

# *Xu Jianqin's Medication Rules of Safflower in the Treatment of Diabetes Mellitus and Its Complications Based on the Traditional Chinese Medicine Inheritance Assistance Platform*

Wu Yun<sup>1,a</sup>, Qu Kai<sup>2,b</sup>, Zhou Ting<sup>1,c</sup>, Ding Yanlin<sup>1,d</sup>, Xie Lei<sup>1,e</sup>, Xu Jianqin<sup>2,f,\*</sup>

<sup>1</sup>Shaanxi University of Chinese Medicine, Xiayang, China

<sup>2</sup>Shaanxi Province Hospital of Traditional Chinese Medicine, Xi'an, China

<sup>a</sup>1357544245@qq.com, <sup>b</sup>1813537577@qq.com, <sup>c</sup>542195424@qq.com, <sup>d</sup>1961902508@qq.com,

<sup>e</sup>1018711076@qq.com, <sup>f</sup>xjq0516@163.com

\*Corresponding author

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**Abstract:** Our purpose is to investigate the clinical application of Xu Jianqin, chief physician, in the treatment of diabetes mellitus and its complications based on data mining. Our method was to collect 222 medical records of chief physician Xu Jianqin's outpatient clinic that contained safflower in the treatment of diabetes and its complications (including 74 cases of safflower in the treatment of diabetes and 148 cases of safflower in the treatment of diabetic complications). The "TCM Inheritance Auxiliary platform (V2.5)" was used to mine and analyze the syndrome distribution, core medication, association rules and cluster analysis of the data. The results of this study were as follows: there are 128 traditional Chinese medicines were included in 222 data collected. Among the medical records of safflower treatment for diabetes and its complications, there were 7 safflower dosage frequency  $\geq 10$  times, which were 12g, 6g, 9g and 15g in descending order, respectively. There were 12 kinds of symptoms  $\geq 50$  times of safflower in the treatment of diabetes and its complications. In the two databases, there are 26 kinds of drug combination patterns, 13 kinds of drug combination patterns, 44 association rules, 25 association rules, and 3 core combinations were obtained by association rules and cluster analysis, respectively. We concluded that by summarizing the rules of Doctor Xu's application of safflower in the treatment of this disease, we analyzed that safflower can remove the visible stasis and prevent the stagnation that has not yet formed, so as to provide reference value for the clinical application of safflower in the later stage.

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia, and the global diabetes map released by the International Diabetes Federation (IDF) shows that 537 million adult diabetic patients have been diagnosed worldwide in 2021, and the number of patients is increasing compared with 2019 [1-2]. China has the largest number of adults with diabetes. In the past 10 years (2011-2021), the number of patients with diabetes in China has increased by 56%, and it is

predicted that this number will reach 174.4 million by 2045<sup>[3]</sup>. How to effectively prevent and treat it has become a hot spot and difficulty in current research.

Xu Jianqin, chief physician of the research group, is a famous doctor of traditional Chinese medicine in Shaanxi Province and a national chief physician of level I. Based on many years of clinical experience and academic accumulation, Dr. Xu proposed that the key pathogenesis of diabetes and various changes in the later stage is mainly based on spleen does not evacuate subtle material throughout body<sup>[4]</sup> and triple energizer dysfunction. However, the pathological products of spleen disharmony can be basically classified into two categories: phlegm and blood stasis. So phlegm and blood stasis are mutually causal, and blood stasis runs through the whole course of diabetes<sup>[5]</sup>. Therefore, in the treatment of diabetes and its complications, Dr. Xu attaches importance to activating blood circulation and Xuanton on the basis of regulating the spleen and stomach function. Modern studies have shown that safflower can treat metabolic diseases by regulating metabolism-related pathways, especially relieving and protecting complications associated with diabetic blood stasis<sup>[5-6]</sup>.

## **1. Materials and Methods**

### **1.1 Data Sources**

The prescriptions of this study were obtained from the medical records of Xu Jianqin Traditional Chinese Medicine Studio of Shaanxi Provincial Hospital of Traditional Chinese Medicine who were first diagnosed with "type 2 diabetes (diabetes)" and various complications of diabetes from June 1, 2020 to June 1, 2022.

### **1.2 Prescription screening**

#### **1.2.1 Inclusion criteria:**

(1) The selected medical records must contain prescriptions reflecting safflower treatment of diabetes and its complications; (2) The selected medical records must have complete symptoms and syndromes, complete prescription composition, and complete drug dose; (3) The selected medical records must be based on oral decoction of traditional Chinese medicine.

#### **1.2.2 Exclusion criteria:**

(1) Prescriptions for treatment with only Chinese patent medicine or western medicine; (2) Prescription for free-decoction granules; (3) Repeated prescription; (4) Prescriptions for combining Chinese patent medicine or western medicine treatment.

### **1.3 Collation results**

According to the above inclusion criteria, there are 222 datas were obtained after collation, and the data were entered into database 1 and database 2 according to the disease name of diabetes and diabetic complications, respectively.

### **1.4 Drug specifications**

Refer to the Chinese *Pharmacopoeia* 2020<sup>[7]</sup> for the name of traditional Chinese medicine (TCM), we unify the name of traditional Chinese medicine of the formula.

## 1.5 Data analysis

We using the "TCM Inheritance Computing Platform (V2.5)" to statistically analyze the medical record data that meet the inclusion criteria, and mainly applies two major modules: "statistical report" and "data analysis", in the software to explore the formula rules in the treatment of diabetes and its complications.

## 2. Results

### 2.1 Statistical analysis

There are 128 herbs were included among 222 prescriptions in databases 1 and 2. In the statistical analysis → medical record analysis → syndrome statistics, we can obtain the frequency distribution of syndromes of safflower in the treatment of diabetes, with a total of 7 syndromes at frequencies  $\geq 10$  times, as shown in Table 1. Through data analysis → formula analysis → medicinal herb dosage input safflower, we can obtain the dosage and frequency of safflower in the treatment of diabetes and its complications. The dosage of safflower is in the range of 6 to 15 g. In the "data analysis" module, we input TCM syndromes to filter out the data of the corresponding syndrome types. Inputting "safflower" in the template of "dosage of medicinal flavor", we can obtain the dosage rule of safflower of the corresponding syndrome type, as shown in Table 2.

Table 1: Frequency of syndrome types of safflower in the treatment of diabetes (frequency  $\geq 10$ ).

Number	Syndrome type	Frequency (times)	Frequency (%)
1	Phlegm-blood stasis syndrome	54	24.32
2	Deficiency of both qi and yin	40	18.01
3	Dampness-heat syndrome	32	14.41
4	Qi deficiency and blood stasis syndrome	30	13.51
5	Deficiency of both spleen and kidney	23	10.36
6	Spleen deficiency and dampness syndrome	12	5.40
7	Deficiency of Yin and Yang	11	4.95

Table 2: Dosage of safflower in different syndromes.

Numbe	Syndrome type	dosage (g)
1	Phlegm-blood stasis syndrome	12
2	Deficiency of both qi and yin	6(9)
3	Dampness-heat syndrome	12(15)
4	Qi deficiency and blood stasis syndrome	12
5	Deficiency of both spleen and kidney	6
6	Spleen deficiency and dampness syndrome	12

Among the 148 prescriptions in database 2, there are 118 herbs were included in total. Through the statistical report → medical case analysis → Western medicine disease statistics module, we can get the disease frequency distribution of safflower treatment of diabetic complications, which were diabetic peripheral neuropathy, diabetic retinopathy, diabetic nephropathy, diabetic peripheral vascular disease, and diabetic heart disease from high to low.

### 2.2 Prescription and symptom analysis

Among 222 prescriptions of safflower for diabetes and its complications in databases 1 and 2, the frequency of use of each herb was obtained by data analysis → formula analysis → frequency

statistics, of which 11 herbs were used more than 100 times, as shown in Table 3. Through data analysis → medical record analysis → symptom analysis to obtain the frequency of occurrence of symptoms in safflower treatment of diabetes and its complications, there are 12 symptoms with frequency of occurrence  $\geq 50$  times, and the top 5 symptoms are dark red tongue, insomnia and dreaminess, dry mouth, fatigue, and blurred vision.

Table 3: Frequency of medication in treatment formulas for diabetes and its complications (frequency > 100 times).

Num	Herbs	Fre (times)	Fre (%)	Num	Herbs	Fre (times)	Fre (%)
1	Safflower	222	100	7	Coptis chinensis	136	61.26
2	Astragalus	186	83.78	8	Rehmannia glutinosa	112	50.45
3	Yam	184	82.88	9	Amomum villosum	111	50
4	Cornus officinalis	156	70.27	10	Radix Pseudostellariae	110	49.55
5	Jiangcan	152	68.47	11	Atractylodes	107	48.2
6	Epimedium	139	62.61				

In database 1, the association rule in Formula Analysis sets the number of degrees of support as 35 and of the confidence as 0.9. The corresponding analysis results were obtained by "medication pattern", "rule analysis", and "network display", respectively. Among them, there were 26 drug combination patterns in the "medication pattern", the highest frequency was safflower - astragalus, which appeared 47 times and contained 5 herbs, namely safflower, astragalus, yam, silkworm, and cornus officinalis. In the "rule analysis", there were 44 association rules and 5 with confidence  $\geq 0.98$ , as shown in Table 4.

Table 4: Association rule analysis of safflower for diabetes drug combinations (confidence  $\geq 0.98$ ).

Numbe	Association Rules	Confidence
1	Safflower, Cornus officinalis -> yam	1
2	astragalus, Jiangcan -> Safflower	1
3	yam, Jiangcan -> Safflower	1
4	Safflower, Cornus officinalis, astragalus -> yam	1
5	Jiangcan -> Safflower	0.98

Table 5: Core Drug Combination Statistics of Carthamus tinctorius for Diabetic Complications (Frequency > 110).

Num	Drug combination	Fre (times)	Num	Drug combination	Fre (times)
1	Safflower, yam	130	8	Cornus officinalis, yam	112
2	Safflower, astragalus	129	9	Safflowe, Cornus officinalis, astragalus	112
3	Safflower, astragalus, yam	122	10	Safflowe, Cornus officinalis, yam	111
4	Safflower, Jiangcan	120	11	yam, Jiangcan	110
5	Safflower, Cornus officinalis	114	12	Safflowe, yam, Jiangcan	110
6	astragalus, yam	114	13	Cornus officinalis, astragalus, yam	110
7	Cornus officinalis, astragalus	113			

Of the 148 formulas in database 2, the number of support degrees was set at 110 and confidence 0.9 in the same way as above, and a total of 13 core drug combinations of safflower for the treatment of diabetic complications were obtained, including 5 herbs in Table 5, and 25 association rules.

In database 1 and 2, we setted the support level as 70, 110 and 180 respectively, with the confidence level of 0.9. Select "Network Presentation" to obtain the corresponding network display diagram (as Figure 1-3). When the support degree is greater than 70 or 110, the compatibility of safflower involves drugs such as invigorating qi, nourishing yin, invigorating spleen, clearing heat, dryness and dampness; while the support degree is greater than 180, the compatibility of safflower only involves invigorating qi, nourishing yin, and dredging collaterals drugs.

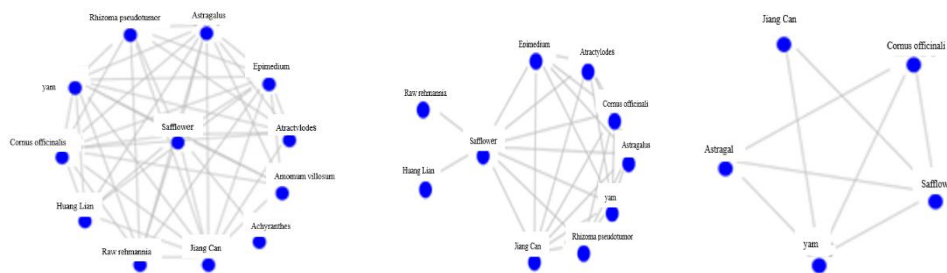


Figure 1: Support > 70. Figure 2: Support > 110. Figure 3: Support > 180.

In databases 1 and 2, there are 3 core combinations were obtained through the "novel formula analysis" template with a correlation of 8 and a penalty of 2, as shown in Table Table 6. Click "Network Presentation" to obtain the corresponding network display diagram as shown in Figure 4.

Table 6: Cluster Analysis Core Set.

Num	Novel formula combination
1	Staghorn cream _ atractylodes _ Achyranthes _ Centipede
2	Angelica root _ Jiangcan _ yam _ Peach kernel _ Chuanxiong
3	Pinellia ternata _ Cornus officinalis _ Epimedium _ Tangerine peel _ Licorice root _ Poria cocos _ Jiangcan

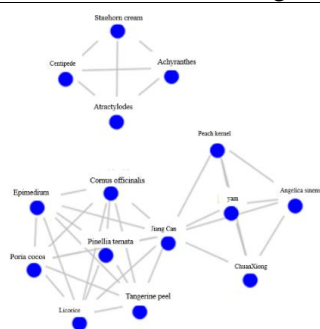


Figure 4: Cluster analysis display diagram.

### 3. Discussion

The relationship between diabetes and blood stasis first appeared in the *Huang Di Nei Jing*, and the Causality between blood stasis leading to diabetes and Chronic diabetes can lead to blood stasis was clarified in the *Lingshu • Five Changes Chapter* and the *Yi Xue Ru Men • Diabetes*, respectively [8-9], which further confirmed that blood stasis is the whole process of diabetes. So Dr. Xu mostly used safflower in the treatment of diabetes and its complications, and grasped its dose very flexibly in order to better play the therapeutic effect of safflower. Dr Xu, has always attached importance to protecting the function of spleen and stomach and promoting circulation in the treatment of diabetes and its complications. And safflower can not only dissipate tangible blood stasis, but also prevent unformed stagnation, not only blood circulation, but also nourish blood, so the dosage of safflower has a pivotal role in Dr.Xu treatment of diabetes and its complications.

### 3.1 Tracing and Modern Studies on *Carthamus tinctorius*

*Carthamus tinctorius*, the ancient name of red and blue flowers, was originally contained in the *Kai Bao Ben Cao*. It has the effect of preventing dampness, qi stagnation, phlegm coagulation lead to blood stasis. *Carthamus tinctorius* not only through the unfinished stagnation, but also eliminating the blood stasis<sup>[10]</sup>. Li Dongyuan pointed out in his "*Lan Shi Mi Zang · Xiaoke Men*" and "*Huo Fa Ji Yao · Xiaoke Zheng*" that: "Those with blood deficiency use the blood medicine, which can carry out blood and nourish blood, so the blood medicine has the function of tonifying blood ". Therefore among the 9 prescriptions for the treatment of diabetes, there are 5 prescriptions containing safflower<sup>[11-12]</sup>, which shows that safflower has a historical origin in the treatment of diabetes in ancient times. In addition, the "*Ben Cao Gang Mu*", "*Yao Xing Ge Kuo Si Bai Wei*" and other ancient books have records that large doses of safflower can promote blood circulation, and small doses of safflower can nourish blood<sup>[13-14]</sup>. Modern pharmacological studies have shown that safflower can protect myocardial cells by inhibiting the expression of inflammatory factors, inhibiting a variety of pathological stimuli, and regulating mitochondrial function<sup>[15]</sup>, and its active component, safflower yellow pigment, can not only improve the hypoxic state during neural stem cell injury and promote the repair and regeneration of nerves in vitro<sup>[16]</sup>, but also improve blood flow by regulating thrombin activity and time, inhibiting platelet aggregation, promoting local thrombolysis, and inhibiting vascular endothelial cell proliferation<sup>[17-18]</sup>. Moreover, safflower yellow pigment can reduce glomerular injury by inhibiting ER stress and apoptosis, and protect renal function through antioxidant, inhibitory inflammatory factors, and promoting blood circulation and removing blood stasis pathways<sup>[19-20]</sup>.

### 3.2 Analysis of the application law of safflower

From the distribution of TCM syndrome types of safflower in the treatment of diabetes and its complications and the dosage of safflower in each syndrome type, it can be seen that safflower can be used not only to treat various blood stasis syndromes, but also for some deficiency syndromes. And in syndromes with obvious blood stasis symptoms, the dosage of safflower is generally 12 g. If heat excess to blood stasis, blood stasis and heat entanglement can increase the dosage of safflower to 15 g. While in deficiency syndromes, the dosage of safflower is generally 6 g, and its use of "Small doses of safflower have the effect of tonifying deficiency". It can be increased to 9 g if accompanied by deficiency heat, which purpose is to prevent unformed blood stasis, avoid dampness, qi stagnation, phlegm coagulation to blood stasis. From the classification of western medicine diseases, *carthamus tinctorius* can prevent and treat diabetic complications through its effect of removing blood stasis and preventing blood stasis.

From the frequency distribution of drugs, the top 5 herbs in the database were Safflower, *Astragalus membranaceus*, Yam, *Cornus officinalis*, Jiangcan. In which small doses of safflower are the effect of warming blood vessels, and large doses of safflower are the effect of promoting blood circulation and removing blood stasis. *Astragalus membranaceus* and Yam replenish the qi of spleen and lung, emphatically replenish the spleen qi, *Cornus officinalis* tonifies the liver and kidney, which is in line with the treatment ideas of Dr. Xu that based on invigorating qi and nourishing yin, regulating the spleen and stomach, promoting blood circulation and promoting dredging throughout the whole process.

Based on entropy clustering of complex systems, there are 3 core drug combinations of Dr Xu for the treatment of diabetes and its complications, which evolving three groups of new prescriptions. The first prescription reflected the treatment concept of both patency and tonifying. The staghorn cream warmed the kidney, fried atracylodes invigorated the spleen, supplemented with *achyranthes* and centipede for promoting blood circulation and dredging collaterals. In the second prescription, *Angelica sinensis* and Yam invigorating qi and tonifying blood, Peach kernel and *Chuanxiong* promote qi and blood circulation, compatibled Jiangcan can expell wind and



reduce phlegm. The third prescription came from the change of Liujunzi soup. Supplemented the spleen and kidney on the basis of protecting the spleen and stomach, and pay attention to dredging while tonifying. Three new prescriptions pay attention to the spleen and stomach care, and tonifying combined with dredging, so that supplement without greasy, through without injuring the basis.

In summary, this study uses the traditional Chinese medicine inheritance computing platform (V2.5) to explore the clinical application rule of safflower in the treatment of diabetes and its complications based on data mining. Xu Jianqin, chief physician, safflower treatment of diabetes is not only to improve the clinical symptoms, but also to prevent and treat its various complications.

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