

On the Medication Rules in Shang Han Lun Based on Complex Network Analysis

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Abstract

Aim: To explore the medication rules in Shang Han Lun based on complex network analysis methods. **Methods:** Prescriptions were extracted from Shang Han Lun to establish a database. After standardizing the data, software was developed using Python to perform statistical analysis on medication frequency, relationships between drugs, and core drugs. **Results:** The appearance frequency of roasted licorice, cassia twig, jujube, ginger, and peony was relatively high in the 112 prescriptions in Shang Han Lun. The main prescriptions for Taiyang disease were Guizhi Tang and Mahuang Tang. The core drugs for Shaoyang disease and combined diseases were licorice, jujube, ginger, *Scutellariae* radix, and cassia twig. The core drugs for Yangming disease were rhu-barb, licorice, *Fructus aurantii* Immaturus, and *Magnoliae* Officinalis. The main prescription for Taiyin disease was Guizhi Tang with modifications. For Shaoyin disease, the main medications were those for restoring Yang and reversing adverse flow or nourishing Yin and clearing heat. The core drugs for Jueyin disease were licorice, *Scutellariae* radix, *Angelicae sinensis* radix, cassia twig, gypsum fibrosum, *Paeoniae* alba, and dried ginger. **Conclusion:** Complex network methods can analyze the medication characteristics and relationship characteristics of Shang Han Lun, which is meaningful for further analysis of the medication compatibility characteristics and syndrome differentiation medication rules in Shang Han Lun.

Keywords

Complex Network Method, Shang Han Lun, Cluster Analysis Method

1. Introduction

Shang Han Lun is the first medical work in China that perfectly integrates theory with practice with principles, methods, prescriptions, and medications. To study

the principle of syndrome differentiation and treatment, as well as the rules of drug compatibility in Shang Han Lun can provide a basis for the development of new prescriptions based on classical formulas.

With the advancement of sciences, study on Shang Han Lun has gradually evolved from qualitative interpretation to quantitative analysis, such as using data mining, deep learning, machine learning and other methods to analyze the compatibility and medication rules of Shang Han Lun. In recent years, some progress has been made in the application of complex network analysis methods in the study of Shang Han Lun. Liang [1] constructed a multi-layer binary network model of “Mechanism-method-prescription-medicine” and proposed an index of “drug influence”. Through analysis, it was found that the core drugs for Taiyang disease are cassia twig and peony, while the key drugs for Taiyin disease are ginger and licorice. Jueyin disease relies mainly on dried ginger and *Asarum*. Shao *et al.* [2] established a multi subnet model for six-channel diseases, and proposed a concept of “differential diagnosis degree” to analyze the topological characteristics of symptoms for six meridian diseases. Wu *et al.* [3] identified the core drug pairs (such as Huanglian-Huangqin) of Dahuang Huanglian Xiexin Tang through a complex network, and analyzed their mechanism of improving renal fibrosis through the AGEs-RAGE pathway. Sun [4] proposed a classification method of prescriptions and syndromes combining approximate reasoning and support vector machine (SVM) to achieve quantitative analysis of traditional Chinese medicine syndrome differentiation. Tang *et al.* [5] used complex network analysis to demonstrate that the drug pairs of ephedra-almond medicine exert antiviral effects through the ACE2 receptor network, verifying the application value of traditional Chinese medicine formulas in modern infectious diseases. Geng *et al.* [6] revealed the differences in antiemetic effects between ginger (targeting 5-HT₃ receptors) and dried ginger (targeting H₁ receptors) through PPI network analysis. Guo *et al.* [7] studied the nodes in the knowledge graph of Yangming disease in Shang Han Lun through complex network, excavated potential knowledge, and explored the key points of differentiation of Yangming disease. Li and Sui [8] used complex network to establish drug subnets for the sixth channel of Taiyang, Yangming, Shaoyang, Taiyin, Shaoyin, and Jueyin, respectively, and analyzed the topological properties of each drug subnet such as node degree and network connectivity. It is found that the main drugs to treat Taiyang disease and Taiyin disease are cassia twig, peony, jujube, ginger, and licorice; the main drugs for treating Yangming disease are rhubarb, ginseng, and almonds; the main drugs for treating Jueyin disease are dried ginger, *Angelica sinensis*, and *Asarum*; the main drugs for treating Shaoyin disease are Fuzi and *Poria cocos*; The treatment of Shaoyang disease is only based on data from Xiaochaihu decoction. According to the calculation of common nodes between any two channels, the prescriptions for treating Taiyang, Yangming, Jueyin, and Shaoyin diseases have many identical drugs, while the data for the Taiyin and Shaoyang disease drug subnets is limited and

mostly composed of a small amount of new drugs added to other channels' prescriptions.

Although previous researchers have conducted extensive study on the rules of syndrome differentiation and treatment in Shang Han Lun. However, there is still limited study on exploring the medication rules based on complex network analysis methods and the classification of the six channels. This study adopts the complex network analysis method to study the characteristics of formula compatibility in Shang Han Lun. Firstly, an overall prescription analysis is conducted. Then the prescriptions in Shang Han Lun are analyzed according to the six channels. that is, the study focuses on the drug sub networks of the overall, Taiyang, Yangming, Shaoyang, Taiyin, Shaoyin, Jueyin, Sanyang, Sanyin diseases, and analyzes their medication rules, drug effects, and relationships between drugs.

2. Data Acquisition and Analysis Method

In order to explore the medication rules of Shang Han Lun, this article conducted complex network analysis and cluster analysis on the 112 prescriptions in Shang Han Lun. Statistical and network analysis were performed using software written in Python language, and the results were visualized at last.

The data used in this article were all from relevant classics related with Shang Han Lun [9]-[11]. We collected and compiled information on 112 prescriptions involved in Shang Han Lun, including 3 parts (the upper, middle, and lower parts) on identifying and treating the pulse syndrome of Taiyang disease, and 5 parts on identifying and treating the pulse syndrome of Yangming, Shaoyang, Taiyin, Shaoyin, and Jueyin diseases, totaling 8 parts and 381 paragraphs.

The paragraph numbers are based on the new edition of Shang Han Lun by the Chongqing Society of Traditional Chinese Medicine [8]. Among them, 1 - 178 paragraphs are related to Taiyang diseases, 179 - 262 paragraphs are related to Yangming diseases, 263 - 272 paragraphs are related to Shaoyang diseases, 273 - 280 paragraphs are related to Taiyin diseases, 281 - 325 paragraphs are related to Shaoyin diseases, and 326 - 381 paragraphs are related to Jueyin diseases.

3. Complex Network Analysis

3.1. Introduction of Method

Complex network analysis is a perspective and method for studying complex systems, which focuses on the structure of individual interactions within the system. By calculating the topological features such as average degree, network diameter, average path length, and average clustering coefficient of nodes in the network, as well as the characteristics of dispersion, concentration, and density between elements, the distribution pattern of elements between things is described [11]. From the perspectives of openness, hierarchy and complexity, traditional Chinese medicine has the same characteristics as complex networks, which is also the basis for using complex networks to analyze traditional Chinese medicine data.

The use of complex network technology to explore the rules of traditional Chi-

nese medicine's syndrome differentiation and treatment, as well as the formulation of medication, is an effective way to reveal the inherent complex relationships of traditional Chinese medicine [12]. The node degree is one of the criteria for determining the importance (centrality) of traditional Chinese medicine nodes in network analysis. The larger the node degree is, the more times it appears in combination with other nodes, and the higher the centrality of the node is, making it more important in the network [13]. The betweenness centrality refers to the frequency at which any node(drug) appears on the shortest path of the network, reflecting the degree of hub of the node(drug) in the network connection compatibility [14]. The above two indexes can measure the importance of nodes of traditional Chinese medicine in complex networks. The more frequent the node compatibility, the denser the lines between the combinations, and the greater the node degree, the stronger the compatibility and combination ability of traditional Chinese medicine nodes.

The method used in this paper was to extract prescriptions from the classic Shang Han Lun first and then establish a database. After standardizing the data, Python language is used to develop the software for complex network analysis, and then statistical analysis on medication frequency, node degree of each drug, connection strength between drugs, core drugs, etc. were performed.

3.2. Results for Total Prescriptions

3.2.1. Frequency

In this section, a complex network analysis was conducted on all 112 prescriptions containing 90 types of traditional Chinese medicine. The data on the frequency of use, node degree, and edge weight of each medicine were obtained. This allows for the analysis of the importance of each medicine, as well as the strength of connections between two drugs.

It is found that those with a usage frequency of more than 10 times are by analysis: Licorice 66 times (accounting for 58.9%), *Cinnamomum cassia* 41 times (36.6%), Jujube 38 times (33.9%), Ginger 37 times (33%), *Paeonia lactiflora* 21 times (18.8%), Ginseng 20 times (17.9%), Dried Ginger 20 times (17.9%), *Pinellia ternata* 18 times (16.1%), Aconitum 17 times (15.2%), *Scutellaria baicalensis* 15 times (13.4%), Rhubarb 15 times (13.4%), *Ephedra sinica* 13 times (11.6%), *Coptis chinensis* 12 times (10.7%), *Poria cocos* 11 times (9.8%), *Atractylodes macrocephala* 10 times (8.9%).

As can be seen, these drugs are mainly from Guizhi Tang and Mahuang Tang. Please note the importance of these two formulas in Shang Han Lun. The proportion of licorice, cassia twig, jujube, and ginger is significantly higher than other drugs, indicating the widespread use of these drugs in all formulas and their applicability to various diseases.

Among the above drugs, licorice has a slightly cool nature and is good at clearing heat and detoxifying. It is often used for treating heat toxic ulcers and sore throat; Honey roasted licorice has a warm nature and focuses on tonifying the spleen, nourishing Qi, and relieving pain. It is suitable for spleen and stomach

weakness, palpitations, and shortness of breath. It belongs to heart meridian, lung meridian, spleen meridian, and stomach meridian. Guizhi has a spicy, sweet, and warm taste, and belongs to the heart, lungs, and bladder meridians. Jujube has a sweet and warm taste, and belongs to the spleen, stomach, and heart meridians. It has the effects of nourishing the middle and Qi, nourishing blood and calming the mind, generating fluids and moistening dryness, and harmonizing medicinal properties. *Paeonia lactiflora* has a bitter and sour taste, with a slight coldness. It belongs to the liver and spleen meridians and has the effects of nourishing blood, regulating meridians, tonifying Yin, stopping sweating, softening the liver, relieving pain, and calming liver Yang. Ginseng has a sweet, slightly bitter, and slightly warm taste, and belongs to the spleen, lung, heart, and kidney meridians. It has the effects of tonifying vital energy, nourishing the spleen and benefiting the lungs, generating fluids and quenching thirst, calming the mind and improving intelligence, and harmonizing medicinal properties. *Pinellia ternata* has a pungent and warm taste, is toxic, and belongs to the spleen, stomach, and lung meridians. It has the effects of drying dampness, resolving phlegm, reducing nausea and vomiting, dispelling stagnation, and reducing swelling when using externally. Ginger has a pungent taste, a slight warmth, and belongs to the lung meridian. It has the effects of sweating, relieving external heat, and dispersing wind and cold. Dried ginger has a pungent and hot taste, and belongs to the spleen, stomach, kidney, heart, and lung meridians. It has the effects of warming the middle and dispelling cold, returning Yang and promoting blood circulation, and warming the lungs and promoting diuresis. Fuzi has a pungent and sweet taste, a hot and toxic nature, and belongs to the heart, spleen, and kidney meridians. Ginseng has a sweet and slightly bitter taste, a slightly warm nature, and belongs to the spleen, lungs, heart, and kidney meridians. It can tonify the kidneys and invigorate the essence, nourish the spirit, and greatly replenish the Qi. It is the strongest Qi tonifying medicine. *Scutellaria baicalensis* has a bitter and cold taste, and belongs to the lungs, gallbladder, spleen, large intestine, and small intestine meridians. It has the effects of clearing heat, drying dampness, purging fire, detoxifying, stopping bleeding, and stabilizing pregnancy. Huanglian has a cold taste, and belongs to the spleen, stomach, liver, gallbladder, and large intestine meridians. It has the effects of clearing heat, drying dampness, purging fire, and detoxifying. Ephedra has a pungent, slightly bitter taste, and warm nature. It belongs to the lung and bladder meridians and has the effects of sweating, dispelling cold, promoting lung function, relieving asthma, promoting diuresis, and reducing swelling. Rhubarb has a bitter and cold taste, and belongs to the spleen, stomach, large intestine, liver, and pericardium meridians. It has the effects of purging and attacking accumulation, clearing heat and fire, removing blood stasis and promoting meridian circulation, and relieving dampness and yellowing. *Poria cocos* has a sweet and mild taste, a calm nature, and belongs to the heart, lungs, spleen, and kidney meridians. It has the functions of promoting diuresis and dampness, strengthening the spleen and stopping diarrhea, calming the heart and mind, resolving phlegm and stopping

cough. *Atractylodes macrocephala* has a bitter and sweet taste, a warm nature, and belongs to the spleen and stomach meridians. It has the effects of tonifying Qi and spleen, drying dampness and promoting diuresis, stopping sweating, and stabilizing pregnancy.

The functional descriptions of the principal herbs in terms of their nature, taste, meridian tropism, and therapeutic effects indicate that the commonly used herbs in the Shang Han Lun encompass a comprehensive range of functions, including tonifying deficiency, promoting diuresis and resolving dampness, activating blood and resolving stasis, releasing the exterior, and warming the interior.

3.2.2. Node Degree

The total number of nodes is 90, the number of connected edges is 557. The node degrees are as follows: The licorice is 55, Guizhi 48, ginger 46, jujube 43, ginseng 38, dried ginger 35, *Paeonia lactiflora* 31, *Pinellia ternata* 31, *Poria cocos* 29, *Scutellaria baicalensis* 29, rhubarb 29, *Ephedra sinica* 27, *Angelica sinensis* 24, aconitum and *Coptis chinensis* 22, almond, *Atractylodes macrocephala* and gypsum 21, *paeonia lactiflora* 20, *Asarum* and oyster 19, colla corii asini and *Bupleurum chinense* 17, *Anemarrhena asphodeloides* and *Fructus aurantii* immaturus 16, magnolia officinalis and hemp seed 14, *Phellodendron chinense* 13, cohosh, asparagus, and verbena officinalis; dragon bone and *Alisma* 12, Wu Zhuyu, Gualou root, and Shuqi 11, minium 10, Sichuan pepper, black plum, sake, raw ground, japonica rice, *Gardenia*, kudzu root, and *Ophiopogon japonicus* are all 9, *Euphorbia kansui* and medulla *Tetrapanacis* 8, *Schisandra chinensis* and red bean 7, bamboo leaves, stems, pork cocos, ocher, *Ophiopogon japonicus*, Shanglu roots, peach kernels, seaweed, spiral flowers, purple bark, roasted licorice, and glutinous rice are all 6, scallion white, white honey, stems, and maltose are all 5, human urine, *Gallus gallus domesticus*, talc, cinnamon, fermented black beans, and pig bile are all 4, *Hirudo*, *Tabanus*, Chinese bulbul, *Daphne genkwa*, *Euphorbia pekinensis*, *Halloysitum rubrum* are all 3, fruit of *Trichosanthes kirilowii*, raw aconite and Yinchen 2, female loin, male loin, *Platycodon grandiflorum*, pedicellus melo, limonitum and egg are all 1.

3.2.3. Edge Weight

Licorice-jujube 32, jujube-*Fructus aurantii* 26, cassia twig-jujube 23, licorice-radix *Paeoniae alba* 15, ginger-radix *Paeoniae alba* 13, Ginseng-jujube 10, jujubes-radix *Paeoniae alba* 15, Licorice-Ephedra 9, jujubes-*Scutellaria baicalensis* 8, cassia twig-licorice 8, dried ginger-licorice 7, cassia twig-*Scutellaria baicalensis* 7, licorice-*Scutellaria baicalensis* 7, almonds-ephedra 6.

Aconiti Radix-licorice, *Coptis chinensis*-*Scutellaria baicalensis*, licorice-*Pinellia ternata*, cassia twig-radix *Paeoniae alba*, licorice-*Poria cocos*, licorice-*Paeonia lactiflora* pall, *Pinellia ternata*-*Scutellaria baicalensis*, *Pinellia ternata*-radix bupleuri, jujube-radix bupleuri, *Rheum officinale*-mirabilite, ginger-*Scutellaria baicalensis*, *Atractylodes macrocephala*-*Poria cocos*, *Scutellaria baicalensis*-radix bupleuri, and ginger-radix bupleuri are all 5.

Cassia twig-*Poria cocos*, cassia twig-almonds, cassia twig-oysters, cassia twig-ginger, ginseng-*Pinellia ternata*, ginseng-licorice, dried ginger-jujube, ginseng-radix bupleuri, *Coptis chinensis*-*Pinellia ternata*, *Coptis chinensis*-jujube, licorice-ginger, gypsum-ephedra, *Paeonia lactiflora*-*Scutellaria*, licorice-gypsum, ginger-*Ephedra sinica*, ginger-*Paeonia lactiflora*, jujube-almond, *Rheum officinale*-*Fructus aurantii* immaturus, ginger-almond, and are all 4; the rest are all 2.

It can be seen that the frequency of appearance in the 112 prescriptions of Shang Han Lun of prepared licorice (Figure 1), cassia twig, jujube, ginger, *Paeonia lactiflora* pall is relatively high, such as the prepared licorice appears 64 times, the cassia twig and jujube 38 times, the ginger 36 times, etc. It is in line with Zhang Zhongjing's actual medication principles. Zhongjing harmonized the Yingqi and Weiqi through the whole treating process, while also caring for the middle-Jiao to harmonize the five organs [1].

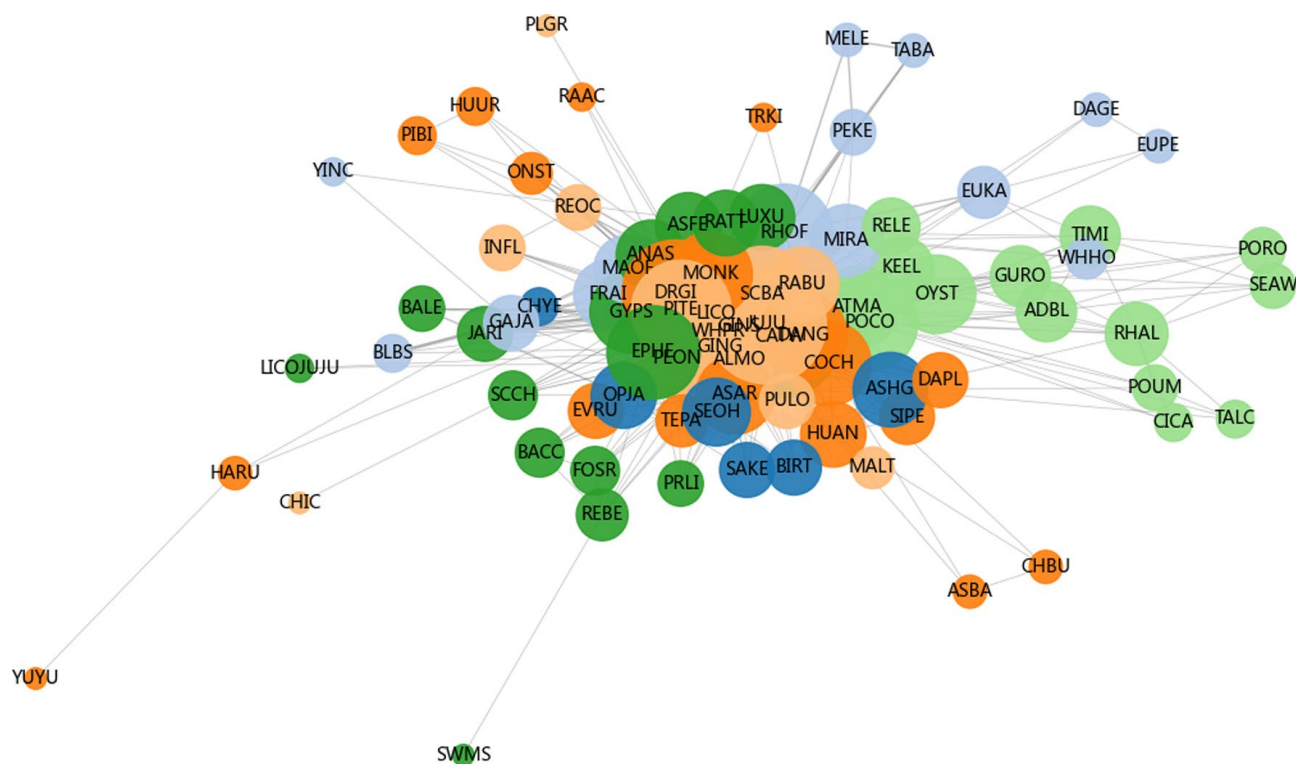


Figure 1. Network for the total prescription.

3.2.4. Cluster Analysis

During clustering analysis, the scree plot was first obtained using the considered data to determine the number of cluster; then K-means method was used to process clustering. When the prescriptions of each cluster were obtained, we can analyze the characteristics of each cluster according to the drugs of these prescriptions and compare the function and medication rules among different clusters. The criteria used to label clusters is determined by the K-means distance. K-means clustering is an unsupervised machine learning algorithm whose core objective is to

partition a dataset into K mutually exclusive clusters, such that the data points within each cluster are as similar as possible, while the data points between different clusters are as different as possible. Here, K-means clustering will automatically assign every formula to the appropriate cluster once we set the number of clusters.

It can be seen that 6 clusters should be selected according to the scree plot (Figure 2(a)). However, the clustering results are not distinctly separated. Moreover,

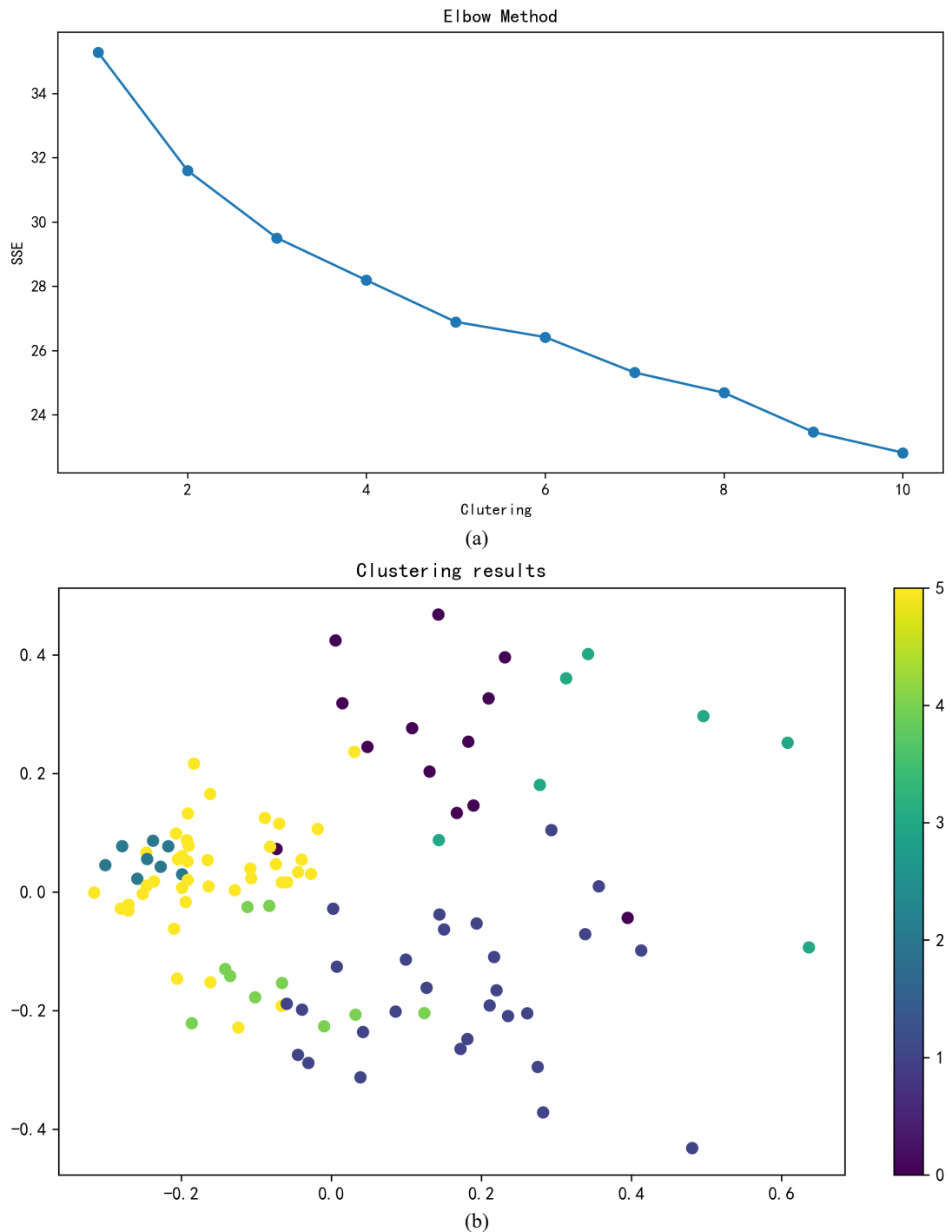


Figure 2. The clustering results of the total prescription. (a) Scree plot; (b) clustering plot.

examining the specific clustering of each drug, these 6 clusters do not correspond to drugs from the six meridians (Taiyang, Shaoyang, Yangming, Taiyin, Shaoyin, and Jueyin) (**Figure 2(b)**). It indicates that within diseases categorized by the six meridians, symptoms often overlap, as the medication principles of Shang Han Lun are based not only on the six-meridian classification but also on symptom patterns.

3.3. Taiyang Chapter

3.3.1. Usage Frequency and Node Degree

Licorice 42 times, cassia twig 30 times, ginger and jujube 26 times, ginseng, dried ginger and *Pinellia ternata* 11 times, *Paeonia lactiflora* 10 times, *Aconiti Radix* and *Rheum officinale* 9 times, *Coptis chinensis*, almond and *Ephedra sinica* 8 times, *Poria cocos* and *Scutellaria* 7 times, *Atractylodes macrocephala* and fructus *Gardeniae* 6 times, *Paeonia lactiflora* pall 5 times, while magnolia officinalis, peach kernel, mirabilite, *Euphorbia kansui*, gypsum, radix bupleuri, dragon Bone, oyster and sojæ semen praeparatum only has 3 times; *Hirudo*, *Tabanus* and *Fructus aurantii* immaturus only have 2 times, all the rest have only 1 time. It can be seen that compared with the statistical data of overall prescription, the main drugs are basically the same. The importance of *Paeonia lactiflora* in treating Taiyang diseases has increased because the *Paeonia lactiflora* has the taste of bitter, sour and slightly sold, benefits for the liver meridian and spleen meridian. It has the effects of tonifying Yin, stopping sweating, softening the liver, and relieving pain.

The total nodes are 60 and the connection edges are 321. The node degrees are as follows: cassia twig 36, licorice 41, ginger 39, jujube 36, ginseng 26, *rheum officinale* 24, *Pinellia ternata* 24, *Paeonia lactiflora* and *Poria cocos* 18, almond 19, *Ephedra sinica* and dried ginger 17, *Scutellaria* and radix bupleuri 14, *Aconiti Radix* and *Paeonia lactiflora* pall 13, oyster, *Atractylodes macrocephala* dragon Bone and *coptis chinensis* 12, red lead and magnolia officinalis 10.

Sake, raw *Rehmannia glutinosa*, *Ophiopogon japonicus*, seed of hemp, colla corii asini and *Fructus aurantii* immaturus are all 9. Both *Euphorbia kansui* and mirabilite are 8. *Schisandra chinensis*, fructus *Gardeniae*, *Asarum* and gypsum are all 7. ruddle, peach kernel, inula flower, bark of Chinese catalpa, red bean, *Forsythia suspensa*, prepared licorice and twig and leaf of antifebrile *Dichroa* are all 6. Maltose, white honey and draba are all 5. Rhizoma *Alismatis*, *Cinnamomum cassia* and *Polyporus umbellatus* are all 4. *Daphne genkwa*, *Pueraria lobata*, sojæ semen praeparatum, *Euphorbia pekinensis*, *Hirudo* and *Tabanus* are all 3. raw *Aconiti Radix*, *Trichosanthes* fruit and *Phellodendron* are all 2. Halloysitum rubrum and Yu Yu Liang (limonitum) are all 1.

Licorice-jujube 21 jujube-ginger 18 cassia twig-jujube 16 licorice-*Paeonia lactiflora* 9 jujube-*Paeonia lactiflora* 8 ginger-*Paeonia lactiflora* and ginseng-jujube are all 7; dried ginger-ginseng, licorice-*ephedra sinica* and cassia twig-licorice are all 5; both of almond-*ephedra sinica* and dried ginger-licorice are 6; dried ginger-jujube, cassia twig-*Pinellia ternata*, cassia twig-almond, cassia twig-ginger, cassia

twig-*ephedra sinica*, licorice-*poria cocos*, *Pinellia ternata*-*Scutellaria*, *Pinellia ternata*-*Coptis chinensis*, jujube-*Scutellaria*, jujube-almond, jujube-*Coptis chinensis*, *Scutellaria*-*Coptis chinensis*, both of licorice-ginger and ginger-almond are 4; licorice-gypsum, licorice-*Aconiti Radix*, licorice-*Scutellaria*, licorice-*Coptis chinensis*, licorice-*Paeonia lactiflora* pall, *Pinellia ternata*-radix bupleuri, ginseng-*Pinellia ternata*, ginseng-ginger, dried ginger-*Coptis chinensis*, cassia twig-ginseng, *Rheum officinale*-mirabilite, gypsum-*Ephedra sinica*, fructus *Gardeniae*-sojae semen praeparatum, cassia twig-oyster, cassia twig-*Poria cocos*, jujube-radix bupleuri, *rheum officinale*-peach kernel, oyster-dragon Bone, ginger-radix bupleuri, *Atractylodes macrocephala*-*Poria cocos*, licorice-ginseng, licorice-*Pinellia ternata* and licorice-almond are all 3; the rests are 2 (Figure 3).

It can be seen that the cassia twig, licorice, ginger, jujube, ginseng, *Rheum officinale*, *Pinellia ternata*, *Paeonia lactiflora* are the core drug among them, and licorice-jujube, jujube-ginger, cassia twig-jujube, licorice-*Paeonia lactiflora*, jujube-*Paeonia lactiflora*, ginger-*Paeonia lactiflora* and ginseng-jujube form the core drug pair, which corresponds to the characteristics of Taiyang disease. Taiyang disease primarily manifests as exogenous wind-induced-cold pathogens invading the body's superficial regions, leading to a struggle between healthy Qi and pathogenic factors at the body surface. This results in dysfunction of the Ying (nutritive) and Wei (defensive) Qi, with its core pathogenesis being "disharmony" between Ying and Wei Qi, and stagnation of Wei Yang. The treatment of Taiyang disease is mainly based on the "sweating" method, which uses sweating to eliminate the evil

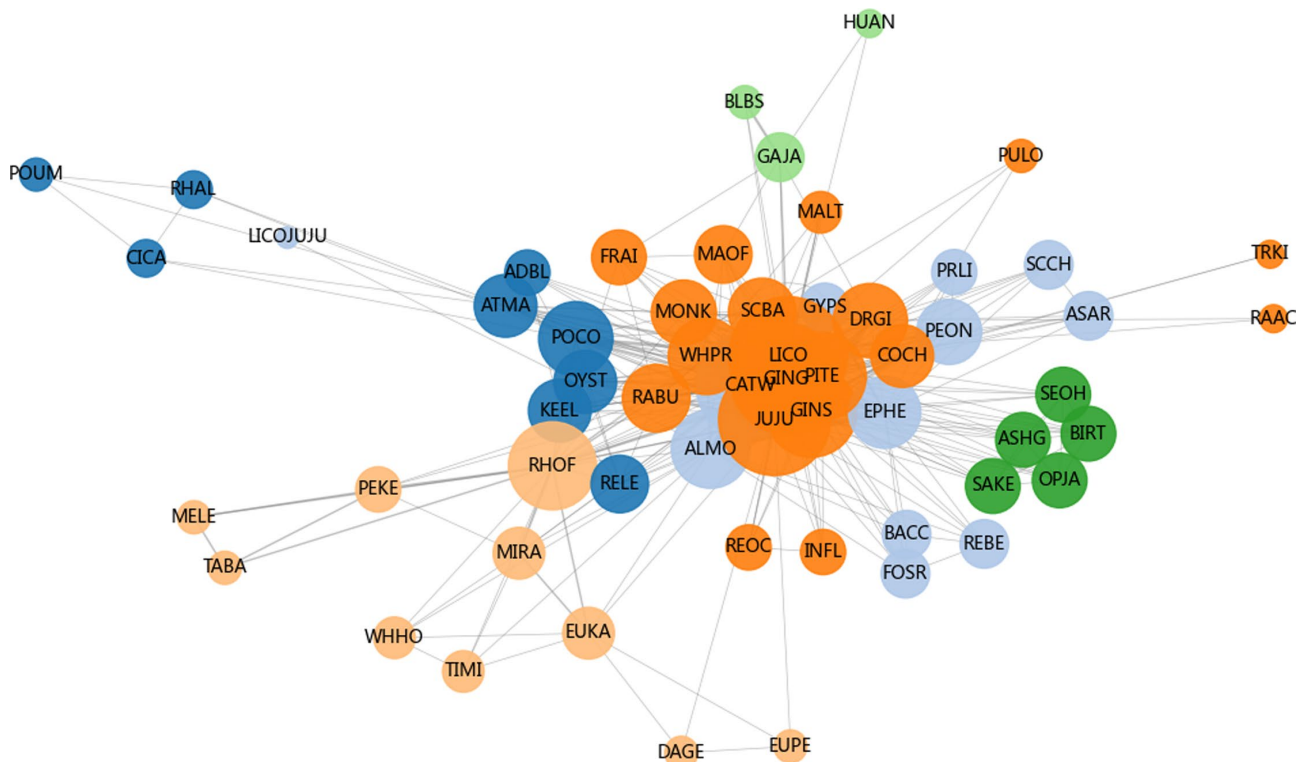


Figure 3. Network for the prescription in Taiyang Chapter (in which HARU-YUYU is a separate connection and is not shown).

from the body surface. The main formulas are Cassia Twig Tang and *Ephedra Sinica* Tang.

3.3.2. Cluster Analysis

It can be seen that 5 clusters were selected, and there is little overlap between the cluster data, indicating that there is a high degree of differentiation between each prescription, or in other words, the corresponding symptoms of each prescription are clearly different, and the drugs used are also different (Figure 4).

The following formulas belong to the same category: Banxia Xiexin Tang with the function of harmonizing liver and spleen, balancing cold and heat, dissolving masses and resolving stagnation). Dachaihu Tang with the function of the harmonizing and resolving Shao Yang, clearing heat and draining repletion and soothing liver and harmonizing stomach. Xuanfu Daizhe Tang for treating the stomach deficiency, phlegm obstruction and rebellious Qi failing to descend. Chaihu Guizhi Tang with the function of harmonizing Shao Yang. Chaihu Longgu Muli Tang with the function of calming the spirit and tranquilizing the mind, leveling liver and subduing Yang. Banxia Tang: balancing cold and heat, dissolving masses and resolving stagnation.

The following formulas belong to the same category: Tao He Cheng Qi Tang whose function is to drain heat and remove blood stasis, promote bowel movement and relieve pain. Di Dang Tang with the function of resolving stasis and clearing heat in lower Jiao, used for mania, rigid lower abdomen, spontaneous urination, and amenorrhea. Shi Zao Tang with the function of draining water retention caused by fluid accumulation in the chest and ribs, treating generalized edema and ascites. Da Xian Xiong Tang with the function of draining heat and expelling fluid, indicated for hard fullness and pain in the chest with associated rigidity. Da Xian Xiong Wan is for chest hardness, fullness, and pain accompanied by neck stiffness, a modified pill formulation of Da Xian Xiong Tang.

The following formulas belong to the same category: Si Ling San with the function of promoting diuresis and removing dampness. Gui Zhi Ren Shen Tang whose function is to warm the Middle, dispel cold, resolve exterior and tonify the spleen. Gui Zhi Sheng Jiang Da Zao Gan Cao Tang with the function of warming the channels, dispelling cold, harmonizing the nutritive and defensive Qi, strengthening the spleen and harmonizing the Middle. Gui Zhi Fu Zi Gan Cao Gan Jiang Da Zao Tang with the function of warming Yang, resolving exterior, dispelling cold and relieving pain. Gui Zhi Fu Ling Sheng Jiang Gan Cao Tang with the function of warming Yang and transforming Qi, Strengthening the spleen and removing dampness, harmonizing the nutritive and defensive Qi. Fu Ling Gui Zhi Da Zao Gan Cao Tang with functions of warming Yang and transforming fluids, calming rebellious Qi and descending reversal. Gui Zhi Fu Zi Tang with the function of dispelling wind, warming the channels, assisting Yang and transforming dampness. Bai Zhu Fu Zi Tang with the function of warming Yang and dispelling cold, strengthening the spleen and removing dampness. Bai Zhu Gui Zhi Fu Zi Gan Cao Tang having the function of warming Yang and dispelling

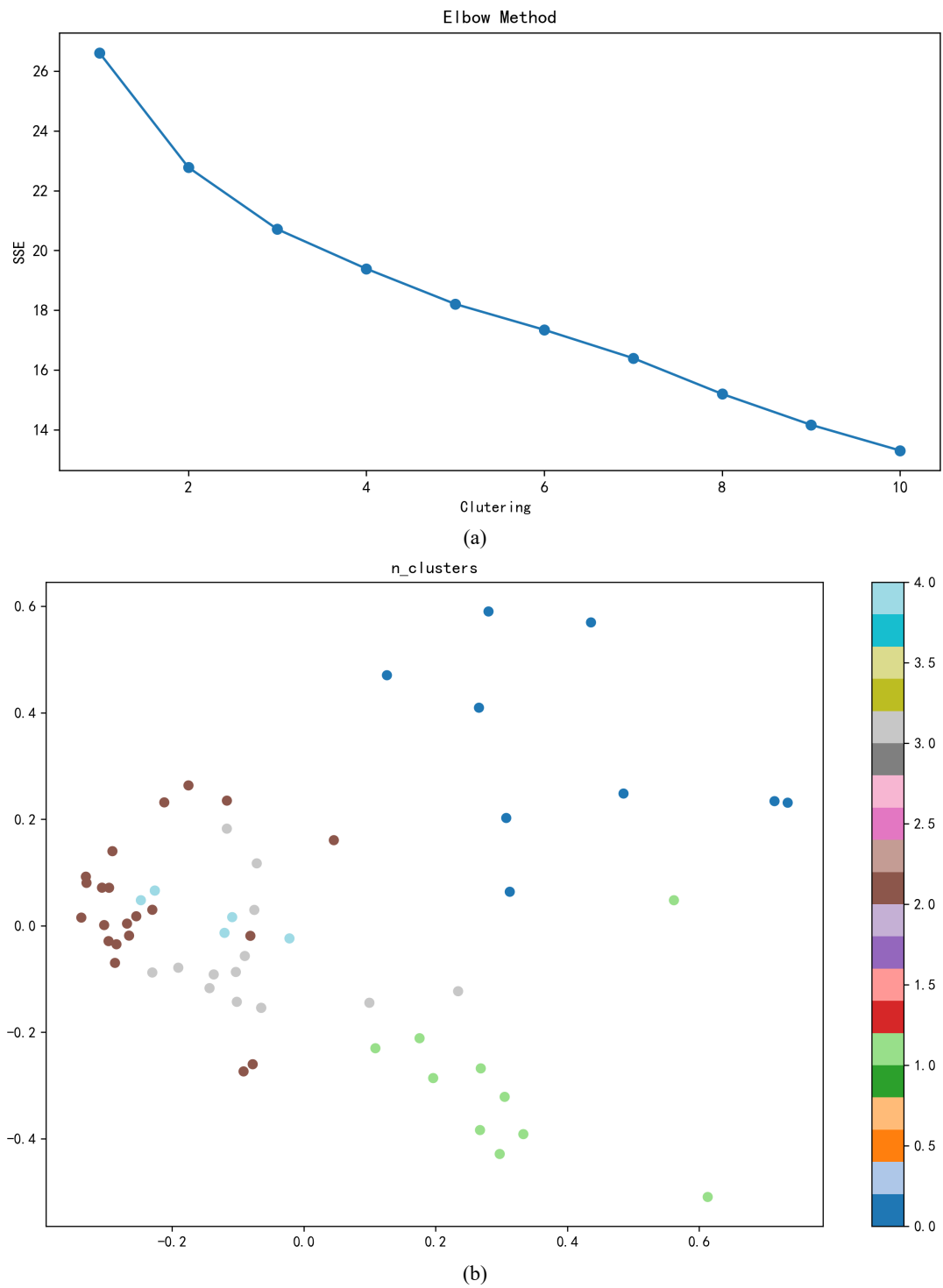


Figure 4. The clustering results of the prescription in Taiyang Chapter. (a) Scree plot; (b) clustering plot.

cold, removing dampness and relieving pain. Fu Ling Gui Zhi Bai Zhu Gan Cao Tang having the function of warming Yang and transforming fluids, strengthening the spleen and removing dampness. Gui Zhi Gan Cao Long Gu Mu Li Tang having the warming and unblocking the heart Yang, calming the spirit and subduing rebellious Qi. Gui Zhi Gan Cao Long Gu Mu Li Tang for the condition of

insufficiency of heart Yang. Fu Ling Si Ni Tang having the regulating spleen and stomach deficiency-cold or internal obstruction due to cold-dampness.

The rest are one category.

The Taiyang disease varies greatly with the course of the disease and presents multiple symptoms, so its medication can be divided into multiple types.

3.4. Shaoyang Combination Chapter

3.4.1. Use Frequency

Licorice 7 times, jujube 6 times, ginger 5 times, *Scutellaria* and cassia twig 4 times, *Pinellia ternata*, *Paeonia lactiflora* and *Pueraria lobata* 3 times, radix bupleuri, *Ephedra sinica*, *Paeonia lactiflora* pall, fructus *Melothriae* and red bean 2 times, ginseng, dried ginger, oyster and radix *Trichosanthis* 1 time (Figure 5).

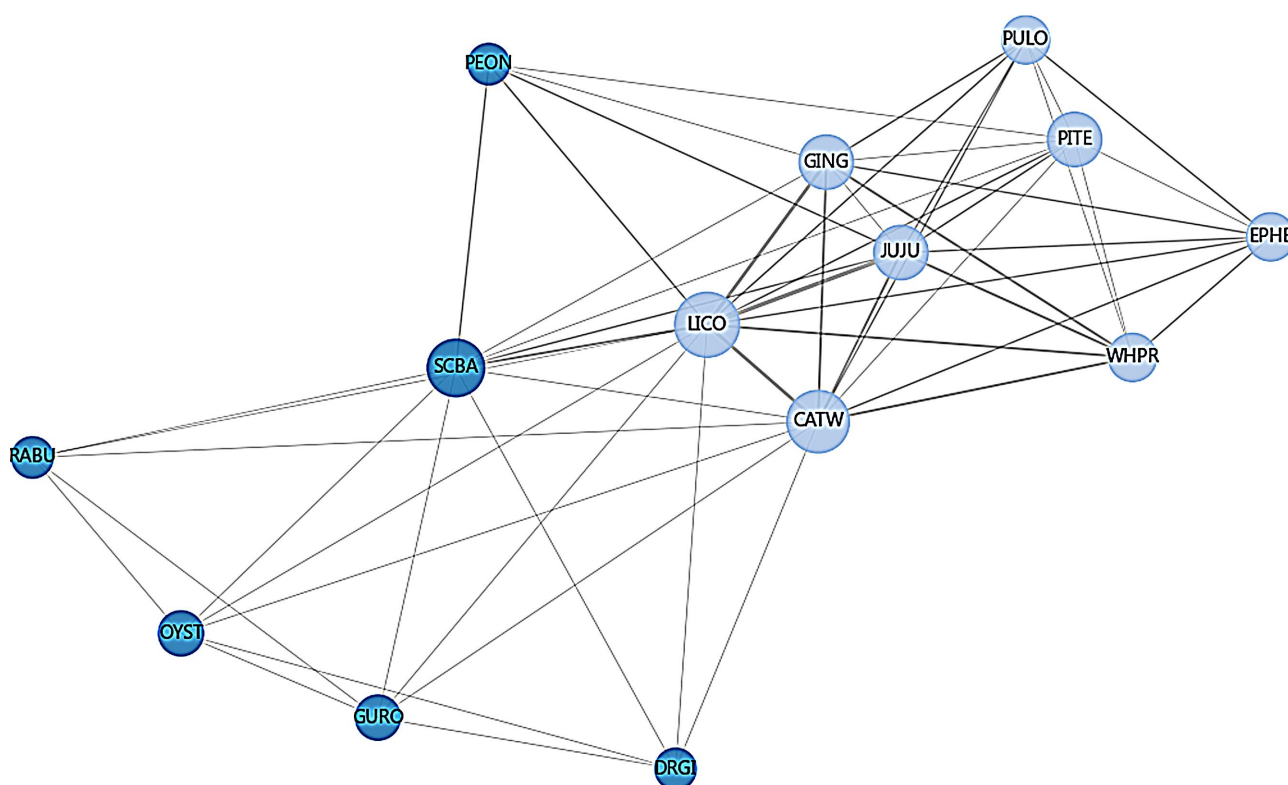


Figure 5. Network for the prescription in Shaoyang Chapter (in which REBE-SWMS is a separate connection and has not been drawn.)

The total nodes are 16 and the connection edges are 57. The node degrees are as follows: licorice 13, cassia twig 12, *Scutellaria* 10, *Pinellia ternata*, ginger and jujube 9, *Pueraria lobata*, *Paeonia lactiflora* and *Ephedra sinica* 7, dried ginger, radix *Trichosanthis*, oyster and radix bupleuri 6, *Paeonia lactiflora* pall 5, fructus *Melothriae* and red bean 1.

The connection weights: jujube-licorice 5, cassia twig-licorice and ginger-licorice 4, ginger-jujube, ginger-cassia twig, jujube-cassia twig, jujube-*Paeonia lactiflora*, cassia twig-*Paeonia lactiflora*, ginger-*Paeonia lactiflora*, licorice-*Paeonia*

lactiflora and licorice-*Scutellaria* 3, *Pinellia ternata*-jujube, *Pinellia ternata*-licorice, ginger-*Pueraria lobata*, ginger-*Ephedra sinica*, jujube-*Pueraria lobata*, jujube-*Paeonia lactiflora* pall, jujube-*Ephedra sinica*, jujube-*Scutellaria*, *Pueraria lobata*-cassia twig, *Pueraria lobata*-licorice, *Pueraria lobata*-*Paeonia lactiflora*, *Pueraria lobata*-*Ephedra sinica*, cassia twig-*Ephedra sinica*, licorice-*Paeonia lactiflora* pall, licorice-*Ephedra sinica*, *Scutellaria*-radix bupleuri and *Paeonia lactiflora*-*Ephedra sinica* are all 2.

It can be seen that there are relatively a few prescriptions for Shaoyang and combined diseases, but in which the licorice, jujube, ginger, *Scutellaria*, cassia twig are still the core drugs. The core drug pairs are jujube-licorice, cassia twig-licorice, ginger-licorice, ginger-jujube, ginger-cassia twig, jujube-cassia twig, jujube-*Paeonia lactiflora*, cassia twig-*Paeonia lactiflora*, ginger-*Paeonia lactiflora*, licorice-*Paeonia lactiflora*, licorice-*Scutellaria*.

3.4.2. Clustering Analysis

It can be seen that the clustering differences are more obvious, which may be due to the fact that these prescriptions include Shaoyang disease and the combined disease of Shaoyang and Taiyang and Yangming, with significant differences between them (Figure 6).

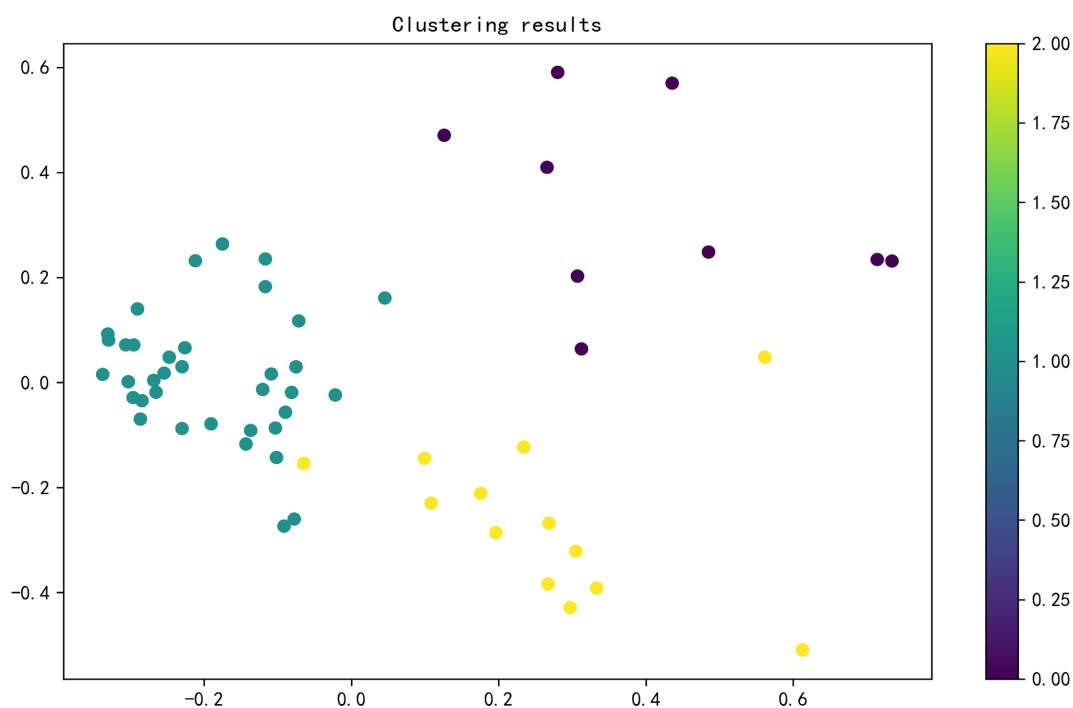


Figure 6. The clustering results of the prescription in Shaoyang Chapter.

The following decoctions belong to the same category Banxia Xiexin Decoction (harmonizing liver and spleen, balancing cold and heat, dispersing nodules), Dachaihu Decoction (resolving Shaoyang, clearing heat and purging excess, soothing liver and harmonizing stomach), Xuanfu Daizhe Decoction (treating stomach deficiency with phlegm obstruction and rebellious qi), Chaihu Guizhi Decoction (resolv-

ing Shaoyang and harmonizing the nutritive and defensive qi), Chaihu Longgu Muli Decoction (calming the spirit and stabilizing the mind, soothing the liver and subduing yang), and Banxia Decoction (balancing cold and heat, dispersing nodules).

The following are the same category: Gui Zhi Fu Zi Tang (functions are to dispel wind, warm the meridians, assist Yang, and transform dampness). Gui Zhi Hou Po Xing Zi Tang (functions are to harmonize the nutritive and defensive Qi, regulate Qi, transform phlegm, and relieve cough and wheezing). Xiao Jian Zhong Tang (to warm the Middle, tonify deficiency, harmonize the Interior, and relax urgency). Zhi Gan Cao Tang (to nourish Yin and blood, benefit Qi and warm Yang, restore pulse and calm palpitations). Ma Huang Lian Qiao Chi Xiao Dou Tang (to release the exterior, disperse pathogenic factors, clear heat, and promote dampness elimination to reduce jaundice). Ma Huang Xing Ren Gan Cao Shi Gao Tang (Pungent-Cooling and to ventilate, clear the Lung, and relieve wheezing). Gui Zhi Ma Huang Ge Ban Tang has the characteristics of pungent-warm and lightly dispersing to induce a light sweat and release the exterior). Da Qing Long Tang (to release the exterior, disperse cold, harmonize the nutritive and defensive Qi, clear heat, and generate body fluids). Gui Zhi Er Ma Huang Yi Tang (to release the muscles, disperse pathogenic factors, and harmonize the nutritive and defensive Qi). Fu Ling Gui Zhi Bai Zhu Gan Cao Tang (to warm Yang, transform fluids, strengthen the spleen, and promote dampness elimination). Gui Zhi Gan Cao Long Gu Mu Li Tang (to warm and unblock heart Yang, calm the spirit and subdue restlessness)

The others are the other category.

Shaoyang disease refers to the syndrome characterized by pathogenic invasion of the Shaoyang gallbladder viscera. Dysfunction of the pivotal mechanism, unfavorable channel Qi, alternate attacks of chill and fever, bitter mouth and dry throat, and dizziness are the main syndromes. The core treatment method is to reconcile with Shaoyang, and the representative formula is Xiao Chaihu Tang. The characteristic of Taiyang Shaoyang syndrome is the coexistence of Taiyang surface syndrome and Shaoyang syndrome, where downward or upward pathogenic heat can cause abdominal pain and vomiting. The *Scutellaria* decoction (*Scutellaria*, *paonia lactiflora* pall, licorice, jujube) is suited for diarrhea. If the patient shows vomiter syndrome, the *Scutellaria* plus *Pinellia ternata* and ginger decoction is suited; The characteristics of Shaoyang-Yangming combined disease include diarrhea with retained food accumulation, The pulse shows a slippery-rapid or deep-firm characteristics, and the Dachengqi decoction is for the case of full pulse. These characteristics are confirmed with the core drugs of licorice, jujube, ginger, *Scutellaria*, cassia twig. Xiao Chaihu Tang is only used for Shaoyang disease and rarely used in all comorbidities.

3.5. Yangming Chapter

3.5.1. Use Frequency

Rheum officinale 5 times, licorice, *Fructus aurantii* immaturus and magnolia of-

ficinalis 3 times, *anemarrhena asphodeloides*, gypsum, japonica rice and mirabilite 2 times, ginseng, *polyporus umbellatus*, *poria cocos*, rhizoma *Alismatis*, colla corii asini, talc, Yinchén, fructus *Gardeniae*, pig gall, seed of hemp, almond and *paeonia lactiflora* pall are all 1 time (Figure 7).

The total nodes are 19, the number of connection edges is 39. The node degrees are as follows: *Rheum officinale* 9, magnolia officinalis and *Fructus aurantii* immaturus 6, licorice, almond, seed of hemp and *Paeonia lactiflora* pall 5, mirabilite, rhizoma *alismatis*, talc, colla corii asini, *Polyporus umbellatus* and *Poria cocos* 4, japonica rice, *Anemarrhena asphodeloides* and gypsum 3, fructus *Gardeniae* and Yinchén 2.

The weights of the connection edges are as follows: magnolia officinalis-*Rheum officinale* and *Fructus aurantii* immaturus-*Rheum officinale* 3, *Rheum officinale*-mirabilite and magnolia officinalis-*Fructus aurantii* immaturus 2.

There are also relatively a few drugs for Yangming disease, with a total of 19 nodes, which is far less than 90 for all 112 nodes and 60 for Taiyang disease. The drugs with high frequency of use are *Rheum officinale*, licorice, *Fructus aurantii* immaturus, magnolia officinalis. The node degrees of these drugs are also higher than other drugs.

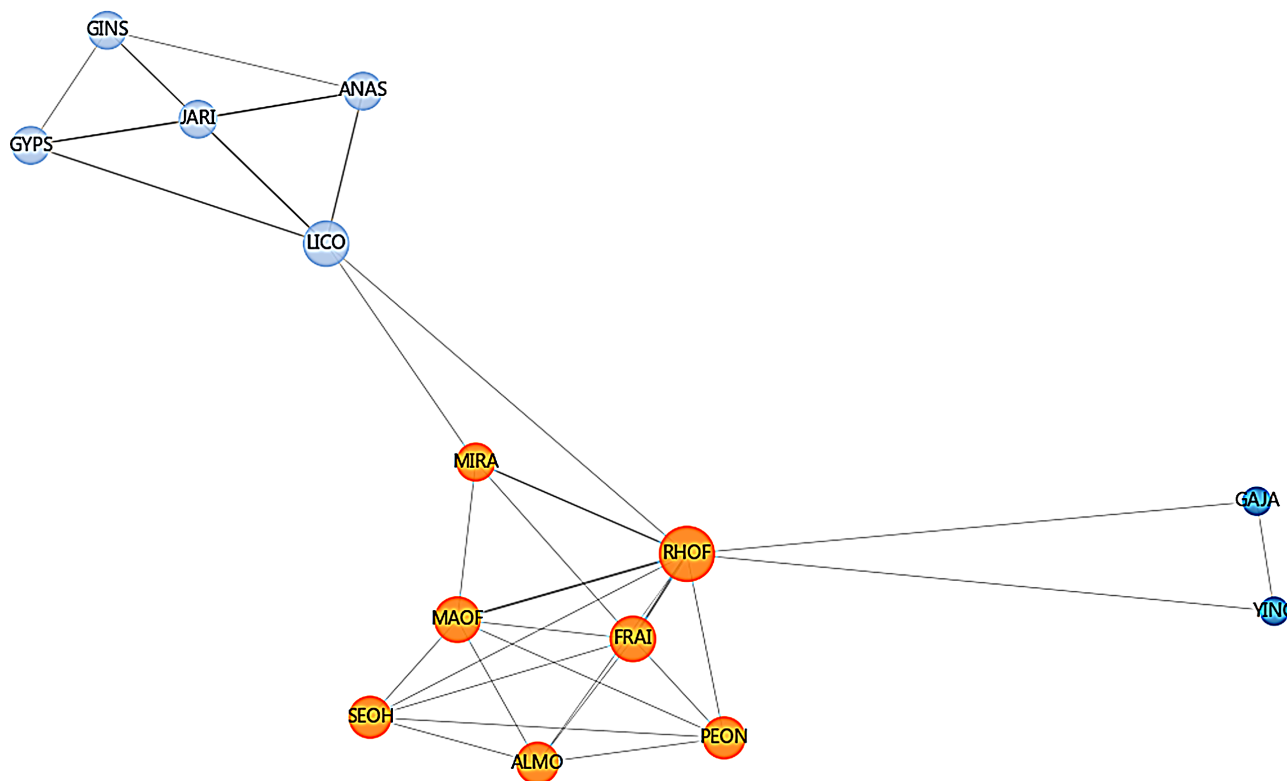


Figure 7. Network for the prescription in Yangming Chapter

3.5.2. Clustering Analysis

It can be seen that there are relatively few prescriptions for Yangming disease, but the differences between clusters are still quite obvious (Figure 8).

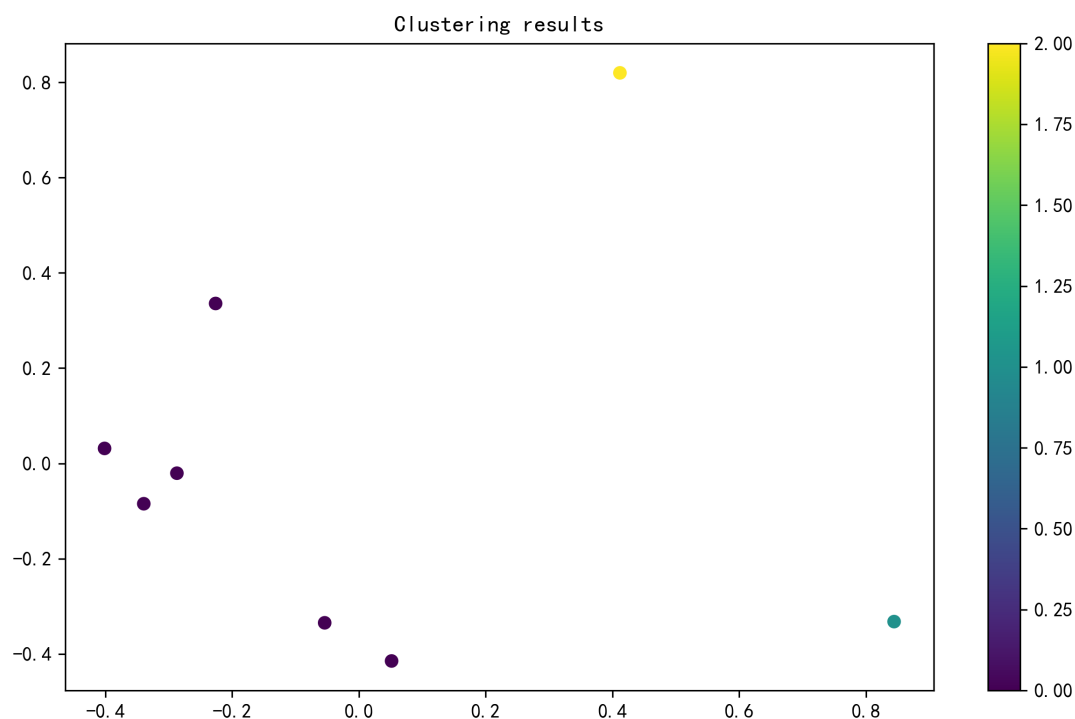


Figure 8. The clustering results of the prescription in Yangming Chapter.

Maren Pill belongs to Category I (laxative for constipation), the rest fall into Category II.

Yangming disease belongs to the stage of internal heat syndrome characterized by excessive Yang heat during the development of exogenous diseases, and its core pathogenesis is excess of stomach and intestine (excess heat in the stomach and large intestine). Yangming disease can be divided into two types meridian syndrome and organ syndrome, with the former usually being more severe than the later. The pathogenesis of Yangming meridian syndrome is characterized by excessive pathogenic heat, which fills the Yangming meridian and has not yet formed dry feces with the intestinal waste. The representative formula is Baihu Tang (gypsum, *Anemarrhena asphodeloides*, japonica rice, licorice) which has the function of clearing heat and generating fluids. If the syndrome changes to heat disturbance to the chest and diaphragm, the decoction of cape jasmine and fermented soybean is suited. For both Qi and Yin injuries, it'd better to choose white tiger decoction plus ginseng. For water-heat intermingling in the lower energizer, the *Polyporus umbellatus* decoction is suitable. The pathogenesis of Yangming Fu syndrome involves the internal transmission of pathogenic heat to the large intestine, where it combines with waste matter, leading to stagnation of Fu-Qi. The representative formula is Dachengqi Decoction (*Rheum officinale*, magnolia officinalis, *Fructus aurantii immaturus*, mirabilite), a strong purgative that resolves sensation of fullness, dryness, and solid stagnation. Xiaochengqi Decoction is the mild purgative and is primarily used to treat stagnation and sensation of fullness with solid accumulation. Tiaowei Chengqi Decoction (*Rheum officinale*, Mirabilite, Licorice) is a kind of slight purgative and is primarily used to treat dryness-

heat syndromes.

The results obtained by the above analysis that the *Rheum officinale*, licorice, *Fructus aurantii* immaturus, magnolia officinalis are the core drugs precisely reflects the pathogenesis and therapeutic characteristics of Yangming disease.

3.6. Taiyin Chapter

Cassia twig, *Paeonia lactiflora*, licorice, ginger and jujube are all 2 times, *Rheum officinale* 1 time.

The total nodes are 6 and the connection edges are 15. The node degrees are as follows: jujube, *Rheum officinale*, cassia twig, licorice, ginger and *Paeonia lactiflora* are all 5 (Figure 9).

The medications for Taiyin disease are fewer than those for Yangming disease, with only 6 nodes, primarily based on variations of Cassia Twig Decoction.

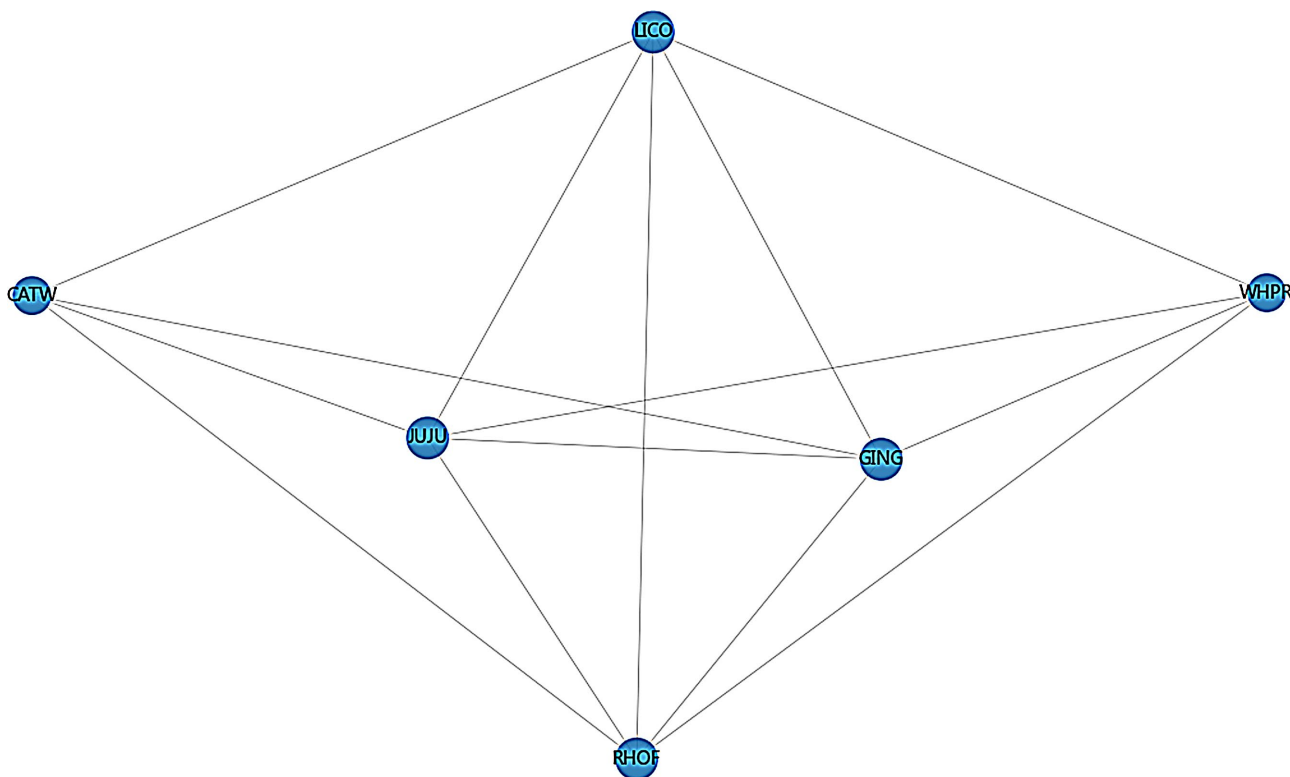


Figure 9. Network for the prescription in Taiyin Chapter.

Because there are few prescriptions, cluster analysis cannot be performed.

The core pathogenesis of Taiyin disease is spleen-stomach deficiency-cold with dysfunction of transportation and transformation. Its essence lies in the spleen's characteristics of deficiency, cold, and dampness, with the fundamental pathological mechanism being spleen-Yang decline, internal excess of cold-dampness, impaired transformation, and disordered ascending-descending functions. The fundamental pathological characteristics of Taiyin disease are internal deficiency-cold, and its treatment principle should be "warming", primarily focusing on

warming Yang to dispel cold and strengthening the spleen to resolve dampness. This is why the main formulas for this condition are still based on variations of Cassia Twig Decoction as the foundational prescription.

3.7. Shaoyin Chapter

3.7.1. Usage Frequency

Aconiti Radix 7 times, licorice, dried ginger, *Paeonia lactiflora* 3 times, scallion white 3 times, *Ephedra sinica*, *Poria cocos*, ginseng, *Atractylodes macrocephala*, ginger, *Pinellia ternata* 2 times; *Asarum*, *Evodia rutaecarpa*, jujube, urina pueri, pig gall juice, *Paeonia lactiflora* pall, *Coptis chinensis*, colla corii asini, *Scutellaria*, egg yolk, halloysitum rubrum, japonica rice, pork skin, *Platycodon grandiflorum*, cassia twig, *Gallus gallus domesticus*, *Fructus aurantii* immaturus and radix bupleuri 1 time (Figure 10).

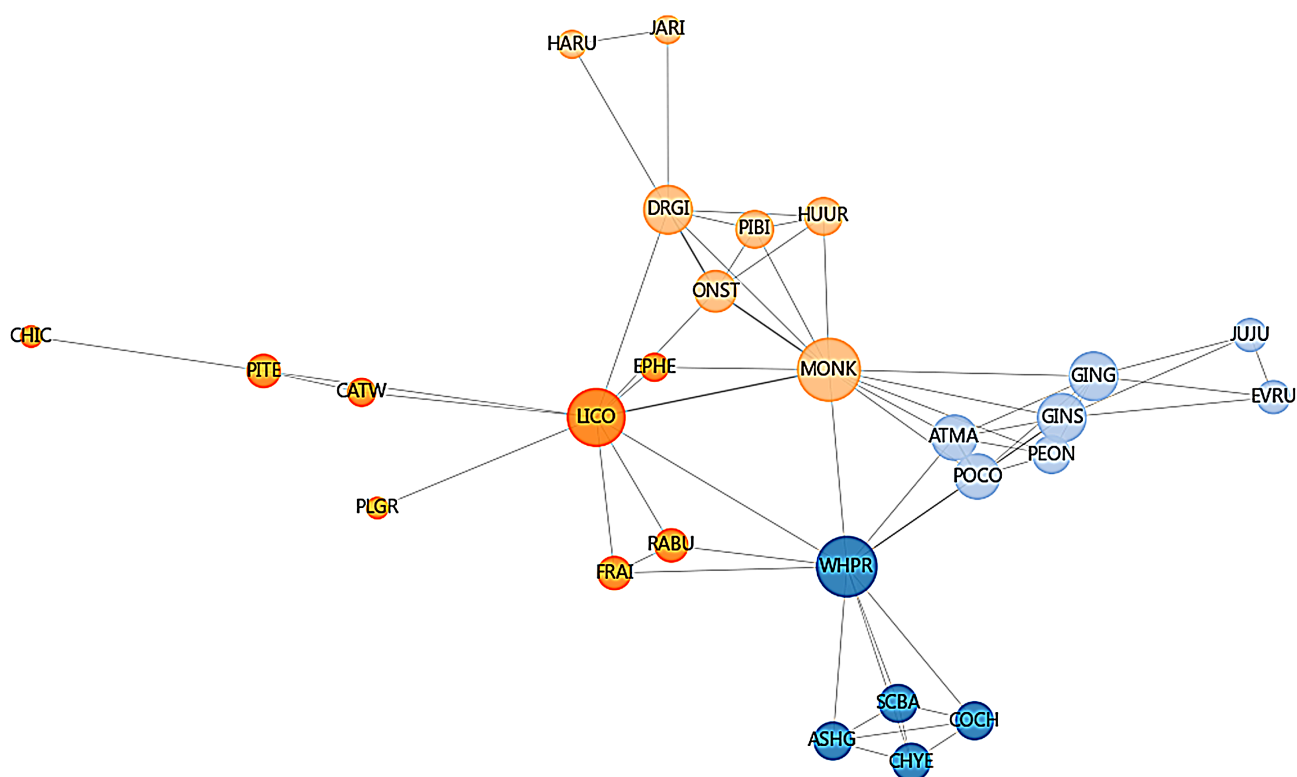


Figure 10. Network for the prescription in Shaoyin Chapter.

It can be seen that the usage frequency of *Aconiti Radix*, licorice, dried ginger, *Paeonia lactiflora*, scallion white is high.

The total nodes are 27 and the connection edges are 62. The node degrees are as follows: *Aconiti Radix* 12, *Paeonia lactiflora* 11, licorice 10, dried ginger, ginseng and ginger 7, *Atractylodes macrocephala* and *Poria cocos* 6, scallion white 5, urina pueri, pig gall juice, *Coptis chinensis*, *Paeonia lactiflora* pall, colla corii asini, egg yolk and *Scutellaria* are all 4, *Evodia rutaecarpa*, jujube, *Pinellia ternata*, *Fructus aurantii* immaturus and radix bupleuri are all 3, cassia twig, japonica rice, hal-

loysitum rubrum and *Ephedra sinica* 2, *Gallus gallus domesticus* and *Platycodon grandiflorum* 1.

The weights of the connection edges are as follows: *Atractylodes macrocephala-poria cocos*, licorice-*Aconiti Radix* and dried ginger-scallion white 2, the rest are all 1.

Compared to Taiyin disease, Shaoyin disease involves more medicinal ingredients and node degrees, but the edge weights are generally smaller, indicating that pairwise co-occurrence of drugs is less frequent in different prescriptions.

The herbs with significant influence in the network of Shaoyin syndrome are *Aconiti Radix*, *Paeonia lactiflora*, licorice, ginger, ginseng, *Atractylodes macrocephala*, *Poria cocos*. An analysis of the actual medication patterns in Shaoyin syndrome reveals that this condition represents a critical stage in the progression of exogenous diseases, characterized by deficiency, Yin, and coldness. Therefore, its treatment often employs the combination of *Aconiti Radix* and *Paeonia lactiflora* pall to warm Yang, regulate water metabolism, and promote urination.

Moreover, Shaoyin syndrome encompasses both the heart and kidney organs and their associated meridians. Since kidney Yang deficiency can lead to water retention and fluid accumulation, its treatment often employs *Aconiti Radix* to tonify fire and reinforce Yang, disperse cold and resolve dampness, and additionally use *Poria cocos* to promote diuresis and drain dampness.

3.7.2. Clustering Analysis

It can be observed that the distinctions among Shaoyin syndrome clusters are quite evident, indicating that the disease can also be clearly categorized into these types, leading to significant differences in the medications used (Figure 11).

Wu Zhu Yu Tang (to warm the Middle and dispel cold, tonify deficiency and descending counterflow) belongs to Category I. Fu Zi Tang (to warm the channels and dispel cold, strengthen the spleen and remove dampness) and Zhen Wu Tang (to warm Yang and promote urination) belong to Category II. Ma Huang Fu Zi Gan Cao Tang (to assist Yang and resolve exterior symptoms), Zhu Fu Tang (to nourish Yin and moisten dryness, benefit the throat and relieve pain), Gan Cao Tang (to clear heat and detoxify, relieve urgency and pain), Jie Geng Gan Cao Tang (to clear heat and detoxify, benefit the throat and transform phlegm), Gui Zhi Gan Cao Ban Xia Tang (to warm and unblock heart Yang, transform phlegm and descend counterflow), and Ku Sha Tang (to dispel phlegm and disperse nodules, reduce swelling and benefit the throat) belong to Category III. The rest fall into Category IV.

Shaoyin syndrome represents a critical stage of externally contracted diseases, where the pathological mechanism involves decline of heart-kidney Yang Qi or fire excess from yin deficiency. The Shaoyin includes the Hand Shaoyin Heart Meridian and the Foot Shaoyin Kidney Meridian. The heart governs fire, while the kidney governs water. Their coordination maintains Yin-Yang balance. The fundamental treatment principles are as follows:

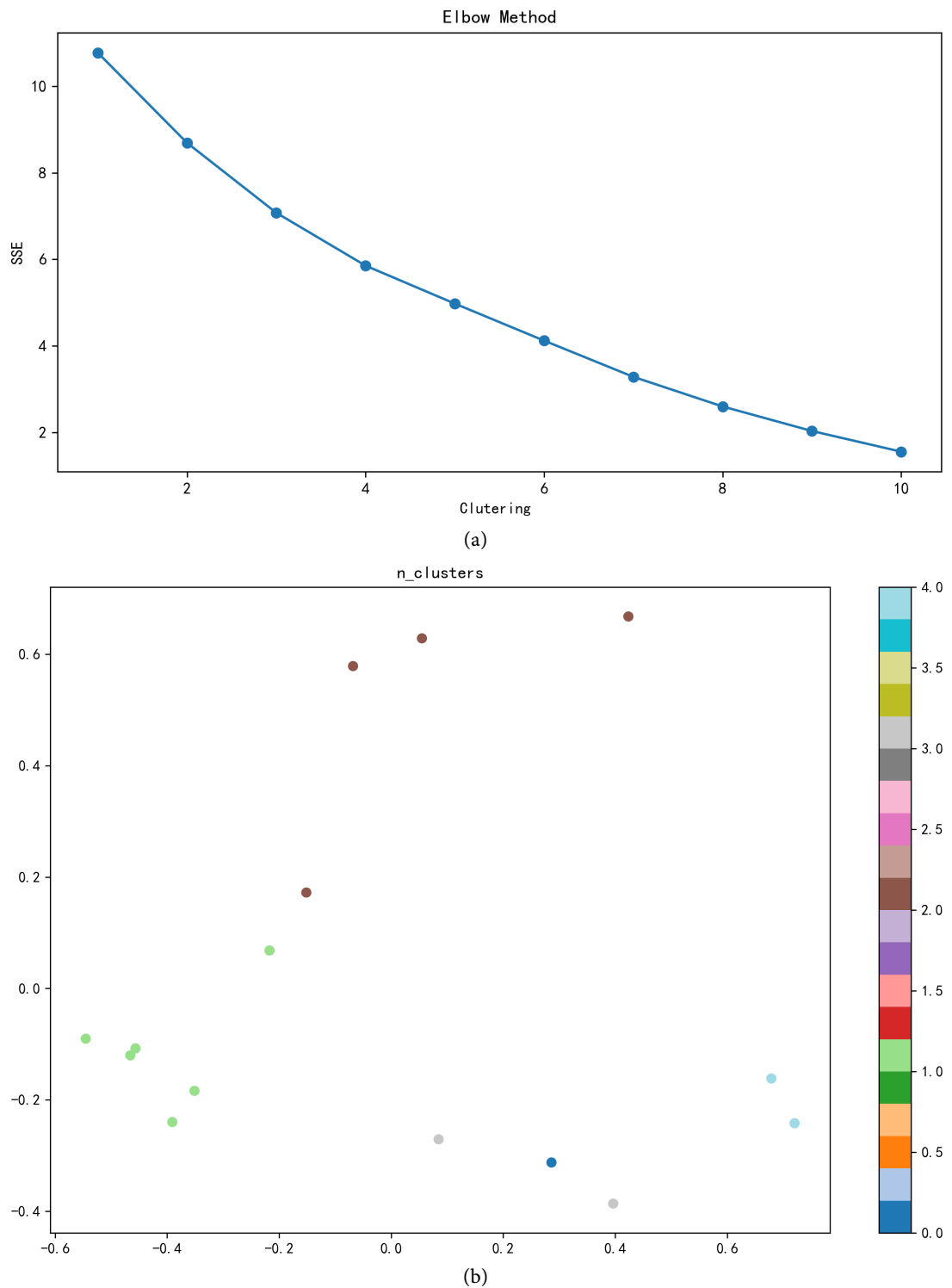


Figure 11. The clustering results of the prescription in Shaoyin Chapter. (a) Scree plot; (b) clustering plot.

For the cold-type transformation, the focus is on restoring Yang and reversing collapse, emphasizing supporting Yang Qi.

For the heat-type transformation, the priority is nourishing Yin and clearing heat, with attention to preserving Yin fluids.

3.8. Jueyin Chapter

3.8.1. Usage Frequency

The usage frequencies of drugs are as follows: licorice 6 times, ginseng 5 times, dried ginger, cassia twig and *angelica sinensis* 4 times, *Asarum*, *Coptis chinensis*, *Paeonia lactiflora*, jujube and *Scutellaria* 3 times, *Phellodendron*, *Tetrapanax* pith, ginger, gypsum, *Atractylodes macrocephala* and *Pinellia ternata* 2 times, the rest are all 1 time (Figure 12).

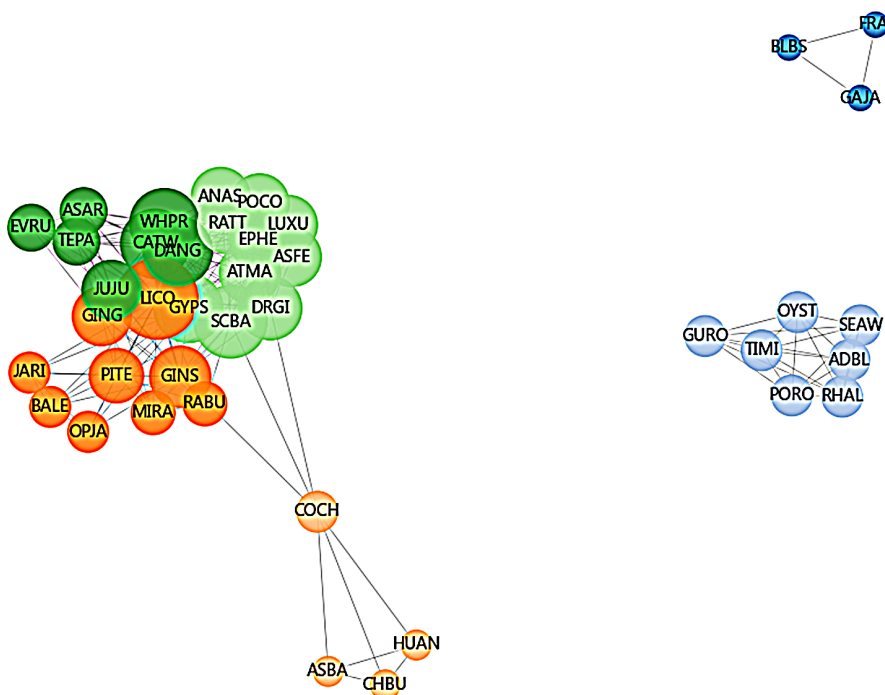


Figure 12. Network for the prescription in Jueyin chapter.

The total nodes are 42 and the connection edges are 198. The node degrees are as follows: licorice 25, *Scutellaria* 20, *Angelica sinensis*, cassia twig, gypsum and *Paeonia lactiflora* 18, dried ginger 15, *Atractylodes macrocephala* and ginseng 14, *Poria cocos*, cimicifuga rhizome, asparagus officinalis, *Ophiopogon* rhizome, *Anemarrhena asphodeloides*, jujube, ginger and *Ephedra sinica* 13, *Pinellia ternata* 11, *Evodia rutaecarpa*, *Asarum* and *Tetrapanax* pith 8, mirabilite and radix bupleuri 7, japonica rice, leaf of henon bamboo, *Ophiopogon* tuber, *Phytolacca* root, radix *Trichosanthis*, Hai Zao, *Coptis chinensis*, rhizoma *Alismatis*, draba seed, twig and leaf of antifebrile *Dichroa* and oyster 6, pulsatillae radix, ash bark and *Phellodendron* 3, *Fructus aurantii* immaturus, fructus *Gardeniae* and sojae semen praeparatum 2, Nü Kun and Nan Kun 1.

The weights of the connection edges are as follows: ginseng-licorice, jujube-licorice, licorice-*Angelica sinensis* and licorice-cassia twig, *Angelica sinensis*-cassia twig, cassia twig-*Paeonia lactiflora* and *Angelica sinensis*-*Paeonia lactiflora* 3; *Pinellia ternata*-licorice, jujube-*Angelica sinensis*, jujube-cassia twig, jujube-*Paeonia lactiflora*, jujube-*Asarum*, jujube-*Tetrapanax* pith, dried ginger-licorice, lic-

orice-ginger, licorice-*Tetrapanax* pith, licorice-gypsum and licorice-*Asarum*, *Angelica sinensis*-*Asarum*, *Angelica sinensis*-*Tetrapanax* pith, cassia twig-*Asarum*, cassia twig-*Tetrapanax* pith, *Paeonia lactiflora*-*Asarum*, *Paeonia lactiflora*-*Tetrapanax* pith and *Asarum*-*Tetrapanax* pith 2.

It can be seen that the usage frequencies of licorice, ginseng, dried ginger, cassia twig, *angelica sinensis* are higher than the others, in which the others are the main ingredients of Cassia Twig Decoction besides *Angelica sinensis*. Most medications are used only once, indicating that the symptoms of Jueyin disease are diverse and require different treatments. Those with more node degrees are licorice, *Scutellaria*, *Angelica sinensis*, cassia twig, gypsum, *Paeonia lactiflora*, dried ginger, *Scutellaria*, gypsum, *Paeonia lactiflora*. These drugs demonstrate high compatibility with other drugs, but their edge weights are relatively low, indicating that the use of drug pairs appears infrequently across different formulas.

3.8.2. Clustering Analysis

There are relatively few formulas for Jueyin disease, and the distinctions between clusters are not very clear, indicating that the differences in its clinical manifestations are subtle (Figure 13).

Jueyin disease is the final stage of the six-channel syndromes in Shanghan Lun, characterized by the disharmony of Yin and Yang Qi and the intermingling of cold and heat. Its core pathogenesis involves liver wind carrying cold and heat internally disturbing the body, manifesting as complex syndromes of upper heat and lower cold, with alternating cold and heat. The fundamental therapeutic principle is to harmonize Yin and Yang, which involves combining cold and warm herbs, using acrid-sweet flavors to support Yang, and sour-bitter flavors to consolidate Yin. To restrain liver wind and extinguish internal wind, sour-astringent herbs are prioritized to calm liver wind. This is the reason that the usage frequencies of licorice, *Scutellaria*, *Angelica sinensis*, cassia twig, gypsum, *Paeonia lactiflora*, dried ginger are high.

3.9. Three Yang Chapter

3.9.1. Usage Frequencies of the Herbs

Three Yang is defined as the total of the Taiyang Channel, Shaoyang Channel and Yangming Channel. So in this section the characteristics of key herbs and drug pairs associated with the Three Yang Channels are analyzed. The usage frequencies are as follows: Licorice is 52 times, cassia twig 34 times, jujube 32 times, ginger 31 times, *Rheum officinale* and *Pinellia ternata* 14 times, *Paeonia lactiflora* and ginseng 13 times, dried ginger 12 times, *Scutellaria* 11 times, *Ephedra sinica* 10 times, both of *Aconiti Radix* and almond 9 times; *Poria cocos*, *Coptis chinensis*, *paeonia lactiflora* pall are all 8 times; fructus *Gardeniae* 7 times, both of *Atractylodes macrocephala* and *magnolia officinalis* 6 times; mirabilite, gypsum, radix bupleuri, *Fructus aurantii immaturus* are all 5 times; both *Pueraria lobata* and oyster 4 times; peach kernel, *Euphorbia kansui*, dragon bone, sojae semen praeparatum are all 3 times; *Polyporus umbellatus*, rhizoma *Alismatis*, *Hirudo*, *Tabanus*, colla corii asini,

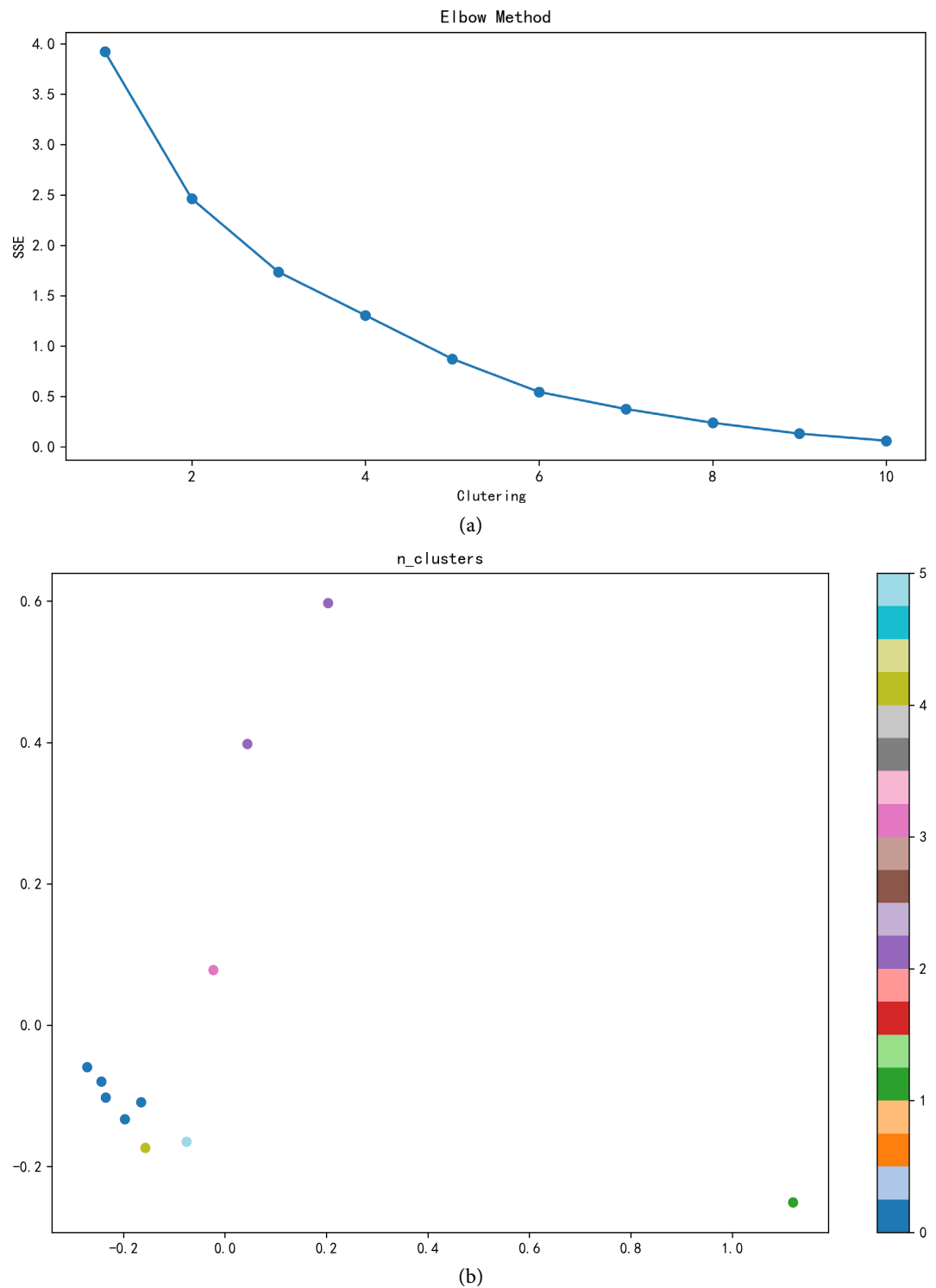


Figure 13. The clustering results of the prescription in Jueyin Chapter. (a) Scree plot; (b) Clustering plot.

seed of hemp, red bean, *Anemarrhena asphodeloides*, japonica rice are all 2 times; the others are 1 time (Figure 14).

The total nodes are 66 and the connection edges are 368. The node degrees are as follows: licorice 44, ginger 40, cassia twig 38, jujube 37, both of *Rheum officinale*

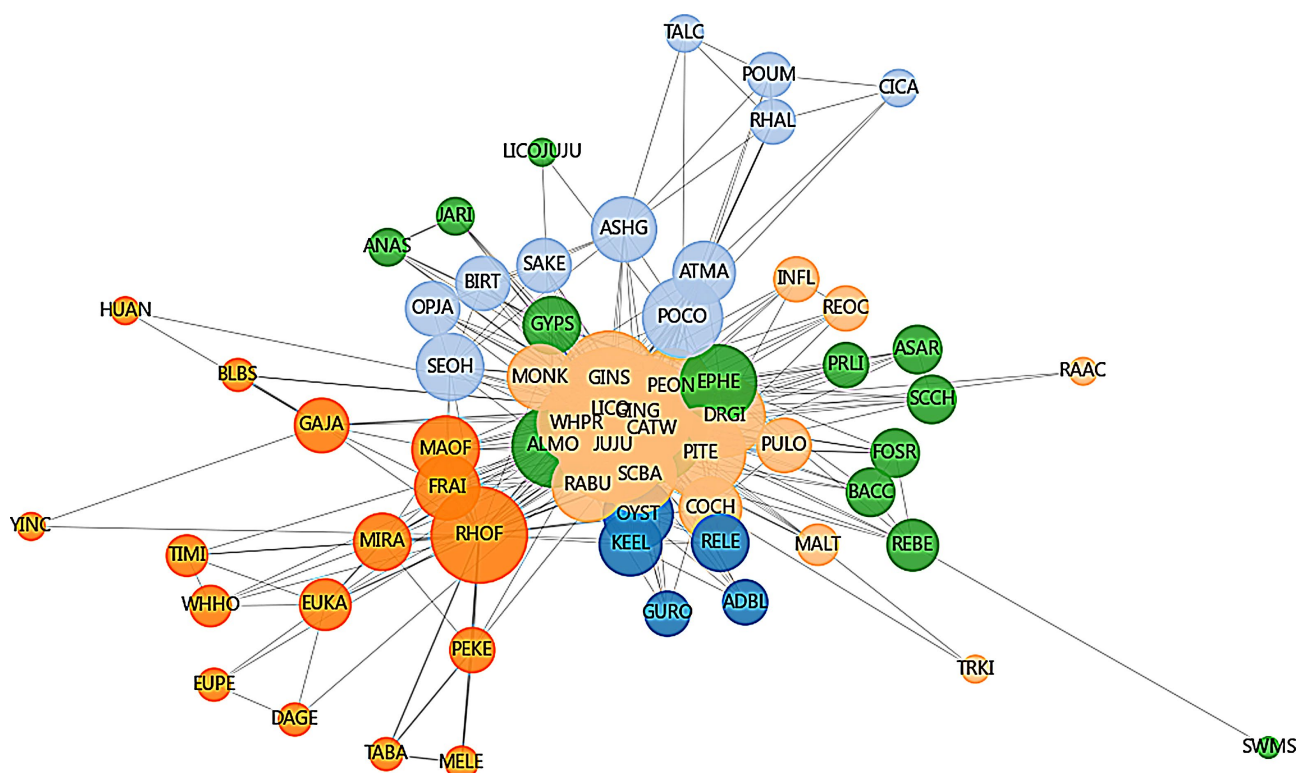


Figure 14. Network for the prescription of three Yang (HARU-YUYU is independently connected so is not drawn.)

and ginseng are 29, *Pinellia ternata* 25, almond 21, *Poria cocos* 20, dried ginger 20, *Paeonia lactiflora* 19, *Paeonia lactiflora* pall 18, *Ephedra sinica* 18, *Scutellaria* 17, radix bupleuri 16, oyster 15, both of *magnolia officinalis* and seed of hemp are 14, colla corii asini, *Aconiti Radix* and *Fructus aurantii immaturus* are 13; *Atractylodes macrocephala*, dragon Bone and *Coptis chinensis* are 12; red lead, gypsum and mirabilite are 10; *Ophiopogon japonicus*, fructus *Gardeniae*, *Pueraria lobata*, sake and raw *Rehmannia glutinosa* are 9; *Euphorbia kansui* 8, red bean, *Schisandra chinensis* and *Asarum* are 7; prepared licorice, rhizoma *Alismatis*, *Polyporus umbellatus*, ruddle, twig and leaf of antifebrile *Dichroa*, peach kernel, radix *Trichosanthis*, inula flower, bark of Chinese catalpa, jujube and *Forsythia suspensa* are all 6; maltose, white honey and draba are 5; *Anemarrhena asphodeloides*, talc, *Cinnamomum cassia* and japonica rice are 4; *Daphne genkwa*, *Hirudo*, *Tabanus*, *Euphorbia pekinensis* and sojæ semen praeparatum are 3; both of *Trichosanthes* fruit and *Phellodendron* are 2; fructus *Melothriae*, both of raw *Aconiti Radix* and Yinchen are 2; both of halloysitum rubrum and Yu Yu Liang are 1.

The weights of connection edges are as follows: licorice-jujube 27, jujube-ginger 22, cassia twig-jujube 19, licorice-*Paeonia lactiflora* 12, jujube-*Paeonia lactiflora* 11, ginger-*Paeonia lactiflora* 10, ginseng-jujube 8, jujube-*Scutellaria* and licorice-*Ephedra sinica* are 7, almond-*Ephedra sinica*, dried ginger-licorice, cassia twig-*Ephedra sinica*, licorice-*Scutellaria* are 6, *Rheum officinale*-mirabilite, licorice-*Paeonia lactiflora* pall, dried ginger-ginseng, cassia twig-licorice, licorice-*Pinellia ternata*, *Pinellia ternata*-*Scutellaria* are 5, dried ginger-jujube, licorice-*Poria cocos*,

Pinellia ternata-Coptis chinensis, *Pinellia ternata-radix bupleuri*, *Rheum officinale-Fructus aurantii immaturus*, jujube-*Coptis chinensis*, cassia twig-almond, jujube-almond, jujube-radix bupleuri, licorice-ginseng, cassia twig-oyster, licorice-ginger, cassia twig-ginger, ginger-almond, ginger-radix bupleuri, ginger-*Ephedra sinica*, *Scutellaria-radix bupleuri*, *Scutellaria-Coptis chinensis* and ginger-*Scutellaria* are all 4, the rest are less than 4.

It can be seen that the drugs with high usage frequency are licorice, cassia twig, jujube, ginger, *Rheum officinale*, *Pinellia ternata*, *Paeonia lactiflora*, ginseng, dried ginger, *Scutellaria*, and *Ephedra sinica*, which is just correspondent with those with high node degree. The weights of the connection edges of licorice-jujube, jujube-ginger and cassia twig-jujube is significantly higher than that of other herb pairs, this can explain the importance of these drugs in treatment of Three Yang disease. The reason is that the common characteristic of the Three Yang diseases (Taiyang, Yangming, and Shaoyang) is the body's defensive energy is intact and exuberant pathogenic influence. It is shown as excess-heat syndrome. The fundamental treatment principles are as follows For Taiyang Disease "Resolve through sweating", using pungent-warm herbs to release the exterior; for Yangming Disease "Treat heat with cold", employing heat-clearing or purgative methods; for Shaoyang Disease Harmonize the pivot mechanism.

3.9.1. Clustering Analysis

It can be seen that there is overlap among the formula clusters for the Three Yang Diseases (Taiyang, Yangming, Shaoyang), making distinctions difficult. This suggests that the differences between their subtypes are not significant, and the medications used are often similar (Figure 15).

3.10. Three Yin Chapter

3.10.1. Usage Frequency

Three Yin is defined as the total of the Taiyin Channel, Shaoyin Channel and Jueyin Channel. So in this section the characteristics of key herbs and drug pairs associated with the Three Yin Channels are analyzed. The usage frequencies are as follows: licorice 14 times, *Paeonia lactiflora* and *Aconiti Radix*, dried ginger 8 times, cassia twig and ginseng 7 times, ginger and jujube 6 times, *Asarum*, *Atractylodes macrocephala*, *Coptis chinensis*, *Scutellaria*, *Pinellia ternata* and *Angelica sinensis* 4 times, *Ephedra sinica*, *Poria cocos* and scallion white 3 times, japonica rice, *Fructus aurantii immaturus*, radix bupleuri, *Phellodendron*, *Tetrapanax pith* and gypsum 2 times, The others are all 1 times. Those with high usage frequency used in three Yang disease are used infrequently in three Yin disease such as *Rheum officinale*, *Anemarrhena asphodeloides* are used only 1 time, radix bupleuri 2 times, *ephedra sinica* 3 times (Figure 16).

The total nodes are 56 and the connection edges are 285. The node degrees are as follows: licorice 30, *Paeonia lactiflora* and cassia twig 26, dried ginger 25, ginseng and *Angelica sinensis* 24, *Scutellaria* 22, ginger and *Aconiti Radix* 19, gypsum 18, *Poria cocos* and *Atractylodes macrocephala* 17, *Asarum* 16, *Ephedra*

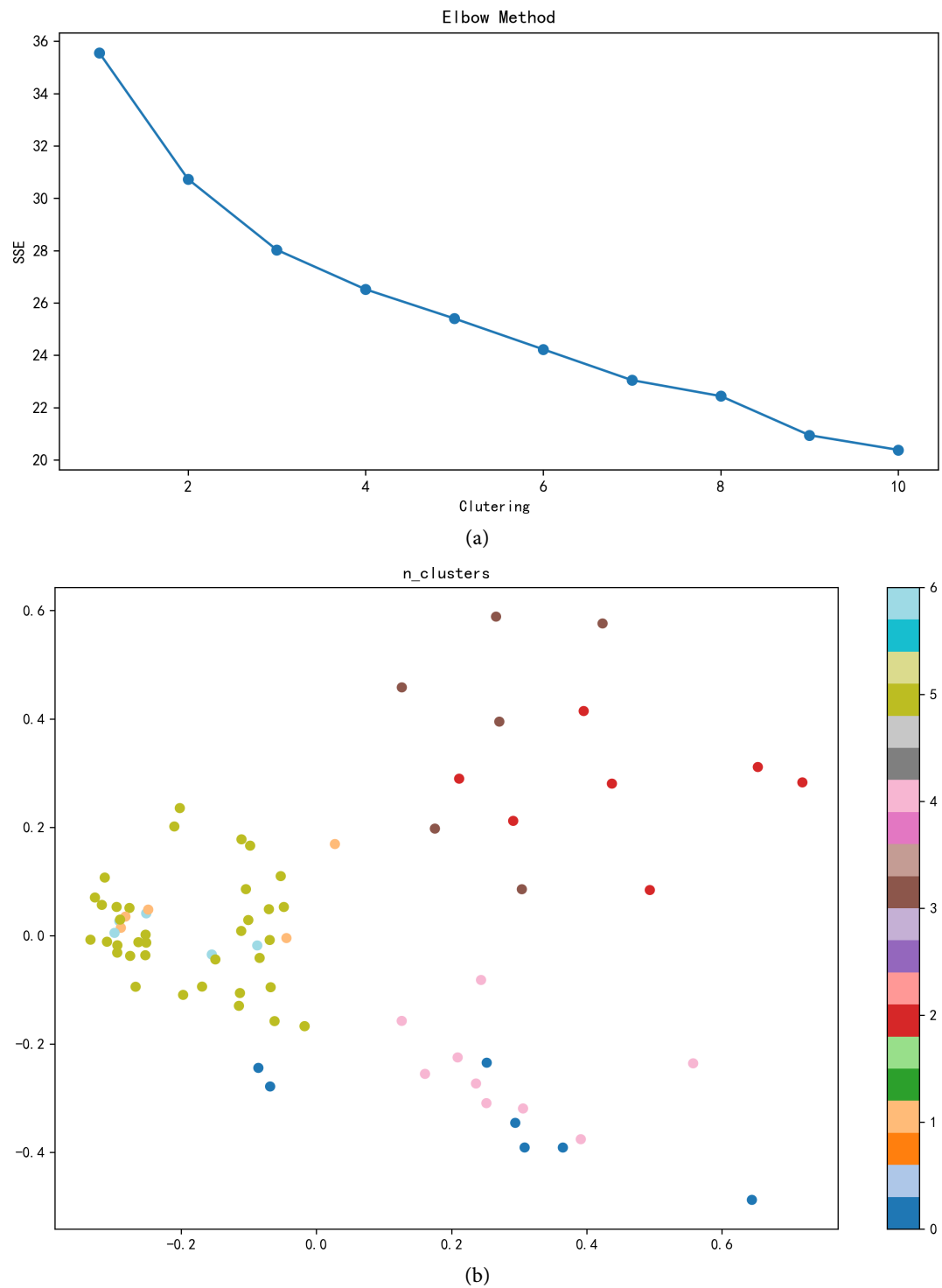


Figure 15. The clustering results of all the prescription in three Yang Chapter. (a) Scree plot; (b) clustering plot.

sinica 15, jujube and *Coptis chinensis* 15, *Pinellia ternata*, cimicifuga rhizome, asparagus officinalis, *Anemarrhena asphodeloides* and *Ophiopogon* rhizome 13, *Phellodendron* 11, Wu Mei, radix bupleuri and Sichuan pepper 9, japonica rice, *Tetrapanax* pith and *Evodia rutaecarpa* 8, mirabilite 7, *Ophiopogon* tuber, *Phytolacca*

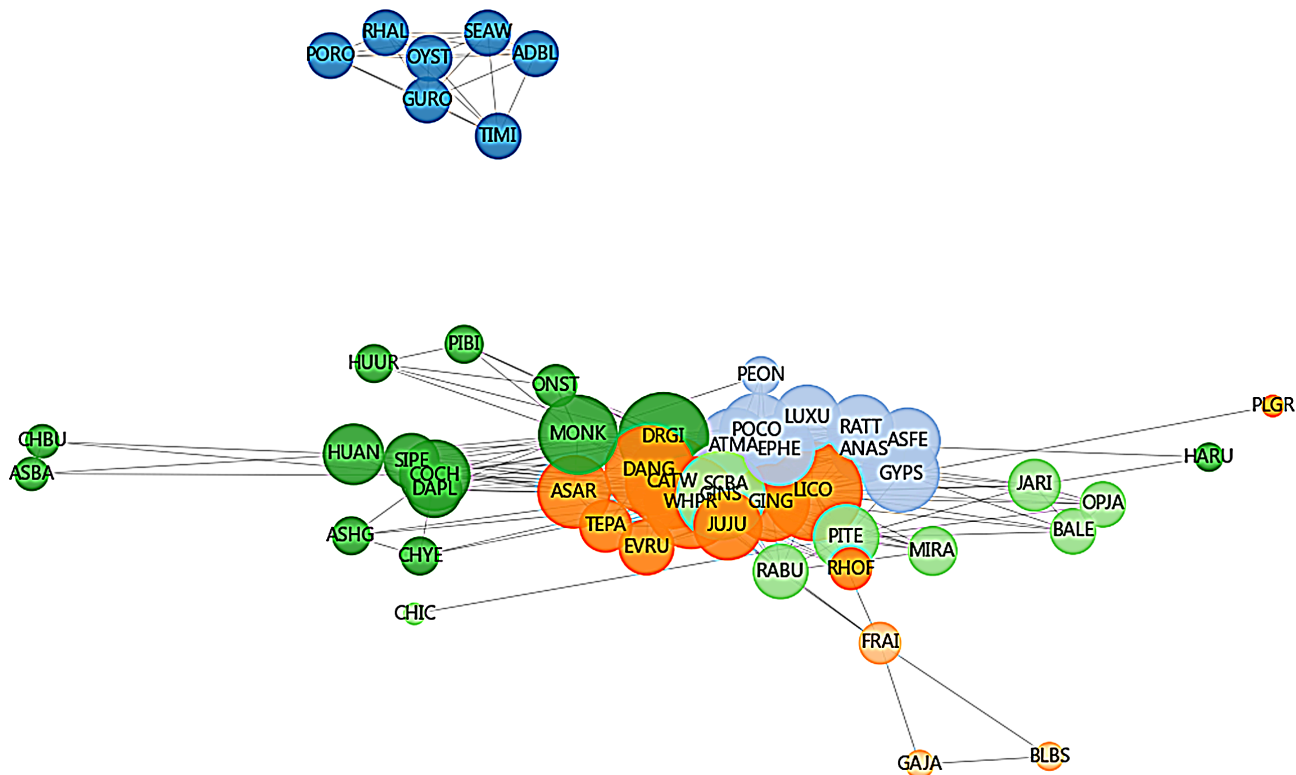


Figure 16. Network for the prescription of all three Yin Chapter.

root, radix *Trichosanthis*, Hai Zao, leaf of henon bamboo, rhizoma *alismatis*, draba seed, twig and leaf of antifebrile *Dichroa* and oyster 6, *Rheum officinale*, scallion white and *Fructus aurantii immaturus* 5, *Paeonia lactiflora* pall, colla corii asini, egg yolk, urina pueri and pig gall juice 4, pulsatillae radix, ash bark and *Evo-dia rutaecarpa* 3, fructus *Gardeniae*, sojæ semen preparatum and halloysitum rubrum 2, *Gallus gallus domesticus*, Nü Kun, Nan Kun and *Platycodon grandiflorum* 1.

The weights of the connection edges are as follows: jujube-licorice 4, *Pinellia ternata*-licorice, jujube-ginger, jujube-*Paeonia lactiflora*, ginseng-licorice, licorice-ginger, *Angelica sinensis*-licorice, *Angelica sinensis*-*Paeonia lactiflora*, cassia twig-jujube, cassia twig-licorice, cassia twig-*Paeonia lactiflora* and cassia twig-*Asarum* 3, the rest are all 2.

The node degree of licorice is still the largest, e.f., the most important. the second largest drugs are *Paeonia lactiflora*, cassia twig, dried ginger, ginseng, *Angelica sinensis*, *Scutellaria*, ginger and *Aconiti Radix*, gypsum, *Poria cocos* and *At-ractylodes macrocephala*, *Asarum*, *Ephedra sinica*, jujube, *Coptis chinensis*. The weights of the connection edge are all relatively small. The largest is jujube-licorice with value of 4. This indicates that these herb pairs are rarely used together across all syndromes, which can be explained by the pathogenesis and medication characteristics of the three Yin diseases The three Yin Diseases (Taiyin, Shaoyin, and Jueyin) are a collective term in the six meridians syndrome differentiation system of treatise of Shang Han Lun, representing three types of Yin syndromes Taiyin

disease (spleen Yang deficiency), Shaoyin disease (heart-kidney deficiency), and Jueyin disease (cold-heat complex). Their common characteristic is deficient healthy Qi with remaining pathogenic Qi, manifesting as deficiency-cold or cold-heat complex syndromes. The treatment principles are as follows Warm the middle jiao and disperse cold for Taiyin disease; as for the Shaoyin disease, restore Yang to rescue from collapse for cold-transformation syndrome and nourish Yin and clear heat for heat-transformation syndrome; Harmonize Yin-Yang and combine cold-heat therapies for Jueyin disease.

3.10.2. Clustering Analysis

The clustering of prescriptions for three Yang diseases shows clear distinctions, indicating significant differences among subtypes, with markedly varied therapeutic approaches (Figure 17).

4. Conclusions

This study employs complex network theory to classify the prescriptions in Shang Han Lun based on Six Meridian Syndrome Differentiation, constructing subnetworks of medicinal patterns for Taiyang, Yangming, Shaoyang, Taiyin, Shaoyin, and Jueyin syndromes. Subsequently, complex network analysis is performed, utilizing metrics such as node degree, edge weight, and prescription frequency to evaluate the importance of herbs, inter-drug relationships, and core medications in the network.

It can be seen that the frequency of occurrence of prepared licorice, cassia twig, jujube, ginger, *Paeonia lactiflora* pall in the 112 prescriptions of Shang Han Lun is generally high, for example, prepared licorice occurs 64 times, cassia twig and jujube 38 times, ginger 36 times, etc.

This aligns with Zhang Zhongjing's actual therapeutic principles, as he consistently applied the "harmonizing Ying and Wei" method in treating Shang Han, while also nourishing the middle jiao (spleen/stomach) to achieve harmony among the five organs.

The Taiyang disease primarily manifests as external wind-cold pathogens invading the body's surface, with its core pathogenesis being "dysfunction of Ying and Wei (nutritive and defensive Qi), with Wei-Yang (defensive Yang) constrained". Therefore, its treatment focuses on "diaphoresis" (sweating therapy), with the primary formulas being the Cassia Twig Decoction and Ephedra Decoction.

Shaoyang syndrome refers to pathogenic factors invading gall bladder of Shaoyang and pivotal mechanism dysfunction. Thus, harmonizing Shaoyang is the core therapeutic principle. Minor Bupleurum Decoction (Xiao Chaihu Tang) is the representative formula. When Shaoyang is complicated by Taiyang or Yangming syndromes, purgative formulas like Chengqi Tang are required to eliminate internal heat accumulation.

It is correspondent that licorice, jujube, ginger, *Scutellaria*, and cassia twig are the core drugs.

The core pathogenesis of Yangming disease lies in the excess-heat disorders of

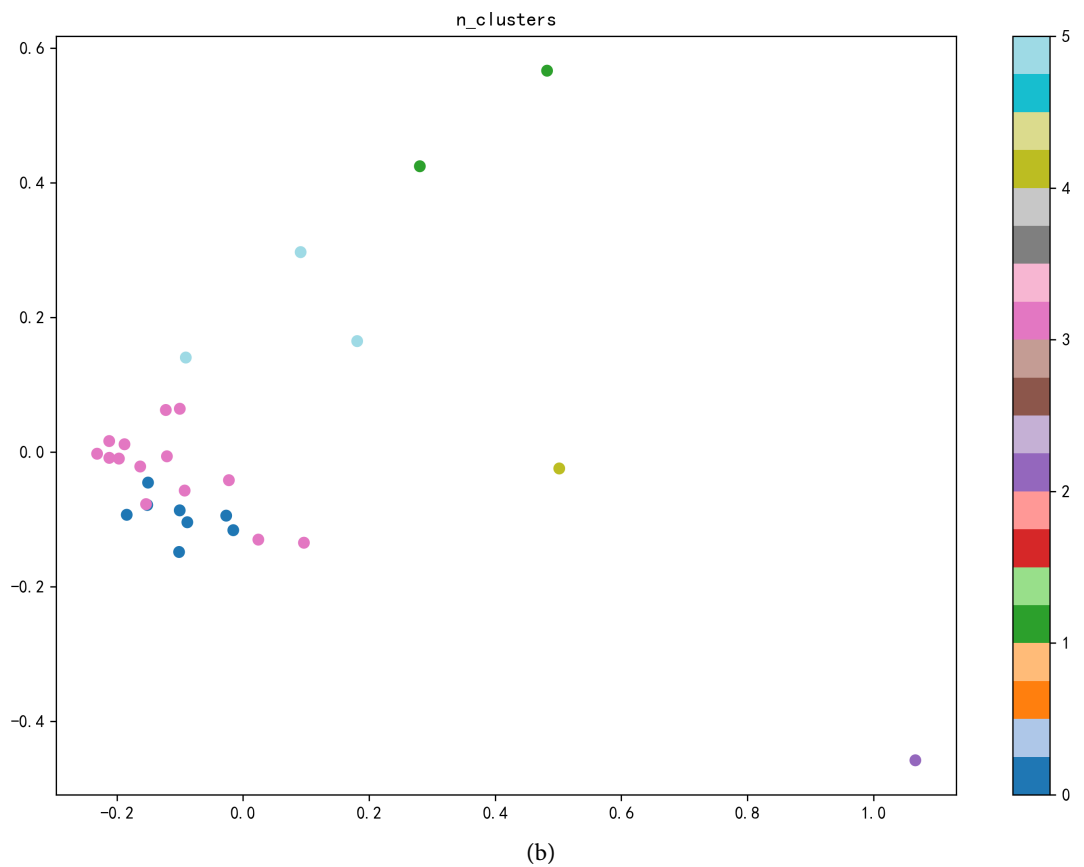
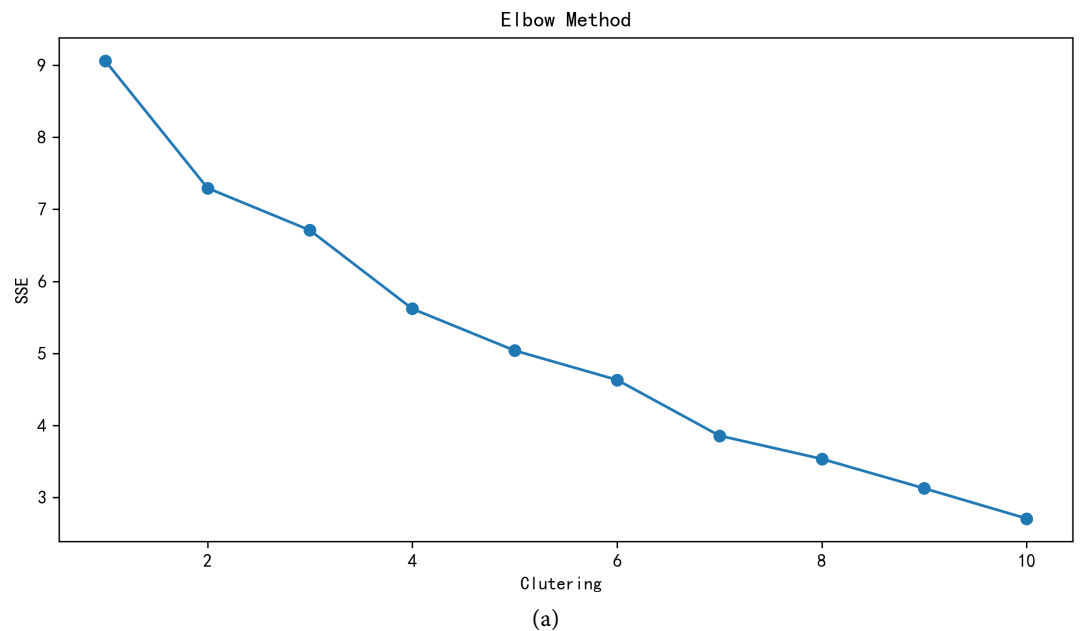


Figure 17. The clustering results of the prescription in all three Yang Chapter. (a) Scree plot; (b) clustering plot.

the stomach and large intestine. The representative formulas are Baihu Decoction and Chengqi Decoction. Therefore, the conclusion that the herbs obtained by analysis—*Rheum officinale*, licorice, and *Fructus aurantii* immaturus—are key

medicinal ingredients precisely reflects the pathogenesis and therapeutic characteristics of Yangming disease.

The core pathogenesis of Taiyin disease is spleen-stomach deficiency-cold with impaired transportation and transformation, hence the treatment principle focuses on warming Yang to dispel cold, strengthening the spleen to resolve dampness. This explains why the primary formulas for this condition are still based on modifications of Cassia Twig Decoction.

Shaoyin disease is a critical stage of externally contracted illnesses progressing to heart-kidney deficiency and decline. The fundamental therapeutic principles are: For the cold-type transformation, the focus should be on restoring Yang and reversing collapse. For the heat-type transformation, the emphasis should be on nourishing Yin and clearing heat.

The core pathogenesis of Jueyin disease is “liver wind carrying cold-heat internally disturbing”, and its fundamental therapeutic principle is “harmonizing Yin and Yang”. That is why licorice, *Scutellaria*, *angelica sinensis*, cassia twig, gypsum, *Paeonia lactiflora*, and dried ginger are used more commonly.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Appendix: Correspondence of Original Text and Abbreviation

Full name	Abbreviation	Full name	Abbreviation	Full name	Abbreviation
<i>Atractylodes macrocephala</i>	ATMA	Peony	PEON	<i>Anemarrhena asphodeloides</i>	ANAS
<i>Cinnamomum cassia</i>	CICA	Gypsum	GYPS	Japonica rice	JARI
Cassia twig	CATW	<i>Pinellia ternata</i>	PITE	Talc	TALC
White peony root	WHPR	<i>Halloysitum rubrum</i>	HARU	Yinchen	YINC
Licorice	LICO	Yu yuliang	YUYU	Gualou root	GURO
Ginger	GING	Radix bupleuri	RABU	Sweet melon stem	SWMS
Jujube	JUJU	<i>Fructus aurantii Immaturus</i>	FRAI	<i>Evodia rutaecarpa</i>	EVRU
monkshood	MONK	Inula flower	INFL	Onion stalk	ONST
ginseng	GIN	Red ochre	REOC	Human urine	HUUR
Dried ginger	DRGI	<i>Trichosanthes kirilowii</i>	TRKI	Pig's bile	PIBI
<i>Pueraria lobata</i>	PULO	Keel	KEEL	Chicken yellow	CHYE
<i>Coptis chinensis</i>	COCH	Red lead	RELE	<i>Platycodon grandiflorum</i>	PLGR
<i>Scutellaria baicalensis</i>	SCBA	Oyster	OYST	Chicken	CHIC
<i>Magnolia officinalis</i>	MAOF	Asini corii colla	ASHG	Dark plum	DAPL
Almond	ALMO	Seed of hemp	SEOH	Danggui	DANG
Peach kernel	PEKE	Birthplace	BIRT	Sichuan pepper	SIPE
<i>Rheum officinale</i>	RHOF	<i>Ophiopogon japonicus</i>	OPJA	<i>Tetrapanax papyriferus</i>	TEPA
Mirabilite	MIRA	Sake	SAKE	Asparagus fern	ASFE
Medical leech	MELE	Raw aconite	RAAC	Rattletop	RATT
<i>Tabanus</i>	TABA	<i>Gardenia jasminoides</i>	GAJA	Luxuriant	LUXU
<i>Daphne genkwa</i>	DAGE	Black bean sauce	BLBS	Chinese bulbul	CHBU
<i>Euphorbia pekinensis</i>	EUPE	Red bean	REBE	Ash bark	ASBA
<i>Euphorbia kansui</i>	EUKA	Bark of Chinese catalpa	BACC	Poke root	PORO
Ting Mi	TIMI	Huangbai	HUAN	Seaweed	SEAW
<i>Forsythia suspensa</i> root	FOSR	Prepared licorice	PRLI		
Bamboo leaf	BALE	<i>Ophiopogon japonicus</i>	OPJA		