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Efficacy of traditional Chinese medicine combined with anti-vascular endothelial growth factor in the treatment of wet age-related macular degeneration：A systematic review and network Meta-analysis

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中药联合抗 VEGF 治疗湿性年龄相关性黄斑变性的疗效：系统评价与网状 Meta 分析

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摘要

目的:评价中药联合玻璃体腔内注射抗血管内皮生长因子(VEGF)与单纯抗 VEGF 药物治疗湿性年龄相关性黄斑变性(wAMD)的疗效。

方法:检索中国知网、万方、维普、中国生物医学库 CBM、Pubmed、Web of Science、Cochrane Library、Embase 八大数据库,发表于建库以来至 2022-04-20 所有中英文文献。选取研究对象为 wAMD 患者,研究方法为比较中药联合抗 VEGF 药物与单纯抗 VEGF 药物治疗的临床随机对照实验研究。采用的结局指标为最佳矫正视力(BCVA),黄斑中心凹厚度(CMT)。采用传统 Meta 和网状 Meta 分析对数据进行统计。

结果:在 617 项确定的研究中,39 项纳入分析,涉及 28 种口服中药,2757 名参与者。在提高 BCVA 方面,中药联合抗 VEGF 药物治疗优于单纯抗 VEGF 药物治疗($MD=0.07$, $95\%CI$:$0.05\sim0.09$)。生蒲黄汤(SPD)在治疗后 1、2mo 最佳,血府逐瘀胶囊(XZC)在治疗后 3mo 最佳。在降低 CMT 方面,中药联合治疗效果更好($MD=-25.32\mu m$, $95\%CI$:$-30.06\sim-20.57$)。当归明目汤(DMD)在治疗 1mo 后效果最好。补肾活血汤(BHD)在 2mo 时疗效最好。二陈二黄汤 (EED) 在 3mo 时疗效最好。

结论:与单纯抗 VEGF 治疗相比,中药联合治疗可改善 BCVA,降低 CMT。然而,纳入的文献多为小样本、单中心、单盲随机对照试验,文献质量总体较低。

关键词:湿性年龄相关性黄斑变性(wAMD);中医药;抗血管内皮生长因子;网状 Meta 分析

Abstract

• AIM：To evaluate the clinical efficacy of traditional Chinese medicine （ TCM ） combined with intravitreal injection of anti - vascular endothelial growth factor （VEGF） or anti-VEGF medicines alone in the treatment of wet age-related macular degeneration （wAMD）.

• METHODS：A total of eight databases were searched for relevant literatures in English and Chinese， including Chinese National Knowledge Infrastructure （CNKI）， Wanfang， CQVIP， SinoMed， PubMed， Web of Science， Cochrane Library， Embase. Taking patients with wAMD as research objects， the Chinese and English clinical randomized controlled trials （RCTs） published from the databases' inception to April 20， 2022， which compared TCM combined with anti - VEGF drugs with anti - VEGF drugs alone were selected. The outcome indicators were best corrected visual acuity （BCVA） and central macular thickness （ CMT ）. Traditional Meta and network Meta analysis were used to examine the data.

• RESULTS：There were 39 eligible studies among the 617 retrieved articles， involving 28 oral administration of Chinese herbal medicines and 2 757 participants. For BCVA improvement， results of TCM combination therapy were

more favorable than anti-VEGF alone (*MD*=0.07, 95%*CI*: 0.05~0.09). Sheng Puhuang Decoction (SPD) ranked highest in 1 and 2mo after treatment, and Xuefu Zhuyu Capsule (XZC) ranked highest in 3mo after treatment. In terms of reducing CMT, TCM combination therapy were better (*MD*=-25.32 μm, 95%*CI*: -30.06~-20.57). Danggui Mingmu Decoction (DMD) ranked the highest in 1mo after treatment. Bushen Huoxue Decoction (BHD) ranked the highest in 2mo. Erchen Erhuang Decoction (EED) ranked the highest in 3mo.

• CONCLUSIONS: Compared with anti-VEGF treatment alone, TCM combination therapy led to improved BCVA and reduced CMT. However, most of the included literature is small-sample, single-center, single-blind RCTs with an overall low quality.

• KEYWORDS: wet age-related macular degeneration (wAMD); traditional Chinese medicine (TCM); anti-vascular endothelial growth factor; network Meta-analysis

INTRODUCTION

A ge-related macular degeneration (AMD) is a neurodegenerative disease characterized by progressive and irreversible loss of central vision, leading to blindness. According to the World Health Organization, AMD is currently the third leading cause of blindness worldwide[1]. It is estimated that the number of people suffering from this disease will increase to 288 million by 2040[2]. AMD is divided into dry and wet, with wet AMD (wAMD) having the heaviest impact on vision acuity (VA). Due to the application of anti-vascular endothelial growth factor (VEGF) drugs, it has made a breakthrough progress in the early 21st century. Currently, it is used as the first-line therapy for the treatment and stabilization of most wAMD worldwide[3]. However, despite the success of anti-VEGF therapy, one third of patients with wAMD did not improve their VA [4]. As the treatment samples continue to grow, there is a differential response to the efficacy of anti-VEGF drugs in a small number of patients. Frequent intravitreal injections result in poor patient compliance and aggravate the mental and financial burden of patients[5].

In recent years, a large number of randomized controlled trials (RCTs) have demonstrated that the long-term effectiveness and safety of traditional Chinese medicine (TCM) in the treatment of wAMD are positive[6-44]. It is used as an important means of adjuvant anti-VEGF therapy. Anti-VEGF drugs have a single target of action, while the composition of TCM are complex which can inhibit choroidal neovascularization (CNV) from multiple pathways and targets, promote the absorption of hemorrhage, edema and

exudation, and improve the visual function of patients to a certain extent, making up for the deficiency of anti-VEGF in other treatments. However, the optimal role of TCM in wAMD has not been determined.

In this context, there is much interest in the potential benefits of combination treatment consisting of TCM and anti-VEGF drugs-strong physiological and clinical rationale lends support to such a strategy. A series of clinical experiments have evaluated the efficacy and safety of TCM combined with anti-VEGF in the treatment of wAMD. In order to assess the differences in role and efficacy between two types of therapies objectively, this study used traditional Meta and network Meta-analysis to verify the effectiveness of TCM combination therapy as well as to compare the efficacy and safety of different Chinese herbs combined with anti-VEGF therapies in wAMD, so as to provide evidence-based medicine (EBM) basis for selecting the best treatment plan for patients.

METHODS

Protocol and Registration The registration number: CRD42022329338.We followed the Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses (PRISMA) and its protocols and the PRISMA-extension statement for network meta-analysis to report the current results[45].

Eligible Criteria The main inclusion criteria were follows: 1) individuals who suffered from wAMD and were over 45 years old were included; 2) the treatment group had anti-VEGF drug therapy combined with TCM that have different dosage forms; 3) the control group was treated with anti-VEGF; 4) the main outcome includes best corrected visual acuity (BCVA) and central macular thickness (CMT). The included literature included at least one of the above outcome indicators; 5) limited RCTs in the languages of Chinese and English.

The studies meeting one of the following criteria would be excluded: 1) not-RCTs, cohort studies, observational and retrospective studies, case experience; 2) animal experiments or *in vitro* trials; 3) repeated literatures in Chinese and English or data published with seriously incorrect studies; 4) interventions not matching, including other Western medical treatments such as PDT, TTT or other Chinese medical treatments, such as acupuncture, physiotherapy, acupoint injection and acupoint application; 5) the outcome measures required for this study were not included.

Search Methods and Strategies We searched the relevant literature imposed on English and Chinese in eight databases, including CNKI, CQVIP, Wanfang database, Sinomed, PubMed, Web of Science, Cochrane Library, Embase. The retrieval time was from the database establishment to April 20, 2022. We applied language restrictions in Chinese and English. We used the following combined text and MeSH terms: "wet macular degeneration", "macular degeneration", "traditional Chinese medicine", "Chinese herb", "vascular endothelial growth factor", "VEGF", "Conbercept", "Ranibizumab", "bevacizumab", "randomized controlled trial" and so on.

Study Selection and Data Collection Process　All included studies were imported into NoteExpress 3. 5. 0 document management software, which was first used to select and exclude duplicate publications. And then two researchers read the titles and abstracts of the literature according to the inclusion and exclusion criteria to screen the desired literature initially. Finally, download the full text of literature and read them again to determine the eventually included studies and extract the data. In the process of literature screening, if two researchers encountered disagreements, the 3rd researcher verified and negotiated to solve the problems. The contents of the extracted literature included：1）basic information of the included literature, such as name of the first author, year of publication, and type of study；2）basic characteristics of the study patients, including the mean age, total number/effective number of patients in the treatment and control groups, interventions, and follow-up time；3）baseline data and final outcome measures of the outcome indicators in the included studies；4）key risk factors in the risk of bias assessment.

Statistical Analysis　Traditional meta–analysis was performed using Review Manager 5.3. Data of continuous-type variables were expressed as mean difference（MD）. Effect sizes were expressed as 95% confidence interval（CI）. I^2 test is used to judge the study level of the heterogeneity. If $I^2 \geq$ 50% or $P < 0.1$, a random effects model was used to incorporate heterogeneity. If $I^2 < 50\%$ or $P > 0.1$, a fixed-effects model was used to ignore the heterogeneity.

Network Meta–analysis was performed using Stata 16. 0 software, calling ado program files and install mvmeta and network Meta program packages to fit multiple regression models for network meta-analysis[46-47]. Draw a network map to represent comparative relationships between interventions. Then, the network meta–analysis was performed using mvmeta command, and ranking probability for each intervention calculated. Finally, a comparison–correction funnel plots was established to identify whether small sample effects or evidence of publication bias exist. Different recording methods of BCVA in the literature are uniformly converted to the international standard visual acuity（IS VA）by the following formula[48]：LogMAR = Lg（1/IS VA）. Approximate early treatment diabetic retinopathy study（ETDRS）letter scores = $85 + 50 \times$ lg（Snellen fraction）. Approximate ETDRS letter scores $= 85 - 50 \times$ LogMAR.

Risk of bias　The included studies were all RCTs, so the Risk of Bias assessment tool in the Cochrane manual was selected to evaluate the quality of the included studies. It contains selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. It will be independently evaluated by two researchers. If there are any differences during the process, they will be settled by third party researcher.

RESULTS

Study Selection　A total of 617 articles were initially searched, 456 articles were obtained by filtering, and 384 articles were excluded by reading the titles and abstracts of the articles in the primary screening. After the first screening 72 articles met the criteria were downloaded and read in full-text for re – screening. Finally, 39 original articles were incorporated, including 3 English and 36 Chinese articles. The specific flow chart is detailed in Figure 1.

Study Characteristics　A total of 39 studies involving 28 TCM interventions, were all two – arm trials and the basic characteristics of the included studies are illustrated in Table 1.
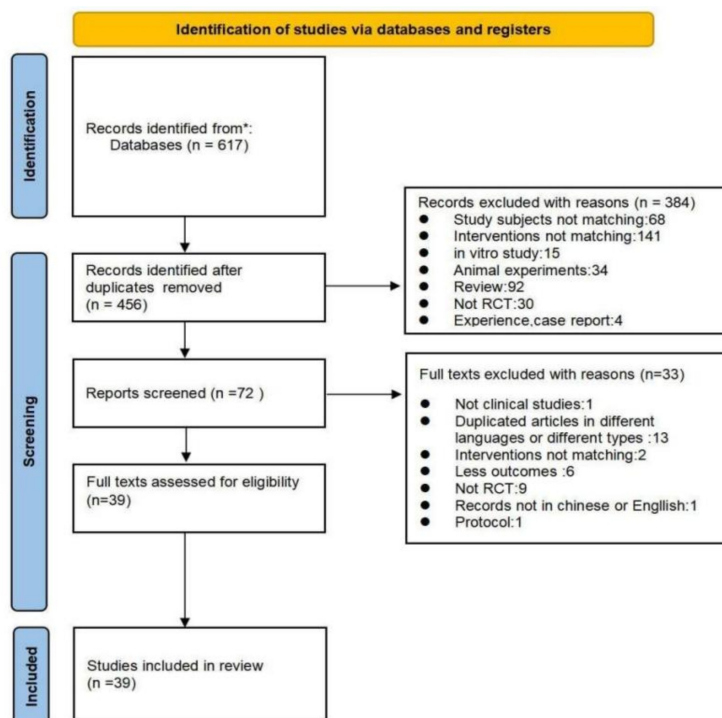

Figure 1　The PRISMA flowchart for study selection.　* CNKI：231；WanFang：88；CQVIP：58；Sinomed：178；PubMed：16；WOS：4；Cochrane Library：4；Embase：38.

Table 1　Baseline characteristics of identified studies and enrolled patients

Rank	Study	Interventions	Average age	Total number/effective number	Follow-up time	Outcomes
1	Jin M 2018	IVR+ZQMT	NA	108/96	1~6mo	②⑥⑦
		IVR+Placebo	NA	36/32		
2	Luo D 2019	IVR+HBOD	66.74±8.53	38/38	1~6,12mo	①②③
		IVR	66.51±8.02	37/37		④⑦⑧
3	Pan HT 2020	IVR+cFXST	59.00±4.00	19/19	1,3mo	①②
		IVR+Placebo	63.40±3.60	19/19		
4	Huang Y 2017	IVB1.5mg+YFD	69.34±8.19	38/38	1wk,1,3,6mo	①②⑧
		IVB1.5mg	70.63±7.81	38/38		
5	He FJ 2017	IVC+BYD	57.10±3.82	20/20	3mo	①②③
		IVC	57.50±4.98	20/20		④⑦⑨
6	Zhou X 2018	IVC+BHD	63.24±12.68	29/29	1~3mo	①②④⑨
		IVC	62.45±13.76	29/29		
7	He YY 2020	IVR+BLP	70.43±10.46	30/30	1,3mo	①②⑨
		IVR	70.20±10.57	30/30		
8	Zhou WX 2020	IVC+ASSBP	67.69±5.48	30/30	1~3mo	①②③④
		IVC	68.66±5.48	30/30		
9	Gong Y 2021	IVC+DMD	58.03±3.20	30/30	1wk,1,3,6mo	①②④⑥⑦
		IVC	59.13±3.01	30/30		
10	He L 2020	IVR+CDDP	68.50±2.20	37/37	2mo	①②④⑩
		IVR	69.10±2.40	37/37		
11	Wu AH 2021	IVR+tFXST	63.18±8.48	60/60	1,3mo	①②⑧
		IVR	63.89±8.77	60/60		
12	Deng J 2019	IVR+GTD	64.78±8.41	27/27	1~3mo	①②④⑥⑨
		IVR	63.29±6.92	28/28		
13	Lin YM 2020	IVC+GDD	63.23±7.65	30/30	2mo	①②③
		IVC	60.47±7.75	30/30		④⑧⑨
14	Li J 2017	IVC+GDD	67.93±5.56	30/30	2mo	①②③⑩
		IVC	68.00±6.22	30/30		
15	Xu C 2019	IVR+HMT	65.30±12.10	48/48	3,6mo	①②③
		IVR	68.20±15.40	48/48		
16	Wu J 2020	IVR+HMT	59.41±5.50	50/50	3mo	①②③④
		IVR	60.96±6.99	49/49		
17	Zhuang P 2021	IVR+MSWD	63.17±7.48	41/41	3mo	①②⑤⑨
		IVR	63.57±7.91	41/41		
18	Zhao YX 2021	IVR+HOD	68.10±6.30	28/28	3mo	①②③
		IVR	67.60±6.30	28/28		⑦⑧⑩
19	Wang YL 2021	IVC+JSD	66.98±8.88	30/30	3mo	①②④⑦⑧⑨
		IVC	67.45±7.83	30/30		
20	Pu WX 2021	IVC+XZC	NA	25/25	1,3mo	①②⑧
		IVC	NA	25/25		
21	Zhou LY 2020	IVR/IVC+Saffron	71.68±7.06	22/22	3mo	②⑧⑩
		IVR/IVC	74.22±7.52	23/23		
22	Yu LB 2019	IVR+cFXST	67.40±8.10	30/30	3mo	①②⑦
		IVR	67.70±8.30	30/30		
23	Zhou ZY 2021	IVC+LHF	71.15±13.19	20/20	1,3,6mo	①②⑥⑧
		IVC	68.45±7.31	20/20		
24	Yu L 2020	IVC+LHF	70.40±7.40	40/20	1, 6, 12mo	①②⑥
		IVC	69.80±7.20	40/18		
25	Wang XD 2019	IVR+LD	66.27±7.67	30/30	3mo	①②③
		IVR	67.60±6.79	30/30		④⑧⑩
26	Yan XL 2019	IVR+MXT	67.60±7.90	100/100	3mo	①②⑤
		IVR	65.90±7.70	100/100		

Table 1　Baseline characteristics of identified studies and enrolled patients（continued）

Rank	Study	Interventions	Average age	Total number/effective number	Follow-up time	Outcomes
27	Qin L 2019	IVR+MXT	65.97±5.85	40/40	3mo	①②⑤⑧
		IVR	65.97±5.85	40/40		
28	Wu XR 2021	IVR+QGD	71.00±8.06	30/30	1，3mo	①②⑨ ⑩⑦⑧
		IVR	69.83±10.14	30/30		
29	Lu FR 2021	IVC+SWD	67.38±5.73	23/23	1～3mo	①②⑩
		IVC	66.89±6.19	23/23		
30	Jiang PF 2020	IVC+SMT	62.56±8.27	35/35	1～3mo	①②⑧
		IVC	61.98±8.82	35/35		
31	Wu QL 2014	IVR+SMT	65.00±7.05	20/20	3mo	①②④
		IVR	65.00±7.05	20/20		
32	Wu QL 2016	IVR+SMT	66.00±7.15	39/39	3mo	①②④
		IVR	65.00±7.05	38/38		
33	Chen JM 2020	IVC+SPD	64.10±8.31	30/30	1～3mo	①②④
		IVC	66.43±8.27	30/30		
34	Bai YX 2018	IVR+SD	54～73（66.27）	57/57	1mo	②④⑤
		IVR	54～73（66.27）	57/57		
35	Wang X 2019	IVR+EED	65.85±5.35	26/26	3mo	①②④
		IVR	65.62±5.78	26/26		
36	Pan HL 2019	IVR+HMT	67.50±2.30	40/40	3mo	②④⑧⑩
		IVR	68.50±2.50	40/40		
37	Jiang Y 2020	IVR+HMT	66.20±1.70	60/60	3mo	①②⑩
		IVR	57.90±1.80	60/60		
38	Wang JJ 2019	IVR+cFXST	59.17±4.03	19/19	1，3mo	①②
		IVR	63.35±3.65	19/19		
39	Cheng MM 2021	IVR+YYD	62.12±2.32	35/35	3mo	①⑨⑩
		IVR	61.12±2.62	35/35		

IVB：Intravitreal injection of bevacizumab；IVR：Intravitreal injection of ranibizumab；IVC：Intravitreal injection of conbercept；NA：none；ZQMT：Zhixue Quyu Mingmu Tablet；HBOD：Huangban Bianxing One Decoction；cFXST/tFXST：Fufang Xueshuantong Capsule/Tablet；YFD：Yiqi Fuming Decoction；BYD：Bugan Yishen Decoction；BHD：Bushen Huoxue Decoction；BLP：Bushen Lishui Prescription；ASSBP：Addition and Subtraction of Shenling Baizhu Powder；DMD：Danggui Mingmu Decoction；CDDP：Compound Danshen Dropping Pill；GTD：Gegen Tuichi Decoction；GDD：Guishao Dihuang Decoction；HMT：Hexue Mingmu Tablets；MSWD：Modified Siwu Wuzi Decoction；HOD：Huangban One Decoction；JSD：Jianpi Shenshi Decoction；XZC：Xuefu Zhuyu Capsule；LHF：Liangxue Huayu Formula；LD：Liujunzi Decoction；MXT：Mingmu Xiaomeng Tablets；QGD：Qihuang Granule Decoction；SWD：Sanren Decoction and Wendan Decoction；SMT：Sanxue Mingmu Tablets；SPD：Sheng Puhuang Decoction；SD：Self-draft Decoction；EED：Erchen Erhuang Decoction；YYD：Yangying Yiqi Decoction；①BCVA；②CMT；③Area of retinal hemorrhage；④Fluorescence leakage area；⑤Quality of life assessment；⑥Average number of injections；⑦Security analysis；⑧Adverse events；⑨TCM symptom score；⑩Clinical efficacy.

Risk of bias within studies　Of the 39 included studies，a total of 17 studies[7, 9-12, 15-16, 21-22, 24, 27, 31, 33, 37-38, 43-44] used the random number table method，4 items[13, 19-20, 36] used the random number grouping method，and 2 items[29-30] adopted simple random grouping method，all of which were grated as "low risk"；16 studies[6, 8, 14, 17-18, 23, 25-26, 28, 32, 34-35, 39-42] were unclear about the grouping method and they were classified as "uncertain risk". All studies did not report whether the study met allocation concealment，so they were rated as "uncertain risk"；2 studies[6, 8] which used a double-blind setting were assessed as "low risk"，the rest did not mention a blinded setting and were judged as "uncertain risk". Only one study[37] in the data were highly biased and did not comply with the reality，which was rated as high risk. The others had complete data without selective reporting of findings and other biases and were considered as "low risk". See Figure 2 for

details.

Composition of the traditional Chinese medicine within studies　A number of 28 TCM were involved in the 39 papers about the study，and their formula compositions and efficacy were analyzed.

Results of Meta-analysis

Traditional meta-analysis　A total of 12 papers reported VA changes at 1mo，7 papers included at 2mo and 29 papers at 3mo after treatment. Meta-analysis of the random effects model showed there is a statistically significant difference between TCM combined therapy compared with anti-VEGF alone（$MD=0.07$，95%CI：0.05～0.09，$P<0.00001$）. It is indicated that TCM combination therapy was more effective than anti-VEGF therapy in improving BCVA. See Figure 3A. A total of 15 publications reported CMT changes at 1mo after treatment，8 papers reported CMT changes at 2mo and 27

literatures at 3mo. Using the random-effect model, the forest plot showed a statistically significant difference between TCM combined therapy than anti-VEGF therapy alone ($MD = -25.32\mu m$, 95% CI: -30.06~-20.57, $P<0.00001$), which indicated traditional Chinese herbals combination therapy was more effective than anti-VEGF therapy in reducing CMT. See Figure 3B.

Network Meta-analysis

Evidential network A total of 34 studies reported BCVA involving 23 different TCMs. 38 studies reported CMT including 25 different TCMs. The blue dots in the evidence network diagram represent the various interventions, and the

size of the circles indicates the number of studies that was eventually incorporated in each intervention; the line between the two dots represents the existence of a direct comparison between 2 interventions, and the thickness of the line segment represents the amount of studies included. There were differences in clinical and methodological characteristics among the included studies, so the differences between direct comparison results and indirect comparison results need to be considered. The inconsistency model is considered only when a closed loop is formed. There are no closed loops in this study; hence, no ring inconsistency test was required. Evidence network as shown in Figure 4.
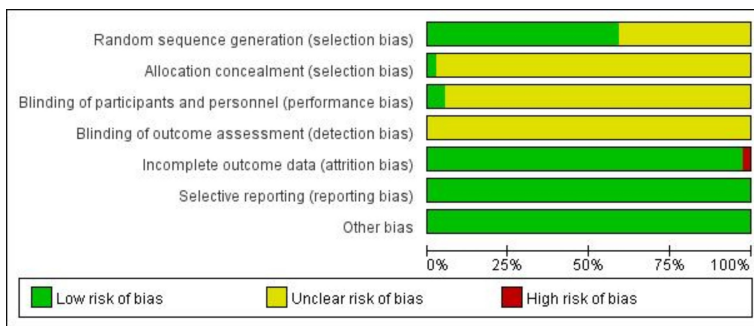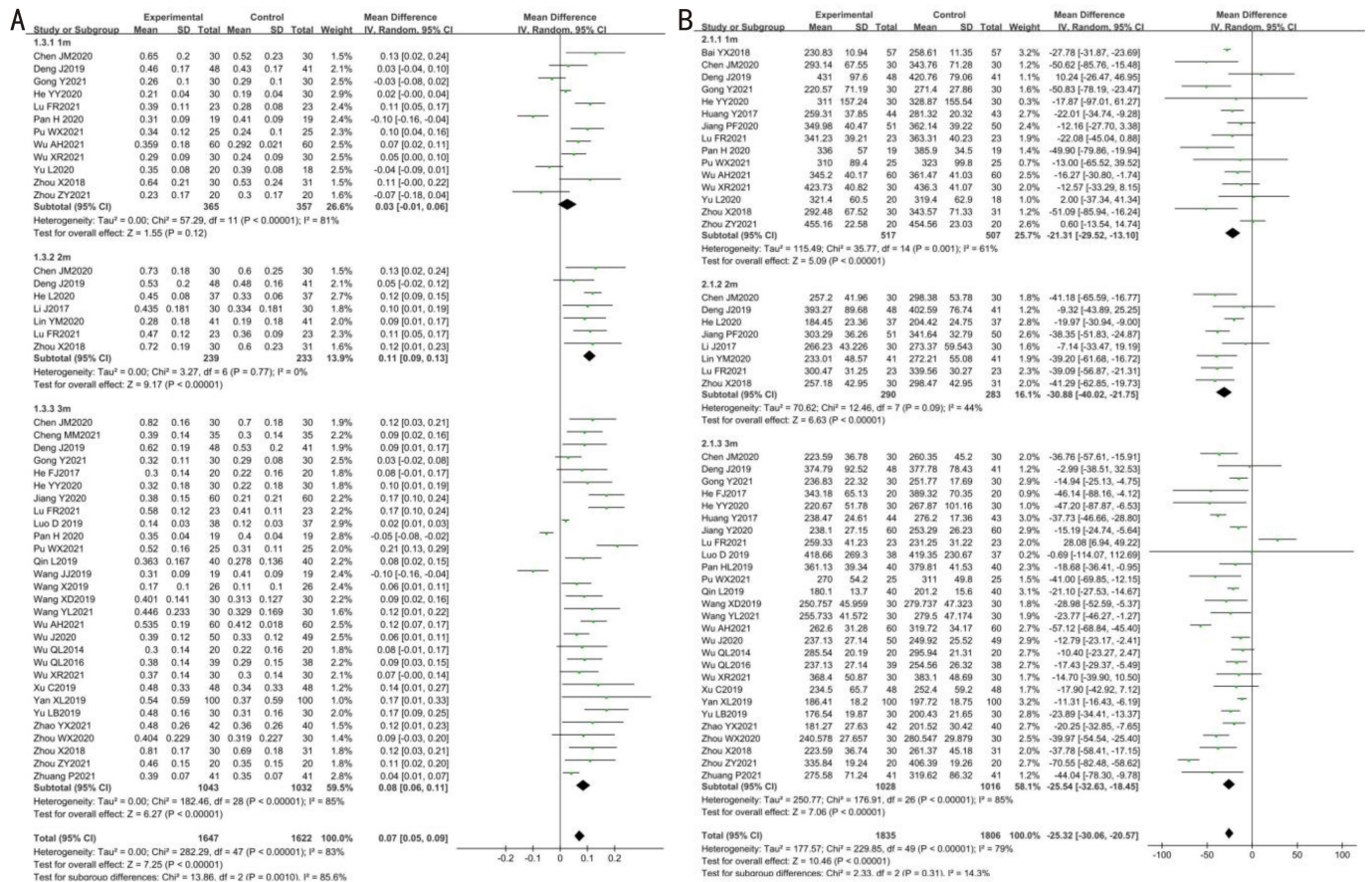

Figure 2　Risk of bias assessment.

Figure 3　Forest graph of best corrected visual acuity（A）and central macular thickness（B）.

Probability Ranking By comparing the therapeutic effects of different TCMs on wAMD, probability ranking of the included outcomes were conducted. When 1mo after treatment, the surface under the cumulative ranking curve （SUCRA） of BCVA was Sheng Puhuang Decoction （SPD;

87.0% ）> Sanren Decoction and Wendan Decoction （SWD; 83.3% ）> Bushen Huoxue Decoction （BHD; 80.1% ）> Xuefu Zhuyu Capsule （XZC; 79.9% ）> Qihuang Granule Decoction （QGD; 59.3% ）> Gegen Tuichi Decoction （GTD; 46.2% ）> Bushen Lishui Prescription （BLP; 43.6% ）> Fufang

Xueshuantong Capsule/Tablet (cFXST/tFXST; 28. 5%) > anti-VEGF (25.9%) > Danggui Mingmu Decoction (DMD; 11.4%) > Liangxue Huayu Formula (LHF; 4.6%), see Figure 5A; At 2mo post-treatment, the SUCRA ranking of BCVA was SPD (72.2%) > Compound Danshen Dropping Pill (CDDP; 71.1%) > BHD (66.8%) > SWD (62.1%) > Guishao Dihuang Decoction (GDD; 50.8%) > GTD (25.1%) > anti-VEGF (1.9%), see Figure 5B; At 3mo post-treatment, the SUCRA ranking of BCVA was XZC (96. 5%) > SWD (89.8%) > BHD (69.6%) > SPD (68.5%) > Huangban One Decoction (HOD; 66.5%) > Jianpi Shenshi Decoction (JSD; 65.3%) > LHF (63.2%) > Hexue Mingmu Tablets (HMT; 61.0%) > BLP (58.3%) > Mingmu Xiaomeng Tablets (MXT; 57.6%) > GTD (53.7%) > Yangying Yiqi Decoction (YYD; 53.6%) > Liujunzi Decoction (LD; 52.4%) > Sanxue Mingmu Tablets (SMT; 52. 0%) > Addition and Subtraction of Shenling Baizhu Powder (ASSBP; 50.3%) > Bugan Yishen Decoction (BYD; 47.8%) > QGD (42.3%) > Erchen Erhuang Decoction (EED; 35.6%) > Modified Siwu Wuzi Decoction (MSWD; 24.3%) > DMD (20.3%) > Huangban Bianxing One Decoction (HBOD; 14.5%) > anti-VEGF (6.3%) > cFXST/tFXST (0.6%), see Figure 5C; The order of reducing CMT efficacy at post-treatment 1mo was: DMD (88.0%) > BHD (87. 2%) > SPD (86. 2%) > Self-draft Decoction (SD; 66.7%) > cFXST/tFXST (55.7%) > Yiqi Fuming Decoction (YFD; 54.4%) > SWD (54. 2%) > BLP (47.7%) > XZC (40.7%) > QGD (37. 8%) > SMT (36.8%) > anti-VEGF (16.3%) > LHF (16.0%) > GTD (12.5%), see the following Figure 5D; The order of reducing CMT efficacy at post-treatment 2mo was: BHD (77.6%) > SPD (76.4%) > SWD (73.7%) > SMT (72.7%) > GDD (43.9%) > CDDP (31.3%) > GTD (20.1%) > anti-VEGF (4.5%), see Figure 5E; The ranking of CMT reduction efficacy at 3mo after treatment was: EED (88.1%) > BLP (81.0%) > MSWD (79.3%) > ASSBP (78.8%) > XZC (77.3%) > YFD (75.7%) > BHD (74.7%) > SPD (73.1%) > LD (60.3%) > cFXST/tFXST (55.9%) > JSD (52.2%) > HOD (45.7%) > QGD (36.8%) > HBOD (36.5%) > DMD (34.8%) = MXT (34. 8%) > HMT (34.3%) > SMT (33.0%) > GTD (24.8%) > anti-VEGF (14. 7%) > SWD (4.5%) > BYD (4.0%), see Figure 5F.

Publication bias   For comparison correction funnel plots, the effect size of each index was plotted on the horizontal coordinate and the standard error was plotted on the vertical coordinate. As shown in Figure 6, the dots in the funnel plot of BCVA were distributed roughly on both sides of the midline and concentrated in the upper part, with an asymmetric distribution, indicating a possible small sample effect or publication bias. And the points in the funnel plot of CMT were distributed roughly on both sides of the midline and concentrated in the upper part, with an symmetric distribution approximately, indicating that a small sample effect or publication bias is less likely.

Adverse Reactions   A sum of 13 RCTs reported adverse reactions involving 857 patients. The study results indicated no significant heterogeneity ($P = 0. 99$, $I^2 = 0\%$). The differences were statistically significant ($RR = 0.48$, $95\%CI$: $0.30 \sim 0.76$, $P < 0.01$), which indicated the safety of the TCM combined with anti-VEGF was good, as shown in the Figure 7. Ten items of these[9, 16, 18, 20, 25, 27, 31, 35-36, 38] have reported the adverse reactions, containing transient intraocular pressure (IOP) rises, conjunctival congestion, dry eyes, ocular pruritus, and mild gastrointestinal reactions in the treatment group. Generally the symptoms will relieve spontaneously after observation or medication. A total of 2 studies[26, 33] have reported on CNV recurrence in patients in the treatment group, patients are advised to continue with anti-VEGF therapy or combined with TCM, the recurrence rate in the control group was higher than that in the treatment group.
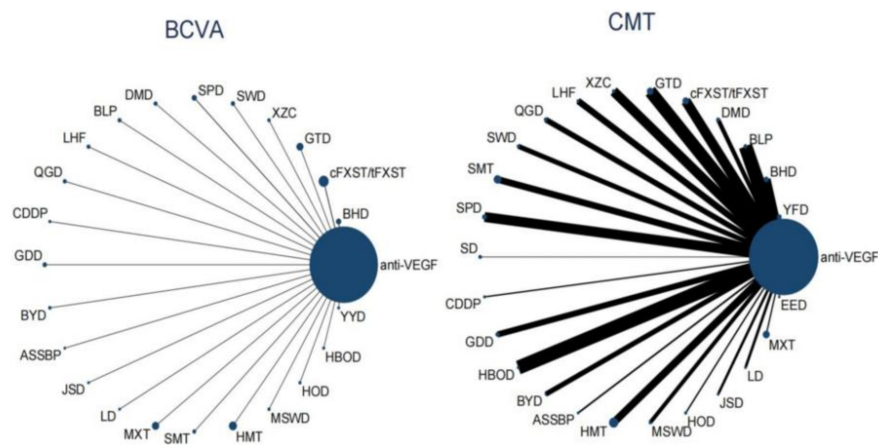

Figure 4   Network maps.   HBOD: Huangban Bianxing One Decoction; cFXST/tFXST: Fufang Xueshuantong Capsule/Tablet; YFD: Yiqi Fuming Decoction; BYD: Bugan Yishen Decoction; BHD: Bushen Huoxue Decoction; BLP: Bushen Lishui Prescription; ASSBP: Addition and Subtraction of Shenling Baizhu Powder; DMD: Danggui Mingmu Decoction; CDDP: Compound Danshen Dropping Pill; GTD: Gegen Tuichi Decoction; GDD: Guishao Dihuang Decoction; HMT: Hexue Mingmu Tablets; MSWD: Modified Siwu Wuzi Decoction; HOD: Huangban One Decoction; JSD: Jianpi Shenshi Decoction; XZC: Xuefu Zhuyu Capsule; LHF: Liangxue Huayu Formula; LD: Liujunzi Decoction; MXT: Mingmu Xiaomeng Tablets; QGD: Qihuang Granule Decoction; SWD: Sanren Decoction and Wendan Decoction; SMT: Sanxue Mingmu Tablets; SPD: Sheng Puhuang Decoction; SD: Self-draft Decoction; EED: Erchen Erhuang Decoction; YYD: Yangying Yiqi Decoction.
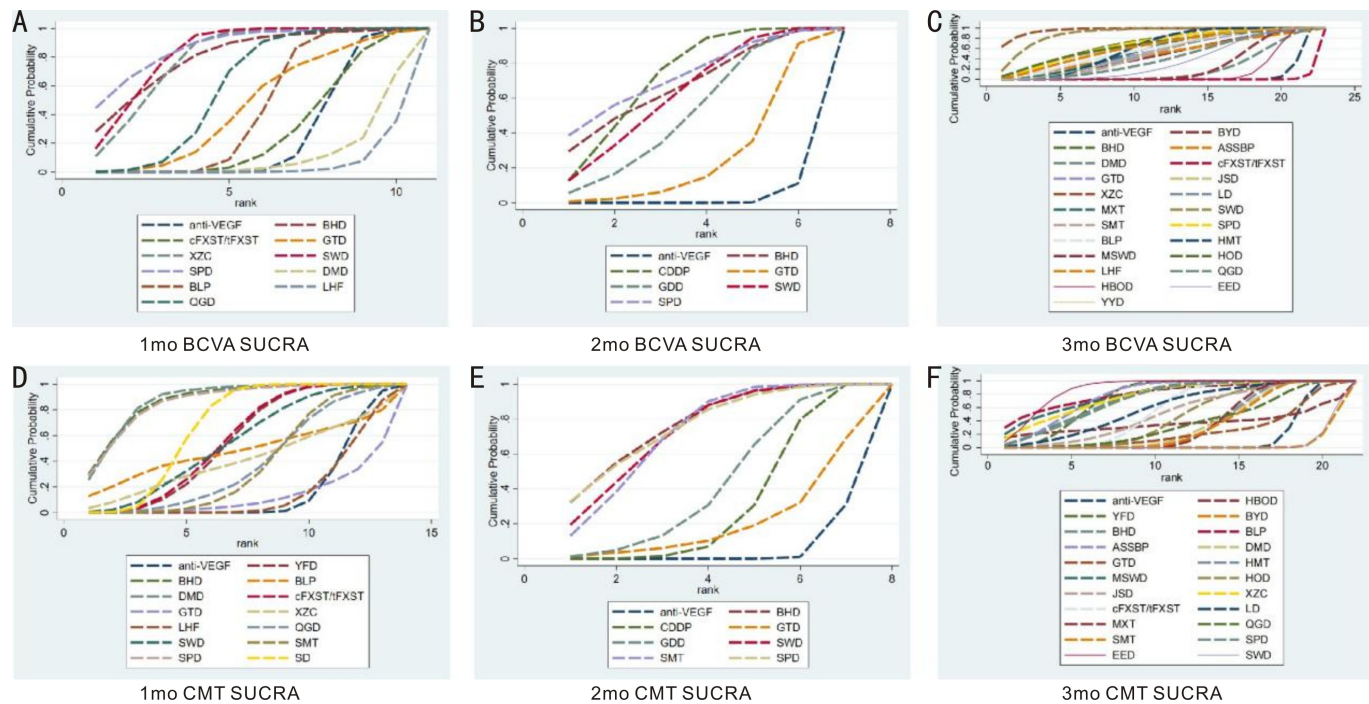
Figure 5　Probability ranking curve　HBOD:Huangban Bianxing One Decoction;cFXST/tFXST:Fufang Xueshuantong Capsule/Tablet;
YFD:Yiqi Fuming Decoction;BYD:Bugan Yishen Decoction;BHD:Bushen Huoxue Decoction;BLP:Bushen Lishui Prescription;ASSBP:
Addition and Subtraction of Shenling Baizhu Powder;DMD:Danggui Mingmu Decoction;CDDP:Compound Danshen Dropping Pill;GTD:
Gegen Tuichi Decoction;GDD:Guishao Dihuang Decoction;HMT:Hexue Mingmu Tablets;MSWD:Modified Siwu Wuzi Decoction;HOD:
Huangban One Decoction;JSD:Jianpi Shenshi Decoction;XZC:Xuefu Zhuyu Capsule;LHF:Liangxue Huayu Formula;LD:Liujunzi
Decoction;MXT:Mingmu Xiaomeng Tablets;QGD:Qihuang Granule Decoction;SWD:Sanren Decoction and Wendan Decoction;SMT:
Sanxue Mingmu Tablets;SPD:Sheng Puhuang Decoction;SD:Self-draft Decoction;EED:Erchen Erhuang Decoction;YYD:Yangying Yiqi
Decoction.

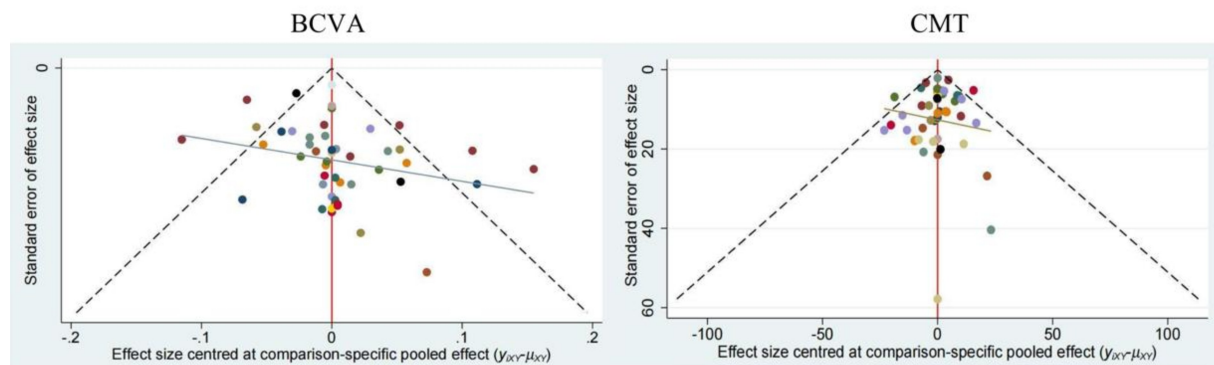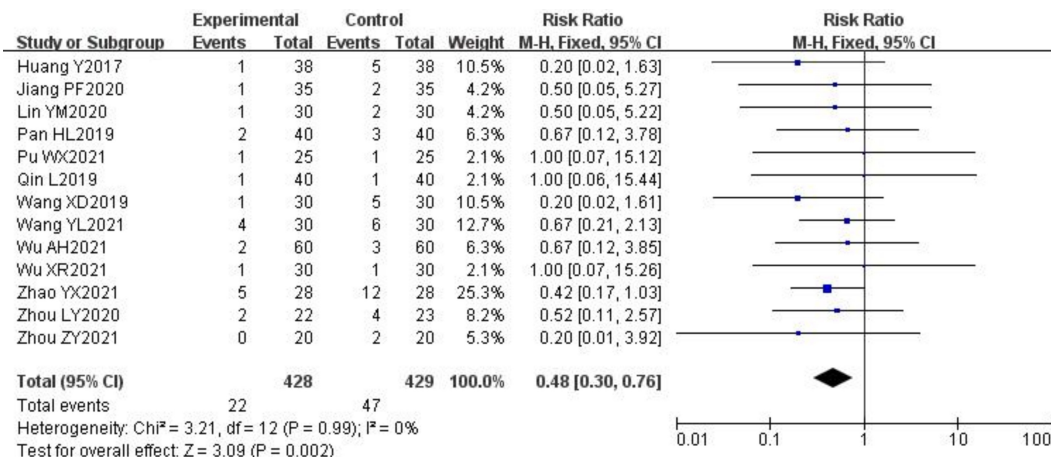**Figure 6　Funnel plot of best corrected visual acuity and central macular thickness.**

Figure 7　Adverse reactions forest graph.

Only one study[28] reported that one patient with coronary atherosclerotic heart disease did not take oral TCM as measured developed pre-heart area pain, chest tightness. Considered causing by the underlying disease, can be relieved after rest. The other patient gave feedback of poor VA recovery after treatment. Given that the large range of wAMD lesions, the CNV was gradually fibrotic or scarring, resulting in poor outcomes.

DISCUSSION

Over the past 20 years, the modality of treatment for wAMD has changed significantly, from primarily laser photocoagulation, photodynamic therapy (PDT), and transpupillary thermotherapy (TTT) to anti-VEGF drug therapy, representing a turning point in the therapy of wAMD[49]. To date, the first-line treatment for wAMD is intravitreal injection of anti-VEGF drugs. The regimens for the use of anti-VEGF drugs, which are not conclusive at home and abroad, are mainly used in fixed interval regimens, 3+PRN and T&E[50]. However, there are some limitations of the short intraocular half-life and physiologic VEGF inhibited[51]. This treatment modality is not durable and hence requires frequent intravitreal injection. Monthly anti-VEGF therapy imposes a large burden of treatment and follow-up on patients, in addition to the poor compliance of most patients, making it difficult to achieve long-term follow-up in actual clinical practice[52]. Despite the promising visual effects of anti-VEGF drug treatment, intensive retreatment may not be sustainable in the long term[53-54]. Thereby, our most important goal is to maintain the best possible visual effect while reducing the burden of treatment, and combination of treatment strategies should be further explored.

AMD is a multifactorial disease, and recent studies have shown that autophagic dysfunction of RPE cells, aging, oxidative stress, lipid metabolism, chronic and abnormal inflammatory responses, angiogenesis and complement system activation play a key role in the development of wAMD[55-56]. The target of anti-VEGF drugs action is single, and not all patients can benefit from them. TCM compounds have the characteristics of many components and complex pharmacological mechanism, which can inhibit angiogenesis, anti-inflammation, hemostasis and detumescence from multiple channels and targets. The inclusion of three anti-VEGF drugs comprises conbercept, ranibizumab and bevacizumab in the context of this search. It is well-evidenced that the effect of anti-VEGF drugs is the identical[57-58]. Accordingly, we indirectly compared the therapeutic effects of different Chinese herbal medicines through a network meta-analysis, with the aim of providing new ideas and EBM basis for clinical treatment of wAMD. Our results showed that the combination of TCM and anti-VEGF therapy could better improve BCVA and reduce CMT in patients with fewer adverse effects compared with anti-VEGF therapy. These datum support the combination of TCM and anti-VEGF as a treatment strategy that can improve wAMD.

The wAMD is a refractory eye disease, and the TCM believes that the AMD is a Tong Shen disease. There is no clear corresponding disease name for AMD in our ancient medical texts. According to the characteristics of different stages of the disease, the disease can be attributed to the category of eye diseases such as Shizhan Hunmiao, Shizhi Ruqu, Yunwu Yijing, Bao Mang[59]. The Standards for Diagnosis and Treatment has a similar description："If a person is older than 50 years and the blurred vision, despite the treatment does not return to the bright. It seems like the moon is overlooking, the innate vital Qi is gradually declining and the natural vision is progressively losing". This disease is mainly caused by old age and physical weakness, and the visceral vital essence cannot reach the eyes, resulting in the loss of nourishment for the eyes, which manifests as Shizhan Hunmiao. Based on the theory of the Internal Meridian, "The central yellow extends through the spleen", Da-Fu Chen proposed that macular is in the middle, yellow in color, belongs to the Spleen Channel of Foot-Taiyin and depends on the spleen and stomach to moisten in the six meridians of ophthalmology in TCM[60]. When the macular areas hemorrhage, or macular edema led to the distortion of visual objects, belong to Shizhi Ruqu. If macular hemorrhage enters into the vitreous, the patient appears to have black shadows in the visual field and cloudy vitreous, which is called Yunwu Yijing. When the macular area bleeding volume is large enough to cause a sudden loss of vision or even not see anything. Then it is called Bao Mang. The wAMD is based on deficiency of liver and kidney, and the pathological products such as phlegm, dampness, blood and stasis are the symptoms, involving the liver, spleen and kidney. Different conditions and different stages, the treatment should be differentiated according to the individual differences of patients.

TCM has unique advantages in the treatment of this disease. Through overall adjustment and syndrome differentiation and treatment, patients are given personalized diagnosis and treatment plan. The combination of disease identification and syndrome identification, as well as overall and localized treatment, can improve the clinical efficacy of AMD patients. In this paper, the combination effect of 28 different TCMs combined with anti-VEGF for wAMD was analyzed through a literature search, and we indirectly compared the effects within various herbal medicines. Ultimately, we found that TCM combination therapy could protect visual function, and reduce complications, thus improving the quality of patient's survival and reducing economic costs. Jin and Chen[61] developed a clinical application guideline for the treatment of wAMD with Chinese patent medicines in 2020. It is recommended that in the early stage of CNV, when visual distortion or sudden loss of vision occurs in the early stage of bleeding, accompanied by soreness and weakness of the waist and knees, dry throat and mouth, heartburn, red tongue with little coating, and counted pulse, take ZQMT or HMT. For those with fatigue, dry throat, dry mouth, take the cFXST. The CNV bleeding phase was treated with ZQMT combined with anti-VEGF.

Previous basic experimental studies and clinical application studies have found that the potential value of single and compound Chinese herbs and acupuncture treatment to inhibit CNV. Qin et al[62] observed that acupuncture combined with salvia injection ocular iontophoresis for wAMD, and the results found that compared with acupuncture alone, combined treatment can significantly reduce VEGF levels, IOP and CMT, improve macular function and VA, with definite efficacy. Lu et al[63] explored the inhibition effect of ginsenoside RG3 on CNV from both in vivo and in vitro tests and showed that ginsenoside RG3 could inhibit CNV formation. In addition, there are also curcumin, Radix Rehmanniae, Mucuna pruriens, Scutellaria baicalensis, ginsenoside, Ginkgo biloba extract and herbal compound that have made some progress in experimental studies and clinical aspects of CNV inhibition[64]. Dr. Cao[65-66], a member of our team, used 532nm laser photocoagulation to induce brown Norway rats CNV models and found that DAG/PKC/MAPK/ NF-κB signaling pathway plays an important role in the process of CNV. At the same time, clinical experiments were also observed that the therapeutic effect of nAMD combined with the GDD and conbercept is more advantageous compared with anti-VEGF alone, which can improve the systemic symptoms of patients and reduce the serum TLR3 levels.

Based on the previous research basis, this paper once again verified the effectiveness and safety of TCM in the treatment of wAMD, and analyzed the comparative efficacy of 28 different Chinese herbal medicines. The results of the network meta-analysis in this paper showed that the drugs with the best efficacy in improving BCVA after 1, 2 and 3mo of treatment were SPD and XZC; the best drugs for reducing CMT were DMD, BHD and EED. It can be showed that the treatment of wAMD with TCM is based on activating blood circulation, removing blood stasis and stopping bleeding, as well as tonifying the liver, benefiting the kidney and strengthening the spleen to resolve turbidity. Previously, it was indicated that many active ingredients of Chinese medicine have prominent pharmacological effects such as antioxidant, anti-inflammatory, anti-aging, and anti-apoptotic, which can prevent or block the occurrence and development process of AMD through different pathways[67]. The active ingredients of TCMs have the advantage of multi-target and multi-pathway collaborative regulation, its potential in the prevention and treatment of wAMD is constantly being explored and developed. Nevertheless, there is still a certain gap in new drugs transformation and clinical application. At present, most of the research on the prevention and treatment of AMD stay in the drug screening stage. In the prospective future, it is expected to conduct in-depth research on the pharmacology and mechanism of action of Chinese medicine, and continuously improve and strengthen preclinical studies and large-scale clinical validation trials.

It's true that there have been some studies published like this, but this study has its advantages and differences, for example, the included studies in this paper are comprehensive and extensive, including all the literature on different dosage forms of herbal medicine combined with anti-VEGF for wAMD. And the different recording methods of visual acuity in the literature were combined and transformed into IS VA, which is comparable. In this manuscript, the BCVA and CMT are used as the main outcomes to compare the best effect of the action of different kinds of TCM. It can guide clinical practice, individualize treatment to reduce the number of frequent anti-VEGF injections, improve compliance, reduce patients' economic burden, achieve optimal outcomes, and provide an evidence-based basis for the application of TCM.

Limitations This paper still has the following shortcomings, to begin with, the quality of the included literature is not high, and they are unclear about the description of how the random grouping sequence is generated, the detailed description of allocation concealment. Only two studies set placebo controls, and the rest of clinical trials were not placebo-controlled and not blinded, which reduces the credibility to a certain extent. In recent years, the reporting specifications of SPIRIT-TCM, an extended version of TCM, and CONSORT, a compound Chinese medicine, have been published for clinical trials in TCM[68-69]. Generally, based on the low quality of the literature included in this study, we should strictly follow the above reporting guidelines to provide a reliable basis for clinical practice in the future. Second, all included studies were positive results, and there was a degree of publication bias. Third, only literatures in Chinese and English languages were included, there were no more than three foreign language papers among them. All experiments were conducted in China, with some geographical and linguistic bias. Fourth, lack of intention to treat (ITT) analysis of clinical trials[70]. The ITT issue was ignored by many investigators in the TCM clinical trials reported in the present study. Only participants who completed the study were subjected to final analysis, which neglected the issue of adherence leading to unreliable conclusions. Fifth, the survey did not form a closed loop, and there were no direct comparison results between different TCMs to determine the consistency of the direct and indirect comparison results, which reduced the credibility and stability to some extent. It is imperative to expand the clinical trials involving pairwise comparisons of Chinese herbal medicines in order to enhance the level of evidence and provide guidance for future clinical medication use. After this, there are a lack of unified diagnostic criteria and syndrome differentiation of TCM. Last, TCM included different pharmaceutical forms such as soup, tablet, capsule and pill. Since the dosage forms are restricted, traditional Chinese patents could not be added or subtracted with evidence types, so there exists heterogeneity.

CONCLUSIONS

In summary, TCM combined with anti-VEGF drugs for the treatment of wAMD has remarkable improvement over anti-VEGF in terms of effectiveness and safety. Chinese medicine has certain advantages in combining disease identification with syndrome differentiation, symptom treatment with root cause

healings. The treatment of wAMD through the combination of traditional Chinese and western medicine can promote abundant Qi and Blood，nourish macular，and improve the local microenvironment，so as to achieve the purpose of enhancing the curative effect and reducing the recurrence[71]. In the future，it is still necessary to carry out multi-center，large sample and prospective clinical RCTs around this project.

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