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Exploring the medication pattern of Sun Simiao's Thousand Gold Formula for the treatment of infertility based on data mining techniques

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Abstract

Objective: To explore the medication and compounding rules of Sun Simiao's Qianjin Fang for infertility in Tang Dynasty by using data mining technology and relying on the Chinese Medicine Inheritance Auxiliary Platform System (V2.5). **METHODS:** The Chinese herbal prescriptions in Qianjinfang for infertility were collected, and their drug composition was sorted out and screened, and the prescription database was constructed by the Traditional Chinese Medicine Inheritance Auxiliary Platform System (V2.5). Frequency analysis, correlation rule and cluster analysis were used for the statistical analysis of the data. **Results:** A total of 19 prescriptions and compound prescriptions were included, involving 90 kinds of Chinese medicines; the total frequency of the medicines was 288 times, of which the top 5 high-frequency Chinese medicines were XiXin, Renseng, Gan Jiang, Angelica sinensis and Rehmannia glutinosa. **Conclusion:** The formulas were mainly characteristic by breaking down the channels, tonify the kidney and warming the yang, clearing dampness and heat in the lower energizer, nourishing the yin, drying dampness and killing dampness, or supplementing to greatly tonify the vital energy, ease the liver and relieve depression, tranquility the mind, and clearing the collateral and dispersing the knots.

Keywords: Infertility; Sun Simiao; Qianjin Fang; medication pattern; data-mining

Infertility refers to those who have not contraceptives after marriage, have normal sexual life,

cohabitation for 2 years without conception[1]; or have had a pregnancy, no contraception and 1 year without conception, known as infertility. The former is primary infertility, which is referred to as "total infertility" and the latter as "intermittent" in "The Essential Formula of the Thousand Golden Jewellery for Emergency Preparation"[2] . When one of the spouses has congenital or acquired anatomical or functional defects that cannot be corrected and cannot lead to conception, it is called absolute infertility; those who can still conceive after appropriate treatment are called relative infertility.

Sun Simiao was a famous Chinese medicine practitioner in the Sui and Tang dynasties, honored as the "King of Medicine", and his main works include the "Thousand Gold Recipes for Emergencies" and the "Thousand Gold Wings", which are collectively known as the "Thousand Gold Recipes". Sun Simiao, a famous doctor in the Tang Dynasty, believed that "human life is most important, and there is a precious thousand jin, a party to help, the virtue is more than this", so the two medical books are titled "thousand jin" two words. The "Preparing for the emergency Qianjin to be prescribed (referred to as Qianjin Fang)"[3] , a systematic summary of the achievements of medical science before the Tang Dynasty, has a high academic level and clinical value, known as China's earliest encyclopedic of medical science[4] . Infertility is a complex disease involving multiple disciplines, with causes covering five major categories: female ovulation disorders, pelvic pathology, male infertility, immune factors and unknown causes. Infertility is not only a medical problem, but also a social problem. In recent years, the incidence of infertility has risen as the age of marriage and childbearing has been delayed. As we all know, Chinese medicine has unique advantages in the field of gynaecologist diseases, and exploring the theory and characteristics of infertility treatment in Qian Jin Fang is undoubtedly of great theoretical significance and clinical guidance value for the treatment of infertility in Chinese medicine[5].

1 Information and methodology

- 1.1 Source: Compilation of prescriptions for the treatment of infertility contained in the Tang Dynasty medical text Qianjinfang (千金方), a total of 19 prescriptions were included in the study.
- 1.2 Data standardization The names of the included Chinese medicines were standardized according to the standards of the Pharmacopoeia of the People's Republic of China[6] and the Chinese Materia Medica[7] . For example, the name of *Dioscorea* spp. was changed to yam; and the names of Dungeness Park, Squid Bone, Park Nitrate, White Gum, Mung Meng and Ziwei were changed to Houpu, Cuttlebone, Mangnit, Deer Antler Gum, Purple Ginseng and Lingxiao Flower respectively. For some special medicines not included in the Pharmacopoeia and the Traditional Chinese Medicine, such as Ge Shang Ting Chang, ulcer, grub. Refer to the efficacy of the original text in which they are found.
- 1.3 **Data analysis** Use the "Data Analysis Module" in the TCM Inheritance Support System

v2.5 for "Frequency Statistics", "Analysis of Formulas", "Analysis of New Formulas", and so on. Data Analysis Module" in TCM Inheritance Support System v2.5

1.4 To extract the data source, enter "Gynaecological Infertility" in "Chinese Medicine Diseases" to search for the prescription and extract it.

1.5 Frequency statistics of drugs were analysed and frequency of all drugs in the extracted formulae were analysed and derived in descending order.

1.6 Analysis of the pattern of formulas

1.7 The analysis mainly includes the frequency of drug use, the four qi and five flavour of the drug, the distribution of basic drugs, and then on this basis, association rule analysis and cluster analysis, to obtain the common drug combinations and new combinations of drugs, to explore Sun Simiao's treatment of infertility with the law of prescription and use of drugs.

2 Results

2.1 There are 19 infertility prescriptions in Qian Jin Fang, involving 90 flavours of traditional Chinese medicine, with a cumulative frequency of 288. There are 6 flavours of medicines that have been used ≥ 8 times or more, and in descending order of frequency, they are: Xin Xin (fine acrid), Ginseng (*Panax ginseng*), Gan Jiang (dried ginger), Angelica sinensis (Chinese angelica), Dihuang (root rhubarb), Schizandra chinensis (*Schizandra chinensis*).

See table 1.

table 1 chinese medicine with a frequency of ≥ 8

Serial number	medicine	Frequency of occurrence	Serial number	medicine	Frequency of occurrence
1	asarum	9	4	danggui	8
2	ginseng	9	5	Shengdi	8
3	ganjiang	8	6	schisandra chinensis	8

2.2 Statistics on the four qi, five flavours and meridians of the drugs in the infertility formulae in the Qianjin Fang. The "four qi" of the medicines were analysed, and it could be seen that warm medicines were in the first place (107 times), followed by cold medicines (55 times), flat medicines (49 times), hot medicines (25 times) and cool medicines (1 time), as shown in Table 2.

table 2 Four gas distribution

Serial number	Four properties	Frequency	Serial number	Four properties	Frequency
1	warm	107	4	hot	49
2	cold	55	5	cool	25
3	flat	55			

The analysis of the "five flavours" of the drugs shows that the sweet drugs are the main ones (139 times), followed by the pungent drugs (106 times), bitter drugs (103 times), sour drugs (24 times), salty drugs (17 times) and astringent drugs (8 times). See Table 3

Table 3 Five taste distribution

Serial number	Five taste	Frequency	Serial number	Five taste	Frequency
1	sweet	139	4	sour	24
2	pungent	106	5	salty	17
3	bitter	103	6	astringent	8

Analysis of the drugs to the meridians showed that they were most frequently attributed to the kidney meridian (133 times), followed by the liver meridian (113 times), heart meridian (108 times), spleen meridian (89 times), lung meridian (84 times), stomach meridian (73 times), large intestine meridian (25 times), gallbladder meridian (13 times), pericardium meridian (8 times), and urinary bladder meridian (7 times), respectively. See Figure 1

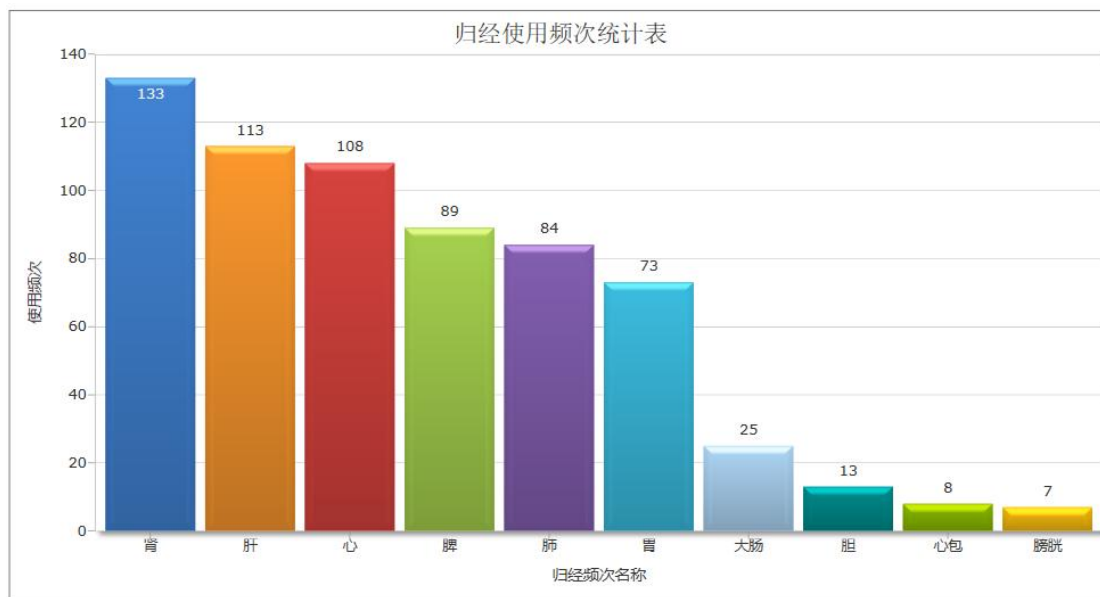


Fig. 1 Statistical chart of the frequency of use of the attributes

2.3 The formulas of Qianjinfang for treating infertility were analyzed by drug association rules, with support set to 5 and confidence level 0.6. 57 drug combinations could be obtained. Sorted by frequency, the top 6 combinations in terms of support were *Angelica sinensis* - *Ginger*, *Angelica sinensis* - *Cynanchum officinale*, *Panax ginseng* - *Cynanchum officinale*, *Panax ginseng* - *Angelica sinensis*, *Cuscuta chinensis* - *Fructus schisandrae chinensis*, and *Radix et Rhizoma Ligustici Chuanxiong* (see Table 4 for details). The confidence level was set to 0.75, and 18 sets of association rules were analysed, as shown in Table 5. The correlations between the drugs were displayed by networking, as shown in Table 4

Table 4 Analysis of two kinds of drug combination mode

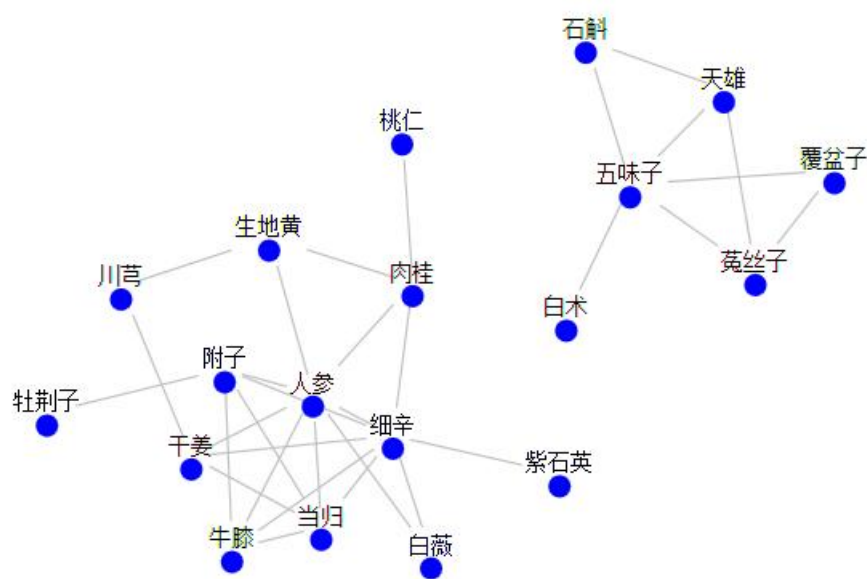
Serial number	Drug model	Frequency	Serial number	Drug model	Frequency
1	danggui, ganjiang	7	4	ginseng, danggui	7
2	danggui, asarum	7	5	dodder, schisandra chinensis	6
3	ginseng, asarum	7	6	shengdihuang, ligusticum wallichii	6

Table 5 Association rule analysis results (confidence coefficient ≥ 0.75)

Serial number	rule	confidence coefficient	Serial number	rule	confidence coefficient
1	danggui->asarum	0.875	10	ginseng, danggui->asarum	0.85714

2	ganjiang->danggui	0.875	11	danggui ,ganjiang->ginseng	0.8571
3	danggui->ganjiang	0.875	12	ginseng,danggui->ganjiang	0.8571
4	danggu->ginseng	0.875	13	danggui,ganjiang ->asarum	0.8571
5	ligusticum wallichill->shengdihuang	0.85714	14	danggui,asarum ->ganjiang	0.85
6	aconite->mujingzi	0.85714	15	ginseng ->danggui	0.7778
7	ginseng,asarum ->Towtooth AchyranthesRoot	0.85714	16	asarum ->ginseng	0.77
8	danggui,asarum->ginseng	0.85714	17	ginseng->asarum	0.77
9	ginseng,asarum->danggui	0.85714	18	asarum ->danggui	0.77

Fig. 2 Display of the network of related Chinese medicine combinations



2.4 Cluster analysis of drugs in the treatment of infertility formulae in Qianjinfang was carried out by setting the correlation degree to 5 and the penalty degree to 2. A total of 7 groups of core drug groups were obtained from the analysis. They were schizandra - raspberry - tianxiong, angelica - hyssop - Houpu, xinxing - ginseng - bei shashen, schizandra - dodder - ginseng, cinnamon - poria - mudanpi, raspberry - tianxiong - pterodactyls macrophage, and zingier officialese - dendrology - antler velvet. Five new prescription combinations were obtained, see Table 6 for details.

Table 6 New formulation analysis table

Serial number	new formulation
1	schisangra chinensis-Fupenzi-Tianxiong-Baizhu
2	danggui-Towtooth AchyranthesRoot-Houpu-Rougui
3	schisangra chinensis-Dodder-ginseng-Fupenzi
4	Rougui-Fuling-Mudanpi-ginseng
5	Mujingzi-Dendrobe-Cartialgenous-Fuling

3 Discussion

The etiology of infertility is complex and varied, in clinical treatment, attention should be paid to the combination of dialectical disease and dialectical evidence, and add and subtract according to the evidence, qi stagnation is given to qi medicines (Xiangsui, Chenpi, etc.) to dredge the liver and regulate the qi. For deficiency of qi and blood, tonic medicines (ginseng, antler gelatin, etc.) should be given.

Analysis of the medicines in the formula Individual medicines used more than 5 times include Sinapis, Radix Panax Ginseng, Radix et Rhizoma Ginger, Radix Angelicae Sinensis, Radix et Rhizoma Dioscoreae, Fructus Schisandraeae, Cortex Cinnamomi, Radix Achyranthis Bidentatae, Rhizoma Ligustici Chuanxiong, Radix Pseudostemonis. Medicines used more frequently than 3 to 4 times include Hou Pu, Hua Pepper, Dry Ginger, Poria, Dendrobium, Gentiana Macrophyllae, Ziyang Shi, Fenghuang, and Cortex Eucommiae. The drugs have the following properties: tonifying qi and blood, assisting yang and warming the uterus, tonifying kidney and yang, promoting blood circulation and removing blood stasis.

3.1.1 Medicines for tonifying Qi and Blood Ginseng is sweet, bitter and slightly warm, and belongs to the Lung, Spleen and Heart meridians. It can replenish vital energy, tonify the Qi of the spleen and lungs, and promote the production of fluids, making it an important medicine for tonifying the spleen. It has the function of tonifying Qi to generate and regulate Blood. It is used to treat long-term blood loss due to weakness of the spleen qi, or deficiency of qi and blood due to weakness of the spleen qi, which is unable to produce blood. Di Huang belongs to the liver and kidney meridians, is sweet and warm, and can nourish yin and benefit the essence to produce blood, and is an important medicine for nourishing blood and nourishing deficiency.

3.1.2 Yang-aiding and warming drugs Cinnamon is pungent, sweet and hot, and belongs to the kidney, spleen, heart and liver meridians. It is used to replenish fire and help yang, disperse cold

and relieve pain, warm up the meridians and pass through the veins, and draw fire back to the source of energy, and is a key drug in treating cold impotence in the uterus and failure of the life gate fire. Xin Xin is pungent and warm, belonging to the lung, kidney and heart meridians, dispersing cold, dispelling wind and relieving pain, and opening the orifices. It can enter the lung meridian to disperse wind-cold in the surface, and enter the kidney meridian to remove the cold in the interior. It is pungent, sweet and hot, and belongs to the heart, kidney and spleen meridians. It can restore yang and save the body, tonify fire and help yang, dispel cold and relieve pain, help heart yang upwards, warm spleen yang in the middle, and tonify kidney yang downwards, and cure impotence and slippery semen due to deficiency of kidney yang and failure of fire in the life gate, infertility due to uterine coldness, and cold pain in lumbar and knee.

3.1.3 Drugs that tonify the kidney and yang Niu Knee and Cortex Eucommiae both belong to the Liver and Kidney meridians, and have the functions of tonifying the liver and kidney and strengthening the muscles and bones. Cortex Eucommiae can support and strengthen the root of the liver and kidney, while *Achyranthes Bidentata* invigorates blood circulation and promotes menstruation, induces diuresis and lymphatic flow, and induces blood to flow downward, treating amenorrhoea and dysmenorrhoea caused by stagnation of blood.

3.1.4 Drugs for promoting blood circulation and eliminating blood stasis *Angelica sinensis*, *Rhizoma Ligustici Chuanxiong* and *Rhizoma Dioscoreae*, based on Four Substances Soup, can tonify and regulate blood circulation, treating menstrual disorders caused by deficiency of the Chong Ren, pain in the lower abdomen caused by cold and stagnation of the Lower Jiao, hardness of the obstruction in the abdomen, and leakage in the middle of the menstrual flow in the case of deficiency of the Kidneys and lack of solidity of the Chong Ren. The combination of medicines can tonify blood without stagnating blood, move blood without destroying blood, and there is dispersal in tonification, which is an important formula for regulating menstruation by tonifying and invigorating blood.

In the Thousand Gold Formula, the four qi of the drugs are warm, the five flavours are sweet and pungent, and the attributed meridians are the kidney meridian and the liver meridian for the first time. Through the analysis of the core drugs attributed to the meridian, function and main treatment, it can be found that the treatment of infertility is mostly based on four aspects: deficiency of qi and blood, cold uterus, stagnation of the uterus, and deficiency and decline of kidney qi, and this is the main line running through the whole process of identifying and applying treatments, and adding and subtracting according to the evidence. If there is deficiency of kidney yang, insufficient essence and blood, deficiency of the channels of Chong Ren, no power to warm and warm the uterus, resulting in prolonged infertility, the treatment is to tonify the spleen and kidneys, and to warm and nourish the uterus. If cold pain in the lower abdomen is accompanied by obstruction in the abdomen, irregular menstrual flow, internal stagnation of blood stasis and obstruction of the uterus, resulting in failure to conceive, the treatment is to

expel blood stasis, regulate menstruation and assist in conception[8].

In the treatment of infertility in the Thousand Golden Formulas, emphasis is placed on treating both men and women together. Sun Simiao believes that "Yin and Yang are in harmony, the two qi are in contact with each other, and Yang applies to Yin" in order to get a child, and he points out that the reason for childlessness should be found in both husband and wife.[9] "All people without children, when the couple for the five labours and seven injuries, deficiency and illnesses caused by the heir of the disaster, so there is no heir", which in the ancient times of the husband is shocking, may not be accepted by the majority of the people, but now seems to be a very objective and scientific point of view. In terms of etiology, he believed that infertility was caused by "deficiency of qi and blood, and weakness of kidney qi", and the main method of treatment was to warm the meridians to eliminate blood stasis and warm the qi and blood. He proposed that the treatment of infertility for men should be based on essence and tonifying the kidneys; for women, blood should be the mainstay and regulating menstruation should be the first priority. "The way of fertility begins with the search for a child, the method of searching for a child, the man is noble in purity of mind and desire, in order to nourish its essence; the woman should be calm and determined in order to nourish its blood". In the treatment also advocates the same treatment for men and women, "the calamity of heirloom, the method of treatment, men serve seven son of the San, women serve purple Shimendong Pills, and sit on the medicines swinging cell soup, there are no children also". The treatment of women since the establishment of all non-production and intermittent long non-production of thirty years, the whole formula to activate the blood as the main, get rid of the uterus blood and evil, the attack down the force is very fierce, after the day after the "heart of the blood and cold red pus such as a small soybean juice", still have to guide the medicine, with the sit-guide formula (raspberry pods, Cornu Cervi Pantomimic, Angelica insistence, Manchurian officinale, Fructose schisandrae chines, Gan Ginger, Rheum illustrious, alum stone, Ron salt, Sichuan pepper for the end of a silk bag, three inches long, the woman in the yin, once a day), "must be under the green and yellow cold juice", make sure that the cold juice drain, and then "you can be lucky to defend". At the same time in the administration of flexible ways, soup, pills, baths and combustion and use.

By analysis the pattern of the formula and the characteristics of the medication used in the formula for seeking children, it is believed that before the Tang Dynasty, the etiology and pathogenesis of infertility were mainly discussed and treated in six aspects, namely, deficiency of qi and blood, insufficiency of the liver and kidneys, deficiency of kidney qi, coldness of the uterus, deficiency of yin and internal heat, and stagnation of the cystic uterus. With the continuous development and progress of society, the etiology and mechanism of infertility have also increased. The incidence of menstrual disorders and infertility caused by liver depression and emotional disorders has gradually increased; the sufficient material conditions of life, unclean diet, eating fat, sweet and thick flavour, phlegm-dampness internal obstruction, and

spleen-dampness loss of movement leading to menstrual disorders and infertility has become an important morbidity factor.

4 Summary

To sum up, infertility is not an independent disease and is caused by many gynaecologist diseases. Infertility is caused by kidney deficiency as the root cause and stagnation of qi, blood stasis, phlegm and dampness as the symptoms. "Nourishing the kidney is the mainstay," "treating the belt is the first step," "phlegm and blood stasis are treated together," "men and women are treated together," and a combination of external treatment and acupuncture treatment, acupuncture and combustion, etc. The treatment of infertility in the Thousand Gold Formula has unique insights. The treatment methods and medicines are of high significance in the current clinical practice.

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Appendix

Asarum-细辛	Fupenzi-覆盆子
Ginseng-人参	Tianxiong-天雄
Ganjiang-干姜	Baizhu-白术
Danggui-当归	Houpu-厚朴
Shengdi-生地	Rougui-肉桂
Schisandra chinensis-五味子	Fuling-茯苓
Dodder-菟丝子	Mudanpi-牡丹皮
Shengdihuang-生地黄	Cartia lgenous-鹿茸
Four properties-四气	Dendrobe-石斛
Five tastes-五味	
Warm-温	
Cold-寒	
Flat-平	
Hot-热	
Cool-凉	
Sweet-甘	
Sour-酸	
Bitter-苦	
Pungent-辛	
Salty-咸	
Astringent-涩	
Mujingzi-牡荆子	

Aconite-附子

Ligusticum Wallichill-川芎

Two tooth Achyranthes root-牛膝