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Herb Co-Occurrence Network Analysis of Formulas and Herbs in Systematic Differentiation of Warm Diseases

Wenjing Lu

Faculty of Engineering, Computing and Mathematics, The University of Western Australia, Perth, Australia
Email: xblu@imech.ac.cn

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Abstract

Aim: Based on the method of complex network analysis, this study explores the medication patterns in the systematic differentiation of warm diseases (Wen Bing Tiao Bian). **Method**: From the book Wen Bing Tiao Bian, extract prescriptions and establish a database. After normalizing the data, develop software using Python to perform statistical analysis on medication frequency, drug relationships, and core herbs. **Results**: The total drugs used in the Three Jiao are 250. The drugs of the top 10 node degrees are as follows: ginseng, white peony root, *Poria cocos*, licorice, radix rehmanniae praeparata, almond, *Evodia rutaecarpa*, Danggui, fennel, *Scutellaria baicalensis*. The drugs can be divided into 5 clusters. The total drugs used in the upper warmer are 154. The drugs with high frequencies are licorice, almond, ginseng, fennel, clove and musk, radix rehmanniae praeparata, Danggui, Sichuan pepper, *Evodia rutaecarpa*, *Ophiopogon japonicus*, rosewood heart wood, faeces trogopterorum, ginger etc. The total drugs used in the middle warmer are 133. The drugs of the top 10 frequencies are as follows: licorice, *Scutellaria baicalensis*, *Magnolia officinalis*, *Poria cocos*, ginseng, dried orange peel, *Coptis chinensis*, *Pinellia ternata*, ginger, radix scrophulariae, talc, gypsum. The total drugs used in the Xia Jiao are 157. The drugs of the top 10 frequent are: poria cocos, ginseng, white peony root, radix rehmanniae praeparata, licorice, Danggui, ass hide glue, cassia twig, *Evodia rutaecarpa*, chicken egg yolk. This study is meaningful for further analysis of the drug compatibility characteristics and syndrome-differentiation-based medication patterns in Wen Bing Tiao Bian. **Conclusions**: Complex network methods can analyze the medication characteristics and relationship characteristics of Wen Bing Tiao Bian, which is meaningful for further analyzing the medication compatibility characteristics and syndrome differentiation medication rules in Wen Bing Tiao Bian.

Keywords

Complex Network Analysis, Wen Bing Tiao Bian, Clustering, Medication Pattern

1. Introduction

The Wen Bing Tiao Bian, a comprehensive systematic differentiation of warm diseases by Wu Jutong of the Qing dynasty, established the "Three Burners Differentiation" system and systematically consolidated the clinical experiences of physicians such as Ye Tianshi. Its pharmacological framework is centered on the core principle of "preserving Yin fluids and protecting Yang Qi" [1]. In recent years, under the backdrop of integrating classical theories with modern scientific and technological advancements, the research paradigm has shifted from traditional textual collation and empirical summation toward multidimensional explorations including mechanism elucidation, clinical evidence evaluation, and dosage form innovation.

Zhang *et al*. [2] proposed a three-dimensional network analysis framework for Wen Bing prescriptions of "pathogenesis-target-pathway". They also discussed the application and potential role of network pharmacology in the Chinese herbal medicine. The developing tendency of network pharmacology is also summarized.

Yang *et al*. [3] organized 281 cases of Wu Jutong treating warm diseases. A total of 281 prescriptions were involved, from which 133 Chinese herbal medicines were extracted, with a total frequency of 2,625 occurrences. There were 24 high-frequency herbs, among which the top 5 most frequently used were *Ophiopogon japonicus*, *Rehmannia glutinosa*, *Forsythia suspensa*, *Lonicera japonica*, and *Scutellaria baicalensis*. The nature of the herbs was primarily cold, warm, and neutral; the flavors were predominantly bitter, sweet, and pungent; and the meridian tropisms mainly belonged to the Lung, Stomach, Heart, and Spleen meridians. Based on *Ophiopogon japonicus*, *Rehmannia glutinosa*, *Forsythia suspensa*, and *Lonicera japonica*, the core herbal formula was formed.

Sun *et al*. [4] studied the medication rules of damp-heat diseases in Wen Bing Tiao Bian selecting a total of 87 prescriptions and involving 167 Chinese herbal medicines with a cumulative frequency of 569 occurrences. Among the Three Jiao patterns, warm diseases characterized by damp-heat in the Middle Jiao were predominant; specifically, within summer-heat warm disease, latent summer-heat, and damp-warm disease, damp-warm disease was the most common. The frequently used herb natures and flavors were primarily bitter and warm. The meridian tropisms mainly targeted the Spleen, Lung, and Stomach meridians. Commonly used herbs included *Pinellia ternata*, *Poria cocos*, ginseng, *Magnolia officinalis*, *Scutellaria baicalensis*, *Prunus armeniaca*, and *Coptis chinensis*. Frequent association combinations identified were: ginseng and *Coptis chinensis* leading to *Zingiber officinale* and *Pinellia ternata*; *Aurantium aurantium* leading to *Coptis*

chinensis; and *Pinellia ternata* with *Scutellaria baicalensis* leading to *Coptis chinensis*. Principal component analysis revealed that clinically common herbs for treating damp-heat warm diseases include heat-clearing and dampness-drying herbs (*Scutellaria baicalensis*, *Coptis chinensis*), Qi-moving and dampness-drying herbs (*Magnolia officinalis*, *Citrus reticulata*, *Aurantii Fructus*, *Pinellia ternata*, *Prunus armeniaca*), and bland-permeating dampness-leaching herbs (*Poria cocos*, talci, *Tetrapanax papyrifer*, *Coix lacryma-jobi*).

Wang *et al*. [5] studied the medication rules for damp-warm disease in Wen Bing Tiao Bian. They selected 6 prescriptions and 22 Chinese herbal medicines for the Upper Jiao, 45 prescriptions and 81 herbs for the Middle Jiao, and 21 prescriptions and 72 herbs for the Lower Jiao. The results showed that in the Upper Jiao, heat-clearing herbs, diuretic dampness-leaching herbs, and phlegm-resolving, cough-suppressing and asthma-relieving herbs accounted for a cumulative frequency of 73.33%. In the Middle Jiao, diuretic dampness-leaching herbs, heat-clearing herbs, dampness-transforming herbs, and Qi-regulating herbs reached a cumulative frequency of 55.32%. In the Lower Jiao, tonifying deficiency herbs, interior-warming herbs, diuretic dampness-leaching herbs, and heat-clearing herbs comprised a cumulative frequency of 62.17%.

Liu *et al*. [6] used the Traditional Chinese Medicine Inheritance Computing Platform (TCMICS), the frequency statistics, property-taste-meridian analysis, herbal efficacy evaluation, clustering analysis, and association rule mining were performed on the herbal data extracted from the Wen Bing Tiao Bian. A total of 43 target prescriptions were identified. The predominant herbal properties were warm, followed by cold and neutral. The most common tastes were sweet, followed by bitter and pungent. The meridians most frequently targeted were the Spleen, Lung, Heart, and Kidney. The most frequent herbal efficacy category was tonifying deficiency, followed by astringing and clearing heat. The four core herbs most frequently combined with Ginseng, in descending order of frequency, were *Ophiopogon japonicus*, processed glycyrrhiza, Danggui, and donkey-hide gelatin. Liao *et al*. [7] screened the active components and related targets of Yinqiao by traditional Chinese medicine system pharmacology database and analysis platform (TCMSP). Then the disease-related targets of URTI, Gene ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were carried. They got the main active ingredients such as (-)-phillygenin, luteolin, quercetin, kaempferol and the key targets involved IL-6, TP53, MAPK1, APP, VEGFA, TNF and found 121 KEGG related pathways.

Tang *et al*. [8] employs network pharmacology and molecular docking to investigate the shared molecular mechanisms underlying Yin Qiao San's application in treating different diseases with the same method—namely, acute upper respiratory infection in children (AURIC) and viral myocarditis in children (VMC). The primary findings reveal that Yin Qiao San exerts its therapeutic effects on AURIC and VMC primarily through key targets including STAT3, RELA, TNF, MAPK3, and AKT1, mediated by major bioactive components such as quercetin,

kaempferol, luteolin, naringenin, and stigmasterol. These components modulate multiple signaling pathways, including the cancer-related pathways, PI3K/AKT signaling, TNF signaling, AGE/RAGE signaling, IL-17 signaling, and TLR-like receptor signaling pathways.

Tan *et al*. [9] retrieved the active ingredients and corresponding targets of the medicinal components in the Jianpi Yiqi Formula from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP). A protein-protein interaction (PPI) network, GO enrichment analysis, KEGG enrichment analysis and molecular docking were performed. They found that the Jianpi Yiqi Formula may exert a potential therapeutic effect on pediatric SS via core targets including STAT3, AKT1, and MAPK3.

Wang *et al*. [10] analyzed the medicinal herb usage in Shanghan Lun and Wen Bing Tiao Bian to investigate the inheritance relationship between the two classical works. The study revealed that among the 110 formulas in Shanghan Lun and 200 formulas in Wen Bing Tiao Bian, a total of 255 distinct herbal substances were involved (77 from Shanghan Lun and 251 from Wen Bing Tiao Bian). Among herbs used with a frequency of ≥30, in addition to commonly used herbs such as licorice, ginger, and jujuba, the top herbs in Shanghan Lun were cassia twig and white *Paeonia lactiflora*; in Wen Bing Tiao Bian, they were ginseng, poria cocos, white *Paeonia lactiflora*, *Ophiopogon japonicus*, *Pinellia ternata*, and *Rehmannia glutinosa*. When combining the herb usage across both texts, the ranked list of herbs with frequency ≥30 was: white *Paeonia lactiflora*, cassia twig, ginseng, *Pinellia ternata*, poria cocos, dried ginger, *Scutellaria baicalensis*, *Aconitum carmichaelii*, *Coptis chinensis*, *Ophiopogon japonicus*, *Magnolia officinalis*, *Prunus armeniaca*, *Rheum palmatum*, and *Rehmannia glutinosa*.

Zhang *et al*. [11] conducted statistical analysis on the drugs in the Chapter of Upper Energizer of Systematic Differentiation of Warm Diseases. The number, use frequency, frequencies of four properties and five flavors, texture of different parts of the drugs were analyzed. There are 58 items and 46 formulas, involving 11 diseases names of wind warm, warm heat, pestilence, warm toxin, winter warm, summer warm, latent summer heat, damp warm, cold damp, warm malaria and autumn dryness. Tang *et al*. [12] explored the core drug combinations and compatibility patterns of pungent drugs in Wenbing Tiaobian for treating warm pathogen diseases and systematically collected formulas containing pungent drugs from Wenbing Tiaobian. Using the TCMICS 3.5, frequency statistics, property, taste and meridian tropism analysis and association rule mining on extracted herbal data were conducted to identify core drug combinations. They found that the pungent herbs treat Upper Jiao syndromes by exerting the effects of expelling pathogens through outward penetration and clearing heat, act on Middle Jiao syndromes via the mechanisms of pungent-opening and bitter-downbearing as well as dampness resolution, and manage Lower Jiao syndromes with the combined actions of purgative downward conduction and tonification.

Through analysis of Wen Bing Tiao Bian, Wen *et al*. [13] identified 72 formulas

in the "Xia Jiao Chapter" involving 162 distinct medicinal substances. For Warm-Heat type warm diseases, the high-frequency herbs are: licorice, white peony root, phiopogon root, prepared rehmannia root, donkey-hide gelatin, oyster shell, hemp seed, turtle carapace, tortoise plastron, ginseng. These primarily comprise Yin and blood nourishing agents. For Damp-Heat type warm diseases, the high-frequency herbs are: ginseng, poria cocos, white peony root, prepared aconite root, coptis rhizome, dried ginger, cassia twig, pinellia rhizome, Danggui, smoked plum, etc. These primarily comprise Qi supplementing and interior warming agents. For Cold-Damp type disorders, the high-frequency herbs are: prepared aconite root, poria cocos, cassia twig, licorice, Magnolia mark, dried ginger, galangal rhizome, fennel seed, tangerine peel, green tangerine peel, etc. These primarily comprise interior warming and Qi regulating agents.

Although considerable research has been conducted on the patterns of syndrome differentiation and treatment in Shanghan Lun, studies employing complex network analysis to explore medication rules based on the San Jiao differentiation classification in Wen Bing Tiao Bian remain scarce. This study adopts complex network analysis to separately examine subnetworks of prescriptions for the upper, middle, and Xia Jiao, as well as the overall prescription network, aiming to uncover medication patterns, the roles of individual herbs, and their interrelationships in Wen Bing Tiao Bian. This work can provide references for better treatment of warm diseases in the future

2. Material and Method

To investigate the medication patterns in the Wen Bing Tiao Bian, this study performed complex network analysis and clustering analysis on the prescriptions in Wen Bing Tiao Bian. All statistical computations and network analyses were conducted using software written in Python, with visualization of results carried out accordingly. The data used in this study were exclusively derived from relevant classics of the Wen Bing Tiao Bian [1] [14] [15]. All data normalization procedures are performed based on the annotated edition of Wen Bing Tiao Bian documented in Reference [15]. A comprehensive collection and statistical analysis of the 215 screened prescriptions in Wen Bing Tiao Bian, in which the Upper Jiao includes 50 prescriptions, Middle Jiao 93 prescriptions and Lower Jiao 72 prescriptions. During the inclusion process of the 215 prescriptions, only one copy of duplicate prescriptions is retained. Prescriptions with only one single herb modified from the original formula are excluded. All herbs using different medicinal parts of the same plant, as well as raw and processed herbal products, are distinguished as separate medicinal ingredients. For example, fresh ginger and dried ginger are classified as distinct herbs, raw hyacinth bean and hyacinth bean are regarded as the same herb, while Tinglizi (Descurainiae Semen) and Tingli (Drabae Herba) are treated as two separate herbs. Fried Qu and fried Shenqu are considered the same herb, and "Zhuyu" refers specifically to Evodiae Fructus (Wu Zhuyu). Prepared licorice root and raw licorice root are collectively referred to as licorice.

Schizonepeta herb and carbonized schizonepeta herb are referred to as schizonepeta. Pear peel and pear flesh are collectively referred to as pear.

3. Complex Network Analysis

3.1. Introduction of Method

As an integrated multidisciplinary concept, network pharmacology, which is based on system biology and polypharmacology, affords a novel network mode of multiple targets, multiple effects, complex diseases and replaces the magic bullets by magic shotguns. Chinese herbal medicine (CHM) has been recognized as one of the most important strategies in complementary and alternative medicine. Though CHM has been practiced for a very long time, its effectiveness and beneficial contribution to public health has not been fully recognized. Also, the knowledge on the mechanisms of CHM formulas is scarce.

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 [16]. 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 Chinese 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 [17]. 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 is, and the higher the centrality of the node is, making it more important in the network [18]. 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 [15]. 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. In this paper, each node represents a single standardized Chinese herbal medicine entity, meaning one distinct herb corresponds to exactly one node. The node degree is defined as the number of edges directly connected to the corresponding node, which represents the total number of direct associated objects of that entity. For every co-occurrence of two Chinese herbal medicines in the same prescription, the corresponding edge weight is incremented by 1. The final edge weight is defined as the total cumulative co-occurrence count of the two

herbs across all 215 prescriptions. The network adopts undirected edges, and no additional weight filtering threshold is set. During the clustering analysis, the implementation from the network library in Python 3.8.5 was used.

3.2. The Upper Jiao

3.2.1. The Degrees of Nodes

The total nodes are 154, The total edges are 1823 (Figure 1).

The drugs of the top 10 of the node degree are licorice 79, almond 76, ginseng 70, fennel, clove and musk 63, radix rehmanniae praeparata, Danggui and sichuan pepper 57, *Evodia rutaecarpa* 56, *Ophiopogon japonicus* 51, rosewood heart wood and faeces trogopterorum 50, ginger 49, white peony root 44. The bottom 10 are: *Magnolia officinalis* and red peony 13, Szechwan chinaberry fruit, folium Isatidis, radix bupleuri and loquat leaf 12, *Tetrapanax papyriferus*, lotus leaf, bark of luffa, sevenlobed yam rhizome, turtle shell, pear skin, puffball, desert cistanche, Chinese wolfberry, pilose antler, pearl, carborundum and watermelon peel 11, benzoin, silver foil, peucedani radix, fructus aurantii, carapax eretmochelydis, amber, buffalo horn and *Perilla frutescens* 10, radix isatidis, bombyx batryticatus and *Salvia miltiorrhiza* 9, red bean, donkey-hide gelatin, *Sesamum orientale*, *Belamcanda chinensis*, *Canella winterana*, cardamonfruit and chrysanthemum 7, *Itoa orientalis*, radices trichosanthis, raw lentil beans, *Polygonatum odoratum* and bulb of thun-berg fritillary 6, seed-coat of green gram, semen benincasae, lotus seed and reed stem 5, water chestnut juice, lotus root juice, pear juice and Chinese mosla herb 4, muskmelon base 2.

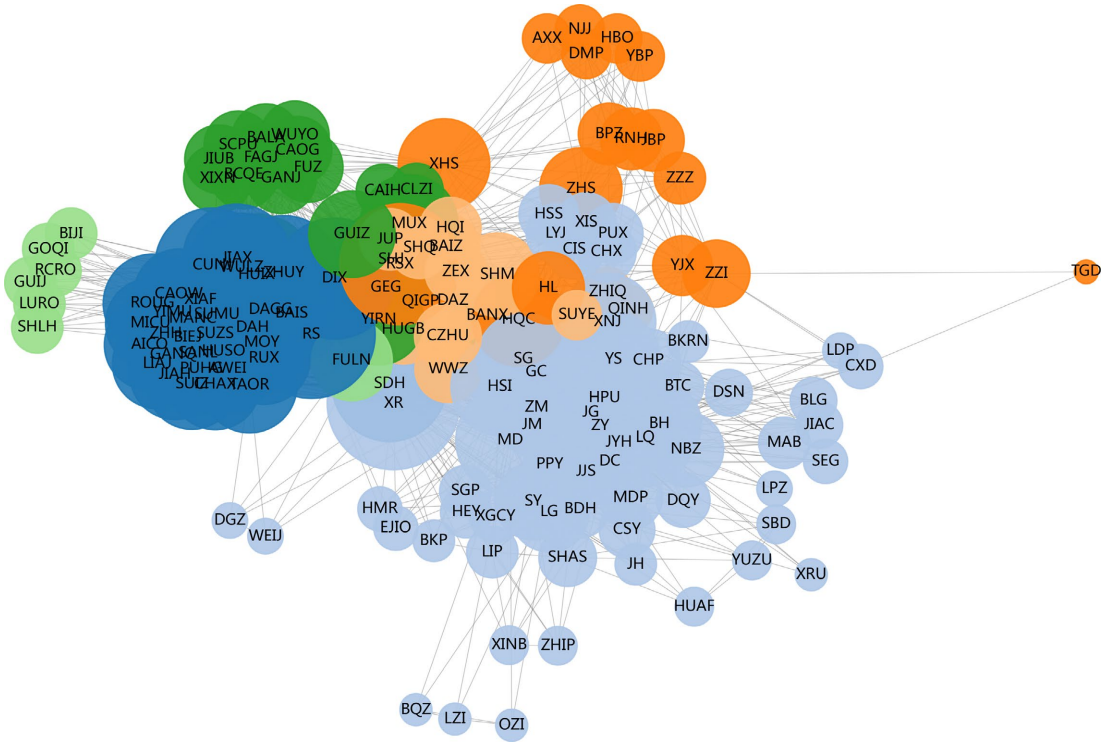


Figure 1. Network for the prescription of Upper Jiao.

The edge weights over 1 are shown in Table 1. The rest edge weights are 1. It means that the edge weights are either 2 or 1.

Table 1. The edge weights of the Upper Jiao network.

SDH-MD	2	SHJ-GUIZ	2	ZY-LQ	2
SDH-YS	2	JG-LG	2	ZY-XNJ	2
GC-JG	2	JG-LQ	2	ZY-DSN	2
XR-JG	2	ZY-JYH	2	NBZ-MAB	2
MD-ZY	2				

3.2.2. Cluster Analysis of the Upper Jiao

For the clustering analysis, the K-means implementation from the sklearn.cluster library in Python 3.8.5 is adopted. The edge weights (*i.e.*, the co-occurrence counts of herbal medicines) are incorporated into the clustering calculation. A random seed of 42 is set to ensure result reproducibility. All disconnected components in the network are included in the unified clustering workflow. Nodes are allowed to belong to multiple clustering modules based on their co-occurrence relationships, and the optimal clustering partition is finally selected using the modularity index.

It can be divided into 6 clusters. *Acorus tatarinowii*, betel nut, lindera root, *Amomum tsao-ko*, monkshood, dried ginger, *Allium macrostemon*, *Asarum*, cassia twig, radix bupleuri, toosendan Fructus are the first cluster; Chinese wolfberry, desert cistanche, turtle shell, pilose antler, carborundum are the second cluster. Benzoin, ox horn, *Eretmochelys imbricata*, amber, silver foil are the third cluster. Radix scrophulariae, dried orange peel, *Tetrapanax papyriferus*, *Salvia miltiorrhiza*, *Magnolia officinalis*, gypsum, licorice, talc, *Anemarrhena asphodeloides*, japonica rice, loquat leaf, spica schizonepetae, black bean sauce, hyacinth bean flower, moutan cortex, folium isatidis, paeoniae radix rubra, white amomun pericarp, donkey-hide gelatin, seed of flax are the fourth cluster. Yu Jin, pearl, *Gardenia jasminoides*, ox horn, hawksbill turtle, silver foil, amber are the fifth cluster. The rest form the sixth cluster.

3.3. Middle Jiao

3.3.1. The Degrees of Nodes of the Middle Jiao Network

The total nodes are 133. The edges are 1092. The drugs of the top 10 node degrees are: licorice 62, *Scutellaria baicalensis* 53, *Magnolia officinalis* 48, poria cocos 47, ginseng 44, dried orange peel 43, *Coptis chinensis* 42, *Pinellia ternata* 42, ginger 41, radix scrophulariae 41, talc 40, gypsum 38 (Figure 2).

The drugs of the bottom 10 node degrees are: ash bark 10, japonica rice 10, caulis bambusae in taeniam 10, papaya 9, myristicae semen 9, peucedani radix 9, Szechuan lovage rhizome 9, sea cucumber 9, pericarpium trichosanthis 9, *Angelica pubescens* 9, *Atractylodes lancea* 9, notopterygium root 9, silkworm excrement 8, red bean 8, orange red, lotus seed 8, *Forsythia suspensa* 8, *Evodia rutaecarpa* 7, divaricate saposhnikovia root 7, *Tribulus terrestris* 7, semen raphani 7, soybean

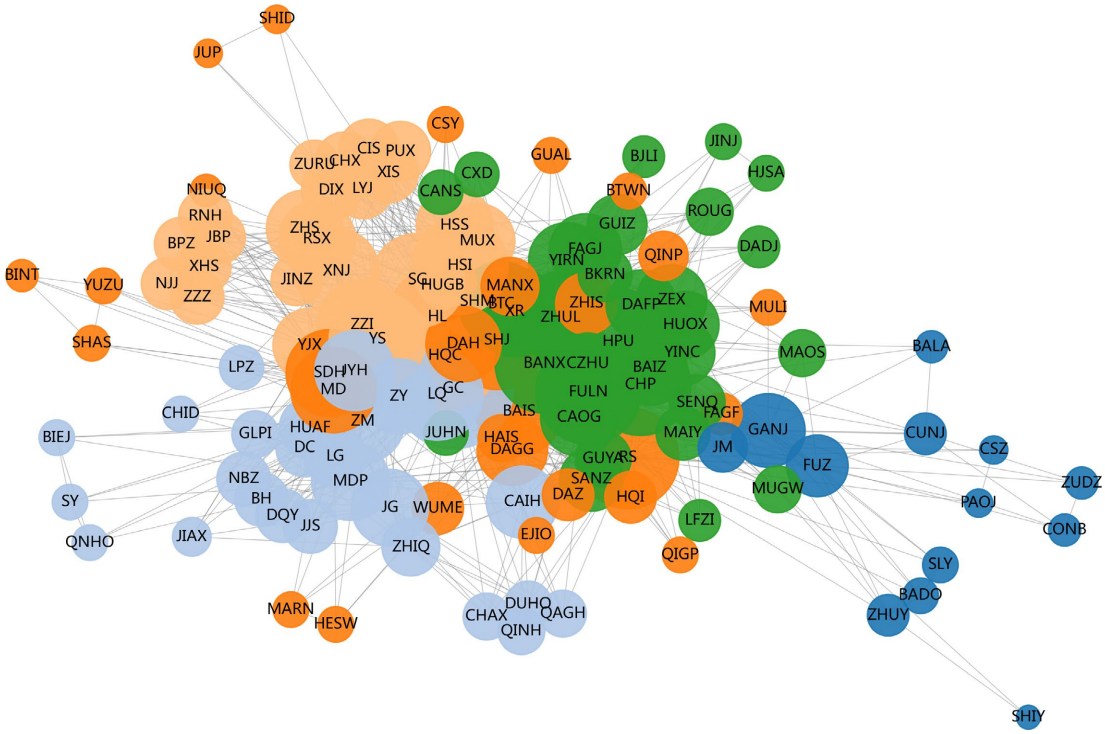


Figure 2. Network for the prescription of Middle Jiao.

roll 7, Sichuan pepper 7, *Dalbergia odorifera* 6, *Croton tiglium* 5, polygoni multiflori radix 5, *Trichosanthes kirilowii* 5, citri Reticulatae pericarpium viride 5, turtle carapace 5, *Polygonatum odoratum* 5, red bean 5, Pulsatilla 5, red peony 5, donkey-hide gelatin 5, hecaoya 5, *Lygodium japonicum* 5, chicken gizzard membrane 5, seed of hemp 5, adenophora root 5, oyster 5, *Artemisia annua* 5, mulberry leaves 5, betel nut 4, rock sugar 4, fistular onion stalk 4, suis fellis pulvis 4, *Achyranthes bidentata* Blume 4, halloysitum rubrum 3, common ginger 3, orange peel 3, persimmon calyx 3, salt 2, milk 1, white sugar 1 (Table 2).

Table 2. Node degree of Middle Jiao.

GC	62	MDP	26	FUZ	16	BPZ	12	CXD	8	JINJ	5
HQC	53	CAOG	25	HUAF	16	JBP	12	JUHN	8	MARN	5
HPU	48	HSS	25	ZHIS	16	XHS	12	LPZ	8	SHAS	5
FULN	47	SHM	25	LG	16	ZZZ	12	LQ	8	MULI	5
RS	44	YIRN	25	CZHU	16	RNH	12	ZHUY	7	QNHO	5
CHP	43	JG	25	GUIZ	15	WUME	11	FAGF	7	SY	5
HL	42	ZY	25	CHX	15	DAZ	11	BJLI	7	BALA	4
BANX	42	ZHS	25	DIX	15	JINZ	11	LFZI	7	BINT	4
SHJ	41	RSX	25	PUX	15	HQI	11	DADJ	7	CONB	4
YS	41	MUX	24	XIS	15	NJJ	11	CUNJ	7	ZUDZ	4
HSI	40	BAIZ	24	CIS	15	QINP	10	JIAX	6	NIUQ	4

Continued

SG	38	DAH	24	LYJ	15	JM	10	BADO	5	CSZ	3
ZHUL	35	GANJ	23	DC	14	ZURU	10	HESW	5	PAOJ	3
ZZI	35	YJX	23	ZHIQ	14	MUGW	9	GUAL	5	JUP	3
XR	34	CAIH	22	MANX	14	ROUG	9	QIGP	5	SHID	3
BAIS	33	FAGJ	22	GUYA	13	QINH	9	BIEJ	5	SHIY	2
LQ	32	DAGG	21	SENQ	13	CHAX	9	YUZU	5	NIUR	1
SDH	32	ZEX	21	MAIY	12	HAIS	9	CHID	5	BAIT	1
MD	32	DAFP	21	BH	12	GLPI	9	BTWN	5		
BTC	31	HUGB	20	DQY	12	DUHO	9	CSY	5		
XNJ	31	HUOX	19	JJS	12	MAOS	9	EJIO	5		
ZM	30	YINC	18	NBZ	12	QAGH	9	SLY	5		
JYH	28	SANZ	17	BKRN	12	CANS	8	HJSA	5		

3.3.2. The Edge Weights of the Middle Jiao Network

Poria cocos (FULN)-*Tetrapanax papyriferus* (BTC) 4, *Scutellaria baicalensis* (HQC)-ginger (SHJ) 2, bamboo juice (ZHUL)-*Tetrapanax papyriferus* (BTC) 2. Table 3 shows the edge weights equal or larger than 2. The rest are all 1.

Table 3. The edge weights more than 1.

FULN-BTC	4	HQC-SHJ	2	ZHUL-BTC	2	GC-JYH	2
GANJ-CUNJ	2	SHJ-CAOG	2	BTC-BKRN	2	HPU-BTC	2
GANJ-FUZ	2	SHJ-ZHIS	2	BTC-HSI	2	HPU-FULN	2
RS-FUZ	2	SHJ-ZZI	2	BTC-LQ	2	FULN-HSI	2
RS-SHJ	2	ZM-HUAF	2	BTC-SG	2	FULN-MAIY	2
BAIS-HL	2	CAOG-FULN	2	BTC-XR	2	FULN-ZHUL	2
BAIS-HQC	2	FAGJ-BTC	2	LG-JYH	2	YS-MD	2
DAGG-SHJ	2	FAGJ-FULN	2	SDH-MD	2	ZY-MD	2
GC-SHJ	2	FULN-DAFP	2	YS-JYH	2	MD-JYH	2

3.3.3. Cluster Analysis of the Middle Jiao Network

It can be divided into 5 clusters.

Radix bupleuri, *Tetrapanax papyriferus*, bamboo juice, almond, *Pinellia ternata*, poria cocos, *Pericarpium arecae*, ginger, rhizoma alismatis, ginseng, atractlodis rhizoma, *Amomum tsao-ko*, white cardamom kernel, coix Seed, cassia twig, hawthorn, agastache, medicated leaven, malt, silkworm excrement, red bean, *Tribulus terrestris*, semen raphani are the same cluster.

Clove, sodium nitrate, magnet, rhinoceros horn, eaglewood, antelope's horn, talc, licorice, aucklandiae radix, white peony root are the same cluster.

Rehmanniae radix praeparataa, *Ophiopogon japonicus*, radix scrophulariae,

reed root, honeysuckle flower, bamboo leaf, golden juice, moutan cortex, *Trichosanthes kirilowii* pollen, folium isatidis, peppermint, burdock fruit, spica schizonepetae, *Forsythia suspensa*, lotus seed are the same cluster.

Milk (NIUR)-white sugar (BAIT) are connected separately and are not drawn.

3.4. Lower Jiao

3.4.1. The Connection Degree of Nodes

The total nodes are 157. The edges are 1556. The drugs of the top 10 node degrees are as follows: poria cocos 82, ginseng 76, white peony root 75, radix rehmanniae praeparata 61, licorice 56, Danggui 50, ass hide glue 48, cassia twig 47, *Evodia rutaecarpa* 46, chicken egg yolk 45 (Figure 3).

The drugs of the bottom 10 node degrees are as follows: Chinese bulbul 3, almond 3, tabanus 3, medical leech 3, rice vinegar 2, euphorbia pekinensis 2, white mustard seed 2, euphorbia kansui 2, asparagus fern 2, Yu Yuliang 2, milk 1, white sugar 1 (Table 4).

Table 4. The connection degree of nodes of Lower Jiao.

FULN	82	NIUQ	35	CUNJ	21	ZHUL	10	LIUH	5
RS	76	HQC	35	HUGB	21	JG	9	ZY	5
BAIS	75	DUZO	33	ZUGS	20	RDKO	9	YINC	5
SDH	61	FUZ	32	HSS	19	SBD	9	YITN	5
GC	56	ZISY	32	SHJ	18	SHAR	9	YJSI	5
DAGG	50	LUJO	32	XNJ	18	MAHW	9	BINT	4
EJIO	48	BIJI	31	QIGP	17	ZM	8	YUZU	4
GUIZ	47	GUIY	31	PAOJ	15	JIUZ	8	BQZ	4
HUIX	47	LNGU	31	CHX	15	CAOG	8	LG	4
ZHUY	46	SPXO	31	DIX	15	HULB	8	OZI	4
JZH	45	WUZG	31	PUX	15	QINP	7	CANS	4
BANX	43	XYSN	31	RSX	15	BALA	7	ZOJZ	4
BIEJ	43	DAH	31	SHM	15	BADO	7	CSZ	4
LPZ	43	HPU	30	YS	15	CLZI	7	JM	4
XIS	42	MDP	30	ZHS	15	DIYU	7	DANC	4
GANJ	42	TAOR	29	CIS	15	WUYO	7	TONB	4
BUGZ	41	MUX	28	HSI	15	YGPI	7	LZI	4
GUIJ	41	CAIH	28	LYJ	15	GAOL	6	QNHO	4
TUSZ	41	BAIZ	25	XIXN	15	ZXHT	6	SHAS	4
QINS	40	HL	24	DAZ	14	SUZS	6	BTWN	3
MULI	39	TLZI	23	YIRN	14	XFHA	6	XR	3
LURO	39	CHP	23	MAOS	14	XIAF	6	MANC	3

Continued

RCRO	38	FONW	22	SANY	14	HUOX	5	SUIZ	3
WWZ	38	LXHA	22	ZHIS	12	SHUQ	5	MICU	2
BAIM	37	QAGL	22	LIAJ	12	MANX	5	DAJI	2
GOQI	37	QUMA	22	JYH	12	RNZB	5	BJZI	2
BJLI	37	SHIW	22	SANZ	12	ZHEL	5	GANS	2
YYZI	37	TUBC	22	MARN	11	MUGW	5	TIND	2
BAOY	37	WUME	22	BAJT	11	JUHN	5	YUYL	2
HAIS	37	SEG	22	FUPZ	11	WULZ	5	NIUR	1
WUGJ	37	SUFU	22	ROUG	10	JUP	5	BAIT	1
MD	35	SG	22						

3.4.2. The Edge Weights of the Lower Jiao Network

The edge weights are as follows: white peony root - ass hide glue 9, white peony root-*Ophiopogon japonicus* 8, white peony root - birthplace 8, ass hide glue - phiopogon japonicus 7, ass hide glue raw rehmannia 7, ophiopogon japonicus - birthplace 7, white peony root - licorice 6, white peony root - dried ginger 6, ass hide glue - licorice 6, white peony root - seed of hemp 5 (Table 5).

Table 5. The edge weights of drug network in Lower Jiao.

BAIS-EJIO	9	GUIZ-SHJ	5	HUIX-LURO	4	BIEJ-MULI	3	DUZO-HUIX	3
BAIS-MD	8	MARN-SDH	5	MARN-MD	4	BIEJ-SDH	3	DUZO-LURO	3
BAIS-SDH	8	BAIS-FULN	4	MULI-SDH	4	BIEJ-MARN	3	FULN-LPZ	3
EJIO-MD	7	BAIS-GUIZ	4	TUSZ-LURO	4	BJLI-GUIJ	3	FULN-QINS	3
EJIO-SDH	7	BAIS-HL	4	GOQI-GUIJ	3	BUGZ-LURO	3	FULN-LURO	3
MD-SDH	7	BAIS-HQC	4	BAIS-DAZ	3	CUNJ-GANJ	3	FUZ-BAIZ	3
BAIS-GC	6	DAGG-RS	4	BAIS-MDP	3	CUNJ-HL	3	FUZ-RS	3
BAIS-GANJ	6	DAGG-LURO	4	BAIS-RS	3	DAGG-DUZO	3	LPZ-QINS	3
EJIO-GC	6	DAZ-GC	4	BAIS-SHJ	3	DAGG-FUZ	3	LPZ-RS	3
BAIS-MARN	5	FULN-FUZ	4	BANX-GANJ	3	DAGG-HUIX	3	MDP-DAH	3
EJIO-MARN	5	FUZ-LURO	4	BIEJ-EJIO	3	DAZ-SHJ	3	MDP-SDH	3
FULN-RS	5	GC-SHJ	4	BIEJ-MD	3	DAZ-GUIZ	3	RS-WWZ	3
GC-RS	5	GC-GUIZ	4						

3.4.3. The Cluster Analysis of the Lower Jiao Network

It can be divided into 5 clusters. exocarpium citri rubrum, faeces trogopteri, sulfur, toosendan fructus, lindera root, croton tiglium, betel nut, pericarpium citri reticulatae viride, galangal, calcitum, aucklandiae radix, mirabilite, musk, clove, antelope's horn, eaglewood, cinnabar, cimicifugae rhizoma are the same cluster.

Ailanthus root bark, sanguisorba officinalis, bamboo juice, atractylod, seed of Chinese honeylocust, fenugreek, silkworm excrement, white sugar, yamaimo, raspberry, hawthorn, amur cork-tree, honeysuckle flower, papaya, *Coptis chinensis*, *Ophiopogon japonicus*, atractylodes macrocephala, common ginger, asari radix et rhizoma are the same cluster.

Fennel, achyranthes bidentata, cornus officinalis, psoralen, semen cuscutae, cistanches herba, American ginseng, keel, sevenlobed yam rhizome, longan, mantidis ootheca, sheep kidney, sea cucumber, turtle shell, hen egg yolk, pig's bone marrow, *Evodia rutaecarpa*, lotus seed are the same cluster.

Dried ginger, scutellaria baicalensis, cassia twig, fructus aurantii immaturus, rheum officinale, peach kernel, Meng Chong, medical leech, saltpeter are the same cluster (Figure 3).

Milk (NIUR)-white sugar (BAIT) and euphorbia kansui (GANS)-white mustard seed (BJZI)-euphorbia pekinensis (DAJI) are connected separately respectively and not drawn in the figure.

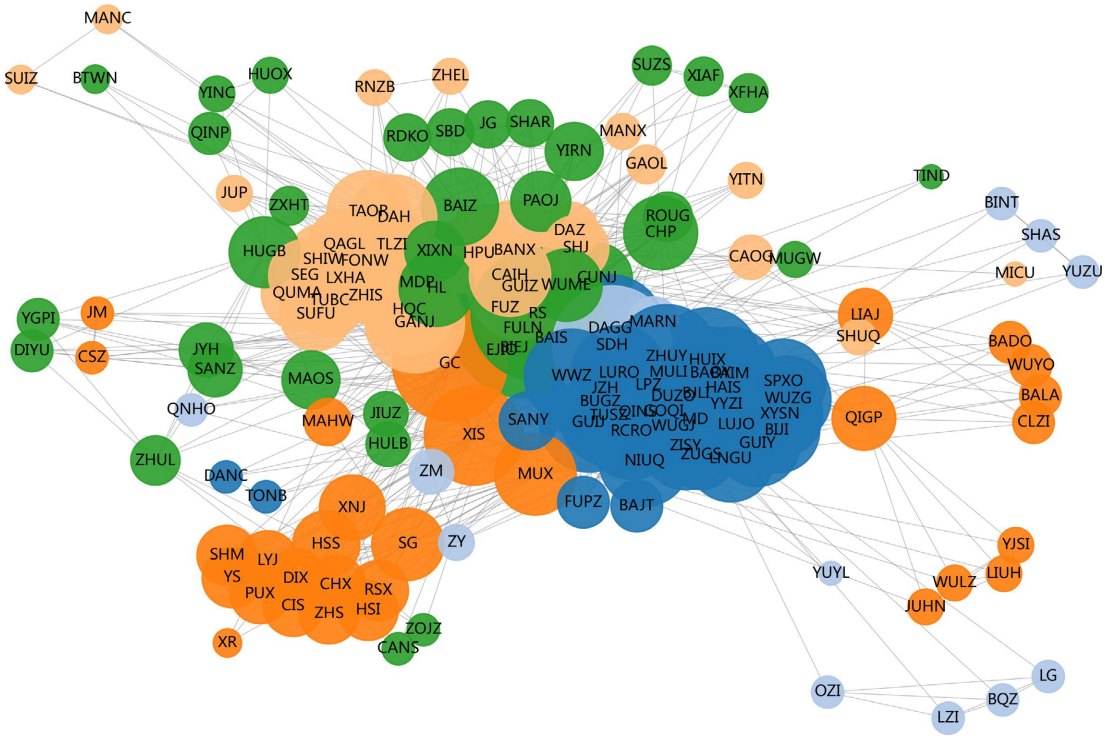


Figure 3. Network for the prescription of Lower Jiao.

3.5. The Total of the Three Jiao

3.5.1. The Connection Degree of Each Node

The total nodes are 250. The total edges are 3541.

The drugs of the top 10 node degrees are as follows: ginseng 131, white peony root 115, poria cocos 111, licorice 111, radix rehmanniae praeparata 104, almond 98, *Evodia rutaecarpa* 95, Danggui 93, fennel 90, *Scutellaria baicalensis* 82 (Figure 4).

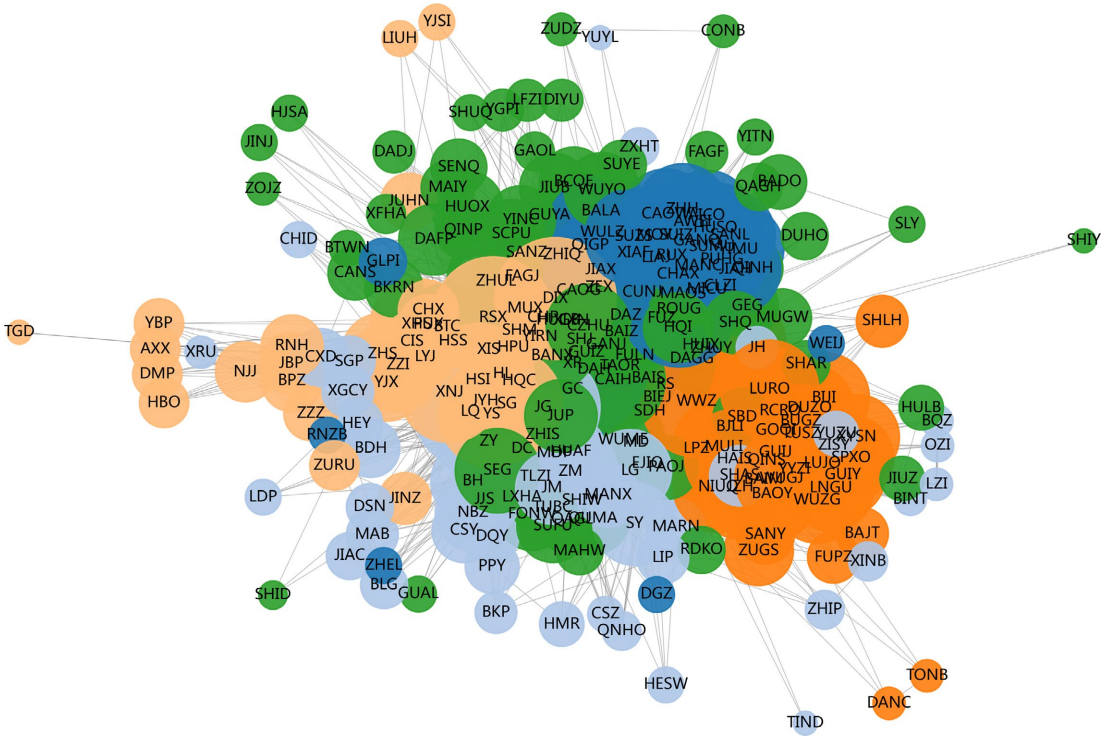


Figure 4. Network for the prescription of all the three Jiao.

The drugs of the bottom 10 node degrees are as follows: rock sugar 4, water chestnut juice 4, lotus root juice 4, seed of Chinese honeylocust 4, onion stalk 4, pig's bile 4, mussel 4, urine of boys under twelve 4, pear juice 4, Chinese mosla herb 4, kaki calyx 3, NaCl 2, asparagus fern 2, Yu Yuliang, sweet melon stem 2 (Table 6).

Table 6. The node degree of all the three Jiao.

RS	131	XNJ	43	GUIY	31	RNH	16	YUZU	8
BAIS	115	XIS	42	LNGU	31	QINH	15	JIUZ	8
FULN	111	HAIS	42	SPXO	31	CHX	15	HMR	8
GC	111	BUGZ	41	WUZG	31	PUX	15	HULB	8
SDH	104	RCRO	41	XYSN	31	CIS	15	FAGF	7
XR	98	ZHUL	41	BH	30	LYJ	15	LFZI	7
ZHUY	95	TUSZ	41	SEG	30	SHAS	15	BKP	7
DAGG	93	LURO	41	CZHU	30	NJJ	15	DADJ	7
HUIX	90	GOQI	40	ZHS	29	MARN	14	DIYU	7
HQC	82	QINS	40	WUME	29	MUGW	14	JH	7
BANX	78	XIAF	40	LG	29	SBD	14	YGPI	7
MD	76	SUZS	40	SY	29	CXD	14	GAOL	6
BIEJ	75	FAGJ	39	HSS	27	BDH	14	ZXHT	6

Continued

DAH	73	ZY	39	SANZ	26	BKRN	14	ZHIP	6
GUIZ	71	ZM	38	BALA	26	SANY	14	QNHO	6
HPU	70	ZZI	38	YJX	25	GUYA	13	XINB	6
SHJ	70	DC	38	NBZ	24	QINP	13	XFHA	6
CUNJ	69	MICU	37	WUYO	24	JUHN	13	HESW	5
GANJ	64	RUX	37	TLZI	23	SENQ	13	GUAL	5
DIX	63	BAIM	37	FONW	22	BADO	12	LDP	5
RSX	63	YYZI	37	LXHA	22	CANS	12	CHID	5
CHP	62	BAOY	37	QAGL	22	MAIY	12	BTWN	5
TAOR	60	MOY	37	QUMA	22	DQY	12	SHUQ	5
YIRN	60	WUGJ	37	SHIW	22	ZZZ	12	CSZ	5
HL	56	XHS	36	TUBC	22	PPY	12	RNZB	5
ROUG	56	DAZ	36	HUOX	22	BAJT	11	ZHEL	5
JIAX	56	AICO	35	SUFU	22	FUPZ	11	DGZ	5
JG	55	YIMU	35	JM	22	HEY	11	SLY	5
HSI	55	AWEI	35	JUP	22	SGP	11	HJSA	5
WULZ	55	BIJI	35	ZHIS	21	LIP	11	JINJ	5
LQ	54	HUSO	35	HUAF	21	MAB	11	LIUH	5
EJIO	53	NIUQ	35	JJS	21	JINZ	11	WEIJ	5
MUX	53	SUIZ	35	DAFP	21	SHLH	11	YITN	5
WWZ	53	QIGP	35	ZUGS	20	XGCY	11	YJSI	5
FUZ	52	ZEX	35	BCQE	20	AXX	10	BINT	4
SG	52	CAOW	35	ZHIQ	20	YBP	10	BQZ	4
LPZ	50	GANQ	35	MAOS	20	DMP	10	OZI	4
MDP	50	JIAH	35	JIUB	20	HBO	10	ZOJZ	4
HUGB	49	MANC	35	SCPU	20	ZURU	10	CONB	4
JYH	49	PUHG	35	YINC	20	SUYE	10	ZUDZ	4
YS	48	SANL	35	HQI	20	RDKO	9	DANC	4
CAOG	47	SUMU	35	CLZI	17	SHAR	9	TONB	4
CAIH	46	ZHH	35	PAOJ	17	BLG	9	LZI	4
JZH	45	SHM	34	CSY	17	JIAC	9	XRU	4
LIAJ	44	DUZO	33	MANX	17	GLPI	9	SHID	3
BJLI	44	BTC	33	BPZ	16	DSN	9	SHIY	2
GUIJ	44	ZISY	32	JBP	16	DUHO	9	TIND	2
CHAX	43	LUJO	32	GEG	16	MAHW	9	YUYL	2
MULI	43	XIXN	31	SHQ	16	QAGH	9	TGD	2
BAIZ	43								

3.5.2. The Edge Weights of All the Three Jiao

The edges weights are as follows: birthplace - *Ophiopogon japonicus* 11, birthplace-white peony root 9, birthplace - ass hide glue 7, dried ginger - white peony root 7, ginseng - licorice 7, white peony root - licorice 7, white peony root - *Scutellaria baicalensis* 7, ass hide glue - licorice 7, ass hide glue-*Ophiopogon japonicus* 7, ginseng - Danggui 6 (Table 7).

Table 7. The edge weights over 2.

SDH-MD	11	TUSZ-LURO	4	CUNJ-GUIZ	3	MUX-LYJ	3	SHM-YS	3
SDH-BAIS	9	LQ-ZY	4	CUNJ-HL	3	MUX-CHX	3	BTC-HSI	3
SDH-EJIO	7	BIEJ-EJIO	3	DAGG-DAZ	3	MUX-PUX	3	HSI-CIS	3
GANJ-BAIS	7	BIEJ-MD	3	DAGG-DUZO	3	MUX-RSX	3	HSI-CHX	3
RS-GC	7	BIEJ-MDP	3	DAGG-FUZ	3	MUX-SHM	3	HSI-DIX	3
BAIS-GC	7	BIEJ-MULI	3	DAZ-BAIZ	3	MUX-XIS	3	HSI-LYJ	3
BAIS-HQC	7	BIEJ-MARN	3	DUZO-LURO	3	MUX-YS	3	HSI-PUX	3
EJIO-GC	7	SDH-NIUQ	3	EJIO-HL	3	MUX-SG	3	HSI-RSX	3
EJIO-MD	7	SDH-SG	3	FULN-CAOG	3	MUX-XNJ	3	HSI-XNJ	3
RS-DAGG	6	SDH-SHAS	3	FULN-HSI	3	RCRO-LURO	3	HSI-YS	3
RS-FULN	6	HUIX-DUZO	3	FULN-JG	3	SHJ-JUP	3	HSI-SG	3
BAIS-HL	6	ZHS-CHX	3	FULN-LPZ	3	SHJ-ZHIS	3	ZY-JYH	3
DAZ-GC	6	ZHS-CIS	3	FULN-QINS	3	XIS-CHX	3	JYH-LG	3
SDH-MDP	5	ZHS-DIX	3	FULN-RCRO	3	XIS-CIS	3	JYH-YS	3
SDH-MARN	5	ZHS-GC	3	FULN-ZHUL	3	XIS-DIX	3	SG-CHX	3
HUIX-LURO	5	ZHS-HSI	3	FULN-MAOS	3	XIS-HSI	3	SG-CIS	3
RS-BAIS	5	ZHS-HSS	3	GC-BAIZ	3	XIS-HSS	3	SG-DIX	3
RS-FUZ	5	ZHS-LYJ	3	GC-CHX	3	XIS-LYJ	3	SG-LYJ	3
BAIS-FULN	5	ZHS-MUX	3	GC-CIS	3	XIS-PUX	3	SG-PUX	3
BAIS-GUIZ	5	ZHS-PUX	3	GC-DIX	3	XIS-SG	3	SG-RSX	3
DAGG-LURO	5	ZHS-RSX	3	GC-HSI	3	XIS-SHM	3	SG-XNJ	3
DAZ-SHJ	5	ZHS-SG	3	GC-JYH	3	XIS-RSX	3	SG-YS	3
EJIO-MARN	5	ZHS-SHM	3	GC-MD	3	XIS-XNJ	3	YS-CHX	3
FUZ-BAIZ	5	ZHS-XIS	3	GC-PUX	3	XIS-YS	3	YS-CIS	3
GC-GUIZ	5	ZHS-XNJ	3	GC-RSX	3	XR-SG	3	YS-LYJ	3
MARN-MD	5	ZHS-YS	3	GC-SG	3	XR-BTC	3	YS-DIX	3
BIEJ-SDH	4	GANJ-BANX	3	GC-SHM	3	ZM-SG	3	YS-PUX	3
DAH-MDP	4	GANJ-CUNJ	3	GC-XIS	3	HSS-CHX	3	YS-RSX	3
SDH-MULI	4	GANJ-HL	3	GC-XNJ	3	HSS-CIS	3	DIX-CHX	3

Continued

HUIX-DAGG	4	RS-EJIO	3	GC-YS	3	HSS-DIX	3	DIX-CIS	3
GANJ-FUZ	4	RS-MD	3	GC-HSS	3	HSS-HSI	3	DIX-PUX	3
RS-BAIZ	4	RS-CHP	3	GC-LYJ	3	HSS-LYJ	3	DIX-LYJ	3
RS-SHJ	4	RS-DAZ	3	GC-MUX	3	HSS-PUX	3	DIX-XNJ	3
RS-WWZ	4	RS-LPZ	3	GUIJ-LURO	3	HSS-RSX	3	RSX-CHX	3
BAIS-DAGG	4	RS-PAOJ	3	GUIZ-HPU	3	HSS-SHM	3	RSX-CIS	3
BAIS-DAZ	4	GOQI-GUIJ	3	HL-JYH	3	HSS-XNJ	3	RSX-LYJ	3
BANX-GC	4	GOQI-RCRO	3	HPU-BTC	3	HSS-YS	3	RSX-PUX	3
BANX-GUIZ	4	GOQI-LURO	3	HQC-MUX	3	HSS-SG	3	RSX-XNJ	3
BANX-HQC	4	BAIS-BANX	3	HQC-SHJ	3	JG-LG	3	CHX-PUX	3
CHP-FULN	4	BAIS-WUME	3	LPZ-QINS	3	JG-LQ	3	CHX-CIS	3
DAGG-SHJ	4	BAIS-CAIH	3	MD-JYH	3	SHM-CHX	3	CHX-LYJ	3
DAZ-GUIZ	4	BANX-CAIH	3	MD-LG	3	SHM-CIS	3	CHX-XNJ	3
FULN-BTC	4	BJLI-GUIJ	3	MD-SHAS	3	SHM-HSI	3	PUX-CIS	3
FULN-FUZ	4	BUGZ-LURO	3	MD-YS	3	SHM-LYJ	3	PUX-LYJ	3
FULN-LURO	4	CHP-BAIZ	3	MD-SG	3	SHM-SG	3	PUX-XNJ	3
FUZ-LURO	4	CHP-DAZ	3	MUX-CIS	3	SHM-DIX	3	CIS-LYJ	3
GC-JG	4	CHP-GC	3	MUX-DIX	3	SHM-PUX	3	CIS-XNJ	3
HL-HUGB	4	CUNJ-DAGG	3	MUX-HSI	3	SHM-RSX	3	LYJ-XNJ	3
MD-ZY	4	CUNJ-FUZ	3	MUX-HSS	3	SHM-XNJ	3	CSZ-JM	3
SHJ-CAOG	4								

3.5.3. The Cluster Analysis of All the Three Jiao

It can be divided into 5 clusters. schisandra chinensis, raw lentil beans, pilose antler, seven lobed yam rhizome, cuttlebone, abalone, keel, yamaimo, pig bone marrow, raspberry, sheep kidney are the same cluster.

Bamboo juice, four stamen stephania root, musk, magnet, calcitum, fructus aurantii immaturus, *Magnolia officinalis*, *Scutellaria baicalensis*, honeysuckle flower, talc, gypsum, *Forsythia suspensa*, radix scrophulariae, cinnabar, gardenia jasminoides, Yu Jin, cimicifugae rhizoma, eaglewood, cow bezoar, gold foil, borneol, pearl, caulis bambusae in taeniam, golden juice are the same cluster.

4. Compared with the Prescription Features of Shang Han Lun

In analysis, 112 prescriptions in Shan Han Lun and 215 prescriptions in Wen Bing Tiao Bian were adopted respectively. The prescriptions in Shang Han Lun were categorized into six types according to the Six Meridians, while those in Wen Bing Tiao Bian are analyzed in three categories based on the Three Jiaos.

The total drugs recorded in Wen Bing Tiao Bian are 250 while 90 in Shang Han Lun. In Shang Han Lun, the appearance frequency of roasted licorice, cassia twig, jujube, ginger, and peony was relatively high. The top 10 used drugs in Wen Bing Tiao bian are as follows: ginseng, white peony root, poria cocos, licorice, radix rehmanniae praeparata, almond, *Evodia rutaecarpa*, Danggui, fennel, *Scutellaria baicalensis* [19].

5. Discussion

The three sub-network analyses in Section 3 demonstrate that the Three Jiao classification system in Wen Bing Tiao Bian does not correspond to a single homogeneous repertoire of herbal combinations, but rather three distinct and characteristic co-prescription pairing patterns.

In terms of the relative density against network size, the Upper Jiao network exhibits the tightest node connectivity (154 nodes and 1823 edges in total). Its core herbs are mostly varieties that are light in nature, dispersing in action, aromatic, or specifically directed to the Lung meridian—Glycyrrhizae Radix (79 occurrences), Armeniacae Semen (76), Ginseng Radix (70), Foeniculi Fructus, Caryophylli Flos and Moschus (63), Rehmanniae Radix Praeparataa, Angelicae Sinensis Radix and Zanthoxyli Pericarpium (57), Evodiae Fructus (56), and Ophiopogonis Radix (51). This result fully aligns with Wu Jutong's therapeutic principle for the Upper Jiao of "releasing the exterior, diffusing the Lung, clearing heat and resolving phlegm". The Middle Jiao network contains 133 nodes and 1, 092 edges, with its core formulations centred on bitter-cold heat-clearing, Qi-regulating and dampness-transforming herbs (Scutellariae Radix 53, Magnoliae Officinalis Cortex 48, Poria 47, Coptidis Rhizoma 42, Pinelliae Rhizoma 42, Zingiberis Recens Rhizoma 41, Scrophulariae Radix 41, Talcum 40, Gypsum Fibrosum 38), which is consistent with the Middle Jiao's therapeutic focus on "clearing heat, transforming dampness and harmonizing the centre". The Lower Jiao network comprises 157 nodes and 1556 edges, where the dominant herbs shift to tonifying, Yin-nourishing and blood-enriching medicinal materials (Poria 82, Ginseng Radix 76, Paeoniae Radix Alba 75, Rehmanniae Radix Praeparataa 61, Glycyrrhizae Radix 56, Angelicae Sinensis Radix 50, Asini Corii Colla 48, Cinnamomi Ramulus 47, Evodiae Fructus 46, and Gallus Ovum Vitellus 45), corresponding to the Lower Jiao therapeutic strategy of "nourishing the Liver and Kidney, restoring the pulse and extinguishing wind". In the pooled Three-Jiao network (250 nodes, 3541 edges, divided into 5 clusters), Ginseng Radix becomes the connectivity hub (with a degree of 131), which precisely echoes the consistent therapeutic thread of "protecting stomach Qi and preserving body fluids" that runs through all three Jiao layers. Taken together, the above results indicate that Jiao attribution not only predicts the distribution of different core herb categories, but also reflects the tightness of inter-herb associations and the variation characteristics of maximum co-occurrence weights of herb pairs.

At the same time, it should be noted that the analytical results of this study are

affected by the following factors:

The first is the interference from formula size. A prescription containing n herbs generates $n(n-1)/2$ unordered herb pairs. As a result, both the total number of edges and the weight of each individual edge increase with the number of ingredients in the prescription. An herb that frequently appears in large compound formulas will accumulate a high node degree and edge weight even if its pairing affinity with other herbs is not strong. This effect is clearly observed in our results: in the Upper Jiao sub-network, all edges with a weight greater than 1 have an exact value of 2 (**Table 1**). The vast majority of the 1823 edges carry only the minimum weight of 1, and only a small number of herb pairs show repeated co-occurrence. In contrast, the weight distribution of the pooled Three-Jiao network drops steeply from 11 to 4, and then extends into a long tail of edges with a weight of 3 (**Table 7**). Since the clustering step is also performed on these weighted edges, the influence of prescription length further permeates the clustering results (the Upper Jiao network yields 6 clusters, while the other three networks each produce 5 clusters). Therefore, conclusions such as "Poria is the herb with the highest connectivity in the Lower Jiao network" essentially indicate that Poria co-occurs with the largest number of distinct partners, and this outcome is partly a consequence of formula size. Future studies can separate genuine herbal compatibility rules from mere high-frequency co-occurrence phenomena by normalizing weights within each individual prescription (for example, using $1/(n-1)$ transformation, or introducing Jaccard coefficient and association strength scaling), setting support or weight thresholds, and comparing the observed network with degree-preserving randomized null models.

The second limitation lies in the coverage scope of the dataset. Following the annotated edition of Wen Bing Tiao Bian [15], this study excluded duplicate records and near-identical prescriptions that differ from an existing formula by only a single herb, and finally retained 215 screened prescriptions: 50 for the Upper Jiao, 93 for the Middle Jiao, and 72 for the Lower Jiao. All three Jiao strata are covered by samples, but the herb inventory is curated according to predefined inclusion rules rather than being exhaustively collected. The final total number of herbs (250 in the pooled network, 154, 133 and 157 for the Upper, Middle and Lower Jiao respectively) is entirely determined by these inclusion criteria. Previous literature has fully demonstrated how such selection decisions affect results: Yang *et al.* [3] mined 281 medical cases and obtained 133 herbs, Sun *et al.* [4] analysed 87 prescriptions and identified 167 herbs, Wang *et al.* [5] included 6/45/21 prescriptions for the three Jiao corresponding to 22/81/72 herbs, Liu *et al.* [6] [7] incorporated 43 target prescriptions through the TCMICS platform, and Wen *et al.* [13] collected 72 formulas and 162 ingredients exclusively in the Lower Jiao chapter. The 72-prescription count of our Lower Jiao stratum exactly matches that reported by Wen *et al.* [13], and the total of 250 herbs in our pooled inventory is highly close to the 251 herbs of Wen Bing Tiao Bian recorded by Wang *et al.* [10].

Third, the accuracy of the herb inventory fully depends on the rigour of nomenclature standardization. In this study, different medicinal parts, raw products and processed products are listed as separate entries (for example, Zingiberis Recens Rhizoma and Zingiberis Rhizoma are set as independent nodes), while some variants under different aliases are merged (raw Lablab Semen and fried Lablab Semen are combined). "Tinglizi" (Descurainiae Semen) and "Tingli" are split into separate nodes, "Shenqu" and "fried Shenqu" are merged, and the term "Zhuyu" is explicitly restricted to Evodiae Fructus. Every such naming decision will alter the network structure. For instance, separating fresh ginger from dried ginger will distribute the Upper Jiao (49), Middle Jiao (41) and Lower Jiao occurrences of ginger across two nodes, and lower the weight of every pair that contains this herb; merging them, on the contrary, will raise both the node degree and the corresponding edge weights.

Fourth, although the patterns obtained in this study are mutually consistent with previous research, they do not directly prove any pharmacological effect. The core position of Ginseng Radix in the pooled network (degree 131) and its high-frequency co-occurring herbs Ophiopogonis Radix and Glycyrrhizae Radix are highly consistent with the ginseng-centred combinations extracted by Liu *et al.* [6] (Ophiopogonis Radix, Glycyrrhizae Radix Praeparataa, Angelicae Sinensis Radix and Asini Corii Colla), and also in line with the high ranking of Ginseng Radix, Poria and Paeoniae Radix Alba reported by Wang *et al.* [10]. The dominance of Coptidis Rhizoma, Scutellariae Radix, Magnoliae Officinalis Cortex and Pinelliae Rhizoma in the Middle Jiao agrees with the damp-heat medication rules summarized by Sun *et al.* [4], and the light, dispersing and aromatic core herbs in the Upper Jiao also match the herb texture, nature and flavour analysis conducted by Zhang *et al.* [11]. However, when the dataset or analytical method differs, the "core herbs" reported in previous studies will also vary, which means that the derived regularities are fully dependent on the adopted dataset and analytical approach.

Co-occurrence records document textual associative links in the literature, rather than direct pharmacological interactions. Herbs may be prescribed together to harmonize the overall medicinal property of a formula, correct its unpleasant taste, or moderate its harsh potency, while the current network does not incorporate any information on dosage, preparation methods, action targets or clinical endpoints. Therefore, the so-called "core herbs", the strongest "compatibility pairs" (Paeoniae Radix Alba - Asini Corii Colla with a weight of 9 and Paeoniae Radix Alba - Ophiopogonis Radix with a weight of 8 in the Lower Jiao sub-network; Rehmanniae Radix Praeparataa - Ophiopogonis Radix with a weight of 11 in the pooled network) and the clustering assignments should all be interpreted as hypotheses about Wu Jutong's prescribing logic, rather than direct evidence of herb synergy, efficacy or safety. Subsequent analysis needs to carry out three lines of work: first, integrating network pharmacology target prediction and molecular docking technology to analyse candidate herb pairs and their major active com-

ponents; second, conducting pharmacological experimental validation in cell or animal models for the herb pairs with high topological strength and clinical plausibility (such as the Yin-nourishing Lower Jiao pairs and the Ginseng-Ophiopogon-Glycyrrhiza core combination); third, performing retrospective or randomized clinical evaluation on the formulas that embody the above patterns. The current analysis remains a descriptive, hypothesis-generating map of the formulation regularities in Wen Bing Tiao Bian, but cannot be directly equated to definitive conclusions about pharmacological compatibility or clinical application.

6. Conclusions

This study employs complex network theory to analyze the formula composition patterns, core herbs, inter-herb connectivity, and herb clustering in the systematic differentiation of warm diseases, categorized into four groups: Upper Jiao, Middle Jiao, Lower Jiao, and the overall prescription.

The total nodes are 154 and the total edges are 1823 of the networks formed by the drugs in the upper warmer. The drugs of the top 10 node degrees are as follows: licorice 79, almond 76, ginseng 70, fennel, clove and musk 63, Radix rehmanniae Praeparata, Danggui and Sichuan pepper 57, *Evodia rutaecarpa* 56, *Ophiopogon japonicus* 51, rosewood heart wood and faeces trogopterorum 50, ginger 49, white peony root 44. The drugs can be divided into 6 clusters. The edge weights greater than 1 are all 2 (Table 1), and the remaining edges have weight 1.

The total nodes are 133 and the total edges are 1092 of the networks formed by the drugs in the middle warmer. The drugs of the top 10 node degrees are as follows: licorice 62, *Scutellaria baicalensis* 53, *Magnolia officinalis* 48, *Poria cocos* 47, ginseng 44, dried orange peel 43, *Coptis chinensis* 42, *Pinellia ternata* 42, ginger 41, Radix Scrophulariae 41, talc 40, gypsum 38.

The largest edge weight is 4 (between *Poria cocos* and *Tetrapanax papyriferus*); the other edges with weight ≥ 2 are listed in Table 3, and all remaining edges have weight 1. The drugs in the middle warmer can be divided into 5 clusters.

The total nodes are 157 and the edges are 1556 of the networks formed by the druge in the total drugs in the Xia Jiao. The drugs of the top 10 node degrees are as follows: poria cocos 82, ginseng 76, white peony root 75, radix rehmanniae praeparata 61, licorice 56, Danggui 50, ass hide glue 48, cassia twig 47, *Evodia rutaecarpa* 46, chicken egg yolk 45.

The total nodes are 250 and the total edges are 3541 of the networks formed by the drugs in the total drugs in the Three Jiao. The drugs of the top 10 node degrees are as follows: ginseng 131, white peony root 115, *Poria cocos* 111, licorice 111, radix rehmanniae praeparata 104, almond 98, *Evodia rutaecarpa* 95, Danggui 93, fennel 90, *Scutellaria baicalensis* 82.

The drugs can be divided into 5 clusters. In the pooled network, the largest edge weights are 11 (birthplace-*Ophiopogon japonicus*), 9 (birthplace-white peony root) and 7 (birthplace-ass hide glue, dried ginger-white peony root, ginseng-licorice, white peony root-licorice, white peony root-*Scutellaria baicalensis*, ass hide

glue-licorice and ass hide glue-*Ophiopogon japonicus*), followed by 6 (ginseng-Danggui) (Table 7).

Conflicts of Interest

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

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Appendix: Drug Name Abbreviation Reference

Honeysuckle flower	JYH	Cimicifugae rhizoma	SHM	Raw lentil beans	SBD	Fructus aurantii immaturus	ZHIS	Persimmon calyx	SHID
Forsythia suspensa	LQ	clove	DIX	Radices trichosanthis	HUAF	*Sesamum orientale*	MARN	Seed of Chinese honeylocust	ZOJZ
Peppermint	BH	Sodium nitrate	PUX	Seed coat of green gram	LDP	Oyster	MULI	*Agastache*	HUOX
Burdock fruit	NBZ	Saltpeter	XIS	Seed of flax	HMR	Chicken egg yolk	JZH	Medicated leaven	MAIY
Spica Schizonepetae	JJS	Radix isatidis	BLG	Donkey hide gelatin	EJIO	Sweet wormwood herb	QNHO	Common ginger	PAOJ
Black bean sauce	DC	Puffball	MAB	*Perilla frutescens*	SUYE	Urine of boys under twelve	TONB	Soybean roll	DADJ
Platycodon grandiflorum	JG	Dried orange peel	CHP	Peucedani radix	QINH	Mussel	DANC	Hawthorn	SANZ
Licorice	GC	*Bombyx batryticatus*	JIAC	Fructus aurantii	ZHIQ	*Trichosanthes kirilowi*	GUAL	Woodlouse	SUFU
Bamboo leaf	ZY	Amur cork tree	HUGB	*Evodia rutaecarpa*	ZHUY	Halloysitum rubrum	CSZ	*Pyrrosia lingua*	SHIW
Reed root	LG	*Rheum officinale*	DAH	Radix bupleuri	CAIH	Rock sugar	BINT	Rice grain sprout	GUYA
Mulberry leaves	SY	Frankincense	RUX	White peony root	BAIS	*Achyranthes bidentata* Blume	NIUQ	*Dianthus superbus*	QUMA
Chrysanthemum	JH	Myrrh	MOY	Toosendan fructus	CLZI	Golden juice	JINZ	Chinese trumpet creeper	LXHA
Almond	XR	*Astragalus membranaceus*	HQI	Fennel	HUIX	Sea cucumber	HAIS	Ground beetle	TUBC
Gypsum	SG	Atractlodis rhizoma	CZHU	*Cinnamomum cassia*	ROUG	*Eupatorium*	ZHEL	Honeycomb	FONW
Anemarrhena asphodeloides	ZM	Rhizoma alismatis	ZEX	Radix aconiti kusnezoffii	CAOW	Sediment of human urine	RNZB	Dung beetle	QAGL
Japonica rice	JM	Medicated leaven	SHQ	Turmeric	JIAH	Sorghum	GAOL	*Tribulus terrestris*	BJLI
Ginseng	RS	Orange peel	JUP	Sichuan pepper	CUNJ	Maltose	MYT	Chicken gizzard-membrane	JINJ
Rehmanniae radix praeparataa	SDH	*Atractylodes macrocephala*	BAIZ	*Tabanus*	MANC	White sugar	BAIT	*Lygodium japonicum*	HJSA
Ophiopogon	MD	Danggui	DAGG	Rhizoma	SANL	Milk	NIUR		

japonicus				sparganii					
Radix scrophulariae	YS	Green tangerine peel	QIGP	Cattail pollen	PUHG	Yinchen	YINC	Semen raphani	LFZI
Rhinoceros horn	XNJ	*Pueraria lobata*	GEG	Saffron	ZHH	Bamboo juice	ZHUL	Polygoni multiflori radix	HESW
Pear juice	LZI	*Schisandra chinensis*	WWZ	Sappan wood	SUMU	Dark plum	WUME	Antifebrile dichroa branchlet and leaf	SHUQ
Water chestnut juice	BQZ	Ginger	SHJ	Perilla seed frost	SUZS	Caulis bambusae in taeniam	ZURU	*Angelica dahurica*	BAZI
Lotus root juice	OZI	Jujube	DAZ	Faeces trogopteri	WULZ	Sulfur	LIUH	Yamaimo	SANY
Gardenia jasminoides	ZZI	Chinese mosla herb	XRU	Rosewood heart wood	JIAX	Gypsum	YJSI	Semen euryales	QINS
Sweet melon stem	TGD	*Magnolia officinalis*	HPU	Dried lacquer	GANQ	Orange red	JUHN	*Morinda officinalis*	BAJT
Red bean	CXD	Hyacinth bean flower	BDH	Rhizoma cyperi	XIAF	Asparagus fern	TIND	Raspberry	FUPZ
Birthplace	SDH	Watermelon peel	XGCY	Corydalis	HUSO	Inula flower	XFHA	Notopterygium root	QAGH
Salvia miltiorrhiza	DSN	Bark of luffa	SGP	Medical leech	SUIZ	Atractylod	MAOS	*Angelica pubescens*	DUHO
Coptis chinensis	HL	Lotus leaf	HEY	*Ferula asafoetida*	AWEI	*Polyporus umbellatus*	ZhLN	Ailanthus root bark	YGPI
Moutan Cortex	DQY	*Pinellia ternata*	BANX	Rhizome of chuanxiong	CHAX	Ash bark	QINP	*Sanguisorba officinalis*	DIYU
Lotus seed	LPZ	*Poria cocos*	FULN	Galangal	LIAJ	*Euphorbia kansui*	GANS	Yu Yuliang	YUYL
Cow bezoar	RNH	Coix seed	YIRN	Carbonized mugwort leaf	AICO	*Euphorbia pekinensis*	DAJI	Myristicae semen	DOUK
Musk	ZZZ	Red peony	CSY	Extract of *Leonurus sibiricus*	YIMU	White mustard seed	BJZI	*Eucommia ulmoides*	DUZO
Cinnabar	ZHS	Adenophora root	SHAS	Turtle carapace	BIEJ	Semen cuscutae	TUSZ	Divaricate saposhnikovia root	FAGF
Realgar	XHS	White cardamom kernel	BKRN	Rice vinegar	MICU	Fenugreek	HULB	Chinese bulbul	BTWN
Scutellaria baicalensis	HQC	*Tetrapanax papyriferus*	BTC	Carborundum	SHLH	Psoralen	BUGZ	Nutmeg	RDKO

Yu Jin	YJX	Burdock fruit	NBZ	Pilose antler	LURO	*Allium tuberosum*	JIUZ	*Amomum villosum*	SHAR
Borneol	BPZ	*Belamcanda chinensis*	SEG	Chinese wolfberry	GOQI	Papaya	MUGW	Black bone chicken	WUGJ
Gold foil	JBP	Loquat leaf	PPY	Desert cistanche	RCRO	Pericarpium arecae	DAFP	Abalone	BAOY
Buffalo horn	NJJ	Reed stem	WEIJ	Sevenlobed yam rhizome	BIJI	Furnace soil	ZXHT	Sheep kidney	YYZI
Amber	HBO	Semen benincasae	DGZ	Turtle shell	GUIJ	Onion stalk	CONB	Pig's bone marrow	ZUGS
Hawksbill turtle	DMP	Peach kernel	TAOR	*Amomum tsao-ko*	CAOG	Pig's bile	ZUDZ	Whitish honey	BAIM
Benzoin	AXX	Cassia twig	GUIZ	*Allium macrostemon* bunge	JIUB	*Ephedra*	MAHW	Amethyst	ZISY
Silver foil	YBP	Dried ginger	GANJ	Lindera root	WUYO	NaCl	SHIY	Antler	LUJO
Calcitum	HSS	Monkshood	FUZ	*Acorus tatarinowii*	SCPU	Semen lepidii	TLZI	Mantidis ootheca	SPXO
Magnet	CIS	White amomun pericarp	BKP	Fourstamen stephania root	FAGJ	Hecaoya	SLY	Cuttlebone	WUZG
Talc	HSI	Pear skin	LIP	Betel nut	BALA	*Croton tiglium*	BADO	American ginseng	XYSN
Antelope's horn	LYJ	Bulb of thunberg fritillary	XINB	Cubeb	BCQE	Pericarpium trichosanthis	GLPI	Keel	LNGU
Aucklandiae radix	MUX	*Itoa orientalis*	ZHIP	*Asarum*	XIXN	Silkworm excrement	CANS	Longan	GUIY
Eaglewood	CHX	*Polygonatum odoratum*	YUZU	Mirabilite	MANX				