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Analysis of the Prescription Regularities of Proprietary Chinese Medicines for Insomnia Based on Data mining

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Abstract: *Objective: To analyze the medication characteristics and regularities of proprietary Chinese medicines for the treatment of insomnia, and to provide new ideas for the clinical treatment of this disease and the research and development of proprietary Chinese medicines. Methods: The prescriptions of proprietary Chinese medicines for the treatment of insomnia were collected from"yaoZH" database, and then Excel 2016, and SPSS Modeler18.0 was employed for frequency statistics, correlation analysis and Apriori association rule. Analysis graphs were drawn using Cytoscape to summarize the patterns of medication use Results: A total of 152 prescriptions were finally screened, involving 336 Chinese herbal medicines, with a cumulative frequency of 1433. The top 5 drugs with the highest cumulative frequency were Danggui (3.07%), Fuling (2.86%), Wuweizi (2.86%), Shudihuang (2.58%) and Huangqi (2.37%). The first place of each order of the drug-drug association rule was Danggui→ Zhiyuanzhi, Chaosuanzaoren+ Danggui→ Fuling; the first place of each order of the drug-symptom association rule was Fuling → Insomnia, Fuling + Danggui → Insomnia. In addition, 152 Chinese patent medicines could treat a total of 66 TCM syndromes, and the top 5 syndromes with the highest treatment frequency were Qi and Blood Deficiency Syndrome (16.5%), Liver and Kidney Deficiency Syndrome (10.9%), Heart and Spleen Deficiency Syndrome (5.21%), Qi and Yin Deficiency Syndrome (4.73%), and Liver Yang Hyperactivity Syndrome (4.26%). Conclusion: The treatment of insomnia with proprietary Chinese medicines is focused on nourishing deficiency, and is particularly good at treating insomnia caused by deficiency of Qi and Blood, deficiency of Liver and Kidney or deficiency of Heart and Spleen, and its main treatment symptoms, apart from insomnia, are most often accompanied by palpitations, fatigue, dizziness and memory loss, which can provide a basis for the clinical treatment of insomnia and the development of proprietary Chinese medicines.*

Keywords: *Insomnia; Proprietary Chinese medicines; Law of medication; Data mining*

1. Introduction

Insomnia refers to the difficulty in falling asleep at night, difficulty in maintaining sleep, decreased sleep quality, and daytime fatigue as the main characteristics of a type of disease, which is the most common clinical sleep disorder [1]. Studies have shown that the incidence of insomnia in adults in the Chinese mainland is as high as 57%, and the age of onset tends to be younger. Insomnia also seriously affects normal work and life [2]. At present, the core of western medicine treatment of insomnia is still to regulate the balance of sleep and awakening by using drugs [3], but it needs to be taken for a long time to bring many adverse effects, such as dependence, addiction and withdrawal reactions, which are not easily accepted by patients. Traditional Chinese medicine (TCM) has a long history in the treatment of insomnia, which can be treated by syndrome differentiation and treatment from multiple perspectives such as Yin and Yang, Rong Wei (Ying wei) and zangfu [4], with good curative effect and few side effects. In the process of clinical diagnosis and treatment, reliable Chinese patent medicines have gradually emerged. This article will collect and sort out the composition of Chinese patent medicines and analyze their rules, so as to provide reference for the development of Chinese patent medicines related to insomnia in the future.

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2. Data and Methods

2.1. Data sources

Through the database of Pharmacointelligence website (https: //db.yaozh.com/) from the Pharmacopoeia of the People's Republic of China (2020 edition), the National Drug Standards, the new National Patent Chinese Medicine database with "insomnia" or "insomnia" as the search term to search.

2.2. Inclusion Criteria

(1) Chinese patent medicine for the treatment of insomnia as the core disease, including tablets, capsules, oral liquid, pill;

(2) Chinese patent medicine composed of Chinese herbal extracts;

(3) The "National Drug approval word" approved by the State Food and Drug Administration.

2.3. Exclusion Criteria

(1) Composing repeated prescriptions;

(2) Medicinal wine, plaster and other preparations.

2.4. Data specification and establishment of database

2.4.1. Data specification

(1) The syndrome names involved in the prescription of Chinese patent medicine were standardized according to the Diagnosis of Traditional Chinese Medicine. For example, "qi deficiency and deficiency syndrome" is unified as "qi and blood deficiency syndrome". (2) Unified the names of all the TCM involved according to the 2020 edition of the Pharmacopoeia of the People's Republic of China. For example, "stir-frying Atractylodes Rhizoma" and "stir-frying Atractylodes Rhizoma Rhizoma (stir-frying with bran)" are unified as "stir-frying Atractylodes Rhizoma rhizoma with bran", and the supplementary materials in the prescription, such as starch and vitamins, are removed at the same time.

2.4.2. Establishment of database

Excel 2016 was used to input the name, composition, function and indications of Chinese patent medicine. SPSS Molder 18.0 was used to analyze the association rules of high-frequency drugs, and the Apriori algorithm was used to explore the potential drug and drug-disease combination. The parameter support was set at 10% and the confidence was 80%. SPSS Statistic 25.0 was used for statistical analysis of high-frequency drugs. The above data were entered by two researchers separately and double-checked by a third researcher.

3. Results

3.1. Screening process of Chinese patent medicine prescriptions

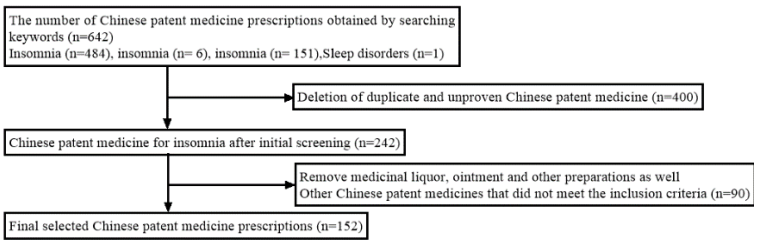

Figure 1: Drug screening process

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Finally, 152 prescriptions of Chinese patent medicine were screened, including 336 TCM, and the total frequency of medicine was 1433 times. See Figure 1.

3.2. High-frequency drug frequency analysis

A total of 152 prescriptions were included, involving 336 Chinese herbs, and the total frequency of drugs was 1433. Among them, the top five drugs were Angelica sinensis (3.07%), Poria coporia (2.86%), Schisandrae fructus (2.86%), Rehmannia radix (2.58%) and Astragalus membranaceus (2.37%), as shown in Table 1.

Table 1: High Frequency Drug Statistics (≥20 times)

Drug	Frequency (times)	Frequency (times)	Drug	Frequency (times)	Frequency (times)
Danggui	44	3.07	Danshen	30	2.09
Fuling	41	2.86	Dihuang	28	1.95
Wuweizi	41	2.86	Gouqizi	28	1.95
Shudihuang	37	2.58	Zhiheshouwu	27	1.88
Huangqi	34	2.37	Dangshen	26	1.81
Maidong	32	2.23	Chaosuanzaoren	25	1.74
Renshen	31	2.16	Chuanxiong	20	1.39

3.3. Analysis of four qi, five tastes and meridians of drugs

Among the 337 herbs, cold (35.8%) and warm (33.0%) were the main four qi agents. The five tastes were mainly sweet (26.1%), bitter (24.3%) and spicy (19.7%). The main meridians entry were liver meridian (21.9%), kidney meridian (15.3%) and heart meridian (13.8%). See Figures 2, 3, and 4.

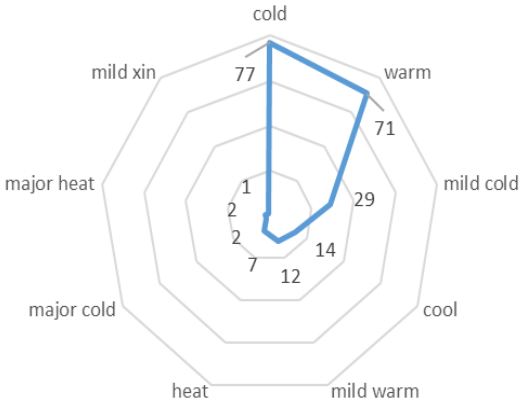

Figure 2: Four qi of drugs

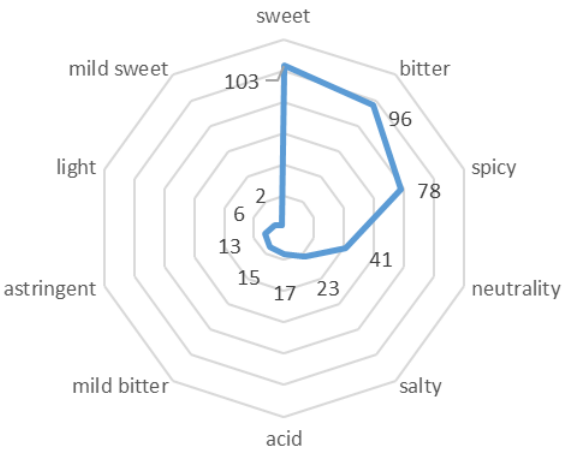

Figure 3: Five tastes of drugs

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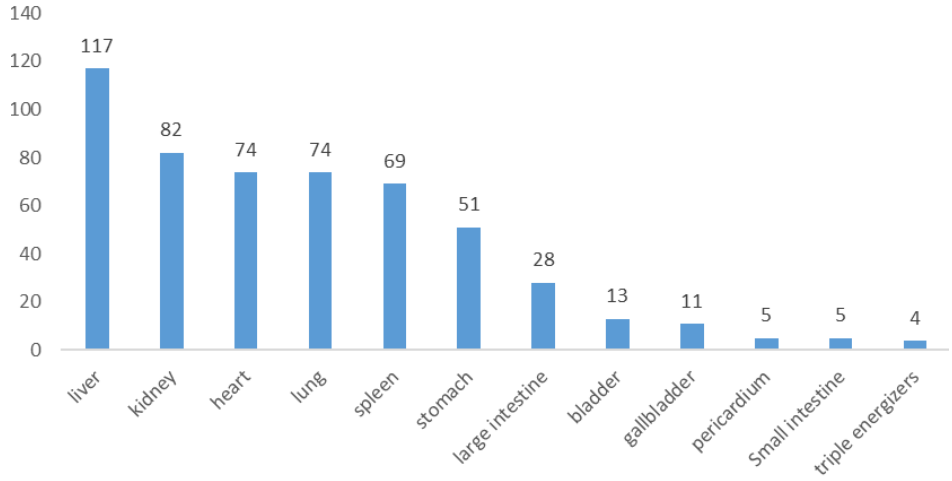

Figure 4: Drug meridian entry

3.4. Analysis of prescription indications

A total of 66 indications of 152 Chinese patent medicines were included. The top three syndromes were deficiency of qi and blood, deficiency of liver and kidney, and deficiency of heart and spleen. See Table 2.

Table 2: Syndrome Statistics (≥5 times)

Syndrome	Frequency (times)	Frequency (%)	Syndrome	Frequency (times)	Frequency (%)
Qi and blood deficiency syndrome	35	16.59	Deficiency of heart and qi	6	2.84
Liver and kidney deficiency syndrome	23	10.9	Spleen and kidney deficiency syndrome	6	2.84
Deficiency of both heart and spleen	11	5.21	Heart and kidney failure	5	2.37
Qi and Yin deficiency syndrome	10	4.74	Yin deficiency of liver and kidney	5	2.37
Hyperthyroidism of liver Yang	9	4.27	Kidney essence deficiency syndrome	5	2.37

3.5. Analysis of core drug association rules

Set the support > 10%, confidence > 60%, and the second-order association rule drug pairs were Danggui → Yuanzhi, Chaosuanzaoren → Zhiyuanzhi, Fuling → Chaosuanzaoren, Shudihuang → Chenpi, Danggui→ Chaosuanzaoren. The third-order association rule drug pair had Chaosuanzaoren + Danggui → Fuling, Chaosuanzaoren + Danggui → Zhiyuanzhi, Shudihuang + Danggui → Maidong, Chaosuanzaoren +Fuling → Danggui, Fuling + Danggui → Chaosuanzaoren. See Tables 3 and 4.

Table 3: Drug-drug second-order association analysis (support > 10%, confidence > 60%)

The former	The latter	Support/%	Confidence/%
Danggui	Zhiyuanzhi	11.18	88.24
Chaosuanzaoren	Zhiyuanzhi	11.18	76.47
Fuling	Chaosuanzaoren	16.45	76.00
Shudihuang	Chenpi	10.53	68.75
Danggui	Chaosuanzaoren	16.45	68.00
Fuling	Zhiyuanzhi	11.18	64.71

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Table 4: Drug-drug third-order association analysis (support > 10%, confidence > 60%)

The former	The latter	Support/%	Confidence/%
Chaosuanzaoren + Danggui	Fuling	11.18	76.47
Chaosuanzaoren + Danggui	Zhiyuanzhi	11.18	70.58
Shudihuang + Danggui	Maidong	10.53	68.75
Chaosuanzaoren + Fuling	Danggui	12.50	68.75
Fuling + Danggui	Chaosuanzaoren	13.15	65.00
Maidong + Wuweizi	Danggui	11.18	64.71
Danggui + Wuweizi	Maidong	11.18	64.71
Maidong + Danggui	Wuweizi	11.84	61.11
Maidong + Danggui	Shudihuang	11.84	61.11

3.6. Drug-symptom association rule analysis

Support > 10%, confidence =100%, drug-symptom third-order association rules were prepared polymonium multitudens + dizziness → insomnia, Chaosuanzaoren + Pachia → insomnia, astragalus + fatigue → insomnia, etc., see Table 5.

Table 5: Drug-symptom third-order association analysis (support > 10%, confidence > 90%)

The former	The latter	Support/%	Confidence/%
Fuling + Danggui	Insomnia	12.82	100.0
Fuling + Chaosuanzaoren	Insomnia	12.18	100.0
Maidong + Danggui	Insomnia	11.54	100.0
Maidong + Wuweizi	Insomnia	10.89	100.0
Shudihuang + Fuling	Insomnia	10.89	100.0
Chaosuanzaoren + Danggui	Insomnia	10.89	94.1
Danshen + Wuweizi	Insomnia	10.89	94.1
Wuweizi + Danggui	Insomnia	10.89	94.1
Shudihuang + Danggui	Insomnia	10.26	100.0

4. Discussion

In this paper, we analyzed the use frequency, four qi and five tastes and meridians of Chinese medicine in the treatment of insomnia, and found that the top three were Angelica sinensis, Poria cohnia and Schisandra chinensis. The most commonly used properties were cold and warm, and the five tastes were sweetness and bitterness, and mainly belonged to the liver meridian and kidney meridian. In Feng Shi Jin Ang Mi Lu (Secret Records of Feng's Jinang), it is recorded that Angelica sinensis is "a medicine for nourishing-blood in the body, but not for activating blood". Later doctors also regarded it as an essential medicine for nourishing-blood. Modern pharmacology points out that the main chemical components of Angelica sinicae are organic components such as volatile oil, polysaccharides, amino acids, and organic acids [5], which can regulate the internal stability of the nervous system by activating the benzodiazepine site of the GABAA receptor and combining with phthalide compounds such as gelispirolide and riligustilide. To achieve sedation, anti-anxiety and neurotrophic effects, so as to prevent insomnia [6]. The nature of the poria is sweet, light and flat, which is beneficial to the water, invigorating the spleen and calming the heart [7]. Pachymia cocos extract (PCET) improves sleep architecture by promoting inhibitory neurotransmission through gamma-aminobutyric acid GABAA receptors [8]. It is based on invigorating the spleen and benefiting the water, which is not equivalent to direct sedation [9]. Schisandrin function can converge solid astringent, benefit qi and body fluid, tonify kidney and calm heart [7], and is widely used in the treatment of neurasthenia and insomnia. The main component of Schisandra chinensis extract is lignan, which is also the most active compound of Schisandra chinensis [10]. It has been confirmed that it can participate in the regulation of hypothalamic 5-HT and 5-HIAA levels in rats, and produce hypnotic effect on insomnia rats [11].

Based on the statistical analysis of the indications of Chinese patent medicines after screening, the top three frequent indications were qi and blood deficiency syndrome, liver and kidney deficiency syndrome and heart and spleen deficiency syndrome. It can be seen that Chinese patent medicines focus on the treatment of insomnia deficiency syndrome. Zhang Ya [12] et al. analyzed the TCM

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syndromes of 1379 patients with insomnia and pointed out that the syndromes of liver depression and fire, Yin deficiency and fire hyperactivity, and deficiency of both heart and spleen were the most common syndromes. Zhang Min [13] et al. collected the information of 1447 patients with insomnia and concluded that the proportion of liver fire disturbance of heart was the highest, followed by the syndrome of stomach qi loss and liver depression and kidney deficiency. Studies have shown that insomnia has the highest correlation with qi deficiency, Yang deficiency, blood stasis and qi stagnation [14]. The occurrence of insomnia is a chronic course [15], and the long-term imbalance of Yin and Yang can cause the accumulation of water, dampness, phlegm, blood stasis and other pathological products, which can be combined with qi, blood, Yin and Yang as a new pathological factor to aggravates insomnia, such as insomnia of qi deficiency and water stagnation, cold water stagnation, and blood stasis and water stagnation [16-18], etc. It is suggested that the treatment of insomnia with Chinese patent medicine still focuses on regulating the deficiency of qi and blood and Yin and Yang of Zangfu organs, and does not pay attention to insomnia caused by pathological products. In addition, there are many types of indications of Chinese patent medicines finally included, and it is still necessary to macro reclassify them to better serve the clinic.

In this study, the drug-drug and drug-symptom association rules were analyzed to reflect the compatibility rules of core drugs in the treatment of insomnia. The second-order drug-drug association rules were Angelica sinensis → preparing gala, Chaosuanzaoren → preparing gala, Poria cocus sinensis → Chaosuanzaoren, cooked rehmannia sinensis → citrus peel, Danggui→ Chaosuanzaoren. The third-order association rules were Chaosuanzaoren + Angelica seed + Angelica seed → Poria cocos, Chaosuanzaoren + Angelica seed + preparing polygala, cooked rehmannia radix + Angelica seed → Ophiolong, Chaosuanzaoren + Pachia cocos → Angelica cocos + Angelica cocos → Chaosuanzaoren. The drug-symptom association rule analysis showed that the core drugs of the third-order rule for insomnia were Poria cocos, Angelica sinensis, Schisandrae fructum, fried jujube kernel, and cooked rehmannia. Angelica sinensis can be replenished for blood deficiency, and can be moistened for blood dryness. The combination of polygala can set the heart and mind at ease, and the combination of jujube kernel can nourish Yin and calm the mind, and nourish the essence and nourish the Yin and blood. Modern medicine has proved [19] that the water extract of jujube seed, Poria codoginseng and Codoginseng can maintain the dynamic balance of excitatory and inhibitory neurotransmitters by regulating the serotonin system in the hypothalamus tissue, so as to improve insomnia. In addition, fried jujube kernel is commonly used in Chinese patent medicine. Jujube kernel achieves the purpose of "effective ripening" in the theory of raw and cooked after frying, and its sedative and hypnotic effect is slightly stronger than that of raw jujube kernel [20]. Tangpi invigorates spleen and regulates qi, compatibility can be filled without retention; Polygala has a protective effect on the central nervous system [21]. By regulating gabaergic signaling pathway, it can induce sedation and hypnosis in elderly rats with insomnia [22]. The core drugs obtained were the constituent drugs of Tianwangbuxindan and Suanzaoren decoction. Xie Guangjing [23] et al confirmed that TianwangBuxin Dan could improve the symptoms of insomnia model rats by regulating the protein expression of Trx system Trx2 and TrxR2. In addition, TianwangBuxin Dan could improve the SCN damage caused by insomnia in rats and reduce the damage of mitochondria, endoplasmic reticulum and other organelles. Zaoren decoction can treat insomnia by regulating the levels of excitatory neurotransmitters and inhibitory neurotransmitters, or affecting other sleep factors [24].

In conclusion, the current Chinese patent medicine is more focused on "tonic" and "nourishment" than "sedative" in the treatment of insomnia. This coincides with Professor Tong Xiao-lin's idea that TCM treats diseases through macro "state regulation", that is, aiming at various disease "states" manifested by the imbalance of Yin and Yang in insomnia, different drugs are used to regulate them through the bias of different drugs, so that Yin and Yang of the body are kept secret and insomnia is gradually alleviated [25]. However, Chinese medicine ignores the "targeting" of insomnia, and uses less target drugs such as keelbone, oyster and other sedative drugs in the prescription. It is difficult to take into account the most obvious symptoms of insomnia, such as difficulty falling asleep, waking up early after light sleep [26], and its accompanying mental and emotional changes, depressive disorders, anxiety disorders, etc. [27]. On the one hand, the composition of Chinese patent medicine is single in the "modulation" of syndrome differentiation, and the influence of liver and stomach pathological changes on sleep is ignored, especially the pathological factors such as liver depression and liver fire. On the other hand, the syndrome differentiation of Chinese patent medicine is not standard, and its indications are various, which cannot reach the height of unifying "syndrome" by "state".

Therefore, it is still necessary to further systematically summarize the characteristics of TCM for insomnia and its accompanying symptoms, strive to realize the combination of TCM and modern medicine at macro and micro levels, and show the advantages of population and multi-target of Chinese

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patent medicine to a greater extent, which is the only way for the development of Chinese patent medicine.

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