Revisión / Review

A revision of Traditional Chinese Medicine in the treatment of polycystic ovary syndrome: Utilizing data mining techniques for disease prevention and management

[Revisión de la medicina tradicional china en el tratamiento del síndrome de ovario poliquístico: utilización de técnicas de minería de datos para la prevención y manejo de la enfermedad]

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Abstract: This study employed data mining to analyze clinical cases of polycystic ovary syndrome (PCOS), PCOS with insulin resistance (PCOS-IR), and insulin resistance (IR), examining their correlations and pathological evolution. A standardized repository was established by searching PubMed and additional medical databases for clinical cases of PCOS, PCOS-IR, and IR. Data mining identified 1,427 PCOS cases (364 Chinese herbal medicines; high-frequency drugs: Radix *Angelicae Sinensis*; key pairs: *Fructus Rubi→Semen Cuscutae*; 5 prescription clusters), 109 PCOS-IR cases (156 Chinese herbal medicines; high-frequency drugs: Poria; key pairs: *Rhizoma Chuanxiong→Radix Angelicae Sinensis*; 4 prescription clusters), and 68 IR cases (125 Chinese herbal medicines; high-frequency drugs: Poria; key pairs: *Radix Bupleuri→Poria*; 4 prescription clusters). The analysis also identified "Phlegm (dampness)" as a shared pathological factor across all conditions, crucially driving PCOS progression. These results suggested the distinct herbal patterns and clusters revealed both therapeutic commonalities and condition-specific strategies.

Keywords: Data mining; Insulin resistance; Phlegm-dampness; Polycystic ovary syndrome; Preventing the development of existing diseases

Resumen: Este estudio empleó minería de datos para analizar casos clínicos de síndrome de ovario poliquístico (SOP), SOP con resistencia a la insulina (SOP-RI) y resistencia a la insulina (RI), examinando sus correlaciones y evolución patológica. Se estableció un repositorio estandarizado mediante la búsqueda en PubMed y otras bases de datos médicas de casos clínicos de SOP, SOP-RI y RI. La minería de datos identificó 1,427 casos de SOP (364 medicamentos herbales chinos; fármacos de alta frecuencia: Radix *Angelicae Sinensis*; pares clave: *Fructus Rubi → Semen Cuscutae*; 5 agrupaciones de prescripciones), 109 casos de SOP-RI (156 medicamentos herbales chinos; fármacos de alta frecuencia: Poria; pares clave: *Rhizoma Chuanxiong → Radix Angelicae Sinensis*; 4 agrupaciones de prescripciones) y 68 casos de RI (125 medicamentos herbales chinos; fármacos de alta frecuencia: Poria; pares clave: *Radix Bupleuri → Poria*; 4 agrupaciones de prescripciones). El análisis también identificó el "Flema (humedad)" como un factor patológico común en todas las condiciones, siendo crucial en la progresión del SOP. Estos resultados sugieren que los patrones y agrupaciones herbales revelan tanto similitudes terapéuticas como estrategias específicas para cada condición.

Palabras clave: Minería de datos; Resistencia a la insulina; Flema-humedad; Síndrome de ovario poliquístico; Prevención del desarrollo de enfermedades existentes

LIST OF ABBREVIATIONS
polycystic ovary syndrome (PCOS)
polycystic ovary syndrome concomitant with insulin resistance (PCOS-IR)
insulin resistance (IR)
Traditional Chinese medicine (TCM)
China National Knowledge Infrastructure (CNKI)
China Biology Medicine (CBM)

INTRODUCTION
Polycystic ovary syndrome (PCOS) is one of the most prevalent reproductive and metabolic disorders globally, with reported prevalence ranging between 8% to 13% (Lim *et al.*, 2019). Its profound impact on menstrual disorders and female infertility underscores its significance as a compelling area of research both domestically and internationally. Studies that have been previously conducted indicate a notable overlap of 44% to 70% between PCOS and insulin resistance (IR), a central aspect in the pathophysiology of patients with PCOS (Diamanti-Kandarakis & Dunaif, 2012). IR increases androgen secretion among patients with PCOS, hinders follicular development, and increases the risk of diverse metabolic complications including endometrial diseases, abnormalities in glucose and lipid metabolism, fatty liver , and long-term cardiovascular disease (Nestler *et al.*, 1998; Munir *et al.*, 2004; Dumesic *et al.*, 2007; Brothers *et al.*, 2010; Qi *et al.*, 2018; Ali & Guidozzi, 2020). Therefore, timely recognition, assessment, and management of IR are essential in delaying the progression of PCOS and reducing the risk of long-term metabolic complications. Currently, metformin is primarily used in Western medicine to treat PCOS-IR by increasing the translocation of the glucose transporters GLUT1 and GLUT4 to cell membranes, activating the AMPK signaling pathway, and reconstructing the role of endogenous insulin-sensitizing molecules, such as adiponectin, in endometrial tissues under pathological conditions; however, its efficacy is tempered by prevalent gastrointestinal side effects, along with concerns regarding its long-term impact on offspring and postnatal development, limiting its clinical use to a certain extent due to the lack of evidence-based medical data on its long-term effects on offspring and postnatal development (Guo *et al.*, 2016; Anonimous, 2018; Given *et al.*, 2018; Hanem *et al.*, 2018; Liu *et al.*, 2020; Zhao *et al.*, 2023). Traditional Chinese medicine (TCM) emerges as a promising avenue for PCOS management, supported by several studies demonstrating its ability to modulate reproductive endocrine function, enhance IR, restore ovarian homeostasis, facilitate ovulation, and enhance fertility prospects. Also, TCM interventions are characterized by their safety profile and limited adverse effects (Ding *et al.*, 2014; Deng *et al.*, 2019; Wang & Liang, 2019; Xu & Zhou, 2020). This study constitutes a systematic analysis of clinical cases of PCOS, PCOS-IR, and IR as treated by distinguished TCM practitioners in contemporary times. Through meticulous examination of their treatment protocols, the objective of this study was to assess the correlation, differences, and evolution among these conditions. Such research endeavors are significant in enhancing the understanding of the disease, refining TCM treatment, and interpreting the essence of disease prevention and intercepting its further progress.

MATERIAL AND METHODS
Data and methods
Data sources
Computer searches were conducted on five major medical databases: China National Knowledge Infrastructure (CNKI), China Biology Medicine (CBM) disc, Wanfang Database, VIP Chinese Scientific and Technical Journal Database (VIP), and PubMed. A combination of subject term search and basic search methods were used, with the search time frame set from the inception of the databases to January 31, 2020.

The Chinese search formula for PCOS was: (Title: "polycystic ovary syndrome" or "PCOS") AND (Title: "case study" or "experience" or "prescription" or "case" or "treatment" or "case"); the English search formula was: (polycystic ovary syndrome [MeSH Terms]) AND (Chinese phytotherapy [Text Word]). A total of 857 relevant documents were retrieved. Following removal of duplicates, initial screening, rescreening, and supplementation, 330 articles met the criteria and were ultimately included.

The Chinese search formula for PCOS-IR was: (Title: "polycystic ovary syndrome" or "PCOS") AND (Title: "insulin resistance" or "hyperinsulinemia") AND (Text: "case study" or "experience" or "prescription" or "case" or "treatment" or "case"); the English search formula was: (polycystic ovary syndrome [MeSH Terms]) AND ((insulin resistance [MeSH Terms]) OR (hyperinsulinemia [MeSH Terms])) AND (Chinese phytotherapy [Text Word]). A total of 122 articles were finally retrieved. Following removal of duplicates, initial screening, rescreening, and supplementation, 28 articles met the criteria and were

finally included.

The Chinese search formula for IR was: (Title: "Insulin resistance" or "Hyperinsulinemia" or "IR") AND (Title: "case study" or "experience" or "prescription" or "case" or "treatment" or "case"); the English search formula was: ((insulin resistance [MeSH Terms]) OR (hyperinsulinemia [MeSH Terms])) AND (Chinese phytotherapy [Text Word]). A total of 106 articles were retrieved. After removing duplicate, initial screening, rescreening, and supplementation, 17 articles met the criteria and were finally included. The specific retrieval and screening process is illustrated in Supplementary Figure No. 1.

Inclusion criteria
① Chinese medicine case studies, case reports, academic experiences, medical theories, and medical discourse were listed in the test case. ② Western medicine diagnoses in the cases included PCOS, IR, or hyperinsulinemia, and both of the above-mentioned diseases. ③ Cases contained symptoms, tongue and pulse analysis, prescriptions, and the composition of Chinese medicine used in the initial diagnosis. ④ If a follow-up medical case revealed changes in symptoms, evidence type, treatment methods, prescriptions, or medication from the previous case, it was recorded as an independent medical case.

Exclusion criteria
① Literature reviews, case reports, animal experiments, and clinical studies were excluded. ② Cases lacking essential information such as symptoms, tongue and pulse analysis, prescriptions, and so on, were excluded. ③ Cases using acupuncture, auricular acupuncture points, dietary therapies, and poultices alone were omitted. ④ Duplicate cases were identified and only the first published instance was retained. ⑤ Abstracts of conference papers inaccessible for full-text retrieval were excluded.

Database construction
Case screening adhered rigorously to the predefined inclusion and exclusion criteria. Relevant prescription details from the selected cases were systematically collected, categorized, and entered into Microsoft Excel 2016 software to construct the database encompassing PCOS, PCOS-IR, and IR medical cases. To uphold data precision, two individuals independently undertook data entry tasks, with the results subsequently subjected to cross-validation upon completion.

Data normalization
Normalized Chinese medicine terminology adhered to the *Chinese Medicine Clinical Case Data Mining Research Data Normalization Standard* for practical implementation (Zhongyi Linchuang Shuju Wajue Yanjin Shuju Guifanhua Biaozhun, 2019). Drug standardization was conducted in accordance with the 2015 edition of the *Pharmacopoeia of the People's Republic of China and the Chinese Pharmacopoeia* (Gao, 2015; Zhonghua Renmin Gongheguo Yaodian, 2015). Examples of this normalization process include: ① Assigning Chinese medicine aliases and common names, such as "Qi Zi" classified as "Gou Qi Zi (*Fructus Lycii*)", and "Xian Ling Pi" as "Yin Yang Huo (*Epimedium* Herb)"; ② Clarifying Chinese medicine concoction or origin names, for instance, "Quan Dang Gui" and "Dang Gui Shen" categorized as "Dang Gui (*Radix Angelicae Sinensis*)", "Chuan Niu Xi" as "*Radix Achyranthis Bidentatae*", and so forth. The data normalization procedure endeavored to uphold the original intentions of the medical practitioners.

Data analysis platform
The data underwent analysis using the data association analysis platform (XMiner V1.0) within the data processing framework of the Medcase V3.8 data record mining system (Yang *et al*., 2016; Su *et al*., 2019). Frequency statistics methodology was used to analyze the frequency of drugs within the cases. Subsequently, reasonable support and confidence levels were established based on the number of formulas encompassed in the cases and pertinent pre-determined parameters. The Apriori algorithm was used to derive association rules, thereby facilitating an examination of dispensing patterns and identification of core drugs within the case formulations. Also, clustering analysis methodology was used to reveal grouping patterns, thereby deriving core combinations and new prescriptions.

RESULTS
General information
The PCOS database comprised 330 articles, encompassing 190 medical practitioners and involving 382 patients, totaling 1,427 consultations. It contained 364 types of TCMs with a cumulative frequency of 21,083 administrations. The PCOS-IR database included 28 articles, involving 22 medical practitioners and 30 patients, which amounted to 109 consultations. It comprised 156 types of TCMs with a cumulative frequency of 1,275 administrations.

Finally, the IR database consisted of 17 articles, with 17 medical practitioners and 22 patients, resulting in 68 consultations. It incorporated 125 types of traditional Chinese medicine, administered cumulatively 852 times (Table No. 1).

Table No. 1
Database Information

Name of the Medical Case Database	Literature: Total number of cases.	Medical Practitioners Total Number of Cases	Patient population and number of cases	Number of Consultations	Chinese Medicine Quantity	Chinese Medicine Total Frequency
PCOS Database	330	190	382	1427	364	21083
PCOS-IR Database	28	22	30	109	156	1275
IR Database	17	17	22	68	125	852

Frequency statistics

The TCMs were ranked based on their frequency of use, and the top 6 medicines with the highest frequency of use in each database were as follows: In the PCOS database: *Radix Angelicae Sinensis*, *Semen Cuscutae*, *Poria*, *Rhizoma Cyperi*, *Rhizoma Atractylodis Macrocephalae*, and *Radix Salviae Miltiorrhizae*. Notably, *Radix Angelicae Sinensis* exhibited the highest frequency of use, accounting for 56.06% of administrations. In the PCOS-IR database: *Poria*, *Radix Angelicae Sinensis*, *Rhizoma Cyperi*, *Semen Cuscutae*, *Rhizoma Atractylodis Macrocephalae*, and *Rhizoma Atractylodis*. Poria emerged as the most frequently used medicine, constituting 52.34% of administrations.

In the IR database: *Poria*, *Radix Codonopsis*, *Rhizoma Atractylodis*, *Radix Glycyrrhizae*, *Radix Bupleuri*, and *Rhizoma Coptidis*. *Poria* was again the most commonly employed medicine, accounting for 53.19% of administrations (Table No. 2).

Table No. 2
Distribution of high frequency drugs

Sequence	PCOS Database			PCOS-IR Database			IR Database		
	Drugs	Frequency	Frequency (%)	Drugs	Frequency	Frequency (%)	Drugs	Frequency	Frequency (%)
1	*Radix Angelicae Sinensis*	800	56.06	*Poria*	56	52.34	*Poria*	25	53.19
2	*Semen Cuscutae*	710	49.75	*Radix Angelicae Sinensis*	46	42.99	*Radix Codonopsis*	21	44.68
3	*Poria*	659	46.18	*Rhizoma Cyperi*	44	41.12	*Rhizoma Atractylodis*	21	44.68
4	*Rhizoma Cyperi*	619	43.38	*Semen Cuscutae*	40	37.38	*Radix Glycyrrhizae*	19	40.43
5	*Rhizoma Atractylodis Macrocephalae*	554	38.82	*Rhizoma Atractylodis Macrocephalae*	40	37.38	*Radix Bupleuri*	18	38.30

6	Radix Salviae Miltiorrhizae	550	38.54	Rhizoma Atractylodis	38	35.51	Rhizoma Coptidis	18	38.30
7	Rhizoma Chuanxiong	513	35.95	Radix Astragali	36	33.64	Radix Astragali	16	34.04
8	Radix Glycyrrhizae	508	35.60	Radix Salviae Miltiorrhizae	33	30.84	Radix Paeoniae Rubra	16	34.04
9	Radix Rehmanniae Preparata	496	34.76	Pericarpium Citri Reticulatae	32	29.91	Radix Angelicae Sinensis	15	31.91
10	Radix Paeoniae Alba	478	33.50	Rhizoma Dioscoreae	30	28.04	Cortex Moutan	14	29.79
11	Radix Achyranthis Bidentatae	440	30.83	Herba Epimedii	30	28.04	Radix Rehmanniae	13	27.66
12	Herba Epimedii	437	30.62	Radix Glycyrrhizae	26	24.30	Herba Epimedii	13	27.66
13	Pericarpium Citri Reticulatae	413	28.94	Radix Codonopsis	26	24.30	Rhizoma Atractylodis Macrocephalae	13	27.66
14	Rhizoma Dioscoreae	407	28.52	Herba Taxilli	25	23.36	Radix Puerariae	13	27.66
15	Radix Dipsaci	393	27.54	Rhizoma Pinelliae	24	22.43	Radix Scutellariae	13	27.66
16	Fructus Corni	363	25.44	Radix Rehmanniae Preparata	24	22.43	Semen Cuscutae	12	25.53
17	Herba Leonuri	358	25.09	Radix Paeoniae Alba	24	22.43	Pericarpium Citri Reticulatae	12	25.53
18	Rhizoma Atractylodis	352	24.67	Rhizoma Chuanxiong	24	22.43	Rhizoma Alismatis	12	25.53
19	Fructus Lycii	344	24.11	Fructus Rubi	21	19.63	Rhizoma Zingiberis	12	25.53
20	Radix Astragali	306	21.44	Caulis Spatholobi	21	19.63	Rhizoma Cyperi	11	23.40

Association rules

The PCOS database was configured with a threshold of ≥ 10% support and ≥ 65% confidence. The top 3 drug pairs exhibiting the highest confidence were *Fructus Rubi→Semen Cuscutae*, *Rhizoma Chuanxiong→Radix Angelicae Sinensis*, and *Fructus Lycii→Semen Cuscutae*. Notably, among the top 20 association rules, *Radix Angelicae Sinensis* featured prominently in 11 cases, indicating its widespread use in PCOS treatment, consistent with its high frequency of use. In the PCOS-IR database, the criteria were set at ≥ 10% support and ≥ 75% confidence. The top 3

drug pairs with the highest confidence were *Rhizoma Chuanxiong→Radix Angelicae Sinensis*, *Rhizoma Alismatis→Poria*, and *Herba Cistanche→Semen Cuscutae*. Among the top 20 association rules, *Radix Bupleuri* was notably prevalent, indicating its frequent inclusion in drug combinations and indicating its key role in PCOS-IR treatment. Finally, in the IR database, the criteria were set at ≥ 20% support and ≥ 80% confidence. The top 3 drug pairs exhibiting the highest confidence were *Radix Bupleuri*→Poria, *Radix Puerariae→Radix Glycyrrhizae*, and *Rhizoma Atractylodis Macrocephalae→Poria*. Among the top 20 association rules, Poria emerged as the most frequently encountered drug in various combinations, underscoring its prominence in IR treatment (Table No. 3).

Table No.3
Set of association rules within the drug set

Sequence	PCOS Database			PCOS-IR Database			IR Database		
	Rule set	Support (%)	Confidence (%)	Rule set	Support (%)	Confidence (%)	Rule set	Support (%)	Confidence (%)
1	*Fructus Rubi→Semen Cuscutae*	12.81	86.89	*Rhizoma Chuanxiong→ Radix Angelicae Sinensis*	25.00	100	*Radix Bupleuri→ Poria*	41.86	100
2	*Rhizoma Chuanxiong→Radix Angelicae Sinensis*	30.99	84.41	*Rhizoma Alismatis→Poria*	15.62	100	*Radix Puerariae→ Radix Glycyrrhizae*	30.23	100
3	*Fructus Lycii→Semen Cuscutae*	19.90	81.29	*Herba Cistanche→Semen Cuscutae*	12.50	92.31	*Rhizoma Atractylodis Macrocephalae →Poria*	30.23	100
4	*Flos Carthami→Radix Angelicae Sinensis*	12.31	80.37	*Radix Bupleuri→ Pericarpium Citri Reticulatae*	11.46	91.67	*Radix Puerariae→ Poria*	30.23	100
5	*Pericarpium Citri Reticulatae→Poria*	21.90	74.63	*Radix Bupleuri→Poria*	11.46	91.67	*Radix Puerariae→ Radix Bupleuri*	27.91	92.31
6	*Radix Achyranthis Bidentatae→Radix Angelicae Sinensis*	22.48	73.02	*Radix Paeoniae Rubra→Poria*	11.46	91.67	*Radix Scutellariae→ Rhizoma Coptidis*	27.91	92.31
7	*Radix Rehmanniae Preparata→Radix Angelicae Sinensis*	25.05	72.02	*Semen Cuscutae→Semen Cuscutae*	19.79	90.48	*Radix Rehmanniae→ Rhizoma Atractylodis*	27.91	92.31
8	*Rhizoma Atractylodis→Poria*	17.97	71.31	*Rhizoma Pinelliae→ Pericarpium Citri Reticulatae*	20.83	83.33	*Pericarpium Citri Reticulatae→ Radix Angelicae Sinensis*	25.58	91.67

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9	Herba Leonuri→Radix Angelicae Sinensis	17.32	70.76	Radix Rehmanniae Preparata→Radix Angelicae Sinensis	20.83	83.33	Radix Salviae Miltiorrhizae→Cortex Moutan	23.26	90.91
10	Fructus Lycii→Radix Angelicae Sinensis	17.25	70.47	Radix Bupleuri→Rhizoma Alismatis	10.42	83.33	Radix Codonopsis→Poria	44.19	90.48
11	Rhizoma Pinelliae→Poria	15.03	69.31	Radix Bupleuri→Radix Glycyrrhizae	10.42	83.33	Radix Rehmanniae→Rhizoma Coptidis	25.58	84.62
12	Radix Bupleuri→Radix Angelicae Sinensis	12.67	68.87	Radix Bupleuri→Radix Angelicae Sinensis	10.42	83.33	Herba Epimedii→Radix Glycyrrhizae	25.58	84.62
13	Rhizoma Cyperi→Radix Angelicae Sinensis	30.28	68.67	Herba Taxilli→Semen Cuscutae	20.83	80.00	Radix Puerariae→Radix Codonopsis	25.58	84.62
14	Radix Codonopsis→Rhizoma Atractylodis Macrocephalae	13.24	67.77	Rhizoma Alismatis→Radix Angelicae Sinensis	12.50	80.00	Radix Glycyrrhizae→Radix Codonopsis	37.21	84.21
15	Herba Lycopi→Radix Angelicae Sinensis	13.31	67.64	Fructus Crataegi→Rhizoma Atractylodis	15.62	78.95	Radix Glycyrrhizae→Poria	37.21	84.21
16	Radix Paeoniae Rubra→Radix Angelicae Sinensis	14.39	67.22	Pericarpium Citri Reticulatae→Poria	26.04	78.12	Radix Bupleuri→Radix Glycyrrhizae	34.88	83.33
17	Radix Morindae Officinalis→Semen Cuscutae	12.17	66.93	Rhizoma Atractylodis Macrocephalae→Poria	32.29	77.5	Pericarpium Citri Reticulatae→Poria	23.26	83.33
18	Radix Dipsaci→Semen Cuscutae	18.68	66.92	Herba Cistanche→Fructus Rubi	10.42	76.92	Rhizoma Alismatis→Poria	23.26	83.33
19	Herba Epimedii→Semen Cuscutae	20.69	66.28	Rhizoma Cyperi→Rhizoma Cyperi	10.42	76.92	Radix Paeoniae Alba→Semen Cuscutae	20.93	81.82
20	Radix Paeoniae Alba→Radix Angelicae Sinensis	22.26	65.34	Rhizoma Atractylodis→Poria	30.21	76.32	Radix Trichosanthis→Radix Rehmanniae	20.93	81.82

Cluster analysis
PCOS database
A systematic clustering methodology was used to analyze the 51 HF drugs for PCOS (frequency > 100), the 47 HF drugs for PCOS-IR (frequency > 7), and the 39 HF drugs for IR (frequency > 4). Clusters were derived from the clustering outcomes to ascertain their directions, and a cluster analysis dendrogram was generated (Figure No. 1; Figure No. 2 and Figure No. 3). Also, the respective types of evidence for each prescription cluster were summarized based on clinical experience (Table No. 4, Table No. 5, Table No. 6).

DISCUSSION
Traditional Chinese Medicine (TCM) does not have a specific term for "PCOS"; however, based on clinical symptoms, PCOS can be categorized under conditions such as "amenorrhea," "infertility," "late menstruation," and "scant menstruation." As early as the records in "Danxi's Heart Method," the description of "phlegm mixed with blood stasis, reversing into a nest-like mass" known as "ke nang" is speculated to be the earliest description of PCOS in TCM. Modern TCM considers that there is a dysfunction of the kidney, liver, and spleen, followed by the obstruction of the penetrating and conception vessels and the uterus by tangible evils such as phlegm dampness and blood stasis. These two factors interact as causes and effects on the body, leading to the development of PCOS, with PCOS-IR being more closely related to kidney deficiency, phlegm dampness, and blood stasis (Munir *et al.*, 2004).

The frequency analysis of medicinal drugs shows that among the top 20 high-frequency drugs commonly used are the following 10: *Angelica sinensis* (Dang Gui), *Cuscuta* seed (Tu Si Zi), *Poria* (Fu Ling), *Cyperi Rhizoma* (Xiang Fu), *Atractylodes macrocephala* (Bai Zhu), *Glycyrrhiza uralensis* (Gan Cao), *Epimedium* (Yin Yang Huo), *Citrus* peel (Chen Pi), *Atractylodes lancea* (Cang Zhu), and *Astragalus membranaceus* (Huang Qi). The high consistency in the use of these drugs reflects the close correlation of their underlying pathological mechanisms. *Angelica sinensis* nourishes and activates blood circulation, *Cuscuta* seed and *Epimedium* tonify the kidney and assist yang, *Poria* and *Atractylodes macrocephala* strengthen the spleen and drain dampness, *Citrus* peel and *Atractylodes lancea* strengthen the spleen, dry dampness, and transform phlegm, *Cyperi Rhizoma* regulates qi, relieves depression, and regulates menstruation, Astragalus membranaceus supplements qi and assists in transforming phlegm and dampness, and *Glycyrrhiza uralensis* supplements the spleen and harmonizes other medicinals. Together, they achieve the effects of tonifying the kidney and spleen, resolving dampness and phlegm, and activating blood circulation. Based on the prescription, it is inferred that "kidney and spleen deficiency with interplay of phlegm and blood stasis" is a common syndrome among the three. "The kidney is the root of phlegm production, and the spleen is the source of phlegm," as stated in "Jingyue Quanshu Phlegm Drink," "Although all five organs can produce phlegm, none can do so without involving the spleen and kidney." This indicates that "phlegm dampness" is a common pathological product and the core pathogenic factor for PCOS, PCOS-IR, and IR, which highly coincides with the Western medical understanding that "IR-centered metabolic disorders are the core pathophysiological basis for the occurrence and development of PCOS" (Anonimous, 2024).

The association rule analysis results show that the basic medicinal pairs for treating PCOS include *Rubus chingii* → *Cuscuta* seed, *Lycium barbarum* → *Cuscuta* seed, *Ligusticum chuanxiong* → *Angelica sinensis*, *Carthamus tinctorius* → *Angelica sinensis*, and *Rehmannia glutinosa* → *Angelica sinensis*. These pairs are believed to have the effects of nourishing the kidney and essence, aiding yang, and activating blood circulation and qi. Based on the knowledge of classical prescriptions, it is inferred that these combinations may be modifications of the Five-Seed Yi Zhong Wan and Tao Hong Si Wu Tang formulas.
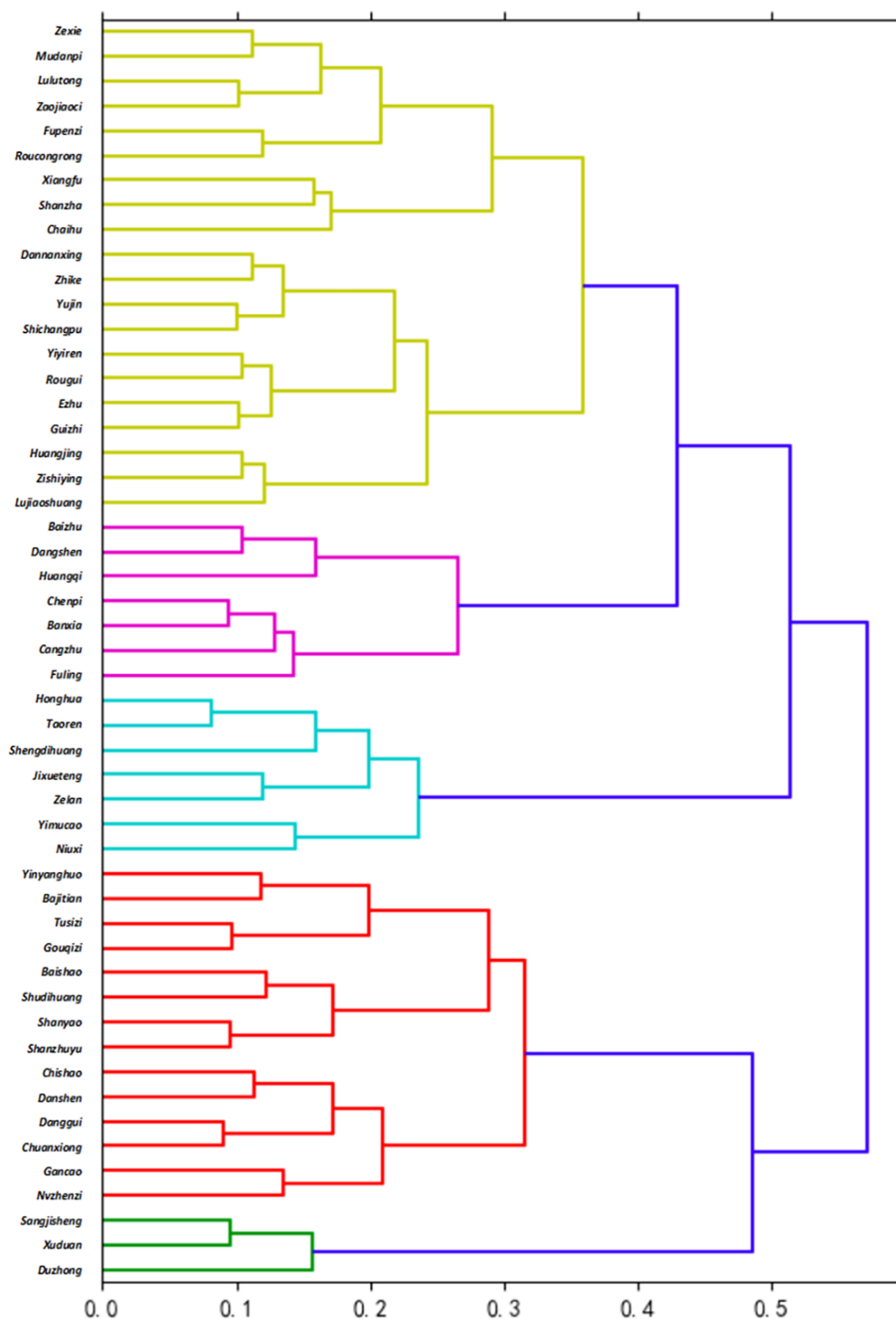
Figure No. 1
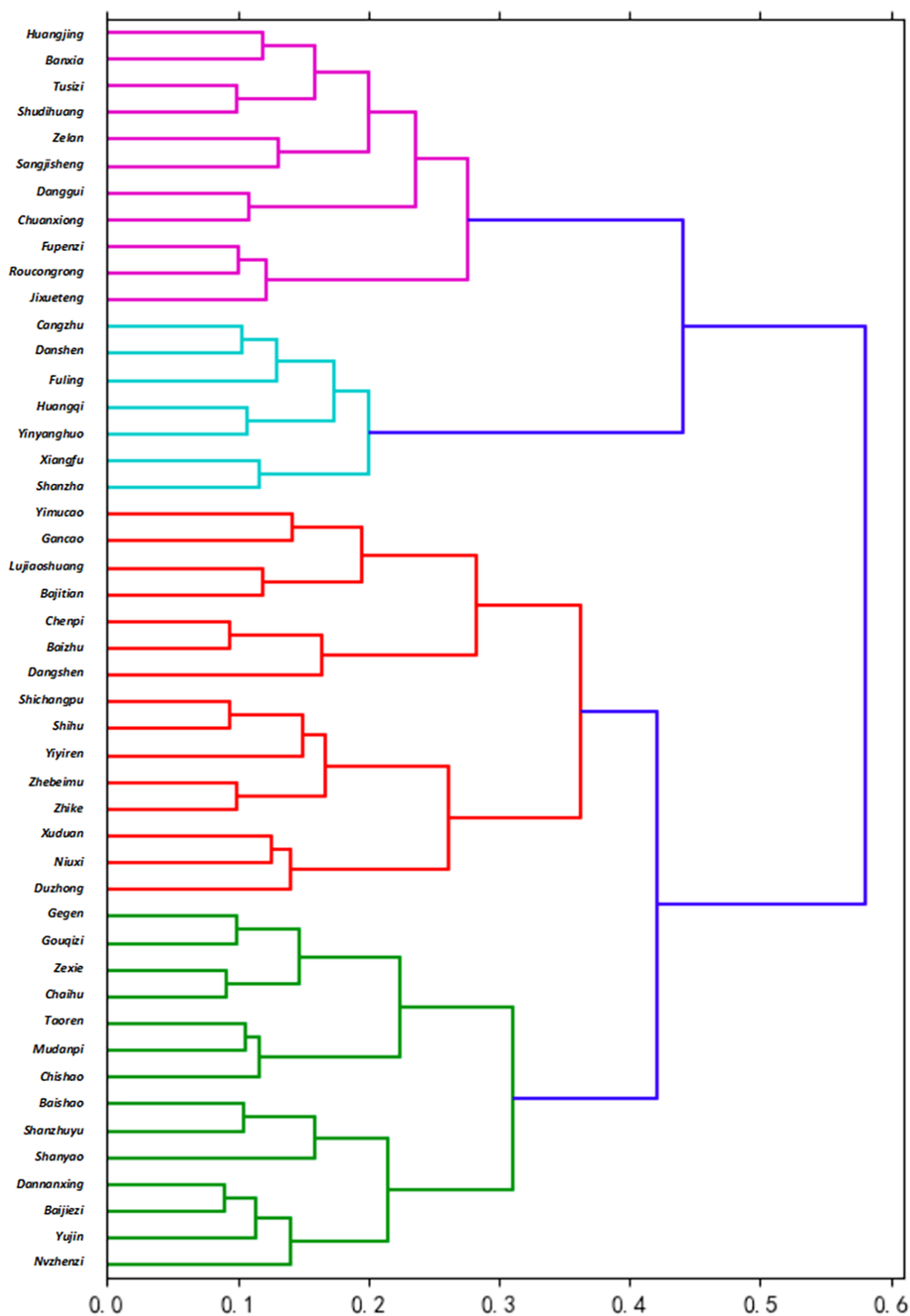**Tree diagram of PCOS high frequency drug clustering analysis**

Figure No. 2
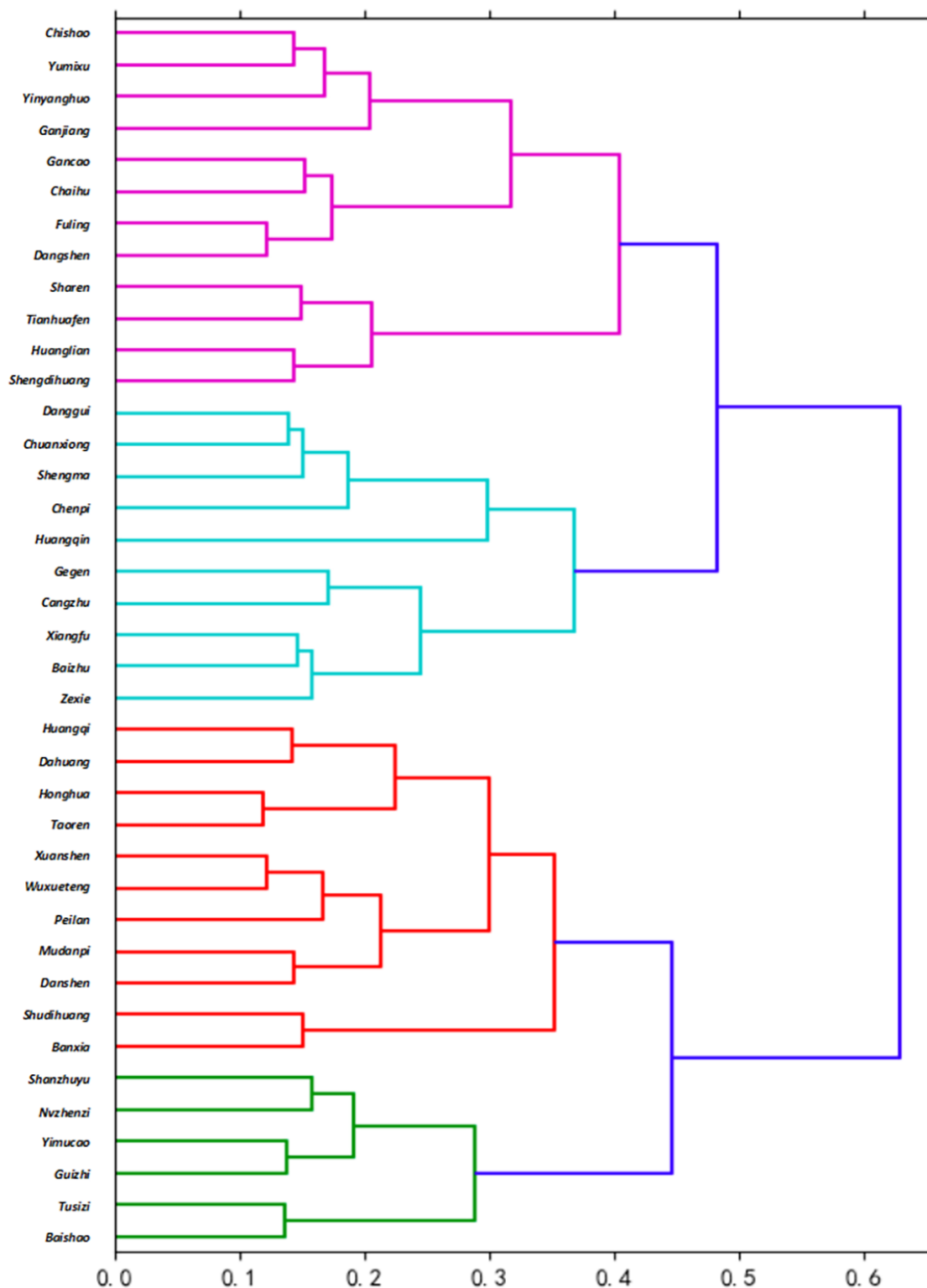**A tree diagram of the PCOS-IR HF drug clustering analysis**

Figure No. 3
A tree diagram of IR high frequency drug clustering analysis

Table No. 4
PCOS high-frequency drug system clustering (frequency amplitude > 100)

Classification	Cluster	Efficacy	Applicable evidence
1st	Herba Taxilli, Radix Dipsaci, Herba Taxilli	Reinforce the liver and kidneys. Warm and tonify the kidney yang.	Kidney yang defciency
2nd	Fructus Ligustri Lucidi, Fructus Corni, Rhizoma Dioscoreae, Radix Rehmanniae Preparata, Fructus Lycii, Semen Cuscutae, Radix Morindae Officinalis, Herba Epimedii, Radix Paeoniae Alba Rhizoma Chuanxiong, Radix Angelicae Sinensis, Radix Salviae Miltiorrhizae, Radix Paeoniae Rubra, Radix Glycyrrhizae	Nourish yin and strengthen kidneys. Tonify and circulate blood.	Kidney defciency and blood stasis
3rd	Semen Persicae, Flos Carthami, Radix Achyranthis Bidentatae, Herba Leonuri, Herba Lycopi, Caulis Spatholobi, Radix Rehmanniae	Circulate blood and overcome stasis. nourish blood and regulate menstruation	Blood stasis and amenorrhoea
4th	Poria, Radix Codonopsis, Rhizoma Atractylodis Macrocephalae, Rhizoma Atractylodis, Rhizoma Pinelliae, Pericarpium Citri Reticulatae, Radix Scutellariae	Strengthen the spleen and tonify the qi. Dry the dampness and transform phlegm.	Spleen deficiency with phlegm dampness
5th	Cornu Cervi Degelatinatum, Fluoritum, Rhizoma Polygonati, Ramulus Cinnamomi, Curcuma Zedoary, Cortex Cinnamomi, Semen Coicis, Rhizoma Acori Graminei, Radix Curcumae, Fructus Aurantii Arisaema Cum Bile, Radix Bupleuri, Fructus Crataegi, Rhizoma Cyperi, Herba Cistanche, Fructus Rubi, Chinese Honeylocust Spine, Beautiful Sweetgum Fruit, Cortex Moutan, Rhizoma Alismatis	Warm Yang and transform phlegm. Transform stasis and unlock collaterals.	Kidney deficiency and phlegm stasis

The basic medicinal pairs for treating PCOS-IR include *Ligusticum chuanxiong → Angelica sinensis*, *Cistanche deserticola → Cuscuta* seed, *Alisma plantago-aquatica → Poria*, *Atractylodes macrocephala → Poria*, and *Atractylodes lancea → Poria*. These pairs are believed to have the effects of nourishing the kidney and yang, activating blood circulation, strengthening the spleen, and resolving dampness and phlegm. Based on the knowledge of classical prescriptions, it is inferred that these combinations may be modifications of the Cistanche Tu Si Zi Wan and Fu Ling Bai Zhu Tang formulas.

The basic medicinal pairs for treating IR include *Bupleurum chinense → Poria*, *Atractylodes macrocephala → Poria*, *Pueraria lobata →* Glycyrrhiza uralensis, *Pueraria lobata → Poria*, and *Codonopsis pilosula → Poria*. These pairs are believed to have the effects of strengthening the spleen, benefiting qi, resolving dampness, clearing heat, and quenching thirst. Based on the knowledge of classical prescriptions, it is inferred that these combinations may be modifications of the Si Jun Zi Tang and Chaihu Ge Gen Tang formulas. Among them, "*Citrus reticulata → Poria*" is a highly

associated rule common to all three, indicating that this pair is the most frequently used in the treatment of the three diseases. *Citrus reticulata*, belonging to the qi-regulating herbs, has a sweet and spicy taste and a warm nature, which can regulate qi, strengthen the spleen, and dry dampness and transform phlegm. Poria, belonging to the diuretic and swelling-reducing herbs, has a sweet and light taste and a neutral nature, which can promote diuresis, resolve dampness, strengthen the spleen, and calm the mind. The combination of *Citrus reticulata* and *Poria* can regulate the flow of qi, strengthen the spleen, and promote the metabolism of water and fat. Studies have shown that the main active component of *Citrus reticulata*, nobiletin (NOB), has protective effects against metabolic and reproductive disturbances in letrozole-induced polycystic ovary syndrome in rats (Ijaz et al., 2023). The main active component of *Poria cocos*, Pachymic acid, may improve insulin resistance and suppress inflammatory responses in PCOS rats by inhibiting the HMGB1/RAGE signaling pathway (Tang *et al*., 2024). Poria cocos oligosaccharides (PCO), may be used as a novel prebiotic in the treatment of glucolipid disorders by reshaping the intestinal bacteria structure (Zhu *et al*., 2022). By inferring the syndrome from the medicine, it further confirms that "phlegm-dampness" is a common pathological product and the core pathogenic factor for all three, which is completely consistent with the conclusions suggested by the high-frequency drug distribution list.

Table No. 5
PCOS-IR clustering of high-frequency drug systems (frequency amplitude > 7)

Cluster class	Cluster value	Efficacy	Applicable evidence
1st	Fructus Ligustri Lucidi, Radix Curcumae, Semen brassicae, Arisaema Cum Bile, Rhizoma Dioscoreae, Fructus Corni, Radix Paeoniae Alba, Radix Paeoniae Rubra, Cortex Moutan, Semen Persicae, Radix Bupleuri, Rhizoma Alismatis, Fructus Lycii, Radix Puerariae	Reinforce the liver and kidneys Circulate blood and transform phlegm	Liver and kidney yin deficiency Comprehensive phlegm stasis
2nd	Eucommia Bark, Radix Achyranthis Bidentatae, Radix Dipsaci, Fructus Aurantii, Bulbus Fritillariae Thunbergii, Semen Coicis, Herba Dendrobii, Rhizoma Acori Graminei, Radix Codonopsis Rhizoma Atractylodis Macrocephalae, Pericarpium Citri Reticulatae, Radix Morindae Officinalis, Cornu Cervi Degelatinatum, Radix Glycyrrhizae, Herba Leonuri	Warm the kidney and strengthen the spleen Transform the phlegm and reduce stasis	Kidney and yang deficiency Damp phlegm with stasis
3rd	Poria, Rhizoma Atractylodis, Fructus Crataegi, Rhizoma Cyperi, Herba Epimedii, Radix Astragali, Radix Salviae Miltiorrhizae	Strengthen the spleen and toifye the qi. Transform phlegm and improve blood circulation.	Spleen deficiency Damp phlegm with stasis
4th	Caulis Spatholobi, Herba Cistanche, Fructus Rubi, Rhizoma Chuanxiong, Radix Angelicae Sinensis, Herba Taxilli, Herba Lycopi, Radix Rehmanniae Preparata Semen Cuscutae, Rhizoma Pinelliae, Rhizoma Polygonati	Tonic for the kidneys and supports the yang Circulate blood and overcome stasis.	Kidney yang deficiency Blood stasis

Table No. 6
IR high-frequency drug system clustering (frequency amplitude > 4)

Cluster class	Cluster value	Efficacy	Applicable evidence
1st	Radix Rehmanniae, Rhizoma Coptidis, Radix Trichosanthis, Fructus Amomi, Radix Codonopsis, Poria, Radix Bupleuri, Radix Glycyrrhizae Rhizoma Zingiberis, Herba Epimedii, Corn Stigma, Radix Paeoniae Rubra	Warm the middle jiao and strengthen the spleen Clear heat and transform dampness in three jiao	Yin deficiency of the spleen and stomach Interior retention of damp-heat
2nd	Rhizoma Alismatis, Rhizoma Atractylodis Macrocephalae, Rhizoma Cyperi, Rhizoma Atractylodis, Radix Puerariae, Radix Scutellariae, Pericarpium Citri Reticulatae, Rhizoma Cimicifugae, Rhizoma Chuanxiong, Radix Angelicae Sinensis	Tonify the spleen, increase yang, and transform dry dampness into phlegm.	Spleen deficiency Phlegm and damp stasis
3rd	Rhizoma Pinelliae, Radix Rehmanniae Preparata, Radix Salviae Miltiorrhizae, Cortex Moutan, Fortune Eupatorium Herb, Gymnema sylvestre, Figwort Root, Semen Persicae, Flos Carthami, Radix et Rhizoma Rhei, Radix Astragali	Circulate blood and overcome stasis. Remove turbidity and detoxify poison.	Blood stasis Muddled and poisonous substance within
4th	Radix Paeoniae Alba, Semen Cuscutae, Ramulus Cinnamomi, Herba Leonuri, Fructus Ligustri Lucidi, Fructus Corni	Reinforce the liver and kidneys. Warm the passages to reduce blood stasis and remove it.	Liver and kidney yin deficiency Blood stasis obstructs the veins

The results of the systematic cluster analysis show that: -- all three primarily employ interventions with traditional Chinese medicine formulas, with the core formulas being small composite formulas, and the use of large composite formulas is relatively less frequent. The common core formulas for all three include Poria cocos, Cyperi Rhizoma, Atractylodes macrocephala, *Glycyrrhiza uralensis*, *Citrus reticulata*, *Atractylodes lancea*, *Ligusticum chuanxiong*, *Angelica sinensis*, *Cuscuta* seed, and *Epimedium*. This formula uses *Atractylodes lancea* and *Citrus reticulata* to strengthen the spleen, dry dampness, and transform phlegm, *Cyperi Rhizoma* to soothe the liver and regulate qi, *Poria cocos*, *Atractylodes macrocephala*, and *Glycyrrhiza uralensis* to tonify the spleen and boost energy, *Angelica sinensis* and *Ligusticum chuanxiong* to nourish blood and activate blood circulation, and *Cuscuta* seed and *Epimedium* to tonify the kidney and assist yang. The combination of these herbs works together to strengthen the spleen and kidney, dry dampness and transform phlegm, activate blood circulation and regulate menstruation, is mainly used for spleen and kidney deficiency, and phlegm-dampness with blood stasis syndrome. Based on the knowledge of classical prescriptions, it is inferred that this formula may be a modified version of Cangfu Daotan Wan and its similar formulas, as stated in "Zhu Lin Nu Ke Zheng Zhi, Volume One": "For those with abundant physique and much phlegm and qi deficiency, whose menstruation only comes every few months, Cangfu Liujun Tang is appropriate, along with Cangfu Daotan Wan." In fact, "Cangfu Daotan Tang" is recommended as the most commonly used prescription for PCOS in the latest Chinese guidelines for the integrated treatment of polycystic ovary syndrome (Chinese Society of Integrated Traditional Chinese and Western Medicine, Obstetrics and Gynecology Committee, 2024). Studies have shown that Cangfu Daotan Tang (CFDT) can alleviate mitochondria-dependent granulosa cell apoptosis in a rat model of polycystic ovary syndrome (PCOS) by inhibiting the ASK1/JNK pathway, thereby improving ovarian function (Jiang

et al., 2022). Another study has shown that Modified Cangfu Daotan Decoction ameliorates polycystic ovary syndrome with insulin resistance via nf-κb/lcn-2 signaling pathway in inflammatory microenvironment (Liu *et al.*, 2022). Further clinical research by our team has confirmed that the modified version of Cangfu Daotan can improve insulin resistance levels and BMI in PCOS-IR infertile patients, increase blood perfusion in the endometrium during the implantation phase, significantly increase clinical pregnancy rates, and improve pregnancy outcomes (Xu *et al.*, 2024). In addition, it is worth noting that kidney yang deficiency and blood stasis are also common syndromes in all three, hence warming kidney yang formulas such as Wu Zi Yan Zong Wan, You Gui Wan, and Er Xian Tang, as well as blood-activating and stasis-removing formulas such as Tao Hong Si Wu Tang and Xue Fu Zhu Yu Tang, become another focus of the compound formula.

CONCLUSION

In summary, kidney and spleen deficiency, along with the presence of phlegm and stasis, represent common core symptoms across PCOS, PCOS-IR, and IR. Treatment strategies primarily focus on tonifying the kidney and spleen, resolving dampness and phlegm, promoting blood circulation, and enhancing blood stasis. *Semen Cuscutae*, *Poria*, *Rhizoma Cyperi*, *Rhizoma Atractylodis Macrocephalae*, *Radix Glycyrrhizae*, *Herba Epimedii*, *Pericarpium Citri Reticulatae*, *Rhizoma Atractylodis*, *Rhizoma Chuanxiong*, and *Radix Angelicae Sinensis* emerge as commonly used high-frequency medicines. The addition and subtraction formula of Cangfu Daotan Wan serves as a common core prescription for these conditions. Notably, "phlegm-dampness" emerges as the common core pathological product and pathogenic factor across PCOS, PCOS-IR, and IR, which corresponds with the concept of insulin resistance in Western medicine. This underscores the key role of "phlegm-dampness" in the development of PCOS and highlights the significance of addressing this factor in disease management.

Effective management of "phlegm-dampness" can significantly prevent the progression of PCOS, leveraging the therapeutic potential of traditional Chinese medicine in disease prevention and management. Leveraging medical cases of PCOS, PCOS-IR, and IR, this study uses data mining methods to assess medication usage patterns for these conditions. Such research holds crucial implications for enhancing diagnosis and treatment approaches by Chinese medicine practitioners, optimizing medication strategies, establishing comprehensive management systems to leverage the benefits of traditional Chinese medicine for PCOS, and ultimately reducing the long-term risk of metabolic complications such as diabetes mellitus and other conditions.

Data Availability
The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

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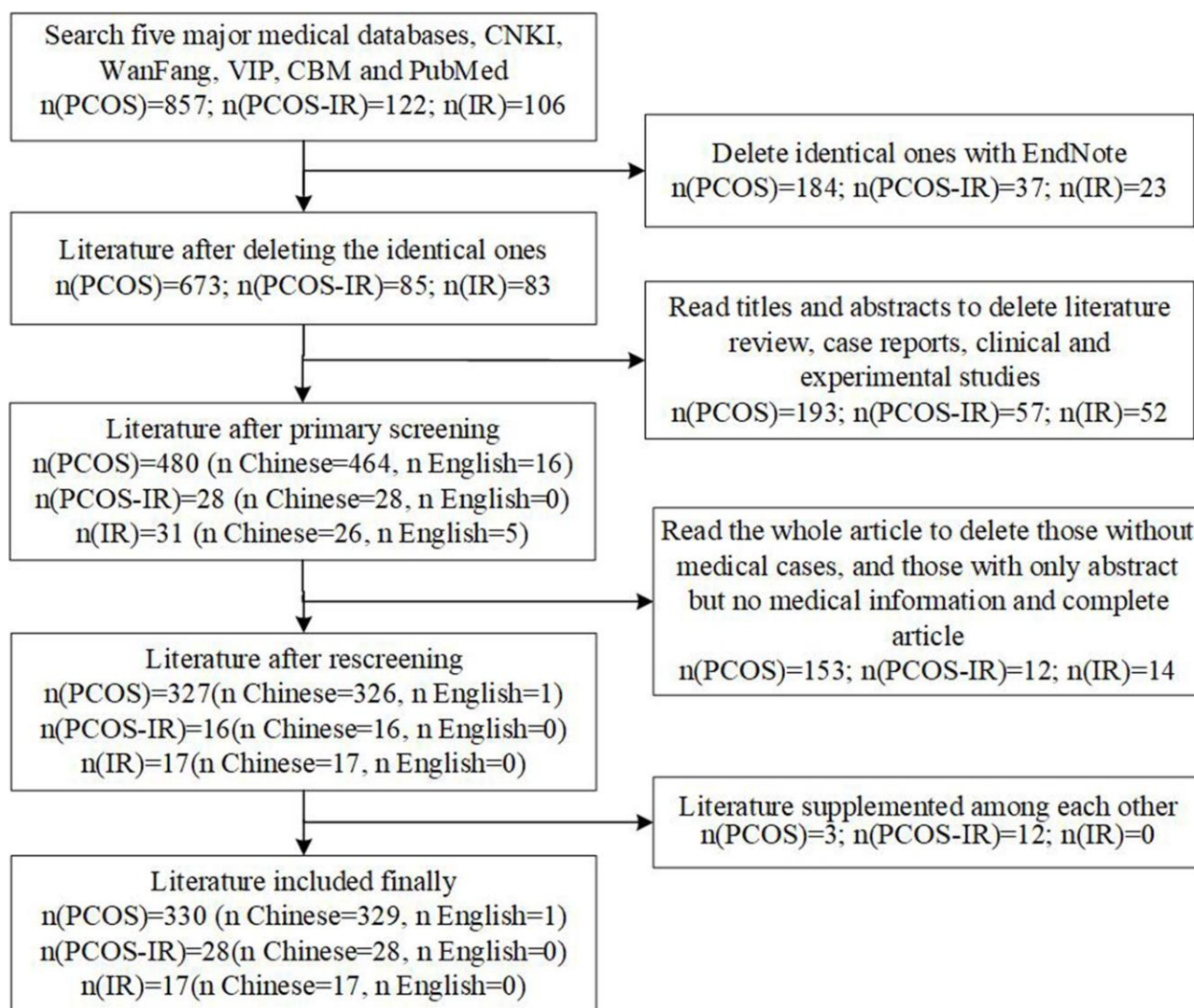
SUPPLEMENTARY MATERIAL

Figure No. S1
Flow chart of literature retrieval

Table No. S1
List of compounds studied

No.	Pinyin Name	Pinyin Name
1	Danggui	Angelicae Sinensis Radix
2	Tusizi	Semen Cuscutae
3	Fuling	Poria
4	Xiangfu	Nutgrass Galingale Rhizome
5	Baizhu	Atractylodis Macrocephalae Rhizoma
6	Cangzhu	Atractylodis Rhizoma
7	Danshen	Salviae Miltiorrhizae Radix et Rhizoma
8	Fupenzi	Rubi Fructus
9	Gouqizi	Lycii Fructus
10	Chuanxiong	Chuanxiong Rhizoma
11	Honghua	Carthami Flos
12	Shudihuang	Rehmanniae Radix
13	Shengdihuang	Rehmanniae Radix
14	Roucongrong	Cistanches Herba
15	Zexie	Alismatis Rhizoma
16	Dangshen	Codonopsis Radix
17	Gancao	Glycyrrhizae Radix et Rhizoma
18	Chaihu	Bupleuri Radix
19	Huanglian	Coptidis Rhizoma
20	Gegen	Puerariae Lobatae Radix
21	Chenpi	Citri Reticulatae Pericarpium
22	Banxia	Pinelliae Rhizoma
23	Yinyanghuo	Epimedii Folium
24	Niuxi	Achyranthis Bidentatae Radix
25	Duzhong	Eucommiae Cortex
26	Xuduan	Dipsaci Radix
27	Sangjisheng	Taxilli Herba
28	Nvzhenzi	Ligustri Lucidi Fructus
29	Chishao	Paeoniae Radix Rubra
30	Shanzhuyu	Corni Fructus
31	Shanyao	Dioscoreae Rhizoma
32	Baishao	Paeoniae Radix Alba
33	Bajitian	Morindae Officinalis Radix
34	Yimucao	Leonuri Herba
35	Zelan	Eupatorium
36	Jixueteng	Spatholobi Caulis
37	Taoren	Persicae Semen
38	Huangqi	Astragali Radix
39	Huangqin	Scutellariae Radix
40	Lujiaoshuang	Cervi Cornu Degelatinatum
41	Zishiying	Flourite Fluoritum
42	Huangjing	Polygonati Rhizoma
43	Guizhi	Cinnamomi Ramulus
44	Ezhu	Curcumae Rhizoma
45	Rougui	Cinnamomi Cassiae Cortex
46	Yiyiren	Coicis Semen
47	Shichangpu	Acori Tatarinowii Rhizoma

48	Yujin	Curcumae Radix
49	Zhike	Aurantii Fructus
50	Dannanxing	Arisaematis Cum Bile
51	Shanzha	Crataegi Fructus
52	Zaojiaoci	Gleditsia sinensis Lam
53	Lulutong	Fructus Liquidambaris
54	Mudanpi	Moutan Cortex
55	Baijiezi	Semen sinapis
56	Zhebeimu	Fritillariae Thunbergii Bulbus
57	Shihu	Dendrobii Caulis
58	Peilan	Eupatorium fortunei
59	Wuxueteng	Gymnema sylvestre
60	Xuanshen	Scrophulariae Radix
61	Dahuang	Rhei Radix et Rhizoma
62	Shengma	Cimicifugae Rhizoma
63	Tianhuafen	Trichosanthis Radix
64	Sharen	Amomi Fructus
65	Ganjiang	Zingiberis Rhizoma
66	Yumixu	Mon Yam Rhizome