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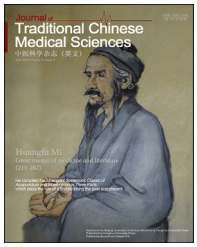

Analysis of active patents to investigate the frequency and patterns of Chinese herbal extract combinations claiming to treat heart disease

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Abstract *Objective:* Using Chinese patents in force to investigate the frequency and patterns of Chinese herbal extract combinations claiming to treat heart disease.
Methods: Patent documents were retrieved from the official website of the State Intellectual Property Office of the People's Republic China. Cluster, frequency, and fuzzy cluster analyses were applied.
Results: A high number of patents in force included high-frequency herbs such as *Salvia miltiorrhiza*, *Panax ginseng*, and *Panax notoginseng*, as well as high-frequency herbal families such as Araliaceae, Leguminosae, Labiatae, and Umbelliferae. Herb pairs such as *P. ginseng* + *Ophiopogon japonicus*, *S. miltiorrhiza* + *Dalbergia odorifera*, and *P. ginseng* + *Schisandra chinensis* are also commonly used, as well as herbal family pairs such as Araliaceae + Liliaceae, Lauraceae + Leguminosae, and Araliaceae + Schisandraceae. Traditional treatment principles for preventing and treating heart diseases was most-commonly based on simultaneously treating the liver and heart and treating the lung and spleen secondarily for choosing herbal combinations.
Conclusion: Most of the high-frequency Chinese herbs in the patents investigated belong to the high-frequency herbal families, and herb pairs were commonly selected to coincide with the commonly-used herbal family pairs. Low-frequency Chinese herbs were also used, but generally belonged to the high-frequency herbal families, and were therefore similar to the high-frequency herbs in terms of traditional categories of taste and channel entered. The results reflect the use of traditional principles of formula composition, and suggest that these principles may indeed be an effective guide for further research and development of Chinese herbal

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extract combinations to prevent and treat heart diseases.

Introduction

In China, traditional Chinese herbs have long been used to treat cardiovascular diseases. In traditional Chinese medicine (TCM), disorders that involve the cardiovascular system fall under the rubric of "heart system disease," and are also comprised of illnesses involving other biomedical systems of the body, in particular mental (psychologic) and brain disorders. According to the World Health Organization, an estimated 17.7 million people died from cardiovascular diseases in 2015, and this number will continue to grow to estimated 22.2 million in 2030.[1] Because heart disease is a serious threat to human health, it has become a focus of research worldwide.

As more and more patients and consumers demand natural, organic, or side-effect free treatments, the use of herbal medicine (also known as botanic medicine, or phytomedicine) is increasingly being used to prevent and treat heart disease. Chinese medicine may have an important contribution to make in this area. However, TCM has still not been accepted in many countries. To a large extent, this is due to problems with safety and stability. Problems may arise when original medicinal plants or decoction pieces (semi-processed, dried and cut herbs) from different geographic regions are used interchangeably without investigating possible differences in medicinal properties. The complex chemical composition of the multi-herb preparations and the lack of clear evidence of their exact mechanisms of action are also important issues.[2,3] Prepared medicines, typically in pill, powder, or capsule form from TCM extracts may be a solution to these problems.[4,5] Herbal extracts are a type of TCM product processed by using a solvent, typically water or ethanol, to release the active chemical constituents.[6] The extract can then be considered to be a substitute for dried plant matter (decoction pieces) or as an active ingredient that can be incorporated into other medicinal products or combination pharmacologic products. Due to these advantages, TCM extracts have become more popular in recent years and prescribing Chinese herbal extract combinations has become a new alternative for herbal administration. As TCM expands worldwide, many TCM research and development units have begun to pay more attention to herbal extracts.

Patent in force, or active patent, refers to a patent that has effective status. Most patent rights cease to exist before their expiration, due to either the low quality of the patent, lack of commercialization, or inadequate profitability after commercialization.[7] Hence the time that a patent is maintained is a reliable indicator of the scientific and technologic innovation capacity and market competitiveness. As one of the most systematic, comprehensive, and active information resources, patent documents should not be overlooked as a source of innovative ideas for new drugs. By studying the technical description of the active patent of a Chinese herbal extract combination, new medical resources, including a patent strategy, can be developed.[8]

To date, TCM patent document research of Chinese and overseas offices has mainly focused on Chinese herbal compounds and extracts to analyze the patentability, patent protection awareness, or simple bibliometric analysis of herbal formulas. Although there has been some research on Chinese herbal compound patents designed to treat cardiovascular diseases, methods have been limited to simple bibliometric analyses. We have not found any systematic statistical analysis and qualitative research on active patents of Chinese herbal extract combinations for preventing and treating TCM heart system disease.

Data mining, which is widely used in TCM research, is a useful tool for investigating the aforementioned patent documents.[9,10] Data mining in the form of cluster analysis and frequency analysis have been applied to the identification of Chinese herbs, studies of the regularity of traditional Chinese medicinal compounds, classification of traditional Chinese herbs among other areas.[11,12]

In this study, we applied frequency analysis, cluster analysis, and fuzzy cluster analysis to explore the combinatorial patterns of Chinese herbal extracts for the treatment of heart system diseases. Our retrieval criteria were the Chinese equivalent of "Chinese herbal extract combination patents". Based on our analysis, suggestions are made for the development of new drugs.

Materials and methods

Patent retrieval and establishment of databases

Patent documents used in this research were retrieved from the official website of the State Intellectual Property Office of the People's Republic of China. There are four query systems that can be accessed through the website. Therefore, we believe the information we obtained is accurate and complete.

According to Chinese patent law, patent applications are published within 18 months after the earliest priority date of the patent application. The patents in this study were all approved, and 2014 was the most recent year with complete coverage of the granted patents. To acquire an objective perspective on TCM extract combination patents, active patents granted from 1995 through 2014 were selected.

Chinese keyword combination was "traditional Chinese medicine OR Chinese herbs OR natural drugs" AND "extract OR extractive". These keyword combinations were identified through literature survey. Initial search targeted

patent titles and abstracts, and after a second round of manual filtering, patent documents meeting the keyword criteria were retrieved.

After retrieval, patent documents were eliminated based on the following exclusion criteria: (1) if proprietary Chinese medicine was recorded in the herbal extract combination patent document; (2) if pharmaceutical drugs were recorded in the patent document; (3) non-human treatment; (4) disorders other than TCM heart system diseases as verified in *Classification and Codes of Diseases and ZHENG of Traditional Chinese Medicine*[13]; (5) Chinese herbal extract combinations that were only extracted with water or ethanol but not separated or purified.

The name, action, property and taste, channel entered, herbal (botanic) family name of Chinese herbs were recorded based on guidelines delineated in *The Dictionary of Medicinal Plants*.[14] A critical part of our investigation was accurately identifying an herbal extract when more than one name is used for the same plant. For example, in our search we used *bai shao* instead of *shao yao* for *Paeonia lactiflora*.

Microsoft Access (2010) was used to create three databases—patent information database (PID), Chinese herb database (CHD), and the combination of Chinese herbal family database (FCD). PID held the patent numbers, approval dates, compositions of the Chinese herbal extract combinations and indications. TCHD held the names, actions, properties and tastes, channels entered, herbal family names and classifications of Chinese herbs listed in the patent document. FCD held the herbal family compositions of the herbal extract combinations.

Investigation of Chinese herbal extract combination patterns using frequency analysis and cluster analysis

Frequency analysis of Chinese herbs and herbal families was performed using IBM SPSS software (version 20.0; IBM, Armonk, NY, USA) and Microsoft (MS) Access. Analysis was carried out on the frequency of the Chinese herb utilization, channel entered, and herbal families included in extract combinations to prevent and treat heart system diseases. The Chinese herbs were then classified based on the families recorded in *The Dictionary of Medicinal Plants*. The frequency of each category was calculated and items from the high-frequency Chinese herbs and high-frequency herbal families were enumerated separately. The two data sets were linked and analyzed to understand the frequency of the Chinese herb utilization, and to prepare for the next steps.

Cluster analysis was then performed using SPSS. First, the query function of MS Access was used to set up the queries that were extracted from the PID and FCD. Following quantization, the Chinese herbs or herbal families included in the queries were binary coded and expressed as 0 or 1 in SPSS (0 = combination does not contain the herb; 1 = combination contains the herb). Cluster analysis of the Chinese herbs or their families was based on Q-type hierarchical cluster, and between-group linkage was chosen as the clustering method. The distance between two variables was based on the squared Euclidean distance. Finally, a dendrogram was created to represent the cluster analysis data. A dendrogram is a visual presentation of the hierarchical categories of a set of items that have shared characteristics.

Fuzzy cluster analysis of herbs in the same family was accomplished with SPSS as well. First, MS Access was used to set up the queries of Chinese herbs that belonged to high-frequency herbal families, and were identified as treatments for heart system disease for further fuzzy cluster analysis (Queries were retrieved from the CHD). After quantization, the name of the Chinese herbs included in the queries were recorded, their properties and tastes and channel entered of the Chinese herbs included in the queries were recorded as the variables and were binary coded and expressed as 0 or 1 in SPSS. (0 = Chinese herb does not have this nature; 1 = Chinese herb has this nature). Fuzzy cluster analysis of the Chinese herbs in the same herbal family was based on Q-type hierarchical cluster, Ward's method was chosen as the clustering method, distance between two variables was based on squared Euclidean distance, and the data shown as a dendrogram.

Results and discussion

Frequency analysis

Chinese herbs and herbal families

During 1995—2014, a total of 1971 Chinese herbs were included in active patents that claimed they could prevent and treat heart system disease. We found that there were 20 Chinese herbs defined as high-frequency herbs for which the utilization frequency number was greater than 20 times (Table 1). These 20 herbs together accounted for approximately 50% of the total. Among them, the most frequently used Chinese herbs were *Salvia miltiorrhiza*, *Panax ginseng*, *Panax notoginseng*, *Astragalus membranaceus*, and *Ligusticum chuanxiong*. These coincided with high-frequency herbal families — of which the four highest-frequency families were Araliaceae, Leguminosae, Labiatae, and Umbelliferae. Sixteen herbal families were identified as high-frequency families, and the utilization frequency number was greater than 30 times for each family (Table 2). These 16 families together accounted for approximately 74% of the total. In addition, there were many Chinese herbs that were used only once or twice, such as *Panax japonicus* (1), *Caragana intermedia* (1), *Leonurus japonicus* (1), *Foeniculum vulgare* (1), *Peucedanum praeruptorum* (2), *Lilium lancifolium* (2) and *Sophora japonica* (2).

The actions of the highest-frequency Chinese herbs have been confirmed by pharmacologic research. Their active ingredients are largely comprised of polyphenols (such as flavonoids and phenolic acids) and saponins, such as astragaloside IV, icariin, ginsenoside, paeoniflorin, total flavonoids from *Dalbergia odorifera*, butein, and salvianolic acid B.[15–17] There are also other active ingredients such as tanshinone II and glycolipid from *Polygala tenuifolia*.[18] Some common herbs are described below.

S. miltiorrhiza. Active constituents are lipid-soluble tanshinone I (Tan I), tanshinone IIA (Tan II A), cryptotanshinone, and dihydrotanshinone as well as water-soluble

Table 1 High-frequency Chinese herbs to prevent and treat heart system disease.

Rank	Latin herb name	Herbal family name	Frequency number
1	*Salvia miltiorrhiza* Bunge	Labiatae	141
2	*Panax ginseng* C. A. Mey	Araliaceae	94
3	*Panax notoginseng* (Burk) F. H. Chen ex C. Chow	Araliaceae	90
4	*Astragalus membranaceus* Bunge	Leguminosae	73
5	Borneolum syntheticum (sourced from *Dipterocarpus turbinatus* C.F.Gaertn)	Lauraceae	66
6	*Ligusticum chuanxiong* Hort.	Umbelliferae	64
7	*Schisandra chinensis* (Turcz.) Baill.	Schisandraceae	60
8	*Ophiopogon japonicus* (Thunb.) Ker-Gawl.	Liliaceae	59
9	*Angelica sinensis* (Oliv.) Diels	Umbelliferae	46
10	*Paeonia lactiflora* Pall.	Ranunculaceae	35
11	*Epimedium brevicornum* Maxim.	Berberidaceae	33
12	*Dalbergia odorifera* T. Chen.	Leguminosae	33
13	*Carthamus tinctorius* L.	Compositae	33
14	*Rehmannia glutinosa* (Gaertn.) Libosch. ex Fisch. et Mey.	Scrophulariaceae	32
15	*Glycyrrhiza uralensis* Fisch	Leguminosae	29
16	*Pueraria lobata* (Willd.) Ohwi	Leguminosae	27
17	*Ginkgo biloba* L.	Ginkgoaceae	25
18	*Poria cocos* (Schw.) Wolf.	Polyporaceae	24
19	*Acorus tatarinowii* Schott	Araceae	21
20	*Polygala tenuifolia* Willd.	Polygalaceae	21

Table 2 High-frequency herbal families to prevent and treat heart system disease.

Rank	Herbal family name	Frequency number
1	Araliaceae	218
2	Leguminosae	190
3	Labiatae	173
4	Umbelliferae	129
5	Medicinal animal components	127
6	Lauraceae	93
7	Ranunculaceae	88
8	Liliaceae	82
9	Compositae	74
10	Schisandraceae	60
11	Rosaceae	45
12	Scrophulariaceae	44
13	Zingiberaceae	38
14	Polygonaceae	37
15	Berberidaceae	33
16	Rubiaceae	30

danshensu and salvianolic acid B (SAB). *S. miltiorrhiza* has been found to have a cardioprotective effect: SAB inhibits platelet adhesion to collagen[19]; Tan IIA downregulates protein expression and the activities of matrix metalloproteinase-2 and 9 and reduces VCAM-1 and 1L-1β levels to suppress increase in the aorta intimal area in rabbits induced with cardiovascular disease by being fed a high-fat-diet.[20]

P. ginseng and *P. notoginseng*. Both of these herbs are used for treating heart system disease. Their extracts — ginsenosides and *P. notoginseng* saponins (PNS) — contain ginsenoside-Rb1, ginsenoside-Rg1 and ginsenoside-Re. Ginsenoside-Rb1 and ginsenoside-Re have been shown to be active ingredients based on their neuroprotective effects and protection against cerebral ischemia-reperfusion injury in rats; the preventive effect of ginsenoside-Rb1 is more significant than the repair effect.[21] PNS appears to promote proliferation, enhance ALP activity and calcium deposition, as well as induce differentiation tendency toward osteoblasts in NIH3T3 cells.[15]

L. chuanxiong.[22,23] In ICR mice, forebrain ischemic injury can be reduced by Z-liguestilide, which is the main lipophilic component of *L. chuanxiong*, indicating that Z-liguestilide may help prevent cardiovascular disease. Angiotensin II-induced VSMC proliferation is significantly inhibited by ferulic acid, which is the active ingredient of *L. chuanxiong*, in a dose-dependent manner, indicating that ferulic acid may help prevent cardiovascular disease.

A. membranaceus.[24] The active ingredients of *A. membranaceus* are *Astragalus* saponins, *Astragalus* polysaccharide, and *Astragalus* flavone. *A. membranaceus* has the highest content of astragaloside IV among all saponins and shows a protective effect against ischemic heart and brain injury.

Additionally, many of the low-frequency Chinese herbs that belong to the high-frequency herbal families have also been identified to have positive effects on the cardiovascular system. The major active ingredients are similar to those of the high-frequency Chinese herbs. Herbal families and their major active ingredients are[18,25–29]: in Araliaceae, the major active ingredients of *P. japonicus* are saponins; in Labiatae, the major active ingredients of *L. japonicus* are flavonoids; in Leguminosae, the major active ingredients of *C. intermedia* are flavonoids, and the major active ingredients of *Psoralea corylifolia* are flavonoids and the meroterpene bakuchiol; in Umbelliferae, the major active ingredients of *F. vulgare* are volatile oils; in Liliaceae, the major active ingredients of *L. lancifolium* are steroidal saponins and polysaccharides.

Channel entered of the Chinese herbs

TCM theory holds that each herb is associated with a channel(s) of the body, that is, the herb's action enters the channel(s). Some call this the herb's meridian tropism. The heart system disease herbs listed in this article are ones in

Table 3 Channel entered frequency of Chinese herbs identified to prevent and treat heart system diseases.

Channel entered	Frequency number (%)
Liver	1174 (20.9)
Heart	1137 (20.5)
Lung	802 (14.4)
Spleen	760 (13.5)
Kidney	605 (10.9)
Stomach	488 (8.5)
Large intestine	231 (4.0)
Pericardium	220 (4.0)
Gallbladder	131 (2.3)
Bladder	46 (0.8)
Small intestine	4 (0.1)
Triple energizer	4 (0.1)

TCM that treat the liver and heart concurrently and treat the lung and spleen for secondary support (Table 3). All of the herbs in Table 1 enter the liver or heart channel, meaning that they have specific effects on the functioning of these channels and can treat diseases associated with these channels. The exceptions are *A. membranaceus*, *Ginkgo biloba*, and *Pueraria lobata*, which act on the lung and spleen channels.

Cluster analysis identifying the most common herb pairs and the most common herbal family pairs

In TCM, herbal prescriptions are combinations of herbs that are chosen based on the patient's condition and the properties of both the individual herbs and the formula as a whole. The herb pair, or two herbs that are combined to increase or decrease certain effects, is the basic unit in a prescription. Our analysis showed that herb pairs commonly-used to prevent and treat heart system disease are: *P. notoginseng* + *S. miltiorrhiza*; *S. miltiorrhiza* + Borneolum syntheticum; *P. ginseng* + *Schisandra chinensis*; *P. ginseng* + *Ophiopogon japonicus*; *S. chinensis* + *O. japonicus*; *S. miltiorrhiza* + *D. odorifera*; *D. odorifera* + Borneolum syntheticum; *L. chuanxiong* + *Carthamus tinctorius*; *Angelica sinensis* + *P. lactiflora*; *L. chuanxiong* + *P. lactiflora*; and *P. tenuifolia* + *Acorus tatarinowii* (Fig. 1). Common three-herb combinations are: *S. chinensis* + *O. japonicus* + *P. ginseng*; *A. sinensis* + *P. lactiflora* + *C. tinctorius*; and *Poria cocos* + *A. tatarinowii* + *P. tenuifolia*.

Common herbal family pairs used for preventing and treating heart system disease are: Araliaceae + Liliaceae; Lauraceae + Labiatae; Schisandraceae + Araliaceae; Umbelliferae + Ranunculaceae; Schisandraceae + Liliaceae; Labiatae + Leguminosae; Lauraceae + Leguminosae; Rubiaceae + Zingiberaceae; Berberidaceae + Scrophul ariaceae; and Zingiberaceae + Ranunculaceae (Fig. 2).

Fuzzy cluster analysis revealed that most of the common herb pairs also belong to common herbal family pairs. However, the common herbal family pairs do not include all of the common herb pairs.

Most of the common herb pairs are derived from classical TCM prescriptions. For example, the prescription Emperor of Heaven's Special Pill to Tonify the Heart (*tian wang bu xin dan*), which dates to 17th century Ming dynasty, contains the herb pairs *O. japonicus* + *P. ginseng* and *P. ginseng* + *S. chinensis*. Another prescription from 19th century Qing dynasty is Drive Out Stasis from the Mansion of Blood Decoction (*xue fu zhu yu tang*), contains the herb

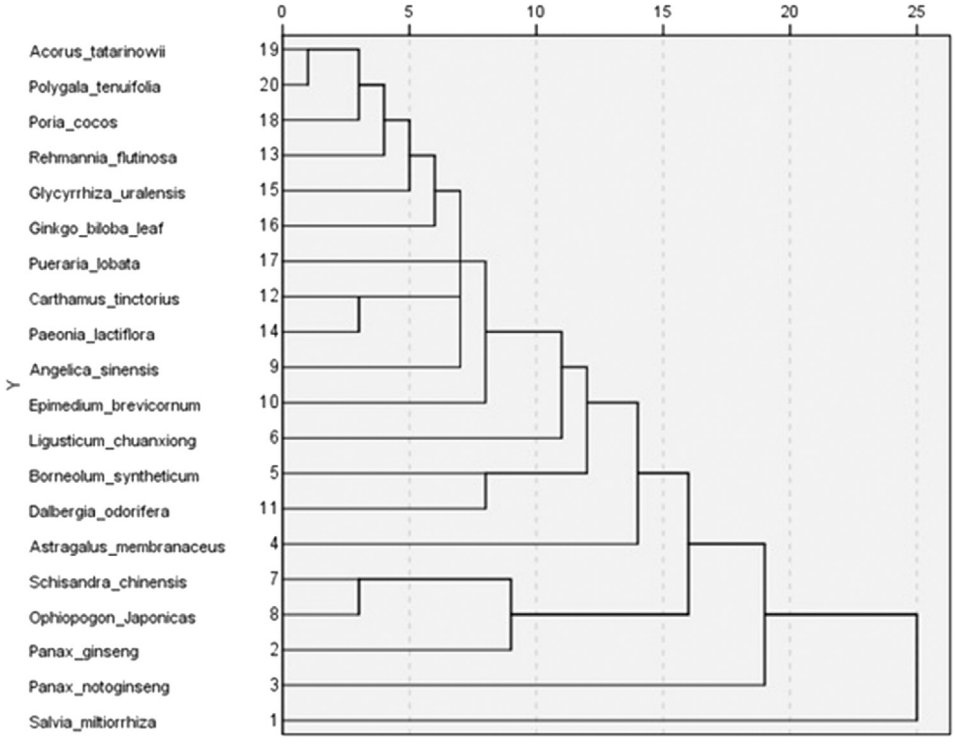

Figure 1 Dendrogram of cluster analysis of Chinese herbal extract combinations to prevent and treat heart system disease.

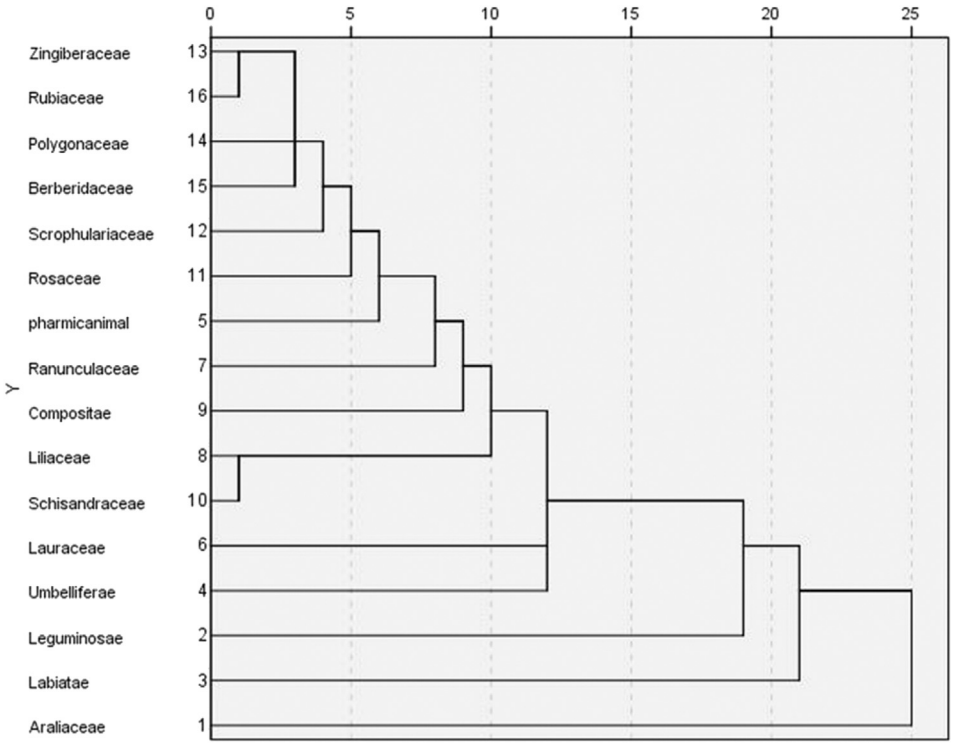

Figure 2 Dendrogram of cluster analysis of herbal families to prevent and treat heart system disease.

pairs *L. chuanxiong* + *C. tinctorius*, *A. sinensis* + *P. lactiflora*, *A. sinensis* + *L. chuanxiong*, and *L. chuanxiong* + *P. lactiflora*. Yet another example is Tonify the Yang to Restore Five [-Tenths] Decoction (*bu yang huan wu tang*), a prescription that also dates to 19th century Qing dynasty, contains the herb pairs *A. membranaceus* + *A. sinensis* and *A. membranaceus* + *P. lactiflora*.[30]

In the tradition of Chinese medicine, it is believed that classical prescriptions have been handed down and persist because they are based on accumulated clinical experience of generations of practitioners. Therefore, the applications and clinical efficacy of herb pairs should not be underestimated. Based on fuzzy cluster analysis of the patents we investigated, we can only speculate on the massive possibility of the combinations of Chinese herb extracts for future research and development.

Fuzzy cluster analysis of Chinese herbs in the same family

Because few Chinese herbs recorded in the patent documents for the prevention and treatment of heart system disease belong to the Lauraceae (4), Schisandraceae (1) and Ranunculaceae families (5), we performed analysis on a select set of families: Araliaceae, Labiatae, Umbelliferae, Liliaceae, and Leguminosae.

Based on fuzzy cluster analysis, some herbs belong to the same category, which is showed similarity in taste and channel entered: in Araliaceae, *P. ginseng*, *Radix ginseng rubra* (steamed *P. ginseng*) and *P. japonicus* belong to the same category (Fig. 3). In Umbelliferae, *L. chuanxiong*, *Ligusticum sinense*, and *F. vulgare* belong to the same category (Fig. 4). In Labiatae, *S. miltiorrhiza* and *A. membranaceus*, *Scutellaria barbata* and *L. japonicus*, *L. japonicus* fruit, *Prunella vulgaris* and *Ajuga decumbens* belong to the same categories (Fig. 5). However, the three categories can also be included under the same larger category when the Chinese herbs from Labiatae are clustered into three categories. In Leguminosae, *P. corylifolia*, *D. odorifera* and *Erythrina variegata*, *A. membranaceus* and *C. intermedia* belong to the same categories (Fig. 6). In Liliaceae, *O. japonicus* and *Fritillaria thunbergii*, *Fritillaria cirrhosa*, *Rohdea japonica* and *Lilium lancifolium* belong to the same categories (Fig. 7).

We found that within the same family, there are many low-frequency Chinese herbs that are similar to high-frequency herbs in terms of taste and channel entered, and many of these herbs have similar active ingredients and applications. For example, *P. ginseng* and *P. japonicus* are both slightly warm in nature, and sweet and slightly bitter in taste, enter the lung and spleen channels, and both have saponins as active ingredients. Their difference is that *P. ginseng* also has affinity for the heart and kidney channels, but *P. japonicus* also has affinity for the liver channel. As another example, *A. membranaceus* and *C. intermedia* are both warm and sweet in taste and enter the spleen channel, and have saponins and flavones as active ingredients. Their difference is that *A. membranaceus* also acts on the lung channel, but *C. intermedia* also acts on the liver channel.

Study limitations

This study has several limitations. First, the database sample size was limited due to the fact that Chinese herbal extract combinations are a new type of formulation developed about 20 years ago. As such, the number of

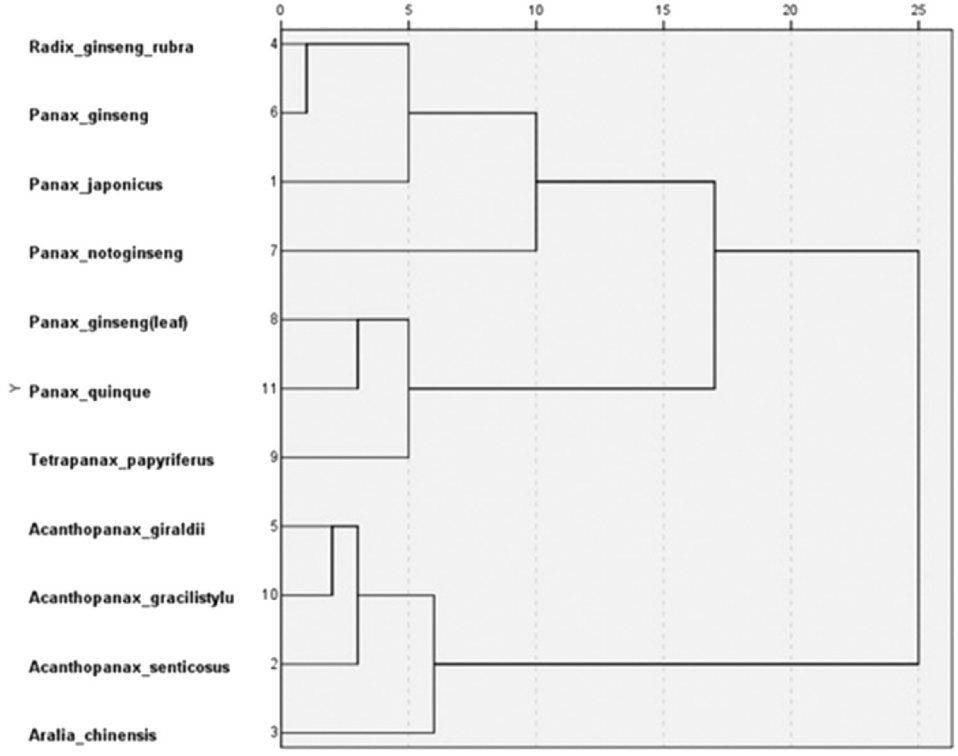

Figure 3 Dendrogram of fuzzy cluster analysis of herbs in the Araliaceae family.

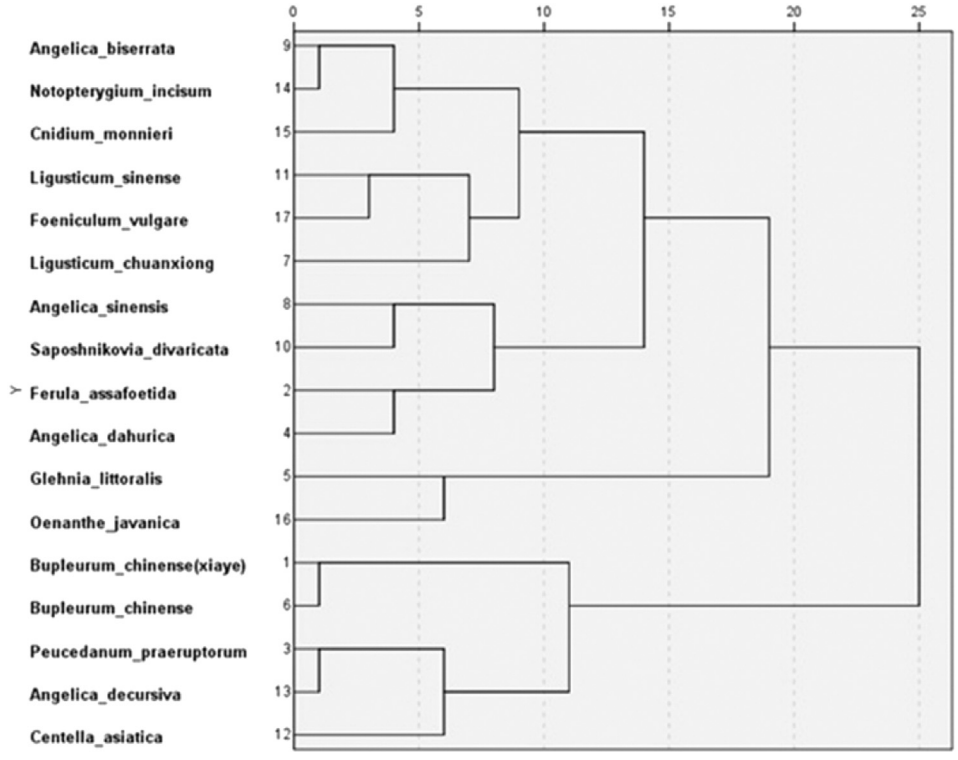

Figure 4 Dendrogram of the fuzzy cluster analysis of herbs in Umbelliferae family.

active patents is limited. Second, the high-frequency Chinese herbs and common herb pairs in this study may not only be used for the prevention and treatment heart system disease. For example, *S. miltiorrhiza* is also commonly used to treat liver system disease. This might be because the extractive fractions in this herb that treat heart system disease are different from the fractions that treat liver system disease. Third, the scope of symptoms is wide.

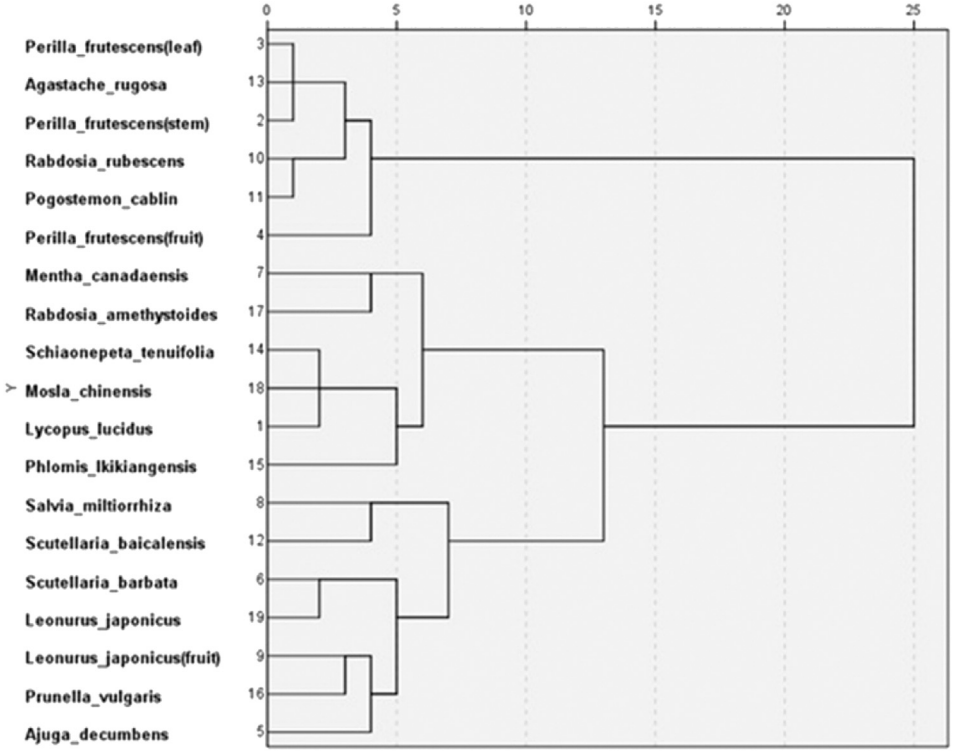

Figure 5 Dendrogram of fuzzy cluster analysis of herbs in the Labiatae family.

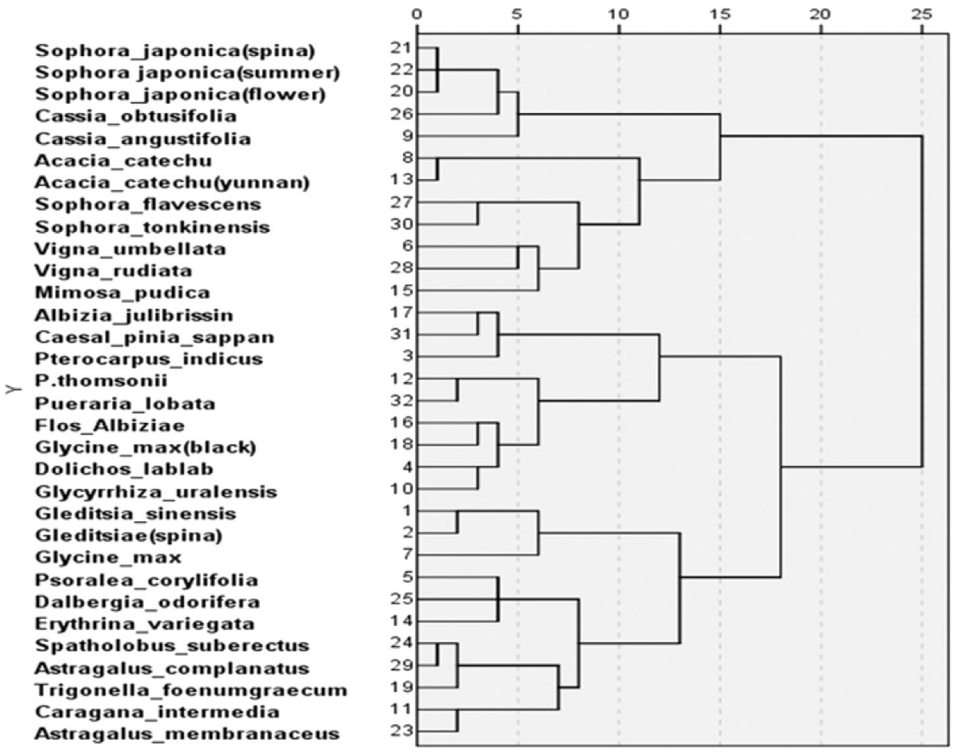

Figure 6 Dendrogram of fuzzy cluster analysis of herbs in Leguminosae family.

According to *Classification and Codes of Diseases and ZHENG of Traditional Chinese Medicine*[13] a professional standard for TCM, heart system diseases encompass many conditions that are considered in biomedicine to belong to other systems of the body such as mental disorders (e.g., depression) and brain disorders (e.g., dementia). Moreover, in TCM, these disorders are often related to each other in terms of traditional categories of disease causation and

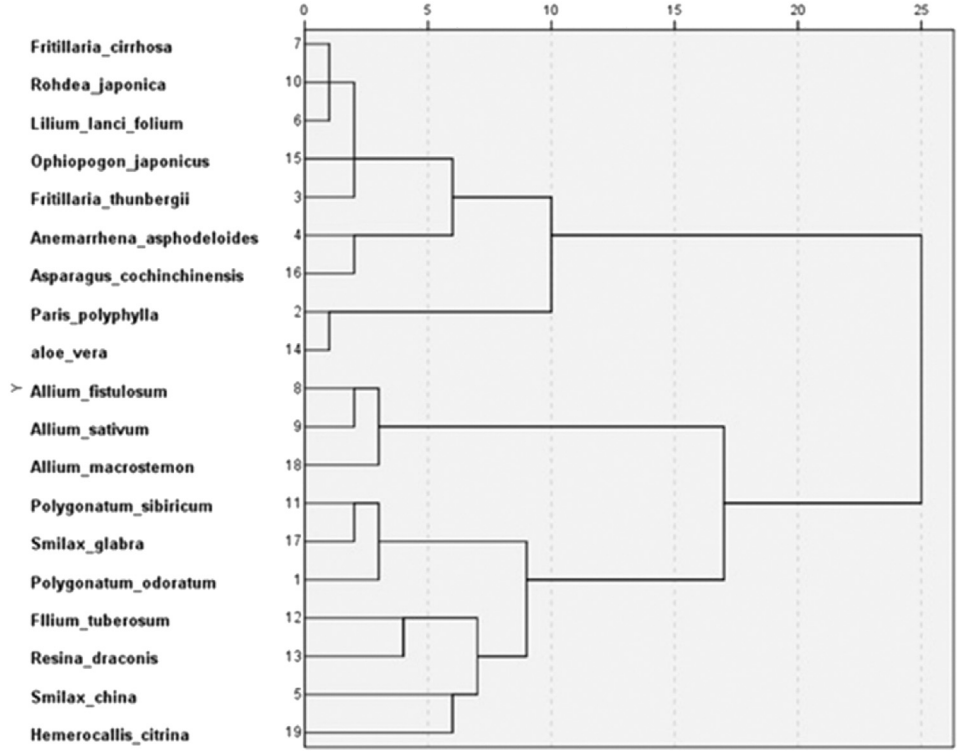

Figure 7 Dendrogram of fuzzy cluster analysis of herbs in Liliaceae family.

development. Thus, further laboratory and clinical studies are needed to confirm which specific biomedical diseases can be prevented and treated with the high-frequency Chinese herbs and common herbal pairs in this study.

Finally, patent documents are a unique scientific and technical literature with advantages and disadvantages. For example, the dosage or the dosage ratio of the herbal extract combinations is typically represented as a numerical range. Therefore, further study is needed to confirm the optimal and specific dosages.

Conclusions

In summary, from the active patents we accessed at the State Intellectual Property Office of the People's Republic of China, common traditional Chinese herbs in herbal extract combinations used to prevent and treat heart system diseases are *S. miltiorrhiza*, *P. ginseng* and *P. notoginseng*. Common herb pairs include *P. notoginseng* + *S. miltiorrhiza*, *S. miltiorrhiza* + Borneolum syntheticum, *P. ginseng* + *S. chinensis*. Herbal extract combinations appear to agree with that of high-frequency herbal families and herbal family pairs. Additionally, the herbs seem to have been selected based on the principles of treating the liver, heart, lung and spleen, as they are understood in TCM.

Furthermore, focusing on low-frequency Chinese herbs that belong to high-frequency herbal families, such as *P. japonicus*, *L. japonicus*, *Caragana intermedia*, and investigating low-frequency herbs combined with high-frequency herbal family pairs may to development new herb pairs and Chinese medicines to prevent and treat heart system diseases.

Because the material foundation of efficacy is more clearly elucidated than the efficacy of a whole Chinese herbal compound, Chinese herbal extract combinations possess higher stability, safety, and controllability. This may explain why foreign patent applications by TCM enterprises have increased in recent years. We conclude that Chinese herbal extract combinations may become a significant medicinal product and that there is great potential for their international development.

Conflict of interests

All authors declare that there is no conflict of interests.

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