Data mining to explore the medication patterns of Dr. Zhou Zequan's cough treatments

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[Abstract]　**Objective**　To use data mining and statistical techniques to analyze the characteristics of combination prescriptions and medications used in the treatment of cough by Dr. Zhou Zequan, the famous and experienced chief physician of Chinese medicine in Xiangtan. **Methods**　The data obtained from patients with cough disease who were treated by Dr. Zhou Zequan were collected from our hospital information system (HIS). These data were analyzed with Excel 2016 and R language software to assess the frequency of drug use, the properties, flavors, and meridian of drugs, and the association rules of the drugs. SPSS v22.0 was used for drug hierarchical clustering analysis. **Results**　A total of 126 medical cases were included, comprising 100 drug prescriptions and 190 drugs. The drugs that were prescribed with high frequency contained licorice, Platycodon grandiflorum, Scutellaria baicalensis, Semen armeniacae amarae, Pericarpium citri reticulatae, and other substances. The flavors of the drugs were mainly bitter, pungent, and sweet; the properties of the drugs were mainly cold and warm; and the target meridians were mainly of the lungs, liver, and spleen. Sixty drug pairs were obtained by correlation analysis, and six new prescriptions were identified by hierarchical clustering analysis. **Conclusion**　The prescriptions had precise efficacy for coughs. The prescription medication patterns were subjected to data mining technology to discover information related to the treatment of cough at the clinical front line. The new prescriptions that were identified with clustering analysis could be used as alternative prescriptions in hospital preparations.

[Key words]　Data mining; Cough; Medication pattern

1　Introduction

Coughing is the most common symptom in patients with respiratory difficulties in community outpatient clinics, and chronic coughing accounts

for more than one-third of the specialist clinics in China[1]. In response to cough, current treatment methods in Western medicine are mostly based on cough suppression, phlegm reduction, use of bronchodilators, and anti-inflammation medications. Treatments with Western medicine alone are mostly ineffective. With the increasing trust in traditional Chinese medicine (TCM) in recent years, acceptance of TCM as a cough treatment has gradually emerged[2-3]. For example, the results of Zhang Xiaoshuang et al.[4], who used ZhiSouSanJiaWei

granules to treat cough after influenza virus infection in qi-insufficient constitutions, showed that after two weeks of treatment, the total effective rate in the experimental group and the control group were 89.86% and 72.46%, respectively, and the total clinical efficacy of the experimental group was significantly higher than that of the control group ($P < 0.05$). Professor Zhou Zequan, the first famous TCM doctor in Xiangtan, has developed excellent prescriptions that have remarkable efficacy in the treatment of acute and chronic cough. In this paper, we compiled his cases that were given cough treatments and explored the rules and characteristics of his prescriptions as references for colleagues in TCM.

2 Methods

2.1 Case screening

Inclusion criteria: Cases were collected from January to June 2020 in the outpatient clinic of the Chinese Medicine Department of our hospital. Patients were diagnosed with a cough according to Western medical diagnostic criteria, including patients with acute and chronic coughs caused by acute infections and conditions after an infection.

Exclusion criteria: Patients with underlying diseases were excluded (including hypertension, coronary heart disease, diabetes mellitus, sequelae of cerebral infarction, etc.).

2.2 Study methodology

2.2.1 Standardization of TCM names:

Standardization of TCM names helped to determine the frequency of drug use more accurately. In this study, the names of drugs in the prescriptions were standardized according to the "Pharmacopoeia of the People's Republic of China (2015 Edition)"[5], the "Dictionary of Traditional Chinese Medicine"[6], and "Traditional Chinese Medicine"[7]. For example, the names of Pinellia ternata, Rhizome Pinelliae Preparata, and Rhizoma Pinellinae Praeparata were unified and modified to Pinellia ternata. Those that changed their medicinal properties after preparation were considered to be two different drugs, such as dried Radix Rehmannia and Radix Rehmannia Preparata.

2.2.2 Data entry and verfication:

The data from our patients with a cough that were treated by Professor Zhou Zequan were collected using the health information system (HIS) in our hospital, including patient name, gender, age, diagnosis, and prescription medication. To ensure that the entered data were accurate, Excel 2016 was used to store the information and one staff member was responsible for entry work, and then another staff member was responsible for reviewing the data after the entry was completed.

2.3 Statistical methods

The statistics on the frequency of drug prescriptions were performed using R (v3.6.2) with the "arules" package. A correlation analysis was performed using the apriori[8-9] function, and the correlation results were visualized using Cytoscape 3.7.2[10-11]. A systematic cluster analysis was performed using SPSS v22.0.

3 Results

3.1 Results of case screening

A total of 156 cases were included in this study. In accordance with the inclusion and exclusion criteria, 126 cases that met the requirements were identified and 100 prescriptions were screened.

3.2 Descriptive analysis

3.2.1 Analysis of the frequency of drug use

The frequency of use for 190 Chinese medicines in the screened 100 prescriptions was assessed. A total of 42 medicines were used

more than 10 times, and the top 5 were licorice, Platycodon grandiflorum, Scutellaria baicalensis, Semen armeniacae amarae, and pericarpium citri reticulatae, see Table 1.

3.2.2 Statistics on the properties, flavors, and meridians of drugs

According to the "Pharmacopoeia of the People's Republic of China (2015 Edition)" and the "Dictionary of Traditional Chinese Medicine", the properties, flavors, and meridians of the drugs involved in the 100 prescriptions were analyzed. The results showed that the drug properties were mostly cold (26.32%) and warm (25.79%); the drug flavors were mostly bitter (54.74%), pungent (45.26%), and sweet (38.95%); and the meridians

were mostly via the meridians of the lungs (50.00%), liver (45.79%), and spleen (31.05%), as shown in Table 2.

3.3 Drug association rules analysis

3.3.1 Calculation of the association rules for the drugs

The R language software "apriori" function was used for a correlation analysis of 190 Chinese medicines, where the support threshold was set at 0.2, the confidence threshold was set at 0.25, and the correlation analysis results were ranked in descending order with the lift degree (lift degree reflects the correlation between A and B in the association rules; lift degree > 1 and higher indicate

Table 1 Statistical results for cough medication frequency (frequency ⩾ 10)

Drug Name	Frequency	Drug Name	Frequency	Drug Name	Frequency
Licorice	75	Flos farfarae	24	Perilla fruit	14
Platycodon grandiflorum	50	Rhizoma atractylodis macrocephalae	18	Thunberg fritillary bulb	15
Scutellaria baicalensis	48	Ephedra sinica	18	Eucommia ulmoides	13
Semen armeniacae amarae	46	Pericarpium trichosanthis	17	Mulberry leaves	12
Pericarpium citri reticulatae	43	Schisandra chinensis	17	Radix bupleuri	11
Pinellia ternata	39	Codonopsis pilosula	17	Fructus forsythiae	11
Aster tataricus	36	Semen raphani	17	Angelica sinensis	11
Periostracum cicadae	32	Rhizoma dioscoreae	17	Mustard seeds	11
Cortex mori radicis	32	Radix peucedani	16	Fritillaria cirrhosa	11
Cynanchum glaucescens	29	Bombyx batryticatus	16	Salvia miltiorrhiza	10
Radix stemonae	26	Psoralea corylifolia Linn	15	Cortex lycii radicis	10
Poria cocos	26	Folium eriobotryae	15	Fructus aurantii	10
Rhizoma phragmitis	26	Semen oroxyli	14	Asarum	10
Perilla leaf	24	Exocarpium citri grandis	14	Lumbricus	10

Table 2 Statistical results of the flavor and properties of the medicines

Drug properties	Proportion / %	Drug flavor	Proportion / %	Meridian	Proportion / %
Cold	26.32	Bitter	54.74	Lung	50.00
Warm	25.79	Pungent	45.26	Liver	45.79
Mild	15.79	Sweet	38.95	Spleen	31.05
Slightly cold	14.74	Salty	6.84	Kidney	25.26
Slightly warm	8.95	Sour	4.74	Heart	22.11
Chill	5.79	Puckery	3.68		
Hot	1.58				
Extremely cold	1.05				
Total	100.00	Total	150.526 3	Total	174.210 5

higher positive correlation; lift degree < 1 and lower indicate higher negative correlation; and lift degree = 1 indicates no correlation; i.e., independent of each other) greater than 2. Then 60 groups of drug combinations commonly used by Professor Zhou Zequan in the treatment of cough were obtained, as shown in Table 3. The analysis indicated that the most used drug combinations included Cynanchum glaucescens, Scutellaria baicalensis => Cortex mori radicis; Cynanchum glaucescens, Platycodon grandiflorum => Aster tataricus; and Radix stemonae => Platycodon grandiflorum.

3.3.2 *Visualization of the drug association rules*

Cytoscape 3.7.2 was used to visualize the association rules with a lift greater than 2. The visualization results are shown in Fig. 1, and the thickness of the edges represents the magnitude of the lift.

3.4 Cluster analysis

SPSS software was used to analyze the

drugs with a frequency of drug use greater than 10 in the prescriptions for the treatment of cough given by Professor Zhou Zequan using systematic clustering analysis. The clustering method included component connections, the squared Euclidean distance was selected for the measurement interval, and the Z score was selected for standardization. The clustering results were combined with clinical knowledge to identify six new prescriptions for the treatment of cough, as shown in Table 4 and Fig. 2.

3 Discussion

Cough is the most common symptom in the pulmonary system, with many causes and a complex pathogenesis[12-13]. Although the disease may be located in the lungs, a cough can be caused by all internal organs. The treatment of cough (especially chronic cough) in Western medicine is not ideal and has many adverse effects. TCM has achieved more significant clinical efficacy through the overall regulation of the patient's internal organs by assessing yin, yang, qi and the blood on the basis of evidence-based treatment.

The top 10 most frequently used Chinese

Table 3 Correlation analysis results for common cough medicines

| Drug Associations	Support Level	Confidence	Lift degree	Frequency
Pericarpium citri reticulatae, Platycodon grandiflorum => Radix stemonae	0.21	0.913 043	3.511 706	21
Cynanchum glaucescens, Scutellaria baicalensis => Cortex mori radicis	0.23	1.000 000	3.125 000	23
Licorice, Scutellaria baicalensis => Cortex mori radicis	0.23	0.851 852	2.662 037	23
Licorice, Cortex mori radicis => Cynanchum glaucescens	0.20	0.769 231	2.652 520	20
Platycodon grandiflorum, Aster tataricus => Rhizoma phragmitis	0.20	0.689 655	2.652 520	20
Cynanchum glaucescens, Platycodon grandiflorum => Aster tataricus	0.20	0.952 381	2.645 503	20
Pericarpium citri reticulatae, Licorice => Perilla leaf	0.21	0.617 647	2.573 529	21
Licorice, Scutellaria baicalensis => Cynanchum glaucescens	0.20	0.740 741	2.554 278	20
Cynanchum glaucescens => Cortex mori radicis	0.23	0.793 103	2.478 448	23
Pericarpium citri reticulatae, Scutellaria baicalensis => Aster tataricus	0.20	0.869 565	2.415 459	20
Pericarpium citri reticulatae, Licorice => Radix stemonae	0.20	0.588 235	2.262 443	20
Licorice, Platycodon grandiflorum => Radix stemonae	0.21	0.583 333	2.243 590	21
Periostracum cicadae, Semen armeniacae amarae => Pinellia ternata	0.20	0.869 565	2.229 654	20
Licorice, Pinellia ternata => Periostracum cicadae	0.22	0.814 815	2.144 250	22
Rhizoma phragmitis => Aster tataricus	0.20	0.769 231	2.136 752	20
Radix stemonae => Aster tataricus	0.20	0.769 231	2.136 752	20
Perilla leaf => Pericarpium citri reticulatae	0.22	0.916 667	2.131 783	22
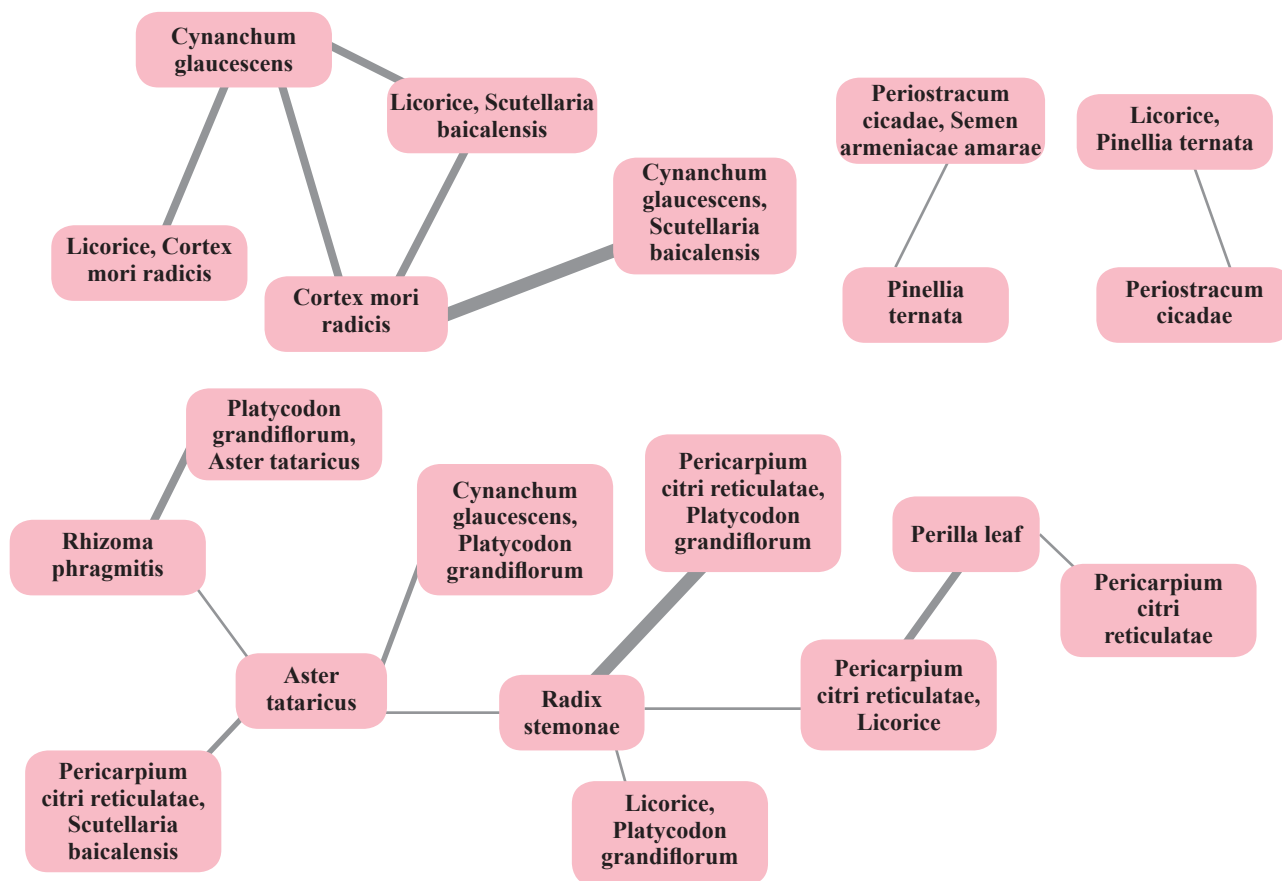
Fig. 1 Visualization results for the association rules with a lifting degree greater than 2

Table 4 New prescriptions for cough treatment identified in the cluster analysis

Prescriptions	Drug composition
Cluster 1	Psoralea corylifolia, Eucommia ulmoides, Semen oroxyli, Rhizoma dioscoreae, Rhizoma atractylodis macrocephalae, Codonopsis pilosula, Poria cocos, Flos farfarae, Pinellia ternate, Mulberry leaves, Semen armeniacae amarae, Pericarpium citri reticulatae, Periostracum cicadae, Licorice
Cluster 2	Platycodon grandiflorum, Aster tataricus, Cynanchum glaucescens, Cortex mori radicis, Radix stemonae, Cortex lycii radicis, Rhizoma phragmitis, Perilla leaf, Scutellaria baicalensis
Cluster 3	Lumbricus, Bombyx batryticatus
Cluster 4	Radix peucedani, Fructus aurantii, Exocarpium citri grandis, Folium eriobotryae, Thunberg fritillary bulb
Cluster 5	Mustard seed, Perilla fruit, Semen raphani, Ephedra sinica, Asarum, Pericarpium trichosanthis, Fritillaria cirrhosa
Cluster 6	Angelicae sinensis, Schisandra chinensis, Salvia miltiorrhiza, Radix bupleuri

medicines were antipyretic and sore-throat relieving medicines (Platycodon grandiflorum, licorice, and Periostracum cicadae), qi-descending, dampness-eliminating, and cough relieving medicines (Semen armeniacae amarae, Pericarpium citri reticulatae, and Pinellia ternata), lung-clearing and dampness-eliminating medicines (Scutellaria baicalensis and Cortex mori), and lung-nourishing and phlegm-relieving medicines (Aster tataricus and Cynanchum glaucescens), reflecting the main principles of treating cough by purging and diffusing the lung, eliminating dampness, and resolving phlegm. Platycodon grandiflorum and licorice ranked as the top two, and the prescription was from Platycodon Grandiflorus Decoction in the Chapter of Consumptive Lung Disease, Pulmonary
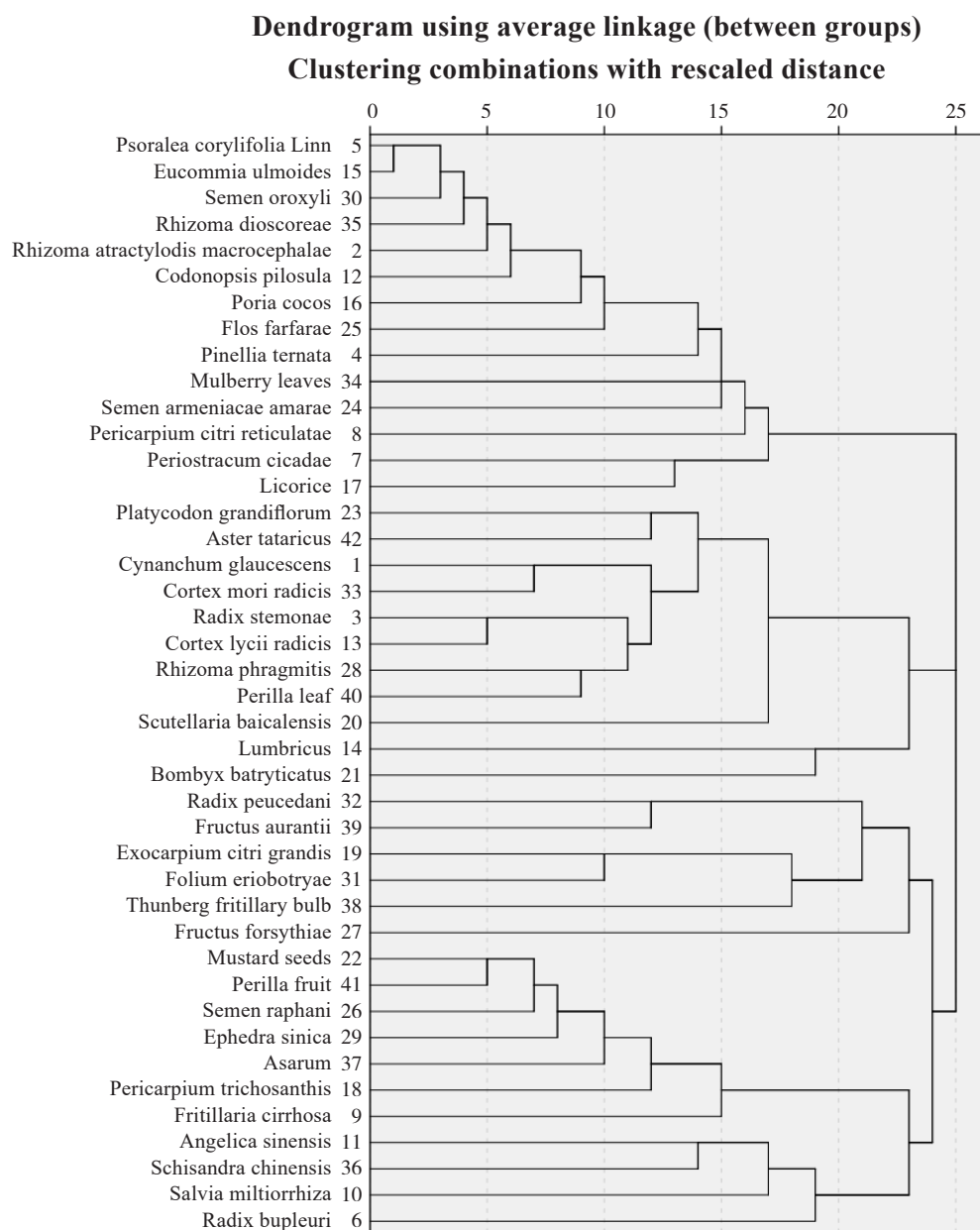
Dendrogram using average linkage (between groups)
Clustering combinations with rescaled distance

Fig. 2 Cluster analysis results for high frequency drugs

Abscess and Cough with Abnormal Rising of Qi in the "Synopsis of Golden Chamber"[14]. The original text is as follows, "People coughing with thoracic fullness, shivering with a rapid pulse, having dry throat without being thirsty, often having opaque saliva and halitosis, and vomiting pus that is like rice porridge for a long time is diagnosed to suffer from pulmonary abscess. It can be treated with Platycodon Grandiflorus Decoction". Platycodon grandiflorum and licorice treat ailments due to cold or exposure and heat toxicity invading from

Shao Yin, attacking the throat, where pharyngalgia and pharyngitis may occur. The wind-heat stagnates in the lung, resulting in a pulmonary abscess and cough. Network pharmacological studies have shown that Platycodon Grandiflorus Decoction mainly works by regulating the excessive inflammatory response of the respiratory tract, improving lung function, inhibiting the overexpression of mucin, and reducing the response of the central nervous system managing cough, ultimately achieving the effect of cough

suppression and phlegm relief[15].

According to Wu Qian, a medical doctor of the Qing dynasty, "The Golden Mirror of Medicine"[16] [General Summary of Cough] states, "Coughs from lung diseases shall have phlegm as well as the sound. With just the sound, it lacks the action of coughing. With just the phlegm, it lacks the sound of cough. The cause of cough is cold, heat, diet and wind". This indicates that the common causes of coughs are cold, heat, diet, and wind. Professor Zhou Zequan used mostly cold and warm medications for cough treatment, followed by mild medications, which is in line with the key point of identifying cold and heat as the causes, as well as the principle of treating the cold with a hot drug and the heat with a cold drug.

Based on the results of the apriori association rule analysis, the common pairs of medicines used by Professor Zhou Zequan to treat cough could be determined. Cortex mori radicis was often combined with Scutellaria baicalensis, Cynanchum glaucescens, and licorice; Aster tataricus was often combined with Cynanchum glaucescens, Pericarpium citri reticulatae, Scutellaria baicalensis, Platycodon grandiflorum, and Rhizoma phragmitis; Radix stemonae was often combined with Aster tataricus, Pericarpium citri reticulatae, Platycodon grandiflorum, and licorice. The correlated drug pairs mostly reflect the characteristics that Professor Zhou Zequan treated coughs, including the combination of cold and warm drugs, which assumes that cough is caused by a mixture of cold and heat, and mostly with a dampness pathogen. In addition, it is consistent with the clinically reported complex pathogenesis of intractable coughs with a combination of excess and deficiency syndromes, and with cold and heat[12]. It is also consistent with the unique climate of Lingnan[17].

Based on the results of unsupervised systematic cluster analysis, six new prescriptions for the treatment of cough were identified. Prescription 1 was Ginseng, Poria, and Atractylodes Macrocephala Powder combined with modified the Two Matured Substances Decoction, which is effective in strengthening the spleen and eliminating dampness, resolving phlegm and relieving cough, warming and nourishing kidney-yang, and is mostly used for dampness caused by deficiency of the spleen and kidney. Prescription 2 is a Zhisou casual treatment combined with modified Xiebai San, which is effective in dispersing wind and clearing the lung, resolving phlegm, and relieving cough, which is mostly used for wind pathogens invading the lung and transforming into the heat syndrome. Prescription 3 is the drug pair of Bombyx batryticatus and Lumbricus, both of which are salty, cold, and mild, which is effective in clearing heat, resolving phlegm, is spasmolytic, and dispels wind. These are mostly used in patients with hot coughs and wind pathogens, and can also be added to the basic formula of TCM differentiation. Prescription 4 is mainly based on the treatment of depressed phlegm, stagnated qi, and heat transmission with Folium eriobotryae and Thunberg fritillary bulb clearing the heat and resolving phlegm, and Radix peucedani, Fructus aurantii and Exocarpium citri grandis moving qi, resolving phlegm, and relieving the cough. Prescription 5 is modified SanZiYangQin Decoction, which is effective in lowering qi, resolving phlegm, eliminating food, relieving superficial cold, and clearing heat. It is used in cases of phlegm congestion, reversed flow of qi, and food stagnation, with superficial cold yet to be resolved and slightly with interior heat syndrome. In this formula, Mustard seed, Perilla fruit, and Semen raphani warm the lung, resolve phlegm, depress qi, and eliminate food. Ephedra sinica and asarum resolve superficial cold and dispel excessive fluid. Pericarpium trichosanthis and Fritillaria cirrhosa clear heat and moisten the lung to resolve phlegm, which at the same time counteracts the harmful effects of Ephedra sinica and asarum by warming dryness and promoting heat. Prescription 6 is mainly based on the theory of qi-stagnation and

blood stasis, with Radix bupleuri detoxifying the liver and relieving stagnation, Angelica sinensis and Salvia miltiorrhiza invigorating and replenishing the blood, and Schisandra chinensis astringing the lung and relieving the cough. Through the above analysis, the new prescriptions obtained by cluster analysis mainly addressed a phlegm-damp cough, heat cough, wind-heat cough, cold cough, and a qi-stagnation and blood-stasis cough.

In this study, the analysis of cough prescription regularity uncovered valuable information and the new prescriptions obtained with the unsupervised systematic clustering algorithm have reference value for the treatment of cough. The results of this study still need to be validated by further clinical studies and studies with large samples.

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