Original Article

Identifying the Chinese herbal medicine used in treating diabetic retinopathy: a data mining analysis

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Abstract: The objective of this study was to identify the frequency and association of Chinese medicine herbs in treating diabetic retinopathy (DR) in the past ten years. A search of the published literature was conducted by using keywords which were commonly associated with diabetic retinopathy, Chinese herbal medicine, Chinese medicine, traditional Chinese medicine and diabetic eye disease in the Chinese National Knowledge Infrastructure (CNKI), PubMed, ScienceDirect, and Springer Link databases. The papers which met inclusion criteria were entered into Microsoft Excel and IBM SPSS Modeler Subscription for a frequency analysis and association rule analysis. There were 25 papers that fit with the criteria. A total of 102 types of Chinese medicines were used in these 25 papers. It was found that the most frequently used Chinese medicine for DR were Dihuang (地黄), Huangqi (黄芪) and Danggui (当归). The top commonly associated Chinese medicine combinations were Huangqi (黄芪) and Dihuang (地黄); Dihuang (地黄) and Danggui (当归); Huangqi (黄芪) and Chuanxiong (川芎). The frequently used Chinese medicine mostly possessed the functions to activate blood, tonify Qi and nourish Yin, this indicated that DR basically had underlying pathological mechanism of "deficiency of Qi and Yin with blood stasis blocking the meridians and collaterals". Treatment principle of DR should consider focusing on tonify Qi and Yin, removing blood stasis, and nourishing the eyes.

Keywords: diabetic retinopathy; diabetic eye disease; Chinese medicine; data mining.

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Introduction

Diabetic retinopathy (DR) is a common and specific microvascular complication of diabetes, which is also a leading cause of vision impairment and blindness across the WHO European Region, with an estimated 950,000 people affected. The severity of the diabetes condition, poor glycemic management, the presence of hypertension, increasing age, sedentary lifestyle and obesity are the key risk factors.[1,2]

The primary approach to reduce the risk of developing and worsening retinopathy formation and progression involves optimal management of blood glucose, blood pressure,

and possibly blood lipids.[3] In western medicine, the initial step in treating DR involves controlling the blood glucose, followed by screening and laser procedures, and surgical intervention if the condition worsens. However, western medicine alone may not completely resolve DR, which is why Chinese medicine can play a significant role in its subsequent treatment.

The terms of diabetic retinopathy in Chinese medicine classic works were known as Que Mu (雀目), Nei Zhang (内障), Bao Mang (暴盲), Shi Zhan Hun Miao (视瞻昏渺) and Yun Wu Yi Jin (云雾移睛) which mean blindness, blurred vision, or visual shadow. In Chinese medicine perspective, DR is caused by innate deficiency body constitution, improper diet, emotion injury, mistreated by warm, heat or dryness nature of herbal decoction, or prolonged Xiao Ke disease (消渴). The pathogenesis of the disease includes deficiency of Qi or Yin in spleen, kidney and liver; blockage of stasis in collaterals and vessels; obstruction of phlegm and dampness; depressive syndrome or abnormal fluid retention in the lymph.[4] The treatment principles should be applied by nourishing Qi and Yin in liver and kidney, activate blood and resolve stasis.[5] The representative formula for DR in Chinese medicine is Ming Mu Di Huang Wan formula (明目地黄丸). This formula is useful in tonifying the kidney Yin and nourish the liver blood, it also enables to help in controlling the hypertension.[6]

Methodology

1. Data collection

Clinical studies and Randomized control trials (RCT) related to Chinese herbal medicine treatment in DR published for last ten years will be collected from various databases including China National Knowledge Infrastructure (CNKI), PubMed, Springer Link and Science Direct. The searching keywords are "Diabetic Retinopathy" or "糖尿病视网膜病变" or "糖尿病眼病" or "Diabetic Eye Disease" and "Chinese Medicine" or "中药 or "中医治疗" or "Traditional Chinese Medicine" or "Chinese Herbal Medicine" and "Randomized Controlled Trials". There were 768 studies in all that were gathered from the mentioned database.

2. Data screening

First data screening process will consist of reading the title and abstract. Then, they will be categorized according to the title, date of publication and database source. In second screening, full text will be read and filtered according to the inclusion and exclusion criteria.

a. Inclusion criteria

1) Subjects involved were diagnosed as Diabetic Retinopathy (DR) following the definition of World Health Organization.[7]

2) RCT trials on human subjects showed statistical significance ($p<0.05$) in the treatment provided in experimental group, which used any kinds of Chinese herbs/herbal formula given orally to the patients, including oral medication, decoction, powder, tablet, syrup, etc. which are fully listed Chinese medicine according to Dictionary of Chinese Medicine《中药大辞典》.

3) Date of publication was between 2012 to 2021.

4) Languages of literature were Chinese or English.

5) Subjects involved were regardless of gender, nationality, ethnicity, and races.

b. Exclusion criteria

1) Duplicate publications, and literature on non-clinical studies such as medical record reviews, editorial articles, retrospective clinical studies, and animal experiments.

2) Clinical studies with unclear statistical analysis.

3) Subject did not list complete composition and dosage of Chinese herbs.

4) The subject involved had other underlying diseases and special conditions, for example, kidney and liver failure, pregnancy, lactation, or having obvious exacerbation or alleviation recently.

5) RCT trials that use Chinese medicine treatments modalities other than Chinese herbal medicine (e.g., acupuncture, Tuina, Qi Gong, moxibustion, cupping, ear acupuncture etc.) or non-Chinese medicine herbal medicine (Japanese, Indian, etc.)

6) Chinese herbs/herbal formula given in non-oral way. (injection/ footbath/ external used cream, paste etc.)

7) Diseases were not clearly diagnosed as DR.

3. Data Analysis

After screening, a total of 25 studies which compliant with inclusion criteria were collected for data analysis. The nomenclature of the herbs was standardized according to Dictionary of Chinese Medicine《中药大辞典》. All data were extracted from prescription into Microsoft Excel to establish a database and the frequency and percentage of each herb was calculated. Association analysis was the main technique in data mining. The support degree and the confidence level was based on the association rules algorithm: Support $(X \rightarrow Y)$ $= P(X, Y)/P(I) = (X \cap Y)/P(I) = num(X \cap Y)/num(I)$, where "I" represents the entire dataset, "num()" represents the frequency or times of specific

or defined dataset. Support degree was used to measure the statistical significance of association rules. Confidence $(X \rightarrow Y) = P(Y|X) = P(X, Y)/P(X) = P(X \cap Y)/P(X)$. Confidence was used as an index to measure the probability that event Y will occur under the condition that event X prior occurs. Association rule analysis was performed using Apriori Algorithms in IBM SPSS Modeler Subscription. Support degree of minimum 15% and confidence degree of minimum 80% were used. The maximum number of antecedent applied was 3.

Results

1. Single herb frequency analysis

A total of 102 types of Chinese herbal medicines were listed for frequency analysis. The results shown that the top 23 Chinese herbal medicine used in treating diabetic retinopathy were Dihuang (地黄), Huangqi (黄芪), Danggui (当归), Chuanxiong (川芎), Danshen (丹参), Gancao (甘草), Honghua (红花), Shanyao (山药), Sanqi (三七), Juhua (菊花), GouQi (枸杞), Taoren (桃仁), Niuxi (牛膝), Nvzhenzi (女贞子), Juemingzi (决明子), Shanzhuyu (山茱萸), Maidong (麦冬), Mudanpi (牡丹皮), Mohanlian (墨旱莲) and Zexie (泽泻). There were 23 herbs in total presented in Table 1 instead of 20 herbs as the 18th-23rd herbs shared the same frequency. The highest frequency used of Chinese herbal medicine was Dihuang (地黄) which carried a frequency of 68% among the herbs.

Table 1 Frequency of the 23 most frequently prescribed Chinese herbal medicine in treating diabetic retinopathy

Ranking	Herbs	Chinese name	Frequency	Percentage %
1	Dihuang	地黄	17	68
2	Huangqi	黄芪	16	64

Table 1 Frequency of the 23 most frequently prescribed Chinese herbal medicine in treating diabetic retinopathy (cont.)

Ranking	Herbs	Chinese name	Frequency	Percentage %
3	Danggui	当归	13	52
4	Chuanxiong	川芎	12	48
5	Danshen	丹参	11	44
6	Gancao	甘草	10	40
7	Honghua	红花	8	32
8	Shanyao	山药	8	32
9	Sanqi	三七	7	28
10	Juhua	菊花	7	28
11	Gouqi	枸杞	7	28
12	Taoren	桃仁	7	28
13	Niuxi	牛膝	6	24
14	Nvzhenzi	女贞子	6	24
15	Juemingzi	决明子	6	24
16	Shanzhuyu	山茱萸	6	24
17	Maidong	麦冬	6	24
18	Mudanpi	牡丹皮	5	20
19	Mohanlian	墨旱莲	5	20
20	Zexie	泽泻	5	20
21	Fuling	茯苓	5	20
22	Puhuang	蒲黄	5	20
23	Dangshen	党参	5	20

2. Herbs combination frequency analysis

The herbs combination with the highest support degree was Huangqi (黄芪)-> Dihuang (地黄), with 68% of support degree. Follow by Dihuang (地黄)-> Huangqi (黄芪), which was with 64% of support degree and Dihuang (地黄)-> Danggui (当归) which was 52% of support degree (Table 2).

Table 2 Association pattern of herbs combinations

No.	Itemset	Support (%)	Confidence (%)
1	Huangqi 黄芪 -> Dihuang 地黄	68.0	70.6
2	Dihuang 地黄 -> Huangqi 黄芪	64.0	75.0
3	Dihuang 地黄 -> Danggui 当归	52.0	76.9
4	Huangqi 黄芪 -> Chuanxiong 川芎	48.0	83.3
5	Dihuang 地黄 -> Chuanxiong 川芎	44.0	90.9
6	Huangqi 黄芪 -> Danshen 丹参	44.0	72.7
7	Dihuang 地黄 -> Danshen 丹参	40.0	70.0
8	Danggui 当归 -> Gancao 甘草	40.0	70.0
9	Huangqi 黄芪 -> Gancao 甘草	40.0	70.0
10	Dihuang 地黄 -> Danshen 丹参 Huangqi 黄芪	40.0	80.0
11	Huangqi 黄芪 -> Chuanxiong 川芎 Dihuang 地黄	40.0	80.0
12	Huangqi 黄芪 -> Danggui 当归 Dihuang 地黄	40.0	70.0
13	Dihuang 地黄 -> Chuanxiong 川芎 Huangqi 黄芪	36.0	88.9
14	Dihuang 地黄 -> Danggui 当归 Huangqi 黄芪	36.0	77.8
15	Taoren 桃仁 -> Honghua 红花	32.0	87.5

The associated patterns between the herb's combinations were shown in the web graph in Figure 1. Thicker lines in the web graph indicated a greater bonding between paired herbs, whereas thinner lines indicated a weaker bonding relationship between herbs matched.
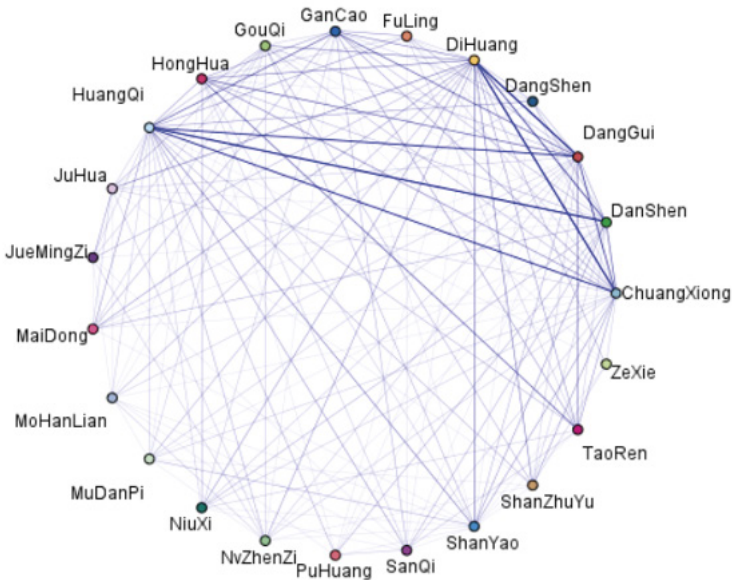

Figure 1 Web graph for association patterns of herbs combinations

3. Chinese medicinal efficacies and properties of frequently used herbs

Based on the classification of medical efficacies analysis (Table 3), the blood activating herbs were the most frequent used Chinese medicine for treating DR. Based on the classification of medical efficacies analysis (Tables 4 and 5), the highest proportion of the herbs used were neutral and sweet in taste.

Table 3 Chinese medicinal efficacies of frequency of the 23 prescribed Chinese herbal medicine

Medical efficacies	Chinese medicine	Number (n)
Blood activating	Chuanxiong (川芎), Danshen (丹参), Honghua (红花), Taoren (桃仁), Niuxi (牛膝)	5
Qi tonic	Huangqi (黄芪), Gancao (甘草), Shanyao (山药), Dangshen (党参)	4
Yin tonic	Gouqi (枸杞), Nvzhenzi (女贞子), Maidong (麦冬), Mohanlian (墨旱莲)	4

Table 3 Chinese medicinal efficacies of frequency of the 23 prescribed Chinese herbal medicine (cont.)

Medical efficacies	Chinese medicine	Number (n)
Heat clearing	Dihuang (地黄), Juemingzi (决明子), Mudanpi (牡丹皮)	3
Diuretic	Zexie (泽泻), Fuling (茯苓)	2
Haemostatic	Sanqi (三七), Puhuang (蒲黄)	2
Blood tonic	Danggui (当归)	1
Exterior releasing	Juhua (菊花)	1
Astringent	Shanzhuyu (山茱萸)	1

Table 4 Chinese medicinal properties (nature) of frequency of the 23 prescribed Chinese herbal medicine

Medical properties (nature)	Chinese medicine	Number (n)
Neutral	Gancao (甘草), Shanyao (山药), Gouqi (枸杞), Taoren (桃仁), Niuxi(牛膝), Fuling (茯苓), Puhuang (蒲黄), Dangshen (党参)	8
Slightly cold	Danshen (丹参), Juhua (菊花), Juemingzi (决明子)	5
Cold	Dihuang (地黄), Mohanlian (墨旱莲), Zexie (泽泻)	3
Slightly warm	Huangqi (红花), Sanqi (三七), Shanzhuyu (山茱萸)	3
Warm	Danggui (当归), Chuanxiong (川芎), Honghua (红花)	3
Cool	Nvzhenzi (女贞子)	1

Table 5 Chinese medicinal properties (flavour) of frequency of the 23 prescribed Chinese herbal

Medical properties (flavour)	Chinese medicine	Number (n)
Sweet	Taoren (桃仁), Huangqi (黄芪), Gancao (甘草), Shanyao (山药), Dangshen (党参), Gouqi (枸杞), Nvzhenzi (女贞子), Maidong (麦冬), Mohanlian (墨旱莲), Dihuang (地黄), Juemingzi (决明子), Zexie (泽泻), Fuling (茯苓), Sanqi (三七), Puhuang (蒲黄), Danggui (当归), Juhua (菊花)	17
Bitter	Danshen (丹参), Taoren (桃仁), Niuxi (牛膝), Nvzhenzi (女贞子), Dihuang (地黄), Juemingzi (决明子), Mudanpi (牡丹皮), Juhua (菊花)	8
Pungent	Chuanxiong (川芎), Honghua (红花), Mudanpi (牡丹皮), Danggui (当归)	4
Sour	Niuxi (牛膝), Mohanlian (墨旱莲), Shanzhuyu (山茱萸)	3
Slightly bitter	Maidong (麦冬), Sanqi (三七)	2
Salty	Juemingzi (决明子)	1
Bland	Fuling (茯苓)	1

Discussion

The top 3 Chinese herbal medicine used in treating DR are Dihuang (地黄), Huangqi (黄芪) and Danggui (当归). Shengdihuang (生地黄) is suitable for those with deficiency of heat due to Yin and fluids deficiency as well as to clear heat in the Ying blood, stop the bleeding due to blood heat, resolve thirst due to heat of Xiao Ke. With the function of cooling blood, it could be effective on stopping the bleeding in the eyes and treating proliferative diabetic retinopathy with dot and blot hemorrhages. Shudihuang (熟地黄) can nourish kidney water, replenish true Yin, produce essence and blood, and brighten the eyes. So, it can be used on diabetic retinopathy with liver and kidney Yin deficiency syndrome. In modern research, the hypoglycemic effect of Dihuang (地黄) which contains oligosaccharide that can alleviate diabetic weight loss and significantly reduce blood glucose and blood lipid levels, which can delay the progression of diabetes and prevent the occurrence of complications.[8] Huangqi (黄芪) brings medical efficacies along to tonify Qi, nourish the blood vessels and the muscles around the eyes.

Pharmacological research has proved that Huangqi (黄芪) with its active ingredients not only have certain hypoglycemic effect, but also has a good effect on the prevention and treatment of its complications. Huangqi (黄芪) polysaccharide has a two-way regulating effect on blood sugar, which can improve glucose tolerance and increase serum insulin level, and at the same time it can reduce plasma glucagon level. This herb is useful in inhibiting high glucose from apoptosis of retinal cells and has a protective effect on retinal ganglion cells.[9] Danggui (当归) can tonify blood, strengthen the muscles of eye, smoothen the liver Qi to nourish the eye and activate the blood to promote blood circulation of the eye. Hence, it can be widely used in cases of blood deficiency, or Qi-blood stagnation or obstructions in the blood vessels of eye, so it is effective in treating diabetic retinopathy as blood stasis and blood deficiency are common pathogenesis for DR.[10] In modern research, Danggui (当归) can remove blood stasis and promoting new eyesight by inducing hematopoietic cell production, anti-free radical, antioxidant, anti-coagulant, hemostatic and inhibited retinal ganglion cell apoptosis. Thus, it is the main herb used for diabetic retinopathy to invigorate blood stasis, nourish blood, and moisten the eye.[11]

The top frequent herbs combination used in DR are Huangqi (黄芪) and Dihuang (地黄), Huangqi (黄芪) and Chuanxiong (川芎), Dihuang (地黄) and Danggui (当归). Huangqi (黄芪) and Dihuang (地黄) are appropriate to be used together to treat the patients with fluid injuries in the body and internal heat due to Xiao Ke. The combination of Huangqi (黄芪) and Dihuang (地黄) appears in representative formula such as the Xiao Ke Wan (消渴丸). Xiao Ke Wan is commonly used in the treatment of Qi and Yin deficiency type of diabetes mellitus.[12] The combination of Huangqi (黄芪) and Chuanxiong (川芎) may improve the underlying cause of Qi deficiency in Xiao Ke, and at the same time ensure smooth blood flow for the treatment of Xiao Ke. The combination of Huangqi (黄芪) and Chuanxiong (川芎) appears in representative formula such as Jiang Tong Tang (降酮汤) which can help to reduces intraocular pressure,[13] increases blood flow to the eye, reduces high blood viscosity, and reduces retinal hemorrhage. Dihuang (地黄) and Danggui (当归) can break up blood stagnation, tonify blood deficiency, nourish blood, tonify deficiencies, remove stasis and regenerate new blood to the eye. As retinal hemorrhage is a common clinical manifestation in patients with diabetic retinopathy which is considered as a blood stasis in Chinese Medicine perspective, this combination can help to ensure the smooth flow of the circulation in the eye. The representative formula such as Shao Yao Di Huang Wan (芍药地黄丸) might help to relieve eye pain, swollen eye, and stasis in the eye.[14]

The blood activating type of herbs are most used for treating DR. The prolonged illness of Xiao Ke could lead to the process of development of internal stasis or stagnation of blood, and obstruction of the eye-loop and eye ligaments. Hence, the blood-activating herbs are widely used in breaking the Qi stagnation and move blood, remove blood stasis and nourish the eyes.

Neutral and sweet herbs are most frequently used as they possess characteristics of tonic, slow down and harmonize. As deficiency syndrome is one of the main pathogeneses of DR, those herbs with sweet taste are mostly used to benefit Qi and tonify essences to the eyes, alleviate eye pains as well as assist to harmonize all medicinal properties. Those herbs with neutral in nature are normally combined along with sweet medicine for treating diabetic retinopathy. Chinese medicinal herbs with neutral property can assist the main herbs to have better efficacies performance.[14]

Limitations

The dosage of Chinese herbal medicines used, and their concoction methods may have different effects on the results. Those herbs used and herbs combinations are not classified based on the syndrome differentiation method, so these are the limitations which will be further explored in the future of studies.

Conclusion

The Chinese medicine mentioned above which supported by RCT studies mostly possess the functions to activate blood, tonify Qi and nourish Yin, this indicates that DR basically has underlying pathological mechanism of "deficiency of Qi and Yin with blood stasis blocking the meridians and collaterals". Thus, the treatment principle of DR should consider focusing on tonify Qi and Yin, remove blood stasis, and nourishing the eyes.

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นิพนธ์ต้นฉบับ

การศึกษากฎเกณฑ์ของยาที่ใช้บ่อยในการรักษาภาวะเบาหวานขึ้นจอประสาทตาด้วยศาสตร์การแพทย์แผนจีนโดยการวิเคราะห์เหมืองข้อมูล

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มหาวิทยาลัยการแพทย์นานาชาติ ประเทศมาเลเซีย

บทคัดย่อ: การศึกษาครั้งนี้เป็นการสำรวจชุดข้อมูลวรรณกรรมในช่วง 10 ปีที่ผ่านมาที่เกี่ยวกับการรักษาภาวะเบาหวานขึ้นจอประสาทตา (DR) เพื่อหาความถี่และความสัมพันธ์ของสมุนไพรจีนที่ใช้บ่อยในการรักษา โดยใช้คำสำคัญที่เกี่ยวข้องกับภาวะเบาหวานขึ้นจอตา ยาสมุนไพรจีน ศาสตร์การแพทย์แผนจีน และโรคตาจากเบาหวาน ใน the Chinese National Knowledge Infrastructure (CNKI), PubMed, ScienceDirect และ ฐานข้อมูล Springer Link เอกสารที่ตรงตามเกณฑ์การคัดเลือกเข้าจะถูกป้อนลงใน Microsoft Excel และ IBM SPSS Modeler Subscription สำหรับการวิเคราะห์ความถี่และการวิเคราะห์กฎการเชื่อมโยง ซึ่งเข้าเกณฑ์จำนวน 25 บทความ มีการใช้ยาจีนทั้งหมด 102 ชนิด พบว่ายาสมุนไพรจีนที่ใช้บ่อยที่สุดในการรักษา DR ได้แก่ ตี้หวง (地黄), หวงฉี (黄芪) และ ตังกุย (当归) และคู่ยาสมุนไพรจีนที่ใช้ร่วมกันที่พบบ่อยที่สุด ได้แก่ หวงฉี (黄芪) และตี้หวง (地黄), ตี้หวง (地黄) และตังกุย (当归), หวงฉี (黄芪) และชวนซยง (川芎) ยาจีนที่ใช้บ่อยมักมีสรรพคุณในการช่วยให้เลือดไหลเวียนได้ดีขึ้น บำรุงชี่ และเสริมอิน จากผลการศึกษาแสดงให้เห็นว่า DR โดยทั่วไปมีกลไกทางพยาธิวิทยาพื้นฐานของ "ชี่และอินพร่อง ทำให้เลือดคั่ง อุดกั้นเส้นลมปราณ" ดังนั้นหลักการรักษาของ DR ควรเน้นไปที่การบำรุงชี่และอิน ขจัดเลือดคั่ง และบำรุงดวงตา

คำสำคัญ: ภาวะเบาหวานขึ้นจอประสาทตา; โรคตาจากเบาหวาน; ยาจีน; เหมืองข้อมูล

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原创论文

基于数据挖掘探讨中医治疗糖尿病视网膜病变的常用药物规律

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摘要： 本文旨在使用文献数据挖掘，探讨十年来中医治疗糖尿病视网膜病变（DR）的常用药物规律。我们使用与糖尿病视网膜病变、中药、中医和糖尿病眼病等常用相关的关键词，于 CNKI、PubMed、ScienceDirect 和 Springer Link 数据库中进行了文献搜索，将符合纳入标准的文献被录入 Microsoft Excel 和 IBM SPSS Modeler 订阅版进行频率分析和关联规则分析。在纳入的 25 篇治疗 DR 的论文中，一共涉及 102 种中药，其中治疗 DR 最常用的中药是地黄、黄芪和当归，常见的中药组合包括黄芪和地黄、地黄和当归、黄芪和川芎。最常用的中药大多具有活血、益气和滋阴的功能，这研究结果表明 DR 基本上具有"气阴不足，血瘀阻络"的潜在病因病理机制，因此在治疗 DR 时应考虑采用补益气阴，疏通血瘀，濡养眼睛的药物。

关键词： 糖尿病视网膜病变；糖尿病眼病；中药；数据挖掘

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