



## Research article

# Analysis of medication rule of Traditional Chinese Medicine in treating depression based on data mining

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## ABSTRACT

**Objective:** Depression is a mental disorder characterized by persistent feelings of sadness, decreased interest or pleasure in activities and reduced energy. As a highly prevalent disorder, it seriously endangers the psychosocial functioning of patients. Many scholars have conducted clinical studies on the treatment of depression using different herbal remedies, but there are no studies that integrate these remedies to explore the general medication rule. This study aims to explore the medication pattern of Traditional Chinese Medicine (TCM) treatment for depression through data mining methods, so as to provide scientific theoretical basis and reference for clinical treatment and new prescription development.

**Methods:** Based on the PRISMA principle, 121 articles involving 10810 patients with depression of TCM treatment were collected. We then performed frequency, association rule, and hierarchical clustering analysis of Chinese herbs using Microsoft Excel 2016, SPSS Modeler 18.0 and IBM SPSS Statistics 23.

**Results:** Among the 270 herbs collected, the three most frequently occurring herbs are Gancao, Chaihu, and Shaoyao. The categories of high-frequency herbs are mainly deficiency-tonifying, Qi-regulating and blood-activating and stasis-eliminating herbs. Through the Apriori algorithm, we mined 21 herbal groups of association rules, and among which the combination of Chaihu-Shaoyao-Gancao has the highest level of support. Furthermore, five novel clustering combinations were identified, predominantly derived from Xiaoyao-San, Chaihu-Shugan-San, Sini powder, Kaixin-San and Chaihu-Jia-Longgu-Muli Decoction.

**Conclusion:** The current study not only concluded the frequent combinations but also developed five new drug cluster combinations for depression, which can provide evidence-based references for the future clinical treatment and is helpful to understand the potential pharmaceutical mechanism from the properties, tastes, meridian tropisms and categories. The clinical effectiveness of these combinations needs to be verified by future study.

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## 1. Introduction

Depression is a common, chronic mental health problem with a global prevalence of 4.4–5 percent [1]. Depression is characterized by a loss of interest in daily activities, low self-worth, disappointment, sadness, and hopelessness [2]. While major depressive disorder (MDD) is a more severe form of depression and is often life-threatening [3]. According to the 2013 Global Burden of Disease Study, major depressive disorder (MDD) is the second leading global cause of disability life expectancy (Global Burden of Disease Study 2013 [4]). The population-attributable risk for depression and all-cause mortality is 12.7 %, and the population-attributable risk for depression and suicide is 11.2 % [5].

However, the specific mechanisms and treatments for depression are still being explored. It is generally believed that depression is caused by a complex interaction of genetic vulnerability and unfavorable environmental events [6]. Yet, specific genetic or non-genetic events remain poorly defined [7]. So far it is still unclear for the exact etiology and pathological mechanisms of depression, but several hypotheses about the mechanism of depression have been proposed and synthetic antidepressants have been introduced to treat patients. Initially, modern medicine exerted tremendous efforts in developing new treatments to target new potential areas beyond the monoamine hypothesis. However, none of these attempts were successful in developing any truly novel drugs [8]. Drugs based on the monoaminergic systems are far from ideal for the treatment of depression. With the discovery that the NMDA receptor antagonist ketamine rapidly improves depression, attention has again turned to novel drugs that target the glutamatergic system [9,10]. Although these drugs have shown some therapeutic promise with rapid-acting antidepressants and clinical studies, they currently still carry the potential for drug abuse and neurotoxicity [11]. Traditional Chinese Medicine (TCM) has been used as a complementary and alternative treatment for depression because it is perceived to have fewer side effects, is less expensive, facilitates long-term chronic conditioning, and allows for individualized treatment.

TCM is attracting increasing attention as an approach to meet the demand for higher remission rates, quicker onset of action, sustained antidepressant effects, and fewer adverse reactions [12,13]. TCM, an empirical medicine developed in China over thousands of years, emphasizes the integrity of the human body and the physical or emotional effects of the external environment on internal stability, and dynamic balance is its basic principle. In TCM, all diseases are caused by an imbalance in homeostasis, which may be due to various social or environmental factors. Therefore, treatment aims at restoring internal balance. Based on a “systemic” view, a typical treatment in TCM treats the body as a whole and cures the disease not only by alleviating symptoms but also by restoring internal balance [6]. According to TCM, depression is caused by an imbalance in organ systems that ultimately leads to brain dysfunction, and it is viewed as a multifactorial disorder with multiple pathomechanisms in different patients. Depression may be caused by stagnation of “Qi” (Positive Qi) in the body, imbalances in blood circulation, “heat” (inflammation), dampness, and phlegm. TCM practitioners usually identify the main causes of depression that are specific to each patient and treat them with acupuncture or medication. Releasing stagnant life energy is the general principle of treatment for depression [2]. It can be replenished by invigorating the blood, reducing inflammation or dissolving phlegm, and removing dampness. The systemic, multi-drug, multi-target approach of TCM is fully compatible with the multifactorial pathophysiology of depression. Many TCM empirical antidepressant formulas are widely used in East Asia to treat patients with depression. Clinical studies have shown that these antidepressant formulas are effective [14].

In specific clinical treatments, the antidepressant formulas employed in TCM vary. For instance, Bupleurum (Chaihu)-based formulas and Sour Jujube Nut Formulas are two relatively effective and commonly used formulas for the treatment of depression. However, the ingredients in these two formulas are quite distinct. Only licorice and Ligusticum wallichii (Chuanxiong), which are among the most basic ingredients in Sour Jujube Nut Formulas, appear in the Bupleurum-based formulas [15,16]. Meanwhile, in the treatment of depression with Chinese herbs, the formulas also tend to be adjusted according to the specific symptoms of the patients ([17,18][19]). It is unknown whether these specific ingredients, are associated with some specific manifestations of depression. Therefore, only exploring common prescription patterns can provide us with a global view of prescription regularity [20]. Analyzing the general composition of these formulas and exploring the patterns behind the formulas has important implications for the better use of herbal medicine in the treatment of depression.

Currently, little literature has attempted to apply statistical methods to systematically analyze the composition of herbal medicines for depression. Some scholars have summarized some common formulas or ingredients for the treatment of depression based on their experience [2,21], and there are review articles concluding the potential mechanisms of herbal antidepressants [22] and the role of antidepressants in oncology patients with depressive symptoms [23], but none of these articles used mathematical statistics to deeply study the medication pattern of herbal medicine for depression.

Therefore, this paper will comb through the diverse studies on the treatment of depression by TCM, and explore as well as summarize the appropriate prescription patterns for the treatment of depression via scientific and rigorous statistical methods, thereby providing a practical and effective theoretical foundation for clinical treatment.

## 2. Materials and methods

### 2.1. Data collection

Data for this study were meticulously gathered from the China Biomedical Database (CBM), China Journals Database (CNKI), Wanfang Database, VIP Chinese Science and Technology Journals Database (VIP), PubMed and EMBase English databases while the language is restricted to English and Chinese. The period for data collection spanned be from January 1, 2000 to March 1, 2024, Search terms such as to “depression”, “Chinese Herbal Medicine (CHM)”, “Traditional Chinese Medicine (TCM)”, “prescription analysis”, to

refine the search results, logical operators ‘AND’ and ‘OR’ were systematically applied.

## 2.2. Selection criteria

### 2.2.1. Inclusion criteria

- (1) Regardless of whether the study employed blinded or not, the report must meet the criteria for a randomized controlled trial (RCT) of TCM in the treatment of depression. The study design should clearly outline the randomization process and, if applicable, the blinding methods used to ensure unbiased results
- (2) Patients must be diagnosed with depression. The diagnosis must have been established using standardized diagnostic tools, such as the Hamilton Depression Rating Scale (HAMD), the Diagnostic Efficacy Criteria of Traditional Chinese Medicine, or other recognized measures for depressive symptoms.
- (3) The study’s findings should demonstrate that that the effective rate of the TCM treatment group (including TCM monotherapy and the combination of TCM and western medicine) was greater than 80 %, and there was a significant difference of efficacy between the treatment group and the control group ( $p < 0.05$ ).
- (4) The treatment method of the experimental group shall include the use of Traditional Chinese Medicine, such as Traditional Chinese Medicine decoction, tablets, capsules, powders, etc. The control group could receive no treatment, simple control, placebos, or other treatments used to improve depressive symptoms.
- (5) The composition and dosage of the TCM formulations used in the study must be fully documented, providing detailed information on the ingredients and their respective quantities in the prescription.

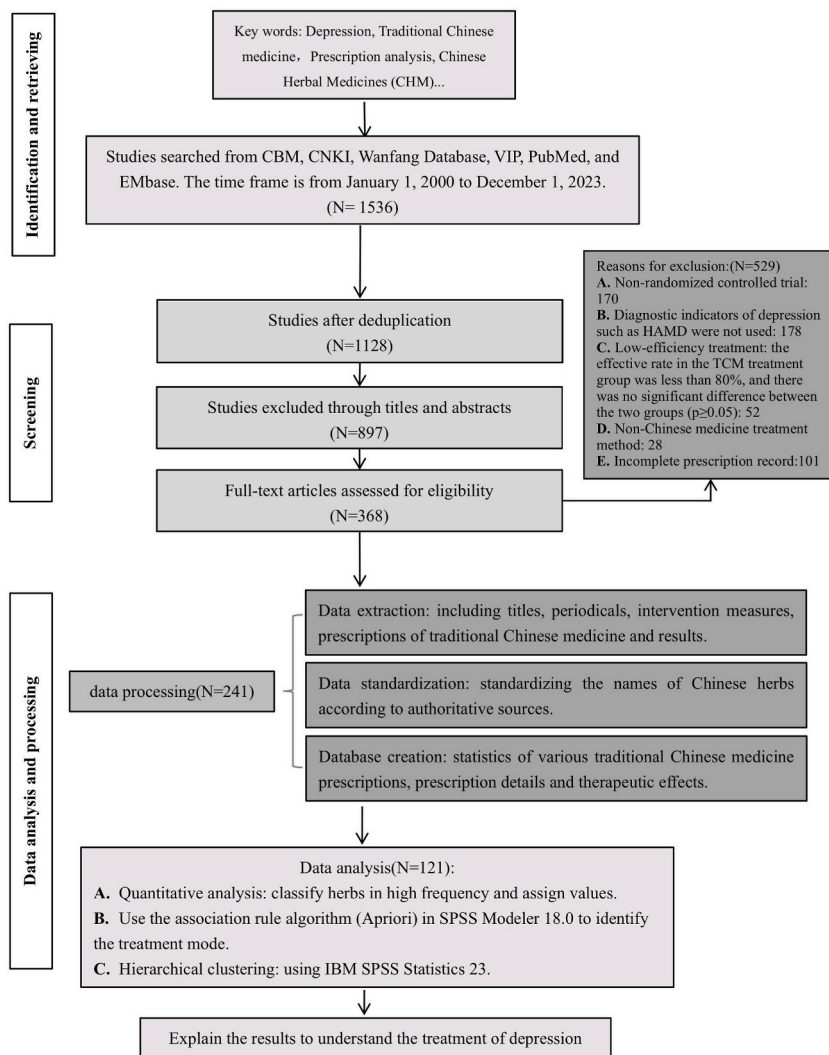


Fig. 1. Screening process. PRISMA flow diagram. Adapted from Guang-hui Liu et al. (2023 [24]).

### 2.2.2. Exclusion criteria

- (1) General descriptive literature and theoretical studies on network pharmacology that focus on the etiology and mechanisms of depression are excluded. These types of literature do not provide empirical data on treatment outcomes and therefore do not meet the criteria for inclusion.
- (2) Case reports, systematic reviews or meta-analyses, and animal experiments on the treatment of depression. These forms of literature do not offer direct clinical evidence relevant to the efficacy of treatments in human populations and thus are not suitable for inclusion.
- (3) Studies focusing on the treatment of depression that is complicated by other psychiatric or organic disorders are excluded. This criterion is set to ensure that the analysis is focused solely on depression without the confounding influence of other conditions.
- (4) Studies in which the literature only mentions the name of a prescription without specifying the exact drugs used, or where the records of Traditional Chinese Medicine components in the formula are incomplete, are excluded.

### 2.3. Screening process

We aggregated all collected articles into EndNote 21.0 and used EndNote 21.0 screening to remove duplicate articles, and then excluded some articles (e.g., pathology-related descriptive articles, review articles, articles with incomplete prescriptions, etc.) according to the exclusion criteria. The remaining articles were then shortlisted for articles that met our inclusion criteria. Finally, we checked the above-mentioned literature that met the standards and obtained 121 TCM prescriptions. The current study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 statement. The study protocol was approved by the ethical review committee at the authors' institution (IRB NO. H24099). The entire screening process, along with the number of articles retained at each step, is illustrated in Fig. 1.

### 2.4. Data processing

#### 2.4.1. Data cleaning

Based on The Dictionary of Chinese Medicines [25] and The Pharmacopoeia of the People's Republic of China [26], we standardized the names of TCM herbs in the literature screened for the treatment of depression. For example, sour jujube kernel, sour jujube and fried sour jujube kernel were standardized as Spine Date Seed, and licorice and roasted licorice were standardized as Radix Glycyrrhizae. This standardization was crucial to ensure consistency across the dataset and to facilitate subsequent analysis.

The contents of the standardized and organized 121 groups of herbal formulas were entered into an Excel spreadsheet to create a database, which recorded the names of the prescriptions, the literature sources, the herbal formulas, and the therapeutic effects. And the high frequency TCM herbs with a frequency greater than 8 were classified according to properties, tastes, meridian tropisms, and efficacy categories, and processed by the quantitative method of dichotomous classification, assigning the value of each herb according to "no = 0, yes = 1"[27–29]. Two independent authors entered the data independently, and then the initial data entered by the two authors were pre-analyzed and summarized, and in case of inconsistency of the pre-analyzed data, both parties checked and calibrated each other.

#### 2.4.2. Data mining

We used Microsoft Excel 2016 to perform frequency analysis of descriptive statistics of TCMs, calculating the frequency of the properties, tastes, meridian tropisms and efficacy categories of each herb in high-frequency Chinese herbal medicine.

Association rule algorithm is a commonly used technology in data mining for TCM symptom treatment, which can find out the associated individual data, and when certain symptoms always appear at the same time, a certain pathogenesis pattern can be found [30]. Here, we used Apriori algorithm in SPSS Modeler 18.0 to perform association rule analysis for high-frequency Chinese herbs. The Apriori algorithm is one of the most influential algorithms in association rule analysis, which can effectively mine the knowledge implicit in the data [31]. The metrics that often need to be focused on in association rule analysis are support, confidence and lift. By setting the appropriate support and confidence conditions, the connection between the attributes of TCM data can be obtained from the medical data, and some effective treatment rules can be derived [32]. In previous articles on TCM treatment of various diseases, the minimum support level was set ranging from 3 to 30 and the minimum confidence level was set ranging from 70 to 90 [33–36]. Based on the reference of previous literature settings and the actual situation of the prescriptions we obtained, we set the minimum support to 15, the minimum confidence level to 85, and the lift to greater than 1.

Association rule analysis helps us to uncover implicit links between herbs, while cluster analysis can also assist us in identifying patterns of herb use across different prescriptions for treatment. Cluster analysis is an unsupervised data analysis method that classifies samples based on the internal structure of the data. Hierarchical clustering analysis is a commonly used clustering algorithm in the current research of Traditional Chinese Medicine [37], which can visually display the clustering results with tree diagrams [38]. Herein, we conducted a hierarchical cluster analysis of high-frequency Chinese herbs using IBM SPSS Statistics 23.

### 3. Result

#### 3.1. Frequency analysis

After conducting a literature search and collecting data, we obtained 121 prescriptions involving 10810 patients, including 270 kinds of herbal medicines, with a cumulative frequency of 1142 herbal medicines. Among the 270 Chinese herbal medicines, 30 (11.11 %) had a frequency of more than 8, which was high frequency, accounting for 67.69 % of the cumulative frequency (Table 1). The high-frequency herbal medicines were Radix Glycyrrhizae (Gancao), Radix Bupleuri (Chaihu), and Radix Paeoniae Alba (Shaoyao).

#### 3.2. Properties, tastes, and meridian tropisms

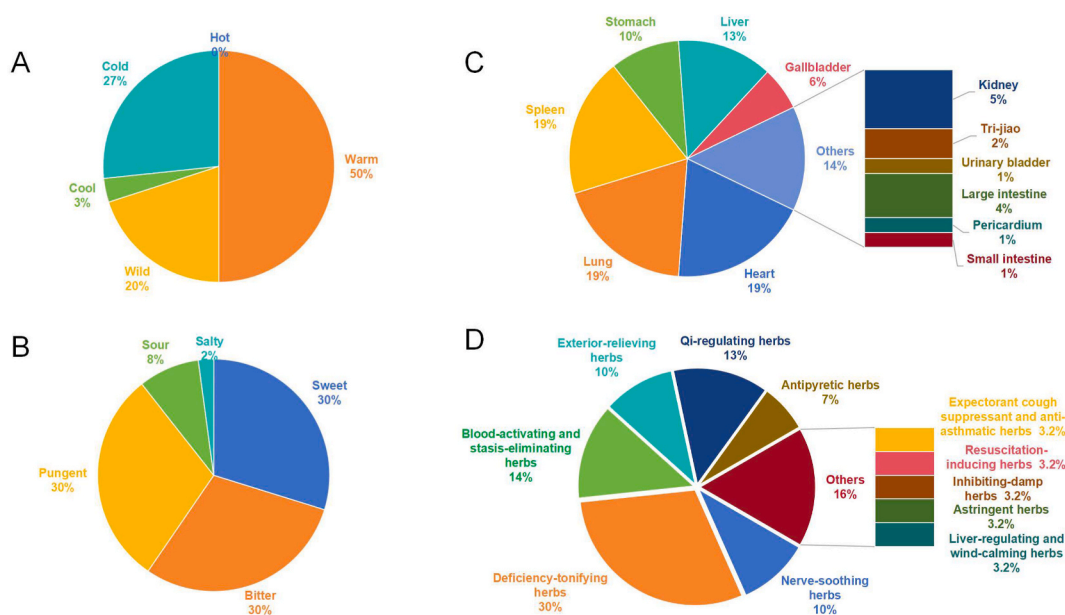
Due to there is only one property per herb so the total frequency of the herb properties in high-frequency herbs was 30. Warm herb were used 15 times (50 %), followed by cold [8 times (26.7 %)] and wild [6 times (20 %)] herbs, and almost no cool and hot herbs were used (Fig. 2 a). Due to each herb has many tastes so the total frequency of herb tastes was 47 times. Bitter herbs, spicy herbs, and sweet herbs were each used 14 times (29.79 %), indicating equal frequency. However, sour and salty tastes were mentioned infrequently (Fig. 2 b). Due to there are many kinds of tropisms for each herb so the total frequency of herb meridian tropism was 84 times. The heart meridians, spleen meridians, and lung meridians had the highest occurrence, were each used 16 times (19.05 %). The liver meridians occurred 11 times (13.10 %), and stomach meridians were mentioned 8 times (9.52 %). The gallbladder meridian, kidney meridian, Tri-jiao meridian, urinary bladder meridian, large intestine meridian, pericardial meridian, and small intestine meridian are also frequently used in herbs, with a combined proportion reaching 20 % (Fig. 2 c).

**Table 1**

High-frequency herbs used to treat depression.

No.	Herb	Properties	Tastes	Meridian Tropisms	Frequency	<sup>a</sup> Proportion
1	Radix Glycyrrhizae (Gancao)	Mild	Sweet	Heart/Lung/Spleen/Stomach	67	0.0587
2	Radix Bupleuri (Chaihu)	Cold	Bitter/Pungent	Lung/Liver/Gallbladder	65	0.0569
3	Radix Paeoniae Alba (Shaoyao)	Cold	Bitter	Spleen/Liver	60	0.0525
4	Indian Buead Tuckahoe (Fuling)	Mild	Sweet	Heart/Lung/Spleen/Kidney	53	0.0464
5	Chinese Angelica (Danggui)	Warm	Sweet/Pungent	Heart/Spleen/Liver	40	0.0350
6	Szechwan Lovage Rhizome (Chuanxiong)	Warm	Pungent	Liver/Gallbladder/Pericardium	34	0.0298
7	Nutgrass Galingale Rhizome (Xiangfu)	Mild	Sweet/Bitter/Pungent	Spleen/Liver/Tri-jiao	32	0.0280
8	Wenchow Turmeric Root Tuber (Yujin)	Cold	Bitter/Pungent	Heart/Lung/Liver	31	0.0271
9	Spine Date Seed (Suanzaoren)	Mild	Sweet/Sour	Heart/Liver/Gallbladder	31	0.0271
10	Largehead Atractylodes Rhizome (Baizhu)	Warm	Sweet/Bitter	Spleen/Stomach	28	0.0245
11	Tangerine Peel (Chenpi)	Warm	Bitter/Pungent	Lung/Spleen	27	0.0236
12	Albizia julibrissin (Hehuan)	Mild	Sweet	Heart/Liver	26	0.0228
13	Gardenia (Zhizi)	Cold	Bitter	Heart/Lung/Tri-jiao	24	0.0210
14	Fructus Aurantii (Zhike)	Warm	Pungent	Spleen/Stomach/Large intestine	22	0.0193
15	Pinelliae Rhizoma (Banxia)	Warm	Pungent	Lung/Spleen/Stomach	20	0.0175
16	Jujubae Fructus (Dazao)	Warm	Sweet	Heart/Spleen/Stomach	20	0.0175
17	Acorus tatarinowii (Shichangpu)	Warm	Bitter/Pungent	Heart/Stomach	20	0.0175
18	Tiger Lily (Baihe)	Cold	Sweet	Heart/Lung	18	0.0158
19	Scutellaria baicalensis (HuangQin)	Cold	Bitter	Lung/Spleen/Gallbladder/Large intestine/ small intestine	17	0.0149
20	Zingiberis Rhizoma Recens (Shengjiang)	Warm	Pungent	Lung/Spleen/Stomach	17	0.0149
21	Membranous Milkvetch Root (HuangQi)	Warm	Sweet	Lung/Spleen	16	0.0140
22	Codonopsis Radix (Dangshen)	Mild	Sweet	Lung/Spleen	15	0.0131
23	Polygalae Radix (Yuanzhi)	Warm	Bitter/Pungent	Heart/Lung/Kidney	14	0.0123
24	Cassia bark tree Twig (Guizhi)	Warm	Sweet/Pungent	Heart/Lung/Urinary bladder	13	0.0114
25	Schisandrae Chinensis Fructus (Wuweizi)	Warm	Sweet/Sour	Heart/Lung/Kidney	13	0.0114
26	Salviae Miltiorrhizae (Danshen)	Cold	Bitter	Heart/Liver	12	0.0105
27	Immature Bitter Orange (Zhishi)	Cold	Bitter/Pungent/Sour	Spleen/Stomach/Large intestine	11	0.0096
28	Ostrea gigas Thunberg (Muli)	Cool	salty	Liver/Gallbladder/Kidney	9	0.0079
29	Ginseng Root (Renshen)	Warm	Sweet/Bitter	Heart/Lung/Spleen	9	0.0079
30	Safflower (Honghua)	Warm	Pungent	Heart/Liver	9	0.0079

<sup>a</sup> The proportion refers to the percentage of a herb's frequency in the total frequency of all herbs.



**Fig. 2.** a. The total frequency of the herb properties. b. The frequency of the herb tastes. c. The frequency of the herb meridian tropisms. d. Categories frequency for TCMs.

### 3.3. Herb efficacy categories

TCMs have different levels of effectiveness depending on how they are combined. Therefore, it can be classified according to the efficacy of its characteristics. The total frequency and ratio of each herbal medicine class are shown in Fig. 2 d. Among them, deficiency tonic drugs are the most commonly used, accounting for 30 %, followed by blood-activating and stasis-eliminating herbs at 14 %, Qi-regulating herbs closely followed at 13 %, and then exterior-relieving and nerve-soothing herbs, which both accounted for 10 %.

### 3.4. Association rule algorithm and network display

The Apriori algorithm was used to analyze the association rules of 30 high-frequency herbs, and we obtained 21 herbal association rules. We set the minimum support level to 15, which means that there is at least a 15 % probability that both items in the data will appear at the same time. The minimum confidence level is set to 85, which means that there is at least an 85 % probability that the

**Table 2**  
Association rules of TCMs for depression.

No.	Former item	Latter item	Support	Confidence	Lift
1	Radix Bupleuri	Radix Paeoniae Alba and Radix Glycyrrhizae	36.364	86.364	1.633
2	Radix Paeoniae Alba	Chinese Angelica and Radix Bupleuri	22.314	92.593	1.899
3	Radix Glycyrrhizae	Indian Buead Tuckahoe and Radix Paeoniae Alba and Radix Bupleuri	19.008	86.957	1.57
4	Radix Glycyrrhizae	Fructus Aurantii	18.182	90.909	1.642
5	Radix Bupleuri	Indian Buead Tuckahoe and Radix Paeoniae Alba and Radix Glycyrrhizae	18.182	90.909	1.719
6	Radix Bupleuri	Fructus Aurantii	18.182	86.364	1.633
7	Radix Bupleuri	Wenchow Turmeric Root Tuber and Radix Glycyrrhizae	18.182	86.364	1.633
8	Radix Bupleuri	Wenchow Turmeric Root Tuber and Radix Paeoniae Alba	17.355	95.238	1.801
9	Radix Paeoniae Alba	Chinese Angelica and Indian Buead Tuckahoe	17.355	90.476	1.856
10	Radix Paeoniae Alba	Nutgrass Galingale Rhizome and Radix Bupleuri	17.355	85.714	1.758
11	Radix Bupleuri	Chinese Angelica and Indian Buead Tuckahoe	17.355	85.714	1.621
12	Radix Paeoniae Alba	Fructus Aurantii and Radix Glycyrrhizae	16.529	90	1.846
13	Radix Bupleuri	Fructus Aurantii and Radix Glycyrrhizae	16.529	90	1.702
14	Radix Glycyrrhizae	Tangerine Peel and Radix Bupleuri	16.529	85	1.535
15	Radix Bupleuri	Szechwan Lovage Rhizome and Radix Paeoniae Alba	16.529	85	1.607
16	Radix Bupleuri	Szechwan Lovage Rhizome and Radix Glycyrrhizae	16.529	85	1.607
17	Radix Glycyrrhizae	Fructus Aurantii and Radix Bupleuri	15.702	94.737	1.711
18	Radix Bupleuri	Chinese Angelica and Indian Buead Tuckahoe and Radix Paeoniae Alba	15.702	94.737	1.791
19	Radix Paeoniae Alba	Fructus Aurantii and Radix Bupleuri	15.702	89.474	1.835
20	Radix Bupleuri	Tangerine Peel and Radix Glycyrrhizae	15.702	89.474	1.692
21	Radix Paeoniae Alba	Nutgrass Galingale Rhizome and Radix Glycyrrhizae	15.702	89.474	1.835

latter item will occur when the former item occurs. The lift is set to greater than 1, which means that the two items are positively correlated. It was found that Radix Bupleuri (Chaihu), Radix Paeoniae Alba (Shaoyao) and Radix Glycyrrhizae (Gancao) were the most correlated (Table 2).

Furthermore, we utilized SPSS Modeler 18.0 to generate a network diagram of the association rules (Fig. 3). In a network diagram, the thicker the line, the stronger the correlation between herbs, and the thinner the line, the weaker the correlation. We found a strong correlation with Radix Bupleuri (Chaihu) and Indian Buead Tuckahoe (Fuling), Radix Glycyrrhizae (Gancao) and Indian Buead Tuckahoe (Fuling), Radix Bupleuri (Chaihu) and Chinese Angelica (Danggui), Radix Paeoniae Alba (Shaoyao) and Chinese Angelica (Danggui), Radix Bupleuri (Chaihu) and Wenchow Turmeric Root Tuber (Yujin). The results showed that Radix Paeoniae Alba (Shaoyao), Radix Bupleuri (Chaihu), Radix Glycyrrhizae (Gancao), Chinese Angelica (Danggui), and Indian Buead Tuckahoe (Fuling) had the best effect on the treatment of depression.

### 3.5. Cluster analysis

In addition, we selected 30 herbal medicines for hierarchical cluster analysis with SPSS 23.0. This method can show the compatibility and combination rules of different Chinese medicines, by which we obtained five new drug clustering combinations that can be used as clinical guidance and reference for new formula development. Cluster 1 includes: Cassiabarktree Twig (Guizhi), Ostrea gigas Thunberg (Muli), Scutellaria baicalensis (HuangQin), Pinelliae Rhizoma (Banxia), Jujubae Fructus (Dazao), Zingiberis Rhizoma Recens (Shengjiang), Tiger Lily (Baihe). Cluster 2 includes: Wenchow Turmeric Root Tuber (Yujin), Albizzia julibrissin (Hehuan), Codonopsis Radix (Dangshen), Polygalae Radix (Yuanzhi), Membranous Milkvetch Root (HuangQi), Schisandrae Chinensis Fructus (Wuweizi), Ginseng Root (Renshen), Salviae Miltiorrhizae (Danshen), Safflower (Honghua), Immature Bitter Orange (Zhishi), Acorus tatarinowii (Shichangpu), Gardenia (Zhizi), Spine Date Seed (Suanzaoren). Cluster 3 includes: Tangerine Peel (Chenpi), Fructus Aurantii (ZhiQiao), Nutgrass Galingale Rhizome (Xiangfu), Szechwan Lovage Rhizome (ChuanQiong). Cluster 4 includes: Radix Bupleuri (Chaihu), Radix Paeoniae Alba (Baishao), Radix Glycyrrhizae (Gancao). And cluster 5 includes: Indian Buead Tuckahoe (Fuling), Chinese Angelica (Danggui), Largehead Atractylodes Rhizome (Baizhu). The tree diagram from cluster analysis of TCMs was shown in Fig. 4.

## 4. Discussion

### 4.1. Analysis of properties, tastes, meridian tropisms and categories

Based on the basic theory of TCM, this paper makes a dialectical analysis of depression. From the perspective of TCM, depression is a group of syndromes with the main symptoms of emotional disorder, depression, and upset caused by long-term stagnation of liver Qi, disharmony between spleen and stomach and stagnation of Qi and blood. In the theory of TCM, Four Qi and Five Tastes [39] refer to the medicinal properties and tastes of TCM. Four Qi includes cold, cool, wild, warm and hot. Five tastes mean sour, bitter, sweet,

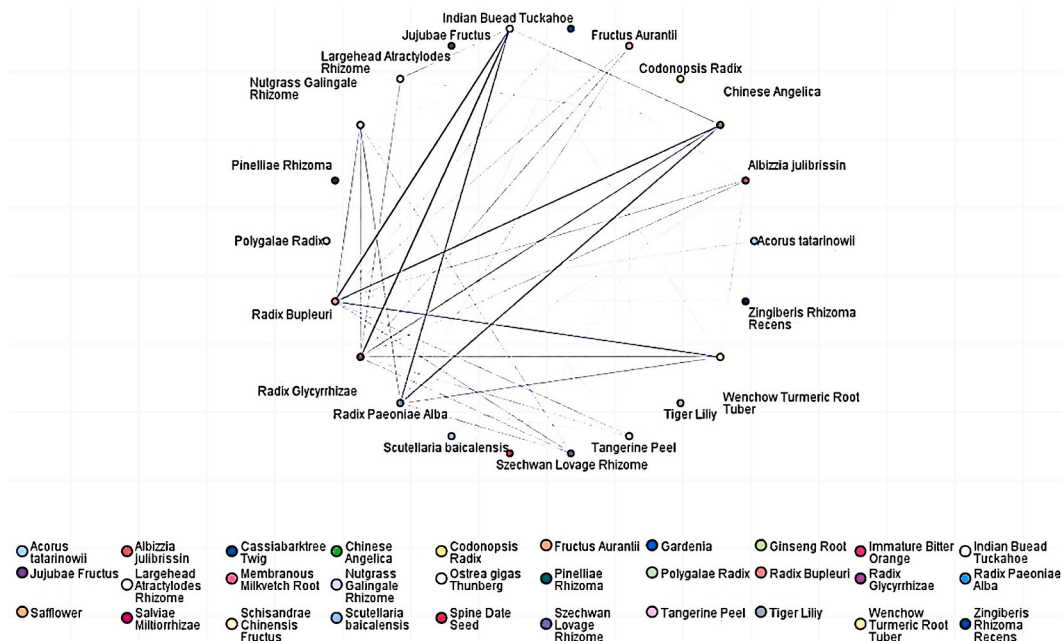
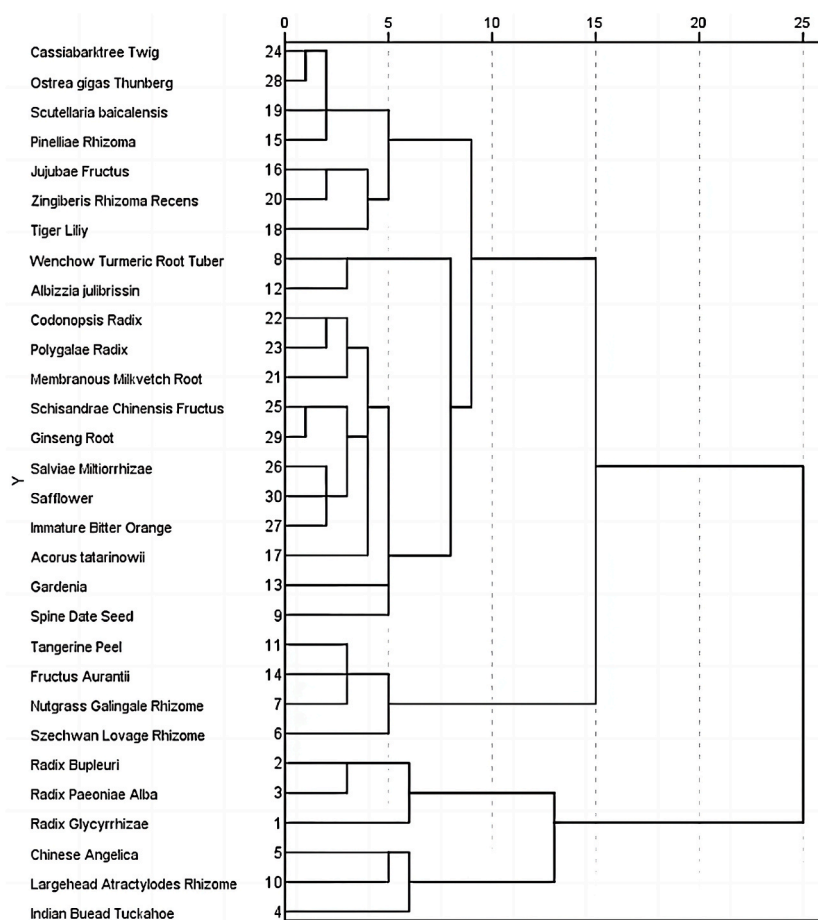


Fig. 3. The network diagram of TCMs.



**Fig. 4.** Tree diagram from cluster analysis of TCMs. The number on the abscissa indicates the order of the frequency of high-frequency medicinal materials from more to less. The ordinate represents the hierarchy of cluster analysis. The larger the number, the more macroscopic it is, the higher the hierarchy it contains, and the smaller the number, the finer the classification and the more dispersed the commonness of each element.

pungent and salty. In accordance with the principle of compatibility in Chinese herbal medicine [40], incorporating the Four Qi and Five Tastes can provide a better treatment for depression. Combined with our research results, it is found that the herb properties of wild and cool are the most commonly used, and the taste is mainly sweet, bitter and pungent. Among the high-frequency herbs, those with pungent taste, such as Radix Bupleuri (Chaihu), are characterized by horizontal dispersion, which can promote blood circulation, remove blood stasis and dredge the inside and outside. Drugs with bitter taste, such as Radix Paeoniae Alba (Shaoyao), have the power of removing blood stasis and lowering blood circulation [41]. In the frequency analysis of meridian tropism, we found that the herbs of heart meridian, spleen meridian and lung meridian were used most frequently. TCMs entering the lung meridian, such as high-frequency herbs Radix Glycyrrhizae (Gancao), Radix Bupleuri (Chaihu) and Indian Buead Tuckahoe (Fuling), have the functions of resolving phlegm, relieving cough and asthma, clearing away heat, relieving exterior syndrome and tonifying deficiency [42]. According to the analysis of category frequency series in our study, deficiency-tonifying herbs such as Radix Glycyrrhizae (Gancao), Radix Paeoniae Alba (Shaoyao) and Chinese Angelica (Danggui) are most commonly used to treat depression. Tonifying herbs can regulate the nervous immune system through the intestinal brain axis, reduce the pruning of synapses by microglia, and produce the mechanism of antidepressant effect. Qi-regulating herbs such as Fructus Aurantii (Zhihe) are also relatively commonly used, which can promote the regulation of neurotrophic and neuroendocrine functions and thus play an antidepressant role [43].

#### 4.2. Association rule analysis

The results of association rule analysis show that Radix Bupleuri (Chaihu), Radix Paeoniae Alba (Shaoyao) and Radix Glycyrrhizae (Gancao) have the highest correlation in herbal collocation (Table 2-No.1) and show the highest support. This phenomenon shows that the combination of the three has significant co-occurrence in the clinical practice of treating depression in Traditional Chinese Medicine [44]. As the main components of Xiaoyao Powder [41], Chaihu Shugan Powder [45] and Jieyu Pill [46], these three ingredients have the functions of soothing the liver and relieving depression, nourishing the heart and calming the nerves, improving the disorders of nervous, endocrine and immune functions, and resisting depression and anxiety [47]. And in the control group



experiment, compared with western medicine antidepressants, the side effects are smaller. There is also a strong relationship between Radix Paeoniae Alba (Shaoyao) and Chinese Angelica (Danggui) and Radix Bupleuri (Chaihu) (Table 2-No.2). The combination of Radix Bupleuri (Chaihu) and Chinese Angelica (Danggui) has shown excellent effect in improving Qi and blood stagnation in the body. As the main medicinal materials in Traditional Chinese Medicine prescriptions for relieving depression such as anshen decoction [48] and Xiaochaihu decoction, they can relieve sleep problems and protect the spleen. In addition, there are significant correlations between Radix Glycyrrhizae (Gancao) and Indian Buead Tuckahoe (Fuling), Radix Paeoniae Alba (Shaoyao) and radix bupleuri (Chaihu) (table 2-No.3). It shows that they may have a positive impact on some physiological processes when used at the same time. For example, in the prescription of Xiaoyao Powder, this medicinal material can be used to reduce the level of serum pilocarpine, warm and tonify Yang Qi, promote the circulation of Qi to relieve depression, and enhance neuroplasticity and anti-apoptosis ability, and can treat symptoms such as deficiency of Yang Qi and poor Qi flow [49]. The correlation between Radix Glycyrrhizae (Gancao) and Frutus Aurantii (Zhike) (Table 2-No.4) is also high. This is consistent with the principle of “harmonizing medicinal properties and promoting efficacy” in the theory of Traditional Chinese Medicine [50]. The relationship between Radix Bupleuri (Chaihu) and Indian Buead Tuckahoe (Fuling), Radix Paeoniae Alba (Shaoyao) and Radix Glycyrrhizae (gancao) (table 2-No.5) is equally significant, and it is very likely that they will have a better effect in treating depression when used together, and may have a synergistic effect when compatible. Through the in-depth analysis of association rules, we can understand the pharmacological basis of these herbal combinations more comprehensively, which provides scientific guidance for the rational application of Chinese herbal medicines.

#### 4.3. Cluster analysis

Cluster 1 and Cluster 2 together happen to be the main prescription of Xiaoyao San (XYS). The results of cluster 1 include Radix Glycyrrhizae (Gancao), Radix Bupleuri (Chaihu), and Radix Paeoniae Alba (Shaoyao), and the results of cluster 2 are Indian Buead Tuckahoe (Fuling), Chinese Angelica (Danggui), and Largehead Atractylodes Rhizome (Baizhu). It is worth noting that the results of Cluster 1 and Cluster 2 are derived from cluster analysis, but it's very coincidental that these two clusters together happen to be the formula of Xiaoyao San (XYS), the most frequently used Traditional Chinese Medicine prescription for the treatment of depression [51]. Since the invention of YYS in the Song Dynasty, its efficacy has gradually evolved from the treatment of “blood deficiency” to “liver depression and spleen deficiency” through the research of Traditional Chinese Medicine doctors in the past dynasties [52]. According to the theory of modern Traditional Chinese Medicine, the most common clinical syndrome of depression is liver depression and spleen deficiency syndrome, which is consistent with the treatment mechanism of YYS [53]. Biochemically, previous studies have shown that YYS can reverse the reduction of brain-derived neurotrophic factor (BDNF) caused by chronic immobilization stress (CIS), thus acting as an antidepressant-like effect [54]. Moreover, animal studies have shown that YYS and its derivative prescriptions can improve abnormal behavior in depressed rats by downregulating hyperactivity of the hypothalamic-pituitary-adrenal axis (HPA axis) [55] as well as modulating the levels of monoamine neurotransmitters in the hippocampus of the brain [56,57].

Cluster 1 and Cluster 3 together happen to be the main prescription of Chaihu Shugan San (CHSGS). Chaihu Shugan San (CHSGS) originated from the “Jingyue Quanshu” of Ming Dynasty, which is derived from the Sini powder, and the whole formula is composed of seven kinds of herbs in cluster 1 and cluster 3 coincidentally, including Radix Glycyrrhizae (Gancao), Radix Bupleuri (Chaihu), Radix Paeoniae Alba (Shaoyao), Nutgrass Galingale Rhizome (Xiangfu), Szechwan Lovage Rhizome (Chuanxiong), Tangerine Peel (Chenpi), and Fructus Aurantii (Zhiqiao). Sini powder has a significant effect in the clinical treatment of depression [58], its prescription is composed of cluster 1 plus Immature Bitter Orange (Zhishi). The three herbs in cluster 1 can soothe the liver and regulate Qi, and Zhishi can break the Qi and dredge the meridians, so as to achieve the effect of Sini powder to soothe the liver and relieve depression. Cluster 1 in CHSGS plays the role of soothing the liver and invigorating the blood [59], combined with the effect of cluster 3 to strengthen the spleen and regulate Qi, thereby alleviating depressive symptoms. Modern pharmacology also demonstrated that CHSGS can ameliorate depressive-like behavior by inhibiting the hepatocerebral inflammatory axis [60]. In addition, paeoniflora, a pharmacodynamic substance from Shaoyao, can play an antidepressant role in CHSGS by altering the expression of the monoamine neurotransmitter 5-HT receptors [61], promoting neuroprotection [62], and increasing the hippocampal levels of BDNF [63].

Cluster 4 happens to be the main prescription of Kaixin San (KXS). Cluster 4 consists of 13 kinds of herbs, among which Acorus tatarinowii (Shichang pu), Ginseng Root (Renshen), and Polygalae Radix (Yuanzhi) are the main ingredients of Kaixin San (KXS). KXS is mainly used to treat symptoms such as sadness, restlessness, forgetfulness, and palpitations, which are very similar to the symptoms of depression in modern medicine [64]. It treats depression by regulating the spleen and liver, nourishing the heart and calming the nerves according to the theory of Traditional Chinese Medicine. Renshen, the main ingredient in KXS, can reduce depression levels in rats by modulating the HPA axis [65], and the chemicals isolated from Yuanzhi have also been shown to act as triple monoamine reuptake inhibitors to exert their antidepressant effects in KXS [66]. Additionally, it can be seen that the herbs in Cluster 4 mainly consist of nerve-soothing, deficiency-tonifying, and blood-activating medicines, with flavors being bitter and sweet, primarily attributed to the Heart and Lung meridians. In Traditional Chinese Medicine (TCM) theory, the heart governs the mind and consciousness, while the lungs govern the regulation of Qi (vital energy) [67], and the functional states of the heart and lungs directly affect emotional and mental well-being. Moreover, depression in TCM is often attributed to the retention of Qi [68] and cardiopulmonary malfunction [69]. Therefore, the combination of medicines in Cluster 4 can harmonize the function of the heart and lungs through their synergistic efficacy, thus achieving the purpose of treating depression.

Cluster 5 overlaps with the main recipe of Chaihu-Jia-Longgu-Muli Decoction (CLMD), namely Pinelliae Rhizoma (Banxia), Jujubae Fructus (Dazao), Scutellaria baicalensis (HuangQin), Zingiberis Rhizoma Recens (Shengjiang), Cassiabarktree Twig (Guizhi) and Ostrea gigas Thunberg (Muli). HuangQin clears liver fire, Guizhi warms the meridians, and Dazao and Shengjiang can benefit and harmonize Qi [70]. Chaihu and Longgu are also the main components of CLMD, Chaihu can relieve the liver, while Longgu and Muli

can calm the mind. The whole formula of CLMD has the effect of promoting Qi and dredging the liver, calming the mind and alarm, draining heat and resolving phlegm [71]. As a famous Traditional Chinese Medicine formula, its efficacy in treating depression and related symptoms is beyond doubt [72]. Clinical and pharmacological experimental studies have also shown that CLMD can exert antidepressant effects through multiple targets and several levels [73]. In addition to the six main components of CLMD, the herb Tiger Lily (Baihe) is also found in cluster 5. Baihe is known to nourish the yin of the heart and lungs and tonify the Qi of the heart and lungs [74], with a long history of use in the treatment of ancient delirium tremens. Modern network pharmacology has also proved that Liliium saponin, the main active component of Baihe, can exert antidepressant effects [75]. Consequently, these seven herbs in Cluster 5 may complement each other to achieve the antidepressant effect of nourishing the liver, heart and lungs, promoting blood circulation and tranquilising the mind.

In this study, data mining methods such as descriptive statistical analysis, association rule algorithm, and cluster analysis were applied to mine and analyze the data of 121 prescriptions for treating depression. Since it is based on the literature data of real clinical treatment, we have identified the clinical pattern and core drug combinations of TCM treatment of depression through data mining, so the results of this mining can not only promote researchers to further theoretically explore and validate the effective mechanism of the related core drugs on the treatment of depression, but also to a certain extent, provide a new basis for the clinical treatment of depression, and also provide a new drug research and development, as well as a possible direction for new drug development. Specifically, there are many different perspectives on the mechanisms of depression and the rationale for the treatment of depression with TCM, and the combination of clinical medications may reflect the rationale for these mechanisms at a practical level. Our findings also have the potential for better efficacy and fewer side effects than existing empirical treatment protocols. Particularly when it comes to individualizing treatment for patients with depression, the new medication combinations have the potential to help achieve precision medicine based on personalized tailoring. In addition, new effective drug combinations can reduce unnecessary waste of medical resources, lower treatment costs, bring new sources of income for enterprises, and provide clues for drug repositioning and accelerate the development process of the prepared prescription of CTM for depression. However, there are still some shortcomings in the current study: First, as the saying goes, "the only criterion for judging the truth is actual practice", although we have derived the core combination of new formulas for the treatment of depression, their antidepressant efficacy needs to be further verified by clinical research. Furthermore, when we initially screened the articles, we only considered the significance of the efficacy and did not take the significance of the side effects into account, which is an aspect that could be improved in future studies. In terms of the data we collected various types of depression, moreover, future studies could conduct in-depth data mining and research on a specific type of depression. One last point that must be mentioned is that, as we all know, the treatment of Chinese medicine is dialectical, and the identification of evidence is a basic principle that Chinese medicine must follow in diagnosing diseases and treating them. In other words, Chinese medicine treatment should emphasize individualized treatment methods. Even for the same disease, the treatment methods vary from person to person and change according to the evidence. However, many of the collected articles do not contain descriptions of patient symptoms, and the methods of describing symptoms vary so differently, from those based on TCM categorization to those based on the symptoms of Western patients with depression. Therefore, it is difficult to summarize and analyze the specific symptoms of different patients. Here, we also call on researchers to describe the symptoms of patients in detail in future studies of TCM prescription therapy so as to facilitate the summarization and analysis. Despite these shortcomings, the findings of this paper are still innovative and deserve to be recognized.

## 5. Conclusion

In conclusion, this study is based on published literature and data mining of real clinical medications used in the treatment of depression with TCM, which provides scientific and reasonable references and potential possibilities for the treatment of depression with TCM. The results showed that the main herbs used to treat depression in TCM were deficiency-tonifying, Qi-regulating, and blood-activating herbs, and the therapeutic methods mainly followed the principles of strengthening the spleen and benefiting Qi, invigorating blood to guide stagnation, nourishing the heart and tranquilising the mind, and dispelling the liver. Besides, this study discovered five core clustering combinations for the treatment of depression as new remedies, and relationships between these combinations and existing prescriptions (such as XYS, CHSGS, and CLMD, etc.) were revealed, but the clinical validity of these combinations needs to be further verified.

## CRedit authorship contribution statement

**Jin Yang:** Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Shuai Wang:** Writing – review & editing, Writing – original draft, Resources, Investigation, Data curation. **Zhen Zhang:** Writing – original draft, Visualization, Resources, Investigation, Data curation. **Junjie Huang:** Writing – original draft, Resources, Investigation, Data curation. **Weihai Chen:** Writing – review & editing, Visualization. **Zhan Xu:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2024.e39245>.

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