prescription patterns and herbal combinations of the herbal formulae recommended for the treatment of COVID-19. This study may provide new insights and ideas for clinical research in the future.

Keywords: coronavirus 19, disease stage, herbs pairing, prescription pattern, network graph

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Introduction

The coronavirus disease responsible for the current pandemic is an acute respiratory illness caused by a new strain of coronavirus (COVID-19). As of 29 March 2021, COVID-19 has affected approximately 127 million people worldwide and the number is still growing every day.[1] COVID-19 is classified into four stages based on their clinical manifestation: the mild stage is classified by mild symptoms such as fever and respiratory symptoms with no signs of radiographic findings of pneumonia; the moderate stage by similar symptoms of fever and respiratory symptoms with radiographic findings of pneumonia; the severe stage by the onset of respiratory failure requiring mechanical ventilation; and the recovery stage.

Although both Food and Drug Administration (FDA)-approved antiviral drugs and several types of vaccines are currently available, many alternative treatments are still being proposed as an adjunctive treatment for COVID-19. It has been reported that herbal medicines could be considered an alternative approach for the treatment and prevention of COVID-19.[2,3] Recent systematic review articles also

concluded that herbal medicine showed significant effects in increasing the total effective rate and alleviating the symptoms.[4–6]

Network science is a field where complex networks are studied and represented by nodes and edges.[7] Network analysis, derived from network science, uses the mathematical language of graph theory to depict relationships among analyzed variables, and such analyses are often presented using visualization techniques.[8] In recent years, network analysis has been used in the field of complementary and alternative medicine. Several acupuncture studies used complex network analysis to examine the distribution pattern of acupoints selection and the regularities of acupoint combinations.[9,10] Herbal studies also integrate complex network analysis techniques to investigate herb–target interactions and herbal combination regularities among herbal formulae.[11–14]

In this study, we applied network analysis to determine the prescription pattern and combination of herbs used in the herbal formulae recommended for the treatment of COVID-19. To analyze the distribution pattern of herbs, we computed the data extracted from available treatment guidelines and visualized the network based on each disease stage.

Materials and Methods
Data Sources
In our previous study,[15] we collected and summarized the composition of herbs used in the herbal formulae recommended by the official guidelines for the treatment of COVID-19 (26 Chinese guidelines and two Korean guidelines), which comprised a total of 142 herbal formulae with 416 herbs. The names of the herbs are standardized based Pharmacopoeia of the People's Republic of China (Appendix 1). To identify useful herbal combinations used in the treatment of COVID-19 for each disease stage, we included all the herbal formulae and herbs of our previous study in this network analysis.

Network Analysis
Network analyses were performed using Netminer v.4.4.3. b (Cyram Inc, Seoul, Korea) for each disease stage.

Mutual Information (MI) Value and Distance-Based Mutual Information Model (DMIM) Score
The mutual information (MI) value between herbs x and y was calculated using $MI(x,y) = P(x,y) * \log\left(\frac{P(x,y)}{P(x)*P(y)}\right)$.

$P(x,y) = (\sum_{i=1}^{m} I(x,y,i))/m$ is the coincidence frequency of x and y, where m is the total number of formulas and $I(x, y, i)$ is the indicator function of x and y that shows whether herb x and y were used together in formula i. Here, $(x) = \sum_{i=1}^{m} I(x,i)/m$ is the frequency of herb x and this formula also applies to P(y). The higher the value of MI between the herbs, the stronger the correlation between them is.[16]

Distance-based mutual information model (DMIM) scores between herbs x and y were defined as score $(x,y) = MI(x,y)/d(x,y)$. DMIM combines the MI value and the average distance between herbs, where the distance between herb x and herb y in the ith formula was defined as $d(x, y, i) = |B(x, i) - B(y, i)|$. The average distance of herb x and herb y in the dataset was computed using $d(x,y) = \sum_{i=1}^{m} (I(x,y,i) * d(x,y,i))/ \sum_{i=1}^{m} (x,y,i)$. DMIM describes the tendency of herb x and herb y to form a herb pair.[16] Similarly, the higher the DMIM score between the herbs, the higher the tendency of the herbs to form a pair.

Modularity Analysis
To analyze the modular structure of the herb combination network, the algorithm introduced by Newman,[17] which maximizes modularity with a greedy approach, was applied to a high-frequency herb pair matrix. The modularity (Q) can be written as $Q = (1/4m) \sum ij [Aij - Pij](gi, gj)$, where A$ij$ = 1 if there is an edge joining node i and j and 0; otherwise, Pij was defined as $k_i k_j/2m$. k_i and K_j are the degree of each node and m is the number of edges in the networks; δ(gi, gj) = 1 if node i and j belong to the same group and δ(gi, gj) = 0 otherwise. Modules are then formed for the nodes that are highly interconnected among themselves.

Degree, Betweenness, and Closeness Centrality Analysis
We computed the degree, betweenness, and closeness centralities for all nodes (herbs) at each disease stage. The degree of centralization index defines the variability of individual centrality scores. The higher the degree of centralization index is, the more centralized the overall network is. The betweenness centrality defines the extent to which a node lies between all other pairs of nodes on their

paths. Here, the more times a node appears in the paths, the higher its centrality is. The closeness centralization index is a measure of the variability of individual closeness centrality scores. The higher the closeness index, the shorter the average distance of the node to all other nodes.[18]

Network Visualization

In this study, Netminer v4.4.3.b. (Cyram Inc, Seoul, Korea) was used to generate the networks to visualize relationships among herbs. We used a spring layout that uses dynamic theory to visualize the degree and betweenness centrality analysis for different stages of COVID-19. Each module is presented in a different color for clarity purposes. The size of the nodes is depending on the number of frequency and the density of the edges between the nodes represent the strength of their correlation.

Results

This study used DMIM techniques to examine the relationships among the 416 herbs included. All possible herbal pairs were examined and the most frequently used herbal pairs were identified for each disease stage. We also identified the patterns in the combinations of herbs and illustrated the modular structure using a spring layout.

Mild Stage

Of the 36 herbal formulae with a total of 90 herbs analyzed in this stage, we identified 12 herb pairs with the highest frequency of use (DMIM score > 0.69). The six herb pairs with the highest DMIM score were *Atractylodis rhizoma–Amomi tsao-ko fructus, Arecae semen–Amomi tsao-ko fructus, Pinelliae rhizoma–Amomi fructus rotundus, Coicis semen–Amomi fructus rotundus, Massa medicata fermentata–Crataegi fructus, and Polyporus–Alismatis rhizoma* (Table 1).

The frequency, degree, betweenness, and closeness centralities of each herb used in the mild stage treatment of COVID-19 were analyzed (Table 2). Sixteen herbs with a frequency of use of eight or more were identified, with *Armeniacae semen amarum* the most frequently used herb. In the modularity analysis, the 16 herbs were categorized into three modules (Figure 1). The first module (Figure 1, red nodes) included *Poria sclerotium, Magnoliae cortex, Coicis semen, Citri reticulatae pericarpium, Armeniacae semen amarum*, and *Agastachis herba*. The second module (Figure 1, green nodes) included *Scutellariae radix, Platycodonis radix, Glycyrrhizae radix et rhizoma,*

Forsythiae fructus, Bupleuri radix, and *Arctii semen*. The third module (Figure 1, blue nodes) included *Ephedrae herba, Atractylodis rhizoma, Arecae semen*, and *Amomi tsao-ko fructus*.

Moderate Stage

A total of 35 herbal formulae and 105 herbs were analyzed and 10 herb pairs with a high frequency of use (DMIM score > 0.85) were identified. The seven pairs of herbs with the highest DMIM scores were included *Polyporus–Zingiberis rhizoma recens, Asari herba–Aurantii fructus, Alismatis rhizoma–Armeniacae semen amarum, Armeniacae semen amarum–Asteris radix, Belamcandae rhizoma–Cinnamomi ramulus, Zingiberis rhizoma recens–Asari herba*, and *Aurantii fructus–Citri reticulatae pericarpium* (Table 1).

We also analyzed the frequency, degree, betweenness, and closeness centralities for each herb and identified 17 herbs with a frequency of use of seven or more for this disease stage. Once again, *Armeniacae semen amarum* was the herb with the highest frequency of use (Table 2). The 17 herbs were also categorized into three modules (Figure 2). The first module (Figure 2, red nodes) included *Agastachis herba, Armeniacae semen amarum, Glycyrrhizae radix et rhizoma, Coicis semen*, and *Persicae semen*. The second module (Figure 2, green nodes) included *Gypsum fibrosum, Forsythiae fructus, Lonicerae flos, Mori radicis cortex, Scutellariae radix,* and *Lepidii seu descurainiae semen*. The third module (Figure 2, blue nodes) included *Cicadae periostracum, Ephedrae herba, Atractylodis rhizoma, Amomi tsao-ko fructus, Arecae semen*, and *Trichosanthis fructus*.

Severe Stage

In the severe disease stage, we analyzed 42 herbal formulae comprising 127 herbs and identified 12 frequently used herb pairs (DMIM score > 0.88). The seven herb pairs with the highest DMIM score were *Ossa draconis* and *Concha ostreae–Magnetitum, Magnetitum–Fluoritum, Dioscoreae rhizoma–Lilii bulbus, Lycii fructus–Psoraleae fructus, Bambusae succus–Jujubae fructus, Zingiberis rhizoma recens–Dioscoreae rhizoma*, and *Psoraleae fructus–Cuscutae semen* (Table 1).

Following the frequency, degree, betweenness, and closeness centrality analyses for each herb, we identified 20 herbs with a frequency of use of nine or more at the severe disease stage. *Bubali cornu* was found to be the most frequently used herbs in the herbal formulae

Table 1 Top Distance-Based Mutual Information Model (DMIM)-Extracted Herbal Pairs

Disease Stage	Herb Pairs	DMIM Score
Mild	*Atractylodis rhizoma–Amomi tsao-ko fructus*	0.90784
	Arecae semen–Amomi tsao-ko fructus	0.90784
	Pinelliae rhizoma–Amomi fructus rotundus	0.90784
	Coicis semen–Amomi fructus rotundus	0.90784
	Massa medicata fermentata–Crataegi fructus	0.90784
	Polyporus–Alismatis rhizoma	0.90784
	Arctii semen–Platycodonis radix	0.86461
	Atractylodis rhizoma–Arecae semen	0.86461
	Forsythiae fructus–Platycodonis radix	0.69737
	Lonicerae flos–Arctii semen	0.69737
	Pinelliae rhizoma–Coicis semen	0.69737
	Amomi fructus rotundus–Tetrapanacis medulla	0.69737
Moderate	*Polyporus–Zingiberis rhizoma recens*	0.92644
	Asari herba–Aurantii fructus	0.92644
	Alismatis rhizoma–Armeniacae semen amarum	0.92644
	Armeniacae semen amarum–Asteris radix	0.92644
	Belamcandae rhizoma–Cinnamomi ramulus	0.92644
	Zingiberis rhizoma recens–Asari herba	0.92644
	Aurantii fructus–Citri reticulatae pericarpium	0.92644
	Talcum–Artemisiae scopariae herba	0.85237
	Curcumae longae radix–Acori tatarinowii rhizoma	0.85237
	Glycyrrhizae radix et rhizoma–Talcum	0.85237
Severe	*Ossa draconis and Concha ostreae–Magnetitum*	1.08217
	Magnetitum–Fluoritum	1.08217
	Dioscoreae rhizoma–Lilii bulbus	1.08217
	Lycii fructus–Psoraleae fructus	1.08217
	Bambusae succus–Jujubae fructus	1.08217
	Zingiberis rhizoma recens–Dioscoreae rhizoma	1.08217
	Psoraleae fructus–Cuscutae semen	1.08217
	Uncariae ramulus cum uncis–Forsythiae fructus	0.92757
	Forsythiae fructus–Phellodendri cortex	0.92757
	Lilii bulbus–Zingiberis rhizoma	0.88148
	Zingiberis rhizoma–Lycii fructus	0.88148
	Trogopterorum faeces–Allii macrostemi bulbus	0.88148

(*Continued*)

Table 1 (Continued).

Disease Stage	Herb Pairs	DMIM Score
Recovery	*Ossa draconis and Concha ostreae–Magnetitum*	1.08217
	Magnetitum–Fluoritum	1.08217
	Dioscoreae rhizoma–Lilii bulbus	1.08217
	Lycii fructus–Psoraleae fructus	1.08217
	Bambusae succus–Jujubae fructus	1.08217
	Zingiberis rhizoma recens–Dioscoreae rhizoma	1.08217
	Psoraleae fructus–Cuscutae semen	1.08217
	Uncariae ramulus cum uncis–Forsythiae fructus	0.92757
	Forsythiae fructus–Phellodendri cortex	0.92757
	Lilii bulbus–Zingiberis rhizoma	0.88148
	Zingiberis rhizoma–Lycii fructus	0.88148
	Faeces trogopterori–Allii macrostemi bulbus	0.88148

recommended for treating severe COVID-19 (Table 2). Similar to the other disease stages, the 20 herbs were categorized into three modules (Figure 3). The first module (Figure 3, red nodes) included *Ginseng radix, Aconiti lateralis radix praeparata, Corni fructus, Bubali cornu, Moschus, Aquilariae lignum, Aucklandiae radix, Cinnabaris*, and *Bezoar bovis*. The second module (Figure 3, green nodes) included *Borneolum, Realgar, Coptidis rhizoma, Scutellariae radix*, and *Gardeniae fructus*. The third module (Figure 3, blue nodes) included *Gypsum fibrosum, Glycyrrhizae radix et rhizoma, Rhei radix et rhizoma, Armeniacae semen amarum, Trichosanthis fructus*, and *Ephedrae herba*.

Recovery Stage

We analyzed a total of 29 herbal formulae and 94 herbs for the disease recovery stage. The twelve herb pairs with the highest frequency of use were identified (DMIM score > 1.08). The seven pairs of herbs with the highest DMIM score were *Ossa draconis* and *Concha ostreae–Magnetitum, Magnetitum–Fluoritum, Dioscoreae rhizoma–Lilii bulbus, Lycii fructus–Psoraleae fructus, Bambusae succus–Jujubae fructus, Zingiberis rhizoma recens–Dioscoreae rhizoma*, and *Psoraleae fructus–Cuscutae semen*.

Table 2 Frequency, Degree, Closeness and Betweenness Centralities of Herbs

Rank/Stage	Herbal Medicine	Frequency, N (%)	Centrality		
			Degree	Closeness	Betweenness
Mild					
1	*Armeniacae semen amarum*	25 (5.7)	0.8	0.83333	0.39127
2	*Magnoliae cortex*	20 (4.6)	0.53333	0.65217	0.10635
3	*Glycyrrhizae radix et rhizoma*	19 (4.4)	0.33333	0.57692	0.00952
4	*Forsythiae fructus*	19 (4.4)	0.53333	0.65217	0.17143
5	*Platycodonis radix*	15 (3.4)	0.2	0.51724	0
6	*Agastachis herba*	15 (3.4)	0.26667	0.53571	0.13333
7	*Ephedrae herba*	15 (3.4)	0.53333	0.65217	0.06111
8	*Atractylodis rhizoma*	14 (3.2)	0.4	0.57692	0.01349
9	*Scutellariae radix*	14 (3.2)	0.33333	0.57692	0.13333
10	*Amomi tsao-ko fructus*	13 (3.0)	0.33333	0.53571	0.00238
11	*Coicis semen*	13 (3.0)	0.2	0.5	0
12	*Citri reticulatae pericarpium*	11 (2.5)	0.06667	0.35714	0
13	*Arecae semen*	11 (2.5)	0.26667	0.51724	0
14	*Bupleuri radix*	11 (2.5)	0.06667	0.375	0
15	*Poria sclerotium*	11 (2.5)	0.26667	0.53571	0.00635
16	*Arctii semen*	8 (1.8)	0.06667	0.40541	0
Moderate					
1	*Armeniacae semen amarum*	31 (6.9)	0.875	0.88889	0.25139
2	*Ephedrae herba*	30 (6.7)	0.9375	0.94118	0.37639
3	*Gypsum fibrosum*	25 (5.6)	0.4375	0.64	0.01667
4	*Glycyrrhizae radix et rhizoma*	21 (4.7)	0.5	0.66667	0.03681
5	*Scutellariae radix*	21 (4.7)	0.4375	0.64	0.01875
6	*Atractylodis rhizoma*	15 (3.4)	0.4375	0.61538	0
7	*Lepidii seu descurainiae semen*	14 (3.1)	0.25	0.55172	0
8	*Coicis semen*	13 (2.9)	0.1875	0.53333	0
9	*Forsythiae fructus*	12 (2.7)	0.3125	0.59259	0
10	*Agastachis herba*	11 (2.5)	0.1875	0.53333	0
11	*Amomi tsao-ko fructus*	10 (2.2)	0.25	0.55172	0
12	*Arecae semen*	10 (2.2)	0.25	0.55172	0
13	*Persicae semen*	9 (2.0)	0.125	0.51613	0
14	*Cicadae periostracum*	8 (1.8)	0.125	0.51613	0
15	*Lonicerae flos*	8 (1.8)	0.0625	0.4	0
16	*Mori radicis cortex*	8 (1.8)	0.1875	0.55172	0
17	*Trichosanthis fructus*	7 (1.6)	0.0625	0.5	0
Severe					
1	*Bubali cornu*	23 (3.9)	0.78947	0.82609	0.4347
2	*Glycyrrhizae radix et rhizoma*	22 (3.8)	0.31579	0.59375	0.12573
3	*Moschus*	21 (3.6)	0.68421	0.65517	0.07115
4	*Gypsum fibrosum*	21 (3.6)	0.31579	0.59375	0.2271
5	*Aconiti lateralis radix praeparata*	20 (3.4)	0.36842	0.57576	0.02437
6	*Cinnabaris*	20 (3.4)	0.68421	0.65517	0.07115
7	*Corni fructus*	17 (2.9)	0.31579	0.55882	0.01462
8	*Ginseng radix*	14 (2.4)	0.26316	0.51351	0
9	*Borneolum*	13 (2.2)	0.42105	0.55882	0.00585
10	*Scutellariae radix*	13 (2.2)	0.36842	0.54286	0
11	*Armeniacae semen amarum*	13 (2.2)	0.26316	0.43182	0.01949

(Continued)

Table 2 (Continued).

Rank/Stage	Herbal Medicine	Frequency, N (%)	Centrality		
			Degree	**Closeness**	**Betweenness**
12	*Rhei radix et rhizoma*	12 (2.0)	0.15789	0.39583	0
13	*Aucklandiae radix*	11 (1.9)	0.21053	0.5	0
14	*Gardeniae fructus*	11 (1.9)	0.36842	0.54286	0
15	*Ephedrae herba*	11 (1.9)	0.15789	0.41304	0
16	*Aquilariae lignum*	10 (1.7)	0.21053	0.5	0
17	*Realgar*	10 (1.7)	0.42105	0.55882	0.00585
18	*Coptidis rhizoma*	10 (1.7)	0.36842	0.54286	0
19	*Bezoar bovis*	9 (1.5)	0.21053	0.5	0
20	*Trichosanthis fructus*	9 (1.5)	0.15789	0.39583	0
Recovery					
1	*Glycyrrhizae radix et rhizoma*	20 (6.6)	0.69231	0.76471	0.45
2	*Poria sclerotium*	17 (5.6)	0.69231	0.76471	0.19957
3	*Ophiopogonis radix*	17 (5.6)	0.38462	0.61905	0.07564
4	*Citri reticulatae pericarpium*	16 (5.3)	0.69231	0.76471	0.19957
5	*Atractylodis macrocephalae rhizoma*	12 (4.0)	0.23077	0.56522	0
6	*Codonopsis radix*	11 (3.7)	0.46154	0.65	0.06239
7	*Lophatheri herba*	9 (3.0)	0.15385	0.46429	0
8	*Amomi fructus*	9 (3.0)	0.30769	0.5	0
9	*Pseudostellariae radix*	8 (2.7)	0.15385	0.46429	0
10	*Astragali radix*	8 (2.7)	0.07692	0.44828	0
11	*Pinelliae rhizoma*	7 (2.3)	0.07692	0.44828	0
12	*Pinelliae rhizoma praeparatum*	7 (2.3)	0.23077	0.48148	0
13	*Astragali radix praeparata cum melle*	7 (2.3)	0.30769	0.5	0
14	*Agastachis herba*	6 (2.0)	0.15385	0.46429	0

After analyzing the frequency, degree, betweenness, and closeness centralities for each herb, we identified 14 herbs with a frequency of use of six or more, and *Glycyrrhizae radix et rhizoma* had the highest frequency of use (Table 2). The 14 herbs were categorized into two modules based on our modularity analysis (Figure 4). The first module (Figure 4, red nodes) included *Pinelliae rhizoma, Ophiopogonis radix, Lophatheri herba, Glycyrrhizae radix et rhizoma, Pseudostellariae radix*, and *Astragali radix*. The second module (Figure 4, green nodes) included *Poria sclerotium, Citri reticulatae pericarpium, Pinelliae rhizoma praeparatum, Codonopsis radix, Atractylodis macrocephalae rhizoma, Astragali radix praeparata cum melle, Amomi fructus*, and *Agastachis herba*.

Discussion

The results of our network analyses provide insights into the prescription pattern, therapeutic logic, and combinations of herbs used in the herbal formulae recommended for the treatment of each stage of COVID-19.

To understand the combination rule embedded in the herbal formulae recommended for COVID-19, we used DMIM scores to compute the tendency of two herbs to form a pair. Interestingly, we found that the herb *Glycyrrhizae radix et rhizoma* only appears in one herb pair (*Glycyrrhizae radix et rhizoma–Talcum*, Table 1), even though this herb appears in the list of herbs with high frequency of use for every disease stage (Table 2). This showed that the DMIM method was able to avoid the pitfalls of other analytical methods by quantitatively computing the frequency and MI value of the herbs, and the "between-herb-distance" in the herbal formulae.

In the theory of traditional medicine (TM), the syndrome differentiation of the four stages of COVID-19 includes "cold-dampness and stagnation lung syndrome" and "dampness and heat-accumulation lung syndrome" for the mild stage; "dampness and stagnation lung
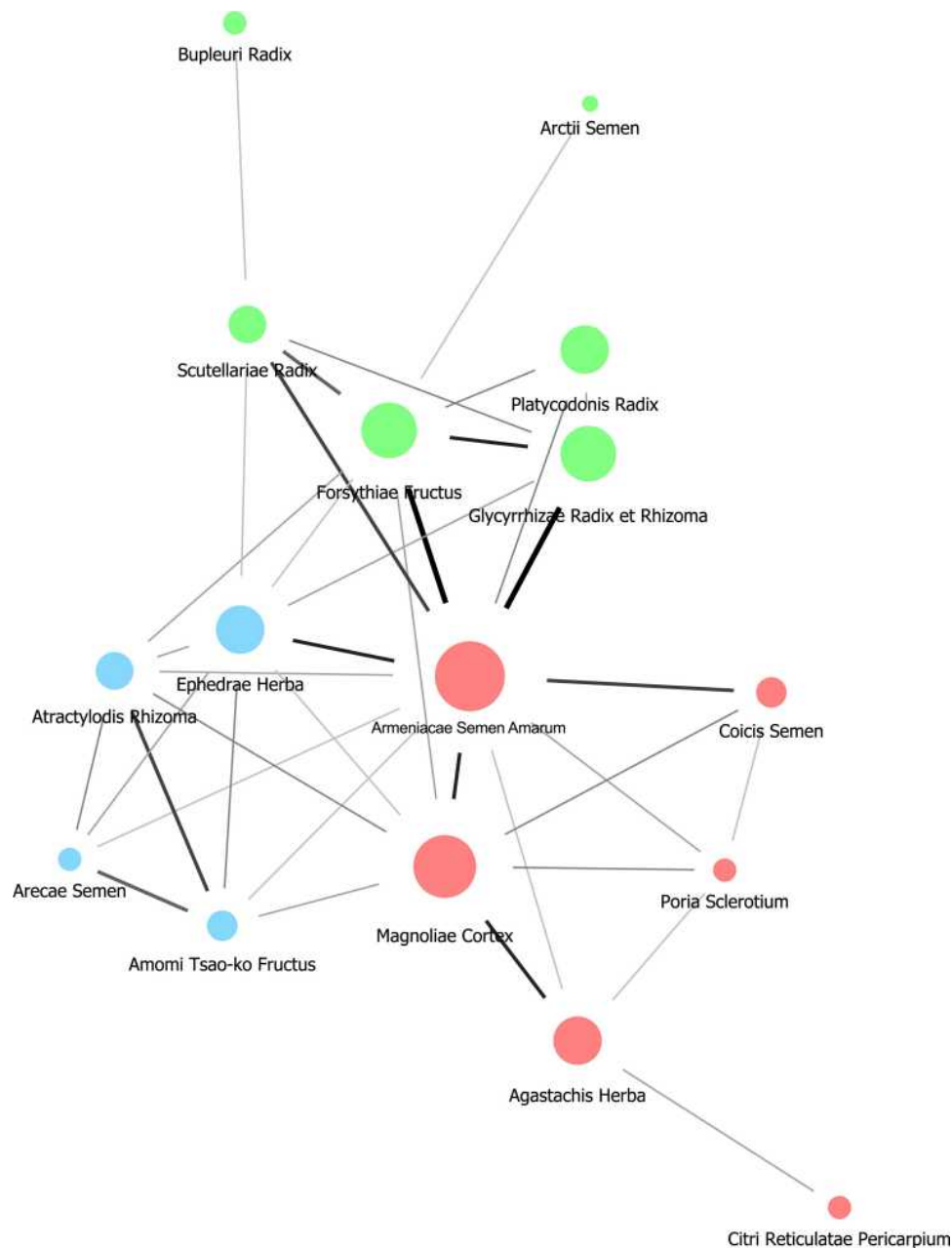
Figure 1 Herb network for mild stage.

syndrome" and "cold dampness lung syndrome" for the moderate stage; "plague poison and lung-closing syndrome", " syndrome of flaring heat in Qifen and Yingfen", and "syndrome of inner blocking causing collapse" for severe stage, and "lung and spleen Qi deficiency syndrome" and "Qi and Yin deficiency syndrome" for recovery stage.[19] In terms of herbal medicine, herbs can be generally classified into cold/cool herbs and hot/warm herbs. Cold-natured herbs have Yin properties such as clearing heat, purging fire, and dispelling toxic and

mainly used for heat-related syndromes, whereas warm-natured herbs have Yang properties such as expelling cold, tonifying Qi, and restoring Yang and mainly used for cold-related syndromes.[20] Therefore, the therapeutic principle and herbal formulae/herbs used vary across each disease stage according to the syndrome differentiation.

In the mild stage of COVID-19, the herbs with the highest frequency of use were mainly warm-natured and can be classified into lung, spleen, and stomach meridians.
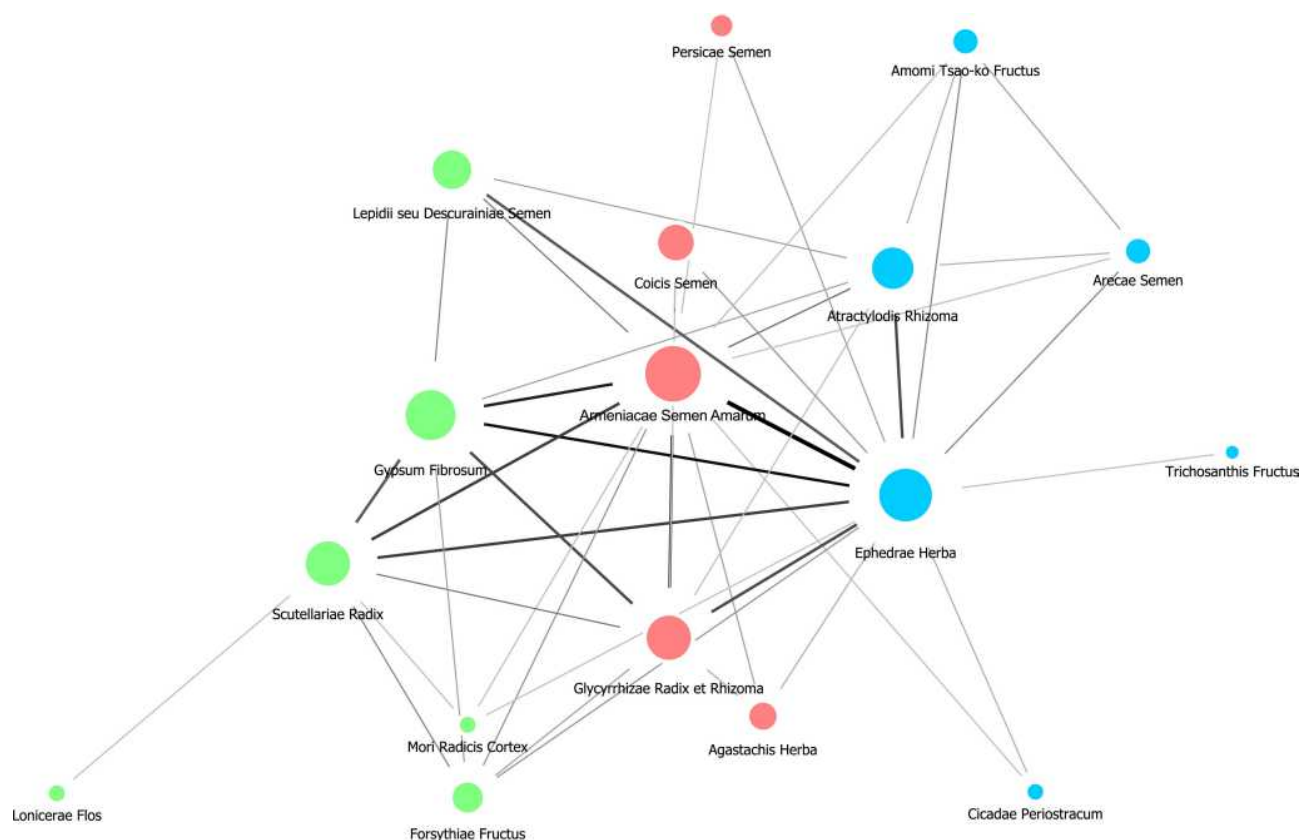
Figure 2 Herb network for moderate stage.

The main TM therapeutic principle of these herbs can be summarized as releasing the exterior and resolving dampness, corresponding with the symptoms of mild COVID-19 such as fever (ie due to external pathogenic factors) and cough (ie due to dampness). In contrast, the herbs with high frequency of use at the moderate stage of COVID-19 are partly warm-natured and partly cold-natured. Similar to the mild stage, these herbs can be mainly classified into lung, spleen, and stomach meridians. The main TM therapeutic principle for the moderate stage can be summarized as clearing heat, drying dampness, and suppressing the cough. This also corresponds with the symptoms of moderate COVID-19 resulting from pathogenic factors of heat, such as fever, sore throat, and pneumonia, and dampness, such as cough, shortness of breath, myalgia, fatigue, and diarrhea.

For both mild and moderate stages, the herb *Armeniacae semen amarum* was the most frequently recommended. Based on our findings, we inferred that most herbal formulae recommended in the mild and moderate stages are modified using "Ma Xing Shi Gan" decoction as the basic formula. "Ma Xing Shi Gan" decoction has been reported to

have a broad spectrum of inhibitory activity against the entry of the influenza virus and have a significant effect of reducing pulmonary inflammation.[21,22] "Ma Xing Shi Gan" decoction is composed of four herbs including *Ephedrae herba, Armeniacae semen amarum, Gypsum fibrosum*, and *Glycyrrhizae radix et rhizoma*. A study exploring the active compounds of *Ephedrae herba* found several key components such as β-sitosterol, estrone, and stigmasterol have potential therapeutic effects on viral-induced respiratory infections.[23] Wang et al also revealed that *Armeniacae semen amarum* has nine active compounds regulating eight targets, with amygdalin as the major effective component and a candidate compound for COVID-19 treatment.[24] The herb *Gypsum fibrosum* is also shown to have an antipyretic effect with calcium as its main active component.[25] A study by Niu et al also identified that compounds such as quercetin, glabridin, and gallic acid present in *Glycyrrhizae radix et rhizoma* may regulate angiotensin-converting enzyme 2 (ACE2) for the treatment of COVID-19.[26]

For the severe stage of COVID-19, the herbs with high frequency of prescription were partly warm-natured and partly cold-natured herbs, including herbs with an
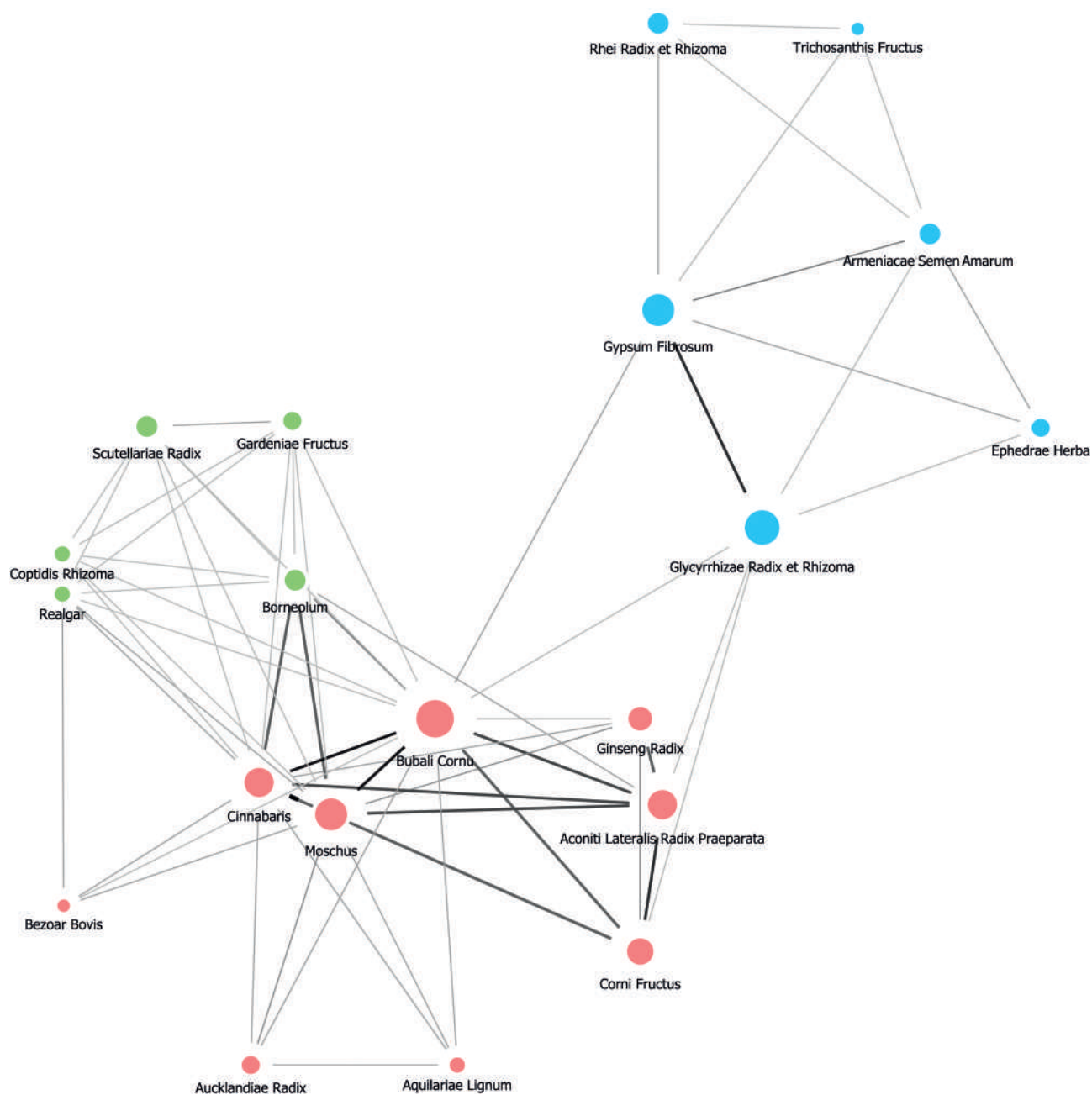
Figure 3 Herb network for severe stage.

extreme-warm-nature and extreme-cold-nature. These herbs can be primarily classified into lung, spleen, and heart meridians. The main TM therapeutic principle can be characterized as clearing heat, dispelling phlegm, and opening the orifices, corresponding to the symptoms of severe COVID-19 such as pneumonia (ie due to heat), comatose due to respiratory failure and shock (ie due to excessive phlegm and closing of orifices). According to a retrospective cohort study, the most frequently observed complication in COVID-19 patients is sepsis, followed by multiple organ failure, and septic shock.[27] This elucidates our findings as the high frequency of recommendation and pairing of herbs in the severe stage are mainly compositions of herbal medicines like "Angong Niuhuang" pill, "Zhi Bao Dan", "Zi Xue San", and "Su He Xiang" pill, which are frequently prescribed during life-threatening conditions. Among the top herbs used in the severe stage, *Bubali cornu* has also shown to have antipyretic
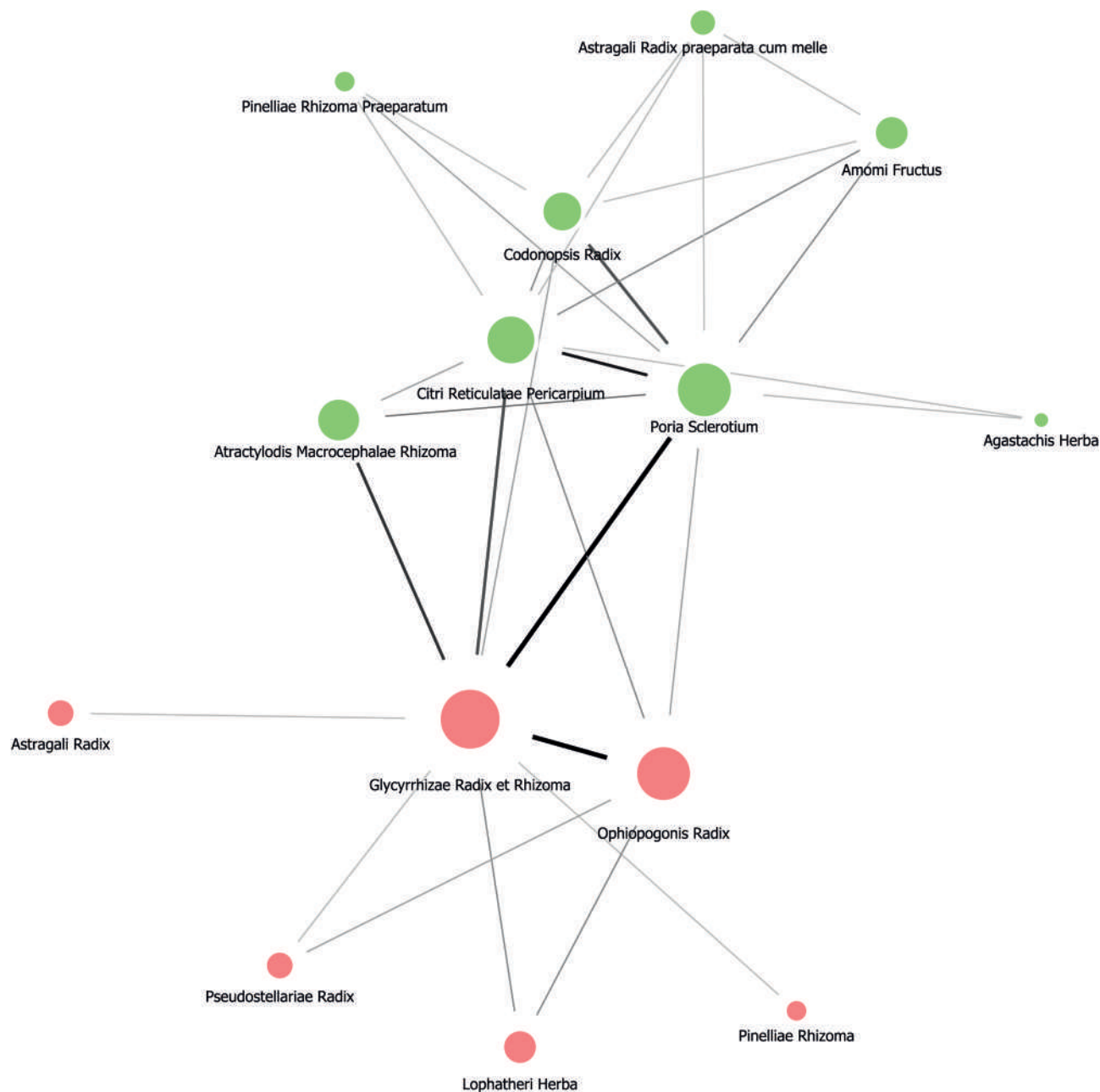
Figure 4 Herb network for recovery stage.

compound[28] and *Aconiti lateralis radix praeparata* has played a potential role in treating heart failure due to its high alkaloid contents.[29]

For the recovery stage, the herbs with high frequency of prescription were mainly warm-natured and can be classified as lung and spleen meridians. The main TM therapeutic principle can be summarized as tonifying qi and resolving dampness. In this stage, the symptoms are often milder after treatment, where the fever has subsided and respiratory symptoms, such as a cough or shortness of breath, have improved. Hence, the recommended herbs and TM therapeutic principles during the recovery process are focused on nourishing the body and improving prolonged mild symptoms. A study by Ko et al reveals that tonifying herbs such as *Glycyrrhizae radix et rhizoma, Ophiopogonis radix, Atractylodis macrocephalae rhizoma, Codonopsis radix*, and *Pseudostellariae radix* could enhance ATP-generation capacity.[30] This also corresponds with our findings as these herbs are also among the top frequently used herbs in the recovery stage.

In addition, we found that the herbs with the highest frequency of use for every stage in our analysis comprised of the composition of herbs in the "Qingfei Paidu" decoction. The "Qingfei Paidu" decoction is a basic herbal formula consisting of 21 herbs included in the Chinese treatment guidelines as the primarily recommended formula that applies to all stages of COVID-19. The "Qingfei Paidu" decoction is reported to have 129 active compounds that can act on many targets to inhibit the entry and replication of SARS-CoV-2, suggesting a potential effect in treating COVID-19.[22,31,32] Recent studies have shown that the "Qingfei Paidu" decoction has significant effects on alleviating the symptoms and reducing multi-organ failure in COVID-19.[33–35] Notably, "Ma Xing Shi Gan" decoction is part of the fundamental composition in the "Qingfei Paidu" decoction and may contribute to the overall efficacy of the "Qingfei Paidu" decoction.[22] Hence, we believe that the "Qingfei Paidu" decoction comprised of the herbs with high frequency of use across all disease stages and the modification of "Ma Xing Shi Gan" decoction, which is also the core herbal composition of "Qingfei Paidu" decoction, is the main herbal formula recommended for treatment of COVID-19.

Conclusion

Our results present the preliminary prescription pattern, therapeutic logic, and herbal formulae recommended in the treatment guidelines for COVID-19 using a network analysis approach. As there are numerous herb pairs with similar DMIM scores across the disease stage, we are unable to identify the herb pair with the highest potential in treating COVID-19. However, we found that the four herbs of "Ma Xing Shi Gan" decoction including *Ephedrae herba*, *Armeniacae semen amarum*, *Gypsum fibrosum*, and *Glycyrrhizae radix et rhizoma* seem to each play a potential role in every stage of COVID-19. Future studies may consider focusing on the mechanism and metabolic pathway for these herbs for the treatment of COVID-19. We hope that this study may provide insights and research ideas for related clinical research in the future.

Data Sharing Statement

Data will be made available upon reasonable request.

Author Contributions

All authors (L.A., H.W.L., A.K., J.Y.C., and M.S.L) made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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