Spotlight on the traditional medicine in prevention and treatment of diabetes in the aging population

Edited by
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Spotlight on the traditional medicine in prevention and treatment of diabetes in the aging population

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Table of
contents

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Editorial: Spotlight on the traditional medicine in prevention and treatment of diabetes in the aging population

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Editorial on the Research Topic
Spotlight on the traditional medicine in prevention and treatment of diabetes in the aging population

1 Introduction

As the global population ages, diabetes has become a growing public health problem. According to the World Health Organization, diabetes affects approximately 425 million people globally, with a particularly high prevalence among the elderly population (1). Diabetes is not only a chronic disease, but its complications pose a serious threat to patients' quality of life (2, 3). In this context, it is particularly important to explore and evaluate the application of traditional medicine in the prevention and treatment of diabetes. This Research Topic aims to provide insights into the potential and challenges of traditional medicine in the management of diabetes in the elderly. We have brought together a series of high-quality research findings covering a wide range of aspects such as diabetic foot problems, neurological complications, and the roles and mechanisms of traditional Chinese medicine in the management of diabetes in the elderly. These studies not only provide empirical support for traditional medicine in diabetes management, but also offer new perspectives on our understanding of its deeper mechanisms of action.

The mission of this editorial is to distill and reflect the best of the scholarship presented in this Research Topic and to present readers with a comprehensive picture of the application of traditional medicine in the treatment of geriatric diabetes. We are confident that these selected studies will shed new light on the field of diabetes care and promote in-depth thinking and innovative practice of comprehensive treatment programs for geriatric diabetes.

2 Diabetic foot problems

Diabetic foot problems, especially diabetic foot ulcers (DFUs) and infections, are common complications in elderly diabetic patients, seriously affecting their quality of life, and prognosis (4). The included articles focus on the use and effectiveness of herbal medicine in the treatment of diabetic foot problems. A prospective study by Zhao et al. revealed the potential of Chinese medicine Shengji ointment combined with the pineapple protease (bromelain) in promoting healing of diabetic foot ulcers, and identified key risk factors for healing, including plantar ulcer location, low hemoglobin levels, high body mass index (BMI) and high creatinine levels. The significance of this study is that it provides a valuable predictive model to assist healthcare professionals in assessing treatment efficacy and personalizing treatment strategies for each patient and may help to improve patient prognosis by integrating herbal treatments into routine clinical practice. The study by Yang G. et al. compared the efficacy and cost-effectiveness of Fufang Huangbai Fluid hydropathic compress (FFHB) with conventional antimicrobial calcium alginate wound dressing (ACAWD) in the treatment of diabetic foot infections. It was found that FFHB had significant advantages in promoting wound healing, inhibiting bacterial proliferation, and reducing local inflammation and edema, and showed greater cost-effectiveness compared with ACAWD, providing a safe and cost-effective pharmacological treatment option for mild diabetic foot infections. These studies not only demonstrate the potential of TCM in the treatment of diabetic foot complications, but also provide a scientific basis for future clinical practice.

3 Diabetic neurological complications

Diabetic neurological complications, including diabetes-associated cognitive decline (DACD) and diabetic peripheral neuropathy (DPN), are common problems among older diabetic patients, severely affecting their cognitive function and ability to perform daily activities (5). A systematic review and meta-analysis by Su et al. assessed the efficacy and safety of combined Chinese and Western medicine in the treatment of DACD, showing significant advantages of combined Chinese and Western medicine in improving glycemic control and cognitive function. The study by Yu et al. explored the mitigating effects of bergenin on high glucose-induced neuroinflammatory injury at the molecular level, using zebrafish, mouse microglial cell line (BV2 cells) and rat models for evaluation. The results showed that bergenin redirects glucose metabolism, attenuates inflammatory responses, and prevents high-glucose-induced neuronal damage through PPAR-γ/NF-κB pathway intervention, providing new perspectives and potential therapeutic strategies for the treatment of diabetes associated cognitive impairment (DACI). The studies by Zhang X. et al. and Fu et al. assessed the efficacy and application prospects of acupuncture and TCM in the treatment of DPN through systematic evaluation and evidence mapping methods, respectively. These studies provide new perspectives for understanding the mechanisms of diabetic neurologic complications and offer diverse therapeutic strategies for clinical management.

4 Role and mechanism of traditional Chinese medicine in the treatment of geriatric diabetes mellitus

Traditional Chinese medicine (TCM) plays an important role in the treatment of geriatric diabetes mellitus, and its multi-targeted and individualized therapeutic features provide new therapeutic options for geriatric diabetes mellitus patients. The study by Lei et al. delved into the pharmacodynamic components and molecular mechanisms of Yuquan pill in the treatment of type 2 diabetes mellitus (T2DM) through a multi-omics analysis, providing a scientific basis for understanding the role of TCM. It was found that Yuquan pill was able to reduce the levels of triglycerides, cholesterol, nitric oxide and malondialdehyde in T2DM rats, as well as increase the levels of high-density lipoprotein cholesterol, and had a protective effect on the liver and kidney. Zhang Q. et al. systematically reviewed the clinical application of TCM in the treatment of geriatric diabetes mellitus, pointed out the shortcomings of the current study, and provided guidance for future study design. Yang X. et al.'s study, on the other hand, explored the role of TCM in the improvement of clinical symptoms and glycemic control from the perspective of the clinical characteristics and pathogenesis of geriatric diabetes mellitus, and emphasized the important value of TCM in the management of geriatric diabetes mellitus. value of TCM in the management of geriatric diabetes mellitus. Together, these studies advance the understanding of the roles and mechanisms of TCM in the management of geriatric diabetes and provide a wealth of information and guidance for clinical practice.

5 Conclusion and outlook

Overall, the studies included in this Research Topic profoundly reveal the multifaceted role of traditional medicine in the management of geriatric diabetes, particularly in the management of diabetic foot problems and neurologic complications. Through in-depth analyses of the pharmacodynamic components of herbal compounds, the clinical effects of traditional treatments, and the potential mechanisms of TCM for glucose regulation and complication prevention, these studies provide valuable insights into personalized treatment strategies for geriatric diabetes. By mapping out a comprehensive picture of traditional medicine in the treatment of diabetes and understanding how these treatments interact with a patient's specific condition, we are able to design more effective and personalized treatment plans for older patients with diabetes. It is important to note that clinical translation of these findings and a deeper understanding of the biological mechanisms are critical to their successful application to practical treatment strategies. Therefore, future work should include further clinical trials and mechanistic studies to confirm the actual effectiveness and application potential of these traditional treatments.

In conclusion, by deeply exploring the therapeutic potential of traditional medicine and combining it with

modern medicine, we are expected to significantly improve the effectiveness of geriatric diabetes treatment and open up new therapeutic avenues. This approach not only demonstrates new prospects for the treatment of geriatric diabetes, but also provides a new direction for future therapeutic practice, especially in improving patients' quality of life and delaying disease progression.

Author contributions

LJ: Writing – original draft. HC: Writing – original draft. XZ: Writing – original draft. JT: Writing – original draft. JZ: Writing – original draft. QZ: Writing – original draft. SL: Writing – review & editing. JS: Writing – review & editing. GY: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Predictive factors and clinical efficacy of Chinese medicine Shengji ointment in the treatment of diabetic foot ulcers in the elderly: a prospective study

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Objective: This study aims to investigate the predictive factors and efficacy of traditional Chinese medicine Shengji Ointment in the treatment of diabetic foot ulcers in the elderly population, with the intent of formulating an effective predictive model for deep diabetic foot ulcer healing. The importance of this research lies in its provision of new perspectives and tools for addressing the severe health impact of diabetic foot ulcers in the elderly population, considering the complexity and diversity of its treatment methods.

Methods: The study includes 180 elderly patients with Wagner grade 3–4 diabetic foot ulcers that involve the tendon or fascia. The dependent variable is the initiation time of granulation tissue development. Independent variables encompass demographic information, a treatment strategy including Shengji Ointment, pre-treatment trauma assessment data, routine blood count, and biochemical index test results. Lasso regression is employed for variable selection, and Cox regression is utilized for the construction of a prediction model. A nomogram is generated to authenticate the model.

Results: The Chinese Medicine treatment approach, ulcer location, creatinine levels, BMI, and haemoglobin levels are identified as independent predictors of granulation tissue development in diabetic foot ulcers. The combined treatment of Chinese herbal Shengji ointment and bromelain positively influenced granulation tissue development. The location of plantar ulcers, impaired renal functionality, obesity, and anaemia are established as independent risk factors that might influence the speed and probability of ulcer healing. The area under the time-dependent ROC curve fluctuates between 0.7 and 0.8, demonstrating substantial discrimination and calibration of the model.

Conclusion: The study ascertains that a combined treatment strategy incorporating Shengji Ointment demonstrates greater effectiveness than the use of cleansing gel debridement alone in facilitating the healing of Wagner grade 3 or higher diabetic foot ulcers. Furthermore, the predictive model developed in this research serves as a valuable tool in evaluating the efficacy of Chinese Medicine treatments like Shengji Ointment for diabetic foot ulcers in

the elderly. It aids clinicians in effectively assessing and adjusting treatment strategies, thereby proving its significant application value in clinical practice.

1 Introduction

Diabetic foot stands as a serious complication among diabetic patients, thereby constituting a significant public health concern. It correlates with elevated rates of disability, recurrence, protracted hospital stays, complex clinical management, and an unfavorable long-term prognosis (American Diabetes Association, 2018). Among the various presentations of diabetic foot, diabetic foot ulcers (DFUs) are the most common, with three-fourths of diabetic foot patients suffering from severe foot infections. This results in a 10–30 times higher incidence of lower extremity amputations in patients with DFUs compared to the general population (Trautner et al., 1996), contributing to the majority of amputations among diabetic patients—accounting for over 85% of instances (Chinese Society of Medical Sciences et al., 2019a). The Wagner grade is broadly employed to evaluate the classification of DFUs (Trautner et al., 1996). As per a nationwide study, 45% of 669 patients were diagnosed with Wagner grade 3 or higher, with the overall amputation rate nearing 20% (Jiang et al., 2015). Moreover, a gradual decline in wound healing rate was observed with an increasing Wagner grade (Fei et al., 2012). Patients who have undergone amputation of one limb bear a high risk of developing amputation of the contralateral limb. Furthermore, 30%–50% of initial amputations lead to subsequent amputations within 1–3 years. Patients with diabetes mellitus saw the greatest increase in amputation rates, rising from 10 per 100 patients with lower extremity ulcers in 2005 to 28 per 100 patients in 2013 (Humphries et al., 2016). These findings underscore a surging prevalence of DFUs involving deeper tissues, such as the tendon fascia, thereby emphasizing the urgent need for more effective treatments to improve prognosis.

DFUs are traditionally managed through physical debridement, wound repair, wound decompression, and negative pressure therapy. The formation of granulation tissue is recognized as a reliable indicator of wound healing (Lin et al., 2005; Valenzuela-Silva CM et al., 2013). However, the effectiveness of these treatment strategies differs among various types of DFUs. Bacteria adhere to the wound surface, proliferate, establish a biofilm, and gradually impair the normal tissue. Once formed, eradicating the biofilm becomes challenging with conventional treatments, including antibiotics and physical debridement (Sanchez et al., 2013; Kalan et al., 2016). Patients with deep ulcers generally exhibit a poorer prognosis, and over-treatment of deep ulcers that expose tendons could potentially culminate in the loss of limb function (Mohajeri-Tehrani et al., 2016; Chinese Society of Medical Sciences et al., 2019b).

The potential role of Chinese herbal medicine in promoting superficial ulcer healing and mitigating disability has been explored as a prospective treatment strategy for diabetic foot, as supported by previous studies (Guo, 2005; Liu et al., 2021). The combined traditional Chinese medicine treatment involves two types of medicine—Shengji ointment and bromelain, originating from Zhang Tianlei's "Compendium of Ulcerology."

Shengji ointment (Chinese patent medicine with China Food and Drug Administration approval number: Z12020345) consists of Angelica sinensis (Oliv.) Diels (Apiaceae; Angelicae sinensis radix), Rehmannia glutinosa (Gaertn.) DC. (Orobanchaceae; Rehmanniae radix), Gypsum Fibrosum [main component: $CaSO_4$], Crinis Carbonisatus (known as Xue-yu-tan in Chinese), calamina and beeswax. The names of the plants were verified on http://www.plantsoftheworldonline.org. Shengji ointment (30 g per bottle, lot number: YW202000285) was supplied by Tianjin Darentang Jingwanhong Pharmaceutical Co., Ltd., (Tianjin, China), with an expiration period of 36 months. The drug adheres to the quality standards set by the National Medical Products Administration (NMPA) National Drug Standard Revision Approval (2001ZFB0067) and NMPA Supplementary Drug Application Approval (2017B02035).

Ultra-performance liquid chromatography with quadrupole time-of-flight mass spectrometry instrument (UPLC-QTOF-MS)

was used to identify the components of Shengji ointment. The chemical analysis follows the standards established by the ConPhyMP statement (Heinrich et al., 2022). The UPLC fingerprints show that the active ingredients of Shengji ointment include Azelaic acid, N-butylidenephthalide, 3-N-butylphthalide, Palmitoleic acid, Ligustilide, Linolenic acid, Linoleic acid, Palmitic acid, Oleic acid. Detailed information on the botanical drug extraction and formulation process, quality control methods, and UPLC chromatogram of Shengji ointment ingredients can be found in Supplementary Appendix S3.

The pineapple protease (bromelain), sourced from Shantou Olive Pharmaceutical Co., Ltd., (Guangdong, China), has a 24-month expiration period. It is approved by China Food and Drug Administration (approval number: H44024825) and has been widely used as a complementary treatment for Hypercholesteremic, combined hyperlipidemia and cardiovascular disease (CVD) in China. The combined treatment process involves the enzymatic decomposition of the fibrin clot at the inflamed area, sparing the basal sore surface bed from mechanical debridement damage, and establishing a moist healing environment for the sore surface with Shengji ointment.

However, the low quality of existing studies restricts their ability to provide high-quality clinical evidence-based findings. Through this multi-center clinical trial, we sought to determine whether combined Chinese Medicine treatment constituted an independent protective factor for wound healing. Our aim was to establish a practical predictive tool for clinical management by examining the factors associated with the healing of deep DFUs. Simultaneously, we endeavored to devise a clinical prediction model for patients with Wagner grade 3-4 injuries involving the tendon or fascia tissue.

2 Materials and methods

2.1 Design and participants

Data for this study were derived from a multicenter, open-label, randomized controlled trial. This research assessed the treatment outcomes of 180 patients with diabetic foot ulcers, who were enrolled from four hospitals in Tianjin and Shanxi between 1 January 2021, and 31 December 2021. Adult patients who satisfied the following criteria were included: 1) diagnosed with diabetic foot disease and Wagner grade 3–4 ulcers exposing tendon tissue; 2) fasting blood glucose ≤10 mmol/L; 3) targeted ulcer debridement area ranging between 1 and 20 cm² (for patients with multiple lesions, the largest ulcer was deemed the target lesion); 4) an ankle-brachial index ≥0.5 on the side of the limb harboring the ulcer; 5) voluntary participation and signed informed consent. Patients were excluded from the study if they met any of the following criteria: 1) presence of malignant lesions and severe infection within the ulcer; 2) severe uncontrolled hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg); 3) severe malnutrition (serum albumin level <28 g/L or hemoglobin <90 g/L or platelet count <50 × 10⁹/L); 4) allergic disposition or allergies to the constituents of the treatment under investigation and reference drugs; 5) cognitive dysfunction that impeded fully informed consent or an inability to complete the trial or comply with its requirements, according to the researcher's judgment.

2.2 Interventions

In the intervention group, patients received a combined topical treatment regime comprising Chinese herbal Shengji ointment and bromelain. In the control group, a hydrocolloid dressing was applied to cover the wound. Both groups received treatment once every 24 h for a 4-week period, alongside routine medical and surgical treatment (including glycemic control, blood pressure reduction, lipid regulation, antiplatelet medication, debridement, and others). No additional Chinese or Western drugs relevant to ulcer treatment (such as vasodilators including lipid microsphere prostaglandin injections, beraprost sodium, cilostazol, and others; antiplatelet drugs such as aspirin and clopidogrel; anticoagulant drugs such as unfractionated heparin or low-molecular-weight heparin, and oral anticoagulants; or TCM or proprietary Chinese medicine, topical

Treatment	Treatment 1 in the intervention group: Shengji ointment	Treatment 2 in the intervention group: Pineapple protease (bromelain)	Treatment in the control group: Comfeel* plus wound dressing
Size	30 g/bottle	10,000 units	25 g/piece
Formulation	Ointment	Tablet	Hydrocolloid dressing
Usage and dosage	For external use. The ointment will be spread on skimmed cotton and applied to the affected area	For external use. It will be applied to exposed tendons and areas with necrotic tissue	Apply Comfeel® dressing to the ulcer. Ensure the dressing height is at the level of the surrounding skin. Then, apply a layer over the ulcer and surrounding area
Route of administration	Topical	Topical	Topical
Frequency of administration	Once every 24 h	Once every 24 h	Once every 24 h
Treatment course	4 weeks	4 weeks	4 weeks
Manufacturer	Tianjin Darentang Jingwanhong Pharmaceutical Co., Ltd., Tianjin, Tianjin, China	Shantou Olive Pharmaceutical Co., Ltd., Shantou City, Guangdong, China	Coloplast Group, Humblebaek, Denmark

TABLE 1 Demographics and baseline information. Comparison of baseline characteristics in the modeling and validation groups.

Variables	Modelling group	Validation group	p
N	126	54	
Age (years)	64.64 ± 10.30	62.23 ± 11.20	0.213
Duration of the illness (in months)	9.25 ± 18.13	5.04 ± 8.88	0.075
Height (cm)	168.51 ± 7.81	168.64 ± 7.51	0.923
Body weight (kg)	68.99 ± 11.80	69.66 ± 12.73	0.763
Fasting blood glucose (mmol/L)	6.80 ± 1.64	6.91 ± 2.05	0.725
Postprandial 2H glucose (mmol/L)	10.48 ± 1.68	10.38 ± 2.05	0.772
Red blood cell count (10^{12}/L)	4.14 ± 0.57	4.16 ± 0.61	0.819
White Blood Cell Count (10^9/L)	7.10 ± 3.12	7.49 ± 2.20	0.459
Haemoglobin (g/L)	121.11 ± 20.46	121.67 ± 19.25	0.881
Platelets (10^9/L)	266.92 ± 82.84	273.18 ± 95.65	0.692
Alanine aminotransferase (ALT) (U/L)	24.36 ± 54.66	18.10 ± 9.97	0.574
Aspartate aminotransferase (AST) (U/L)	20.85 ± 22.84	16.90 ± 6.67	0.7
Total bilirubin (umol/L)	8.96 ± 4.59	7.10 ± 4.43	0.001
Direct bilirubin (umol/L)	2.89 ± 1.88	3.41 ± 1.82	0.069
Indirect bilirubin (umol/L)	6.24 ± 3.88	3.55 ± 2.78	<0.001
Total protein (g/L)	68.38 ± 6.96	67.92 ± 7.14	0.718
Albumin (g/L)	38.51 ± 5.45	38.14 ± 4.06	0.697
Creatinine (umol/L)	74.77 ± 51.25	73.87 ± 30.47	0.811
Uric acid (umol/L)	300.54 ± 97.43	304.26 ± 97.36	0.835
Maximum depth (cm)	0.65 ± 0.74	0.42 ± 0.40	0.102
Ulcer area (cm²)	8.70 ± 6.22	6.45 ± 5.78	0.028
Ulcer volume (cm³)	3.78 ± 6.52	2.24 ± 3.81	0.051
Percentage of granulation (%)	29.63 ± 24.80	43.59 ± 28.78	0.008
Percentage of decay (%)	43.25 ± 28.78	33.38 ± 32.43	0.038
Percentage of crust (%)	27.27 ± 26.23	23.18 ± 23.12	0.357
Area of granulation tissue within the wound (cm²)	2.35 ± 2.63	2.76 ± 3.15	0.486
Total wound area (cm²)	8.74 ± 6.25	6.45 ± 5.78	0.026
Ankle brachial index (ABI)	0.78 ± 0.09	0.82 ± 0.10	0.035
Whether granulation occurred			0.107
No	8 (6.35%)	0 (0.00%)	
Yes	118 (93.65%)	54 (100.00%)	
Treatment			0.745
Hydrocolloid dressing	62 (49.21%)	28 (51.85%)	
Shengji ointment and bromelain	64 (50.79%)	26 (48.15%)	
Ulcer location			0.127
Dorsum of foot	26 (20.63%)	17 (31.48%)	
Toe	69 (54.76%)	21 (38.89%)	

(Continued on following page)

TABLE 1 (*Continued*) Demographics and baseline information. Comparison of baseline characteristics in the modeling and validation groups.

Variables	Modelling group	Validation group	p
Plantar	31 (24.60%)	16 (29.63%)	
Gender			0.645
Male	70 (55.56%)	32 (59.26%)	
Female	56 (44.44%)	22 (40.74%)	
Marital status			0.562
Unmarried	2 (1.59%)	2 (3.7%)	
Married	114 (90.48%)	46 (85.19%)	
Divorced	2 (1.59%)	2 (3.70%)	
Widowed	6 (4.76%)	4 (7.41%)	
Unknown	2 (1.59%)	0 (0.00%)	
Educational level			0.518
Illiterate	2 (1.59%)	0 (0.00%)	
Primary education	16 (12.70%)	7 (12.96%)	
Lower secondary	41 (32.54%)	21 (38.89%)	
High School	24 (19.05%)	8 (14.81%)	
College	5 (3.97%)	4 (7.41%)	
University and above	1 (0.79%)	2 (3.70%)	
Not available	37 (29.37%)	12 (22.22%)	
Wagner Grading			0.086
Grade 3	74 (58.73%)	39 (72.22%)	
Grade 4	52 (41.27%)	15 (27.78%)	

antibiotics, and others, which promote muscle growth and act as astringents in sore treatment) were allowed during the trial. This restriction extended to biological treatments (like stem cell therapy, topical autologous platelet-rich plasma, and TCM or Chinese herbal tonics with functions similar to the trial treatment).

2.3 Outcomes

Our primary outcome was the time to granulation, as new granulation is closely linked with ulcer treatment prognosis. Granulation time (in days) was defined as the period from the enrolment day to the emergence of new granulation tissue within the wound. This study was a non-blinded clinical trial; an independent evaluator captured images of the target ulcer. Using 3D scanning, we obtained the wound surface topography. We then utilized the inSight® platform (eKare, Inc., Fairfax, VA, United States) to identify different tissue types and measure the areas they covered. This approach effectively controlled bias in efficacy evaluation arising from the non-blinded methodology. Additionally, we assessed demographic data, medical and allergy history, vital signs, blood routine, C-reactive protein, urine routine, liver and renal function, and wound assessments.

2.4 Allocation

We employed the central randomized MagMinDA clinical trial grouping system for participant enrollment. This process ensured the implementation of randomization concealment, effectively averting the introduction of selection bias.

This study received ethical approval from the Medical Ethics Committee of the Second Affiliated Hospital of Tianjin University of Chinese Medicine (Approval number: 2020-006-01). It was also registered with the China Clinical Trials Registry (Registration number: ChiCTR2000039327) on 23 October 2020.

2.5 Data capture

This study utilized an Electronic Data Capture (EDC) system to gather patient case information and test examination data. To ensure patient privacy, any personally identifiable information was encoded and processed before data extraction and analysis.

The analysis incorporated 35 variables, encompassing demographic data such as gender, age, marital status, and education level. It also considered physical characteristics such as height, weight, blood glucose levels, and routine pre-treatment blood tests, including red blood cell

FIGURE 1
Lasso regression results. **(A)** presents the tuning parameter (lambda) selection in the lasso model using 10-fold cross-validation via the lambda.min and lambda.1se criteria. The *y*-axis represents the partial likelihood deviance, the lower *x*-axis indicates log (λ), and the upper *x*-axis represents the number of variables included in the model. **(B)** showcases the LASSO coefficient profiles of the variables. The *y*-axis represents the value of the coefficient, and the lower *x*-axis denotes log (lambda).

count, white blood cell count, hemoglobin, and platelet count. Pre-treatment biochemical indicators of liver and kidney function—namely, glutamic transaminase, glutamic oxaloacetic transaminase, total bilirubin, direct bilirubin, indirect bilirubin, total protein, albumin, creatinine, and uric acid—were also assessed.

Furthermore, a detailed analysis was conducted on wound assessment information, such as the maximum ulcer depth, ulcer area, ulcer volume, tissue type (granulation tissue/necrotic/crust), specific wound location, the area of granulation tissue within the ulcer, Wagner classification, and the ankle-brachial blood pressure ratio of the ulcerated limb.

2.6 Analysis methods

In this study, data analysis was undertaken using R version 4.1.2. Quantitative metrics were reported as the mean ± standard deviation. The statistical tests employed included the independent *t*-test for variables with a normal distribution and the Wilcoxon rank-sum test for variables with a skewed distribution. Qualitative metrics were expressed in terms of frequencies and percentages and were analyzed using the Chi-square test with a significance level set at α = 0.05.

The modeling group utilized data from centers 1, 3, and 4, while the external validation group used data from center 2. Considering the small sample size and a large number of predictor variables, lasso regression was employed for variable screening in the modeled data. λ was selected using 10-fold cross-validation of lasso regression, where the corresponding λ was the lasso screening variable criterion in this study when the mean error value was at its minimum.

After variable screening based on lasso regression, Cox regression clinical prediction models were developed, and regression coefficients, standard error values, HRs, 95% confidence intervals, and *p*-values were computed for each variable in the model. Nomograms were also plotted. External validation was conducted using the equation fit data derived from the modeling set. Model evaluation was performed on both modeled and validated data sets. Model discrimination was evaluated using the area under the time-dependent ROC curve (AUC), which is generally considered moderately discriminatory between 0.70–0.80.

3 Study results

3.1 Baseline analysis

This study enlisted a total of 180 participants, with 126 assigned to the modeling group and 54 to the validation group. A comparative analysis of the demographic and baseline data between the two groups was conducted, and the results are detailed in Table 1.

3.2 Lasso regression variable screening

In this research, we assessed 35 potential factors implicated in the formation of granulation tissue. The Lasso method was employed to identify the variables exerting the most significant impact on the outcome. The optimal λ parameter in the Lasso model

FIGURE 2
Results of the Cox proportional hazard model analysis. The forest plot depicted in this figure provides the Hazard Ratio (HR), the 95% Confidence Intervals (CIs), and the *p*-value of the HR for each selected covariate included in the Cox model.

was ascertained through ten-fold cross-validation. The vertical line in Figure 1A represents the optimal value with the smallest λ and its standard error (SE). The optimal model value was established to be $\lambda = 0.1047$ and $\log(\lambda) = -2.2566$. The Lasso regression process highlighted treatment, ulcer location, hemoglobin, creatinine, the proportion of the decaying area, Body Mass Index (BMI), disease duration, albumin, and the ankle-brachial index as critical variables. The coefficient profiles for all variables are illustrated in Figure 1B.

3.3 Construction of the Cox proportional hazard regression model

A multi-factorial Cox proportional hazard regression model was constructed based on the independent variables identified via the lasso regression analysis. The time until granulation tissue formation served as the dependent variable, as depicted in Figure 2. The treatment approach, ulcer location, creatinine levels, Body Mass Index (BMI), and hemoglobin were identified as independent factors affecting the production of granulation tissue in diabetic foot ulcers. The combined treatment of Chinese herbal Shengji ointment and bromelain positively influenced granulation tissue development. Conversely, plantar ulcers, impaired renal function, obesity, and anemia were found to negatively impact granulation tissue formation. The results of the Cox proportional hazard model

analysis are shown in Figure 2, and the predictive model nomogram is displayed in Figure 3.

3.4 Model evaluation

This study utilized the bootstrap method for both internal and external validation of the model. The accuracy of the model's predictions was evaluated through time-dependent receiver operating characteristic curve analysis. The area under the curve (AUC) for the model group data set ranged between 0.7 and 0.8, demonstrating the model's substantial predictive capability for the occurrence of granulation tissue in patients with diabetic foot ulcers post-treatment. These findings are depicted in Figure 4.

4 Discussion

4.1 Combined therapy with Chinese medicine may foster wound healing in diabetic foot ulcers (DFUs) of Wagner grade 3 or higher

Shengji ointment stimulates metabolism through a multitude of biochemical reactions such as hydrolysis, enzymatic digestion,

FIGURE 3
Nomogram of the prediction model. In the nomogram, each variable corresponds to a specific score. By summing up the scores for all variables, a total score can be calculated. This total score can then be used for the prediction of outcome variables.

acidification, saponification, and esterification, resulting in bactericidal and anti-inflammatory effects. It maintains a moderate level of immune response and controls the partial inflammatory response, a cornerstone for damage repair (Xu and Xiao, 2003). Moreover, it promotes the growth of fresh granulation and skin regeneration, maintains the trauma's regenerative environment, encourages the contraction of the trauma, and facilitates epidermal cell differentiation, reproduction, migration, covering the trauma, ultimately leading to trauma healing (Ma and Ju, 2013).

Recent pharmacological studies propose its potential to mitigate inflammation by downregulating TNF-α and IL-6 proteins in wounded tissues (Sun et al., 2021). Furthermore, it may amplify the expression of VEGF protein within these tissues, fostering angiogenesis and enhancing microcirculation at the wound site, which subsequently aids wound healing (Song et al., 2020). The outcomes of some clinical trials imply that Shengji ointment exhibits excellent efficacy in skin ulcers that are hard to heal (Zhang, 2017; Xie, 2020). It has been found that the repair and regeneration of skin tissue damage correlate with the change in collagen content, and the type I/type IV collagen ratio can effectively reflect the tissue repair in patients (Ye, 2018).

Shengji ointment can enhance the type I/type IV collagen ratio and hasten collagen synthesis, thus promoting wound healing. The clinical manifestations include pus coverage on the wound surface, rapid growth of the wound edge, redness of the granulation tissue, easy bleeding when touched, and the emergence of "skin islands" in the center of the wound (Li et al., 2013). When applied externally to the ulcer surface, Shengji

Ointment forms a protective film that isolates the wound surface from the external environment, reduces contamination, and possesses an anti-infective effect believed to be related to the activation of macrophages and enhancement of phagocytosis (Lu et al., 2018).

Meanwhile, bromelain, a protease derived from the pineapple plant, is another vital component in the treatment regimen, especially for DFUs exhibiting exposed tendon necrosis. Bromelain is extracted from the natural plant pineapple stem or unripe fruit, with the primary component being a large class of sulfhydryl protease, which includes phosphodiesterase, glycosidase, peroxidase, etc., and functions to hydrolyze proteins (Pereira et al., 2023). Bromelain works by breaking down collagen fibers, liquefying necrotic tendon and fascial tissues, and facilitating the removal of necrotic tissue while preserving the surrounding healthy skin, thereby creating an ideal environment for wound healing. Furthermore, it removes trauma-induced fibrin or clots, improves local circulation, reduces swelling and inflammation, and inhibits platelet aggregation, collectively accelerating blood flow and promoting wound healing (Ramundo and Gray, 2008; Zhang et al., 2012).

Our results have underscored the effectiveness of a combined treatment approach involving Traditional Chinese Medicine. The utilization of Chinese herbal Shengji ointment alongside bromelain appears to foster granulation tissue development, thereby expediting the healing process. This suggests that integrating Traditional Chinese Medicine into conventional treatment strategies for DFUs may provide enhanced therapeutic outcomes.

FIGURE 4
Time-Dependent ROC Curves. **(A)** This panel shows the results of the time-dependent ROC curve for the modeling group. The *x*-axis represents time, while the AUC and its 95% Confidence Intervals (CIs) are plotted on the *y*-axis. **(B)** This panel displays the results of the time-dependent ROC curve for the validation group. Similar to **(A)**, time is represented on the *x*-axis and the AUC along with its 95% CIs is plotted on the *y*-axis.

4.2 Ulcer location, hemoglobin, creatinine, and BMI are identified as independent risk factors for Wagner grade 3 or higher DFUs

Our study observed that plantar ulcers presented a greater healing challenge compared to toe and dorsum ulcers in patients with non-ischemic DFUs and controlled infection. Some research suggests that reducing plantar pressure may expedite DFU healing (Caravaggi et al., 2007); however, decompression therapy should not be solely relied upon for treating plantar ulcers but may be considered to reduce ulcer recurrence rates (Reiber et al., 2002).

Hemoglobin, acting as a nutritional status indicator, offers a partial reflection of a patient's health condition. A national dietary survey exposed common misunderstandings about dietary management among diabetes patients and their families, such as believing in numerous food contraindications and advocating for extreme restrictions on consuming animal products, potentially leading to an insufficient intake of high-quality protein (Lin and Fan, 2006). When blood glucose is under robust control, dietary restrictions can be eased during the early stages of DFUs. As the disease progresses, patients should be encouraged to adopt a high-protein diet to aid in ulcer healing. In the late stages, when the ulcer fails to heal for an extended period and multiple debridements and dressing changes cause bleeding, active nutritional therapy emphasizing a high-protein diet and other nutritional intakes become necessary (Wei et al., 2015). Consequently, the clinical management of DFU patients should focus on personalized medical nutrition therapy, maintaining blood glucose levels within effective limits while strengthening nutritional support, particularly a high-protein diet. An appropriate dietary plan should be crafted for DFU patients at different stages, and dietary structure should be optimized to increase the protein intake proportion to facilitate DFU healing.

The study found that an increased BMI prolongs DFU healing time. Research also suggests that a high BMI is a significant risk factor for a diabetic foot, associated with increased foot pressure and adipokine accumulation-mediated vascular injury (Sohn et al., 2011). Furthermore, several studies indicate that BMI is linked with the development and prognosis of multisystem diabetes complications (Yang et al., 2017; Jia, 2020; Yang et al., 2020; Zhang et al., 2022), and suitable BMI control might improve the overall diabetes outcome.

High creatinine levels were identified as an independent risk factor for wound healing in diabetic foot patients without a history of chronic kidney disease. Research indicates that renal damage in diabetic foot patients becomes more severe as Wagner grade increases (Ding et al., 2015), possibly due to wound or recurrent infection-induced inflammatory factor release leading to renal damage (Game et al., 2013). This suggests that early multidisciplinary combination therapy should be administered to patients with Wagner grade 3 or higher to minimize the risk of progression to end-stage renal disease.

4.3 Limitations and future directions

While this study's rigorous screening criteria—which excluded patients with Wagner grades 1–2 and those with co-infections, malnutrition, and poor lower extremity circulation—increased the internal validity by reducing confounding factors, it also limited the sample size. This strict selection process enhanced the study's precision, but it also restricted the generalizability of the results.

Additionally, discrepancies in certain baseline variables (such as total bilirubin, indirect bilirubin, decay percentage, total wound area) were noticed during the external validation of the model, leading to a decrease in the area under the ROC curve for the externally validated model. This suggests that while the prediction model holds value, it still necessitates further refinement and validation using a larger and more diverse patient dataset. Moreover, the endpoint of this study is the formation of granulation tissue, and we hope that future research will focus on long-term survival indicators of patients.

Despite these limitations, the study provides valuable insights into the treatment of DFU, laying the groundwork for future research aimed at creating a more accurate clinical prediction model that could significantly enhance the prognosis and quality of life for patients with diabetic foot ulcers.

5 Conclusion

Through the application of Lasso regression and multi-factor Cox regression, this study successfully constructed a valuable predictive model. This model represents a potent tool for healthcare professionals to assess treatment efficacy and individualize treatment strategies for patients suffering from Wagner grade 3-4 diabetic foot ulcers. The ability to adapt and optimize treatment according to the specific needs and conditions of each patient is crucial in enhancing patient outcomes.

In this patient population, we discovered that the combined therapy of Chinese medicine ointment acted as an independent protective factor for wound healing. Conversely, plantar ulceration, reduced hemoglobin, elevated body mass index, and high creatinine levels were identified as independent risk factors. Collectively, these factors demonstrated predictive power for the outcomes of diabetic foot ulcers.

However, it is important to note that the findings of this study should be cautiously extrapolated as it excluded patients with severe infection or poor blood supply. These limitations underscore the need for more comprehensive and diverse samples to enhance the predictive model.

Despite these limitations, this study offers valuable insights into the treatment of deep diabetic foot ulcers in elderly patients with diabetes, underscoring the potential for integrating Chinese Medicine into treatment plans. With further validation and refinement, our predictive model could potentially be incorporated into routine clinical practice, contributing to improved patient outcomes.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Medical Ethics Committee of the Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine. The studies were conducted in

accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

H-YG and YZ conceptualized the research and composed the initial draft of the manuscript. SS conducted the statistical analyses. H-YG, X-YD, Q-NL, and RG were responsible for the manuscript's drafting. W-YC performed the analysis of the drug composition. Z-HL, X-FL, H-YG and YZ revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1236229/full#supplementary-material

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Elucidating the pharmacodynamic mechanisms of Yuquan pill in T2DM rats through comprehensive multi-omics analyses

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Background: Yuquan Pill (YQW) is a modern concentrated pill preparation of six herbs, namely, Ge Gen (*Pueraria lobata* Ohwi), Di huang (*Rehmannia glutinosa* Libosch.), Tian Huafen (*Trichosanthes kirilowii* Maxim.), Mai Dong (*Ophiopogon japonicus* (L. f.) Ker Gawl.), Wu Weizi (*Schisandra chinensis* (Turcz.) Baill.) and Gan Cao (*Glycyrrhiza uralensis* Fisch.). It is extensively used to treat type 2 diabetes-related glucose and lipid metabolism disorders. But what's the pharmacodynamic substance and how it works in the treatment of Type 2 diabetes mellitus (T2DM) are still unclear.

Purpose: The purpose of this study is to determine the likely pharmacological components and molecular mechanism of YQW's intervention on T2DM by combining serum pharmacochemistry, network analysis and transcriptomics.

Methods: The efficacy and prototypical components of blood entry were determined after oral administration of YQW aqueous solution to T2DM rats induced by high-fat feed and low-dose streptozotocin (STZ), and the key targets and pathways for these compounds to intervene in T2DM rats were predicted and integrated using network analysis and transcriptomics techniques.

Results: In diabetic rats, YQW can lower TG, CHO, NO, and MDA levels ($p < 0.05$) while increasing HDL-C levels ($p < 0.01$), and protecting the liver and kidney. 22 prototype components (including puerarin, daidzein, 3′-methoxypuerarin, and liquiritigenin, among others) were found in the serum of rats after oral administration of YQW for 90 min, which might be used as a possible important ingredient for YQW to intervene in T2DM rats. 538 YQW pharmacodynamic components-related targets and 1,667 disease-related targets were projected through the PharmMapper database, with 217 common targets between the two, all of which were engaged in regulating PI3K-Akt, MAPK, Ras and FoxO signal pathway. Finally, the mRNA expression profiles of liver tissues from rats in the control, model, and YQW groups were investigated using high-throughput mRNA sequencing technology. YQW can regulate the abnormal expression of 89 differential genes in a disease state, including 28 genes with abnormally high expression and 61 genes with abnormally low expression. Five

common genes (Kit, Ppard, Ppara, Fabp4, and Tymp) and two extensively used regulatory pathways (PI3K-Akt and MAPK signaling pathways) were revealed by the integrated transcriptomics and network analysis study.

Conclusion: The mechanism of YQW's intervention in T2DM rats could be linked to 22 important components like puerarin, daidzein, and glycyrrhetinic acid further activating PI3K-Akt and MAPK signaling pathways by regulating key targets Kit, Ppard, Ppara, Fabp4, and Tymp, and thus improving lipid metabolism disorder, oxidative stress, and inflammation levels in T2DM rats. On the topic, more research into the pharmacological ingredient foundation and mechanism of YQW intervention in T2DM rats can be done.

1 Introduction

About 425 million people in the world suffer from diabetes, of which T2DM and its complications affect the great majority of them (Guariguata et al., 2014; Thomas, 2022). According to statistics published by the International Diabetes Federation, by 2045, there will be around 629 million individuals worldwide with diabetes, of which T2DM patients account for more than 90% of the total (Forouhi et al., 2018; Kapoor et al., 2021). T2DM is a chronic disease impacted by the environment, genetics, and multiple genes. T2DM and its severe effects, such as kidney damage, nerve damage, retinopathy, and cardiovascular disease, are a serious hazard to human health worldwide (Bhatti et al., 2016; Kanter and Bornfeldt, 2016). Diabetes currently has no remedy anywhere in the planet. Only hypoglycemic drugs, a nutritious diet, regular exercise, self-monitoring blood sugar dynamics, and psychological modifications can help diabetics alleviate their symptoms and prevent difficulties (Kirchner et al., 2013; Ning et al., 2022). Traditional Chinese Medicine (TCM) has a long history of treating diabetes (Zheng et al., 2021). According to TCM, the main causes of DM are yin-jin deficiency, as well as excessive dryness and heat. Patients with a qi and yin deficiency, dryness and heat, vein and tendon obstruction, and tendons and vein dystrophy are common in TCM clinical diagnosis and therapy, causing injury to the viscera and organs. To improve the overall condition of T2DM patients and achieve a better curative effect, TCM techniques such as tonifying qi, nourishing yin, and clearing away heat should be used to exert the effects of nourishing yin, promoting body fluid production, quenching thirst, relieving vexation, invigorating qi, and harmonizing the middle warmer (Chen et al., 2016; Wong, 2016).

YQW is a modern polyherbal formulation modified from Yuquan Powder in Volume II (Diabetes) of the ancient book Zhongfutang Public Selection Recipe, which made up of six medications: *Pueraria lobata* (Willd.) Ohwi (gegen), *Rehmannia glutinosa* (Gaertn.) DC. (dihuang), *Ophiopogon japonicus* (Thunb.) Ker Gawl. (maidong), *Trichosanthes kirilowii* Maxim./*Trichosanthes rosthornii* Harms (tian huafen), *Schisandra chinensis* (Turcz.) Baill. (wu weizi) and *Glycyrrhiza uralensis* Fisch./*Glycyrrhiza inflata* Batalin/*Glycyrrhiza glabra* L. (gancao). Gegen is a monarch drug that enhances fluid production, quenches thirst, and reduces fever. It belongs to the lung and stomach meridians (Chen et al., 2016). Ministerial remedies dihuang nourishing yin; tian huafen, thirst-quenching, heat-clearing and fire-purging; wu weizi nourishes qi,

produces body fluid, and astringes astringent, both of which are complementary drugs (Tan et al., 2017). Gancao clears heat and toxic materials, tonifies spleen, invigorate qi, and is used as an agent in YQW, which can be used to harmonize various drugs (Liu et al., 2021). YQW has been shown to treat symptoms of T2DM patients in clinical trials. Gegen has pharmacological effects of lowering blood sugar and regulating blood lipid (Liu et al., 2022b); dihuang can lower blood sugar and diuresis (Li et al., 2022a; Yang et al., 2022b); maidong can not only lower blood sugar (Li et al., 2022a), but also has many important pharmacological effects such as anti-myocardial ischemia. The majority of current studies, however, are focused on YQW's therapeutic efficacy in the treatment of T2DM. There has been no conclusive research or conclusion as to what the material base of its complete prescription is or how to use it to treat T2DM.

Therefore, this subject systematically analyzed the potential pharmacodynamic substances and mechanism of YQW intervention in T2DM rats using the serum pharmacochemistry research method, combining with network analysis and transcriptomics technology.

2 Materials and methods

2.1 Reagents and materials

Yuquan Pill (batch No. 200401, Chengdu Jiuzitang Jinding Pharmaceutical Co., Ltd., China); Metformin Hydrochloride Tablets (batch No. H20023370, Bristol-Myers Squibb., China); Streptozotocin (batch No. 18883-66-4, Shanghai yuanye Bio-Technology Co., Ltd., China); Uralose (CAS No. #51-79-6, Shanghai yuanye Bio-Technology Co., Ltd., China); Citric Acid-Sodium Citrate Buffer (batch No. L10S11G124133, Shanghai yuanye Bio-Technology Co., Ltd., China); 45% High-fat feed (batch No. D12451. SPF (Beijing) Biotechnology Co., Ltd., China); NO assay kit (batch No. E1030. Beijing Pulley Gene Technology Co., Ltd., China); MDA test kit (batch No. 20201106. Nanjing Jiancheng Bioengineering Institute, China); mass spectrometry grade methanol, acetonitrile and formic acid (Thermo Fisher Company, United States); ultrapure water (A.S.WATSON TM LIMITED); ME155DU electronic balance (METTLER TOLEDO, China); JA 2003B electronic balance (Shanghai Yueping Scientific Instruments Co., Ltd., China); KQ-300DB ultrasonic cleaning machine (Kun

Shan Ultrasonic Instruments Co., Ltd., China); high-speed desktop refrigeration centrifuge (Shanghai Anting Scientific Instrument Factory, China); Pipette (Eppendorf, Germany); Fully automated biochemistry analyser (BECKMAN COULTER); EPOCH enzyme labeller (BioTek); Eclipse Ti-E laser confocal microscope (NIKON, Japan); Panoramic section scanner, 3DHISTECH (HUNGARY); ACQUITY I-CLASS UPLC (Waters, United States), SYNAPT G2-Si Q-TOF MS (Waters, United States).

2.2 YQW aqueous/alcohol solution preparation

2.0 g of YQW (Concentrated Pill) powder were weighed and ultrasonic extracted for 20 min with 20 mL of 75% methanol solution (240 W, 25 kHz). The mixture was centrifuged twice at 13,000 r/min for 15 min each time after cooling to room temperature and the supernatant was removed.

2.3 Animal experiments

2.3.1 Experimental animals

SPF grade SD rats (male, 4 weeks old, 100 ± 10 g) were acquired from SPF (Beijing) Biotechnology Co., Ltd. (Production license number: scxk (Beijing) 2019-0010, Quality certificate of experimental animals: No. 1103242011017624). These rats were cared and treated according to the regulations and general recommendations of China Laboratory Animal Management Regulations, and approved by the Animal Ethics Committee of Beijing University of Traditional Chinese Medicine (No. BUCM-4-2020081003-3147; Date: 10-08-2020).

2.3.2 Animal grouping and modeling

After 1 week of adaptive feeding in a standard environment, 10 rats were randomly selected as the control group and the remaining rats were fed 45% high-fat feed as the modeling group using the random number approach. The modeling rats received a single intraperitoneal injection of STZ 35 mg/kg (Jawale et al., 2016) after 5 weeks, while the control rats received an identical volume of citric acid-sodium citrate buffer (0.01 mol/L, pH 4.5). A random blood glucose measurement of 16.7 mmol/L was regarded a successful modeling 72 h after injection (Yang et al., 2022c). Then, based on their blood glucose levels, we separated successfully modeled rats into four groups: Model group, Metformin (Met) group, YQW high-dose (YQW-H) group, and YQW low-dose (YQW-L) group. On the basis of the model group, varied concentrations of YQW (YQW-H group: 3.95 g/kg; YQW-L group: 0.99 g/kg) and positive medication (Met group: 0.34 g/kg) were administered to the administration groups. The rats' activity, body weight, and physiological conditional were all monitored during the intervention.

2.3.3 The effect of YQW on serum biochemical indexes and organ indexes

Finally, all rats were sacrificed using anesthetics following a 12-h fast, in accordance with laboratory animal ethics. To get the serum, a blood sample was taken from the abdominal aorta

and centrifuged at 3,000 r/min for 15 min at 4°C. The supernatant was taken out of the mixture and split. A completely automated biochemical analyzer was used to assess blood glucose, TG, CHO, HDL-C, LDL-C, and SOD. NO and MDA were also measured according to the kit's specifications, and the remaining serum was kept at −80°C until needed. The splenic glands were removed and washed with saline after the rats were executed, and the blood was removed from the surface with filter paper before being weighed on an electronic balance and the splenic index calculated.

2.3.4 Histopathological observation

The liver and kidney were embedded in paraffin, dehydrated, and stained with H&E, and examined under a light microscope at 20 and 200 magnification after being fixed in 4% paraformaldehyde for 48 h.

2.3.5 Data processing

The data is presented as continuous variables or qualitative descriptions depending on the type of data. GraphPad Prism 5 software was used to process the continuous variables, and the results were reported as mean ± SD. A statistically significant difference was defined as $p < 0.05$.

2.4 Pharmaceutical chemistry research on serum

2.4.1 Method of administration to rats

Blood was taken from the inner orbital canthus of the rats in the dosing group at 45 min after oral administration in the morning; at 90 min, the rats in each group were anesthetized with 25% urethane (m/V) by intraperitoneal injection (dose administered was 0.4 mL/100 g) and blood was taken from the abdominal aorta.

2.4.2 Blood samples pretreatment

To obtain the drug-contained serum, the whole blood was centrifuged at 3,000 r/min (4°C, 15 min) after standing for 30 min. The sera of rats in each group were pooled at 45 and 90 min, then 1,000 μL of the combined serum were added 3 times of acetonitrile, vortex for 2 min, centrifuged at 3,000 r/min (4°C, 15 min), and then blew dry with nitrogen at 40°C and redissolved with 100 μL methanol (enrichment 10 times). Finally, the redissolution fluid was centrifuged at 12,000 r/min (4°C, 15 min), and the supernatant was separated for sample injection analysis using UPLC-Q-TOF/MS.

2.4.3 Chromatographic and mass spectrometric conditions

Chromatographic column: Waters ACQUITY BEH C18 column (2.1 mm × 100 mm, 1.7 μm); flow rate: 0.3 mL/min; column temperature: 35°C; injection volume: 5.0 μL.mobile phase: 0.1% formic acid in water (A) - acetonitrile (B); gradient elution procedure: (1) condition 1: 0–2 min, 5% B ~ 5% B; 2–17 min, 5% B ~ 98% B; 17–20 min, 98% B ~ 98% B; 20–23 min, 98% B ~ 5% B; 23–25 min, 5% B ~ 5% B; (2) condition 2: 0–8 min, 2% B ~ 9% B; 8–18 min, 9% B ~ 32% B; 18–20 min, 32% B ~ 89% B; 20–35 min,

89% B ~ 100% B; 35–37 min, 100% ~ 2%B; 37–40 min, 2% B ~ 2% B (Note: condition 1 was used to collect the chromatogram of the YQW solution, and condition 2 was used for the collection of the rat *in vivo* blank and drug-contained serum).

In both positive and negative ionization modes, an electrospray ionization source (ESI) was used for mass spectrometry analysis. Leucine-enkephalin was employed as an external reference for real-time calibration to guarantee that correct mass numbers were collected for each component of the molecule during data capture, yielding fragment ions m/z 556.2721 $[M+H]^+$. As an auxiliary spray ionization and desolventizing gas, high purity N_2 was utilized. The drying gas flow rate was 10 mL/min, the N_2 temperature was 120°C, the nebulisation chamber air pressure was 310 kPa, the desolventizing nitrogen flow rate was 900 L/h, the cone hole backblast nitrogen flow rate was 50 L/h, the capillary ionisation voltage was 500 V, the cone hole voltage was 40 V, the collision energy was 40–65 eV, and the data acquisition range was m/z 50-1200Da.

2.4.4 Establishment of the YQW database

To collect information on the chemical composition of six herbs in YQW, the following online databases were used: TCMID (http://www.megabionet.org/tcmid), TCMSP (http://tcmspw.com/tcmsp.php), ETCM (http://www.ehbio.com/ETCM), BATMAN-TCM (http://bionet.ncpsb.org/batman-tcm/). By means of TCM database, the exclusive database of YQW was created, and information on the chemical composition of the six herbs was collected, including chemical names, molecular formulas, structural formulae, and molecular weights.

2.4.5 Identification of chemical composition

Masslynx V4.1 (Waters, United States) and UNIFI were utilized to process data and the unique database of YQW were used to identify chemical compositions. The major chemical composition of YQW was then identified and confirmed by extracting fragment ions and comparing it to relevant literature data based on the retention time (RT) and mass spectrum information of each chemical component under positive and negative ion modes.

2.4.6 Acquisition of the target

The PharmMapper database (http://www.lilab-ecust.cn/pharmmapper/) was employed to anticipate the appropriate chemical component-targets in the prescription given above. Then, the GeneMANIA (http://genemania.org) protein interaction analysis tool was used to predict the indirect targets connected to the direct targets. Finally, the Uniport (http://www.uniprot.org/) database was used to convert all targets into conventional gene names.

The term "type 2 diabetes" was used to found the targets associated to T2DM by searching the Comparative Toxicogenomics Database (http://ctdbase.org/), Therapeutic Target Database (http://db.idrblab.net/ttd/), and GeneCards (http://www.genecards.org/) illness databases. The CTD database was filtered by looking for reported targets associated with T2DM that were tagged with "marker/mechanism"; the TTD database was filtered by looking for databases that clearly contained the disease "type 2 diabetes"; and the GeneCards database was filtered by having

a relevance score of 26 or higher. Then, in Uniport, T2DM-targets were changed into the standard gene name. The targets of YQW in the treatment of T2DM were determined by intersecting the T2DM and composition targets.

2.4.7 Protein-protein interactions (PPI) analysis

To obtain the PPI network, the YQW targets in the therapy of T2DM were submitted to the String (https://cn.string-db.org) analysis platform. The network topology of the PPI network was then analyzed using Cytoscape 4.6.1 (National Institute of General Medical Sciences, United States). According to the Degree value, the top five targets were chosen as critical objectives.

2.4.8 GO and KEGG enrichment analysis

All of the above-mentioned targets were uploaded to the String analysis platform's "Multiple Proteins" section, and "*Rattus norvegicus*" was chosen for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) studies. The top 10 pathways in KEGG Pathways with different classification functions were chosen based on their p values and imported into the Omicshare (https://www.omicshare.com/) platform for pathway enrichment analysis to create a bubble map of signaling pathways; at the same time, the top 10 pathways in BP, CC, and MF were chosen based on their p values and imported into the microbiology online database to investigate the possible mechanism of YQW.

2.4.9 Construction of the "TCM-component-target" network

Using the merge integration function, the "TCM-Component-Target" network was built in Cytoscape 4.6.1.

2.5 Transcriptomic studies

2.5.1 RNA extraction, quality control and RNA sequencing

Shanghai Personal Biotechnology Co., Ltd. (http://www.personalbio.cn/) extracted and analysed nine samples from the three groups of rats. Electrophoresis, gel imaging system, and Agilent 2100 biological analyzer were used to ensure the quality, quantity, purity and integrity of the RNA samples. Finally, the Illumina HiSeq 2500 was used to sequence the samples.

2.5.2 Expression differential gene analysis

DESeq was used to perform differential gene expression analysis, and differentially expressed genes were evaluated for expression difference multiplicity $|log2FoldChange| > 1.5$ and significance $p < 0.05$. In each comparison group, the number of upregulated differential genes and downregulated differential genes was counted.

2.5.3 Functional enrichment analysis

Two-way cluster analysis was performed by using the R language Pheatmap software package on the concatenated sets of differential genes and samples from all comparison groups, clustering according to the expression levels of the same gene in different samples and the

FIGURE 1
Therapeutic effect of YQW in STZ-induced T2DM rats. **(A)** The condition of each group: a1: the control group; a2: the model group; a3: the administration group. **(B)** The biochemical indexes of rats in each group. **(C)** HE staining of rat livers in each group:1:x20; 2:x200. **(D)** HE staining of rat kidney in each group:1:x20; 2:x200. Values are presented as the mean $\pm$ SD. $^{\#\#\#}p < 0.001$, $^{\#\#}p < 0.01$, $^{\#}p < 0.05$ versus the control group. $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$ versus the model group.

expression patterns of different genes in the same sample, using the Euclidean method to calculate distances and the hierarchical clustering longest distance method (Complete Linkage) for cluster analysis. In addition, GO enrichment analysis was performed using top GO and KEGG enrichment analysis was performed using the cluster profiler in this experiment.

2.6 Integration analysis of transcriptomic and network analysis

In this section, the back-regulated differential genes obtained from transcriptomics sequencing were integrated and analyzed with the major targets of YQW for the treatment of T2DM, taking the shared targets or shared pathways to understand the mechanism of action of YQW intervention in T2DM rats.

3 Results

3.1 Therapeutic effect of YQW in STZ-induced T2DM rats

Rats in the control group had normal drinking, diet and excretion, clean fur, good mental state and active behavior. On the contrary, the rats in the model group had obvious excessive drinking, excessive urination, thin body, rough and wet fur, poor mental state and wet bedding, which needed to be changed every day. As shown in Figure 1A, after 4 weeks of intervention, YQW group can obviously improve the mental state of rats, with smooth hair, reduced urine output and clean bedding. In addition, As shown in Figure 1B, compared with the control group, the blood glucose (GLU) of rats in the model group increased ($^{###}p < 0.001$), indicating that the modelling was successful. The GLU of rats in the Met group decreased ($^{**}p < 0.01$), indicating a better hypoglycaemic effect, while the GLU in the YQW-L and YQW-H groups showed a trend of decrease compared with the model group, but there was no significant difference compared with the model group. In addition, the YQW-L group reduced TG and CHO levels in T2DM rats ($^{*}p < 0.05$) and was more effective than the Met group. Besides, compared with the model group, NO level was reduced in the Met and YQW-L groups ($^{*}p < 0.05$), but there was no statistical significance in the YQW-H group. Compared with the model group, SOD level was increased in the Met group ($^{**}p < 0.01$). Compared with the model group, the YQW-L group ($^{*}p < 0.05$) showed a significant decrease in MDA level, while the Met group and YQW-H groups showed no statistically significant decrease. These results showed that the YQW-L group was able to regulate the increase in serum NO and MDA levels and the decrease in SOD levels in rats, and enhance the antioxidant capacity of rats. Finally, compared with the model group, the Met groups showed an increase in spleen index ($^{*}p < 0.05$), and the YQW-L and YQW-H groups showed a tendency to increase, although there was no statistical difference, the original data could be found in Supplementary Tables I–IV. Then, the liver and kidney tissues of rats in each group were stained with HE. As shown in Figure 1C, in the control group, the liver lobules were clearly structured, the hepatic cords were neatly arranged, the hepatocytes were rich in cytoplasm, the morphology was normal, the hepatic sinusoids were not significantly dilated or extruded, and there was no obvious inflammation. On the contrary, in the model group, there was a large amount of hepatocyte steatosis around the confluent area, round vacuoles

FIGURE 2
The basic peak ion current diagram of chemical composition of YQW. **(A)** Positive ion mode of 75% alcohol extract of YQW. **(B)** Positive ion mode of water extract of Yuquan pill. **(C)** Negative ion mode of 75% alcohol extract of YQW. **(D)** Negative ion mode of water extract of YQW.

of different sizes were visible in the cytoplasm, and there were many focal infiltrations of lymphocytes around the confluent area. In the Met group, mild fatty degeneration of hepatocytes and small round vacuoles in the cytoplasm of the liver were seen locally, and focal infiltration of lymphocytes was seen in many places accompanying with reduced inflammation. Compared with the model group, mild fatty degeneration of hepatocytes around the confluent area and small round vacuoles in the cytoplasm of the liver were seen in the YQW-L and YQW-H group accompanying with no obvious inflammation. As for the kidney tissue, As shown in Figure 1D, the control group showed uniform staining, clear demarcation of the renal cortical medulla, normal glomerular morphology and structure, no obvious inflammation, a large number of tubular lumen with shed epithelial cells. However, the model group showed localized tubular atrophy with more lymphocytic infiltration, and more tubular lumen with shed epithelial cells. The Met

TABLE 1 Table of prototype components identification of YQW in blood.

NO.	RT (min)	Formula	Theoretical m/z	Observed m/z	Mass error (ppm)	Adducts	MS/MS	Component	Structure	Source
1	1.49	$C_{10}H_{13}N_5O_4$	268.1046	268.1034	4.5	$[M+H]^+$	203.0520 $[M+H-NH_3-H_2O-CH_3O]^+$ 136.0606 $[M+H-C_5H_9O_4]^+$	adeninenucleoside		Maidong
2	2.28	$C_{12}H_{16}O_3$	247.0737	247.0755	−7.3	$[M+K]^+$	NA	elemicin		Wuweizi
3	2.88	$C_{21}H_{16}O_6$	365.1025	365.1043	−4.9	$[M+H]^+$	305.0849 $[M+H-CH_3-CHO_2]^+$	gancaonin f		Gancao
4	9.74	$C_{21}H_{20}O_9$	417.1186	417.1172	3.4	$[M+H]^+$	161.0174 $[M+H-C_{12}H_{12}O_3]^+$ 297.0752 $[M+H-C_4H_8O_4]^+$ 267.0648 $[M+H-C_5H_{10}O_4-H_2O]^+$	puerarin		Gegen
5	10.96	$C_{15}H_{10}O_4$	255.0657	255.0646	4.3	$[M+H]^+$	NA	daidzein		Gegen
6	12.35	$C_{21}H_{20}O_{10}$	433.1135	433.1121	3.2	$[M+H]^+$	365.1037 $[M+H-4H_2O]^+$ 137.0228 $[M+H-C_6H_{11}O_5-C_8H_5O_2]^+$	genistein 7-glucoside		Gegen
7	12.54	$C_{15}H_{12}O_4$	257.0814	257.0805	3.5	$[M+H]^+$	137.0228 $[M+H-C_8H_8O]^+$	liquiritigenin		Gancao

TABLE 1 (*Continued*) Table of prototype components identification of YQW in blood.

NO.	RT (min)	Formula	Theoretical m/z	Observed m/z	Mass error (ppm)	Adducts	MS/MS	Component	Structure	Source
8	14.06	$C_{21}H_{22}O_9$	441.1162	441.1145	3.9	$[M+Na]^+$	NA	liquiritin		Gancao
9	14.15	$C_{16}H_{26}O_7$	331.1757	331.1721	10.9	$[M+H]^+$	167.0818 $[M+H-H_2O-C_{10}H_{15}O]^+$	schizonepetoside a		Wuweizi
10	15.74	$C_{15}H_{12}O_4$	257.0814	257.0806	3.1	$[M+H]^+$	137.0228 $[M+H-C_8H_7O]^+$	isoliquiritigenin		Gancao
11	19.43	$C_{30}H_{44}O_4$	491.3137	491.3181	−9.0	$[M+Na]^+$	317.2108 $[M+H-C_{10}H_{16}O]^+$	glabrolide		Gancao
						$[M+H]^+$	217.1177 $[M+H-C_{16}H_{25}O_2]^+$			
12	19.76	$C_{23}H_{28}O_6$	401.1964	401.1953	2.7	$[M+H]^+$	162.0212 $[M+H-C_{14}H_{20}O_3]^+$	gomisin n		Wuweizi
13	20.24	$C_{22}H_{24}O_7$	401.1600	401.1593	1.7	$[M+H]^+$	341.1011 $[M+H-C_3H_6O]^+$	gomisin r		Wuweizi

TABLE 1 (*Continued*) Table of prototype components identification of YQW in blood.

NO.	RT (min)	Formula	Theoretical m/z	Observed m/z	Mass error (ppm)	Adducts	MS/MS	Component	Structure	Source
14	20.59	$C_{30}H_{44}O_5$	485.3276	485.3276	0	$[M+H]^+$	119.0851 $[M+H-H_2O-CH_3-C_{20}H_{24}O_4]^+$	liquoric acid		Gancao
15	20.9	$C_{10}H_{16}O$	153.1279	153.1270	5.9	$[M+H]^+$	NA	citral		Wuweizi
16	21.09	$C_{30}H_{46}O_4$	471.3474	471.3463	2.3	$[M+H]^+$	184.1467 $[M+H-C_{19}H_{27}O_2]^+$	glycyrrhetinic acid		Gancao
17	19.44	$C_{23}H_{30}O_5$	409.1991	409.1957	8.3	$[M+Na]^+$	209.0477 $[M+Na-C_{10}H_{14}-C_3H_7]^+$	robustadial a (Thomas, 2022)		Wuweizi
18	19.45	$C_{22}H_{22}O_{10}$	491.1190	491.1188	0.4	$[M+HCOO]^-$	NA	3′-methoxypuerarin (Thomas, 2022)		Gegen

TABLE 1 (*Continued*) Table of prototype components identification of YQW in blood.

NO.	RT (min)	Formula	Theoretical m/z	Observed m/z	Mass error (ppm)	Adducts	MS/MS	Component	Structure	Source
19	20.45	$C_{15}H_{22}O$	219.1749	219.1743	2.7	$[M+H]^+$	105.0694 $[M+H-C_3H_5-C_4H_5O]^+$	nootkatone (Thomas, 2022)		Wuweizi
20	20.98	$C_{28}H_{48}O_2$	439.3552	439.3564	−2.7	$[M+Na]^+$ $[M+H]^+$	303.2309 $[M+H-C_8H_{17}]^+$	vitamin e (beta) (Kapoor et al., 2021)		Wuweizi
21	21.08	$C_{30}H_{46}O_4$	469.3318	469.3316	0.4	$[M-H]^-$	233.1538 $[M-H-C_{15}H_{23}O_2]^+$	18alpha-glycyrrhetinic acid (Thomas, 2022)		Gancao
22	36.48	$C_{48}H_{78}O_{17}$	925.5161	925.5083	8.4	$[M-H]^-$	581.3095 $[M-H-C_2H_2O_3-C_{19}H_{28}O]^+$	kaikasaponin iii (Thomas, 2022)		Gegen

FIGURE 3
The basic peak ion current diagram of prototype components of YQW in different doses. (A) Positive ion mode of medicated serum in YQW-H group. (B) Positive ion mode of medicated serum in YQW-L group. (C) Negative ion mode of medicated serum in YQW-H group. (D) Negative ion mode of medicated serum in YQW-L group.

group showed more tubular dilatation and a small amount of tubular epithelial cytoplasmic vacuolation, with no obvious inflammation. As for the YQW-H and YQW-L groups, the kidney tissue showed uniform staining, clear demarcation of the renal cortical medulla, normal glomerular morphology and structure, no obvious inflammation, and little tubular epithelial cytoplasmic vacuolation compared with the model group.

3.2 Qualitative analysis of the chemical composition of YQW

75% methanolic and aqueous extracts of YQW were analysed respectively in positive and negative ion mode and the basal peak ion flow diagrams are shown in Figure 2. The mass spectral data of them were collected and automatically matched and identified by the UNIFI data processing system to obtain the retention time, precise molecular weight, error and high-energy fragmentation ion peak information of each peak.

A preliminary characterization of the 116 components in YQW was carried out by combining database comparison and literature reports. Among them of 20 components were derived from Gegen, 4 components from Dihuang, 3 components from Tianhuafen, 10 components from Maidong, 21 components from Wuweizi, and 58 components from Gancao. The main components include 59 flavonoids, 10 lignans, 9 triterpenes, 6 phenylpropanoids, 5 terpenoid, 5 steroids and 4 fatty acid, etc. The results are shown in Supplementary Material.

3.3 Qualitative analysis of *in vivo* blood entry prototype components of YQW

Blank serum and YQW-containing serum were analysed in positive and negative ion mode according to the analytical conditions established in the UPLC-Q-TOF/MS technique, and the base-peak ion flow diagrams and the table of incoming blood prototype components are shown in Table 1 and Figure 3 respectively.

The retention time, precise molecular weight, error and high-energy fragmentation ion peak information of each peak were obtained by comparing the ion flow maps of blank serum and YQW-H and YQW-L containing serum. UNIFI data processing system was used to automatically match and identify them. Combined with the results of the *in vitro* chemical composition characterization, a preliminary characterization of the 22 prototypical components of YQW into blood after high and low administration to T2DM rats was carried out. They were listed in Table 2. So these blood entry prototype components may be potential important substances of YQW in the intervention of T2DM rats.

3.4 Retrieval results of targets, "TCM-component-target" network and functional analysis

The 197 direct common targets were obtained by integrating 22 chemical composition targets and T2DM targets. The Venn diagram results are shown in Figure 4A. Then 197 targets were uploaded to the GeneMANIA protein interaction platform for analysis and 20 indirect targets was obtained. The inverse pharmacophore screening also revealed that all the 22 blood entry prototypes are important ingredients in YQW for the treatment of T2DM. Based on the Degree value, the top5 targets, namely, Akt1, Alb, Tp53, Casp3 and Src, were selected as the key

TABLE 2 The table of blood components in YQW.

NO.	Component	Formula	Source
1	puerarin	$C_{21}H_{20}O_9$	Gegen
2	daidzein	$C_{15}H_{10}O_4$	Gegen
3	genistein 7-glucoside	$C_{21}H_{20}O_{10}$	Gegen
4	3′-methoxypuerarin	$C_{22}H_{22}O_{10}$	Gegen
5	kaikasaponin iii	$C_{48}H_{78}O_{17}$	Gegen
6	adeninenucleoside	$C_{10}H_{13}N_5O_4$	Maidong
7	elemicin	$C_{12}H_{16}O_3$	Wuweizi
8	schizonepetoside a	$C_{16}H_{26}O_7$	Wuweizi
9	gomisin n	$C_{23}H_{28}O_6$	Wuweizi
10	gomisin r	$C_{22}H_{24}O_7$	Wuweizi
11	citral	$C_{10}H_{16}O$	Wuweizi
12	robustadial a	$C_{23}H_{30}O_5$	Wuweizi
13	nootkatone	$C_{15}H_{22}O$	Wuweizi
14	vitamin e (beta)	$C_{28}H_{48}O_2$	Wuweizi
15	gancaonin f	$C_{21}H_{16}O_6$	Gancao
16	liquiritigenin	$C_{15}H_{12}O_4$	Gancao
17	liquiritin	$C_{21}H_{22}O_9$	Gancao
18	isoliquiritigenin	$C_{15}H_{12}O_4$	Gancao
19	glabrolide	$C_{30}H_{44}O_4$	Gancao
20	liquoric acid	$C_{30}H_{44}O_5$	Gancao
21	glycyrrhetinic acid	$C_{30}H_{46}O_4$	Gancao
22	18alpha-glycyrrhetinic acid	$C_{30}H_{46}O_4$	Gancao

targets of YQW for the treatment of T2DM. The "TCM-Chemistry," "Chemistry-Direct Target" and "Direct Target-Indirect Target" property files were imported into Cytoscape V3.8.0. The network diagram of "TCM - component - direct target - indirect target" was constructed by the Merge integration function, and the results were shown in Figure 4B. The GO bioassay was visualised on the MicrolifeInfo platform, as shown in Figure 4C. The enrichment analysis of the KEGG signalling pathway based on *p*-values was carried out on the Omicshare platform to obtain bubble maps. The KEGG pathway enrichment analysis showed that of the 203 individual signalling pathways obtained, the top 20 signal transduction process were shown respectively in as shown in Figure 4D.

3.5 Transcriptomics

3.5.1 Identification of differential genes

To further understand the multifaceted mechanism of action of YQW-L inT2DM rats, RNA sequencing analysis were performed to obtain the mRNA expression of each sample in the control, model and YQW-L groups. By comparing the differential gene expression in each group, the screening revealed that the YQW-L group could

FIGURE 4
Bioinformatics analysis of potential active compound targets. **(A)** Venn diagram of chemical composition target of YQW-target of-T2DM. **(B)** Cross-mapping of "Traditional Chinese Medicine-Composition-Target" Network. The green circle in the picture represents the taste of TCM; Orange hexagon represents the chemical composition, and its size represents the Degree value; The middle diamond represents the direct target, the pink diamond represents the indirect target, and its size and color intensity represent the Degree value. It indicates the degree of interaction between target proteins, and its thickness indicates the value of Combine score. The thicker the edge, the greater the value of Combine score. **(C)** GO enrichment analysis of potential targets of YQW. **(D)** Enrichment analysis of KEGG pathway of YQW's potential target. The abscissa is Rich Factor, and the larger the value, the greater the enrichment degree; The ordinate is the top 20 pathways with high enrichment degree; The color from red to purple indicates that the *p*-value is getting bigger and bigger, and the enrichment is becoming more and more obvious.

reverse the abnormally high expression of 28 genes and the abnormally low expression of 61 genes the modle group compared with the normal group. The differential gene regressions are shown in Table 3.

Additional differential gene Venn diagrams and cluster analysis heat maps were used to represent the number of differential genes between the comparison groups, the overlap between the comparison groups and the correlation of expression between 9 individual samples in the three groups. The differential gene expression histogram and the cluster analysis heat map for each group were shown in Figures 5A, B. In comparison to the control group, 471 genes in the model group were highly expressed and 360 genes were low expressed using bioinformatics analysis technologies. In comparison to the YQW group, the model group had 79 highly expressed genes and 227 low expressed genes. In the normal group, 261 genes were highly expressed and 424 genes were low expressed as compared to the YQW group. At the same time, the cluster analysis thermogram revealed that following injection, some

genes in T2DM rats' liver tissue tended to call back to the control group, compared to the control group.

3.5.2 Results of GO, KEGG pathway analysis

In this section, the expression of differential genes in the model group compared to the normal group (i.e., in the disease state) and the differential genes back-regulated in the YQW-L group compared to the normal group were analysed respectively for GO Term enrichment. In addition, KEGG processes are mainly divided into metabolic processes, environmental information processing processes, disease processes, tissue system processes and cellular processes. The differential genes and the KEGG enrichment analysis of the retraced genes in the model group compared to the normal group (i.e., in the disease state) were also shown in Figures 5C, D. In comparison to the control group, the Toll 20 pathways in the model group primarily include Rap1 signaling, AGE-RAGE signaling pathway in diabetic complications, amino acid and nucleotide sugar metabolism, MAPK signaling pathway, nuclear factor-B

TABLE 3 The table of differential gene identification.

Gene	Up	Down	Gene	Up	Down
Pcdh18	√		Ccnf	√	
Hhex	√		LOC108348128	√	
Tmem164	√		Dnah8	√	
Gpsm2	√		Rhoh	√	
Sorbs3	√		Tnfrsf4	√	
R3hcc1l	√		LOC100912564	√	
Dsc2	√		Wfdc21	√	
Pcare	√		Nrg1	√	
AABR07012583.2	√		LOC103694879	√	
Dbp	√		Dck	√	
Wdr92	√		Cxcl14	√	
Cele2a	√		Acad10		√
Nptx2	√		Tymp		√
Epb42	√		Tgif1		√
AABR07021804.1	√		Mgat4a		√
Spata46	√		Rasgef1b		√
Mmel1	√		Ppard		√
Chka		√	Rarres1		√
Foxo1		√	Ppp1r13l		√
AABR07063279.1		√	Pkib		√
Kit		√	Ptpdc1		√
Arntl		√	Gsn		√
Thbs1		√	Bcl2l11		√
Steap3		√	Jdp2		√
Fam89a		√	Coq8a		√
Serpina5		√	Esrrg		√
Per1		√	Noct		√
Tsku		√	Nav3		√
Samd4a		√	Pax8		√
Gstt1		√	Foxp1		√
Ppargc1a		√	Slc45a3		√
Gckr		√	Col27a1		√
Pkdcc		√	Tsc22d3		√
Wfdc2		√	Fam169b		√
Sox5		√	Stard4		√
Foxo3		√	Fzd7		√
Hes1		√	Ppara		√
IL10		√	Sdc4		√

TABLE 3 (Continued) The table of differential gene identification.

Gene	Up	Down	Gene	Up	Down
Pfkfb3		√	Cep85l		√
Zbtb16		√	Rgs9bp		√
Gpatch4		√	Veph1		√
AABR07040840.1		√	Tfap4		√
Baiap2l1		√	Cyp4f39		√
Fabp4		√	Lgsn		√
Lpin1		√			

signaling pathway, toll-like receptor signaling pathway, PI3K-AKT signaling pathway, and so on.

3.5.3 Results of integration analysis

Five shared targets of Kit, Ppard, Ppara, Fabp4 and Tymp were obtained by crossing the targets of pharmacodynamic components and disease predicted by network analysis with the differential targets obtained by transcriptome sequencing. And the shared passway were PI3K-Akt and MAPK signal pathway. As shown in Figure 6, this shared target and pathway could be a potential key target and pathway for YQW in the treatment of T2DM.

4 Discussion

4.1 Analysis of low hypoglycemic effect of TCM

Diabetes is a chronic disease with various consequences, and its prevalence is quickly increasing over the world, putting people's health at risk (Nolan et al., 2011). The T2DM rats model was effectively duplicated in this study by giving them a high-fat diet for 5 weeks and injecting STZ intraperitoneally once (Sun et al., 2019). The modeling rate was 85%, and the model rats had random blood glucose of ≥16.7 mmol/L. The increase and decrease of blood glucose values in the clinical diagnosis and treatment of diabetes can be utilized as a key criterion for determining the severity and control of diabetes, so blood glucose lowering is the most critical loop in diabetes treatment (Mian et al., 2019). Our findings show that the blood glucose value of Met group decreased significantly after 4-week drug administration treatment of T2DM rats in each group. However, compared with the model group, the blood glucose value of the YQW group, whether the high-dose group or the low-dose group, showed a downward trend, but there was no significant difference. According to our literature survey, YQW is frequently used in conjunction with other TCM or western drugs in the clinical treatment of diabetes. The administration takes a little longer, about 8 weeks on average. As a result, it is still unclear if it can dramatically lower blood sugar levels in a short period of time or on its own, and more research is needed. Furthermore, findings from studies such as the United States diabetes prospective show that reducing blood sugar alone does not prevent all problems from occurring, nor does it allow all complications that have already happened to be properly treated. TCM has a high reputation for

FIGURE 5
Bioinformatics analysis of genes related to treatment of T2DM with YQW. **(A)** Histogram of differential gene expression in each group. Red indicates upward adjustment and blue indicates downward adjustment; M represents the model group, NS represents the control group, and L represents the low-dose YQW administration group **(B)** Heat map of cluster analysis of different genes in each group. Blue represents the control group, red represents the model group, and green represents the low-dose YQW administration group. **(C)** GO analysis chart of differential genes in disease state. **(D)** Differential KEGG enrichment map.

preventing and treating diabetes and its chronic consequences, although TCM has less glucose-lowering efficacy compared to western treatment (Liu et al., 2019; Wang et al., 2021a). Clinical studies have found that combining Chinese and Western medicine can shorten the time required for blood glucose to return to normal, reduce the use of Western medicine, reduce the adverse effects of Western medicine and improve symptoms such as excessive drinking, excessive urination and weight loss. Unlike single administration of Western medicine, combined TCM can take advantage of TCM's multi-target and multi-linking effects, allowing for non-hypoglycemic diabetic treatment (Lian et al., 2015). Although the YQW group did not achieve a significant glucose reducing impact in a short period of time, it can play a role in diabetes treatment by controlling lipid metabolism abnormalities and oxidative stress levels, among other things, just like the results in our experiments.

4.2 Analysis of potential pharmacological substances of YQW

In addition, we created a YQW composition database with 495 components in order to elucidate the effective substances of YQW. The blood components of high and low dose YQW samples were examined based on the *in vitro* chemical properties of YQW. The precise mass number, retention period, and lysis rules were used to identify 22 chemical compounds in the blood prototype components. Flavonoids, lignans, and triterpenoids may be viable therapeutic chemicals for regulating lipid metabolism and antioxidation, such as puerarin (Zhu et al., 2010; Guo et al., 2019), gomisin n (Yun et al., 2017; Takanche et al., 2020) and glycyrrhetinic acid (Kalaiarasi and Pugalendi, 2009), according to prototype components discovered in blood research. In this section, UPLC-Q-TOF/MS technology was combined with the UNIFI data matching analysis platform to establish a rapid, sensitive, accurate, and selective blood component identification method of YQW (Zhang et al., 2021; Zhou et al., 2021), which provided reliable data and information for the follow-up network analysis to investigate the effective substances and mechanism of YQW in the treatment of T2DM.

4.3 Interpretation of biological significances

The integrity and systematicness of network analysis, as well as the interactions between medications and drugs and targets, tend to be congruent with TCM's basic characteristics, which is in keeping with Chinese medicine's understanding of disease nature (Wang et al.,

FIGURE 6
Full-text summary diagram.

2021b; Yang et al., 2022a). Therefore, applying network analysis technology to the study of the material basis and mechanism of TCM compounds can not only meet the urgent need for systematic research in TCM, but also reflect a new trend in biomedical systematic research in the era of big data (Li et al., 2022b). Previous research has shown that candidate compounds found in the serum of rats treated with TCM can be identified as active chemicals in network pharmacological analysis (Shao et al., 2022). The PI3K-Akt, MAPK, and FoXO signal pathway may be implicated in the therapeutic mechanism of YQW in treating T2DM, according to a comprehensive analysis of 538 targets and 1,667 genes associated to T2DM from 22 blood components. High-throughput mRNA sequencing technology has been used to reveal molecular mechanisms and predict biomarkers in complicated diseases including diabetes and cancer in recent years (Li et al., 2022c; Reuter et al., 2015). The YQW group can reverse the abnormal expression of 89 genes in the model group, according to our findings. These distinct genes regulate glucose and lipid metabolism, as well as anti-inflammation and anti-oxidation, mostly through the PI3K-Akt and MAPK signaling pathways, and are linked to the formation and progression of T2DM.

Furthermore, studies have revealed that islet cells produce insulin after eating. Insulin first attaches to the appropriate receptors on the cell surface, activates IRS, and transmits the insulin signal from outside the cell to the cell, and then phosphorylates FI3Kto activate Akt. The PI3K-Akt signal pathway plays a major role in lipid metabolism and glucose homeostasis by modulating growth factor signals, and it is the primary channel for insulin signal transduction. Diabetes is caused by an abnormal PI3K-Akt signal pathway. It contains important proteins that help insulin regulate cell metabolism. Insulin activates PTK and

phosphorylates tyrosine residues in IRS-2, allowing p-IRS-2 to bind to PI3K and catalyze the conversion of PIP2 to PIP3. PIP3, as a second messenger, activates Akt, which subsequently controls a number of downstream proteins, including FoxO1, to stimulate glycogen production (Benchoula et al., 2021; Liu et al., 2022; Priyanka et al., 2022; Wang et al., 2022). GLP-1 can induce islet cell proliferation and suppress cell apoptosis, increase islet cell number, improve islet cell function, and stimulate insulin secretion by modulating the MAPK signaling system. The Glp-1-mediated MAPK pathway is one of the diabetes research hotspots because it plays a vital role in islet cell repair. ERK is an essential subtype of the MAPK family that is activated by phosphorylation after being induced by glucose and plays a role in islet cell proliferation and differentiation (Brown et al., 2021; El-Sayed et al., 2021). In recent years, several effector organs have been involved in research on the mechanism of anti-diabetes based on the PI3K/Akt and MAPK signaling pathways (Zhang et al., 2020). This work focused on the transcriptome of rat liver tissue and used multi-tissue and verification studies to better clarify the mechanism of YQW in the treatment of T2DM.

4.4 Deficiencies and limitations

In vitro and *in vivo*, no reference material was employed to verify YQW's component identification, numerous active components or components with isomerism were not found, and the main active components were not quantitatively examined. As a result, in the prediction of network analysis, 22 prototype components were

treated identically, which differs from the theory and characteristics of traditional Chinese medicine compound in clinical illness therapy. Pueraria lobata, Glycyrrhiza uralensis Fisch., Schisandra chinensis, and Ophiopogon japonicus were among the 22 prototyped components. In Rehmannia glutinosa and Trichosanthis Radix, no significant active components were discovered. On the one hand, this could be due to the fact that Rehmannia glutinosa is primarily a polysaccharide component, but Trichosanthis Radix is primarily composed of protein components, which do not exist as prototyped components once they enter the bloodstream. It could, on the other hand, be related to a lack of component identification. In addition to the prototype components in blood, the metabolites in YQW's drug-containing serum must be identified further, allowing for a more thorough identification of beneficial chemicals.

Furthermore, only the expected findings from network analysis and transcriptomics results are merged and studied in the investigation of action mechanism, and five essential targets and linked important pathways require more in-depth analysis and experimental verification.

5 Conclusion

In summary, YQW groups can reverse the abnormally low or abnormally high expression of some genes. The active ingredients in YQW, such as puerarin, daidzein and glycyrrhetinic acid, may further activate the signalling pathways of PI3K/Akt, FoxO and AMPK by regulating the important proteins FoxO3, IL10, Ppargc1a and FoxO1, thereby reducing the level of inflammation, regulating lipid metabolism and protecting liver and kidney tissues. Five common targets, namely, Kit, Ppard, Ppara, Fabp4 and Tymp, were obtained by analyzing the targets screened with network pharmacology and the differential genes sequenced with transcriptomics, all of which were reversed after YQW administration ($p < 0.05$). This result suggests that the active ingredient in YQW may improve the lipid metabolism disorder, oxidative stress and inflammation by regulateing these 5 key genes in T2DM rats. This study looks into the potential pharmacodynamic substances and mechanism of YQW in the treatment of T2DM, but how to explain the pharmacodynamic substance basis and mechanism of YQW in the treatment of T2DM in a systematic and comprehensive manner still requires a lot of detailed research.

Data availability statement

The data presented in the study are deposited in the NCBI repository, accession number: SRP471298:PRJNA1039142.

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Ethics statement

The animal study was approved by the Animal Ethics Committee of Beijing University of Traditional Chinese Medicine. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

YLei: Writing–original draft, Investigation, Methodology, Visualization. JH: Conceptualization, Writing–review and editing. ZX: Data curation, Writing–review and editing. CW: Supervision, Writing–review and editing. YLi: Data curation, Writing–review and editing. YH: Data curation, Writing–review and editing. CL: Project administration, Writing–review and editing. RY: Project administration, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Glossary

BP	Biological process
CHO	Cholesterol
CC	Cellular component
CTD	the Comparative toxicogenomics database
DM	Diabetes mellitus
FoXO	Forkhead box transcription factor O
GLU	Glucose
GO	Gene ontology
GLP-1	glucagon-like peptide-1
HDL-C	High density liptein cholesterol
HE	Hematoxylin-eosin
KEGG, IR	Insulin resistance; Kyoto encyclopedia of genes and genomes
LDL-C	Low density liptein cholesterol
MDA	Malondialdehyde
MAPK	Mitogen-activated protein kinase
MF	Molecular function
Met	Metformin
NO	Nitric oxide
PPI	Protein protein interaction
PKB	Protein kinase B
PI3K	Phosphatidylinositol 3-kinase
PIP2	Phosphatidylinosital biphosphate
PIP3	Phosphatidylinosital triphosphate
STZ	Streptozotocin
SOD	Superoxide dismutase
SI	Spleen index
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglyceride
TTD	Therapeutic target database
UPLC-Q-TOF/MS	Ultra performance liquid chromatography-quardrupole time-of-flight mass spectrometry
YQW	Yuquan pill

Efficacy and safety of the integration of traditional Chinese medicine and western medicine in the treatment of diabetes-associated cognitive decline: a systematic review and meta-analysis

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Objective: In order to offer possible therapeutic treatment evidence for diabetes-associated cognitive decline (DACD), we thoroughly evaluated the effectiveness and safety of combining Traditional Chinese Medicine (TCM) and Western Medicine (WM) in the current study.

Methods: The present study employed a comprehensive search strategy across multiple databases, namely, PubMed, EMBASE, Web of Science, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Data, Chinese Scientific Journals Database (VIP), and Chinese Biomedical Literature Database (CBM), to identify relevant articles published until July 2023. Subsequently, a systematic review and meta-analysis of randomized controlled trials (RCTs) were conducted to assess the efficacy and safety of integrating TCM with WM for the treatment of DACD. The literature included in this study was assessed using the GRADE criteria and the Cochrane Handbook for Systematic Reviews of Interventions. Statistical analysis was conducted using RevMan 5.4 software.

Results: A total of 20 RCTs involving 1,570 patients were ultimately included in this meta-analysis. The pooled results demonstrated that the integration of TCM and WM therapy significantly enhanced the overall effectiveness rate compared to WM therapy alone [OR = 4.94, 95% CI (3.56, 6.85), $p < 0.00001$]. Additionally, the combination therapy resulted in reductions in fasting blood glucose [MD = −0.30, 95% CI (−0.49, −0.10), $p = 0.003$], HbA1c [MD = −0.71, 95%CI (−1.03, −0.40), $p < 0.00001$], TNF-α levels [MD = −8.28, 95%CI (−13.12, −3.44), $p = 0.0008$], and TCM Syndrome Score [MD = −5.97, 95%CI (−9.06, −2.88), $p = 0.0002$]. Meanwhile, the combination therapy had a positive effect on MoCA Score [MD = 2.52, 95% CI (1.75, 3.30), $p < 0.00001$], and MMSE

Score [MD = 2.31, 95% CI (1.33, 3.29), p < 0.00001]. In addition, the safety of the combination therapy was comparable to that of the WM alone [OR = 0.40, 95% CI (0.12, 1.31), p = 0.13].

Conclusion: The integration of TCM and WM therapy outperformed WM alone in DACD treatment. Simultaneously, the combination therapy could improve the therapeutic effect on blood glucose, cognitive function, and inflammation to a certain extent with few adverse effects. However, given the constraints imposed by the quality limitations of the incorporated studies, as well as the potential presence of reporting bias, it is imperative that our findings be substantiated through rigorous, large-scale, randomized controlled trials of superior quality in the future.

GRAPHICAL ABSTRACT

1 Introduction

Diabetes mellitus (DM) is a metabolic disorder that is becoming more prevalent, marked by chronic hyperglycemia and a deficiency in insulin production or sensitivity (Banday et al., 2020). Diabetes mellitus is spreading globally, with an estimated 366 million people in the world by 2030, and thus it has become an urgent and worldwide public health issue threatening human health (Aschner et al., 2021). Neurodegenerative disease is increasingly recognized as an additional complication of diabetes mellitus, in addition to the well-established microvascular and macrovascular complications (Mauricio et al., 2020). Extensive research has demonstrated a correlation between type 2 diabetes mellitus (T2DM) and the development of neurodegenerative diseases such as Alzheimer's disease, vascular dementia, and cognitive impairment (Khaledi et al., 2019; Sutherland et al., 2017; Stoeckel et al., 2016). Notably, T2DM is closely linked to a heightened risk of cognitive impairment, with approximately 60%–70% of T2DM patients experiencing cognitive dysfunction (Gupta et al., 2022; Chatterjee et al., 2016).

Diabetes-associated cognitive decline (DACD) is a prevalent neurological complication of T2DM that primarily presents as cognitive deficits, involving attention and executive functions (Chen et al., 2018). Furthermore, it has gradually become a worldwide health concern due to the advancement of living standards, the acceleration of aging, and the changes in lifestyle (Srikanth et al., 2020). Unfortunately, we remain a shallow understanding on the exact pathogenesis of DACD until now, and thus the range of treatment options is constrained when there is a lack of efficacious and targeted therapeutic medications (Chinese Society of Endocrinology, 2022). The current approach to treating DACD primarily emphasizes the comprehensive management of multiple risk factors, such as blood glucose control, enhancement of cerebral blood supply, and preservation of cognitive function. However, the intricacy of multidrug regimens may engender the likelihood of nonadherence among patients, whereas the prolonged utilization of hypoglycemic agents may escalate the occurrence of adverse effects, including gastrointestinal discomfort, weight gain, and hepatic dysfunction (Chinese Society of Endocrinology, 2021). In light of the unsatisfactory outcomes associated with current treatments, clinicians are taking a closer look at Traditional Chinese Medicine (TCM) as an adjuvant or alternative treatment.

Traditional Chinese medicine therapy is extensive and profound, which has been inherited and applied for more than 2,000 years, is the treasure of Chinese culture. The theory of TCM promotes the principle of "harmony between man and nature" and strives for comprehensive treatment. The people-centered, holistic, and multitarget strategies employed by TCM offer distinct benefits in managing intricate conditions, including DM (Marín-Peñalver et al., 2016). There is no definite disease name of DACD in TCM literature, but according to its clinical characteristics and performance, it is classified as "Xiao Ke" combined with "Chi Dai" or "Jian Wang." In recent years, a substantial body of preclinical (*in vivo/in vitro*) experiments and clinical observation studies has provided evidence supporting the therapeutic efficacy of the integration of traditional Chinese medicine and western medicine in the treatment of DACD. Meanwhile, the potential therapeutic mechanism is still being improved and supplemented, including oxidative stress (Hao et al., 2019), gut microbiota (Zheng et al., 2022), autophagy (Tian et al., 2022), neuroinflammation (Shi et al., 2021), etc. However, most of the published clinical studies are small single-center clinical trials, lacking high-quality systematic evaluation and review of clinical treatment. Efficacy and safety of this treatment must therefore be demonstrated through evidence-based studies. Given the aforementioned constraints, we conducted an extensive review of both domestic and foreign literature to impartially assess the clinical effectiveness and safety of combining TCM and Western Medicine (WM) for patients with DACD, aiming to shed light on clinical treatment approaches.

2 Materials and methods

The review procedure was carried out in accordance with PRISMA guidelines, and it has been submitted to the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) under registration number INPLASY202320072.

2.1 Literature search strategy

To identify relevant studies on biological therapeutic interventions for DACD, an extensive search was conducted across several databases, including China National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Scientific Journals Database (VIP), Chinese Biomedical Literature Database (CBM), PubMed, EMBASE, Web of Science, and Cochrane Library. The retrieval period encompassed the entire duration of databases up until July 2023. No restrictions were placed on language, systemic conditions of participants, or publication year within the scope of this study. The search strategy employed a comprehensive approach, utilizing both MeSH terms and keywords, with a specific emphasis on the topics of "diabetic cognitive impairment" and "traditional Chinese medicine and western medicine." Additionally, the search encompassed intervention measures and diseases associated with these topics, such as proprietary Chinese medicine, Chinese medicine herbs, herbal medicine, diabetic cognitive dysfunction, and diabetic encephalopathy etc. Furthermore, a manual search was conducted in the journal literature available at the Liaoning University of Traditional Chinese Medicine library to complement the initial search and identify any potential omissions. The specific search strategy of each database was shown in Supplementary Material S1.

2.2 Inclusion criteria

The inclusion criteria were established using the PICOS framework, encompassing participant, intervention, comparison, outcomes, and study design.

2.2.1 Types of participants

The study did not impose any limitations based on age, gender, or race. The participants included individuals who had received a

diagnosis of DACD based on a well-defined definition or internationally recognized diagnostic criteria.

2.2.2 Types of interventions

The intervention implemented in this study entailed the integration of TCM and WM. In the treatment group, TCM treatment was exclusively employed as the positive intervention, contrasting with the control group. No limitations were imposed on the dosage or duration of medication.

2.2.3 Types of comparison

The use of WM treatment, including hypoglycemic agents, insulin, nimodipine, donepezil, and others, has been shown to effectively lower blood glucose levels and enhance cognitive function. The control groups in the studies employed the same specifications and dosage of WM as the treatment groups.

2.2.4 Types of outcomes

The primary outcome measure was the total effective rate, while secondary outcomes included fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), MoCA score, MMSE score, TNF-α, TCM syndrome score, and adverse reactions. All included literature reported at least two results from the aforementioned outcomes.

2.2.5 Types of study design

All randomized controlled trials (RCTs) that reported the utilization of TCM in combination with WM for the treatment of DACD were included in this study. No restrictions were placed on publication status or language.

2.3 Exclusion criteria

The exclusion criteria were set as followed. 1) Non-RCTs or animal studies. 2) Control group included methods of TCM, such as acupuncture, Chinese patent medicine, herbal extracts and so on. 3) Repeated publication or repeated clinical data. 4) Original and unpublished data that could not be obtained and extracted after contacting the authors. 5) Outcome effect was not clear: The data were incomplete, the outcome effect was not clear, the statistical method was incorrect, and the data could not provide the mean and standard deviation.

2.4 Baseline characteristics and assessment of included studies

The data extraction process for the studies was conducted by two independent reviewers (Jiren An and Guiyan Sun). To facilitate this process, a study-specific spreadsheet was created in Excel, encompassing variables such as authors, publication date, country, study design, sample size, average age, gender, intervention measures, follow-up duration, and outcome measures. Subsequently, all data were cross-verified and imported into Rev Man software (V.5.4). The Cochrane Handbook for Systematic Reviews was utilized to evaluate the risk of bias in all studies included in this analysis. These studies were categorized as having a low, high, or unclear risk of bias based on seven specific criteria: 1) random sequence generation; 2) allocation

concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessors; 5) incomplete outcome data; 6) selective reporting; and 7) other potential risks of bias. In cases where there was disagreement, a third reviewer investigator (Yufeng Yang) was consulted to reach a resolution.

2.5 Data analysis and synthesis

Statistical analyses were performed using the Review Manager program (version 5.4.1, The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) and Stata software (version 16, The Stata Corporation, College Station, Texas, United States). To measure the effect size, Risk ratio (RR) with 95% confidence intervals (CIs) was used as an evaluation index for dichotomous data, including total effective rate and adverse reaction. Mean difference (MD) or standardized mean difference (SMD) with 95% CI was used as an evaluation index for continuous data, including FPG, HbA1c, MoCA score, MMSE score, TNF-α, AND TCM syndrome score.

Heterogeneity among the outcomes of the included studies was analyzed using the Cochrane Q test, while the magnitude of heterogeneity was determined quantitatively in combination with I^2 (Higgins and Thompson, 2002). If there was no heterogeneity ($p > 0.05$, $I^2 \leq 50\%$), the fixed-effect model was selected; if there was heterogeneity ($p \leq 0.05$, $I^2 > 50\%$), the random-effect model was used. $p < 0.05$ was considered statistically significant.

2.6 Subgroup analyses, sensitivity analyses and publication bias

Subgroup analysis was performed on the clinical characteristics to investigate the causes of clinical heterogeneity. By excluding one study at a time, sensitivity analysis was used to examine whether low-quality studies affected the robustness and stability of the overall meta-analysis. Begg's test funnel plot and Egger's test were used to evaluate publication bias.

2.7 Evaluation of the certainty of the evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool was used to evaluate the quality of cumulative evidence in this review (Goldet and Howick, 2013). By assessing the factors such as the risk of bias, inconsistency, and indirectness, the certainty level of evidence was judged using four categories of "very low," "low," "moderate," and "high."

3 Results

3.1 Literature retrieval process and results

A preliminary literature search turned up a total of 143 publications, and 20 articles (Cai, 2016; Chen et al., 2021; Fu

et al., 2017; Gao et al., 2017; Jin et al., 2015; Li, 2022; Li, 2016; Li et al., 2022; Liu et al., 2016; Mao et al., 2019; Tian et al., 2021; Wang et al., 2016; Wang, 2015; Wang et al., 2015; Yan and Guan, 2019; Yang, 2017; Yu, 2018; Yu et al., 2022; Zhang, 2016; Zhao et al., 2014) that qualified were subsequently found. Figure 1 displayed the search procedures.

3.2 Study characteristics and assessment of risk of bias

All studies were published before July 2023 and conducted in China. Totally, this meta-analysis involved 1,570 participants, of which 788 participants were designated to the experimental group while 782 patients were assigned to the control group. The sample size varied from 30 to 126, with a mean patient age ranging from 59 to 80 years old. and the average course of disease ranged from less than 12 months to more than 17 years. Regarding of the treatment measures, the control group adopted the therapy of western medicine alone, whereas the experimental group received combined treatment with TCM and WM. Specially, western medicine included hypoglycemic drug, antihypertensive drug, hypolipidemic drug, donepezil, nimodipine, oxiracetam citicoline sodium tablets, aspirin enteric-coated tablet, and insulin etc. Meanwhile, a total of 17 types of Chinese herbal medicine were used in the 20 RCTs, all of which were multi-herbal medicines, including Bushen Huoxue decoction, Bushen Huoxue Kaiqiao recipe, Bushen Huoxue recipe, Bushen Jiannao granules, Bushen Jianpi Huoxue recipe, Bushen Yiqi Huoxue recipe, Jiaotai pill, Naoling decoction, Rehmannia decoction, Shenqi Yizhi Jiannao recipe, Xuefu Zhuyu decoction, Yangyi Yizhi decoction, Yiqi Bushen Huoxue recipe, Yiqi Yangyin Huoxue recipe, Yishen Huoxue recipe, Yizhi Mixture, Zishen Qushi Huatan recipe. Among the 20 included studies, the duration of treatment ranged from 2 months to 12 months. In terms of the outcomes, 13 studies mentioned the total effective rate, 10 studies reported the FPG level, 11 studies reported the HbA1c level, 12 studies reported the MoCA score, 11 studies reported the MMSE score, 3 studies reported the TNF-α level, 7 studies reported the TCM syndrome score, and 12 studies reported the adverse reaction. The experimental group and the control group had equivalent pre-treatment data (such as age, sex ratio, outcome indicators, etc.). The basic characteristics of the included studies were summarized in Table 1, and components of Chinese herbal medicine used in the included studies were presented in Table 2.

Assessment of risk biases were outlined as Figure 2. In general, the overall methodological qualities of the included studies were poor to moderate. In terms of random sequence generation, 14 studies provided a sufficient randomization process to generate random sequences with a low risk of bias, whereas the remaining 6 studies supplied unspecific details of randomization, and thus were assessed as unclear risk. None of the included studies explicitly mentioned the use of allocation concealment, which led to unclear risk of bias in the relative domain. Only 1 study described the implementation of single blinding of subjects, which was rated as low risk. None of other included studies explicitly mentioned the use of blind method,

resulting in an unclear associated risk of bias. All studies included in the analysis published complete data regarding the outcomes, leading us to rate the risk of bias as low. Meanwhile, all included RCTs didn't report the bias of selective reporting, thus assessing as low risk. As for other biases, none of the studies provided adequate information for risk judgment, resulting in an unclear risk of bias.

3.3 Meta-analysis results

3.3.1 Meta-analysis of total effective rate

Preliminary data from 13 studies revealed the disclosure of the total effective rate, as illustrated in Figure 3. Following the heterogeneity test ($p = 0.18$, $I^2 = 26\%$), the fixed-effects model was employed for analysis. The findings demonstrated a statistically significant increase in the total effective rate within the experimental group compared to the control group [OR = 4.94, 95% CI (3.56, 6.85), $p < 0.00001$]. Consequently, the combination of TCM and WM exhibited superior efficacy in treating DACD when compared to WM alone.

An additional subgroup analysis revealed that the combination of TCM and WM resulted in a significantly higher total effective rate compared to WM alone for treatment durations of 2 months [$p = 0.77$, $I^2 = 0\%$; OR = 3.01, 95% CI = (1.57, 5.77), $p = 0.0009$], 3 months [$p = 0.16$, $I^2 = 36\%$; OR = 7.47, 95% CI = (4.50, 12.41), $p < 0.00001$], and 6 months [$p = 0.41$, $I^2 = 0\%$; OR = 4.17, 95% CI (2.31, 7.51), $p < 0.00001$].

3.3.2 Meta-analysis of FPG

A total of 10 studies were incorporated into the analysis of FPG, as illustrated in Figure 4. The random effects model was chosen after considering the outcomes of the heterogeneity test ($p = 0.0002$, $I^2 = 72\%$). In comparison to the control group, the combination of TCM and WM demonstrated a significant reduction in FPG levels among patients with DACD [MD = −0.30, 95% CI (−0.49, −0.10), $p = 0.003$].

A subgroup analysis indicated not readily apparent heterogeneity ($p = 0.19$, $I^2 = 40\%$) during the ≤2 month treatment course. On the basis of the fixed effects model, TCM plus WM treatment of DACD was determined to induce a statistically significant effect compared with WM alone [MD = −0.34, 95%CI (−0.57, −0.11), $p = 0.004$]. Regarding the 3-month treatment course ($p = 0.0006$, $I^2 = 79\%$) and 6-month treatment course ($p = 0.06$, $I^2 = 73\%$), heterogeneity was significant, and the statistical analysis using the random effects model indicated that TCM plus WM was superior to the control group in terms of reducing FPG level during the 3-month treatment course [MD = −0.31, 95%CI (−0.46, −0.15), $p < 0.0001$]. However, there was no statistical significance between the two groups during 6-month treatment course [MD = −0.10, 95% CI (−0.22, 0.03), $p = 0.13$].

3.3.3 Meta-analysis of HbA1c

Eleven studies involving a total of 870 patients were included in the analysis, as illustrated in Figure 5. The statistical analysis was conducted using the random effects model, following the heterogeneity test ($p < 0.00001$, $I^2 = 93\%$). The findings of the

FIGURE 1
Flow chart for study selection process.

meta-analysis revealed that the combination of TCM and WM exhibited a greater capacity to decrease HbA1c levels compared to the use of WM alone [MD = −0.71, 95%CI (−1.03, −0.40), $p < 0.00001$].

3.3.4 Meta-analysis of MoCA score

12 studies focused on MoCA scores, as illustrated in Figure 6. The heterogeneity was apparent ($p < 0.00001$, $I^2 = 88\%$); Therefore, the random effects model was selected. In patients with DACD, TCM plus WM significantly improved MoCA scores compared with WM alone [MD = 2.52, 95% CI (1.75, 3.30), $p < 0.00001$].

The MoCA scale consisted of the following 7 items, including visuospatial and executive, naming, attention, language, abstraction, memory and delayed recall, as well as orientation. In the present

study, a total of 5 studies reported on the specific items of MoCA scale in detail. The pooled data of meta-analysis demonstrated the superior effect of TCM plus WM for items other than naming and orientation. The entire summary was provided in Table 3.

3.3.5 Meta-analysis of MMSE score

A total of 11 eligible studies, as illustrated in Figure 7, encompassing 802 patients evenly distributed across two study groups, were included for the purpose of analyzing the MMSE score. The random effects model was chosen for analysis due to the observed heterogeneity ($p < 0.00001$, $I^2 = 95\%$). The combination of TCM and WM demonstrated a significant improvement in MMSE scores among patients with DACD compared to the control group [MD = 2.31, 95% CI (1.33, 3.29), $p < 0.00001$].

TABLE 1 Summary of included studies.

Author (year)	Sample size E/C	Gender (M/F)		Course of disease	Mean age (y) E/C	Co-intervention	Intervention		Duration (months)	Outcomes
		E	C	E/C			E	C		
Cai 2016	24/24	15/9	14/10	9.0 ± .8/9.2 ± 2.0	66.2 ± 4.2/ 66.8 ± 4.5	NR	Yishen Huoxue Recipe + C	Conventional treatment (oral hypoglycemic drug or insulin) and brain neuroprotective drug	3	⑤⑦
Chen et al., 2021	37/37	20/17	19/18	NR	71.56 ± 7.13/ 71.18 ± 7.12	Lifestyle intervention	Naoling Decoction + C	Conventional treatment (oral hypoglycemic drug or insulin) and donepezil (5 mg, qd)	6	①②③④⑤
Fu et al., 2017	40/40	20/20	19/21	17.7 ± 8.4/15.5 ± 7.8	67.2 ± 8.5/ 67.4 ± 9.8	NR	Bushen Huoxue Recipe + C	Conventional treatment (oral hypoglycemic drug or insulin + antihypertensive drug + hypolipidemic drug) and nimodipine (30 mg, tid)	3	①②③④⑧
Gao et al., 2017	60/60	36/24	34/26	NR	62.40 ± 5.95/ 62.08 ± 5.92	NR	Zishen Qushi Huatan Recipe + C	Donepezil (5 mg, qd)	3	①④⑤⑧
Jin et al., 2015	15/15	7/8	9/6	NR	62.5 ± 5.4/ 63.0 ± 5.6	NR	Bushen Huoxue Kaiqiao Recipe + C	Nimodipine (30 mg, tid)	3	①④⑦⑧
Li et al., 2022	63/63	32/31	35/28	7.74 ± 3.82/ 7.31 ± 3.28	62.73 ± 5.12/ 61.46 ± 6.17	NR	Yiqi Yangyin Huoxue Recipe + C	Conventional treatment (oral hypoglycemic drug or insulin + antihypertensive drug) and donepezil (5 mg, qd)	6	①②③④⑤⑥
Li 2016	54/53	30/24	29/24	7.5 ± 2.3/7.4 ± 2.3	61.3 ± 4.7/ 61.2 ± 4.7	NR	Bushen Huoxue Kaiqiao Recipe + C	Nimodipine (10 mg, tid)	3	①④
Li 2022	32/32	21/11	22/10	5.34 ± 0.88/ 5.70 ± 0.97	59.03 ± 7.15/ 60.06 ± 6.58	Lifestyle intervention	Rehmannia Decoction + C	Conventional treatment (oral hypoglycemic drug) and donepezil (5 mg, qd)	6	①②③④⑤⑦⑧
Liu et al., 2016	35/35	16/19	18/17	6.5 ± 2.7/7.1 ± 2.9	65.6 ± 7.6/ 68.2 ± 6.9	NR	Yiqi Bushen Huoxue Recipe + C	Conventional treatment (oral hypoglycemic drug or insulin + antihypertensive drug)	3	①⑤
Mao et al., 2019	30/30	19/11	21/9	10.56 ± 1.43/ 9.21 ± 1.65	60.32 ± 4.51/ 63.25 ± 4.03	Lifestyle intervention	Yangyi Yizhi Decoction + C	Conventional treatment (oral hypoglycemic drug or insulin + antihypertensive drug) and nimodipine (30 mg, tid)	2	①⑤
Tian et al., 2021	40/40	23/17	22/18	8.2 ± 2.8/8.5 ± 3.2	69.5 ± 5.3/ 69.2 ± 5.4	NR	Jiaotai Pill + C	Conventional treatment (oral hypoglycemic drug or insulin) + oxiracetam (0.8 g, tid)	6	④⑥
Wang et al., 2016	53/52	34/19	37/15	7.4 ± 2.4/7.5 ± 2.5	60.2 ± 10.1/ 61.6 ± 10.5	Lifestyle intervention	Bushen Yiqi Huoxue Recipe + C	Metformin (0.5 g, tid) or insulin + citicoline sodium tablets (0.2 g, tid)	12	②③
Wang 2015	30/30	17/13	16/14	11.1 ± 2.9/11.3 ± 2.8	69.3 ± 3.5/ 69.5 ± 3.4	Lifestyle intervention	Bushen Jiannao Granules + C	Conventional treatment (oral hypoglycemic drug or insulin + antihypertensive drug + hypolipidemic drug) and nimodipine (30 mg, tid)	2	①⑤
Wang et al., 2015	57/57	29/28	31/26	7.7 ± 4.4/7.5 ± 4.8	61.1 ± 7.8/ 60.4 ± 7.5	NR	Bushen Huoxue Decoction + C	Conventional treatment (oral hypoglycemic drug or insulin + antihypertensive drug + hypolipidemic drug), nimodipine (30 mg, tid) and bayaspirin enteric-coated (100 mg, qd)	2	②③④⑥

44

TABLE 1 (Continued) Summary of included studies.

Author (year)	Sample size E/C	Gender (M/F) E	Gender (M/F) C	Course of disease E/C	Mean age (y) E/C	Co-intervention	E	C	Duration (months)	Outcomes
Yan and Guan 2019	30/30	18/12	16/14	11.56 ± 4.39/9.83 ± 5.79 (months)	71.37 ± 4.66/70.56 ± 5.26	NR	Yizhi Mixture + C	Conventional treatment (oral hypoglycemic drug or insulin) and citicoline sodium tablets (0.2 g, tid)	2	②③⑤
Yang 2017	30/30	16/14	14/16	6.83 ± 1.64/7.33 ± 2.04	61.63 ± 6.10/62.17 ± 5.27	Lifestyle intervention	Shenqi Yizhi Jiannao Recipe + C	Metformin (500 mg, qd), shagliptin (5 mg, qd) and nimodipine (30 mg, tid)	3	①②③④⑤⑥⑦
Yu 2018	26/25	18/8	16/9	NR	67/66.5	NR	Xuefu Zhuyu Decoction + C	Conventional treatment (oral hypoglycemic drug or insulin)	3	②③
Yu et al., 2022	40/40	23/19	22/20	11.69 ± 2.84/11.05 ± 3.93	71.67 ± 6.09/71.10 ± 6.12	Lifestyle intervention	Bushen Jianpi Huoxue Recipe + C	Conventional treatment (antihypertensive drug + hypolipidemic drug), metformin (500 mg, qd), glicazide (80 mg, bid, if necessary) and aspirin enteric-coated tablet (100 mg, qd)	3	①③④⑦⑧
Zhang 2016	32/33	17/13	14/16	NR	79.67 ± 7.68/80.62 ± 6.42	Lifestyle intervention	Yizhi Mixture + C	Conventional treatment (oral hypoglycemic drug or insulin) and oxiracetam injection (4.0 g, qd)	3	①②③⑤⑥⑦
Zhao et al., 2014	62/58	44/18	40/18	NR	65.5 ± 5.9/64.0 ± 5.8	NR	Bushen Huoxue Kaiqiao Recipe + C	Aspirin (100 mg, qd)	6	④⑦⑧

E, Experimental group; C, Control group; NR, Not reported. Outcome: ① Total effective rate; ② FPG; ③ HbA1c; ④ MoCA, score; ⑤ MMSE, score; ⑥ TNF-α; ⑦ TCM, syndrome score; ⑧ Adverse reaction.

3.3.6 Meta-analysis of TNF-α

Furthermore, three studies specifically focused on the reduction of TNF-α, as illustrated in Figure 8. The random effects model was employed for analysis based on the results of the heterogeneity test ($p < 0.00001$, $I^2 = 93\%$). The meta-analysis results indicated a statistically significant difference between the two groups [MD = −8.28, 95%CI (−13.12, −3.44), $p = 0.0008$]. The findings of this study suggest that the combination of TCM and WM in the treatment of DACD is more effective in reducing TNF-α levels compared to WM alone (Figure 5).

3.3.7 Meta-analysis of TCM syndrome score

Out of the included studies, a total of 7 articles reported improvements in TCM syndrome, as illustrated in Figure 9. Heterogeneity testing was conducted, followed by a meta-analysis using the random-effects model ($p < 0.00001$, $I^2 = 94\%$). The results showed a statistically significant difference with a MD of −5.97 and a 95% CI of (−9.06, −2.88). These findings indicate that the combination of TCM and WM is more effective in treating DACD by improving TCM syndrome ($p = 0.0002$).

3.3.8 Meta-analysis of adverse reactions

Twelve studies within the encompassed literature made reference to the occurrence of adverse reactions, with only six of these studies reporting patients who experienced such reactions. Conversely, the remaining six studies documented no instances of adverse reactions among their respective patient populations. A total of 28 patients in the experimental group had adverse reactions during treatment, including 7 cases of dizziness, 2 cases of headache, 2 cases of gastrointestinal discomfort, 2 cases of facial flushing, 5 cases of nausea and vomiting, 4 cases of diarrhea, 1 case of albuminuria, 1 case of xerostomia, 1 case of fever, 2 cases of restlessness, and 1 case of insomnia; A total of 57 patients in the control group experienced adverse reactions, including 11 cases of dizziness, 7 cases of headache, 10 cases of gastrointestinal discomfort, 6 cases of decreased blood pressure, 1 case of facial flushing, 3 cases of nausea and vomiting, 1 case of diarrhea, 1 case of anemia, 2 cases of albuminuria, 1 case of impaired liver function, 2 cases of impaired renal function, 2 cases of xerostomia, 2 cases of fever, 2 cases of restlessness, 2 cases of insomnia, 2 cases of tinnitus, and 2 cases of constipation. The overall heterogeneity was manifested ($p = 0.007$, $I^2 = 76\%$), and thus the random effects model was selected. The data of meta-analysis showed that the differences were not statistically significant (OR = 0.40, 95% CI [0.12, 1.31], $p = 0.13$) (Figure 10). This observation suggests that the safety of medication administration was comparable between the experimental and control groups, namely, on the basis of WM, the additional use of TCM didn't appear to result in an increase in adverse reactions.

3.4 Sensitivity analysis and publication bias

In order to conduct a sensitivity analysis on the total effective rate, FPG, HbA1c, MoCA score, MMSE score, TCM syndrome score, TNF-α, and adverse reactions, a meticulous item-by-item elimination approach was employed to scrutinize the data extracted from the included literature. No notable alterations were observed in the stability of each study and the combined outcomes of each effect size, thereby affirming the credibility of the data analysis findings.

TABLE 2 Components of Chinese herbal medicine used in the included studies.

Study	Prescription name	Source	Extraction process	Compositions	Usage of preparations	Preparations	Quality control reported?	Chemical analysis reported?
Cai 2016	Yishen Huoxue Recipe	NR	NR	Hornes of Cervus nippon Temminck [Cervidae; Cervi Cornus Colla] 20g, Rehmannig glutinosa Libosch. [Orobanchaceae; Rehmanniae radix praeparata] 20g, Reynoutria multiflora (Thunb.) Moldenke [Polygonaceae; Polygoni multiflori radix] 20g, Lycium barbarum L. [Solanaceae; Lycii fructus] 15g, Polygala tenuifolia Willd. [Polygalaceae; Polygalae Radix] 10 g, Carthamus tinctorius L. [Asteraceae; Carthami Flos] 10 g, Ziziphus jujuba Mill.var.spinosa (Bunge) Hu ex H.F.Chou [Rhamnaceae; Ziziphi Spinosae Semen] 20 g, Ligusticum chuanxiong Hort. [Apiaceae; Chuanxiong rhizoma] 12 g, Salvia miltiorrhiza Bunge [Lamiaceae; Salviae Miltiorrhizae Radix Et Rhizoma] 20g, Acorus calamus var. angustatus Besser [Acoraceae; Acori tatarinowii rhizoma] 12g, Alpinia oxyphylla Miq. [Zingiberaceae; Alpiniae Oxyphyllae Fructus] 12 g	1 package bid po	Decoction	NR	NR
Chen et al., 2021	Naoling Decoction	Shaanxi Traditional Chinese Medicine Hospital	Partially reported[c]	Epimedium brevicornu Maxim. [Ginkgoaceae; Epimedii Folium] 10 g, Rhodiola rosea L. [Crassulaceae; Rhodiolae Crenulatae Radixet Rhizoma] 15g, Cnidium monnieri (L.) Cuss. [Apiaceae; Cnidii Fructus] 10 g, Reynoutria multiflora (Thunb.) Moldenke [Polygonaceae; Polygoni multiflori radix] 20g, Cullen corylifolium (L.) Medik. [Fabaceae; Psoraleae Fructus] 15g, Panax ginseng C.A.Mey. [Araliaceae; Ginseng radix et rhizoma] 15g, Eucommia ulmoides Oliv. [Eucommiaceae; Eucommiae Cortex] 15g, Acorus calamus var. angustatus Besser [Acoraceae; Acori tatarinowii rhizoma] 15 g	200 ml bid po	Decoction	NR	NR
Fu et al., 2017	Bushen Huoxue Recipe	Peking University First Hospital	Partially reported[c]	Cuscuta chinensis Lam. [Convolvulaceae; Cuscutae Semen] 15 g, Lycium barbarum L. [Solanaceae; Lycii fructus] 15 g, Rubus chingii Hu [Rosaceae; Rubi Fructus] 10 g, Schisandra chinensis (Turcz.) Baill. [Schisandraceae; Schisandrae chinensis fructus] 6 g, Plantago asiatica L. [Plantaginaceae; Plantaginis Herba] 5g, Epimedium brevicornu Maxim. [Ginkgoaceae; Epimedii Folium] 10 g, Hirudo niponica Whitman [Hirudo; Hirudo] 3 g	1 package bid po	Decoction	NR	NR
Gao et al., 2017	Zishen Qushi Huatan Recipe	NR	NR	Panax ginseng C.A.Mey. [Araliaceae; Ginseng radix et rhizoma] 20 g, Dioscorea oppositifolia L. [Dioscoreaceae; Dioscoreae rhizoma] 15g, Poria cocos (Schw.) Wolf [Polyporaceae; Poria] 15 g, Salvia miltiorrhiza Bunge [Lamiaceae; Salviae Miltiorrhizae Radix Et Rhizoma] 15 g, Cistanche deserticola Ma [Orobanchaceae; Cistanches Herba] 15 g, Pinellia ternata (Thunb.) Makino [Araceae; Pinelliae rhizoma] 10 g, Amomum longiligulare T.L.Wu [Zingiberaceae; Amomi Fructus] 10 g, Acorus calamus var. angustatus Besser [Acoraceae; Acori tatarinowii rhizoma] 8 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma] 8 g	1 package bid po	Decoction	NR	NR
Jin et al., 2015	Bushen Huoxue Kaiqiao Recipe	NR	NR	Cistanche deserticola Ma [Orobanchaceae; Cistanches Herba] 10g, Acorus calamus var. angustatus Besser [Acoraceae; Acori tatarinowii rhizoma] 5g, Panax notoginseng (Burkill) F.H.Chen [Araliaceae; Notoginseng radix et rhizoma] 2.5 g	1 package tid po	Decocted preparation	NR	NR
Li 2022	Yiqi Yangyin Huoxue Recipe	NR	NR	Panax quinquefolium L. [Araliaceae; Panacis Quinquefolii Radix] 10 g, Rehmannig glutinosa Libosch. [Orobanchaceae; Rehmanniae radix praeparata] 15 g, Ophiopogon japonicus (Thunb.) Ker Gawl. [Asparagaceae; Ophiopogonis radix] 10 g, Schisandra chinensis (Turcz.) Baill. [Schisandraceae; Schisandrae chinensis fructus] 6 g, Carthamus tinctorius L. [Asteraceae; Carthami Flos] 8 g, Ligusticum chuanxiong Hort. [Apiaceae; Chuanxiong rhizoma] 8 g, Atractylodes macrocephala Koidz. [Asteraceae; Atractylodis macrocephalae rhizoma] 15 g, Polygala tenuifolia Willd. [Polygalaceae; Polygalae Radix] 10 g, Actaea cimicifuga L. [Ranunculaceae; Cimicifugae rhizoma] 6 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma] 5 g	1 package bid po	Decoction	NR	NR

TABLE 2 (Continued) Components of Chinese herbal medicine used in the included studies.

Study	Prescription name	Source	Extraction process	Compositions	Usage of preparations	Preparations	Quality control reported?	Chemical analysis reported?
Li 2016	Bushen Huoxue Kaiqiao Recipe	NR	Partially reported[c]	Polygonatum sibiricum Redouté [Asparagaceae; Polygonati Rhizoma] 30g, Rehmannig glutinosa Libosch. [Orobanchaceae; Rehmanniae radix praeparata] 15g, Rehmannia glutinosa (Gaertn.) DC. [Orobanchaceae; Rehmanniae radix praeparata] 15 g, Cistanche deserticola Ma [Orobanchaceae; Cistanches Herba] 15 g, Polygala tenuifolia Willd. [Polygalaceae; Polygalae Radix] 15 g, Acorus calamus var. angustatus Besser [Acoraceae; Acori tatarinowii rhizoma] 5 g, Ginkgo biloba L. [Zingiberaceae; Ginkgo Folium] 10 g, Actaea cimicifuga L. [Ranunculaceae; Cimicifugae rhizoma] 10 g, Panax notoginseng (Burkill) F.H.Chen [Araliaceae; Notoginseng radix et rhizoma] 2.5 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma] 6 g	1 package tid po	Decoction	NR	NR
Li et al., 2022	Rehmannia Decoction	The First Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine	Partially reported[c]	Rehmannia glutinosa (Gaertn.) DC. [Orobanchaceae; Rehmanniae radix praeparata]15g, Gynochthodes officinali How [Rubiaceae; Morindae Officinalis Radix] 15g, Cornus officinalis Siebold & Zucc. [Cornaceae; Corni Fructus] 15g, Dendrobium nobile Lindl. [Orchidaceae; Dendrobii Caulis] 15g, Cistanche deserticola Ma [Orobanchaceae; Cistanches Herba] 15g, Aconitum carmichaelii Debx [Ranunculaceae; Aconiti Lateralis Radix Praeparata] 15g, Polygala tenuifolia Willd. [Polygalaceae; Polygalae Radix] 15g, Neolitsea cassia (L.) Kosterm. [Lauraceae; Cinnamomi Cortex] 15g, Schisandra chinensis (Turcz.) Baill. [Schisandraceae; Schisandrae chinensis fructus] 15g, Poria cocos (Schw.) Wolf [Polyporaceae; Poria] 15g, Ophiopogon japonicus (Thunb.) Ker Gawl. [Asparagaceae; Ophiopogonis radix] 15 g, Acorus calamus var. angustatus Besser [Acoraceae; Acori tatarinowii rhizoma] 15 g, Mentha canadensis L. [Lamiaceae; Menthae Haplocalycis Herba] 10 g, Zingiber offcinale Rosc. [Zingiberaceae; Zingiberis Rhizoma Recens] 5 g, Ziziphus jujuba Mill. [Rhamnaceae; Jujubae Fructus] 5 g	1 package bid po	Decoction	NR	NR
Liu et al., 2016	Yiqi Bushen Huoxue Recipe	First Clinical Hospital Affiliated to Jilin Province Academy of Traditional Chinese Medicine	Partially reported[c]	Panax ginseng C.A.Mey. [Araliaceae; Ginseng radix et rhizoma], Cervus nippon Temminck [Cervidae; Cervi Cornu Pantotrichum], Rehmannig glutinosa Libosch. [Orobanchaceae; Rehmanniae radix praeparata], Panax notoginseng (Burkill) F.H.Chen [Araliaceae; Notoginseng radix et rhizoma], Paeonia suffruticosa Andr. [Paeoniaceae; Moutan Cortex], Acorus calamus var. angustatus Besser [Acoraceae; Acori tatarinowii rhizoma], Polygala tenuifolia Willd. [Polygalaceae; Polygalae Radix]	NR	Granule	NR	NR
Mao et al., 2019	Yangyi Yizhi Decoction	Affiliated Hospital of Hunan Academy of Traditional Chinese Medicine	Partially reported[c]	Astragalus mongholicus Bunge [Fabaceae; Astragali radix] 30g, Trichosanthes kirilowii Maxim. [Cucurbitaceae; Radix Trichosanthis] 30g, Dioscorea oppositifolia L. [Dioscoreaceae; Dioscoreae rhizoma] 15g, Rehmannig glutinosa Libosch. [Orobanchaceae; Rehmanniae radix praeparata] 15g, Cornus officinalis Siebold & Zucc. [Cornaceae; Corni Fructus] 15g, Salvia miltiorrhiza Bunge [Lamiaceae; Salviae Miltiorrhizae Radix Et Rhizoma] 15g, Cistanche deserticola Ma [Orobanchaceae; Cistanches Herba] 15 g, Trigonella foenum-graecum L. [Fabaceae; Semen Trigonellae] 15 g, Ophiopogon japonicus (Thunb.) Ker Gawl. [Asparagaceae; Ophiopogonis radix] 12 g, Euonymus alatus (Thunb.) Siebold [Celastraceae; Ramulus euonymi] 10 g, Pheretima aspergillum (E. Perrier) [Megascolecidae; Pheretima] 10 g, Polygala tenuifolia Willd. [Polygalaceae; Polygalae Radix] 10 g, Citrus medicaL.var. sarcodactylis Swingle. [Rutaceae; Citri Sarcodactμlis Fructus] 10 g	1 package bid po	Decoction	NR	NR
Tian et al., 2021	Jiaotai Pill	Hubei Provincial Hospital of Traditional Chinese Medicine	Partially reported[b]	Coptis chinensis Franch. [Ranunculaceae; Coptidis rhizoma], Neolitsea cassia (L.) Kosterm. [Lauraceae; Cinnamomi Cortex]	4 pills bid po	Pill	Yes	NR

TABLE 2 (*Continued*) Components of Chinese herbal medicine used in the included studies.

Study	Prescription name	Source	Extraction process	Compositions	Usage of preparations	Preparations	Quality control reported?	Chemical analysis reported?
Wang et al., 2016	Bushen Yiqi Huoxue Recipe	NR	NR	Astragalus mongholicus Bunge [Fabaceae; Astragali radix] 20g, Salvia miltiorrhiza Bunge [Lamiaceae; Salviae Miltiorrhizae Radix Et Rhizoma] 20g, Poria cocos (Schw.) Wolf [Polyporaceae; Poria] 15g, Panax ginseng C.A.Mey. [Araliaceae; Ginseng radix et rhizoma] 15g, Lycium barbarum L. [Solanaceae; Lycii fructus] 12 g, Rehmannig glutinosa Libosch. [Orobanchaceae; Rehmanniae radix praeparata] 15 g, Schisandra chinensis (Turcz.) Baill. [Schisandraceae; Schisandrae chinensis fructus] 8 g, Trichosanthes kirilowii Maxim. [Cucurbitaceae; Radix Trichosanthis] 10 g, Ophiopogon japonicus (Thunb.) Ker Gawl. [Asparagaceae; Ophiopogonis radix] 12 g, Dioscorea oppositifolia L. [Dioscoreaceae; Dioscoreae rhizoma] 10 g, Rubus chingii Hu [Rosaceae; Rubi Fructus] 12 g, Alisma plantago-aquatica L. [Alismataceae; Alismatis rhizoma] 12 g	1 package bid po	Decoction	NR	NR
Wang 2015	Bushen Jiannao Granules	NR	NR	Cistanche deserticola Ma [Orobanchaceae; Cistanches Herba] 15 g, Reynoutria multiflora (Thunb.) Moldenke [Polygonaceae; Polygoni multiflori radix] 15 g, Alpinia oxyphylla Miq. [Zingiberaceae; Alpiniae Oxyphyllae Fructus] 12 g, Rehmannia glutinosa (Gaertn.) DC. [Orobanchaceae; Rehmanniae radix praeparata] 15 g, Cornus officinalis Siebold & Zucc. [Cornaceae; Corni Fructus] 15 g, Dioscorea oppositifolia L. [Dioscoreaceae; Dioscoreae rhizoma] 15g, Polygala tenuifolia Willd. [Polygalaceae; Polygalae Radix] 12 g, Acorus calamus var. angustatus Besser [Acoraceae; Acori tatarinowii rhizoma] 10 g	150 ml bid po	Granule	NR	NR
Wang et al., 2015	Bushen Huoxue Decoction	NR	NR	Polygonatum sibiricum Redouté [Asparagaceae; Polygonati Rhizoma] 30 g, Rehmannig glutinosa Libosch. [Orobanchaceae; Rehmanniae radix praeparata] 15 g, Rehmannia glutinosa (Gaertn.) DC. [Orobanchaceae; Rehmanniae radix praeparata] 15 g, Cistanche deserticola Ma [Orobanchaceae; Cistanches Herba] 15 g, Astragalus mongholicus Bunge [Fabaceae; Astragali radix] 30 g, Panax quinquefolium L. [Araliaceae; Panacis Quinquefolii Radix] 10 g, Ginkgo biloba L. [Zingiberaceae; Ginkgo Folium] 15 g, Hirudo niponica Whitman [Hirudo; Hirudo] 2 g, Eupolyphaga sinensis Walker [Eupolyphaga; Eupolyphaga] 10 g, Alisma plantago-aquatica L. [Alismataceae; Alismatis rhizoma] 15 g, Acorus calamus var. angustatus Besser [Acoraceae; Acori tatarinowii rhizoma] 12 g, Polygala tenuifolia Willd. [Polygalaceae; Polygalae Radix] 10 g, Paeonia suffruticosa Andr. [Paeoniaceae; Moutan Cortex] 10 g, Actaea cimicifuga L. [Ranunculaceae; Cimicifugae rhizoma] 10 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma] 6 g	1 package bid po	Decoction	NR	NR
Yan and Guan 2019	Yizhi Mixture	Affiliated Hospital of Shandong University of Traditional Chinese Medicine	NR	Rehmannia glutinosa (Gaertn.) DC. [Orobanchaceae; Rehmanniae radix praeparata] 30 g, Gynochthodes officinali How [Rubiaceae; Morindae Officinalis Radix] 30 g, Codonopsis pilosula (Franch.) Nannf. [Campanulaceae; Codonopsis radix] 12 g, Ophiopogon japonicus (Thunb.) Ker Gawl. [Asparagaceae; Ophiopogonis radix] 15 g, Cuscuta chinensis Lam. [Convolvulaceae; Cuscutae Semen] 30 g, Ziziphus jujuba Mill.var.spinosa (Bunge) Hu ex H.F.Chou [Rhamnaceae; Ziziphi Spinosae Semen] 30 g, Polygala tenuifolia Willd. [Polygalaceae; Polygalae Radix] 6 g, Bupleurum Chinense DC. [Apiaceae; Bupleuri radix] 3 g, Paeonia lactiflora Pall. [Paeoniaceae; Paeoniae Radix Alba] 15 g, Poria cocos (Schw.) Wolf [Polyporaceae; Poria] 5 g, Salvia miltiorrhiza Bunge [Lamiaceae; Salviae Miltiorrhizae Radix Et Rhizoma] 9 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma] 3 g	50 ml bid po	Decoction	NR	NR
Yang 2017	Shenqi Yizhi Jiannao Recipe	Jiangsu Province Hospital of TCM	Partially reported[c]	Pseudostellaria heterophylla (Miq.)Pax ex Paxet Hoffm. [Caryophyllaceae; Pseudostellariae Radix] 10 g, Astragalus mongholicus Bunge [Fabaceae; Astragali radix] 10 g, Poria cocos (Schw.) Wolf [Polyporaceae; Poria] 10 g, Rehmannia glutinosa (Gaertn.) DC. [Orobanchaceae; Rehmanniae radix praeparata] 10g, Cornus officinalis Siebold & Zucc. [Cornaceae; Corni Fructus] 10 g, Panax	NR	Decoction	NR	NR

TABLE 2 (*Continued*) Components of Chinese herbal medicine used in the included studies.

Study	Prescription name	Source	Extraction process	Compositions	Usage of preparations	Preparations	Quality control reported?	Chemical analysis reported?
				notoginseng (Burkill) F.H.Chen [Araliaceae; Notoginseng radix et rhizoma] 5 g, Acorus calamus var. angustatus Besser [Acoraceae; Acori tatarinowii rhizoma] 10 g, Polygala tenuifolia Willd. [Polygalaceae; Polygalae Radix] 6 g, Alpinia oxyphylla Miq. [Zingiberaceae; Alpiniae Oxyphyllae Fructus] 10 g				
Yu 2018	Xuefu Zhuyu Decoction	NR	NR	Prunus persica (L.) Batsch [Rosaceae; Persicae semen] 15 g, Carthamus tinctorius L. [Asteraceae; Carthami Flos] 12 g, Angelica sinensis (Oliv.) Diels [Apiaceae; Angelicae Sinensis Radix] 15 g, Ligusticum chuanxiong Hort. [Apiaceae; Chuanxiong rhizoma] 12 g, Paeonia veitchii Lynch. [Paeoniaceae; Paeoniae Radix Rubra] 15 g, Rehmannig glutinosa Libosch. [Orobanchaceae; Rehmanniae radix praeparata] 15 g, Bupleurum Chinense DC. [Apiaceae; Bupleuri radix] 15 g, Paeonia lactiflora Pall. [Paeoniaceae; Paeoniae Radix Alba] 12 g, Citrus aurantium L. [Rutaceae; Fructus Aurantii] 12 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma] 10 g, Achyranthes bidentata Blume [Amaranthaceae; Radix Achyranthis Bidentatae] 15 g, Astragalus mongholicus Bunge [Fabaceae; Astragali radix] 20 g	200 ml bid po	Decoction	NR	NR
Yu et al., 2022	Bushen Jianpi Huoxue Recipe	NR	Partially reported[c]	Rehmannia glutinosa (Gaertn.) DC. [Orobanchaceae; Rehmanniae radix praeparata] 15g, Lycium barbarum L. [Solanaceae; Lycii fructus] 15g, Achyranthes bidentata Blume [Amaranthaceae; Radix Achyranthis Bidentatae] 15g, Astragalus mongholicus Bunge [Fabaceae; Astragali radix] 20g, Codonopsis pilosula (Franch.) Nannf. [Campanulaceae; Codonopsis radix] 15g, Atractylodes macrocephala Koidz. [Asteraceae; Atractylodis macrocephalae rhizoma] 15g, Angelica sinensis (Oliv.) Diels [Apiaceae; Angelicae Sinensis Radix] 15g, Prunus persica (L.) Batsch [Rosaceae; Persicae semen] 15g, Carthamus tinctorius L. [Asteraceae; Carthami Flos] 12g, Acorus calamus var. angustatus Besser [Acoraceae; Acori tatarinowii rhizoma] 15g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma] 6 g	250 ml bid po	Decoction	NR	NR
Zhang 2016	Yizhi Mixture	Affiliated Hospital of Shandong University of Traditional Chinese Medicine	Partially reported[c]	Rehmannia glutinosa (Gaertn.) DC. [Orobanchaceae; Rehmanniae radix praeparata] 150g, Ophiopogon japonicus (Thunb.) Ker Gawl. [Asparagaceae; Ophiopogonis radix] 75g, Ziziphus jujuba Mill.var.spinosa (Bunge) Hu ex H.F.Chou [Rhamnaceae; Ziziphi Spinosae Semen] 150g, Polygala tenuifolia Willd. [Polygalaceae; Polygalae Radix] 30g, Gynochthodes officinali How [Rubiaceae; Morindae Officinalis Radix] 150g, Cuscuta chinensis Lam. [Convolvulaceae; Cuscutae Semen] 150g, Codonopsis pilosula (Franch.) Nannf. [Campanulaceae; Codonopsis radix] 60g, Bupleurum Chinense DC. [Apiaceae; Bupleuri radix] 15g, Paeonia lactiflora Pall. [Paeoniaceae; Paeoniae Radix Alba] 75g, Poria cocos (Schw.) Wolf [Polyporaceae; Poria] 75g, Salvia miltiorrhiza Bunge [Lamiaceae; Salviae Miltiorrhizae Radix Et Rhizoma] 60g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma] 15 g	50 ml bid po	Decoction	NR	NR
Zhao et al., 2014	Bushen Huoxue Kaiqiao Recipe	NR	NR	Cistanche deserticola Ma [Orobanchaceae; Cistanches Herba] 10g, Acorus calamus var. angustatus Besser [Acoraceae; Acori tatarinowii rhizoma] 5g, Panax notoginseng (Burkill) F.H.Chen [Araliaceae; Notoginseng radix et rhizoma] 2.5 g	1 package tid po	Decocted preparation	NR	NR

NR, not reported; bid, twice a day; tid, three times a day.

[a]Extraction temperature and time and amount of the provoked extract were reported but not the amount of the initial solvent.

[b]Only the amount of provoked extract was reported.

[c]Referred to simply as "boiling."

FIGURE 2
Included studies' risk of bias plot.

FIGURE 3
Total effective rate meta-analysis forest plot.

FIGURE 4
FPG meta-analysis forest plot.

FIGURE 5
HbA1c meta-analysis forest plot. The subgroup analysis revealed that the benefits of TCM plus WM on lowering HbA1c surpassed that of the control group, irrespective of whether the duration was less than or equal to 2 months [p = 0.01, I^2 = 77%; MD = −0.68, 95%CI (−1.27, −0.09), p = 0.02], 3 months [p < 0.00001, I^2 = 94%; MD = −0.86, 95%CI (−1.38, −0.35), p = 0.001] or 6 months [p = 0.11, I^2 = 61%; MD = −0.32, 95%CI (−0.57, −0.07), p = 0.01].

Additionally, Egger's test was conducted for each outcome to evaluate the likelihood of publication bias, with a significance level of p < 0.05 indicating the presence of such bias. The examination disclosed the absence of publication bias across all indicators. A comprehensive review of the literature indicated that all studies were conducted in China and reported favorable results. These details are comprehensively presented in Table 4. Therefore, it was postulated that the presence of publication bias could potentially be associated with geographical location, racial demographics, and the non-publication of negative findings.

3.5 Evidence quality rating of outcome indicators

The GRADE pro software was employed to assess the quality of evidence. The primary outcome measure, total effective rate, demonstrated a moderate level of reliability, whereas the majority

of outcome indicators were deemed to be of low-quality evidence. In addition, two outcome indicators, including TNF-α and AD, were graded as very low-quality evidence (Table 5).

4 Discussion

4.1 Summary of evidence

In recent times, there has been a significant surge in the worldwide prevalence of diabetes mellitus. Data from the World Health Organization has emphasized that the estimated prevalence of diabetes is currently approaching 463 million adults with projection rising to 700 million by 2,045 years (Sun et al., 2022). Concurrently, the cognitive decline linked to diabetes has emerged as a growing area of concern. Substantial evidence has substantiated that DM serves as a significant etiological factor for cognitive impairments, which may subsequently advance to dementia

FIGURE 6
MoCA score meta-analysis forest plot.

TABLE 3 Meta-analysis of the 7 items of MoCA scale.

Outcomes	Meta-analysis results		Effect model	Heterogeneity test	
	MD (95%CI)	p-value		p-value	I² (%)
Visuospatial and Executive	0.54 (0.15, 0.93)	0.007	Random	<0.00001	87
Naming	0.07 (−0.01, 0.14)	0.08	Fixed	0.38	5
Attention	0.57 (0.44, 0.69)	<0.00001	Fixed	0.52	0
Language	0.34 (0.24, 0.45)	<0.00001	Fixed	0.31	17
Abstraction	0.31 (0.07, 0.56)	0.01	Random	<0.00001	90
Memory and Delayed recall	0.39 (0.26, 0.52)	<0.00001	Fixed	0.21	32
Orientation	0.21 (−0.01, 0.43)	0.06	Random	<0.0001	85

FIGURE 7
MMSE score meta-analysis forest plot.

FIGURE 8
TNF-α meta-analysis forest plot.

FIGURE 9
TCM syndrome score meta-analysis forest plot.

FIGURE 10
Adverse reaction meta-analysis forest plot.

(Datusalia and Sharma, 2016). The epidemiological data have long shown that T2DM populations are at significantly higher risk for developing cognitive deficits and dementia compared with healthy individuals (Seto et al., 2015; Bello-Chavolla et al., 2019). Moreover, a meta-analysis of such studies comprising 25 studies found that the T2DM had an approximately 50% and 60% greater risk of

developing DACD and dementia, respectively (Cukierman et al., 2005). However, there is currently no vaccine or specific medicine for DACD. Hence, it is of great significance to identify novel and better anti-DACD drugs and explore new therapeutic schemes.

The application of syndrome differentiation in treatment represents a distinctive feature of the theoretical framework of

TABLE 4 Summary of sensitivity analysis and publication bias.

Indicators	OR/MD fluctuations	95%CI fluctuations	Publication bias (*p*-value)	
			Begg's test	Egger's test
Total effective rate	4.94	(3.56, 6.85)	0.077	0.081
FPG	−0.37	(−0.59, −0.15)	0.721	0.498
HbA1c	−0.99	(−1.43, −0.57)	0.533	0.160
MoCA score	0.99	(0.71, 1.27)	0.837	0.781
MMSE score	0.97	(0.62, 1.32)	1.000	0.141
TCM syndrome score	−1.28	(−1.82, −0.74)	0.213	0.213
TNF-α	−1.35	(−1.98, −0.72)	1.000	0.825
Adverse reaction	0.42	(0.26, 0.69)	0.260	0.366

TCM, and it holds that "Xiao Ke," the signs of which are recognized as common symptoms of diabetes mellitus in modern medicine, is caused by the interaction of multiple factors, including advanced age, poor diet, emotional and mental disorders, viscera deficiency, and the depletion of a long-term illness. Its pathogenesis is determined as dryness-heat due to deficiency of yin, further resulting in disorder of viscera function and insufficiency of Qi and blood, Yin and Yang, gradually developing the combination of blood stasis and phlegm turbidity that may obstruct the meridians of brain, and eventually leading to the onset or aggravate of "Xiao Ke" complicated with "Chi Dai," the symptoms of which are considered as analogous to DACD in modern medicine (Yang et al., 2021).

With an apparent dissatisfaction with the effect of conventional treatments, a growing number of DACD sufferers are turning to alternatives medicine, particularly TCM or integrated TCM and WM. It is of note that the integrated TCM and WM therapy has been shown to be more effective than single conventional treatment in improving the effectiveness of DACD and alleviating the side effects (Cai, 2016; Chen et al., 2021; Fu et al., 2017; Gao et al., 2017; Jin et al., 2015; Li, 2022; Li, 2016; Li et al., 2022; Liu et al., 2016; Mao et al., 2019; Tian et al., 2021; Wang et al., 2016; Wang, 2015; Wang et al., 2015; Yan and Guan, 2019; Yang, 2017; Yu, 2018; Yu et al., 2022; Zhang, 2016; Zhao et al., 2014). To date, integrated TCM and WM therapy for DACD has been reported increasingly, conversely, high-quality meta-analysis remains scarce. Here, we aimed to assess the efficacy and safety of integrated TCM and WM therapy for DACD and provide high quality evidence for its clinical therapeutic effects in this context.

The present meta-analysis incorporated 20 RCTs that met the inclusion criteria and included 1,570 subjects in total. In terms of total effective rate, the meta-analysis indicates that integrated TCM and WM therapy for DACD was superior to that of WM alone, possibly by improving glucose toxicity, membrane signal disorder, homeostasis imbalance, inflammation, oxidative stress injury and vascular diseases (Fiatarone Singh et al., 2014; Tian et al., 2016). Meanwhile, the combination therapy could significantly alleviate the TCM syndrome scores. Moreover, prolonged elevation of blood glucose levels has been demonstrated to exert detrimental effects on cognitive abilities and cerebral morphology (Thal et al., 2012). In our investigation, we evaluated both HbA1c and FPG as a composite

measure to aid in the assessment of glycemic control. We confirmed that compared with WM alone, integrated TCM and WM therapy exhibited advantages in improving fasting plasma glucose and HbA1c levels. In addition, MMSE and MoCA most probably reflected lesion-associated cognitive impairments (Dong et al., 2010). Thus, we selected MMSE and MoCA for assessing cognitive function in the present meta-analysis. Our results demonstrated that the integrated TCM and WM significantly enhanced the MMSE and MoCA scores in DACD patients, indicating that the combination therapy is beneficial for the improvement of cognitive function. It has been reported that inflammation is associated with the onset of T2DM and progression of its complications, especially DACD. TNF-a is a cytokine with pro-inflammatory properties that was related to both T2DM and cognitive decline (Chu, 2013; Khosravi et al., 2013; Martínez-Mármol et al., 2019). Meta-analysis results showed that the combination therapy could lead to a mean greater reduction in TNF-α level, with statistically significant. Regarding safety, it suggested that the safety of integrated TCM and WM therapy was comparable to that of the WM alone.

4.2 Advantages and limitations

To our knowledge, this is the first meta-analysis to quantitatively estimate the beneficial effect of the integration of TCM and WM therapy for DACD, providing better evidence-based evaluation for the domestic and international researchers to understand this issue. Following the Cochrane Collaboration's guidelines, the objective is to derive more comprehensive conclusions. The inclusion of additional outcome measures, like FPG, HbA1c, MoCA score, MMSE score, TNF-α, and TCM syndrome score, enables a multidimensional and multilevel assessment of the effectiveness of integrating traditional Chinese medicine (TCM) and Western medicine (WM) for treating DACD.

Despite our critical evaluation of the currently available evidence, some potential limitations should not be ignored. First and foremost, the methodological quality of our included studies was generally poor. The majority of the included trials were rated as "moderate" or "high" bias risk due to insufficient information on randomization process, allocation concealment, and methods of

TABLE 5 GRADE evidence quality of outcomes included in the literature.

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Experimental	Control	Relative	Absolute	Quality	Importance
			Quality assessment				No. of patients		Effect			
Total Effective Rate												
13	RCT	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	430/494 (87%)	293/493 (59.4%)	OR 4.94 (3.56–6.85)	284 more 1,000 (from 245 more to 315 more)	Moderate	Critical
								66.7%		241 more per 1,000 (from 210 more to 265 more)		
FPG												
10	RCT	Serious[a]	Serious[b]	No serious indirectness	No serious imprecision	None	396	394	-	MD 0.3 lower (0.49–0.1 lower)	Low	Important
HbA1c												
11	RCT	Serious[a]	Serious[b]	No serious indirectness	No serious imprecision	None	436	434	-	MD 0.71 lower (1.03–0.4 lower)	Low	Important
MoCA Score												
12	RCT	Serious[a]	Serious[b]	No serious indirectness	No serious imprecision	None	528	523	-	MD 2.52 higher (1.75–3.3 higher)	Low	Important
MMSE Score												
11	RCT	Serious[a]	Serious[b]	No serious indirectness	No serious imprecision	None	401	401	-	MD 2.31 higher (1.33–3.29 higher)	Low	Important
TNF-α												
3	RCT	Serious[a]	Serious[b]	No serious indirectness	Serious[c,d]	None	160	160	-	MD 8.28 lower (13.12–3.44 lower)	Very low	Important
TCM Syndrome Score												
7	RCT	Serious[a]	Serious[b]	No serious indirectness	No serious imprecision	None	233	229	-	MD 5.97 lower (9.06–2.88 lower)	Low	Important
Adverse Reaction												
6	RCT	Serious[a]	Serious[b]	No serious indirectness	Serious[c]	None	28/247 (11.3%)	57/243 (23.5%)	OR 0.4 (0.12–1.31)	125 fewer 1,000 (from 199 fewer to 52 more)	Very low	Important
								18.6%		102 more per 1,000 (from 159 fewer to 44 more)		

[a]Some study randomization methods, allocation concealment, and blinding are not described.
[b]Heterogeneity is significantly higher.
[c]The 95% Cl crosses the invalid line.
[d]Fewer included articles and observers.

blinding outcome assessors. In particular, double-blinding was not conducted in all of the included studies. When both herbal decoction and WM are used as interventions, it is difficult to perform blinding due to their differences in external characteristics. Moreover, the review found that protocol registration information, quality control and chemical profile were not reported in any of the included studies, which has led to controversial conclusions. Second, despite the fact that sensitivity analysis verified the reliability of our findings, there was substantial heterogeneity in several of them. The clinical diagnosis and treatment of TCM rely on a comprehensive assessment of various factors, including the patient's symptoms, tongue image, and pulse image, known as syndrome differentiation. Subsequently, treatments are tailored based on the identified TCM syndrome type, indicating that patients with distinct syndromes receive different medications, potentially resulting in heterogeneity. Additionally, the variability in composition and dosage of Chinese herbal medicine, along with diverse outcome indicators, may contribute to further heterogeneity in the study results. Furthermore, the presence of diverse western medicine interventions utilized in the control group constitutes an inherent factor contributing to the observed heterogeneity. Third, it is noteworthy that the studies encompassed within this research were exclusively conducted in China and published solely in the Chinese language. Consequently, the validation of our findings becomes imperative in order to ascertain the applicability of TCM in broader samples, diverse countries, and various ethnic groups. Fourth, Chinese clinical trials have become a relatively standardized, safe procedure in the last decade, and thus strict temporal constraints of the present study was made to uphold the study's quality standards. However, this selection process led to the exclusion of a considerable number of studies that did not meet the intervention or diagnostic criteria. Thereafter, the insufficient number of included studies hindered the resolution of heterogeneities. Furthermore, a majority of the included studies had small sample sizes, which appeared to be one risk in exaggerating intervention benefits. Last but no the least, there is a dearth of studies that have presented follow-up data on the combination of TCM and WM in the treatment of DACD. Given the chronic and progressive nature of DACD, characterized by potential fluctuations over an extended period, it is imperative to conduct ongoing follow-up assessments to determine the true efficacy and long-term consequences of this therapeutic approach. Regrettably, the majority of studies have been limited by short treatment durations, with none of them encompassing long-term follow-up observations.

4.3 Implications for clinical practice and future research

Over the past dozen years, the integration of TCM and WM therapy is being increasingly investigated for their use in the treatment of DACD. However, the choice of Chinese herbal medicine is empirical and there is a lack of consensus among clinicians. The evidence available from our study demonstrated the effectiveness and safety of CHM therapy for DACD, which is able to offer a comprehensive and transparent framework for promoting clinical practice guidelines. Importantly, extensive and in-depth data

mining in applying TCM to the treatment of DACD is conducive to inherit the clinical experience of ancient TCM, boost the understanding of the theory and practice of TCM in DACD treatment and enrich the treatment options for treating DACD. The findings from our study provide evidence supporting the efficacy and safety of the above-mentioned therapy for DACD, thereby offering a comprehensive and transparent framework for the promotion of clinical practice guidelines. Notably, the extensive and thorough study in the application of TCM for DACD treatment facilitates the preservation of ancient TCM clinical experience, enhances the comprehension of TCM theory and practice in DACD treatment, and expands the range of treatment options available for DACD management.

In light of our findings and aforementioned limitations, several recommendations can be made for future research and clinical practice. Firstly, it is recommended that multi-center studies with larger sample sizes be undertaken in order to augment the representativeness and reliability of the findings. Secondly, the efficacy of Traditional Chinese Medicine (TCM) hinges upon the precise differentiation and treatment of the syndrome, thus it is advisable to establish an evaluation system for assessing therapeutic effects that aligns with the distinctive attributes of TCM, and to explore pragmatic and discerning indicators for TCM. Thirdly, investigations pertaining to TCM ought to enhance their protocols and prioritize quality control, with particular emphasis on the meticulous implementation of randomization, blinding, and allocation concealment. We advise designing and reporting RCTs of DACD strictly according to the CONSORT 2010 statement (Schulz et al., 2010) and the CONSORT Extension for Chinese Herbal Medicine Formulas 2017 (Cheng et al., 2017). Fourthly, incorporating an appropriate follow-up period that aligns with the characteristics of the disease, in order to conduct longer-term research and clinical trials to confirm the long-term safety of TCM on DACD, explore the optimal dosage, duration of treatment, and potential adverse events, thereby providing valuable clinical insights. Fifthly, considering the research prospects associated with Chinese herbal medicines in the treatment of diabetes and its diverse complications, clinical and animal experimental studies focusing on the active ingredients of Chinese herbal medicines may elucidate the specific effects and intrinsic mechanisms of treating DACD, which could increase the evidence base for the clinical application of TCM in DACD as well as promote the inclusion of TCM in relevant international guidelines.

5 Conclusion

This systematic review has found some promising evidence for the integration of TCM and WM therapy in the treatment of DACD. Compared to WM alone, the integration of TCM and WM therapy appears to show a more favorable therapeutic effect. Meanwhile, it holds great potential in alleviating blood glucose, improving cognitive function, and reducing inflammation.

However, it is crucial to consider the limitations to the evidence base, notably the low methodological quality and small sample sizes of the included studies. These factors highlight the need for further research into the use of TCM for DACD. Specifically, we urgently need high-quality, multi-center studies with larger samples to strengthen the evidence supporting the clinical use of TCM for DACD. This kind of robust research is essential to guide clinical decision-making and to optimize patient care in the future.

Author contributions

JS: Conceptualization, Data curation, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing–original draft, Writing–review and editing. GS: Investigation, Methodology, Software, Supervision, Validation, Writing–original draft, Writing–review and editing. JA: Data curation, Investigation, Methodology, Software, Validation, Writing–original draft, Writing–review and editing. YA: Data curation, Formal Analysis, Investigation, Methodology, Writing–review and editing. JL: Data curation, Formal Analysis, Investigation, Methodology, Writing–review and editing. ZS: Investigation, Methodology, Resources, Software, Visualization, Writing–review and editing. LZ: Investigation, Methodology, Resources, Software, Visualization, Writing–review and editing. SZ: Investigation, Methodology, Writing–review and editing. YY: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing–review and editing. YS: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1280736/full#supplementary-material

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Characteristics of elderly diabetes patients: focus on clinical manifestation, pathogenic mechanism, and the role of traditional Chinese medicine

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Diabetes mellitus has become a major public health issue globally, putting an enormous burden on global health systems and people. Among all diseased groups, a considerable part of patients are elderly, while their clinical features, pathogenic processes, and medication regimens are different from patients of other ages. Despite the availability of multiple therapies and techniques, there are still numerous elderly diabetes patients suffering from poor blood glucose control, severe complications, and drug adverse effects, which negatively affect the quality of life in their golden years. Traditional Chinese Medicine (TCM) has been widely used in the treatment of diabetes for several decades, and its relevant clinical practice has confirmed that it has a satisfactory effect on alleviating clinical symptoms and mitigating the progression of complications. Chinese herbal medicine and its active components were used widely with obvious clinical advantages by multiple targets and signaling pathways. However, due to the particular features of elderly diabetes, few studies were conducted to explore Traditional Chinese Medicine intervention on elderly diabetic patients. This study reviews the research on clinical features, pathogenic processes, treatment principles, and TCM treatments, hoping to provide fresh perspectives on the prevention and management strategies for elderly diabetes.

KEYWORDS

elderly diabetes, traditional Chinese medicine, clinical manifestation, pathogenic mechanism, treatment

1 Introduction

Diabetes mellitus (DM) is characterized by an absolute or relative lack of insulin creation as well as insulin resistance (IR) in target tissues, which leads to hyperglycemia and glucose intolerance (Ma et al., 2022). It can be classified into four types: type 1 diabetes (T1DM), type 2 diabetes (T2DM), gestational diabetes, and diabetes driven by islet disease or medicines (Fan et al., 2022; Yang and Yang, 2022). With an expanding lifespan and conversion in diet structure, the number of patients with diabetes-related high-risk factors increases, which contributes to the increased prevalence of diabetes, especially among elderly people (LeRoith et al., 2019). Elderly diabetes refers to the patients above the age of

TABLE 1 Clinical trials of TCM in complications with elderly diabetes.

Disease	Reported TCM intervention in elderly diabetes	Ref. #
Breast cancer	Di Huang Wan series	Wu et al. (2018)
Hyperglycemia	health management, TCM dietary scheme, TCM syndrome differentiation and treatment, Sini decoction, TCM tea	Xu, 2019; Zhuang (2019), Wang, (2020); Wu et al. (2021), Li Y. et al. (2022), Lin et al. (2023)
IR	Goshajinkigan, Jinlida, TCM syndrome differentiation and treatment	Uno et al. (2005), Tian et al. (2018), Tsai et al. (2020)
CHD and Atherosclerosis	Acupuncture, TCM syndrome differentiation and treatment	Zhang et al. (2008), Fang et al. (2015)
Diabetic foot	ARCC (Angelica, Angelica, Calcined Gypsum and Caleramide), NF3 (Astragali Radix and Radix Rehmanniae)	Ko et al. (2014), Zhong et al. (2022)
DKD	Liu-Wei-Di-Huang-Wan, Qi-Kui granules, TCM syndrome differentiation and treatment	Gong, 2013; Hsu et al. (2014), Wang L. et al. (2023)
DPN	Acupuncture	Meyer-Hamme et al. (2021)
Stroke	TCM syndrome differentiation and treatment, Bu Yang Huan Wu Tang, Tongluo Xifeng formula	Ma and Xia (2017), Tsai et al. (2017), Chiao et al. (2018), Weng et al. (2021)
DR	Mingmu Dihuang decoction, Zhenwu decoction	Zhong, 2018; Li (2022)
Hyperhidrosis	Yupingfeng power	Chang et al. (2021)
Constipation	Modified Sini power, modified Jichuan decoction	Feng and Tong (2009), Li T. et al. (2018)

Abbreviations: Diabetic peripheral neuropathy (DPN); Diabetic kidney disease (DKD); Insulin resistance (IR); Traditional Chinese Medicine (TCM); Diabetic retinopathy (DR).

TABLE 2 Registered clinical trials on the elderly diabetes.

Main ID	Country	TCM intervention	Disease	Expected endpoints	Status
IRCT20201128049510N1	Iran	Mulberry leaf extract	Elderly diabetes	cardiovascular inflammatory markers	Recruiting
ChiCTR2300075132	China	Bushen Tongmai Recipe	Elderly diabetes complicated with ASCVD	Blood lipids, Crouse plaque points, inflammation factor	Pending
RBR-75qb7pp	Brazil	curcumin supplementation	elderly women	glycemic levels, lipid profile and body weight	Recruitment completed
ITMCTR2000003276	China	Sancai powder	Elderly diabetes	blood glucose level, glycemic variability	Pending
ChiCTR2000039049	China	Yi-Jin-Jing	Middle-aged and elderly obese people with pre-Diabetes	Bone mineral density, FGF23 and other markers of bone metabolism	Recruiting
ChiCTR1800020069	China	Qigong and Tai Chi	Middle-aged and elderly diabetes	glycemic levels, C-peptide	Completed
IRCT2015080822466N2	Iran	Herbal combination	pre-diabetic elderly	glycemic levels	Completed
RBR-2sgtn2	Brazil	Green Tea	elderly Metabolic Syndrome	abdominal circumference	Not yet recruiting

sixty, including patients diagnosed with diabetes before the age of sixty and patients diagnosed with diabetes after the age of sixty (Chinese Elderly Type 2 Diabetes Prevention and Treatment of Clinical Guidelines Writing Group et al., 2022). According to prior studies, around 28.8% of Chinese individuals aged 60–69 suffered from diabetes. This figure jumped to 31.8% among those aged over 70, which was significantly higher than young and middle-aged populations (Li et al., 2020). However, the present knowledge, diagnosis, treatment, and self-management capacity of elderly diabetes patients is inadequate, which causes the blood glucose level out of control (Chinese Elderly Type 2 Diabetes Prevention and Treatment of Clinical Guidelines Writing Group et al., 2022). Many people were first diagnosed with diabetes because of serious complications such as ischemic cardiovascular and cerebrovascular

disease. This not only greatly affects patients' quality of life, but also creates an enormous burden on society and the medical system.

Current treatments for diabetes include insulin secretagogues, biguanides, insulin sensitizers, alpha-glucosidase inhibitors, incretin mimetics, amylin antagonists, and sodium-glucose co-transporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptors agonists (Padhi et al., 2020). Though these drugs can enhance insulin sensitivity, promote insulin secretion, and improve metabolic disorders, there are still a large number of patients suffering from poor blood glucose control, serious complications and drug side effects. Previous studies have shown that Traditional Chinese Medicine (TCM) was extremely effective in stabilizing blood glucose fluctuations, preventing the occurrence of brittle diabetes, slowing the development of complications, and enhancing patients' life quality

FIGURE 1
Pathogenesis of elderly diabetes. **(A)**, gut microbiota. The lack of *Firmicutes* and *Bacteroidetes* in the elderly may result in a decrease of SCAFs, and then put the intestines and pancreatic beta cells in a state of immune disorder and inflammation, leading to disorders of blood sugar homeostasis and metabolism. **(B)**, cellular senescence. Aging adipocytes disrupt the insulin signaling pathway by secreting SASP and regulating the expression of aging-related genes. At the same time, reduced volume of brown and beige adipose tissue and significantly reduced expression of genes related to thermogenesis and differentiation both jointly aggravate IR. In senescent islet cells, the expression of Ins1, Pdx1, Mafa, and Neurod1 decreases, and the expression of aging-related markers p16, p21, and SASP increases. **(C)**, oxidative stress, and mitochondrial dysfunction. Changes in skeletal muscle mitochondrial function, reduced ATP synthesis, and increased ROS production may be the causes of skeletal sarcopenia in the elderly with diabetes. Impaired mitochondrial oxidative function in skeletal muscle leads to excessive lipid deposition, increased CER and DAG, and further exacerbates oxidative stress, inflammation and diabetes. **(D)**, Immune and inflammatory. Elderly patients with diabetes are often accompanied by disorders of lipid metabolism, which activates related inflammatory pathways such as JNK and NF-κB, which in turn leads to the activation of pro-inflammatory factors such as NLRP3, caspase-1, TNF-a, CRP, IL-6 secretion and pro-IL-1β, pro-IL-18 cleavage increased. At the same time, the expression of anti-inflammatory factors such as IL-10 is reduced. In terms of immunity, the main manifestations are the shortened duration of immune memory, accumulation of memory T cells, the lack of immune response to neoantigens, and a higher tendency to autoimmunity, further induced the occurrence of IR and diabetes. **(E)**, Epigenetics. Epigenetic research on diabetes mostly focuses on DNA methylation. Methylation of ABCG1, P1, SHOSPHO3, SREBF1 and TXNIP is associated with a higher risk of T2DM; methylation of ABCG1, PHOSPHO3, SOCS1, SREBF2 and TXNIP is associated with T1DM. Different tissues have different methylation sites. In the pancreatic tissue of T2DM patients, the methylation sites are TCF7L2, KCNQ1, THADA, FTO, IRS1, PPARG, PDX1, PAX4 and GLP1R; in the skeletal muscle tissue, the methylation sites are CXCL4, FADS2, MAPK1, PPARGC1A and other sites; in adipose tissue, the methylation sites are ATP10A, IRS1, JARID2, KCNQ1, NDUFB4, PPARG and TCF7L2.

(Tian et al., 2019). Therefore, attention has steadily been drawn to comprehensive regimens with integrative medicine for diabetes.

Pathogenic pathways peculiar to elderly diabetes include gut microbiota disturbance, cell senescence, mitochondrial failure, oxidative stress, and alterations in epigenetic expression. Also, many Chinese herbs (such as *Puerariae Lobatae, Radix Scutellaria baicalensis Georgi, Salvia miltiorrhiza*) play a role in elderly diabetes through the aforementioned mechanisms (Xiao et al., 2020; Wang et al., 2022c; Yingrui et al., 2022; Niu et al., 2023). Furthermore, different Chinese medicine formulations may be chosen for symptomatic therapy based on the stage of diabetes to fully exert the advantage of TCM. Here, we

reviewed the characteristics, pathogenesis and related TCM treatments of elderly diabetes, and analyzed the research status and potential clinical situations.

2 Clinical features in elderly diabetes

2.1 Invisible typical symptoms

The typical symptoms of DM are excessive intake of water and food, urination, and weight loss, which are invisible in elderly

FIGURE 2
TCM interventions and potential mechanisms related to elderly diabetes. Abbreviations: Diabetic peripheral neuropathy (DPN); Diabetic kidney disease (DKD); Insulin resistance (IR).

populations. These symptoms can be important hints for diagnosis in young and middle-aged people, but in elderly people they are masked or manifested with other atypical symptoms due to a variety of factors such as reduced body functions due to natural aging, diseases, medications, and other factors.

It should be noted that polyuria due to DM is an increase in the volume of urine. Many diseases of the elderly, such as prostate enlargement in men and urinary tract infections in women, leads to an increase in the frequency of urination, which can be distinguished from polyuria due to DM. In addition to DM, excessive thirst and intake of water are also common in the elderly (El Osta et al., 2014; Islas-Granillo et al., 2017). Previous studies have shown that the majority of older adults experience hyposalivation or dry mouth, which may be associated with a decrease in the number of teeth in the mouth, aging, the female gender, and other diseases (hypertension, cardiovascular disease, neurologic disorders, and psychological disorders) (van der Putten et al., 2003; Flink et al., 2008; Abdullah, 2015; Ohara et al., 2016). Therefore, diseases with the same characteristics as diabetes tend to mask those symptoms of the elderly, which also shows the limitations of diabetes diagnosis relying on symptoms and physical examination screening.

In elderly groups, the syndromes of diabetes may manifest itself in other forms. Diminished pressure receptor-mediated regulation of thirst in that weakens physical function of Aging body, induces higher thirst osmolality set point (Koch and Fulop, 2017). The symptoms of excessive thirst and drinking could be replaced by fatigue and cognitive deficits (Hoen et al., 2021). Diabetes causes glycation of blood fibrinogen and decreased production of fibrinolytic enzymes, which directly affects fibrinolysis and leads to hypercoagulable state (Ajjan et al., 2013). Excessively coagulated blood increases the risk of stroke, acute coronary syndrome, or intermittent claudication in elderly. Thus, all of these atypical forms of morbidity may act as the initial symptoms of elderly diabetes (Mordarska and Godziejewska-Zawada, 2017).

2.2 High risk of hypoglycemia

Hypoglycemia is more common in the elderly diabetic populations. A cohort study based on 987 elderly diabetic patients showed that about one-third of the elderly patients have hypoglycemia, within 3.3% of cases were severe (Bordier et al., 2015). As well known, hypoglycemia in the elderly is closely related to anti-diabetes regimens like sulfonylureas and insulin (Ling et al., 2021).

Decreased autonomic function due to aging results in a reduced response intensity to hypoglycemic symptoms in elderly diabetic patients. n healthy individuals, aging also allows attenuation of blood glucose recovery and reductions of counter-regulatory responses. For example, emerging warning signals associated with hypoglycemia (such as sweating, shivering, or hunger) generated by stimulation of adrenergic system, may not be present in the elderly

TABLE 3 Representative examples of major anti-diabetic effects of TCM ingredients, herbs and formulations, as well as potential mechanisms related to elderly diabetes.

Bioactive ingredients	Representive herbs	Related formulations	Disease	Beneficial effects	Potential mechanism	Ref. #
Berberine	Huanglian	Gegen Qinlian decoction, Fufang Zhenzhu Tiaozhi capsule, Qijian mixture, Huanglian jiedu decoction	DPN, coronary atherosclerosis, DKD, DCD	modulating inflammation, alleviating apoptosis, and inhibiting EndMT of coronary artery, regulate mitochondrial energy homeostasis	①②③④⑤	Gao et al. (2018), Dong et al. (2019), Meng et al. (2021), Wang et al. (2022b)
Quercetin	-	Not available	DPN	reduces inflammation	①②③④⑤	B et al., 2021; Dhanya (2022), Roshanravan et al. (2023)
Resveratrol	-	Not available	DKD, CHD, obesity, and IR	improves intestinal barrier function and ameliorates intestinal permeability and inflammation	①②③④⑤	Cai et al. (2020), Huang et al. (2020)
Ginsenoside	Panax ginseng, Panax notoginseng	Baihu renshen decoction, Dan-qi prescription, Huanglian Maidong Decoction	Pre-diabetes, hyperglucose, IR and obesity	anti-diabetic, anti-hyperlipidemic, anti-inflammatory, and hepatoprotective	①②③④⑤	Xie et al. (2015), Fan et al. (2019), Zhou et al. (2019), He et al. (2021), Naseri et al. (2022)
ML polysaccharides	mulberry (Morus alba L.) leaves	Sansang Buxu decoction	hyper glucose, and IR	prevent glucolipid metabolism disorders, alleviating liver and kidney damage	①②③④⑤	Chen et al. (2022a), Tang et al. (2023)
Astragaloside	Astragalus membranaceus (Fisch.) Bunge	Huangqi Guizhi Wuwu decoction, Huangqi decoction, Qidan junzhi decoction	DPN, DKD, DR	antioxidant, anti-inflammatory, anti-apoptotic properties, and the roles in enhancement of immunity, attenuation of the migration and invasion of cancer cells and improvement of chemosensitivity	①②③④⑤	Shen et al. (2023a)
Tanshinone	Salvia miltiorrhiza	Danshenyin, Danggui Buxue Decoction, Compound Danshen Dripping Pills	DKD, DR	anti-oxidative stress, anti-inflammatory, anti-EMT effects	③④	Wang et al. (2020a), Zhang et al. (2021b), Guo et al. (2021), Sun et al. (2022)
Wogonin	Scutellaria baicalensis Georgi	Tourexiaozhen formula	DKD	anti-inflammatory, anti-apoptotic, anti-oxidative, and cell cycle regulatory effects	②③④⑤	Wang et al. (2018)

Note: ① Gut microbiota, ② Cellular senescence, ③ Oxidative stress and Mitochondrial dysfunction, ④ Immune and inflammatory, ⑤ Epigenetics.
Abbreviations: Diabetic peripheral neuropathy (DPN); Diabetic kidney disease (DKD); Insulin resistance (IR); Epithelial-mesenchymal transition (EMT); Diabetic cognitive dysfunction (DC); Coronary heart disease (CHD).

(Mordarska and Godziejewska-Zawada, 2017). In addition, negative feedback regulation to glucagon secretion often becomes inadequate and limited.

2.3 Increased incidence of complications and coexisting disorders

In the natural course of diabetes, the incidence of complications increases with the duration of diabetes, making elderly adults at high-risk for microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (coronary heart disease, stroke, peripheral arterial disease) complications of DM (Gregg et al., 2002). It has been shown that the most common cardiovascular complications in

elderly patients with diabetes are coronary heart disease, followed by lower extremity vascular disease, cerebrovascular disease, and heart failure (Sinclair et al., 2015; Bauduceau et al., 2018). Also, gradual loss of skeletal muscle mass, cognitive impairment, depression, urinary incontinence, falls, fractures, and other geriatric syndromes are often comorbid or concomitant. Elderly patients with T2DM have accelerated loss of lean leg mass, muscle strength and functional capacity compared to the normoglycemic group (Leenders et al., 2013). Plasma dipeptidyl peptidase-4 activity was shown to be independently associated with mild cognitive impairment in elderly T2DM (Zheng et al., 2016). Indian survey shows that nearly one-fifth of elderly diabetes patients are suffering from depression, urban living and financial support can prevent the occurrence of depression (Sodhi et al., 2023). Diabetes duration,

neuropathy and albuminuria are risk factors for urinary incontinence in elderly women with diabetes and are particularly associated with severe incontinence (Vischer et al., 2009). Increased risk of hip fracture is seen primarily in patients treated with insulin, while T2DM patients treated with any glucose control medication are consistently at increased risk of non-skeletal fall injuries (Wallander et al., 2017).

Compared to those clinical features of young and middle-aged adults, the problems faced by elderly population, include the characteristics of invisible typical symptoms, high risk of hypoglycemia, and increased incidence of complications and coexisting disorders (macrovascular and microvascular lesions, sarcopenia, cognitive dysfunction, depression, urinary incontinence, falls, and fracture). For these reasons, screening, and prevention of progression from prediabetes to diabetes are particularly important. According to the guideline (LeRoith et al., 2019), fasting glucose and/or HbA1c screening is recommended every 2 years for elderly population without diabetes, lifestyle interventions for those with pre-diabetes, and 2-h oral glucose tolerance test for those with established diabetes. Elderly diabetes patients should also undergo fingertip glucose testing as part of their daily testing regimen and regular cognitive screening.

3 Pathogenesis of elderly diabetes

3.1 Gut microbiota disturbance

Pathogenesis of elderly diabetes (including Gut microbiota disturbance, Cellular senescence, Oxidative stress and mitochondrial dysfunction, Immune and inflammatory, and Epigenetics) has been summarized. Relevant details are indicated at Figure 1. A huge number of microorganisms such as bacteria, archaea, fungi, viruses, and phages habitats in gastrointestinal tract (Wang J. et al., 2023). The gut microbiota prototype forms prenatally, undergo rapid establishment during the neonatal and infancy stages, evolves with growth and becomes virtually stable in adulthood (Zhuang et al., 2019). Changes in the structure and quantity of gut microbiota, which serve as pathogenic mechanisms in chronic noncommunicable illnesses (Illiano et al., 2020), may have an impact on corresponding activities such as food digestion (Paone and Cani, 2020), energy metabolism (Li M. et al., 2022), immunological and genetic modulation (Wiertsema et al., 2021; Xu et al., 2023), as well as the integrity of the intestinal barrier (Adolph et al., 2019; Paone and Cani, 2020).

In 1907, Elie Metchnikoff postulated that one of the factors contributing to the decline in physical health was the gut microbiota and its metabolites (Cavaillon and Legout, 2016). In recent years, there has been a growing awareness of the correlation between gut microbiota and aging process. It had shown that gut microbiota was extremely different between the elderly and young population, manifested by a decrease in species diversity and probiotics, an increase in individual differences and harmful bacteria (Duncan and Flint, 2013; Mangiola et al., 2018). After comparing the gut microbiota between the elderly and young population in South

Korea, Seung Yun Lee et al. found that *Firmicutes*, *Bacteroidetes*, *Cyanobacteria*, *Fusobacteria*, and *Proteobacteria* were more common in young people, while the abundance of *Negativicutes* was higher in the elderly (Lee et al., 2021). Furthermore, Tianyi Li et al. (Li et al., 2019) and Yongcheng Ni et al. (Ni et al., 2018) discovered that *Firmicutes* abundance was positively correlated with blood glucose level and sensitivity to insulin treatment in elderly T2DM patients, while the abundance of anaerobic bacteria (such as *Bacteroidetes*) was negatively correlated. *Firmicutes* are the major butyrate-producing bacteria in the human body, while *Bacteroidetes* are mainly acetate and propionate producers (Tsai et al., 2021). Previous research has revealed that short chain fatty acids, (SCFAs) including acetate, propionate (Chambers et al., 2015a; Wu et al., 2022), and butyrate (Gao et al., 2009; Chang et al., 2014; Mollica et al., 2017; Zhang et al., 2017; 2019; Li Z. et al., 2018; Stachowska et al., 2021) may target G protein-coupled receptors (GPCRs) such as FFAR2、FFAR3、GPR109A on the intestine, pancreatic islets, and immune cells, which may affect the metabolic function (Mayorga-Ramos et al., 2022). It has been demonstrated that SCFAs activate intestinal GPCRs to control the release of glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) (Coppola et al., 2021), which in turn influences insulin secretion and the hypothalamic perception of energy intake. Furthermore, in pancreatic β-cell mitochondria, butyrate can suppress the expression of fission genes (DRP1, FIS1) and fusion genes (MFN1, MFN2, OPA1).

This can not only decrease the production of pro-inflammatory factors (such as IL-6 and TNF-α), but also increase the secretion of anti-inflammatory factors (such as IL-10, IL-4, and IL-11) (Mollica et al., 2017; Xiong et al., 2019; Noureldein et al., 2020; Prause et al., 2021). Hence, the lack of *Firmicutes* and *Bacteroidetes* in the elderly may result in a decrease of SCAFs, and then put the intestines and pancreatic beta cells in a state of immune disorder and inflammation, leading to disorders of blood sugar homeostasis and metabolism.

Besides SCFAs, Shin Yoshimoto et al. investigated metabolic products of gut microbiota in young and elderly groups found that choline, trimethylamine (TMA), N-8-acetylspermidine, 2-hydroxy-4-methylvaleric acid, and 5-methylcytosine were more abundant in elderly individuals (Yoshimoto et al., 2021). These metabolites have been proven to be high-risk factors for geriatric diseases such as metabolic syndrome (Chen et al., 2019; Zhou et al., 2021), cardiovascular disease (Nayak et al., 2020; Li et al., 2021), and tumors (Yin et al., 2022).

In elderly individuals, the administration of *Bifidobacterium* has been observed to regulate intestinal barrier function, exert anti-inflammatory and antioxidant effects, and result in an increased abundance of this organism in stool samples. These effects have been found to be associated with a reduction in fasting blood glucose levels and improvement in insulin resistance among patients diagnosed with T2DM (Schiffrin et al., 2007; Ouwehand et al., 2008). The utilization of *B subtilis natto DG101* in conjunction with suitable medications has demonstrated promising outcomes in the management of T2DM (Cardinali et al., 2020). Additionally, the potential cognitive benefits of probiotics can be attributed to their ability to reduce visceral fat and mitigate inflammation (Azuma et al., 2023).

3.2 Cellular senescence

Cellular senescence is a complicated yet ubiquitous process which is essential for biological embryonic development, tissue remodeling, and wound healing (Huang et al., 2022b). Cellular senescence is often distinguished by a reduction in the capacity for cell division, stoppage of the cell cycle, and the secretion of senescence-associated secretory phenotypes (SASP), which include cytokines, chemokines, growth factors, and proteases (Basisty et al., 2020). These chemicals can be delivered extracellularly via small vesicles, resulting in alterations to intercellular communication and the exertion of regulatory influences on adjacent cells, tissues, and even faraway tissues (Özcan et al., 2016; Terlecki-Zaniewicz et al., 2018). Nevertheless, the onset of age-related diseases is inextricably tied to the process of excessive and protracted senescence (Palmer et al., 2019; Yousefzadeh et al., 2021). Clinical studies revealed that increasing age is one of the risk factors for elderly diabetes, which is closely related to the aging of tissues and organs (Markle-Reid et al., 2018; Kumar et al., 2023).

Studies verified that the cellular senescence of diabetes target organs (such as the adipose tissue and pancreas) might accelerate the occurrence and progression of diabetes. Furthermore, obesity, lipid metabolism problems, and hyperglycemia also exacerbated this process (Narasimhan et al., 2021). Adipose tissue is crucial for storing energy, maintaining body temperature, safeguarding internal organs, and play a role in wound healing, immune as well as endocrine regulation. (Zwick et al., 2018). Nevertheless, the composition and functionality of adipose tissue undergo substantial alterations with aging or serious metabolic stress. These changes include the redistribution of body adipose, an increase in chronic aseptic inflammation, a decline in the function of adipose progenitor cells, heightened lipotoxicity of nearby tissues caused by ectopic fat deposition, diminished secretion and sensitivity of hormones derived from adipose tissue (Palmer and Kirkland, 2016). By secreting SASP and recruiting immune cells, ageing adipocytes may aggravate inflammatory responses and disrupt the insulin signaling pathway, which aggravate IR and raise the risk of T2DM and metabolic syndrome (Khosla et al., 2020). A comparison of adipose tissue between young and elderly people showed that the volume of brown and beige adipose tissue around shoulder blades, blood vessels, and kidneys was smaller in the elderly. Furthermore, the expression of adipose tissue thermogenesis and differentiation related genes (*UCP1, β3AR, FOXA3, C/EBPα* and *PRDM16*) significantly decreased (Ma et al., 2014; Wang et al., 2019; Ikeda and Yamada, 2020; Ou et al., 2022). This may cause the fibrosis of fat precursor cells and reduced the differentiation of beige cells in the elderly, causing more fat to be stored under the skin and around internal organs, inducing and enhancing the risk of metabolic diseases. Aside from functional alterations, adipocytes from elderly people and mice also show increased expression of aging-related genes such as *p16, p21, Gpnmb,* and *p53.* Activation and overexpression of *p53* can lead to DNA damage, downregulation of insulin signaling protein transcription, inflammatory response, and macrophage infiltration, which have been confirmed to be associated with reduced lipogenesis, IR, and the occurrence of diabetes (Vergoni et al., 2016; Lahalle et al., 2021). However, the mechanism of other aging molecules such as *p16* and *p21* induced IR and diabetes is still unclear.

Additionally, it has confirmed that the aging of pancreatic beta cells is also associated with elderly diabetes. Age-related alterations in pancreatic beta cell function include decreased insulin production, decreased beta cell mass, and delayed cell proliferation. These processes might be potential roads that lead to elderly diabetes (Aguayo-Mazzucato, 2020). Cristina Aguayo-Mazzucato et al. compared the pancreatic islets of young and elderly mice and recognized that senescent islet cells accumulated obviously in the elderly mice, companied the downregulation of *Ins1, Pdx1, Mafa, Neurod1*, while aging markers (*p16, p21*), SASP (*Ccl2, Il1a, Il6, Tnf*) expression increased (Aguayo-Mazzucato et al., 2019; Aguayo-Mazzucato, 2020). An analogous pattern can be observed in human beings, where the prevalence of senescent islet β cells will progressively escalate because of IR, obesity, and diabetes.

Intervention strategies in the cell senescence process may be able to ameliorate metabolic problems and the progression of diabetes in the elderly (Tchkonia et al., 2021). Suda et al. and Wang et al. have confirmed that reduced expression of senescent cells and senescence markers in adipose tissue can improve glucose tolerance and insulin sensitivity (Suda et al., 2021). Currently, commonly used anti-aging combination include Dasatinib plus Quercetin (D + Q). This solution can target senescent adipocyte progenitor cells, reducing adipose tissue inflammation, increasing adipose tissue and peripheral insulin sensitivity, as well as promoting adipocyte progenitor cell development, ultimately treating diabetes in the elderly (Hickson et al., 2019; Wang et al., 2022a).

3.3 Oxidative stress and mitochondrial dysfunction

Mitochondria are double-membraned organelles that play a pivotal role in ATP synthesis and energy metabolism. Fatty acids and glucose both contribute to energy metabolism via glycolysis and the tricarboxylic acid cycle. The majority of high-energy electrons are transmitted downstream after combining with the reduced coenzyme (NADH or FADH2) of the respiratory chain in the mitochondria. Thereafter, they combine with oxygen to produce water and ATP (Nolfi-Donegan et al., 2020; Prasun, 2020). However, some electrons are not transferred through the respiratory chain but react directly with oxygen to produce superoxide radicals and hydrogen peroxide (Addabbo et al., 2009). This in turn damages cell membranes, proteins, enzymes, and DNA, leading to cell death. When mitochondrial dysfunction occurs, excessive accumulation of ROS prevents superoxide dismutase and reducing glutathione peroxidase in mitochondria from exerting their antioxidant effects. This process is called oxidative stress (Nolfi-Donegan et al., 2020).

Mitochondrial function weakens with age, owing to lower antioxidant capacity, decreased ATP synthesis, mitochondrial DNA (mtDNA) damage, mitochondrial protein oxidation, decreased electron transport chain efficiency, and worse quality control during mitophagy (Chistiakov et al., 2014). Previous studies have confirmed that mitochondrial dysfunction and oxidative stress in target organs (e.g., skeletal muscle, adipose tissue) are related to elderly diabetes. Sarcopenia, in addition to typical microvascular and macrovascular disorders, has emerged as the third significant complication among older diabetes patients. It is a significant

role in patients' poor quality of life and impairment. Changes in skeletal muscle mitochondrial function, ATP reduced synthesis and increased ROS generation may be possible causes of sarcopenia in elderly diabetes (Izzo et al., 2021). Paul Coen et colleagues discovered that the quantity and function of mitochondria in skeletal muscle were significantly diminished in the elderly when compared to young persons, and that the number of mitochondria in skeletal muscle was positively connected with insulin sensitivity (Coen et al., 2013). Pelletier et al. discovered that the oxidative phosphorylation and oxidation capacities of elderly muscle were diminished, which inhibited oxidative breakdown of lipids in muscles then increased lipid accumulate (St-Jean-Pelletier et al., 2017). Lipid accumulation raises ceramide (CER) and diacylglycerol (DAG) levels, which lower the function of mitochondrial oxidative phosphorylation and disrupting the electron transport chain (Chaurasia and Summers, 2021). As a consequence, substantial volumes of ROS were produced. ROS production activates downstream targets such as the IKKβ/NF-κB and JNK signaling pathways, increases inflammatory factor secretion (TNF-α, TLR2, IL-1), decreases IRS-1 activity, and affects insulin signaling (Michot et al., 2013). Increased levels of inflammation diminish IRS-1 expression and disrupt insulin signaling, resulting in elderly diabetes. Through comparing adipose tissue from young and elderly people, Laura Pelletier et al. found that mitochondrial dysfunction, oxidative stress, and adipocyte dysfunction were more obvious in elderly adipose tissue which accompanied by impaired lipogenesis and insulin sensitivity (L et al., 2021).

3.4 Immune and inflammatory

There are two types of immune systems: innate immunity and adaptive immunity. The complement system and various types of white blood cells (natural killer cells, mast cells, eosinophils, basophils, phagocytic cells, macrophages, neutrophils, and dendritic cells) comprise the innate immune system, which can produce cytokines and recruit immune cells to the site of infection or inflammation, then activate the adaptive immune process via antigen presentation (Daryabor et al., 2020). Adaptive immune cells include B cells and T cells, which mainly participate in humoral immunity and cellular immunity processes (SantaCruz-Calvo et al., 2022). A great number of research over the last 2 decades have demonstrated that immunometabolism is a key mechanism for controlling adaptive and innate immunity (Makowski et al., 2020). That is, metabolic processes can influence immune cell activity, and immunological and inflammatory responses may be the root causes of metabolic diseases.

However, as age increases, the immune system of the elderly will show a senescence state, which is manifested by a shortened duration of immune memory, accumulation of memory T cells, a lack of immune response to neoantigens, a higher tendency to autoimmunity, and a persistent low-grade inflammatory state throughout the body (Franceschi et al., 2018; Bulut et al., 2020; Moskalev et al., 2020). Inflammation can be caused by a variety of factors, including heightened levels of proinflammatory cytokines in the blood flow, disrupted lipid metabolism, alterations in the composition of gut microbiota, compromised immune system

functioning, and the presence of meta-inflammation (Singh and Newman, 2011).

Previous studies have confirmed that the level of cellular inflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and C-reactive protein (CRP) was increased in elderly patients with diabetes, and anti-inflammatory factors such as IL-10 were reduced (Gorska-Ciebiada et al., 2015; Saukkonen et al., 2018; Yang et al., 2018; Leite et al., 2021). These inflammatory factors have been confirmed to have a negative effect on insulin production, secretion and insulin signaling pathway (Shoelson et al., 2006; Akbari and Hassan-Zadeh, 2018), which may induce programmed cell death of pancreatic β cells (Maedler et al., 2009), and aggravate the risk of IR and diabetes. (Wang et al., 2013).

Furthermore, elderly patients with diabetes are often accompanied by abnormalities in lipid metabolism, mainly manifested by high triglycerides, low high-density lipoprotein cholesterol, and elevated small-density low-density lipoprotein cholesterol. (Gyawali et al., 2018). These pro-inflammatory lipids result in the activation of inflammatory signaling pathways, including JNK and NF-κB (Osborn and Olefsky, 2012; Tall and Yvan-Charvet, 2015). Activation of inflammatory signaling pathways lead to increased metabolic inflammatory stress (Hotamisligil, 2017) and promote the activation of NLRP3 (Masters et al., 2010; Wen et al., 2011; Wen et al., 2013) and caspase-1 as well as the cleavage of pro-IL-1β and pro-IL-18 (Wen et al., 2012), thereby aggravating systemic chronic inflammation and inducing the occurrence of IR (Masters et al., 2010).

Anti-inflammation and regulating immune cell function are ways to alleviate insulin resistance and pancreatic β-cell dysfunction. Commonly used drugs include metformin, GLP-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase 4 (DPP4) inhibitors (Jo and Fang, 2021). In addition, IL-1R antagonists can reduce islet inflammation caused by hyperglycemia, thereby improving islet β-cell dysfunction, alleviating insulin resistance and blood sugar homeostasis. However, the clinical efficacy of the above-mentioned drugs for elderly diabetes patients remains to be seen due to a lack of clinical research.

3.5 Epigenetics

Epigenetics is the study of heritable changes in the genetic information of gene-related characteristics that do not involve in modifying the DNA sequence, such as DNA methylation, histone modifications, and non-coding RNA (Allis and Jenuwein, 2016; Ling and Rönn, 2019). Furthermore, several enzymes are involved in post-transcriptional protein modification, such as acetylation, methylation, phosphorylation, and ubiquitination. However, most clinical studies have shown that there is a close relationship between chromatin formation, histone modifications, DNA methylation and gene activity, which have differential epigenetic changes expressed in different target tissues. So, it is difficult to determine which epigenetic phenomenon appears first.

The direct effects of aging on metabolic regulation exacerbate the underlying pathophysiological processes in elderly patients with diabetes. Aging effects interact with diabetes to accelerate the

progression of many common diabetes complications (LeRoith et al., 2019). This is often associated with varying degrees of underlying IR, excess obesity, beta cell dysfunction, and sarcopenia, and increase the complexity of diabetes management in this age group (Bellary et al., 2021). Most of the current epigenetics research in diabetes are focused on DNA methylation. Previous studies have shown that the methylation patterns of diabetic patients are significantly different from those of healthy population, and there are also obvious differences in the methylation sites of different target tissues in patients (Singh et al., 2020). John Chambers et al. followed 25,372 Indian Asians and Europeans and found that methylation of ABCG1, PHOSPHO1, SOCS3, SREBF1 and TXNIP in the blood was associated with a higher risk of future T2DM; in type 1 diabetes Methylation of ABCG1, PHOSPHO3, SOCS1, SREBF2 and TXNIP sites was found (Chambers et al., 2015b). But when it comes to specific tissues, their methylation sites are different. When comparing pancreatic tissue from healthy people and T2D patients, multiple studies have found that TCF7L2, KCNQ1, THADA, FTO, IRS1, PPARG, PDX1, PAX4, and GLP1R sites are methylated, which may be related to the methylation of pancreatic islet β after transcriptional inactivation. Decreased cell secretory function and activation of pro-inflammatory pathways (Dayeh et al., 2016; Suárez et al., 2023). In skeletal muscle, CXCL4, FADS2, MAPK1, PPARGC1A and other sites; in adipose tissue, it shows methylation of ATP10A, IRS1, JARID2, KCNQ1, NDUFB4, PPARG, and TCF7L2.

4 Treatment principles of elderly diabetes

With the decline of pancreatic beta cell function and the increase of IR, the prevalence of diabetes is gradually increasing in the elderly (Motta et al., 2008a; Tekin and Zimmerman, 2020). Common comorbidities in elderly patients with diabetes include chronic kidney disease, cognitive impairment, chronic airway disease, and infection (Fagot-Campagna et al., 2005; Lin et al., 2016). Multiple medications may have adverse effects (Noale et al., 2016), so appropriate management of comorbidities should be included in the guidelines for elderly diabetes patients (Caughey et al., 2010). The challenge of managing elderly diabetes patients is that it is highly heterogeneous (Bennett, 2015), which requires personal assessment of treatment and care options (Munshi et al., 2020), as well as comprehensive education of patients (Tekin and Zimmerman, 2020).

4.1 Western medicine treatment principles and clinical intervention

The target level of blood glucose and the use of anti-diabetes medications should be comprehensively evaluated according to clinical status, risk of hypoglycemia, and complications of diabetes (Scheen et al., 2014). Failure of oral glycemic control therapy is often observed in elderly patients, so insulin is often chosen as the preferred medication (Rajpal et al., 2021). However, the dangers associated with hypoglycemia cannot be ignored. Regimens using DPP-4 inhibitors alone or in combination with

basal insulin have been shown to be safe and effective and may be an alternative to basal injection regimens in elderly patients (Umpierrez and Pasquel, 2017). Reducing the frequency and severity of hypoglycemia is the key to achieving better compliance in elderly patients with diabetes (Motta et al., 2008b). In addition, the participation of family members is the basis for the good treatment effect of elderly diabetic patients (Baig et al., 2015). Besides, aiming to maintain or improve general health, the management goals of elderly patients with diabetes also include the assessment and treatment of atherosclerosis and microvascular disease (Adu-Sarkodie, 2017).

Specific clinical guidelines for T2DM in elderly have been published in Europe and the United States, but they do not specifically address advanced chronic kidney disease in elderly people with diabetes. Elderly patients with diabetes are different from younger patients, mainly due to their frailty and shorter life expectancy, requiring different treatment strategies to be tailored (Abaterusso et al., 2008). Studies have found that in the treatment of elderly diabetic nephropathy, excessive reduction of blood pressure to the current target is unsafe (Williams, 2013). The selection of some specific medications could improve the cure rate, reduce blood glucose, and improve kidney function for diabetic nephropathy in elderly (Cao and Chen, 2021).

Diabetic peripheral neuropathy (DPN) is the main form of neuropathy and a leading cause of disability. Small fiber neuropathy (SFN) can develop in older people with pre-diabetes, prior to large fiber damage (Akbar et al., 2023). The symptoms of DPN consist primarily of spontaneous, intractable pain that is diffuse and persistent and can last for weeks to months. Clinical treatment focuses on alleviating clinical symptoms, improving blood glucose control and cardiovascular risk factors (Yang et al., 2022). Pain in the elderly need arouse attention from clinicians and patients (Marchesi et al., 2024). In pain management, anticonvulsants such as pregabalin and gabapentin are the first-line treatment of choice, followed by amitriptyline, duloxetine, and venlafaxine (Cernea and Raz, 2021). Opioids and related medications are recommended for short-term use during acute exacerbations of pain (Kozma et al., 2012; Feldman et al., 2019; Marchesi et al., 2024). These interventions play an important role in diminishing DPN's symptoms and complications. For patients who do not respond to monotherapy, combination therapy may be beneficial (Rafiullah and Siddiqui, 2022). Basic interventions also include nutritional recommendations (mecobalamin, etc.) and functional exercise (Didangelos et al., 2020; 2021; Seyedizadeh et al., 2020; Shen et al., 2023b; Marchesi et al., 2024). However, diet and exercise are often neglected in the treatment of elderly patients with diabetes. Nutritional recommendations and exercise resistance training based on elderly subjects to increase muscle mass have good value in reducing diabetes parameters (Constans and Lecomte, 2007).

4.2 TCM treatment principles

The comprehensive and holistic management with TCM for diabetes patients is gradually being favored by modern healthcare systems (Xiao and Luo, 2018). The combination of TCM characteristics and western medicine to prevent and treat diabetes becomes a new attempt (Wang et al., 2020b). More and

more studies have emphasized that the bioactive components of TCM participate in those mechanism mentioned above (Nie et al., 2019; Ai et al., 2020; Tang et al., 2021; Huang et al., 2022c). TCM emphasizes Yin and Yang balance and a holistic approach. Chinese herbal medicine bidirectional regulation of body metabolism, to maintain the balance of the body's internal environment. TCM individual treatment focuses on syndrome differentiation, multi-level and multi-target treatment, and patients with diabetes can significantly relieve symptoms under the treatment of TCM theory (Tong et al., 2012).

Clinical TCM classifies diabetes as "Xiaoke" and "Pidan". Some scholars put forward the idea of "state-target" differentiation and treatment (Zhang et al., 2021a), and believe that the stage identification and treatment of elderly diabetes are different from the general diabetes population. According to the different stages of clinical manifestations and pathological changes, syndrome differentiation and treatment can alleviate the symptoms and physique of patients (Wang et al., 2020b). The pathological characteristics of elderly patients with diabetes are gradually becoming weak, accompanied by insufficient digestive ability. Due to long-term nutritional metabolism deficit, often just at the beginning of the disease will see the phenomenon of physical weakness, so elderly diabetes is easy to enter the stage of deficiency, damage, often combined with a variety of complications. TCM believes that most elderly patients are sick for too long and lead to physical weakness, with the gradual loss of Yang physical characteristics, so strong Yang is often the treatment principle of elderly diseases.

TCM believes that most elderly patients have a long course of disease, which leads to physical weakness and gradual imbalance of Qi, Blood, Yin, and Yang. Therefore, the use of TCM intervention strategies, focusing on improving immunity, improving circulation, and reducing inflammation may becoming the key to the treatment of elderly diabetes.

5 TCM treatments of elderly diabetes

Over the past few years, numerous investigations have been carried out to find evidence-based anti-diabetes TCM formulas but few for elderly diabetes. We conducted a literature review on PubMed and CNKI updated until November 2023, for eligible studies on the Traditional Medicine accepted for use in clinical settings by the elderly population with diabetes or diabetic complications. And we searched keywords and Medical Subject Headings (MeSH) terms pertinent to the intervention of interest, such as "elderly diabetes", and "Traditional Medicine". All involved TCM interventions for elderly diabetes were summarized (Table 1).

Though there were insufficient direct clinical proofs on TCM for diabetes and related complications in elderly patients, it is beyond question that TCM addresses the health of the population. Moreover, TCM have provide patient-centered treatment strategies for blood glucose problem that can partly replace western medicine. A meta-analysis reported that TCM could significantly improve glucose control and clinical indices in patients with diabetes and effectively delay the progression of diabetes (Tian et al., 2019). As early as 2015, the first RCT on TCM formula for diabetes and mechanism exploration with gut microbiota was conducted, providing powerful clinical proofs on

this issue (Xu et al., 2015). A traditional Chinese herbal formula, Gegen Qinlian Decoction, can exert similar diabetes-control effects with metformin in a dose-dependent manner (Tong et al., 2011; Xu et al., 2020; Tian et al., 2021).

Also, studies reported in Chinese concentrated on senile disease (such as DKD) and other common symptoms or signs in elderly diabetes like constipation and diabetic gastroparesis. It is obvious that the danger and particularity of elderly diabetes have attracted more attention in recent years, and we've also just seen the size of these settlements balloon. Various TCM interventions could solve a majority of problems for elderly diabetes. And different complications suit for different TCM interventions. For example, acupuncture plays a crucial role on diabetic peripheral neuropathy while TCM exercise therapy (such as Taichi) helps weight loss and muscle function recovery (Jiang et al., 2020; Huang. et al., 2022a; Shen et al., 2023b; Li et al., 2023).

Clinical trials on TCM intervention in elderly diabetes was also retrieved from WHO International Clinical Trials Registry Platform (https://www.who.int/clinical-trials-registry-platform), ClinicalTrials.gov. (https://clinicaltrials.gov/). and Chinese Clinical Trial Registry (https://www.chictr.org.cn/). We noticed that there was an increasing trend in trials on TCM intervention in elderly diabetes (Table 2). Such TCM treatment of elderly diabetes research is currently in progress.

Furthermore, we have reviewed the common mechanism of TCM reported for aging and diabetes, or direct mechanism for elderly diabetes mentioned above. So far, those mechanism could be well implemented by distinctive TCM non-pharmacological approaches (Figure 2) and herbal treatment (Table 3). TCM had the effect of modulating gut microbiota and improving glucose metabolisms in T2DM patients and pre-clinical experiments (Zheng et al., 2021b). Numerous studies reviewed the efficacy and mechanisms of Chinese herbal medicine on DKD, DR, and DPN, which have been reported to be critical for diabetes in the elderly (Lu et al., 2019; Ai et al., 2020; Chen et al., 2022b; Liu et al., 2022). Whlie TCM could give full play to the advantages of multiple targets and intervene in many important mechanisms of elderly diabetes. Take Gegen Qinlian Decoction (GQD) as an example, its prescirption may ameliorate T2DM with hyperlipidemia via enriching beneficial gut microbiota (such as *Blautia* and *Faecalibacterium spp*) and decline harmful gut microbiota which closely related to the occurrence and development of T2DM (Tong et al., 2018). Also, the exosomal miRNA expression profile and signaling pathways related to T2DM was changed obviously following GQD treatment to provide a potential strategy for elderly diabetes. For elderly DKD, Dihong formula, Qi-Kui granules, and treatment based on syndrome differentiation were reported to exert the effect of oxidative stress inhibition and kidney protection.

There were also various natural products (including oleuropein, cyclocarya paliurus polysaccharides, hyperoside, and so on) that do not used in traditional clinical practice, while existed proofs have reported excellent potentials for elderly diabetes considering consistent curative mechanism (Yao et al., 2020; Zheng et al., 2021a; Liu et al., 2021). Quercetin, an important natural flavonoid, not only regulate gut microbiota disorders in diabetes animal models, but also inhibiting oxidative stress and inflammatory responses to restore mitochondrial dysfunction (Yi et al., 2021; Cui et al., 2022). Moreover, there are numerous natural products from TCM used for various diabetes related complications, including DR,

DPN and so on. Furthermore, we categorized and analyzed their main bioactive ingredients (Table 3). This review partly covers the key works on the effects and underlying mechanisms of TCM, herbal ingredients and synergistic effects of constituent compatibility in treating elderly diabetes, providing additional ideas to address this threat.

6 Discussion and prospects

Diabetes is a systemic chronic metabolic disease caused by a combination of genetic, nutritional, environmental, and other factors. With the improvement of living circumstances and the aging of population, diabetes is affecting an increasing number of senior individuals. As a result, early and thorough interventions have substantial therapeutic implications for delaying diabetes development, preserving target organs, preventing complications, and increasing patients' quality of life. Even though a range of medicines is being utilized to treat diabetes, current diabetes management in the elderly is still inadequate.

Diabetic patients in China frequently undergo TCM treatment in addition to conventional care, and the results are frequently superior to conventional treatment alone. Multiple studies have demonstrated that TCM can relieve clinical symptoms and postpone the development of diabetes by regulating exosome secretion and epigenetic expression, as well as enhancing gut microbiota and eliminating oxidative stress. However, due to the unique diagnostic methods of TCM and the complexity of TCM components, as well as the fact that the pathogenesis of diabetes in the elderly differs from that of other age groups, there is still a lack of large-scale, multi-center, randomized, and controlled clinical trials of TCM in the treatment of elderly diabetes. Furthermore, clinical studies have yet to validate several results, although clinical trials have proven improvements in clinical symptoms, the fundamental mechanisms remain unknown. To overcome these limitations, we should conduct additional analyses and searches for key compounds and targets of TCM in the treatment of elderly diabetes. Also, there is an urgent need to clarify the drug dose-response relationship and ensure the reliability of the results through experimental verification in the future. Besides, a high-quality TCM clinical research protocol should be established to facilitate the conduction of large-scale, multi-center, controlled trials, so that to provide stronger evidence for TCM treatment of diabetes in the elderly.

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Conflict of interest

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Supplementary material

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Efficacy and pharmacoeconomic advantages of Fufang Huangbai Fluid hydropathic compress in diabetic foot infections: a comparative clinical study with antimicrobial calcium alginate wound dressing

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Objective: To compare the intervention effects and pharmacoeconomic advantages of Fufang Huangbai Fluid (FFHB) hydropathic compress *versus* Antimicrobial Calcium Alginate Wound Dressing (ACAWD) in the treatment of diabetic foot infections (DFI).

Methods: Patients with DF who were hospitalized in the peripheral vascular Department of Dongzhimen Hospital of Beijing University of Chinese Medicine from December 2020 to February 2022 and met the inclusion and excluding criteria were allocated into the experimental group and control group through minimization randomization. The experimental group was treated with FFHB hydropathic compress for 2 weeks, while the control group was treated with ACAWD for the same duration. The wound healing of both groups was monitored for 1 month post-discharge. Clinical data from all eligible patients were collected, and differences in various indices between cohorts were analyzed.

Results: 22 in the experimental group (including two fell off) and 20 in the control group. After the treatment, the negative rate of wound culture in the experimental group was 30% and that in the control group was 10%, There was no significant difference in the negative rate of wound culture and change trend of minimum inhibitory concentration (MIC) value of drug sensitivity ($p > 0.05$). The infection

control rate of the experimental group was 60%, and that of the control group was 25%. The difference between the two groups was statistically significant ($\chi 2 = 5.013$, $p = 0.025$). The median wound healing rate of the experimental group was 34.4% and that of the control group was 33.3%. There was no significant difference between the two groups ($p > 0.05$). During the follow-up 1 month later, the wound healing rate in the experimental group was higher, and the difference was statistically significant ($p = 0.047$). Pharmacoeconomic evaluations indicated that the experimental group had greater cost-effectiveness compared to the control group.

Conclusion: In the preliminary study, FFHB demonstrated comparable pathogenic and clinical efficacy to ACAWD in the treatment of mild DF infection, and exhibited superior pharmacoeconomic advantages. With the aid of infection control, the wound healing rate in the FFHB group showed notable improvement. Nevertheless, due to the limited sample size, larger-scale studies are warranted to further validate these findings.

Clinical Trial Registration: (https://www.chictr.org.cn/showproj.aspx?proj= 66175), identifier (ChiCTR2000041443).

1 Introduction

Diabetic foot infection (DFI) is not only a significant factor leading to the deterioration of diabetic foot (DF), but it also stands as the most prevalent cause of hospitalization and even amputation in DF patients (Lavery et al., 2007; Ndosi et al., 2018; Tan et al., 2019). A prospective study reported that DFI patients had only a 46% healing rate within 1 year (another 10% of these patients would relapse), a mortality rate of 15%, and an amputation rate of 17% (Tan et al., 2019). If patients become infected, they face a higher likelihood of amputation. Studies by Lavery et al. have shown that the risk of amputation in DF patients with lower limb infection is 154.5 times higher than that in patients without infection (Lavery et al., 2006). A meta -analysis examining risk factors for large amputation in DF patients showed that major amputation in DF patients was associated with infection (OR:2.5295%CI:1.71–3.71) (Wang et al., 2018). The presence of infection makes DFI wounds challenging to heal, which seriously affects the quality of life of patients, occupies a lot of medical resources, and brings a heavy burden to the family and society.

Fufang Huangbai Fluid (FFHB) Comprises five traditional Chinese medicine: Forsythiae Fructus [Oleaceae; Forsythia suspensa fruit], Phellodendri Chinensis Cortex [Rutaceae; Phellodendron amurense bark], Lonicerae Japonicae Flos [Caprifoliaceae; *Lonicera japonica* Thunb flower bud], Taraxaci Herba [Compositae; Taraxacum mongolicum Herb], Scolopendra [Scolopendridae; Scolopendra subspinipes Mutilans whole worm]. The plant names were verified at http://mpns.kew.org/mpns-portal, and the name of Scolopendra was authenticated using the Pharmacopoeia of the People's Republic of China. FFHB is believed to clearing away heat and toxic materials, reducing swelling, and eliminating decay. Studies have shown that the effective rate of treating DF wounds infected with methicillin-resistant *Staphylococcus aureus* with FFHB is 92% (Wang et al., 2019).

Currently, most clinical studies focus primarily on clinical observation to assess FFHB's therapeutic effects, and the research on the effect of FFHB on pathogenic microorganisms of DFI wound is limited to basic medical research. At present, there is still a lack of evaluation on the intervention effect of FFHB on the wound pathogenic microorganisms of real DFI patients.

2 Materials and methods

2.1 Design and participants

Forty-two patients with DF, admitted to the Department of Peripheral Vascular at Dongzhimen Hospital, Beijing University of Chinese Medicine between December 2020 and February 2022, were selected based on the following criteria:

2.1.1 Inclusion criteria

①Patients meeting the diagnostic criteria for diabetic foot; ②Grade 2 according to the Infections Diseases Society of America (IDSA) (Lavery et al., 2007); ③The wound surface was confirmed to be infected by pathogenic microorganisms through culture; ④Glycated hemoglobin ≤8%; ⑤Ages between 18 and 85 years, regardless of gender; ⑥Ankle-brachial index (ABI) ≥ 0.4; ⑦The wound area was within the range of 1 cm × 1 cm–10 cm × 10 cm (If the subjects have ≥2 wounds, the largest one would be considered as the study object); ⑧Patients voluntarily participated in this trial and signed informed consent form.

2.1.2 Exclusion criteria

①Patients who were allergic to FFHB or ACAWD; ②Those who used antibiotics in anyway within 1 week before treatment; ③Severe heart, liver and renal insufficiency that seriously affected the safety and treatment of subjects were ruled out by the investigator; ④Patients with foot ulcer caused by venous, neoplastic, radioactive, simple arterial and other non-diabetic reasons; ⑤Serum albumin <25 g/L; ⑥Hemoglobin <90 g/L; ⑦

Platelet is lower than the lower limit of normal value; ⑧Those who have pregnancy or family planning, or pregnant or lactating women; ⑨Patients with cognitive dysfunction who cannot give full informed consent; ⑩At the discretion of the investigator, the patient was unable to complete the study or to comply with the requirements of the study.

2.1.3 Elimination criteria
①During the trial, the inclusion/exclusion criteria were violated; ②During the experiment, subjects applied drugs or dressings to the affected area that were explicitly identified as having antibacterial properties in their instructions or product literature; ③The subjects received vascular intervention during the experiment.

2.2 Interventions

2.2.1 Treatment method
Subjects were divided into control and experimental groups through minimization randomization.

Both groups were administered a systematic basic medical treatment regimen tailored to individual patient needs. This included a diabetic diet and medications aimed at controlling blood pressure, blood glucose, and lipid levels. It should be noted that the specific medications varied among patients due to the presence of multiple comorbidities and long-term prescriptions. While it is infeasible to list all drugs, they encompassed a broad range of commonly used antihypertensives, antidiabetics, and lipid-lowering agents.

In addition to the basic treatment, FFHB (Shandong Hanfang Pharmaceutical Co., Ltd., commercially available) was used in the treatment group. After treatment, the wound was conventionally wrapped. And the dressing was changed once a day, for a total of 2 weeks. In the control group, in addition to the basic treatment, ACAWD (Lomanos (China) Medical Products Co., Ltd., commercially available) was applied to the wound surface for 2 weeks and then conventionally wrapped. And the dressing was changed once a day. Since the two drugs studied are for external use, professional doctors are required to change the dressing. In the process, they can distinguish the differences. Therefore, this trial is an open clinical study. The wound dressing change methods are detailed in the Supplementary Material S1.

2.2.2 Preparation of FFHB
FFHB is produced by Shandong Hanfang Pharmaceutical Co., Ltd. It contains Forsythiae Fructus 80 g, Phellodendri Chinensis Cortex 40 g, Lonicerae Japonicae Flos 40 g, Taraxaci Herba 40 g, and Scolopendra 2.4 g (Chinese Pharmacopoeia Commission, 2015).

Procedure: Decoct the above ingredients with water for three times, 1 h for the first time, 45 min for the second, 30 min for the third time, combine the decoctions, filter, and concentrate the filtrates to a thin extract with a relative density of 1.10–1.15 (50°C), add ethanol and adjust the concentration of ethanol to 70%, stand for 24 h and filter, recover ethanol to no ethanolic smell in vacuum, add water to 1,000 mL, stir well, store at a low temperature for 24 h, filter, pack and sterilize. The chemical analysis follows the standards established by the ConPhyMP statement (Heinrich et al., 2022). The identification methods are detailed in the Supplementary Material S2.

2.3 Follow-up plan

All patients were discharged after 2 weeks of treatment. If the patient still has an infection, they should continue to use drug anti-infection treatment. Continue to use FFHB or ACAWD, respectively. If the infection has been eliminated, it will be changed to ordinary dressing change treatment. Use saline cotton ball to clean the wound, and cover a proper amount of sterile gauze on it. Then, bandage it with gauze bandage. One month later, the patients in the two groups were followed up by outpatient service or social software, and whether the wounds healed or not was counted, see flowchart for details (Figure 1).

2.4 Observation indicators

2.4.1 Baseline data collection
Before entering the group, demographic data (age and gender) of subjects in both groups, concomitant diseases, bacterial type of infection (Gram staining), ABI and DF ulcer history and ulcer site were collected as baseline data. Efficacy and safety indicators were also assessed for all subjects at baseline (enrollment), at Visit 1 (7 ± 2 days dosing), and at Visit 2 (14 ± 2 days dosing).

2.4.2 Primary efficacy measurements
① Pathogenic microorganism culture: using sterile cotton swab by Levin's method to collect wound secretion of patients, conducting a bacterial culture and drug sensitivity test to observe whether pathogenic microorganisms on the wound surface were eradicated following drug administration;

② Minimum inhibitory concentration (MIC) value: The susceptibility results of cultures were used to detect whether the MIC of pathogenic microorganisms against different antibacterial drugs was changed.

③ Infection control rate: The rate of the IDSA grade of DFI patients decreasing from grade 2 to grade 1. The judgment results were subjected to blind evaluation by clinical experts. If the judgment results are inconsistent, the researcher shall make a new judgment and make an explanation.

2.4.3 Secondary efficacy measurements
① Wound surface area and wound area healing rate: The three-dimensional wound measurement and recording device of eKare inSightTM was used to measure the wound surface area, so that the camera was perpendicular to the wound surface. The deflection angle was less than 15° and the distance to the wound surface was about 40 ± 5 cm, ensuring that the wound surface was located in the center of the display screen. When the device was automatically recognized as 3D mode, the wound surface and the device were kept stationary for photographing. Wound area healing rate = [(baseline wound area—visit wound area)/baseline wound area] × 100%; The wound areas were recorded twice by two researchers and the average value was taken.

② Cost-effect ratio: The direct medical costs (bed cost, nursing cost, consumables cost, drug replacement cost and medication cost) of the two treatment methods were calculated and divided by the negative rate of microbial

FIGURE 1
Flowchart ●: Required item; *: When joining the group, women of childbearing age are examined; ABI: Ankle-brachial index; HCG, human chorionic gonadotropin; IDSA, Infections Diseases Society of America.

culture, infection control rate and wound area healing rate, respectively. The economies of the FFHB and ACAWD were compared by comparing the costs required to obtain the 1% negative rate of microbial culture, 1% infection control rate and 1% wound area healing rate.

③ Wound healing rate: One month after the subjects were discharged from the group, the wound healing of the subjects in the two groups were followed up, and the two researchers made a judgment on whether they healed or not. If there are differences between the two researchers, they can reach an agreement through discussion, or ask the third researcher to make a ruling.

2.4.4 Safety assessments

All adverse events observed during the treatment, including any symptoms and signs, were considered as safety indicators:

1) Drug Allergy: If patients exhibit allergic reactions such as skin itching, papules, erythema, wheals, eczema, or blisters during treatment, they should discontinue treatment immediately. Mild reactions may resolve spontaneously, whereas severe reactions should be managed with antiallergic treatments under medical guidance.

2) Wound Bleeding: In the event of bleeding, immediate compression should be applied to the wound. If the bleeding ceases, treatment may proceed as planned. Should the bleeding persist, the experiment should be halted, and surgical intervention may be necessary to stop the bleeding.

3) Exacerbation of Infection: If there's an escalation in infection, the experiment should be stopped immediately. Affected patients should receive intravenous administration of appropriate antibiotics.

2.5 Allocation

The centralized MagMinDA clinical trial randomization system was utilized for participant enrollment. Stratification factors were determined based on patients' baseline characteristics and factors influencing infection control, such as the bacterial type of infection (determined by Gram staining as G-/G+) and the ABI value (either ≤0.7 or >0.7). Using the minimization algorithm principle, the allocation probability for each patient was calculated. When the first subject was completely randomized, from the second study object, the difference of prognostic factors between the two groups was calculated after the study object was divided into specific groups. According to the principle of minimizing the difference, the research objects were randomly grouped according to the distribution probability. This approach ensured that patients were assigned to the most appropriate treatment group, guaranteeing a balanced distribution of control factors between the groups.

2.6 Statistical method

Experimental data was processed using SPSS 21.0, with measurement data represented as mean ± standard deviation ($\bar{x} \pm s$). The normal distribution test and variance homogeneity test were performed. If the conditions were met, t-test was used. For skewed distribution data that did not meet the conditions, the Kruskal–Wallis Test was performed, expressing the data as median [upper and lower quartiles) (M(P25,P75)]. The count data were subjected to chi-square test. A p-value of <0.05 was considered statistically significant.

TABLE 1 Basic conditions of subjects in the two groups when entering the group.

Index	Experimental group	Control group	Statistic	p-value
Age (mean ± sd)	66.55 ± 11.959	61.55 ± 10.283	t = 1.444	0.156
Gender (male/female, case)	15/7	14/6	$\chi^2 = 0.018$	0.899
Renal insufficiency (none/yes, case)	21/1	19/1	-	1.000
Diabetic peripheral neuropathy (none/yes, case)	6/16	2/18	$\chi^2 = 2.027$	0.155
Hypoproteinemia (none/yes, case)	13/9	16/4	$\chi^2 = 2.143$	0.143
Hypertension (none/yes, case)	9/13	8/12	$\chi^2 = 0.004$	0.952
Hyperlipidemia (none/yes, Cases)	13/9	10/10	$\chi^2 = 0.349$	0.554
Gram staining (G-/G+, case)	17/5	16/4	$\chi^2 = 0.046$	0.830
ABI (>0.7/≤0.7, case)	8/14	10/10	$\chi^2 = 0.795$	0.372
History of amputation (none/yes, Cases)	11/11	9/11	$\chi^2 = 0.105$	0.746
Ulcer site (left foot/right foot, case)	14/8	12/8	$\chi^2 = 0.059$	0.808
Ulcer site (forefoot/midfoot/hindfoot, case)	13/8/1	11/8/1	$\chi^2 = 0.353$	1.000

3 Results

3.1 Comparison of basic conditions of subjects between the two groups when they were enrolled

A total of 42 subjects were included, including 22 in the experimental group and 20 in the control group. All the subjects obtained informed consent. Two patients from the experimental group dropped out due to the COVID-19 outbreak and their failure to strictly follow the dressing change protocol. There were 42 cases in the FAS set and 40 in the PPS set. The FAS set was used for baseline data analysis. The two subjects' dropout was due to completely random deletions, and the deletion rate was low. Thus, the PPS set was employed for follow-up data analysis.

Between the two groups, there were no significant differences in demographic data (age, gender), concomitant diseases, bacterial type of infection (based on Gram staining), ABI, DF ulcer history, or ulcer site ($p > 0.05$) (Table 1).

3.2 Comparison of pathogenic microorganisms and infection control between the two groups

The culture report of pathogenic microorganisms from the subjects was analyzed. If no bacteria were cultured at Visit 2, compared to the baseline data, it was determined as "Yes"; otherwise, it was marked as "NO." The probability of negative wound culture was 30% in the experimental group and 10% in the control group. There was no significant difference between the two groups ($\chi^2 = 1.406$, $p = 0.236$) (Table 2).

The MIC values reported in all pathogenic microorganism drug sensitivity reports during the subject visit period were analyzed. If a change in MIC was observed, it was considered a positive event. There were a total of 32 positive events in the test group and 51 in the control group were obtained. MIC was determined to be increased if

it was higher than its previous value, and was noted to be decreased if it was lower than its previous value. There was no significant difference between the two groups ($\chi^2 = 0.133$, $p = 0.716$) (Table 2).

Relevant data, including wound photos and subject symptoms, were collected to ascertain whether the infection grade of the patients decreased from IDSA2 to 1. The infection control rate for the test group at visit 2 was 60%, while it was 25% in the control group. The difference between the two groups was statistically significant ($\chi^2 = 5.013$, $p = 0.025$), and the effect in the experimental group was superior to that in the control group (Table 2).

3.3 Analysis of wound surface area and wound area healing rate of subjects in two groups

The overall wound area decreased in both groups of subjects. In the intra-group comparison, there was a significant difference between Visit 1 and baseline ($t = 2.437$, $p = 0.025$) and between Visit 2 and baseline in the experimental group ($t = 3.539$, $p = 0.002$). However, there was no statistical difference between Visit 1 and baseline in the control group ($t = 1.421$, $p = 0.177$), and there was a statistical difference between Visit 2 and baseline ($t = 3.012$, $p = 0.007$) (Table 3).

The wound area healing rates of the experimental group and the control group were calculated separately. For both Visit 1 and Visit 2, there was no significant difference between the two groups ($p > 0.05$). The median wound area healing rate in the Visit 2 experimental group was 34.4%, while that in the control group was 33.3% (Table 4).

3.4 Cost-effectiveness analysis of two groups of subjects

Due to limitations in data accuracy, this study only calculated the main direct medical costs for treating DFI wounds in subjects,

TABLE 2 Pathogenic microorganisms and infection control of subjects in two groups.

Index	Experimental group	Control group	Statistic	p-value
Culture without bacteria (yes/no, case)	6/14	2/18	$\chi^2 = 1.406$	0.236
MIC value (increase/decrease, case)	17/15	25/26	$\chi^2 = 0.133$	0.716
Infection downgraded to IDSA1 (yes/no, case)	12/8	5/15	$\chi^2 = 5.013$	0.025

TABLE 3 Comparison of wound surface areas between the two groups within the same group.

Group	Baseline (cm^2)	Visit 1 (cm^2)	Visit 2 (cm^2)	p-value (baseline-visit 1)	p-value (baseline-visit 2)
Experimental group	12.43 ± 9.07	10.32 ± 6.61	8.09 ± 6.39	0.025	0.002
Control group	12.49 ± 11.10	10.83 ± 9.75	8.68 ± 7.49	0.177	0.007

TABLE 4 Wound area healing rates of subjects in the two groups.

Date	Wound healing rate	Experimental group	Control group	Statistic	p-value
Visit 1	N (missing)	19 (1)	15 (5)	$\chi^2 = -0.884$	0.376
	M(P25,P75) (%)	13.6 (-26.7,27.0)	19.0 (1.0,34.8)		
Visit 2	N (missing)	20 (0)	19 (1)	$\chi^2 = -0.337$	0.736
	M(P25,P75) (%)	34.4 (15.0,56.1)	33.3 (19.7,52.2)		

TABLE 5 Direct medical costs for subjects in two groups.

Cost items	Experimental group		Control group	
	Unit price (yuan)	Quantity×Days	Unit price (yuan)	Quantity×Days
Bed fee	50	1 × 14	50	1 × 14
Nursing expenses	26	1 × 14	26	1 × 14
Consumables Fees	0.33	5 × 14	0.33	3 × 14
Exchange medicine fee	24	1 × 14	24	1 × 14
Expenses for medicine	39.2	1 × 14	34 0	1 × 14
Total	1971.9		6,173.86	

including bed fee (normal), nursing fee (level II), consumables fee (gauze and cotton balls), drug replacement fee (incurred during the process of dressing change), and drug cost (the unit price of FFHB is 39.2 yuan, and that of ACAWD is 340 yuan). The total cost for 14 days was 1971.9 yuan in the experimental group and 6173.86 yuan in the control group (Table 5).

From the previous analysis, the probability of negative wound culture was 30% in the experimental group and 10% in the control group. The infection control rate of the experimental group was 60% and that of the control group was 25%. The median wound area healing rate was 34.4% in the experimental group and 33.3% in the control group. Through calculation, we respectively obtained the costs required to achieve 1% negative rate of microbial culture, 1% infection control rate and 1% wound area healing rate in the two groups, with the results kept to two decimal places. The cost to achieve a 1%

negative rate of microbial culture, 1% infection control rate, and 1% wound area healing rate in the experimental group were 65.73, 32.87 and 57.32 yuan, respectively. The control group was 617.39, 246.95 and 185.40 yuan, respectively. The experimental group had more pharmacoeconomic advantages than the control group.

3.5 Wound healing rate of two groups of subjects

After 1 month follow-up, all 20 cases in the experimental group were healed (with a healing rate of 100%), while 15 cases in the control group were healed (the healing rate was 75%). The difference between the two groups was statistically significant ($p = 0.047$) (Table 6).

TABLE 6 Wound healing of two groups of subjects.

Index	Experimental group	Control group	p-value
Wound healed (yes/none, case)	20/0	15/5	0.047

4 Adverse event conditions in both groups

No significant adverse reactions were reported in either group during the trial.

5 Discussion

5.1 Understanding diabetic foot infections (DFI)

In 2019, the International Working Group on Diabetic Foot defined DF as an infection, ulcer or tissue damage in the foot of a patient who was newly diagnosed with diabetes or had a history of diabetes, usually accompanied by lower extremity neuropathy and/or peripheral artery disease, and defined DFI as a clinical manifestation of inflammation in tissues below the ankle in diabetic patients (Bus et al., 2020). DFI is an important factor for the development and deterioration of DF, which consuming vast medical resources, including anti-infection treatment and surgery (Lavery et al., 2006; Hao et al., 2014; Lazzarini et al., 2018). A large portion of DFI wounds fail to heal, which is related to the infection (including osteomyelitis) and/or gangrene development of the foot or lower limb and the increased risk of lower limb amputation (Pecoraro et al., 1990; Adler et al., 1999). Effective and timely treatment of DFI is crucial for promoting wound healing and saving patients' limbs and lives.

5.2 Comparing efficacies of two treatment modalities

In this study, the experimental group used the hydropathic compress method with FFHB coated on medical gauze. In contrast, the control group employed ACAWD combined with silver ion and calcium alginate. Both treatment exhibited antibacterial effects. After absorbing the exudate, ACAWD was similar to FFHB in, maintaining a moist local wound surface. The morphology and mechanism of action of the selected treatments were similar in both groups. Numerous clinical studies have proved that silver ion dressings have a positive effect on DFI (Yang et al., 2021; Luo et al., 2022). In this study, there was no statistical significance between the negative rate of wound culture in the experimental group and that in the control group, proving that for DFI patients with IDSA2 grade, the bactericidal effect of FFHB was comparable to that of ACAWD.

5.3 Exploring FFHB's antibacterial properties and mechanisms

Modern pharmacological studies have demonstrated that FFHB can inhibit S. aureus, Pseudomonas aeruginosa and Proteus

(Sun et al., 2020). The extracts of Taraxacum mongolicum and Honeysuckle Flower showed strong inhibitory activity against Proteus. The centipede medicinal extract has strong inhibitory activity on P. aeruginosa, S. aureus, Proteus, and Klebsiella pneumoniae (Sun et al., 2020). The above basic studies confirmed that FFHB had a positive antibacterial effect, as evidenced in our clinical trials.

MIC refers to the minimum concentration of antibacterial drugs to inhibit the growth of a certain microorganism. Unlike conventional drug sensitivity tests that detect at a single concentration, MIC can quantitatively reflect the drug resistance of pathogenic microorganisms. Therefore, this index is often used for monitoring the drug resistance of pathogenic microorganisms and further guiding clinical medication. If the MIC value of an antibacterial agent against a pathogenic microorganism increase, it is considered that a MIC shift of the antibacterial agent has occurred. If the MIC value reaches a certain limit, it may cause the treatment failure of the antibacterial agent, and exert pressure on clinical treatment of DFI. Studies have shown that antibacterial drugs below the MIC not only enhance the hemolytic activity of S. aureus (Kuroda et al., 2007) but also promote the expression of virulence factors (Shang et al., 2019), but also stimulate the local formation of biofilm (Jin et al., 2020), lead to induce the production of drug-resistant bacteria (Bhattacharya et al., 2017). There was no statistical difference between the two groups, indicating no significant variance between the two drugs in regulating drug resistance of pathogenic microorganisms in DFI infections.

5.4 Clinical improvements and underlying pharmacological mechanisms

If the IDSA is downgraded from level 2 to level 1, it indicates successful for anti-infective therapy. The infection control rate of the experimental group in Visit 2 was 60% and that of the control group was 25%, and the effect of the experimental group was better than that of the control group. This is probably related to the multi-metabolite and multi-target property of FFHB. Its pharmacological effects may not only lie in the direct killing of pathogenic microorganisms, but also be related to the regulation of wound cell molecular biological characteristics, resistance to the formation of bacterial biofilm, and improvement of the wound exudate microenvironment. Further basic research and clinical trial verification are needed to elaborate on the mechanism of FFHB in the treatment of DFI.

The intra-group comparison of wound area at Visit 2 was statistically significant compared with baseline, indicating that the wounds of the subjects in the two groups generally showed a healing trend. Differences for the treatment group at Visit 1 compared to baseline were statistically significant, whereas those for the control group were not. This might be related to the toxicity of silver ions to normal tissues, which slowed the wound healing. Previous research

demonstrated that nano-silver solution could inhibit fibroblasts cultured *in vitro* (FU et al., 2010).

The end point of treatment of diabetic foot should be wound healing, and patients can return to family and society. Infection control is an important step in wound healing. With good antibacterial effect and relatively weak tissue toxicity of FFHB, the wound healing rate of the experimental group was significantly better than that of the control group after 1 month of follow-up.

The basic research of FFHB has shown that it can promote wound healing by inhibiting bacterial reproduction, reducing local inflammation and edema, maintaining a wet healing environment, and promoting wound granulation growth (Zhang et al., 2020; Zheng et al., 2021). Clinical studies have also shown that FFHB can inhibit the body's synthesis of advanced glycation end products to reduce inflammation, remove wound pathogenic microorganisms, control and prevent local infection, promote autolysis of necrotic tissue, and increase the number of growth factors to promote wound healing in diabetic foot (You-shan and Bo-hua, 2014; Wang et al., 2019).

5.5 Economic evaluation: Cost-effectiveness of FFHB vs. ACAWD

Cost-effectiveness analysis aims to identify the most economical treatment plan to achieve a desired treatment outcome. The cost to effect ratio is expressed as the cost required to achieve a unit effect. The cost of pharmacoeconomics includes direct cost, indirect cost and negative cost. Direct costs include both direct medical cost and non-medical expenses. Limited by the precise availability of data, many pharmacoeconomic estimates calculate only direct medical costs. It has been calculated in this study that the cost of the control group was significantly higher than that of the experimental group. From an economic viewpoint, FFHB offered a notable price advantage over ACAWD. In combination with the lack of obvious adverse reactions in both groups of subjects, FFHB was a safe and economical medication for DF mild infection.

5.6 Limitations and future directions

The subgroup analysis of some test indicators, such as MIC trend change for a specific pathogenic microorganism, revealed that more clinical data is necessary to achieve a substantial sample size, and we should expand sample size in future studies. Second, the observation and follow-up time in this trial was relatively short. The wound healing time of most DFI patients was often several months, and the 14-day follow-up time was relatively short. Further prolongation of the observation period is required to demonstrate the long-term efficacy of the test drug. In order to collect complete data on subjects, all subjects included in this study were hospitalized. Outpatients may be considered for inclusion in further studies to make the results more consistent with the real-world situation. Finally, since this study is a clinical trial, there is a lack of verification for the comparison of the *in vitro* antibacterial effects of FFHB and ACAWD.

6 Conclusion

This study compared the effects of FFHB and ACAWD in the treatment of DFI. The results demonstrated that FFHB has significant advantages in promoting wound healing, inhibiting bacterial proliferation, reducing local inflammation and edema, among others. Moreover, when compared to ACAWD, FFHB showed greater cost-effectiveness, offering a safe and economical medicinal choice for mild DF infections.

The study also points out some limitations, such as sample size and follow-up duration, which might influence the conclusions. However, overall, this research provides robust evidence for the application of FFHB in the treatment of DFI and offers valuable guidance for further clinical research and practice.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Dongzhimen Hospital of Beijing University of Chinese Medicine (approval No. DZMEC-KY-2020-40-02). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

GY: Conceptualization, Data curation, Formal Analysis, Writing–original draft. GW: Conceptualization, Resources, Supervision, Writing–original draft. ZL: Formal Analysis, Writing–original draft. LD: Resources, Writing–original draft. NW: Formal Analysis, Writing–original draft. XW: Resources, Writing–original draft. TZ: Resources, Writing–original draft. JZ: Data curation, Writing–original draft, Validation. YL: Data curation, Writing–original draft. TW: Writing–original draft, Resources. YW: Resources, Writing–original draft. HS: Data curation, Writing–original draft. MC: Data curation, Writing–original draft. KZ: Data curation, Writing–original draft. MZ: Data curation, Writing–original draft. XW: Data curation, Writing–original draft. XL: Writing–original draft, Writing–review and editing. SJ: Conceptualization, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1285946/full#supplementary-material

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Mechanism of traditional Chinese medicine in elderly diabetes mellitus and a systematic review of its clinical application

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Objective: Affected by aging, the elderly diabetes patients have many pathological characteristics different from the young people, including more complications, vascular aging, cognitive impairment, osteoporosis, and sarcopenia. This article will explore their pathogenesis and the mechanism of Traditional Chinese medicine (TCM) intervention, and use the method of systematic review to evaluate the clinical application of TCM in elderly diabetes.

Method: Searching for randomized controlled trials (RCTs) published from January 2000 to November 2023 in the following databases: Web of Science, Pubmed, Embase, Cochrane Library, Sinomed, China National Knowledge Internet, Wanfang and VIP. They were evaluated by three subgroups of Traditional Chinese Prescription, Traditional Chinese patent medicines and Traditional Chinese medicine extracts for their common prescriptions, drugs, adverse reactions and the quality of them.

Results and Conclusion: TCM has the advantages of multi-target and synergistic treatment in the treatment of elderly diabetes. However, current clinical researches have shortcomings including the inclusion of age criteria and diagnosis of subjects are unclear, imprecise research design, non-standard intervention measures, and its safety needs further exploration. In the future, the diagnosis of elderly people with diabetes needs to be further clarified. Traditional Chinese patent medicines included in the pharmacopoeia can be used to conduct more rigorous RCTs, and then gradually standardize the traditional Chinese medicine prescriptions and traditional Chinese medicine extracts, providing higher level evidence for the treatment of elderly diabetes with traditional Chinese medicine.

KEYWORDS

elderly diabetes mellitus, traditional Chinese medicine, hypoglycemia, vascular aging, cognitive impairment, osteoporosis, sarcopenia, systematic review

1 Introduction

Diabetes mellitus is a highly prevalent health condition in the aging population. With the aging degree of the population increasing in the past 50 years, the number of older adults (≥65 years old) living with diabetes is expected to grow rapidly in the coming decades and has become the mainstream population of diabetes. Over 25% of people over the age of 65 years have diabetes, and 50% of older adults have prediabetes (Laiteerapong and Huang, 2018; Prevention, 2020). The prevalence of diabetes in adults aged 75–79 years in 2021 is

estimated at 24.0% and is expected to rise to 24.7% in 2045 (IDF, 2021). There are 122.8 million people aged 65–99 years with diabetes worldwide and that number is projected to grow dramatically to 253.4 million in 2045 (IDF, 2017).

It is worth noting that although many available treatment methods can still be considered in healthy elderly individuals when combining hypoglycemic agents to achieve recommended goals, the combination with the lowest risk of hypoglycemia should be considered. Hence, the selection of appropriate hypoglycemic drugs is limited for elderly patients with frailty. In recent years, plant-derived traditional herbal medicine and its phytochemicals have attracted people's attention as a kind of nutrient to prevent the onset and progress of diabetes and its serious complications. Compared with Western medicine, traditional herbal medicine has many advantages in the prevention and treatment of elderly type 2 Diabetes mellitus (T2DM).

It is important to consider the risk of hypoglycemia when combining hypoglycemic agents to achieve recommended goals in healthy elderly individuals. However, the options for selecting appropriate hypoglycemic drugs are limited for frail elderly patients. In recent years, Traditional Chinese medicine (TCM) has gained attention as a nutritional approach to prevent and manage diabetes and its complications. TCM offers several advantages over Western medicine in the context of elderly T2DM management.

Firstly, TCM allows for individualized clinical therapy based on different conditions and constitutions (Zhou et al., 2014a). It views diseases as imbalances within the whole individual rather than isolated organ lesions, emphasizing the regulation of internal and external balance within the body (Qiu, 2007). Secondly, given that diabetes involves complex metabolic disorders and often requires multiple drug treatments, which may increase the risk of hypoglycemia, especially among elderly patients taking sulfonylurea drugs or insulin injections. Traditional herbal medicine can comprehensively regulate bodily functions and support normal glucose metabolism. Importantly, it can replace some pharmaceuticals with severe contraindications for elderly patients, offering better tolerance. Therefore, at present, many elderly diabetic patients who have no obvious response or intolerance to hypoglycemic effects from Western medicine prefer to choose alternative treatment methods, such as herbal medicine or TCM, thus making alternative treatment for diabetes a popular treatment method.

As a result, many elderly diabetic patients who do not respond well to Western medicine or face intolerance to its side effects prefer alternative treatments like herbal medicine or TCM. TCM therapy, with its characteristics of comprehensive regulation, multi-target effects, and personalized medication, has shown remarkable therapeutic efficacy, minimal adverse effects, and a commendable safety profile (Meng et al., 2023). Numerous clinical and basic research studies have provided evidence of TCM's clinical effectiveness in managing diabetes, regardless of age (Shao et al., 2021). For example, in a double-blind, randomized, placebo-controlled study involving 420 patients with impaired glucose tolerance (IGT), it was found that the combination of Tianqi capsule and lifestyle intervention for 12 months reduced the risk of diabetes by 32.1% (Lian et al., 2014). Notably, TCM has a positive impact on elderly diabetes patients by effectively lowering blood glucose levels, reducing the progression of diabetes complications and comorbidities, and significantly extending the lifespan of elderly individuals (Tian et al., 2019). This article reviews the clinical features of elderly diabetes mellitus and the latest clinical applications of TCM in managing elderly diabetes and its complications. It aims to provide insights into supplementary and alternative medicine in the clinical management of chronic diseases in the elderly.

2 The pathological mechanisms in elderly diabetes mellitus

Unlike young patients with diabetes, diabetes in older adults is a highly heterogeneous condition, and diabetic individuals who become old have different characteristics compared to older individuals who become diabetic on functional status, comorbidities, and degree of frailty (Laiteerapong and Huang, 2018) and face particularly difficult challenges (Figure 1). Clinical research has found that older adults with T2DM are frequently associated with cardio-renal challenges and are more likely to have the risk of hypoglycemia in their frail body as well as merge multiple complications and comorbidities which seriously affect the quality of life and lifespan of the elderly (Bellary et al., 2021). The following briefly discusses some clinical features of senile diabetes and outlines its main pathological mechanism.

2.1 The aging process and declining pancreatic function in elderly individuals

As the metabolic capacity of the elderly declines, multiple metabolic disturbances combined with vascular aging contribute to the increasing prevalence of vascular complications in diabetes year by year. Aging increases the susceptibility to T2DM. In both humans and rodent models, glucose-stimulated insulin secretion appears to decrease with advancing age. In humans, this reduction, to some extent, may be associated with decreased expression and function of the GLUT-2 transporter, as well as diminished glucose oxidation (Sun et al., 2023). Furthermore, inadequate inhibition of K^+ efflux and reduced Ca^{2+} uptake (required for insulin granule exocytosis) have been implicated in aging rodent models; however, current human data remain limited. Additionally, a novel contributor to islet cell injury is islet amyloid polypeptide, which is oversecreted along with insulin in insulin-resistant states. This excessive secretion leads to aggregation and amyloid plaque formation, consequently inducing cell apoptosis. This process is particularly prominent in elderly diabetic patients (Gunasekaran and Gannon, 2011).

2.2 The mechanisms of vascular complications in elderly diabetes

Older individuals are more susceptible to the early onset of diabetes vascular complications (Bellary et al., 2021). On the one hand, metabolic disturbances affect vascular endothelial cells, including disruptions in glucose metabolism, lipid metabolism, intestinal microbiota metabolism, inflammation-related

FIGURE 1
During the aging process of the elderly, the β-cells gradually secrete insufficient insulin, accompanied by insulin resistance, leading to an increased risk of diabetes. After diabetes, it can further develop into diabetes complications, such as diabetes retinopathy, diabetes gastroparesis, diabetic kidney disease, diabetes peripheral neuropathy, neurogenic bladder, diabetes foot, etc. At the same time, elderly diabetes patients themselves are prone to hypoglycemia, which is more likely to lead to cardiovascular and cerebrovascular events, and long-term repeated hypoglycemia is easy to cause neurodegenerative diseases. The elderly are also often accompanied by sarcopenia, osteoporosis, etc., and metabolic syndrome can also occur with the decline of metabolic capacity. Elderly diabetes, a series of diabetic complications, and multiple comorbidities will further accelerate the aging of multiple organs, leading to further increased bone fragility, vascular aging, muscle loss, cognitive decline, etc.

metabolites, and the impact of arachidonic acid derivatives on the endothelium (Xue et al., 2023). On the other hand, under the regulation of various cells and their secreted cytokines, key transcriptional regulation pathways such as TLR2/4-NF-κB, p38/MAPK, IL-6/STAT3, and others participate in the immune-inflammatory interactions underlying diabetic vascular complications, ultimately leading to vascular damage and barrier disruption, triggering diabetes-related macrovascular and microvascular complications (Odegaard et al., 2016; Wu et al., 2018).

Specifically, in the context of diabetic nephropathy, high glucose-induced metabolic disturbances and hemorheology lead to impaired renal function. Activation of the Renin-Angiotensin-Aldosterone System (RAAS) results in consequences like glomerular hyperperfusion, hypertension, and high filtration. Simultaneously, there are disruptions in the expression of signaling pathways such as Transforming growth factor-β (TGF-β) signaling pathways, VEGF/VEGFR signaling pathways, Angiopoietin (Ang)/Tie signaling pathways, among others, ultimately driving glomerular fibrosis and progressing towards end-stage pathological conditions like glomerulosclerosis.

Diabetic retinopathy, similarly, is one of the microvascular complications of diabetes. However, due to the high metabolic demand of retinal cells and limited vascular supply, they are particularly sensitive to metabolic disturbances. Structural vascular disruptions are more pronounced in Diabetic Retinopathy (DR) (Yang and Liu, 2022).

Regarding diabetes-related coronary heart disease, it is mainly due to the fact that glucose metabolism disturbances may alter and increase the impact of other risk factors for atherosclerosis. For example, low-density lipoprotein (LDL) is more susceptible to modifications by Advanced Glycation End Products (AGEs) in late-stage glycation. Increased lipoprotein oxidation, increased LDL receptor uptake of LDL protein, and increased platelet aggregation are also disrupted (Madonna et al., 2018). A characteristic feature of macrovascular complications in diabetes is the formation of new blood vessels within plaques. Due to excessive or aberrant neovascularization, there is an increase in capillary density, tissue edema, leading to more frequent arterial atherosclerotic plaque hemorrhage and plaque rupture, along with microvascular dysfunction in the heart (Madonna et al., 2018).

Iron death is a newly discovered iron-dependent regulation of cell death. Research indicates that iron death plays an important role in the pathophysiology and pathogenesis of diabetes and its related complications (Liu et al., 2024). Furthermore, emerging evidence suggests that extracellular vesicle (EVs)-mediated crosstalk between pancreatic islet cells and between organs is involved in the progression of diabetes. EVs derived from β-cells can also affect recipient β-cells and further exert negative effects through autocrine signaling in type 2 diabetes (Wei et al., 2023).

2.3 The pathological mechanisms of comorbidities in elderly diabetes

With the aging of multiple organs, elderly diabetes is often accompanied by other chronic comorbidities. Here, we mainly discuss the pathological mechanisms of several common diabetic comorbidities which include vascular aging, cognitive impairment, loss of muscle, osteoporosis, and hypoglycemia.

2.3.1 Vascular aging

Vascular aging refers to arterial functional, structural, and mechanical changes that occur with aging or age-related metabolic diseases within the cardiovascular system (Ryder et al., 2020; Singam et al., 2020). The prominent structural changes in aging vessels include increased arterial stiffness, reduced compliance, diminished vascular repair and regeneration capacity, and impaired endothelial cell function, ultimately leading to the development of atherosclerosis and calcification (Gopcevic et al., 2021). The inflammation, oxidative stress, autophagy, and the accumulation of AGEs are associated with the entire process of vascular aging.

Oxidative stress is currently recognized as the "ultimate common pathway" for many chronic age-related diseases (Pitocco et al., 2013), as it can disrupt cellular metabolism and homeostasis, leading to endothelial cell damage. Reactive oxygen species (ROS) serve as the major drivers of oxidative stress. T2DM leads to excessive ROS production through various pathways. Early research suggested that glucose could directly stimulate excessive ROS production (Du et al., 1999), but later studies found that high glucose (HG) activates various enzymatic cascades in mitochondria (Rizwan et al., 2020), including the activation of NADPH oxidase (Jansen et al., 2013), NO synthase uncoupling (Sasaki et al., 2008), and the stimulation of xanthine oxidase (Hernandez-Hernandez et al., 2022). Similarly, elderly individuals often have comorbidities such as dyslipidemia and hypertension, which can also induce ROS production.

AGEs are non-enzymatically formed through the condensation of the carbonyl group of reducing sugars with free amino groups in nucleic acids, proteins, or lipids. These compounds then undergo further rearrangement, producing stable and irreversible end products that can alter tissue function and mechanical properties (Twarda-Clapa et al., 2022). AGEs are associated with many age-related diseases and accumulate in various tissues, exerting cytotoxic effects. Research has shown that the AGEs/Receptor for Advanced Glycation End Products (RAGE) signaling pathway plays a central role in diabetic-related atherosclerosis and narrowing processes (Soro-Paavonen et al., 2008; Kopytek et al., 2020). Elevated

glucose levels in T2DM patients can promote the late glycation end-product and collagen cross-linking, resulting in stiff and less hydrolysable collagen proteins, thereby increasing vascular wall stiffness (Aronson, 2003; Reddy, 2004). AGEs stimulate endothelial cells to produce ROS through RAGE activation, and these signaling molecules can activate the NF-κB and downstream signaling pathways (Dorenkamp et al., 2023; Shu et al., 2023). AGEs also inhibit the phagocytic action of macrophages by binding to AGEs receptors, thus promoting inflammation (Du et al., 2023). Additionally, HG-induced AGEs dysregulate the chromatin remodeling through DNA methyltransferases (DNMTs), DNMT1-ten-eleven translocations (TETs), histone modifications, miRNAs, and lncRNAs. This leads to changes in chromatin structure and persistent vascular damage through metabolic memory, ultimately resulting in a chronic inflammatory state and vascular complications (Dhawan et al., 2022).

Autophagy is a critical regulator of cellular metabolism and intracellular homeostasis, playing a crucial role in maintaining the normal function of vascular cells. Autophagy dysfunction has been observed in some age-related diseases such as T2DM (Sehrawat et al., 2023). Reduced autophagic activity not only leads to the delayed and abnormal accumulation of denatured proteins and dysfunctional organelles but also, through various pathways, results in endothelial dysfunction and intimal thickening, exacerbating vascular aging. Autophagy has been shown to play roles in the homeostasis of β-cells, IR, clearance of protein aggregates such as islet amyloid polypeptide, and various insulin-sensitive tissues (Sehrawat et al., 2023).

Moreover, the activation of the inflammasome via the NOD (nucleotide-binding oligomerization domain)-like receptor family, pyrin domain containing 3 (NLRP3) pathway during T2DM can also promote chronic inflammation and exacerbate vascular endothelial cell aging and endothelial dysfunction (Gora et al., 2021).

2.3.2 Cognitive impairment in elderly diabetes

Cognitive impairment is increasingly recognized as a significant comorbidity of diabetes. Diabetes-related cognitive impairment progresses through different stages. The more severe stages, particularly mild cognitive impairment and dementia, often accompanied by progressive deficits, predominantly manifest in elderly individuals (Biessels and Despa, 2018).

Insulin and Insulin-like Growth Factor receptors (IGF) receptors, akin to insulin-like peptides, are expressed in neurons and glial cells, with insulin receptor (IR), insulin-like growth factor 1 (IGF1R), and insulin-like growth factor 2 (IGF2R) signaling through their respective receptors well-expressed in regions such as the hippocampus, striatum, hypothalamus, cerebral cortex, and olfactory bulb (Duarte et al., 2012). In elderly individuals with diabetes, alterations in insulin levels and/or signaling pathways in the brain occur due to cerebral IR. This results in neuronal loss, disruption of peripheral metabolism, and synaptic dysfunction (Wijesekara et al., 2018). Studies have found that impaired brain insulin-PI3K-AKT signaling may promote neurodegeneration in Alzheimer's disease (AD) by downregulating O-GlcNAcylation, subsequently promoting abnormal tau hyperphosphorylation and neurofibrillary degeneration (Liu et al., 2011b). Intravenous or intranasal insulin administration has improved memory function in both humans and animals (Chapman et al., 2018; Wu et al.,

2023b), indicating that compromised insulin signaling pathways may be a primary defect linking AD and T2D.

Currently, a substantial body of research suggests that AD primarily results from an imbalance between the generation and clearance of Aβ, promoting Aβ accumulation in the central nervous system and triggering AD (Hardy and Selkoe, 2002; Selkoe and Hardy, 2016). Hyperglycemic states contribute to cerebral endothelial damage, promote atherosclerosis, affecting cerebral perfusion and function while impeding the clearance of brain metabolites. This may impair the Aβ clearance system, further promoting Aβ deposition in the brain (Hamzé et al., 2022).

2.3.3 Sarcopenia and osteoporosis in elderly diabetes

Sarcopenia is a progressive, systemic skeletal muscle disorder that is associated with an increased risk of adverse outcomes such as falls, fractures, physical disability, and mortality (Schaap et al., 2018).

In elderly patients with T2DM, the pro-inflammatory pathway is activated during the aging process of skeletal muscle. However, due to a decrease in the activity of antioxidant enzymes, the number of mitochondria decreases, and their anti-oxidative capacity decreases, thereby leading to an increase in intracellular accumulation of reactive oxygen species and oxidative stress levels in skeletal muscle (Crescioli, 2020). Besides, low muscle mass is linked to poor blood glucose control (Alabadi et al., 2023). This appears to be a bidirectional relationship, where prolonged exposure of cells and tissues to high blood glucose levels promotes the accumulation of AGEs in skeletal muscle, leading to increased oxidative stress, mitochondrial dysfunction (Ritov et al., 2010; Tabara et al., 2019), and impaired insulin synthesis and metabolism (Gougeon, 2013). All of these factors contribute to muscle damage and a lack of physical activity, ultimately resulting in the loss of muscle mass and function, referred to as muscle wasting syndrome. Therefore, T2DM is also considered a significant predictive factor for sarcopenia (Cruz-Jentoft et al., 2019). In addition, age-related insulin-mediated impaired glucose uptake is related to the gradual deterioration of skeletal muscle structure and function. In the human body, skeletal muscle accounts for over 80% of glucose uptake following oral glucose load, and insensitivity of this organ can lead to IR and elevated blood glucose levels (Merz and Thurmond, 2020). Muscle mass plays a pivotal role in facilitating glucose disposal mediated by insulin, and its reduction can further exacerbate IR (Maliszewska et al., 2019). Potential mechanisms include mitochondrial dysfunction, increased low-grade inflammation, lipid accumulation, and oxidative stress in intramuscular cells, as well as accumulation and decreased autophagy and enzyme activity in aging cells (Jiao and Demontis, 2017; Kalinkovich and Livshits, 2017; Crescioli, 2020; Shou et al., 2020).

The musculoskeletal system is a comprehensive and interconnected system, and diabetic patients with muscle wasting syndrome are more prone to developing osteoporosis, and lower muscle mass and strength, along with higher fat content, can impair bone quality (Herrmann et al., 2020). Due to the long-term blood glucose fluctuations, elderly T2DM patients may experience metabolic disturbances which are unfavorable for bone matrix (HICKMAN et al., 2018). Furthermore, HG levels can lead to osmotic diuresis, and disturbances in calcium-phosphorus metabolism, causing significant loss of trace elements such as calcium and phosphorus, resulting in decreased bone density, decreased levels of bone growth factors and

bone remodeling function (Seyfizadeh et al., 2018; Sinnott-Armstrong et al., 2021). Poor long-term blood glucose control leads to an increase in AGEs which can also lead to abnormalities in bone organic matter metabolism (Zhang et al., 2023).

Overall, the underlying pathophysiological mechanism of bone fragility in diabetes is very complex, including hyperglycemia, oxidative stress, and the accumulation of advanced glycosylation end products, which will damage the characteristics of collagen, increase bone marrow obesity, release inflammatory factors and adipokines from visceral fat, and may change the function of bone cells. Other factors include treatment-induced hypoglycemia, some antidiabetic drugs (such as thiazolidinediones) that have a direct impact on bone and mineral metabolism, and an increased tendency to fall, all of which will lead to an increased risk of fracture in diabetes patients (Napoli et al., 2017).

2.3.4 Hypoglycemia

Clinical research shows that for older patients with diabetes, the result of an intensive hypoglycemic treatment strategy is that the risk of hypoglycemia in patients with T2DM is significantly increased, and the mortality rate with cardiovascular events is increased (Gerstein et al., 2011). As is well known, hypoglycemia is the main cause of myocardial infarction and cardiovascular events, and the regulatory mechanism of hypoglycemia, especially in elderly people, is weakened (Ishikawa et al., 2018). In elderly patients with diabetes, the secretion of incretin is reduced, the storage and release function of glycogen is weakened, the ability of self-regulating hypoglycemia is reduced, the liver and kidney functions are reduced, and multi-drug treatment caused by various chronic comorbidities (including heart disease, stroke, and chronic kidney disease) can increase the risk of severe hypoglycemia (Corsonello et al., 1999; Lipska et al., 2016). The consequences of recurrent hypoglycemic episodes include acute and long-term cognitive changes, arrhythmia and myocardial infarction, severe falls, weakness, and death; For elderly diabetes patients with sympathetic nerve dysfunction, the induction of hypoglycemia is reduced, and asymptomatic hypoglycemia, nonspecific neurological symptoms (improper speech, confusion of thinking, strange behavior) or direct hypoglycemic coma may occur.

3 The mechanisms of TCM in preventing and treating elderly diabetes

The prevalence of diabetes among the elderly is high, and overall blood glucose control is suboptimal. Consequently, the rates of disability and mortality due to complications and comorbidities are elevated. TCM plays a significant role in the treatment of elderly diabetes by improving disorders in glucose and lipid metabolism, controlling risk factors, complications, and comorbidities (Figure 2).

3.1 The mechanisms of TCM in lowering blood glucose and delaying vascular complications

TCM has shown significant efficacy in lowering blood glucose and managing vascular complications in diabetes. Numerous clinical

FIGURE 2
TCM is widely utilized in the treatment of diabetes, its vascular complications, and common comorbidities associated with elderly diabetes. The mechanisms underlying its efficacy have been preliminarily summarized as depicted in the figure below. As illustrated in the figure, traditional Chinese medicine operates through multiple targets and pathways in a synergistic manner to ameliorate diabetes and its related vascular complications and comorbidities. These effects encompass but are not limited to the improvement of oxidative stress, ERS, inflammatory responses, inflammasomes, advanced glycation end products pathways, insulin-related signaling pathways, lipid metabolism pathways, gut microbiota, and bone metabolism, among others.

trials have confirmed the clinical effectiveness of TCM in improving blood glucose levels. The research on the therapeutic mechanisms of TCM has explored a wide range of aspects, including herbal compounds and monomers. For example, berberine, derived from the Chinese botanical drug Huanglian, has become a prominent bioactive compound with potent glucose-lowering effects (Xie et al., 2022). Its therapeutic effect on T2DM was first reported in mice as early as 1986 (Chen and Xie, 1986). Subsequently, extensive research has evaluated the anti-diabetic activity of berberine both *in vitro* and *in vivo* (Han et al., 2021). The anti-diabetic activity of berberine is attributed to its multifaceted mechanisms, including the activation of the AMP-activated protein kinase (AMPK) pathway, activation of GLUT1 and AKT/GLUT4 signaling pathway, enhancement of glucagon-like peptide-1 (GLP-1) levels, upregulation of insulin receptor (InsR) mRNA expression, inhibition of PEPCK and G6Pase expression, suppression of inflammation (IL-1, IL-6, TNF-α, COX-2, and iNOS), and regulation of lipid metabolism, among others (Shrivastava et al., 2023). TCM decoction like Gegen Qinlian

Tang (GQD) have demonstrated their ability to improve high blood sugar and protect pancreatic function by modulating the structure of gut microbiota, thereby restoring intestinal permeability and suppressing inflammation in T2DM rats (Tian et al., 2021). Furthermore, TCM has been proven to synergistically ameliorate multiple metabolic disorders. For instance, the TCM Jinlida (JLD) granules enhance mitochondrial biogenesis and fatty acid oxidation, significantly improving obesity, increased fat content, maintaining glucose and lipid homeostasis, and ameliorating hepatic steatosis and inflammation induced by HFD (Zhang et al., 2019). Recent studies also summarize that Chinese botanical drugs have a significant therapeutic potential in improving T2DM by regulating mitochondrial respiratory chain complexes in various cell types (Zhang et al., 2024).

TCM also demonstrates substantial advantages in preventing and treating vascular complications in diabetes, slowing down vascular aging, and delaying renal lesions. The TCM herbal monomer Danshinone IIA (Tan IIA) can alleviate kidney damage in db/db mice, possibly by inhibiting cell pyroptosis through the

regulation of NLRP3 and thioredoxin-interacting protein (Txnip) expression, thus delaying the progression of diabetic kidney disease (DKD) (Wu et al., 2023a). Dysregulated autophagy is one of the critical mechanisms underlying microvascular complications in diabetes. Emerging research suggests that TCM and their active compounds can improve diabetic kidney damage by regulating autophagy (Liu et al., 2023b). Based on network pharmacology, molecular docking, and experimental validation, a mixture of Schisandra chinensis fruit improved kidney function and pathological changes in DKD rats, possibly by downregulating the AGEs/RAGE signaling pathway, further downregulating the expression of TNF-α, IL-1β, IL-6, upregulating IL-10, among other mechanisms (Li et al., 2023a).

3.2 The mechanisms of TCM in improving the islet function of elderly diabetes patients and diabetes related complications

The experimental study on TCM improving the function of islets in elderly diabetes and diabetes related comorbidities shows that Chinese medicine plays a role in treating elderly diabetes and its complications and comorbidities by regulating the proliferation, apoptosis and differentiation of islet cells, delaying cognitive dysfunction related diseases, regulating bone metabolism and differentiation, and improving muscle loss.

3.2.1 Regulating of pancreatic islet cell proliferation and apoptosis

TCM may treat elderly diabetes by regulating the proliferation and apoptosis of pancreatic islet cells. A TCM formulation known as Shenqi Compound (SQC), composed of Panax Ginseng, Astragali Radix, Rhizoma Dioscoreae, Corni Fructus, Rehmanniae Radix, Salviae Miltiorrhizae Radix et Rhizoma, Radix Trichosanthis, and Rhei Radix et Rhizoma, has been found to significantly control blood glucose levels, inhibit IR, reduce hyperinsulinemia, and protect pancreatic islet hypertrophy. It accomplishes this through alleviating oxidative stress and suppressing inflammation, as well as inhibiting the apoptosis and senescence of β-cells (Yang et al., 2023). Fufang-zhenzhu-tiaozhi formula (FTZ), a patented TCM preparation, has been demonstrated to promote β-cell regeneration by protecting the islets from inflammatory cell invasion, maintaining the number of pancreatic β-cells, and increasing the expression of key markers of new β-cell formation, such as PDX-1, MAFA, and NGN3 (Chen et al., 2023). Research has revealed that Puerarin, an isoflavone derived from the root of Pueraria lobata (Willd.) Ohwi, significantly improves blood glucose stability in high-fat diet-induced diabetic mice by promoting β-cell neogenesis.

Puerarin has demonstrated a significant improvement in blood glucose homeostasis in HFD-induced diabetic mice. Additionally, during the treatment of HFD-fed mice with puerarin, the pancreatic ducts exhibited the presence of markers of new β-cell formation, including insulin, PDX1 (Pancreatic and Duodenal Homeobox 1), and Ngn3 (Neurogenin 3). Moreover, this treatment induced the expression of insulin and PDX1 in the pancreatic ducts,

along with the upregulation of GLP-1R expression, followed by the activation of β-catenin proteins and STAT3 (Wang et al., 2020a).

3.2.2 Slowing vascular aging

Cellular aging is a critical factor in the development of elderly diabetes, while vascular aging is a degenerative condition that occurs in the cardiovascular system as one ages. Research has shown that extracts derived from ginseng, sanqi, and chuanxiong may potentially slow down endothelial cell aging induced by high glucose and high fat (Wang et al., 2020b). This is achieved by enhancing cellular autophagy activity, elevating mitochondrial membrane potential, and reducing the accumulation of DNA damage caused by ROS generation (Wang et al., 2020b). Furthermore, another study discovered that these extracts can lower random blood glucose levels in aging diabetic mice, inhibit the expression of proteins related to the AMPK/mTOR pathway, improve cardiac aging in mice, reduce vascular calcification, and delay vascular aging (Hu et al., 2020).

A considerable number of active components derived from TCM have been demonstrated to inhibit the NLRP3 inflammasome. Published data suggest that many candidate drugs from traditional herbal sources exert anti-inflammatory effects by inhibiting upstream signals of NLRP3, including TXNIP and NF-κB, or by combating oxidative stress, such as promoting Nfr2 signal transduction. Ultimately, these interventions may lead to targeted inhibition of the NLRP3 inflammasome, resulting in the amelioration of oxidative stress, endoplasmic reticulum stress (ERS), inflammatory pathways, and the suppression of pro-inflammatory cytokines. This approach holds promise for improving diabetes and its complications (Bai et al., 2021).

3.2.3 Improving diabetes-related cognitive impairment

Extensive research has confirmed the significant therapeutic effects of TCM on diabetes-related cognitive dysfunction (DCD). Most TCM and their active ingredients can ameliorate DCD by reducing IR, microvascular dysfunction, abnormal gut microbiota composition, inflammation, and damage to the blood-brain barrier, cerebral blood vessels, and neurons under hyperglycemic conditions (Meng et al., 2021). Specifically, the underlying mechanisms involve the regulation of various signaling pathways, such as PI3K/Akt/GSK-3β signaling pathways (Guo et al., 2023), RhoA/ROCK/moesin and Src signaling pathways (Li et al., 2018b), AGEs/RAGE (Wang et al., 2012), NLRP3 inflammasome (Tian et al., 2023), ERS (Chen et al., 2018), and Nrf2/ARE (Liu et al., 2019), among others. These pathways collectively improve IR, synaptic plasticity, and exert anti-inflammatory, antioxidant, anti-ERS, and anti-neuronal apoptosis effects.

Recent studies have shown that Danshinone IIA (TAN) lowers fasting blood glucose (FBG) levels and enhances cognitive and memory function in HFD and streptozotocin (STZ)-induced diabetic animals. The potential mechanism may be related to the modulation of the gut microbiota by TAN. TAN regulates neuronal biomarkers, reduces serum levels of LPS and TNF-α, corrects the reduced abundance of specific microbial taxa in diabetic rats, regulates the abundance of specific microbial taxa to control

pathways related to fatty acid lipid metabolism and biosynthesis, and significantly restores decreased levels of isobutyric acid and butyric acid (Zheng et al., 2022a). Similar studies have also demonstrated the beneficial effects of dendrobium mixture (consisting of Dendrobii Caulis, Astragali Radix, and Rehmanniae Radix) in alleviating DCD by regulating gut microbiota composition (Zheng et al., 2022b).

3.2.4 Improving diabetic osteoporosis

Diabetic osteoporosis (DOP) is a chronic bone metabolic disorder induced by diabetes, and research has shown that TCM can treat DOP by improving bone metabolism and differentiation. In a recent study, Epimedium brevicornum, mainly composed of Epimedium brevicornum polysaccharides, was found to promote bone formation and ameliorate apoptosis by regulating the Bax/Bcl-2 signaling pathway, thus accelerating osteogenesis in osteoblasts in a HG-induced DOP model (Lei et al., 2023). Arabinoxylans (PPCP-1) isolated from the bark of Phedendron chinense Schneid were shown to downregulate the expression of AGEs receptors induced by streptozotocin in the tibia of diabetic rats, thereby improving diabetes-associated osteoporosis (Wang et al., 2021). Anemarrhenae Rhizoma/Phellodendri Chinensis Cortex (AR/PCC) herbal compound has been shown to effectively lower fasting blood glucose levels in diabetic rats, reverse the osteoporotic phenotype, significantly improve trabecular area percentage, trabecular thickness, and trabecular number in vertebral bodies, and reduce trabecular separation (Xu et al., 2022). Another research has found that the AR/PCC herbal compound improved osteogenesis, promoted neurite outgrowth, and enhanced angiogenesis (Fu et al., 2023) by reducing the overexpression of Nlrp3, Asc, Caspase1, Gsdmd, and IL-1β, thus alleviating abnormal activation of apoptosis in vertebral osteoblasts of diabetic rats (Fu et al., 2023). Additionally, it upregulated the antioxidant response protein Nrf2, activating the antioxidant pathway, while simultaneously reducing its negative feedback regulator Keap1 (Fu et al., 2023). Ligustroflavone, an active compound in Ligustrum lucidum (Scrophulariaceae), has been found elevate parathyroid hormone (PTH) levels in diabetic mice, regulate calcium metabolism, and prevent osteoporosis (Feng et al., 2019). Rehmannia glutinosa (Scrophulariaceae) regulated alkaline phosphatase activity and bone alkaline phosphatase levels in diabetic rats, enhancing bone density and improving bone microstructure. Catalpol (CAT), acteoside (ACT), and echinacoside (ECH) extracted from Rehmannia glutinosa promoted bone formation by regulating the IGF-1/PI3K/mTOR signaling pathway (Gong et al., 2019).

3.2.5 Improving diabetic muscle loss

T2DM in the elderly can lead to a decline in muscle mass and grip strength. Skeletal muscle, as one of the largest organs in the human body, is responsible for up to 80% of postprandial glucose uptake (Merz and Thurmond, 2020). Impairments in skeletal muscle glucose uptake and utilization play a critical role in the development of T2DM. Previous research has demonstrated that the combination of Astragalus membranaceus and Dioscorea opposita improves diabetic muscle atrophy by addressing mitochondrial dysfunction mediated by the Rab5a/mTOR pathway (She et al., 2023). Another herbal combination, AR/PCC reverses muscle atrophy in diabetic mice through the Akt/mTOR/FoxO3 signaling pathway (Zhang et al., 2014b).

4 The systematic review of TCM's clinical application for elderly diabetes

4.1 Method

4.1.1 Search strategy and study selection

Relevant studies were identified by searching for papers published from January 2000 to November 2023 in the following databases: Web of Science, Pubmed, Embase, Cochrane Library, Sinomed, China National Knowledge Internet, Wanfang and VIP. Search terms included the following: ("diabetes" or "diabetes mellitus" or "diabetes nephropathy" or "diabetes retinopathy" or "diabetes peripheral neuropathy" or "diabetic cardiomyopathy" or "diabetic gastroparesis" or "diabetic foot" or "diabetes and osteoporosis" or "diabetes and sarcopenia" or "diabetes and coronary heart disease" or "diabetes and arteriosclerosis" or "diabetes and cognitive impairment") and (older or elderly or senile) and ("randomized controlled trial" or "controlled clinical trial" or "random" or "randomly" or "randomized" or "control" or "RCT") and ("TCM" or "traditional Chinese medicine" or "Chinese medicinal herb" or "Chinese herbal medicine" or "decoction" or "formula" or "prescription" or "powder" or "Chinese patent medicine" or "Chinese patent drug" or "Chinese herbal compound prescription" or "granule" or "pill" or "tablet" or "capsule" or "admixture" or "Chinese medicine extract" or "extractive" or "glycosides" or "polysaccharide" or "oil"). The authors of the identified papers were contacted for additional information if necessary.

4.1.2 Inclusion and exclusion criteria

We included clinical studies that satisfied the following criteria: (a) Study participants were diagnosed with elderly diabetes, with or without diabetes nephropathy, diabetes peripheral neuropathy, diabetes retinopathy, diabetes cardiomyopathy, diabetes gastroparesis, diabetes foot, cognitive impairment, osteoporosis, sarcopenia, coronary heart disease, and arterial sclerosis. (b) Sample size ≥60; (c) The study follow-up ≥12 weeks.

We excluded clinical studies with the following features: (a) Studies that were non-randomized; (b) Patients that were enrolled with no definite. (c) Sample size <60; (d) The study follow-up <12 weeks; (e) Non-oral Chinese medicine treatment; (f) TCM treatment based on syndrome differentiation, the therapeutic drugs are uncertain; (g) The control group was not a western drug or the placebo; (h) studies that reported only symptomatic changes in patients without objective laboratory measurements or physical examination; (i) Conference papers or dissertations; (j) Full text not found.

4.1.3 Study selection and data extraction

According to the above design, two reviewers (Qiqi Zhang and Shiwan Hu) searched the online databases listed above and assessed the eligibility of these articles and made decisions on every research (inclusion or exclusion) independently. If they did not reach the same decision, the concerned articles were discussed with a third reviewer (Zishan Jin). Three reviewers (Qiqi Zhang, Shiwan Hu and Zishan Jin) extracted data independently from each study. Differences of extracted data were solved after discussion with a fourth reviewer (Boxun Zhang).

FIGURE 3
Flowchart of database searching and study identification.

4.1.4 Data statistics

All the studies were divided into three subgroups of Traditional Chinese Prescription, Traditional Chinese patent medicines and Traditional Chinese Medicine Extracts for analysis. If there were ≥5 studies included, the frequency of using TCM will be statistically analyzed. For adverse reactions, the frequency and number of symptoms in the control group and intervention group were separately counted. The above analyses were conducted in Microsoft Excel.

4.1.5 Quality assessment and ConPhyMP statement

Quality assessment of all the trials included in this review was independently evaluated by three reviewers (Qiqi Zhang, Shiwan Hu and Zishan Jin) using Jadad Scale (Jadad et al., 1996). Any disagreement was resolved by discussions with a fourth reviewer (Boxun Zhang).

Two researchers (Qiqi Zhang and Shiwan Hu) evaluated all studies on traditional Chinese medicine extracts using the guidelines

outlined in the ConPhyMp statement (Heinrich et al., 2022). If there is any dispute, it shall be determined by the third researcher (Zishan Jin).

4.2 Result

4.2.1 Study inclusion

We searched 26,303 articles from eight databases, and after deleting duplicates, the number of articles was reduced to 18,187. According to the title and abstract of the articles, we excluded 17,254 articles for reasons including animal experiments, case reports or reviews, and not related to TCM treatment of elderly diabetes. Subsequently, we downloaded the full text of the remaining 933 articles for further screening, and according to the inclusion and exclusion rules, we finally included 160 articles. Articles on elderly diabetic gastroparesis were excluded because they were all followed up for less than 12 weeks. An article on elderly diabetes with sarcopenia was also excluded due to its study size <60 participants. The flow chart of the study selection process is shown in Figure 3.

4.2.2 Study characteristics

All the included 160 studies were conducted in China, of which 159 were published in Chinese and 1 in English. The control group in 159 trials were oral western medicine or insulin injection therapy, and the control group in 1 trial was placebo.

4.2.3 TCM for elderly diabetes mellitus and islet function

4.2.3.1 Traditional Chinese Prescription

A total of 28 RCTS, involving 2737 subjects, were conducted on Traditional Chinese Prescription. The age range of the included subjects was between 50 and 93 years, and the duration of the intervention ranged from 12 weeks to 4 months (Supplementary Table S1; Supplementary Table S2). (Xue et al., 2010; Li and Chen, 2011; Fu et al., 2013; Wang et al., 2013; Zhou and He, 2013; Zhu and Li, 2013; Zhou et al., 2014b; Li et al., 2014; Wu and Zheng, 2015; Liu, 2016; Zhao, 2016; Ma, 2017b; Zou, 2017; Ailiyasi and LAI, 2019; Su, 2020b; Dai, 2020; Ding, 2020; Xu et al., 2020; Ni et al., 2021; Wei et al., 2021; Zhu, 2021; Wang, 2022c; Ma and Li, 2022; Sun et al., 2022; Zha, 2022; Zhao and Zhi, 2022; Han, 2023; Jiang, 2023). There were 22 kinds of Traditional Chinese Prescription in the intervention group, of which the most commonly used were Gegen Qinlian Decoction (3 RCTs), Liuwei Dihuang Decoction (2 RCTs), Sanhuang Decoction (2 RCTs), Jiangtangjing Granules (2 RCTs).

The most commonly used drugs included *Astragalus mongholicus Bunge* [Fabaceae, Astragali radix] (20 times), *Dioscorea oppositifolia L.* [Dioscoreaceae, Dioscoreae rhizoma] (18 times), *Pueraria montana* var. *lobata (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep* [Fabaceae, Puerariae lobatae radix] (13 times), *Coptis chinensis Franch.* [Ranunculaceae, Coptidis rhizoma] (12 times), *Rehmannia glutinosa (Gaertn.) DC.* [Orobanchaceae, Rehmanniae Radix] (12 times) (Supplementary Table S3a).

Ni et al. (2021); Sun et al. (2022); Jiang (2023) all conducted experiments using Gegen Qinlian Decoction, and the three studies

all targeted elderly diabetic patients with gastrointestinal dampness and heat syndrome. However, the composition and dosage of Gegen Qinlian decoction in Jiang's study were different from those in the other two trials. Jiang et al. found that Gegen Qinlian Decoction could improve the blood glucose level and islet function of the subjects. Ni et al. and Sun also found that Gegen Qinlian Decoction was beneficial to reduce the lipid metabolism indicators of the subjects.

Zhu (2021); Ma and Li (2022); Zhao and Zhi (2022) all used Liuwei Dihuang Decoction combined with western medicine for the treatment of elderly diabetes, but the composition and dosage of the prescription used in the three studies were different. The results showed that in addition to reducing the blood sugar level of the subjects, the Liuwei Dihuang Decoction used by Zhu could also improve the level of serum inflammatory factors in the patients, and the prescription used by Zhao et al. could also improve the blood lipid index of the patients. Two studies using Sanhuang Decoction in elderly patients with diabetes showed that it can improved blood glucose level, serum inflammatory factors and oxidative stress, as well as HOMA-IR, TC and TG levels (Ailiyasi and LAI, 2019; Wei et al., 2021). Xue et al. (2010); Zhu and Li (2013) used Jiangtangjing Granules and found that compared with conventional western medicine treatment, Jiangtangjing Granules could reduce the indicators of glucose and lipid, regulate the coagulation function of patients, and improve their prethrombotic state.

Of the 28 RCTs, nine studies evaluated measures of islet function, including Gegen Qinlian Decoction, Erban Decoction, self-designed Yangyin Xiaoke Recipe, Sanhuang Decoction, Jingui Shenqi Prescription, Modified Taohe Chengqi Decoction and Yuye Decoction. The results all proved that Traditional Chinese Prescriptions have positive effect on improving islet function in elderly diabetic patients.

4.2.3.2 Traditional Chinese patent medicines

A total of 25 RCTs involving 2338 subjects explored the application of Traditional Chinese patent medicines in elderly diabetes. The age range of the included population ranged from 55 to 89 years, and the intervention period was 12–30 weeks (Supplementary Tables S1; Supplementary Table S2). (Zhang, 2003b; a; Dai and Ou, 2005; Yu et al., 2007; Liu, 2008; Niu and Fang, 2008; Wang and Zhao, 2012; Wu et al., 2012; Hu et al., 2014; Deng et al., 2015; Xia, 2016; Zhao and Yao, 2016; Zhong et al., 2017; Liu and Kang, 2018; Xiao and Zheng, 2018; Bao and Fang, 2019; Hou et al., 2019; Cheng et al., 2020; Jiang et al., 2020; Wu and Shi, 2020; Xiao et al., 2021; Zhao et al., 2021; Li et al., 2022; Han et al., 2023; Li et al., 2023c) The included studies involved a total of 14 Traditional Chinese patent medicines, including Jinqi Jiangtang Tablets (4 RCTs), Jinlida Granules (3 RCTs), Liuwei Dihuang Pills (3 RCTs), Xiaoke Pills (3 RCTs), Shenqi Jiangtang Granules (3 RCTs), Danzhi Jiangtang Capsules (2 RCTs), Yuquan Pills (1 RCT), Shiwei Yuquan Tablets (1 RCT), Jinkui Shenqi Pills (1 RCT), Shenqi Jiangtang Tablets (1 RCT), Xuefu Zhuyu Pills (1 RCT), Maiwei Dihuang Pills (1 RCT), Xuezhikang Capsules (1 RCT), Qiju Dihuang Pills (1 RCT). Among them, Yuquan Pills, Shiwei Yuquan Tablets, Danzhi Jiangtang capsule and Jinkui Shenqi Pills were not included in Pharmacopoeia of the People's Republic of China 2020 (Committee, 2020). In addition,

Shenqi Jiangtang Granules is not included in the Pharmacopoeia, but its Tablets -- "Shenqi Jiangtang Tablets" has been included.

In these Traditional Chinese patent medicines, commonly used drugs included *Rehmannia glutinosa (Gaertn.) DC.* [Orobanchaceae, Rehmanniae Radix] (16 times), *Alisma plantago-aquatica subsp. orientale (Sam.) Sam.* [Alismataceae, Alismatis rhizoma] (12 times), *Dioscorea oppositifolia L.* [Dioscoreaceae, Dioscoreae rhizoma] (12 times), *Astragalus mongholicus Bunge* [Fabaceae, Astragali radix] (11 times), *Poria cocos (Schw.) Wolf Poria* [Polyporaceae, Poria] (11 times) (Supplementary Table S3b). Xiaoke Pills contain glibenuride 0.25 g. Wang and Zhao (2012); Zhong et al. (2017); Xiao and Zheng (2018) explored the efficacy of Xiaoke pills in the treatment of elderly diabetes mellitus. The results showed that Xiaoke pills can reduce the levels of FBG, 2hPBG and HbA1c, and the incidence of hypoglycemia is lower than control group.

Of the 25 RCTs, 10 studies evaluated indicators of islet function, including Danzhi Jiangtang Capsules, Jinlida Granules, Liuwei Dihuang Pills, Maiwei Dihuang Pills, Shenqi Jiangtang Tablets, Shiwei Yuquan Tablets and Yuquan Pills. All studies showed that they could improve the islet function.

4.2.3.3 Traditional Chinese Medicine Extracts

Only one study used Traditional Chinese Medicine Extracts in elderly patients with diabetes. Cheng et al. (2023) applied *Zea mays L.* [Poaceae, corn silk] to elderly patients with newly diagnosed T2DM. Compared with placebo, it was found to reduce FBG and insulin resistance, regulate serum cholesterol levels, and enhance endogenous antioxidant capacity, with no adverse effects on liver and kidney function. Some studies have found that corn silk aqueous extract can inhibit advanced glycation end products (AGEs), and has positive effects on anti-diabetes and anti-aging. However, the pharmacological effects of corn silk against diabetes have been mostly verified *in vivo* or *in vitro* experimental models, and more studies on elderly diabetic patients have not been carried out (Supplementary Table S1; Supplementary Table S2). (Farsi et al., 2008)

4.2.4 TCM for elderly DKD
4.2.4.1 Traditional Chinese prescription

There are 21 RCTs to explore the effect of Traditional Chinese Prescription in elderly DKD, involving a total of 1987 subjects. The age range of the included population ranged from 40 to 80 years, and the intervention duration was 12 weeks– to 24 months (Supplementary Table S4; Supplementary Table S5). (Wen et al., 2006; Gao et al., 2010; Ou et al., 2011; Chen, 2015; Feng et al., 2015; Mi et al., 2015; Zhao et al., 2016b; Chen et al., 2016; Li et al., 2018a; HU and ZHANG, 2018; Jiang et al., 2019; Jin, 2019; Li, 2019; Su et al., 2019; Yang, 2021a; Zhang et al., 2021; Wang, 2022a; Lin, 2022; Zhang et al., 2022; Li et al., 2023b; Feng et al., 2023) Among the 21 studies, three RCTs explored the preventive effect of Traditional Chinese Prescription on DKD in the elderly. After 24 months of follow-up, it was found that compared with the control group, Yiqi Guben Decoction reduced the incidence of DKD in the elderly (Su et al., 2019; Wang, 2022a; Lin, 2022).

Of the other 18 RCTs, 10 studies defined the stage of DKD, and they were mostly applied to stage III or IV. In these studies, a total of 18 prescriptions were involved, and the most commonly used drugs

included *Astragalus mongholicus Bunge* [Fabaceae, Astragali radix] (17 times), *Dioscorea oppositifolia L.* [Dioscoreaceae, Dioscoreae rhizoma] (10 times), *Poria cocos (Schw.) Wolf Poria* [Polyporaceae, Poria] (10 times), *Atractylodes macrocephala Koidz.* [Asteraceae, Atractylodis macrocephalae rhizoma] (9 times), *Cornus officinalis Siebold & Zucc.* [Cornaceae, Corni fructus] (9 times), *Salvia miltiorrhiza Bunge* [Lamiaceae, Salviae miltiorrhizae radix et rhizoma] (9 times) (Supplementary Table S6a).

Both (Zhao et al., 2016b; Li et al., 2018) used Huangqi Guizhiwuwu Decoction to treat DKD in the elderly, but the dosage of them were different. Zhao et al. found that Huangqi Guizhiwuwu decoction can improve blood glucose and kidney function index. Li et al. found that Huangqi Guizhi Wuwu Decoction could reduce the expression of TGF-β gene while improving UAER. Jiang et al. (2019); Li (2019) used Yiqi Yangyin Decoction to observe its efficacy in elderly diabetes, but the composition and dosage were different. Both studies found that Yiqi Yangyin Decoction could improve renal function and reduce the level of inflammation in the body. The prescription Jiang et al. used was also able to lower ET levels, which plays an important role in modulation of glomerular filtration rate and renal blood flow, control of renin release, and regulation of transport of sodium, water, protons, and bicarbonate (Kohan et al., 2011).

4.2.4.2 Traditional Chinese patent medicines

There were 37 RCTs to explore the application of Traditional Chinese patent medicines, involving a total of 3447 subjects. The age range of the included population ranged from 50 to 94 years old and the intervention period was 12 weeks to 6 months (Supplementary Table S4; Supplementary Table S5). (Wang and Su, 2007; Bai et al., 2008; Yi et al., 2009; Hong, 2010; Huang et al., 2010; Shu et al., 2010; Sun et al., 2012a; Sun et al., 2012b; Peng and Guo, 2013; Shen et al., 2013; Zhang et al., 2014a; Huang, 2014; Zhu, 2014; Hu et al., 2016; Li and Wang, 2016; Pan and Shang, 2016; Wang et al., 2016; Xie et al., 2016; Yang and Liu, 2016; Ma, 2017a; Chen, 2018; Hu, 2018; Wang, 2018; Wang and Cao, 2018; Fang et al., 2019; Lin et al., 2019; Shi et al., 2019; Su, 2020a; Li and Zhou, 2020; Zhong et al., 2020; Guo, 2021; Shen et al., 2021; Yu et al., 2021; Wang, 2022b; Xu and Wang, 2022; Liu et al., 2023a; Wang et al., 2023) The studies involved a total of 13 Traditional Chinese patent medicines, including Bailing Capsules (10 RCTs), Compound Danshen Dripping Pills (7 RCTs), Shenyan Kangfu Tablets (4 RCTs), Yishen Huashi Granules (4 RCTs), Jinshuibao Capsules (4 RCTs), Huangkui Capsules (2 RCTs), Bailing Tablets (1 RCTs), Congrong Yishen Granules (1 RCT), Jinlida Granules (1 RCT), Jinshuibao Tablets (1 RCT), Niaoduqing Granules (1 RCT), Qi-Kui Granules (1 RCT), Shen'an Capsules (1 RCT). Bailing Tablets, Qi-Kui Granules, Shen'an Capsules, Niaoduqing Granules, Huangkui Capsules were not included by Pharmacopoeia of the People's Republic of China 2020 (Committee, 2020). Jinshuibao Capsules and Jinshuibao Tablets are both included in Chinese Pharmacopoeia, but they contain different doses of fermented cordyceps sinensis powder. Commonly used medicines include *Cordyceps sinensis (BerK.) Sacc.* [Clavicipitaceae, Cordyceps] (16 times), *Salvia miltiorrhiza Bunge* [Lamiaceae, Salviae miltiorrhizae radix et rhizoma] (12 times), *Alisma plantago-aquatica subsp. orientale (Sam.) Sam.* [Alismataceae, Alismatis rhizoma] (9 times), *Panax ginseng*

TABLE 1 TCM for elderly DR.

Study	Subjects (Age range)	Ages[a]	No. of intervention group/control group	Treatment of intervention group[b]	Dose of intervention group	Treatment of control group	Dose of control group	Duration	Outcomes[c]	Adverse reactions
Traditional Chinese Prescription										
Li et al., 2022 (2)	Elderly DR	control group: 62.97 ± 5.28 years old; intervention group: 63.26 ± 6.01 years old	39/39	Danhuang Mingmu Decoction + Calcium Dobesilate	1 dose, 2/d	Calcium Dobesilate	0.5 g, 3/d	5 months	vision, MD, Macular thickness, Bleeding spot area, Hemangioma volume, FBG, 2hPBG, IGF-1, VEGF	control group: loss of appetite (1), vomit (2); intervention group: loss of appetite (1), vomit (1)
Wei and Gao (2012)	Elderly DR (stage I-III, 58–72 years old)	69.3 ± 5.8 years old	40/40	Zhenwu Decoction + Conventional Western Medicine Treatment	100 mL, 2/d	Conventional Western Medicine Treatment	NM	3 months	vision, ET	NM
Liu et al. (2011a)	Elderly DR (stage I-III, 64–78 years old)	72.6 years old	60/60	Zhenwu Decoction + Conventional Western Medicine Treatment	100 mL, 2/d	Conventional Western Medicine Treatment	NM	3 months	vision, ET	NM
Traditional Chinese patent medicines										
Wang and Du (2020)	Elderly DR (stage I-III, 60–83 years old)	control group: 68.35 ± 6.82 years old; intervention group: 69.52 ± 7.11 years old	44/42	Compound Xueshuantong Capsules†+Calcium Dobesilate	1.5 g, 3/d	Calcium Dobesilate	0.5 g, 3/d	5 months	vision, MD, Macular thickness, Bleeding spot area, Hemangioma volume, WBV, PV, FIB	control group: loss of appetite (2), gastrointestinal discomfort (2); intervention group: nausea (1), gastrointestinal discomfort (1), loss of appetite (1)
Yan and Yuan. (2014)	Elderly DR (stage I-III)	control group: 68.8 years old; intervention group: 65.5 years old	40/60	Compound Danshen Dropping Pills†+Calcium Dobesilate	10 pills, 3/d	Conventional Western Medicine Treatment	NM	6 months	vision, MD, number of hemangioma, bleeding spot area	NM
Zhang and Zhang (2012)	Elderly DR (stage I-III, 64–78 years old)	72.6 years old	30/30	Qiju Dihuang Pills†+Iodizedlecithin + Adenosine triphosphate + Vitamin tablets	8 pills, 3/d	Iodizedlecithin + Adenosine triphosphate + Vitamin tablets	Iodizedlecithin: 3mg, 2/d; Adenosine triphosphate: 40mg, 2/d; Vitamin tablets: 1–2 tablets, 1/d	3 months	vision, ET	NM

[a]Ages were displayed as mean ± standard deviation or mean.
[b]"†" indicated that it was included in Pharmacopoeia of the People's Republic of China 2020.
[c]"*" showed no significant difference between the intervention group and the control group.
Abbreviation: NM, not mentioned; FBG, fasting blood glucose; 2hPBG, 2-h Postprandial blood glucose; TGF-1, transforming growth factor-1; VEGF, vascular endothelial growth factor; ET, endothelin; WBV, whole blood viscosity; PV, plasma viscosity; FIB, fibrinogen; MD, mean defect.

C.A.Mey. [Araliaceae, Ginseng radix et rhizoma] (9 times), *Poria cocos (Schw.) Wolf Poria* [Polyporaceae, Poria] (8 times) (Supplementary Table S6b).

Of the 37 studies, 22 RCTs defined the stage of DKD in the enrolled population. 16 of these studies were applied to patients with stage 3 and below DKD. The positive effects of Jinshuibao Tablets, Niaoduqing Granules, Bailing Capsules, Jinshuibao Capsules, Jinshuibao Capsules and Shenyan Kangfu Tablets on stage 3–5 elderly DKD have been verified.

4.2.4.3 Traditional Chinese Medicine Extracts

There was only one study on the effect of Traditional Chinese Medicine Extracts on elderly DKD (Supplementary Table S4; Supplementary Table S5). Chen et al. (2022) applied Haikun Shenxi Capsule to early elderly patients with DKD and found it could not only improve the kidney function, but also reduce the inflammatory response and the expression of TGF-β1 and MMP-2. Haikun Shenxi Capsule is composed of Fucoidan, which can protect kidney by improving kidney inflammation, anti-oxidation and anti-fibrosis. In addition, Fucoidan can also counteract renal aging by inhibiting the activity of AMPK-ULK1 signaling pathway. (Zahan et al., 2022).

4.2.5 TCM for elderly DR
4.2.5.1 Traditional Chinese Prescription

Three studies explored the role of Traditional Chinese Prescription in elderly DR, involving 276 participants. The age range of the included population ranged from 58 to 78 years and the intervention period was 3 months–5 months (Table 1; Supplementary Table S7). (Liu et al., 2011a; Wei and Gao, 2012; Li, 2022) The three studies involved two Traditional Chinese Prescription, including Danhuang Mingmu Decoction and Zhenwu Decoction.

4.2.5.2 Traditional Chinese patent medicines

Three studies explored the use of Traditional Chinese patent medicines in elderly DR, including 246 participants. The age range of the included subjects ranged from 60 to 83 years old, and the intervention time was 3 months–6 months (Table 1; Supplementary Table S7). (Zhang and Zhang, 2012; Yan and Yuan, 2014; Wang and Du, 2020) The Traditional Chinese patent medicines involved in the three studies included Compound Xueshuantong Capsules, Compound Danshen Dripping Pills and Qiju Dihuang Pills, all of which were included in Pharmacopoeia of the People's Republic of China 2020 (Committee, 2020).

4.2.6 TCM for elderly DPN
4.2.6.1 Traditional Chinese Prescription

Five studies explored the use of Traditional Chinese Prescription in elderly DPN, involving a total of 446 participants. The age range of the included population ranged from 60 to 80 years, and the intervention period was 12 weeks to 3 months (Table 2; Supplementary Table S8). (Liu et al., 2012; Li et al., 2016b; Guo, 2016; Xu and Zhou, 2017; Yang and Xing, 2019) The prescriptions used in these studies vary, and commonly used Chinese medicines include *Astragalus mongholicus Bunge* [Fabaceae, Astragali radix] (4 times), *Spatholobus suberectus Dunn* [Fabaceae, Spatholobi caulis] (4 times), *Achyranthes bidentata Blume* [Amaranthaceae,

Achyranthis bidentatae radix] (3 times), *Angelica sinensis (Oliv.) Diels* [Apiaceae, Angelicae sinensis radix] (3 times), *Carthamus tinctorius L.* [Asteraceae, Carthami flos] (3 times), *Paeonia lactiflora Pall.* [Paeoniaceae, Paeoniae radix rubra] (3 times), *Prunus persica (L.) Batsch* [Rosaceae, Persicae semen] (3 times) (Supplementary Table S9).

4.2.6.2 Traditional Chinese Medicine Extracts

One RCT evaluated the role of berberine in elderly DPN, involving 68 participants. The age range of the included population ranged from 60 to 80 years, and the intervention period was 12 weeks (Table 2; Supplementary Table S8) (Wang and Zhang, 2009). After berberine intervention, not only can reduce FBG, HbA1c and 24h-UTP, but also increase the levels of MNCV and SNCV in elderly diabetic patients. Berberine is an effective component of *Coptis chinensis Franch.* [Ranunculaceae, Coptidis rhizoma]. Studies have found that it may play a role in protecting neurons through various signaling pathways such as Pl3K/Akt/Bcl-2 pathway, Nrf2/HO-1 pathway and MAPK signaling pathway. (Lin and Zhang, 2018).

4.2.7 TCM for elderly diabetic Cardiomyopathies (DCM)

Two studies explored the effect of TCM on DCM in the elderly and included studies of Traditional Chinese Prescription only. A total of 146 participants aged between 60 and 80 years were included in the study. The intervention period was 12 weeks (Table 3; Supplementary Table S10). Xing et al. (2023) applied Yangyin Yiqi Huoxue Recipe to treat elderly DCM complicated with heart failure and found that Yangyin Yiqi Huoxue Recipe could improve heart function while lowering blood sugar, and its mechanism might be related to regulating VEGF expression. Chen (2021) treated the elderly diabetic patients complicated with heart arrhythmia with Zhigancao Decoction and found that it could improve the cardiac autonomic nerve function and reduce the level of inflammation.

4.2.8 TCM for elderly DOP
4.2.8.1 Traditional Chinese Prescription

Nine studies explored the efficacy of Traditional Chinese Prescription in elderly patients with DOP, involving a total of 934 subjects. The age range of the included population ranged from 52 to 84 years, and the intervention duration was 12 weeks to 6months (Table 4; Supplementary Table S11). (Li, 2015; Hu et al., 2017; ZONG and ZHANG, 2017; Li et al., 2018c; LIU et al., 2018; ZHANG, 2019; Xiao, 2020; Yang, 2021b; Lin, 2021) Chinese medicines commonly used in nine prescriptions include *Epimedium sagittatum (Siebold & Zucc.) Maxim.* [Berberidaceae, Epimedii folium] (7 times), *Angelica sinensis (Oliv.) Diels* [Apiaceae, Angelicae sinensis radix] (6 times), *Rehmannia glutinosa (Gaertn.) DC.* [Orobanchaceae, Rehmanniae radix praeparata] (6 times), *Astragalus mongholicus Bunge* [Fabaceae, Astragali radix] (5 times) (Supplementary Table S12).

4.2.8.2 Traditional Chinese patent medicines

Three studies explored the efficacy of Traditional Chinese patent medicines in elderly DOP, involving a total of 256 participants. The age range of the included population ranged from 49 to 75 years, and

TABLE 2 TCM for elderly DPN.

Study	Subjects (Age range)	Ages[a]	No. of intervention group/control group	Treatment of intervention group	Dose of intervention group	Treatment of control group	Dose of control group	Duration	Outcomes[b]	Adverse reactions
Traditional Chinese Prescription										
Yang and Xing (2019)	Elderly DPN of qi deficiency and blood stasis syndrome (65–76 years old)	control group: 68.59 ± 2.12 years old; intervention group: 67.91 ± 2.18 years old	38/38	Modified Buyang Huanwu Decoction + Mecobalamin Injection	250 mL, 2/d	Mecobalamin Injection	0.5–1.0 mg, 1/d	3 months	FBG, 2hPBG, HbA1c, SF, SOD, GSH-Px	control group: headache (1, gastrointestinal discomfort (2), rash (3); intervention group: headache (1, gastrointestinal discomfort (4), rash (3)
Xu and Zhou (2017)	Elderly DPN (60–80 years old)	control group: 66.17 ± 8.10 years old; intervention group: 65.08 ± 9.79 years old	40/40	Yangyinhuoxue Decoction + Mecobalamin	1 dose, 2/d	Mecobalamin Tablets	0.5 mg, 3/d	3 months	SNCV, MNCV	no adverse reaction
Li et al. (2016b) (2)	Elderly DPN (60–72 years old)	control group: 68.68 ± 3.96 years old; intervention group: 62.19 ± 2.93 years old	45/45	Modified Huangqi Guizhi Wuwu Decoction + Mecobalamin	1 dose, 2/d	Mecobalamin Tablets	0.5 mg, 3/d	3 months	FBG, 2hPBG, HbA1c, TC, TG, LDL, HDL, MNCV, SNCV	NM
Guo (2016)	Elderly DPN (61–78 years old)	control group: 69.78 ± 5.96 years old; intervention group: 69.45 ± 5.06 years old	51/51	Compound Qiteng Tongluo Decoction + Epalrestat	1 dose, 2/d	Epalrestat	50 mg, 3/d	12 weeks	EAI, PV, WBV, SNCV, MNCV, FBG, 2hPBG, HbA1c	NM
Li et al., 2012	Elderly DPN	control group: 61.1 ± 65.3 years old; intervention group: 60.3 ± 64.7 years old	49/49	Yiqi Huoxue Tongluo Recipe + Mecobalamin Injection + Vitamin B1	250 mL, 2/d	Mecobalamin Injection + VITAMIN B1 TABLETS	Mecobalamin Injection: 0.5mg, 1/d; VITAMIN B1 TABLETS: 10 mg, 3/d	12 weeks	FBG, MNCV*, SNCV*	NM
Traditional Chinese Medicine Extracts										
Wang and Zhang (2009)	Elderly DPN (60–80 years old)	control group: 67.5 ± 3.5 years old; intervention group: 66.3 ± 4.9 years old	34/34	Berberine + Mecobalamin Tablets	700 mg, 3/d	Mecobalamin Tablets	0.5 mg, 2/d	12 weeks	FBG, HbA1c, 24h-UTP, MNCV*, SNCV*	NM

[a]Ages were displayed as mean ± standard deviation or mean.

[b]"*" showed no significant difference between the intervention group and the control group.

Abbreviation: NM, not mentioned; FBG, fasting blood glucose; 2hPBG, 2-h postprandial blood glucose; HbA1c, glycosylated hemoglobin; SF, serum ferritin; SOD, superoxide dismutase; GSH-Px, Glutathione peroxidase; SNCV, sensory nerve conduction velocity; MNCV, motor nerve conduction velocity; TC, cholesterol; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; EAI, red cell aggregation index; PV, plasma viscosity; WBV, whole blood viscosity; 24hUTP, 24-h urinary protein quantity.

TABLE 3 TCM for elderly DCM.

Study	Subjects (Age range)	Ages[a]	No. of intervention group/control group	Treatment of intervention group	Dose of intervention group	Treatment of control group	Dose of control group	Duration	Outcomes	Adverse reactions
Traditional Chinese Prescription										
Xing et al. (2023)	Elderly diabetes cardiomyopathy with heart failure (60–78 years old)	control group: 67.0 ± 4.3 years old; intervention group: 67.23 ± 3.58 years old	30/30	Yangyin Yiqi Huoxue Recipe + Conventional Western Medicine Treatment	150mL, 2/d	Conventional Western Medicine Treatment	NM	12 weeks	FBG, 2hPBG, HbA1c, VEGF, Cardiac function	no adverse reaction
Chen (2021)	Elderly T2DM with arrhythmia (50–78 years old)	control group: 64.26 ± 8.76 years old; intervention group: 64.32 ± 8.80 years old	43/43	Zhigancao Decoction + Carvedilol Tablets	150 mL, 2/d	Carvedilol Tablets	10–20 mg, 1/d	12 weeks	SBP, DBP, HR, HRV, QTd, hs-CRP, IL-6, TNF-α	NM

[a]Ages were displayed as mean ± standard deviation or mean.
Abbreviation: NM, not mentioned; FBG, fasting blood glucose; 2hPBG, 2-h Postprandial blood glucose; HbA1c, Glycosylated hemoglobin; VEGF, vascular endothelial growth factor; SBP, systolic pressure; DBP, diastolic pressure; HRV, heart rate variability; QTd, QT dispersion; HR, heart rate; CRP, C-reaction protein; IL, interleukin; TNF, tumor necrosis factor.

the intervention period was 24 weeks–26 weeks (Table 4; Supplementary Table S11). (Gao, 2012; Song, 2016; Yu and Xu, 2016) The study involved two kinds of Traditional Chinese patent medicines, Jintiange Capsules and Tangmaikang Granules. Tangmaikang Granules were included in Pharmacopoeia of the People's Republic of China 2020 (Committee, 2020).

4.2.8.3 Traditional Chinese Medicine Extracts

One study explored the efficacy of Chinese herbal extracts in elderly patients with diabetes mellitus combined with osteoporosis. A total of 100 subjects were included. The age of the included population was 69.4 ± 3.7 years old, and the intervention time was 6 months (Table 4; Supplementary Table S11).

After using Qianggu Capsule for intervention, (LUO et al., 2014) found that Qianggu Capsule can reduce pain and improve bone density in elderly DOP patients while improving glucose metabolism. The main component of Qianggu Capsule is *Drynaria roosii Nakaike* [Polypodiaceae, Drynariae rhizoma] total flavone, which has been found to improve DOP by activating BMP2/Smad signaling pathway, promoting bone formation and inhibiting bone resorption (Fang et al., 2023).

4.2.9 TCM for elderly diabetes with cognitive impairment

4.2.9.1 Traditional Chinese Prescription

Six studies explored the efficacy of TCM compounds in elderly patients with diabetes mellitus combined with cognitive dysfunction. A total of 462 participants were enrolled, ranging in age from 50 to 84 years, and the intervention period was 12 weeks to 6months (Table 5). (Zhao et al., 2016a; Liu et al., 2016; Gao et al., 2017; Yan and Guan, 2019; Zhao et al., 2019; Yu et al., 2022) The studies involved five prescriptions, commonly used Chinese medicine including *Rehmannia glutinosa (Gaertn.) DC.* [Orobanchaceae, Rehmanniae Radix] (5 times), *Acorus calamus* var. *angustatus Besser* [Acoraceae, Acori tatarinowii rhizoma] (4 times), *Panax ginseng C.A.Mey.* [Araliaceae, Ginseng radix et rhizoma] (4 times), *Astragalus mongholicus Bunge* [Fabaceae, Astragali radix] (4 times) (Supplementary Table S13; Supplementary Table S14). Three of the studies limited inclusion to participants with mild cognitive impairment.

4.2.9.2 Traditional Chinese patent medicines

Two studies explored the efficacy of Traditional Chinese patent medicines in elderly patients with diabetes mellitus combined with cognitive dysfunction. A total of 196 subjects were included, ranging in age from 60 to 79 years old, and the intervention period was 12 weeks to 3 months (Table 5; Supplementary Table S13). The Traditional Chinese patent medicines involved in the studies included Jinlida Granules and Xiaoke Pills, which are included in Pharmacopoeia of the People's Republic of China 2020 (Committee, 2020). Guo et al. (2020) found that Jinlida Granules can improve MMSE and MoCA scores. Zhao and He (2017) found that Xiaoke Pills had positive effects on cognitive function and blood viscosity in elderly patients with diabetes mellitus accompanied by cerebrovascular disease.

4.2.9.3 Traditional Chinese Medicine Extracts

One study explored the effect of TCM extracts on cognitive dysfunction in elderly diabetic patients, including 190 subjects.

TABLE 4 TCM for elderly DOP.

Study	Subjects (Age range)	Ages[a]	No. of intervention group/control group	Treatment of intervention group[b]	Dose of intervention group	Treatment of control group	Dose of control group	Duration	Outcomes[c]	Adverse reactions
Traditional Chinese Prescription										
Liu et al. (2018)	Elderly DOP	NM	100/100	Bushen Huoxue Prescription + Calcium Carbonate and Vitamin D3 Tablets + Alendronate sodium + Alfacalcidol Soft Capsules	200 mL, 2/d	Calcium Carbonate and Vitamin D3 Tablets + Alendronate sodium + Alfacalcidol Soft Capsules	Calcium Carbonate and Vitamin D3 Tablets: 600 mg, 1/d; Alendronate sodium: 70 mg, 1/week; Alfacalcidol Soft Capsules: 1 ug, 1/d	24 weeks	BMD, P1NP, BGP, Ca*, P*, ALP*	NM
Li et al. (2018b) (2)	Elderly DOP (60–75 years old)	control group: 62.2 ± 3.7 years old; intervention group: 63.4 ± 2.8 years old	40/40	Bushen Yigu Recipe + Calcium Carbonate and Vitamin D3 Tablets	100 mL, 2/d	Calcium Carbonate and Vitamin D3 Tablets	Calcium Carbonate and Vitamin D3 Tablets: 600 mg, 1/d	3 months	BMD	NM
Lin (2021)	Elderly DOP (62–81 years old)	70.2 ± 4.1 years old	60/60	Bushen Zhuanggu Prescription + Calcium Carbonate and Vitamin D3 Tablets + Alendronate sodium	1 dose, 2/d	Calcium Carbonate and Vitamin D3 Tablets + Alendronate sodium	Calcium Carbonate and Vitamin D3 Tablets: 600 mg, 1/d; Alendronate sodium: 10 mg, 1/week	12 weeks	FBG*, HbA1c*, VAS	control group: gastrointestinal discomfort (2); intervention group: rash (1), gastrointestinal discomfort (2)
Zong and Zhang (2017)	Elderly DOP with Spleen and Stomach Qi Deficiency syndrome	control group: 66.60 ± 4.3 years old; intervention group: 65.80 ± 4.2 years old	36/30	Qishu Tanggu Decoction + Bisphosphonate + Calcium Carbonate and Vitamin D3 Tablets+	1 dose, 2/d	Bisphosphonate + Calcium Carbonate and Vitamin D3 Tablets	NM	3 months	BMD	NM
Zhang et al. (2019)	Elderly DOP (56–80 years old)	control group: 61.94 ± 2.73 years old; intervention group: 62.13 ± 2.61 years old	92/92	ShenTong ZhuYu Decoction + Calcium Carbonate and Vitamin D3 Tablets + Yougui Pills	1 dose, 2/d	Calcium Carbonate and Vitamin D3 Tablets + Yougui Pills	Calcium Carbonate and Vitamin D3 Tablets: 1 tablet, 2/d; Yougui Pills: 9 g, 2/d	24 weeks	BMD, BGP, NTX, WBV, FIB, PV, HCT	NM
Xiao (2020)	Elderly DOP (>60 years old)	control group: 68.6 ± 4.6 years old; intervention group: 68.4 ± 4.9 years old	42/42	Tonifying Kidney and Strengthening Bone Prescription + Calcium Carbonate and Vitamin D3 Tablets + Alendronate sodium + Alfacalcidol Soft Capsules	200 mL, 2/d	Calcium Carbonate and Vitamin D3 Tablets + Alendronate sodium + Alfacalcidol Soft Capsules	Calcium Carbonate and Vitamin D3 Tablets: 600 mg, 1/d; Alendronate sodium: 10 mg, 1/week; Alfacalcidol Soft Capsules: 0.5 ug, 1/d	3 months	FBG*, 2hPBG*, HbA1c*, BMD	NM

(Continued on following page)

TABLE 4 (*Continued*) TCM for elderly DOP.

Study	Subjects (Age range)	Ages[a]	No. of intervention group/control group	Treatment of intervention group[b]	Dose of intervention group	Treatment of control group	Dose of control group	Duration	Outcomes[c]	Adverse reactions
Li (2015)	Elderly DOP (52–76 years old)	control group: 65.9 ± 4.3 years old; intervention group: 65.4 ± 4.1 years old	33/32	Traditional Chinese Medicine Formulas + Gliclazide	125 mL, 2/d	Gliclazide	30 mg, 1/d	6 months	VAS, osteodynia relief time	NM
Yang (2021b) (2)	Elderly DOP (65–84 years old)	control group: 73.43 ± 4.63 years old; intervention group: 73.41 ± 4.62 years old	37/37	Zishen Jiangtang Pills + Conventional Western Medicine Treatment + Alendronate sodium	6 g, 3/d	Alendronate sodium	70 mg/week	3 months	FBG, 2hPBG, BMD, Bone-alkaline phosphatase, osteocalcin, β-CTX, Osteoprotegerin	no adverse reaction
Hu et al. (2017)	Elderly T2DM	control group: 65.13 ± 4.44 years old; intervention group: 64.77 ± 4.66 years old	31/30	Zuogui Pills + Alfacalcidol	9 g, 2/d	Alfacalcidol	0.25 ug, 2/d	6 months	FROP-COM, PlNP, β1-CTX, 25-OHD, ALP	NM
Traditional Chinese patent medicines										
Yu and Xu (2016)	Elderly DOP (51–75 years old)	NM	30/30	Jintiange Capsules + Atorvastatin	3 capsules, 3/d	Atorvastatin	10 mg, 1/d	24 weeks	BMD	no adverse reaction
Song (2016)	Elderly DOP (49–74 years old)	NM	50/50	Jintiange Capsules + Atorvastatin+	3 capsules, 3/d	Atorvastatin	10 mg, 1/d	24 weeks	BMD	no adverse reaction
Gao (2012)	Elderly DOP (60–75 years old)	control group: 66.41 ± 6.08 years old; intervention group: 65.62 ± 5.41 years old	48/48	Tangmaikang Granules[†]+Calcium Carbonate and Vitamin D3 Tablets + Alendronate sodium Tablets	5g, 3/d	Calcium Carbonate and Vitamin D3 Tablets + Alendronate sodium Tablets	Calcium Carbonate and Vitamin D3 Tablets: 600 mg, 1/d; Alendronate sodium Tablets: 10 mg, 1/d	26 weeks	BGP, NTX, BMD, Ca*, P*, ALP*	control group: abdominal distension (2); intervention group: nausea (1)

TABLE 4 (Continued) TCM for elderly DOP.

Study	Subjects (Age range)	Ages[a]	No. of intervention group/control group	Treatment of intervention group[b]	Dose of intervention group	Treatment of control group	Dose of control group	Duration	Outcomes[c]	Adverse reactions
Traditional Chinese Medicine Extracts										
Luo et al. (2014)	Elderly DOP	69.4 ± 3.7 years old	50/50	Qianggu Capsules + Atorvastatin + Calcium Carbonate and Vitamin D3 Tablets	1 capsule, 1/d	Calcium Carbonate and Vitamin D3 Tablets + Atorvastatin	Calcium Carbonate and Vitamin D3 Tablets: 1 tablet, 1/d; Atorvastatin: 1 tablets, 1/d	6 months	FBG, 2hPBG, HbA1c, BMI*, VAS, BMD	control group: gastrointestinal discomfort (5); intervention group: gastrointestinal discomfort (7)

[a]Ages were displayed as mean ± standard deviation or mean.
[b]"" indicated that it was included in Pharmacopoeia of the People's Republic of China 2020.
[c]"*" showed no significant difference between the intervention group and the control group.
Abbreviation: NM, not mentioned; BMD, bone mineral density; FBG, fasting blood glucose; VAS, visual analogue scale; BGP, osteocalcin; 2hPBG, 2-h postprandial blood glucose; HbA1c, Glycosylated hemoglobin; NTX, Cross-linked N-telopeptides of type I collagen; P1NP, aminoterminal prepeptide type I procollagen; β1-CTX, β-1 collagen carboxy terminal peptide; BMI, body mass index; ALP, alkaline phosphatase; FIB, fibrinogen; PV, plasma viscosity; HCT, hematocrit; WBV, whole blood viscosity; P, phosphorus; Ca, Calcium; 25-OHD, 25-hydroxyvitamin D; FROP-COM, falls risk for older people in the community; PINP, Type I procollagen amino-terminal peptide; β-CTX, Type I collagen carboxy-terminal peptide.

(Wang, 2012). The age standard of the included population was >60 years old, and the intervention time was 6 months (Table 5; Supplementary Table S13). The study included elderly diabetic patients without cognitive impairment, and found that ginkgo biloba extract can also improve the MMSE, CDR and ADL scores of patients, indicating that it has a positive effect on the cognitive function of elderly diabetic patients.

4.2.10 TCM for elderly diabetes with vascular injury
4.2.10.1 Traditional Chinese Prescription

Three RCTs involving 286 elderly patients with diabetes and vascular sclerosis were conducted. The age range of the included population was 60–79 years, and the intervention duration was 12 weeks to 4 months (Table 6; Supplementary Table S15). Cheng et al. (2019); Guan (2021) applied Modified Huangqi Guizhi Wuwu Tang and Tangmai Tongluo Decoction to treat the elderly diabetic patients with lower extremity vascular lesions, and found that the decoctions could improve the blood flow of dorsal foot artery after 3 months of intervention. After intervention with Yiqi Tongluo Qingre cream, (Liu et al., 2022) found that it could improve arteriosclerosis of common carotid artery, popliteal artery and dorsal foot, and reduce lipid metabolism indicators.

4.2.10.2 Traditional Chinese patent medicines

Four RCTs investigated the efficacy of Traditional Chinese patent medicines in elderly patients with diabetes and vascular sclerosis. A total of 483 subjects were enrolled. The age of the enrolled population ranged from 60 to 81 years, and the intervention time was 12 weeks to 6 months (Table 6; Supplementary Table S15) (SHOU et al., 2012; Wang, 2013; Wang et al., 2017; Yu and Zhang, 2018).The studies involved five Traditional Chinese patent medicines. Naoxintong Capsules, Yixinshu Capsules, Yangxinshi Tablets and Shexiang Baoxin Pills were included in Pharmacopoeia of the People's Republic of China 2020 (Committee, 2020), Maixuekang Capsules was not included.

4.2.10.3 Traditional Chinese Medicine Extracts

Four RCTs involving 432 participants explored the efficacy of Traditional Chinese Medicine Extracts in elderly diabetic patients with vascular sclerosis. The age range of the included population was 60–90 years old, and the intervention time was 12 weeks to 3 months (Table 6; Supplementary Table S15) (Li et al., 2016a; Chen, 2017; Li and Yang, 2017; JIANG et al., 2021). The studies involved 4 extracts, including Panax notoginseng (Burk.) F.H.Chen [Araliaceae, Notoginseng total saponins], Salvia miltiorrhiza Bunge [Lamiaceae, Tanshinones], Ginkgo biloba L. [Ginkgoaceae, Ginkgo leaves extract], Tribulus terrestris L. [Zygophyllaceae, Tribuli fructus]. Both of them are used to treat carotid atherosclerosis.

4.2.11 Safty

Adverse reactions were reported in 72 studies, of which 23 reported no adverse reactions. Among the adverse events studies, there were 48 adverse events in the control group, including 30 symptoms, involving 222 subjects, and common adverse events included hypoglycemia (13 RCTs, 42 subjects), gastrointestinal discomfort (7 RCTs, 19 subjects), dizzy (13 RCTs,

TABLE 5 TCM for elderly diabetes with cognitive impairment.

Study	Subjects (Age range)	Ages[a]	No. of intervention group/control group	Treatment of intervention group[b]	Dose of intervention group	Treatment of control group	Dose of control group	Duration	Outcomes[c]	Adverse reactions
Traditional Chinese Prescription										
Yu et al. (2022)	Elderly T2DM with mild cognitive impairment of deficiency of spleen and kidney combined with blood stasis (61–84 years old)	control group: 71.10 ± 6.12 years old; intervention group: 71.67 ± 6.09 years old	40/40	Bushen Jianpi Huoxue Formula + Aspirin	125 mL, 2/d	Aspirin	100 mg, 1/d	3 months	MoCA, FBG, 2hPBG, HbA1c, HOMA-IR*, CRP	control group: anemia (1), proteinuria (2), abnormal liver function (1), abnormal renal function (2), hypotension (2; intervention group: anemia (0), proteinuria (1), abnormal liver function (0), abnormal renal function (0), hypotension (0)
Gao et al. (2017)	Elderly T2DM with cognitive impairment (50–75 years old)	control group: 62.08 ± 5.92 years old; intervention group: 62.40 ± 5.95 years old	60/60	Chinese Medicine for nourishing kidney, eliminating phlegm and damp + Donepezil	1 dose, 2/d	Donepezil	5 mg, 1/d	6 months	MoCA, MMSE, ADL, MDA, SOD, AchE	control group: dizzy (2), headache (1), hypotension (1), flushed face (0), vomit (1); intervention group: dizzy (3), headache (2), hypotension (0), flushed face (1), vomit (2)
Zhao et al. (2016a) (4)	Elderly T2DM with mild cognitive impairment (60–80 years old)	NM	30/30	Tonifying Deficiency for Dispelling Turbidity and Removing Obstruction in Collaterals Method + Conventional Western Medicine Treatment	100 mL, 2/d	Conventional Western Medicine Treatment	NM	12 weeks	MMSE, ADAS-COG-DVR, adiponectin, Leptin, HOMA-IS	NM
Zhao et al. (2016b) (5)	Elderly T2DM with mild cognitive impairment (60–80 years old)	71.9 ± 8.2 years old	36/36	Tonifying deficiency, removing turbidity and dredging collaterals recipe + Conventional Western Medicine Treatment	150 mL, 2/d	Conventional Western Medicine Treatment	NM	12 weeks	MMSE, ADAS-COG-DVR, A-β, SOD	NM
Liu et al. (2016)	Elderly T2DM with cognitive impairment (60–80 years old)	control group: 68.2 ± 6.9 years old; intervention group: 65.6 ± 7.6 years old	35/35	Yiqi bushen huoxue Decoction + Conventional Western Medicine Treatment	150mL, 2/d	Conventional Western Medicine Treatment	NM	12 weeks	MMSE, CDR, ADL	NM

(Continued on following page)

TABLE 5 (*Continued*) TCM for elderly diabetes with cognitive impairment.

Study	Subjects (Age range)	Ages[a]	No. of intervention group/control group	Treatment of intervention group[b]	Dose of intervention group	Treatment of control group	Dose of control group	Duration	Outcomes[c]	Adverse reactions
Yan and Guan (2019)	Elderly T2DM with cognitive impairment (65–80 years old)	control group: 70.56 ± 5.26 years old; intervention group: 71.37 ± 4.66 years old	30/30	Yizhi Heji + Citicoline Sodium Capsules	50 mL, 2/d	Citicoline Sodium Capsules	0.2 g, 3/d	6 months	MMSE, FBG, 2hPBG, HbA1c, WBC, RBC, Hb, ALT, AST, BUN, Cr	no adverse reaction
Traditional Chinese patent medicines										
Guo et al. (2020)	Elderly T2DM with mild cognitive impairment (60–79 years old)	control group: 68.2 ± 5.8 years old; intervention group: 67.8 ± 5.4 years old	48/48	Jinlida Granules[†]+Sitagliptin	9g, 3/d	Sitagliptin	100 mg, 1/d	3 months	MMSE, MoCA, FBG, HbA1c, IL-1β, IL-6, TNF-α	control group: hypoglycemia (3); intervention group: hypoglycemia (4)
Zhao and He (2017)	Elderly T2DM with cerebral microvascular lesion blood viscosity (61–78 years old)	control group: 67.5 ± 3.6 years old; intervention group: 67.24 ± 4.0 years old	50/50	Xiaoke pill[†]+Metformin	10 pills, 3/d	Metformin	0.75 g, 3/d	12 weeks	cognitive function scores, WBV, PV, HCT, Cell deformation index, Erythrocyte rigidity index, Erythrocyte deformation index	NM
Traditional Chinese Medicine Extracts										
Wang 2012 (2)	Elderly T2DM (>60 years old)	NM	94/96	Ginkgo biloba extract Capsules + Conventional Western Medicine Treatment	0.3 g, 2/d	Conventional Western Medicine Treatment	NM	6 months	MMSE, CDR, ADL, CDT, BDNF, Hcy	NM

[a]Ages were displayed as mean ± standard deviation or mean.

[b]"†" indicated that it was included in Pharmacopoeia of the People's Republic of China 2020.

[c]"*" showed no significant difference between the intervention group and the control group.

Abbreviation: NM, not mentioned; 2hPBG, 2-h postprandial blood glucose; AchE, acetylcholinesterase; ADAS-COG-DVR, Alzheimer disease assessment scale-cog; ADL, Activity of DailyLiving Scale; ALT, alanine aminotransferase; AST, aspartate aminotransferase; A-β, amyloid β-protein; BDNF, serum brain derived growth factor; BUN, blood urea nitrogen; CDR, clinical dementia rating scale;CDT, clock drawing test; Cr, Creatinine; CRP, C-reaction protein; FBG, fasting blood glucose; Hb, Haemoglobin; HbA1c, Glycosylated hemoglobin; WBV, whole blood viscosity; HCT, hematocrit; Hcy, Homocysteine; HOMA, homeostasis model assessment; IL, interleukin; MDA, malondialdehyde; MMSE, minimum mental state examination; MoCA, montreal cognitive assessment; PV, plasma viscosity; RBC, erythrocyte; SOD, superoxide dismutase; TNF, tumor necrosis factor; WBC, leukocyte.

TABLE 6 TCM for elderly diabetes with vascular injury.

Study	Subjects (Age range)	Ages[a]	No. of intervention group/ control group	Treatment of intervention group[b]	Dose of intervention group	Treatment of control group	Dose of control group	Duration	Outcomes[c]	Adverse reactions
Traditional Chinese Prescription										
Cheng et al. (2019)	Elderly T2DM with lower-extremity arterial disease (≤Fontaine stage III, 60–75 years old)	control group: 63.08 ± 9.17 years old; intervention group: 61.53 ± 8.84 years old	64/64	Modified Huangqi Guizhi Wuwu Decoction+Probucolum+Aspirin+Alprostadil Injection	150 ml, 2/d	Probucolum+Aspirin+Alprostadil Injection	Probucolum: 0.5 g, 2/d; Aspirin: 100 mg, 1/d; Alprostadil Injection: 10 ug, 1/d	3 months	ABI, TBI, Dorsal foot artery blood vessel, IL-1, Hcy, TNF-α, hs-CRP, CysC, MDA, SOD, LDL	NM
Guan (2021)	Elderly T2DM with lower limb arterial disease (60–76 years old)	control group: 67.65 ± 5.28 years old; intervention group: 67.63 ± 5.35 years old	39/39	Tangmai Tongluo Decoction+Aspirin+Probucol+Alprostadil Injection	150 ml, 2/d	Aspirin+Probucol+Alprostadil Injection	aspirin: 50 mg, 2/d; Probucol: 0.5 g, 2/d; Alprostadil Injection: 10 ug, 1/d	12 weeks	Blood flow velocity of dorsalis pedis artery, Peak flow velocity of dorsal foot artery blood flow, TNF-α, IL-1, MWD, PWD	NM
Liu et al. (2022)	Elderly patients with T2DM and atherosclerosis (61–79 years old)	control group: 70.2 ± 5.9 years old; intervention group: 69.7 ± 6.1 years old	40/40	Yiqi Tongluo Qingre cream+Conventional Western Medicine Treatment	10 g, 2/d	Conventional Western Medicine Treatment	NM	4 months	TC, TG, LDL, HDL, FIB, ABI, Dorsal foot artery blood vessel, QoL	control group: vomit (3), diarrhea (4), loss of appetite (7), abnormal liver function (3), bleeding (6); intervention group: vomit (0), diarrhea (1), loss of appetite (0), abnormal liver function (0), bleeding (0)
Traditional Chinese patent medicines										
Wang et al. (2013) (2)	Elderly T2DM with arteriosclerosis obliterans of lower limbs (60–81 years old)	control group: 68.5 years old; intervention group: 71.2 years old	58/57	Maixuekang capsule[†]+Yixinshu Capsules+Clopidogrel+Rosuvastatin	3 capsules, 1/d	Clopidogrel+Rosuvastatin	Clopidogrel: 75 mg, 1/d; Rosuvastatin: 10 mg, 1/d	3 months	ERS, FIB, Platelet, HbA1c, LDL	no adverse reaction

TABLE 6 (*Continued*) TCM for elderly diabetes with vascular injury.

Study	Subjects (Age range)	Ages[a]	No. of intervention group/ control group	Treatment of intervention group[b]	Dose of intervention group	Treatment of control group	Dose of control group	Duration	Outcomes[c]	Adverse reactions
Wang et al. (2017)	Elderly T2DM with subclinical atherosclerosis (62–75 years old)	65.6 ± 4.1 years old	55/55	Naoxintong Capsules[†]+Conventional Western Medicine Treatment	3 capsules, 3/d	Conventional Western Medicine Treatment	NM	6 months	C-IMT, PAI-1, β-thromboglobulin, P-selectin	NM
Shou et.al. (2012)	Elderly T2DM with coronary heart disease (≥65 years old)	76.06 ± 4.81	72/76	Shexiang Baoxin Pills[†]+Conventional Western Medicine Treatment	2 pills, 3/d	Conventional Western Medicine Treatment	NM	12 weeks	FBG, HbA1c, TC, LDL, hs-CRP, FIB, ABI, CAVI	no adverse reaction
Yu and Zhang (2018)	Elderly T2DM with coronary heart disease (NM)	NM	55/55	Yangxinshi Tablets[†]+Conventional Western Medicine Treatment	3 tablets, 3/d	Conventional Western Medicine Treatment	NM	12 weeks	Number of angina attacks, 6-minute walking distance, METs	NM
Traditional Chinese Medicine Extracts										
Li and Yang (2017)	Elderly T2DM with carotid atherosclerosis (60–79 years old)	control group: 66.2 ± 4.5 years old; intervention group: 66.5 ± 4.2 years old	75/75	Tanshinone Capsules+Beraprost Sodium	2 capsules, 3/d	Beraprost Sodium	40 ug, 2/d	3 months	FBG, HbA1c, TG, TC, C-IMT, Crouse scores, MCP-1, hs-CRP, TNF-α, ICAM-1, Vascular endothelial cell function	NM
Jiang et al. (2021)	Elderly T2DM with peripheral arterial disease (70–90 years old)	control group: 80.2 ± 6.5 years old; intervention group: 80.8 ± 5.8 years old	50/50	panax notoginseng saponins+Conventional Western Medicine Treatment	100 mg, 3/d	Conventional Western Medicine Treatment+placebo	2 capsules, 2/d	3 months	hs-CRP, IL-6, TNF-α, TC, TG, HDL, LDL, FBG, HbA1c, FIB, C-IMT*	NM

TABLE 6 (*Continued*) TCM for elderly diabetes with vascular injury.

Study	Subjects (Age range)	Ages[a]	No. of intervention group/control group	Treatment of intervention group[b]	Dose of intervention group	Treatment of control group	Dose of control group	Duration	Outcomes[c]	Adverse reactions
Li et al. (2016a) (3)	Elderly T2DM with carotid plaque (60–84 years old)	69.93 ± 6.79 years old	48/48	Xinnao Shutong Tablets+Conventional Western Medicine Treatment	0.52 g, 3/d	Conventional Western Medicine Treatment	Metformin: 0.5–1 g, 2/d; gliclazide sustained-release tablets: 30–60 mg, 1/d; Acarbose: 50–100 mg, 3/d; protamine biosynthetic human insulin injection (pre mixed 30R): NM, 2/d; aspirin: 100 mg, 1/d; atorvastatin calcium: 20 mg, 1/d	12 weeks	C-IMT, Crouse scores, Hcy, hs-CRP, FBG, HbA1c, TC, TG, LDL, HDL	no adverse reaction
Chen (2017)	Elderly T2DM with carotid atherosclerosis (60–75 years old)	control group: 67.4 ± 6.7 years old; intervention group: 67.1 ± 6.9 years old	43/43	Ginkgo biloba leaves+Rosuvastatin calcium	400 mg, 3/d	Rosuvastatin calcium	10 mg, 1/d	3 months	TC, TG, LDL, HDL, NO, ET-1, MDA	control group: diarrhea (1), dizzy (1); intervention group: diarrhea (1), dizzy (2)

[a]Ages were displayed as mean ± standard deviation or mean.

[b]"†" indicated that it was included in Pharmacopoeia of the People's Republic of China 2020.

[c]"*" showed no significant difference between the intervention group and the control group.

Abbreviation: NM, not mentioned; BMD, bone mineral density; FBG, fasting blood glucose; VAS, visual analogue scale; BGP, osteocalcin; 2hPBG, 2-h postprandial blood glucose; HbA1c, Glycosylated hemoglobin; NTX, Cross-linked N-telopeptides of type I collagen; P1NP, aminoterminal prepeptide type l procollagen; β1-CTX, β-1 collagen carboxy terminal peptide; BMI, body mass index; ALP, alkaline phosphatase; ALP, alkaline phosphatase; FIB, fibrinogen; PV, plasma viscosity; HCT, hematocrit; WBV, whole blood viscosity; P, phosphorus; Ca, Calcium; 25-OHD, 25-hydroxyvitamin D; FROP-COM, falls risk for older people in the community; PlNP, Type I procollagen amino-terminal peptide; β-CTX, Type I collagen carboxy-terminal peptide.

18 subjects), loss of appetite (8 RCTs, 18 subjects), diarrhea (9 RCTs, 17 subjects), vomit (9 RCTs, 16 subjects), nausea (9 RCTs, 13 subjects), headache (8 RCTs, 11 subjects); Adverse events occurred in 47 studies in the intervention group, with 26 symptoms and involving 167 participants. Common adverse events included gastrointestinal discomfort (9 RCTs, 24 subjects), dizzy (11 RCTs, 22 subjects), nausea (12 RCTs, 18 subjects), hypoglycemia (10 RCTs, 17 subjects), diarrhea (9 RCTs, 14 subjects), vomit (9 RCTs, 13 subjects), loss of appetite (5 RCTs, 10 subjects), rash (5 RCTs, 9 subjects) (Supplementary Table S16).

4.2.12 Quality assessment and ConPhyMP statement

Jadad scale was used to evaluate the treatment of literatures, and there were 1 study with a score of 5, 13 studies with a score of 4, 61 studies with a score of 3, 82 studies with a score of 2, and 3 studies with a score of 1. Not use blind methods, failure to report dropout and loss of follow-up, and failure to explain the way of randomization performed were the main reasons for the low Jadad score (Supplementary Table S17).

Nine studies about Traditional Chinese Medicine Extracts were evaluated by the ConPhyMP statement. *Zea mays L.* [Poaceae, corn silk] was identified as type B extracts because corn silk was not included in Pharmacopoeia of the People's Republic of China 2020 (Committee, 2020). Other extracts were identified as type A extracts. Detailed evaluation results were shown in the Supplementary Table S18–26.

5 Discussion

The elderly are often complicated with many diseases, and the phenomenon of multiple drug use is common. The study found that the prevalence of polypharmacy is approximately 50% in older people with diabetes and is associated with poor blood sugar control, risk of hypoglycemia, falls, fainting, hospitalization, and risk of death (Pazan and Wehling, 2021). The application of commonly used western anti-diabetic drugs in elderly diabetes seems to have both advantages and disadvantages. Cohort studies showed that metformin reduced the risk of dementia in T2DM patients by 35% over 8 years (Hsu et al., 2011), but a prospective study showed that metformin increased cognitive deterioration and risk of AD (Koo et al., 2019). A population-based nested case study also showed that metformin use was associated with an increased risk of AD (Ha et al., 2021). Clinical studies have shown that TZDs can improve the cognitive function of diabetic patients and reduce the risk of dementia (Watson et al., 2005; Abbatecola et al., 2010; Sato et al., 2011; Heneka et al., 2015; Burns et al., 2021), but there are also studies that the application of TZDs drugs has no significant benefits in improving Alzheimer's disease and delaying Parkinson's disease (Heneka et al., 2015; Burns et al., 2021). The effect of SGLT2i on bone is controversial. Many meta-analyses have shown that SGLT2i does not increase the risk of fracture in patients with T2DM (Tang et al., 2016; Ruanpeng et al., 2017), but there is more evidence that canagliflozin increases the risk of fracture (Watts et al., 2016; Blevins and Farooki, 2017), especially in patients with renal failure, cardiovascular disease, peripheral vascular disease, or neuropathy (Kalaitzoglou et al., 2019). In addition, the positive or negative effects of antidiabetic drugs on

sarcopenia are not fully understood. Epidemiology shows that metformin or TZDs can reduce muscle loss in elderly IFG or T2DM men, but clinical observational studies have found that female skeletal muscle mass is significantly reduced after metformin treatment (Aghili et al., 2014). TCM has the advantages of a wide range of indications and many targets, and many studies have proved that the same prescription has a synergistic effect in the treatment of multiple diseases (Zhang et al., 2020; Yuan et al., 2023). For example, Jinlida Granules improve the islet function, kidney function and cognitive function of elderly diabetic patients. Compound Danshen Dripping Pills have a synergistic effect on improving DKD and DR in the elderly. Many epidemiological studies have verified the correlation between DKD and DR (Park et al., 2019).

In addition, Chinese medicine has certain safety in the treatment of elderly diabetes. The study found that the use of sulfonylureas would increase the risk of severe hypoglycemia by three times (Misra-Hebert et al., 2018). Elderly diabetes patients were older and complicated with a variety of chronic diseases, which was more likely to increase the risk of hypoglycemia caused by sulfonylureas (Sinclair et al., 2015). Compared with the control group, the number of adverse reactions in TCM intervention group was lower, especially the incidence of hypoglycemia was significantly lower than that in the control group.

However, there are still many problems in the clinical research of TCM in elderly diabetes. First, the age criteria for inclusion are different. In the international standard, patients with diabetes whose age is ≥65 years are defined as elderly diabetes (LeRoith et al., 2019; ElSayed et al., 2023), while in the Chinese Clinical Guidelines for the Prevention and Treatment of Elderly Type 2 diabetes (2022) (group, 2022), the age standard is ≥60 years. According to the included literature, it was found that many studies did not adhere to this age criterion although they focused on older patients with diabetes. Second, the subjects were not diagnosed clearly. Only some studies have defined the stage of DKD in the elderly, which may have different effects on the outcome depending on the severity of the patient's disease. Third, the studies design is not rigorous. Most of the study controls were Western drugs, only one study used placebo control. Meanwhile, blind method was not used and the Jadad score was of low quality. Fourth, intervention measures are not standardized. Some studies did not explain the composition or dosage of the Traditional Chinese Prescription. Some of the traditional Chinese patent medicines used in the study were not included in Pharmacopoeia of the People's Republic of China 2020 (Committee, 2020) and the description of the extraction process for traditional Chinese extracts is also not detailed. Both of them led to the unclear method of TCM in the treatment of elderly diabetes. Fifth, no adverse reactions were reported. Some studies have not reported adverse reactions, making it difficult to evaluate the safety of their treatment.

6 Conclusion

The application of TCM in elderly diabetes has the advantages of multi-target and coordinated treatment. TCM can jointly treat various complications and complications caused by aging, and can focus on the unique characteristics of elderly diabetes, such as vascular aging, osteoporosis, cognitive impairment, sarcopenia, etc. However, there are also many problems, including the inclusion of age criteria and

diagnosis of subjects are unclear, imprecise research design, non-standard intervention measures, and its safety needs further exploration. These will lead to the low efficacy and safety of TCM in elderly diabetes. Although there have been many explorations of TCM in the experimental model of elderly diabetes, in the future, the diagnosis of elderly people with diabetes needs to be further clarified. Traditional Chinese patent medicines included in the pharmacopoeia can be used to conduct more rigorous RCTs, and then gradually standardize the traditional Chinese medicine prescriptions and traditional Chinese medicine extracts, providing higher level evidence for the treatment of elderly diabetes with traditional Chinese medicine.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1339148/full#supplementary-material

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Evidence mapping of traditional Chinese medicine in diabetic peripheral neuropathy treatment

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Objective: Diabetic peripheral neuropathy (DPN) stands as a crucial complication of diabetes, significantly affecting patients' quality of life. This study aims to elucidate the evidence distribution from clinical randomized controlled trials (RCTs) on DPN treatment with traditional Chinese medicine (TCM) through evidence mapping.

Methods: A comprehensive search was conducted from January 2017 to October 2022 in databases such as Wanfang (China Online Journals), CNKI (China National Knowledge Infrastructure), VIP (China Science and Technology Journal Database), SinoMed (Chinese Biomedical Literature Database), PubMed, Web of Science, and Cochrane Library. Literature related to the treatment of DPN with TCM was selected. From the 1,229 RCTs identified over the past 6 years, relevant data were extracted. The evidence mapping approach was utilized, and trends in publications, study scales, intervention types, and evaluation indicators were analyzed using descriptive text combined with tables and bubble charts.

Results: Research on the treatment of DPN with TCM is extensive. The publication trend remains relatively stable with predominantly smaller sample sizes. The main treatments encompass oral Chinese medicine and traditional external treatments. The most common evaluation indicators are neurophysiological, efficiency rate, symptom signs, neuropathy scores, and traditional Chinese symptoms, with less focus on psychological status and the ankle-brachial index (ABI).

Conclusion: Shedding light on contemporary research, this study explores the current RCTs evaluating TCM's efficacy in treating DPN. The findings not only highlight the potential role of TCM in addressing diabetic complications but also underscore areas that could benefit from refined research approaches, expanded intervention methods, and broader assessment criteria. Our observations aim to inform and inspire future research directions and clinical practices concerning TCM's role in managing diabetes-associated complications.

1 Introduction

Diabetic Peripheral Neuropathy (DPN) is a prevalent neurological complication of diabetes. Between 11% and 49% of prediabetic patients can exhibit symptoms, even in the disease's preliminary stages (Ziegler et al., 2008; Lee et al., 2015; Won et al., 2017). After a decade of affliction, 60%–90% of diabetic individuals might display various degrees of neuropathic impairments, nearly half of which are categorized as
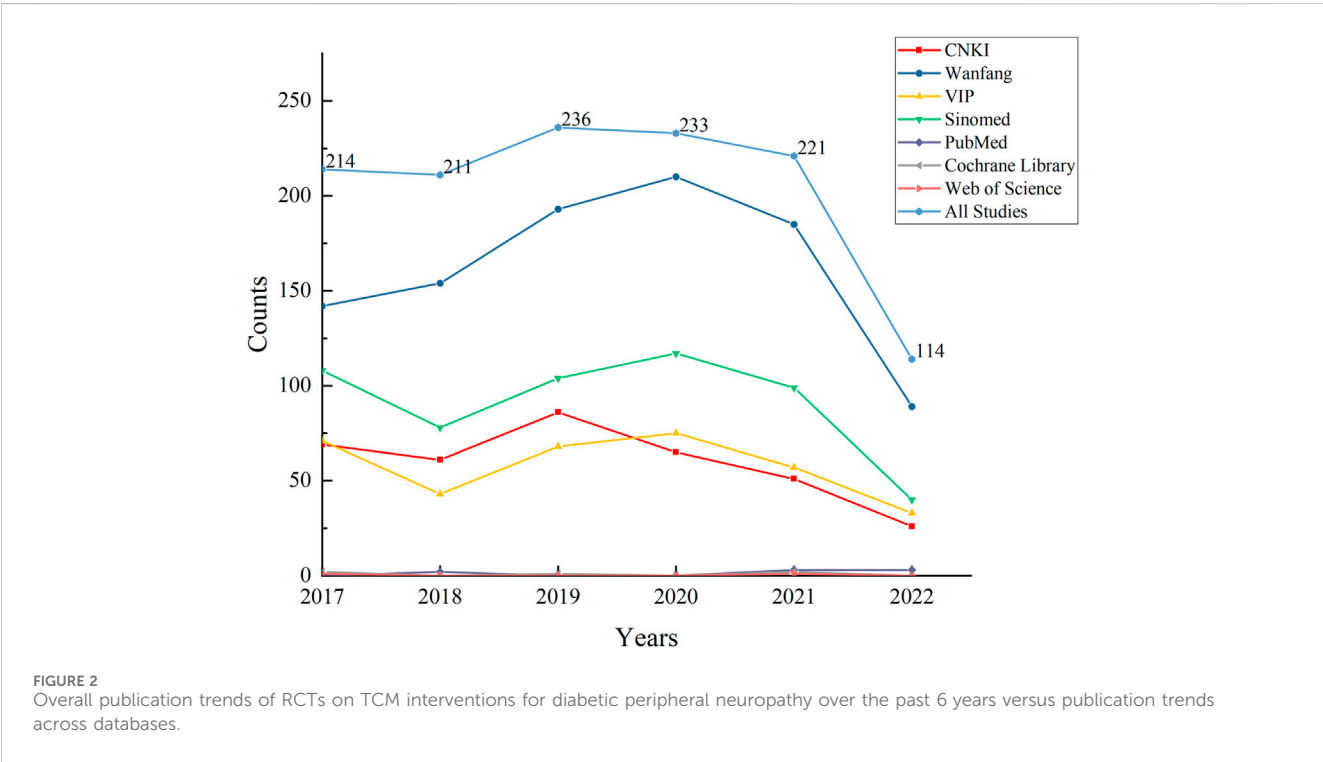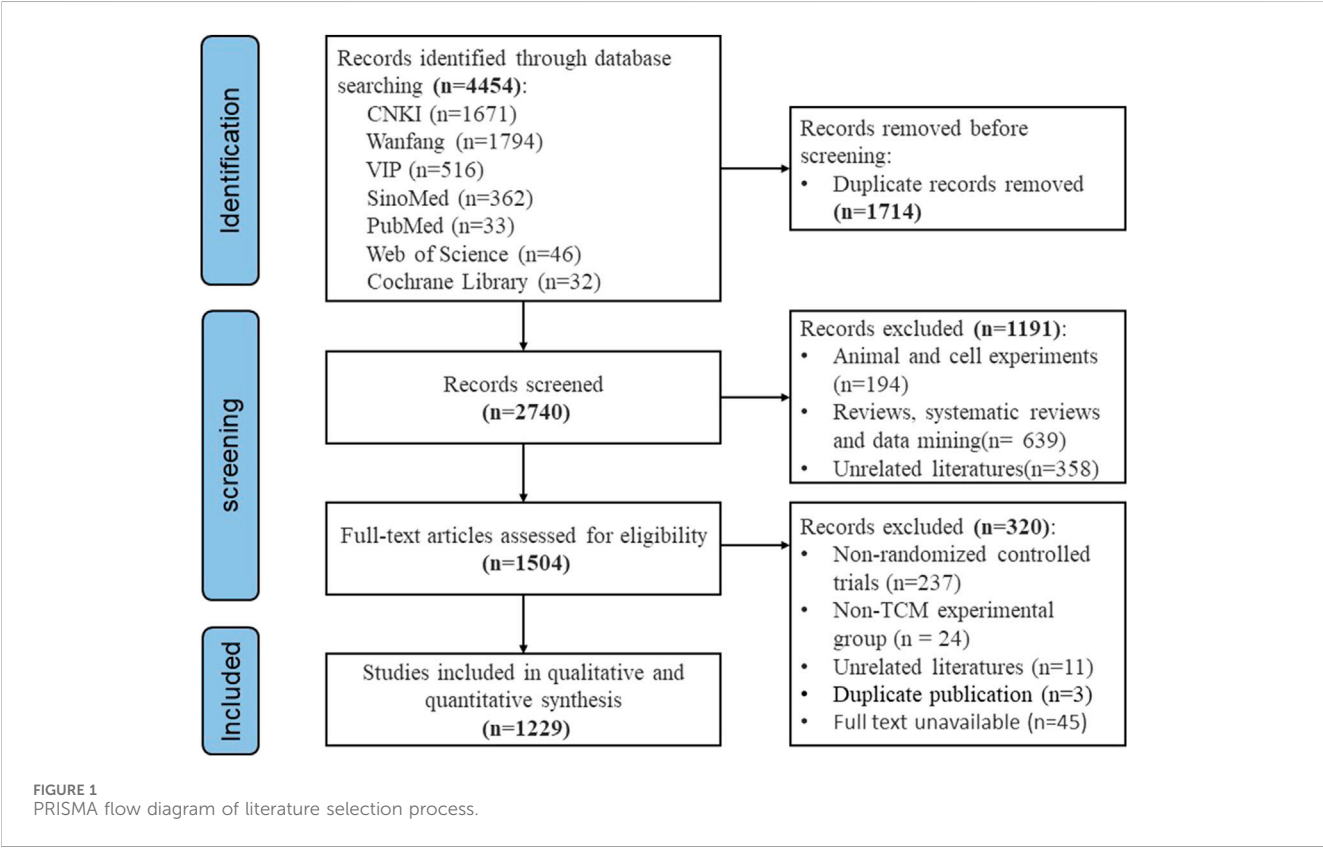

FIGURE 1
PRISMA flow diagram of literature selection process.

FIGURE 2
Overall publication trends of RCTs on TCM interventions for diabetic peripheral neuropathy over the past 6 years versus publication trends across databases.

TABLE 1 Sample sizes of RCTs on TCM interventions for diabetic peripheral neuropathy over the past six years.

Sample size	Number of articles	Proportion (%)
≤50	72	5.86
50–100	891	72.50
100–200	239	19.45
200–500	23	1.87
500–1,000	4	0.33

DPN (Tesfaye et al., 2010). These complications encompass challenges such as balance difficulties, excruciating neuropathic pain, and, in advanced instances, irreversible nerve injuries leading to diabetic foot ulcers and possible amputations (Morrison et al., 2012; Selvarajah et al., 2019). On an individual level, age remains a persistent risk factor for DPN (Liu et al., 2019). As patients age and disease duration elongates, the likelihood of developing DPN intensifies (Cabezas-Cerrato, 1998). On a macro scale, with rapid economic growth coupled with accelerated aging populations, the global number of elderly diabetic patients and those with DPN is anticipated to continually ascend (Yang et al., 2010; Powell et al., 2012; Xu et al., 2013; Wang et al., 2023). In 2019, the population of elderly diabetic individuals (aged 65–99) was approximately 135.6 million, accounting for 19.3%. This number is projected to soar to 195.2 million by 2030 (Brussels, 2019; Saeedi et al., 2019). With many elderly already having underlying conditions, the onset of DPN may precipitate more grave consequences and comorbidities. Consequently, efficacious and economical prevention and treatment strategies, alongside evaluation metrics, are paramount for this group. Traditional Chinese Medicine (TCM) has demonstrated

certain therapeutic efficacy in treating DPN, offering diverse treatments that alleviate symptoms and delay disease progression through multiple targets and pathways (Yang et al., 2022).

With the burgeoning emphasis on high-quality clinical trial research within the TCM realm, there has been an influx of randomized controlled trials (RCTs) exploring diverse TCM interventions for DPN. Yet, an overarching synthesis of evidence in this area is notably absent. Evidence mapping, a methodological tool that traces its origins to Yale University's research on complementary and alternative medicine, mandates a comprehensive retrieval and systemic summation of research attributes and outcomes. By utilizing graphical elucidations, it furnishes a lucid and precise portrayal of the research field's evidence, advancements, and existing challenges (Katz et al., 2003; Li et al., 2011; Schmucker et al., 2013), enhancing the efficacy and applicability of research in the area. This serves researchers, guideline creators, clinical physicians, and other stakeholders (Bragge et al., 2011; Miake-Lye et al., 2016; Li et al., 2019). Our study collates and analyzes RCTs from the past 6 years on multi-method TCM treatments for DPN. By integrating charts with evidence mapping, we offer a comprehensive view of the current state of research in the domain. This also encapsulates its limitations, contributing towards the enhancement of research quality in the field (Bastian et al., 2010), aiming to bridge the gap in research synthesis on evidence.

2 Methods

2.1 Data sources and searches

We systematically searched several databases including Wanfang, China National Knowledge Infrastructure (CNKI), VIP, SinoMed, PubMed, Web of Science, and Cochrane Library
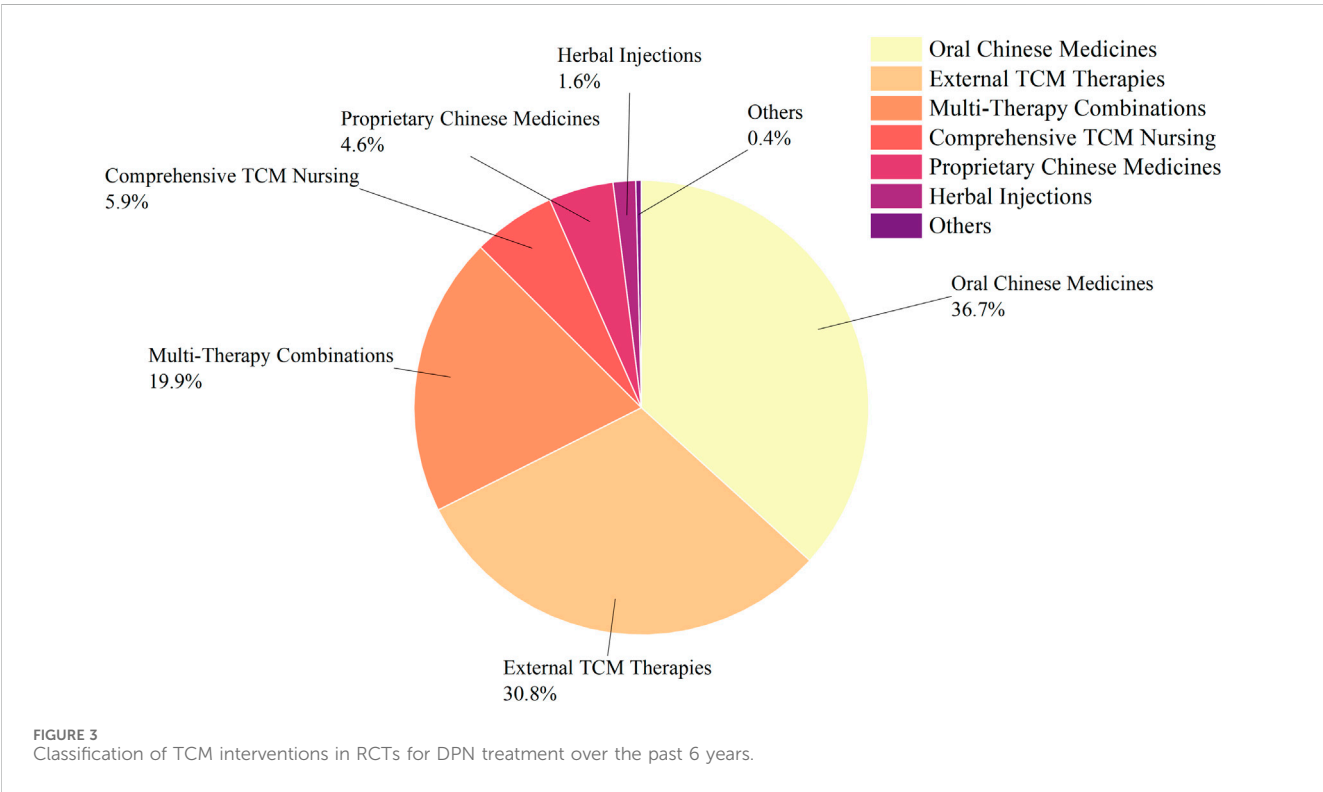

FIGURE 3
Classification of TCM interventions in RCTs for DPN treatment over the past 6 years.

TABLE 2 Frequency of various intervention methods.

Types of interventions	Intervening measure	Counts
Oral Chinese Medicine	Huangqi Guizhi Wuwu Decoction	64
	Buyang Huanwu Decoction	23
	Danggui Sini Decoction	22
	Duhuo Jisheng Decoction	6
	Taohong Siwu Decoction	5
External Treatment of TCM	Acupuncture	68
	Foot Bath	59
	Fumigation Combined With External Washing	46
	External Application	28
	Moxibustion	14
	Foot Bath Combined With Massage	11
	Acupoint Injection	11
	External Wash	11
	External Application Combined With Acupuncture	11
	Foot Bath Combined With External Application	9
	Iontophoresis	8
	Foot Bath Combined With Acupuncture	8
	Fumigation	7
	Fumigation Combined With External Washing And Acupuncture	6
	Massage	5
	Foot Bath Combined With Acupoint Injection	5
	Topical Rubbing	5

for studies on traditional Chinese medicine (TCM) interventions in diabetic peripheral neuropathy (DPN). Considering the increasing attention to TCM treatment aspects in the DPN field in 2017, this approach allowed us to collect a large number of relevant time newer publications to provide a comprehensive reference for future research. The search timeframe was from January 2017 to October 2022, including only Chinese and English articles. Both MeSH terms and free-text terms were used. The search terms included but were not limited to "糖尿病性周围神经病变", "糖尿病周围神经病变", "中医", ""中药", and their English counterparts "Diabetes peripheral neuropathy", "DPN", "traditional Chinese medicine", "herbal medicine", and "TCM". The search strategy for Web of Science was: [TS = (Diabetes peripheral neuropathy) OR TS = (DPN)] AND [TS = (traditional Chinese medicine) OR TS=(herbal medicine) OR TS = (TCM)].

2.2 Study selection

2.2.1 Inclusion criteria

The studies considered for inclusion were clinical RCTs that investigated TCM treatments for DPN. Participants in these studies could be patients diagnosed with DPN, with no restrictions regarding age, gender, disease duration, or comorbidities. The interventions examined in the selected studies could encompass a range of treatments including oral Chinese herbal decoctions, granules, proprietary Chinese medicines, Chinese medicine injections, acupuncture, foot baths, massage, fumigation washing, integrated TCM care, combined TCM therapies, etc.

2.2.2 Exclusion criteria

Studies were excluded if they were duplicated publications, inaccessible full-texts, animal or cellular experiments.

2.3 Data extraction and quality assessment

All identified references were imported into NoteExpress3.7.0 for management. A group of five researchers conducted the literature screening, with one appointed as the team leader. To ensure consistency, 100 papers were pre-screened as a calibration exercise before the main screening, and uniform screening criteria were established. Titles and abstracts were initially screened for relevance. Potentially relevant papers were further assessed by reading the full text. Discrepancies during the screening were resolved through discussions led by the team

TABLE 3 Top 5 oral Chinese medicines: introduction to medicinal plants.

Latin name	Bopomofo	Latin names of plants	Medicinal parts
Radix Astragali	Huangqi	Astragalus membranaceus (Fisch.) Bge. var. mongholicus (Bge.)Hsiao; Astragalus membranaceus (Fisch.)Bge	Root
Angelicae Sinensis Radix	Danggui	Angelicasinensis (Oliv.) Diels	Root
Paeoniae Radix Rubra	Chishao	Paeonia lactiflora Pall. ; Paeonia veitchii Lynch	Root
Pheretima	Dilong	Pheretima aspergillum (E.Perrier); Pheretima vulgaris Chen; Pheretima guillelmi (Michaelsen); Pheretima pectinifera Michaelsen	All
Chuanxiong Rhizoma	Chuanxiong	Ligusticum chuanxiong Hort	Rhizome
Carthami Flos	Honghua	Carthamus tinctorius L	Flower
Persicae Semen	Taoren	Prunus persica (L.) Batsch; Prunus davidiana (Carr.) Franch	Ripe Seed
Paeoniae Radix Alba	Baishao	Paeonia lactiflora Pall	Root
Cinnamomi Ramulus	Guizhi	Cinnamomum cassia Presl	Shoot
Zingiberis Rhizoma Recens	Shengjiang	Zingiber officinale (Willd.) Rosc	Rhizome
Jujubae Fructus	Dazao	Ziziphus jujuba Mill	Ripe Fruit
Asari Radix et Rhizoma	Xixin	Asarum heterotropoides Fr. Schmidt var. mandshuricum (Maxim.)Kitag.; Asarum sieboldii Miq.var.seou1ense Nakai、 Asarum sieboldii Miq	Root and Rhizome
Glycyrrhizae Radix et Rhizoma	Gancao	Glycyrrhiza uralensis Fisch	Root and Rhizome
Tetrapanacis Medulla	Tongcao	Tetrapanax papyriferus (Hook.) K. Koch	stem pith
Angelicae Pubescentis Radix	Duhuo	Angelica pubescens Maxim. f. biserrata Shan et Yuan	Root
Taxilli Herba	Sangjisheng	Taxillus chinensis (DC.) Danser	Leafy Stem Branche
Eucommiae Cortex	Duzhong	Eucommia ulmoides Oliv	Bark
Achyranthis Bidentatae Radix	Niuxi	Achyranthes bidentata Bl	Root
Gentianae Macrophyllae Radix	Qinjiao	Gentiana macrophylla Pall.; Gentiana straminea Maxim.、 Gentiana crassicaulis Duthie ex Burk.; Gentiana dahurica Fisch	Root
Poria	Fuling	Poria cocos (Schw.) Wolf	Mushroom Kernel
Saposhnikoviae Radix	Fangfeng	Saposhnikovia divaricata (Turcz.) Schischk	Root
Ginseng Radix et Rhizoma	Renshen	Panax ginseng C. A. Mey	Root and Rhizome
Rehmanniae Radix Praeparata	Shudihuang	Rehmannia glutinosa Libosch	Tuberous Root
Cinnamomi Cortex	Rougui	Cinnamomum cassia Presl	Bark

leader. Relevant information was extracted using a standardized form, which included publication year, authors, sample size, trial period, combined drugs, interventions (categorized as oral Chinese medicine, proprietary medicine, TCM external treatments, herbal injections, integrated TCM care, multi-therapy combination, and others), and outcome measures.

2.4 Classification of TCM interventions

To provide a clearer picture of TCM treatments for DPN, we categorized the TCM interventions from the included studies into seven types: oral Chinese medicines (including herbal decoctions and granules), proprietary Chinese medicines, external TCM therapies (like acupuncture, foot baths, massages, and fumigation), comprehensive TCM nursing, multi-therapy combinations, herbal injections, and others (which covers TCM exercise therapy and music therapy, etc.).

2.5 Data synthesis and analysis

Descriptive statistics were presented both in text and graphical forms. Graphs were plotted using Origin 2021 software, with trend developments represented using line graphs, category distributions in pie charts, and evidence distributions in bubble charts (Tian et al., 2019).

TABLE 4 Composition, therapeutic effects, and pharmacological actions of oral Chinese medicines.

Oral Chinese medicine	Botanical drugs included	Effect	Action	References
Huangqi Guizhi Wuwu Decoction	Radix Astragali; Cinnamomi Ramulus; Zingiberis Rhizoma Recens; Paeoniae Radix Alba; Jujubae Fructus	Improves coldness, numbness, and pain in the limbs	1.Improves neurological function to prevent diabetic peripheral neuropathy of STZ-induced diabetic rats by attenuating oxidative stress through Nrf2 and Bcl2 activation. 2.Upregulates the expression of β-catenin, cyclin D1, c-cmyc mRNA, downregulates the expression of DKK1 mRNA, and activates the classical Wnt signaling pathway to promote nerve fiber repair and regeneration 3.Prevents chronic OIPN by dynamically regulating intestinal flora homeostasis, thereby ameliorating intestinal barrier damage and reducing serum LPS and relevant inflammatory factor levels in the colon, serum, and DRG.	Zheng et al. (2019), Manman et al. (2022), Zhang et al. (2023)
Buyang Huanwu Decoction	Radix Astragali; Pheretima; Angelicae Sinensis Radix; Paeoniae Radix Rubra; Chuanxiong Rhizoma; Persicae Semen; Carthami Flos	Improves limb numbness	1.Regulates the production of inflammatory cytokines and promotes axonal regeneration after nerve transection of rats 2.promotes growth and differentiation of neural progenitor cells	Sun et al. (2007), Kim et al. (2020)
Danggui Sini Decoction	Paeoniae Radix Alba; Angelicae Sinensis Radix; Cinnamomi Ramulus; Asari Radix et Rhizoma; Tetrapanacis Medulla; Jujubae Fructus; Glycyrrhizae Radix et Rhizoma	Improves coldness, numbness and pain in the limbs	1.Downregulates the expression level of NF-κb protein and m RNA to protect neuronal cells	Cheng (2019)
Duhuo Jisheng Decoction	Angelicae Pubescentis Radix; Taxilli Herba; Eucommiae Cortex; Asari Radix et Rhizoma; Cinnamomi Cortex; Achyranthis Bidentatae Radix; Angelicae Sinensis Radix; Gentianae Macrophyllae Radix; Saposhnikoviae Radix; Rehmanniae Radix Praeparata; Chuanxiong Rhizoma; Ginseng Radix et Rhizoma; Poria; Paeoniae Radix Alba; Glycyrrhizae Radix et Rhizoma	Improves pain and coldness in limbs	Reduces serum MAD levels, elevates GSH-Px levels, improves oxidative stress, repairs the nerve conduction system	Jie et al. (2018)
Taohong Siwu Decoction	Persicae Semen; Carthami Flos; Angelicae Sinensis Radix; Rehmanniae Radix Praeparata; Paeoniae Radix Alba; Chuanxiong Rhizoma	Improves numbness and pain in limbs	1.Upregulates the expressions of autophagy markers (LC3-II/LC3-I and Beclin1) mitochondrial autophagy markers (Parkin and PINK1) after CIRI 2.Regulates the biosynthesis of phenylalanine, tyrosine, and tryptophan, as well as the metabolism of taurine, hypo, taurine, ascorbic acid, alginate, riboflavin, biotin, acid and proline, phenylalanine, and pyrimidine, improving the diversity and abundance and adjusting the structure of the gut microbiota, thereby alleviating the state of blood deficiency and blood stasis	Ji et al. (2022), He et al. (2023)

3 Results

3.1 Study selection

A total of 4,454 articles published over the past 6 years were identified through database searches. Of these, 1,229 RCTs on TCM interventions for DPN were included. The literature screening process and results are depicted in Figure 1.

3.2 Publication trend

From January 2017 to October 2022, we analyzed 1,229 published RCTs of TCM interventions for DPN. Over the five complete years (2017–2021) included, the annual average number of publications was 223, with no significant fluctuations, indicating a plateau in the number of publications. It is evident that Wanfang has indexed the most articles on TCM interventions for DPN. This trend is illustrated in Figure 2.

3.3 Analysis of sample size

An assessment of the scale of the included RCTs revealed a range in sample size from a minimum of 28 to a maximum of 900. The majority of studies had a sample size between 50 and 100, followed by studies with a sample size between 100 and 200. Detailed distributions are presented in Table 1.

TABLE 5 Average duration of intervention and proportion of studies without specified duration.

Intervening measure	Oral Chinese medicine	External TCM therapies	Herbal injections	Proprietary Chinese medicines	Comprehensive TCM nursing	Multi-therapy combinations	Others	All interventions
Average Duration of Treatment (day)	53.39	32.23	32.05	77.07	31.67	40.26	75.20	44.49
Literature Quantity	451	379	20	57	73	244	5	1,229
The Number of Articles without Indicating the Duration of Treatment	24	34	0	2	49	17	0	126
The Proportion of Articles without Specifying the Duration of Treatment	5.32%	8.97%	0%	3.51%	67.12%	6.87%	0%	10.25%

3.4 Positive drug usage

Of the 1,229 included studies, 775 (63.06%) explicitly used positive agents, including mecobalamin, thioctic acid, and prostaglandins. Another 73 studies (5.94%) employed drugs described with phrases like "neurotrophic and circulatory improvement." In contrast, 381 studies (31.00%) either did not use or did not mention positive drugs. These agents generally showed various degrees of improvement in DPN patients' symptoms and signs (Zhang and Ning, 2008; Han et al., 2012; Shin et al., 2013; Ma et al., 2022).

Mecobalamin, an active Vitamin B12 formulation widely used in many parts of the world for DPN treatment, promotes nucleic acid and protein synthesis within neurons. It significantly aids myelin formation and axonal regeneration, repairing damaged nerve cells and improving nerve conduction velocity, ultimately enhancing symptom signs (Sawangjit et al., 2020; Branch Group Of Neurological Complications, 2021).

Thioctic acid, a potent antioxidant, acts by inhibiting lipid peroxidation, enhancing blood flow in neurotrophic vessels, and boosting the activity of the Na + -K + -ATPase enzyme. It directly neutralizes reactive oxygen clusters and free radicals, protecting endothelial function (Ziegler et al., 2011; Han et al., 2012; Branch Group Of Neurological Complications, 2021).

Prostaglandins, physiologically active unsaturated fatty acids, and related compounds can increase cyclic adenosine monophosphate (cAMP) levels in vascular smooth muscle cells, relaxing vascular smooth muscles, reducing blood viscosity, and improving microcirculation (Branch Group Of Neurological Complications, 2021).

3.5 The distribution of TCM therapies

Oral Chinese medicine research dominated with 453 studies (36.86%), followed by external TCM therapies with 378 (30.76%). The remaining categories included multi-therapy combinations (244 studies), comprehensive TCM nursing (73), proprietary Chinese medicines (57), herbal injections (19), and others (5). The distribution is illustrated in Figure 3.

Among the 453 studies with oral Chinese medicine as an intervention: The most frequently occurring interventions (with a frequency of ≥5) are, in descending order: Huangqi Guizhi Wuwu Decoction, Buyang Huanwu Decoction, Danggui Sini Decoction, Duhuo Jisheng Decoction, and Taohong Siwu Decoction.

For the 378 studies involving external TCM therapies: The most frequent interventions (with a frequency of ≥5) are, in descending order: acupuncture, foot bath, fumigation combined with external washing, external application, moxibustion, foot bath combined with massage, acupoint injection, external wash, external application combined with acupuncture, foot bath combined with external application, iontophoresis, foot bath combined with acupuncture, fumigation, fumigation combined with external washing and acupuncture, massage, foot bath combined with acupoint injection, and topical rubbing.

A detailed breakdown of the frequencies for each intervention is presented in Table 2. A comprehensive overview of oral Chinese medicines can be found in Tables 3, 4.
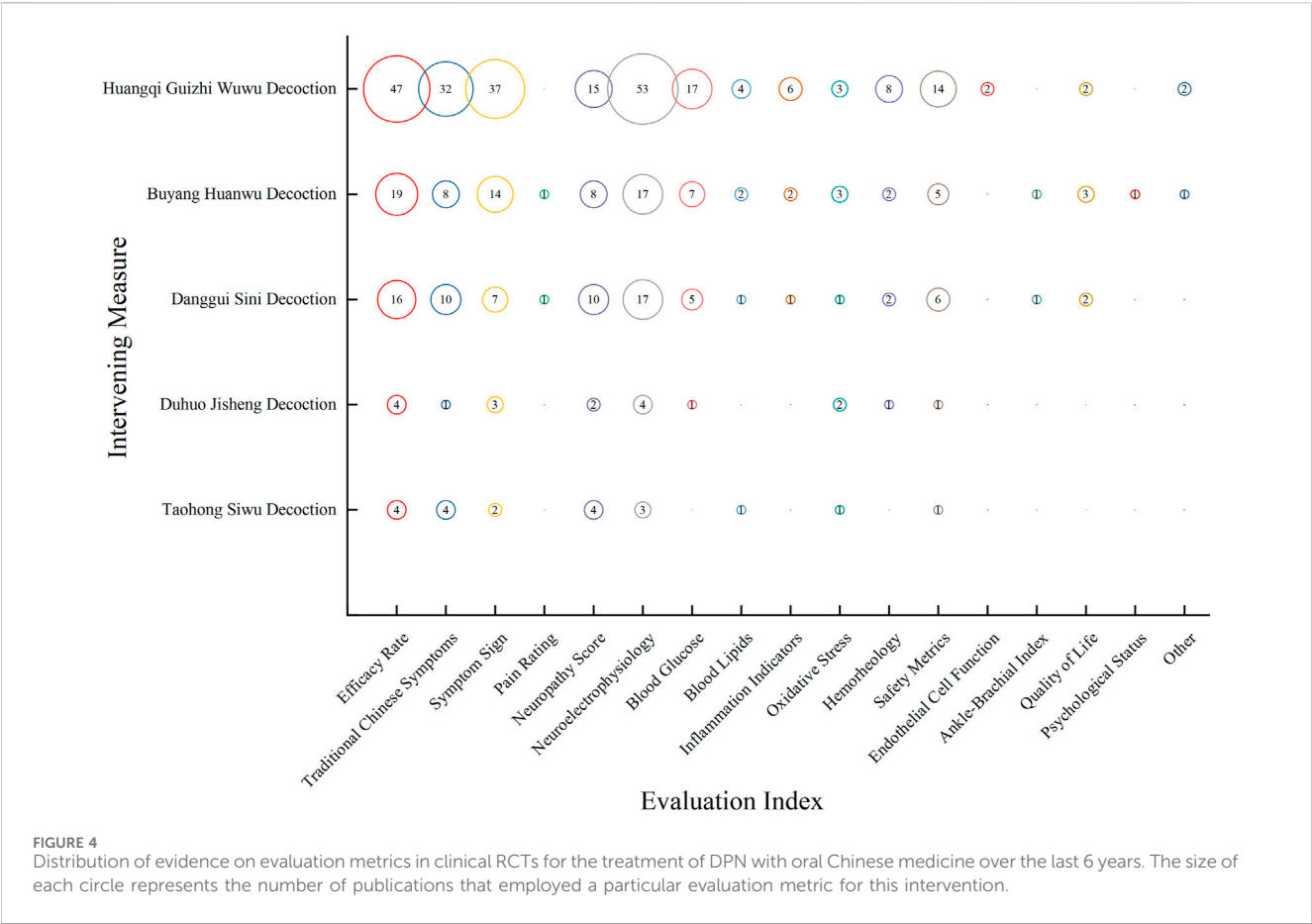
TABLE 6 Details of selected outcome measure categories.

Classification of evaluation indicators	The name of the evaluating indicator
Neurophysiological Evaluations	Motor Nerve Conduction Velocity (MCV), Sensory Nerve Conduction Velocity (SCV), Action Potential Amplitude, etc.
Neuropathy Score	Toronto Clinical Scoring System (TCSS), Toronto Clinical Neuropathy Score (TCNS), Michigan Diabetic Neuropathy Score (MDNS), Michigan Neuropathy Screening Instrument (MNSI), Clinical Symptom Integral Table (CSIT), Total Symptom Score-6 (NTSS-6), Neurological Disability Score (NDS), Neurological Symptom Score (NSS), Total Symptom Score (TSS), Leeds assessment of neuropathic symptoms and signs (S-LANSS),etc.
Safety Indicators	Incidence of Adverse Drug Reactions, Blood Routine, Liver Function, Renal Function, Electrocardiograph, etc.
Hemorheology	Plasma Viscosity, Whole Blood Relative Viscosity (WBRV), Whole Blood Low Shear Viscosity, Whole Blood High Shear Viscosity, RBC Aggregation Index, RBC Deformation Index (RDI), etc.
Indicators of Oxidative Stress	Serum Ferritin (SF), Malondialdehyde (MDA), Superoxide Dismutase (SOD), Glutathione Peroxidase (GSH-Px), Total Antioxidative Capacity (T-AOC), Advanced Glycation End Products (AGEs), Homocysteine (HCY), Cystatin C(Cys-c), etc.
Markers of Inflammation	Interleukin-6(IL-6), Interleukin-1β(IL-1β), Interleukin-18(IL-18), Free Fatty Acid (FFA), TNF-α, NF-κB, NLRP3 Inflammasome, High Mobility Group Box-1 Protein (HMGB1), Toll-like Receptor 2 (TLR2), Toll-like Receptor 4 (TLR4), Myeloid Differentiation Primary Response 88 (MyD88), Lp-PLA2, Prostaglandin F2α(PGF2),etc.
Function of Endothelial Cell	Nitric-oxide (NO), Endothelin (ET), Vascular Endothelial-Derived Growth Factor (VEGF), Nitric-oxide Synthase (NOS), etc.
Living Quality	36-Item Short Form (SF-36), Pittsburgh Sleep Quality Index (PSQI), Diabetes Specificity Quality of Life Scale (DSQL), Nottingham Health Profile (NHP), Sleep State Self-Rating Scale (SRSS), World Health Organization Quality of Life Assessment (WHOQOL-BREF), Activity of Daily Living (ADL), EORTC Core Quality of Life questionnaire (EORTC QLQ-C30), Barthel Index, EuroQol Five Dimensions Questionnaire (EQ-5D), etc.
Pain Score	Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN), the Neuropathy Pain Scale (NPS), etc.
Psychological Status	Self-rating Depression Scale (SDS), Self-Rating Anxiety Scale (SAS), Connor-Davidson Resilience Scale (CD-RISC), Diabetes Distress Scale (DDS), Hamilton Depression Scale (HAMD), etc.

TABLE 7 Evaluation metrics rankings by treatment approach.

Rank	Oral Chinese medicine metrics	External TCM therapies metrics
1	Neuroelectrophysiology	Efficacy Rate
2	Efficacy Rate	Neuroelectrophysiology
3	Symptom Sign	Symptom Sign
4	Traditional Chinese Symptoms	Neuropathy Score
5	Neuropathy Score	Traditional Chinese Symptoms
6	Blood Glucose	Safety Metrics
7	Safety Metrics	Blood Glucose
8	Hemorheology	Pain Rating
9	Oxidative Stress	Quality of Life
10	Inflammation Indicators	Other
11	Blood Lipids	Hemorheology
12	Endothelial Cell Function	Blood Lipids
13	Quality of Life	Inflammation Indicators
14	Other	Oxidative Stress
15	Pain Rating	Ankle-Brachial Index
16	Ankle-Brachial Index	Psychological Status
17	Psychological Status	Endothelial Cell Function

FIGURE 4
Distribution of evidence on evaluation metrics in clinical RCTs for the treatment of DPN with oral Chinese medicine over the last 6 years. The size of each circle represents the number of publications that employed a particular evaluation metric for this intervention.

3.6 Duration of treatment

Of the 1,229 studies, 1,103 (89.75%) specified the duration of treatment, while 126 (10.25%) did not. Among the seven categories of interventions, Comprehensive TCM Nursing had the highest proportion of studies that did not specify the duration at 67.1%. Conversely, Herbal Injections (0%), Others (0%), and Proprietary Chinese Medicines (3.51%) had the lowest proportions of unspecified durations. Among the studies that specified the duration, Proprietary Chinese Medicines had the longest average treatment duration at 77.07 days, while Comprehensive TCM Nursing had the shortest at 31.67 days. See Table 5.

3.7 Outcome measures

A comprehensive analysis of the outcome measures employed in the included RCT studies on TCM treatment for DPN was conducted. These outcome measures were categorized into 17 types, including neurophysiological evaluations, neuropathy scores, safety indicators, hemorheology, etc. Details for some of the outcome measure categories are provided in Table 6.

Based on the assessment metrics utilized in the included RCT, studies on TCM, treatment for DPN, we categorized them into 17 types. The detailed contents for some of these categories are listed in Table 7.

Bubble diagrams indicate that clinical RCTs of common oral Chinese medicine treatments for diabetic peripheral neuropathy often focus on metrics such as Neuroelectrophysiology, Efficacy Rate, and Symptom Sign. In contrast, those metrics like Endothelial Cell Function, Quality of Life, and Ankle-Brachial Index receive less attention, as shown in Figure 4.

Clinical RCTs of prevalent TCM External Treatment pay more attention to Efficacy Rate, Neuroelectrophysiology, and Symptom Sign, while metrics such as Endothelial Cell Function and Psychological Status are often overlooked. Both treatment approaches prioritize Neuroelectrophysiology, Efficacy Rate, and Symptom Sign, with lesser emphasis on Ankle-Brachial Index and Psychological Status, as depicted in Figure 5.

4 Discussion

This study represents the first comprehensive examination of clinical RCTs regarding the TCM treatment of DPN over the past 6 years, using an evidence map approach. Through an in-depth analysis encompassing publication trends, study scale, positive drug usage, intervention categories, duration of treatment, and evaluation metrics, we shed light on the current evidence, research advancements, and challenges in TCM's treatment of DPN. This review aims to guide future RCT research in this domain, assisting in refining both research focus and design.
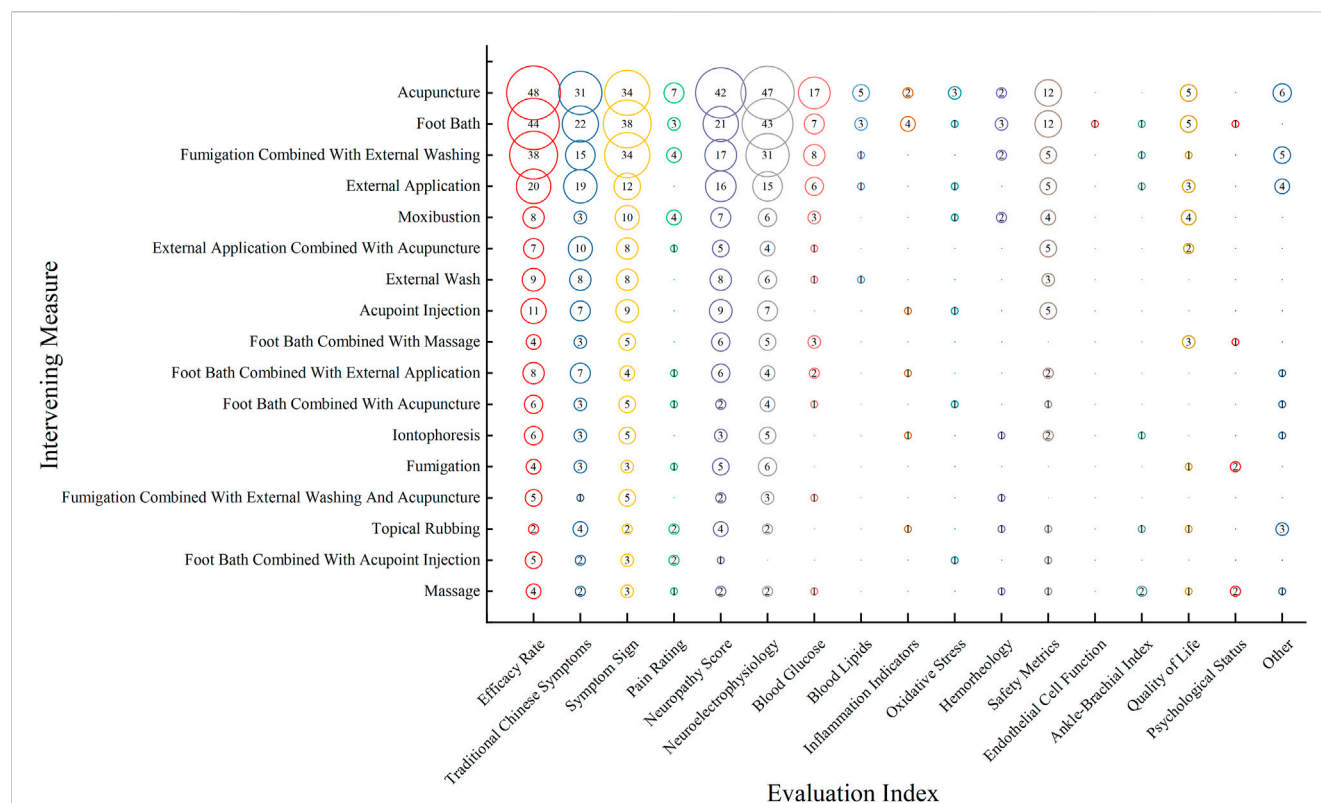
FIGURE 5
Distribution of evidence on evaluation metrics in Clinical RCTs for the treatment of DPN with TCM external treatment over the last 6 years. The size of each circle represents the number of publications that employed a particular evaluation metric for this intervention.

4.1 TCM treatment for DPN: integrative trends and requirements

From the 1,229 RCT articles reviewed, the number of TCM studies addressing DPN has remained relatively stable over the past 6 years. Notably, up to 80% of these studies were of small scale, with sample sizes of fewer than 100 participants. Several studies displayed design flaws such as ambiguous sample sources, insufficient descriptions of randomization and blinding methods, a lack of baseline characteristics for trial participants, and an absence of drug washout periods, all of which could significantly influence the study outcomes.

However, concurrently, we observed a significant trend integration where nearly 70% of the interventions combined modern drugs like metformin, alpha-lipoic acid, and ipragliflozin with TCM. This combination potentially offers a dual therapeutic approach, fully harnessing the rapid and quantitative effects of modern drugs and the holistic and long-term benefits of TCM. For instance, while modern drugs might swiftly stabilize the blood sugar levels in diabetic patients, TCM can provide long-term health benefits by adjusting the overall balance in the body. Additionally, TCM often emphasizes moderating lifestyle habits, dietary practices, and emotional states, crucial aspects that might be overlooked in modern medicinal treatments.

Such integration underscores the advantages of combining traditional and modern medicine, offering patients a more comprehensive and integrative treatment modality. However, studies solely relying on traditional Chinese methods remain scarce. This may reflect an integration trend between TCM and contemporary medicine, suggesting an imperative for more

exclusive TCM clinical trials to ascertain its efficacy. In the future, conducting large-scale, multi-center clinical randomized controlled trials would be valuable to confirm the effectiveness of TCM interventions. Such studies could compare TCM treatments with standard medications to assess non-inferiority, thus offering evidence to back the use of TCM as a standalone option in the prevention and management of diabetic peripheral neuropathy. (Hulley et al., 2017; Wang et al., 2022).

The inconsistency observed in the diagnostic criteria across RCT literature, with some studies providing clear guidelines while others merely confirming a diagnosis of diabetic peripheral neuropathy, underlines the necessity for uniform diagnostic standards in future research. To enhance the rigor and comparability of RCTs, it is crucial to use explicit diagnostic criteria. Researchers are encouraged to consult established guidelines, such as the American Diabetes Association's position statement on Diabetic Neuropathy (Pop-Busui et al., 2017), the Standards of Medical Care in Diabetes-2020 (Association, 2020), and the Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition) (Society, 2021), to ensure consistency and reliability in the field.

4.2 Diversity of outcome measures and the necessity of quantification in TCM syndrome diagnosis

A variety of efficacy evaluation indices were used, with DPN diagnostic-related indices, such as symptom and sign assessment,

neurophysiological tests, and nerve lesion scoring (Fang et al., 2017), as well as TCM syndrome scores and overall efficacy rates being the primary ones. However, attention to the ankle-brachial index and psychological states was notably lacking. As a commonly used composite index, the efficacy rate is frequently applied based on the "Guidelines for Clinical Research of New Chinese Medicines" and "Standards for the Evaluation of TCM Syndromes" and combines various evaluation metrics, causing significant variability between studies and a lack of scientific rigor (Zhang et al., 2020). Future studies should opt for primary, singular symptoms or signs to determine relative objective evaluation criteria. It's also recommended that DPN researchers collaboratively explore a Core Outcome Set (COS) and develop common COS guidelines, aiming to simplify trial design, select efficacy evaluation indices, reduce outcome reporting bias, and minimize inter-study outcome reporting heterogeneity (Clarke, 2007; Yu et al., 2016).

Diagnosis and treatment in TCM are determined by a combination of disease diagnosis, symptoms, and syndrome identification. TCM syndrome is an essential aspect in addition to disease diagnosis and symptomatology. Issues with the TCM syndrome scoring system in RCT studies of TCM treatment for DPN include the lack of scientific quantification of symptom scoring and the subjective nature of efficacy judgments. It's suggested that future research could utilize a scoring system for syndrome efficacy metrics, based on the severity of DPN-related symptoms and signs and the contribution defined by TCM syndrome characteristics, thereby transforming TCM syndrome metrics into objective, quantifiable ones.

4.3 Comprehensive perspectives on DPN-related complications and TCM treatment

DPN and lower limb vascular lesions are pivotal contributors to diabetic foot ulcers. Their severity has been positively correlated (Song, 2018). The ankle-brachial index, a significant measure for evaluating lower limb arterial status, provides considerable prognostic insight for DPN patients (Hinchliffe et al., 2020; Sorber and Abularrage, 2021).

Interestingly, between 26% and 50% of DPN patients also report symptoms of anxiety or depression (Gore et al., 2005; Zhao and Qi, 2022). Persistent symptoms, such as abnormal limb sensations and functional impairments in DPN patients, increase their susceptibility to depressive states. Such depressive conditions not only intensify their pain and numbness but also diminish their motivation to control blood sugar, exacerbating their condition and creating a vicious cycle (DU Shun-Tang et al., 2022).

Several oral TCM medications have demonstrated efficacy in treating diabetes-associated depression by attenuating insulin resistance, mitigating oxidative stress, and modulating the nervous system (Lu et al., 2020). Furthermore, non-pharmacological TCM interventions like acupuncture and massage excel in alleviating pain, anxiety, and depressive symptoms, significantly enhancing patients' quality of life (Yan, 2013; Wang et al., 2018). We recommend that future research on TCM for DPN broaden its scope beyond merely alleviating symptoms to encompass the overall quality of life and mental

health of patients. This approach will contribute to a more holistic evidence base supporting the use of TCM in treating DPN.

Our findings indicate that non-pharmacological treatments like acupuncture and moxibustion, alongside oral Chinese medicine, are increasingly utilized for DPN management. We recommend that future research should focus on conducting more RCTs and meta-analyses specifically on these non-pharmacological Chinese medicine therapies, such as acupuncture for DPN. This approach will enable a more comprehensive evaluation of the effectiveness of non-pharmacological Chinese medicine treatments on DPN.

4.4 Study limitations and future directions

While this study provides substantial evidence for the clinical investigation of TCM in treating DPN, it is not without limitations:

The search scope was confined to clinical randomized controlled trials published in Chinese and English databases over the recent 6 years, resulting in a relatively narrow range of included study types. To gain a more comprehensive understanding of this field, future studies should consider broadening their search criteria to encompass various types of studies and explore other literature sources, such as clinical trial registration platforms.

In illustrating evidence distribution, interventions were categorized and distinguished based on type. This method's shortcoming is that some intervention categories may encapsulate different drugs and operational methods. Furthermore, interventions within the same category might not be uniformly implemented, potentially influencing the research outcomes to varying degrees. No detailed quality assessment was carried out for the included studies, suggesting that the evidence distribution might be affected by biases to some extent.

Building on the previous discussion, we acknowledge the absence of a quantitative synthesis of data as a limitation. Future studies should incorporate quantitative analyses, such as meta-analyses, to provide more definitive conclusions regarding the effectiveness of TCM treatments for DPN. Such efforts will help clarify the magnitude of effects of various TCM treatments and identify promising approaches for further clinical investigation. By addressing these limitations and embracing a more comprehensive research methodology, future research can significantly advance our understanding and application of TCM in treating DPN.

5 Conclusion

This study systematically evaluated the clinical RCTs of TCM in addressing DPN, a significant complication of diabetes, using an evidence mapping approach. Despite the breadth of studies in this area, challenges such as inconsistent trial designs, predominant focus on standalone TCM treatments, varied intervention methods, and restricted evaluation metrics remain (Zhang et al., 2021).

To improve research quality regarding this pivotal diabetes complication, future studies should emphasize rigorous RCT design and apt selection of evaluation criteria. Moreover, establishing an online research database specifically tailored for TCM treatment of DPN—with a standardized literature extraction format—would be beneficial, promoting collaborative

research and facilitating re-assessment of data. By integrating global research expertise, it's essential to advance the synergy of TCM and modern medicine, aiming to enhance therapeutic outcomes and better the quality of life for patients grappling with this complication.

Our research accentuates the profound role of TCM in tackling DPN as a notable diabetes complication, providing meaningful insights for informed medical decisions and optimized clinical practices. This investigation endeavors to bolster the scientific underpinning of clinical practices, aiming to elevate patient satisfaction and understanding of DPN within the larger context of diabetes-related complications.

In conclusion, the potential of TCM in addressing DPN as a significant diabetes complication is evident. We look forward to further research that explores its potential efficacy in this domain.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Author contributions

YF: Writing–original draft, Writing–review and editing. YW: Writing–original draft, Writing–review and editing. ZL: Writing–original draft, Writing–review and editing. KH: Writing–original draft, Writing–review and editing. YG: Writing–original draft. SX: Writing–original draft. QL: Writing–original draft. XL: Writing–original draft, Writing–review and editing. GZ: Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer XG declared a shared parent affiliation with the author(s) YF, YG, and SX to the handling editor at the time of review.

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Acupuncture for the treatment of diabetic peripheral neuropathy in the elderly: a systematic review and meta-analysis

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Background: Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes mellitus, often causing pain or numbness in the patient's limbs and even leading to amputation and death. Elderly patients with DPN usually have higher morbidity and more severe results. Acupuncture has been widely used as an effective treatment for DPN in China. However, the efficacy of acupuncture in the treatment of DPN remains unclear. In this review, we aimed to explore the impact of acupuncture in alleviating symptoms of DPN.

Method and analysis: Six databases were searched from inception to October 2023. We searched Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and three Chinese databases, namely China National Knowledge Infrastructure (CNKI), SinoMed, and Wanfang. All randomized controlled trials related to the effect of acupuncture on DPN will be included. There was no restriction in language or publication year. The primary outcome is the response rate. The secondary outcomes are the Toronto clinical scoring system (TCSS), nerve conduction velocities (NCVs), and blood glucose before and after the treatment. Two researchers will be responsible for the selection of study, data extraction, and assessment of study quality independently. RevMan V5.1.0 software will be used to assess the risk of bias and generate data.

Results: We searched 4518 studies, among which 9 RCTs were considered eligible. Overall, acupuncture treatment had a higher response rate than controls (relative risk (RR), −2.87 [95% confidence interval (CI), −5.27 to −0.48], $p = 0.02$) and significantly alleviated the symptoms of DPN patients, reduced their blood glucose levels, and improved their NCVs compared to the control group. This study will provide a high-quality synthesis of current available evidence for the clinical treatment of DPN with this therapy.

Conclusion: The results suggested that acupuncture might be effective in improving symptoms of DPN in elderly patients. Owing to the overall low quality of the literature included, we need more large-sample, high-quality, and low-bias studies to prove it.

1 Introduction

Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes mellitus (DM). DPN is characterized by the functional loss of cutaneous receptors and proprioceptive sensation (1). Its typical symptoms include numbness and pain, which start most often in the feet and lower legs of DM patients. Up to 50% of diabetic peripheral neuropathies are asymptomatic, which is often missed until the disease progresses further, at which point it is almost irreversible, and should be treated with prompt preventive care (2). In addition, it is a leading cause of lower limb amputation and disabling neuropathic pain, which has a disastrous effect on the quality of life of patients and even leads to a shortened life expectancy (only 2 years on average) (3).

The incidence of DPN among newly diagnosed diabetic patients is 29.4% (4). Age is an independent risk factor for DPN. The incidence of DPN increased significantly with each 10-year increase in age, and diabetic patients older than 60 years of age were significantly associated with the incidence of DPN (4). In addition, older people with DPN experience higher fall risks compared to healthy older people, which can lead to serious consequences. With the progress of global population aging, the number of elderly patients with DPN has further increased, highlighting the need to address this issue in elderly populations (5).

At present, there is still a lack of treatment that targets underlying nerve damage. Prevention and early intervention are the key measures in the care of DPN (2). Appropriate interventions can reduce ulcers by 60% and amputations by 85% in those with high-risk diabetic neuropat (6). Based on the special characteristics of elderly patients with DPN, long-term use of drugs may increase the risk of adverse reactions (7). Therefore, clinical attention is gradually focused on the application of non-pharmacological treatment of elderly patients with DPNs. Acupuncture, a complementary and alternative therapy based on the meridian theory of traditional Chinese medicine, is currently widely used in China for the treatment of DPN. According to reports in the literature, acupuncture is an effective method for treating DPN, can improve nerve conduction velocities (NCVs) and clinical symptoms, and can slow down the development of DPN (8). We conducted a systematic review and meta-analysis to further explore the relationship between acupuncture and DPN.

2 Method

2.1 Literature search

This review was reported following the principles of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) (9). We searched Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and three Chinese databases, namely China National Knowledge Infrastructure (CNKI), SinoMed, and Wanfang, from inception to October 2023. There was no restriction in language or publication year. The search strategy of this study is shown in Supplementary material 1. The flow diagram of the study selection process is shown in Supplementary material 3.

2.2 Study selection and data extraction

We considered RCTs concerning the efficacy of acupuncture treatment of DPN in patients 60 years of age or older. The

intervention was acupuncture treatment. Due to the current lack of consensus and uniform standards on the definition of acupuncture, we adopt the International Organization for Standardization (ISO)'s definition of acupuncture: Acupuncture therapy refers to the entire process of inserting acupuncture needles into the body and applying appropriate maneuvers after the insertion, which involves the healthcare provider's method of selecting acupuncture points (10), including electro-acupuncture, scalp acupuncture, warm acupuncture, fire acupuncture, and needle knife. The control group was pharmacotherapy, other non-pharmacotherapy, or invalid groups. The trial group can be included if it consists of acupuncture and control group therapy. This article excluded studies that compared different types of acupuncture and reported only one single outcome indicator. If additional information or data are required, we will contact the authors of the study.

Two independent reviewers (Huan Yang and Yuan Qin) conducted literature searches separately, initially screened titles and abstracts according to the requirements, and included qualified articles after reading the full text. In case of disagreement, the third reviewer will make the final decision. The two investigators independently extracted data from the eligible literature into the Microsoft Excel spreadsheet and extracted the following data according to the predesigned forms: first author name, publication year, country, study design, participant characteristics, intervention indication, male-to-female ratio, duration of treatment, outcome measures, and adverse events.

2.3 Outcome assessment

The primary endpoint was the response rate. The secondary endpoints included the Toronto clinical scoring system (TCSS), NCVs (median nerve sensory nerve conduction velocity (SNCV), common peroneal nerve MNCV, and common peroneal nerve SNCV), and blood glucose (fasting glucose and glycosylated hemoglobin). The outcome of the patient was divided into three categories-significant effective (no abnormality in neurological examination and disappearance of subjective symptoms), effective (improvement in neurological examination and alleviated subjective symptoms), and ineffective (no improvement in neurological examination and subjective symptoms), and then calculate the response rate: the response rate = significant effective rate + effective rate.

2.4 Risk of bias assessment

The included randomized controlled trials were independently assessed by two evaluators (Huan Yang and Yuan Qin) according to the Cochrane Risk of Bias Assessment Tool. The following items were evaluated: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The overall risk of bias for each study was summarized after evaluating them on three levels: low risk, high risk, and unclear risk. Disagreements were resolved by negotiation, and if no consensus could be reached, the decision was made by a third evaluator.

2.5 Statistical analysis

Statistical analysis was carried out using Review Manage software (V5.1.0, Nordic Cochrane Center, Copenhagen, Denmark). Dichotomous data were presented as relative risk (RR) and continuous data as mean difference (MD) and 95% confidence interval (95%CI). The major assumption of a fixed-effect model is that all effect sizes share a common mean, and thus that variation among data is solely attributable to sampling error (11). This assumption, however, is unrealistic for most meta-analyses; the random-effects model will be used throughout this article.

Heterogeneity among studies was tested by Q-test and I^2-test statistics. If its p-value >0.05 indicates no significant heterogeneity, the differences between the studies are caused by random factors. If the p-value is <0.05, it means significant heterogeneity that the differences between the studies are not random, but rather due to a factor that causes heterogeneity between cases.

3 Result

3.1 Study description

A total of 4158 studies were retrieved in this study; 2513 duplicate studies were screened out, and 1309 studies irrelevant to this study were excluded after further reading of the title and abstract. The complete text was then read, and 327 unqualified studies were screened out according to the inclusion and exclusion criteria of the literature. Nine studies (12–20) were finally included for meta-analysis, and the diagram of the screening process is shown in Supplementary material 3. The included studies were all in Chinese, had a sample size of 751 patients (383 patients in the experimental group and 368 in the control group), treatment durations ranging from 10 days to 3 months, no distinction between type 1 and type 2 DM, and no follow-up. Of the nine studies, all patients were treated with conventional Western medicine, except for one study (19) in the control group, which used walking ladder training (WLT). Except for acupuncture with specimen matching points (20) in one RCT in the experimental group and warm acupuncture (19) in one RCT, millineed needling was used in the other seven studies. The basic characteristics of the included studies are shown in Table 1 and Supplementary material 2.

3.2 Assessment of quality and bias

We used the Cochrane Risk of Bias Assessment Tool to assess the quality of the included papers. Nine studies described the specific randomization scheme in detail with allocation concealment, six studies used random digitization tables (low risk), one study used computerized randomization (low risk), one study used coin-flip randomization (low risk), and one study used an incorrect randomization scheme based on the order of treatment (high risk). None of the nine studies explicitly said whether or not they were blinded (unclear risk). Nine studies had complete outcome data (low risk). In the reporting of outcome selectivity, one study did not define and describe outcomes in advance, and there was a possibility of reporting bias (high risk). Among other biases, it was unclear whether there were other biases in the literature, except for one where the sample size was too small (high risk). The risk of bias in included studies is shown in Supplementary material 4.

3.3 The response rate

A total of eight (12–17, 19, 20) studies evaluated the clinical response rate in the literature, with a total of 670 patients included, and there was no significant heterogeneity among the studies ($p = 0.86$, $I^2 = 0$), which was evaluated using a random-effects model. For the treatment of DPN, the response rate of the experimental group was higher than that of the control group (RR = 4.49, 95% CI: 1.26 [1.17,1.35], $Z = 7.49$, $p < 0.00001$) (Figure 1).

3.4 The Toronto clinical scoring system (TCSS)

A total of four papers (13, 14, 17, 19) evaluated the TCSS. One article did not report pre-treatment data but only reported post-treatment outcomes, and we have not yet contacted the authors to obtain the original data; therefore, this article was excluded. A total of 319 patients were included, and the studies were significantly heterogeneous from each other ($p < 0.00001$, $I^2 = 94\%$), and were evaluated using a random-effects model. For the treatment of DPN, the TCSS score of the experimental group was better than that of the control group, and the difference was statistically significant (MD = −2.87, 95% CI: −5.27 to −0.48, $Z = 2.35$, $p = 0.02$) (Figure 2).

3.5 Nerve conduction velocities (NCVs)

Three studies (14, 16, 20) in the literature evaluated median nerve SNCV and included a total of 239 patients. Three studies (15, 19, 20) evaluated the common peroneal nerve MNCV and included a total of 312 patients. Five studies (14–16, 19, 20) reported the common peroneal nerve SNCV and included a total of 458 patients. All had significant heterogeneity: median nerve SNCV ($p = 0.02$, $I^2 = 73\%$), common peroneal nerve MNCV ($p < 0.00001$, $I^2 = 93\%$), and common peroneal nerve SNCV ($p = 0.001$, $I^2 = 77\%$). A random-effects model was used for all. For the treatment of DPN, the improvements in motor NCVs of the experimental group were better than those of the control group, and the differences were statistically significant: median nerve SNCV (MD = 3.65, 95% CI: 1.60 to 5.71, $Z = 3.45$, $p = 0.0005$), common peroneal nerve MNCV (MD = 6.86, 95% CI: 2.52 to 11.2, $Z = 3.10$, $p = 0.002$), and common peroneal nerve SNCV (MD = 5.06, 95% CI: 3.10 to 7.03, $Z = 5.06$, $p < 0.00001$). Acupuncture effectively improved motor NCVs (Figure 3).

3.6 Blood glucose

Two studies (18, 20) evaluated fasting blood glucose and glycosylated hemoglobin in the literature, and a total of 174 patients were included. There was significant heterogeneity among the studies on fasting blood glucose ($p = 0.0006$, $I^2 = 92\%$) and glycosylated hemoglobin ($p < 0.00001$, $I^2 = 96\%$), which were evaluated using a random-effects model. For the treatment of DPN, the experimental group showed better improvement in fasting blood glucose and glycosylated hemoglobin than the control group, and the difference was statistically significant. The fasting blood glucose of the experimental group was lower than that of the control group (MD = −1.2, 95% CI: −2.34 ~ −0.07, $Z = 2.08$, $p = 0.04$). The HBA1c of the experimental group was lower than that of the control group (MD = −1.45, 95% CI: −2.69 ~−0.21, $Z = 2.28$, $p = 0.02$).

TABLE 1 Characteristics of the included trials.

Study ID	N (T/C)	Age (T/C, years)	Acupuncture intervention	Control intervention	Outcome
Ye xin2020	93 (46/47)	72.13 ± 4.25/72.92 ± 3.73	Specimen matching points acupuncture	Therapeutics	①③④⑤⑥⑦⑧⑨
Chen Hualu2022	119 (60/59)	66.62 ± 5.17/65.71 ± 4.28	Hand and foot warm acupuncture+walking step training	Mecobalamin	①②⑩⑪⑫⑬
Li Lihong2015	30 (15/15)	72 ± 5.82	Acupuncture+Mecobalamin	walking step training	①②⑭
Yu Shaoqing2017	90 (45/45)	60–69/60–68	Acupuncture+Mecobalamin	Mecobalamin	①②⑭
Han Qing2018	64 (34/30)	6.9 ± 3.6/5.6 ± 4.7	Acupuncture+Mecobalamin	Mecobalamin	①②④⑥
Xie Aixian2017	100 (48/52)	70.6 ± 3.2	Acupuncture+DL-Thioctic acid	Mecobalamin	①⑤⑥⑮⑯
Wang Zichun2013	82 (41/41)	77.5 ± 4.3/81.2 ± 2.1	Acupuncture	Mecobalamin+Vitamin B1	①③④⑤⑥⑰⑱
Feng Xiao2018	92 (46/46)	71.5 ± 4.6/71.6 ± 4.7	Acupuncture	Sham-acupuncture	①②
Yu Haoyan2017	81 (43/38)	70.67 ± 4./70.44 ± 4.32	Acupuncture	Sham-acupuncture	⑦⑲

① The response rate, ② the Toronto clinical scoring system (TCSS), ③ median nerve MNCV, ④ median nerve SNCV, ⑤ common peroneal nerve MNCV, ⑥ common peroneal nerve SNCV, ⑦ blood glucose, ⑧ blood lipid, ⑨ inflammatory cytokines, ⑩ Michigan Diabetes Neuropathy Score (MDNS), ⑪ tibial nerve MNCV, ⑫ tibial nerve SNCV, ⑬ hemodynamics, ⑭ pain relief effect, ⑮ Michigan Neurological Screening Inventory (MNSI), ⑯ physical examination score, ⑰ ulnar nerve MNCV, ⑱ ulnar nerve SNCV, and ⑲ treatment satisfaction.
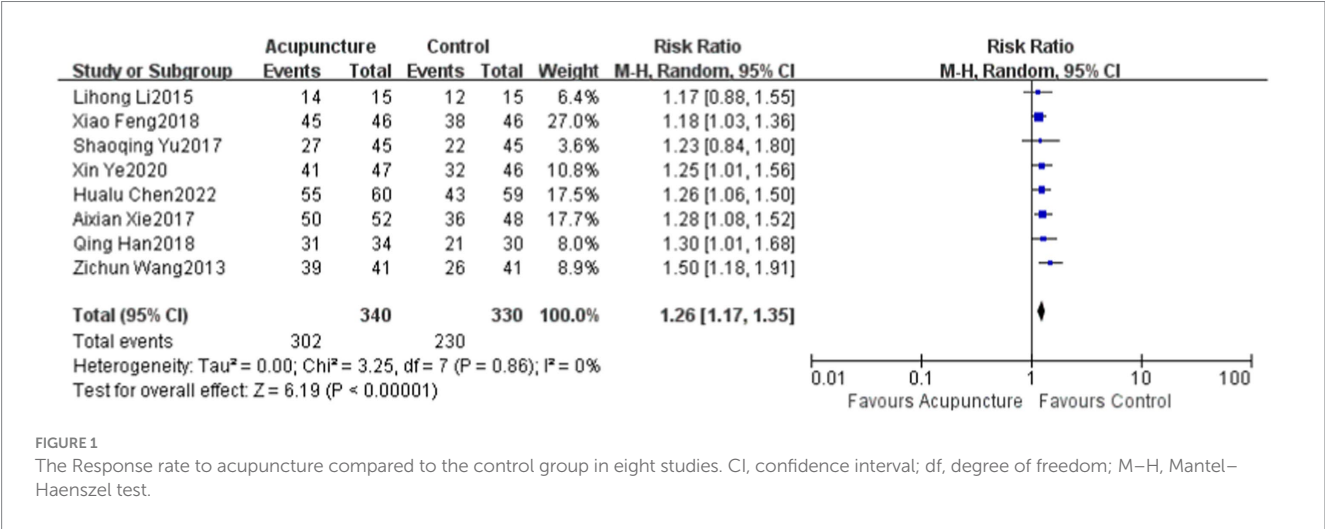

FIGURE 1
The Response rate to acupuncture compared to the control group in eight studies. CI, confidence interval; df, degree of freedom; M−H, Mantel–Haenszel test.
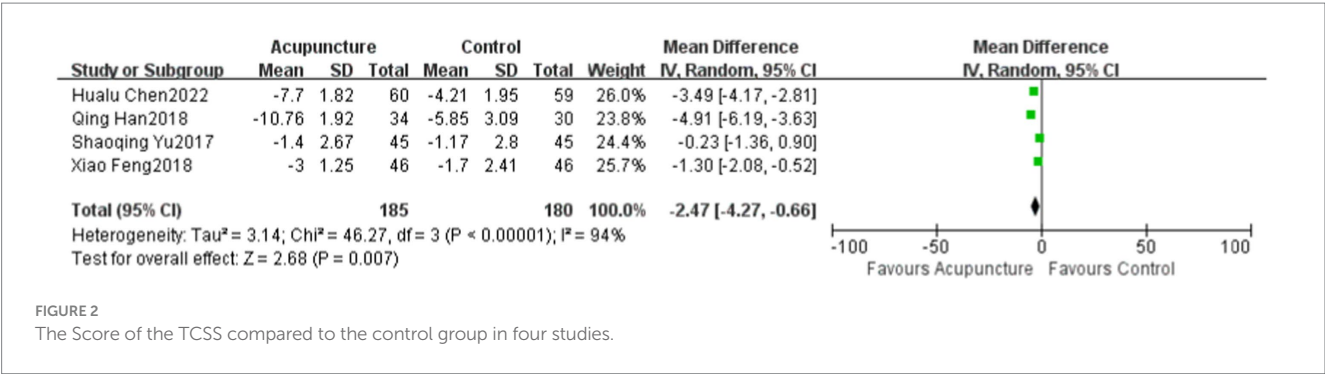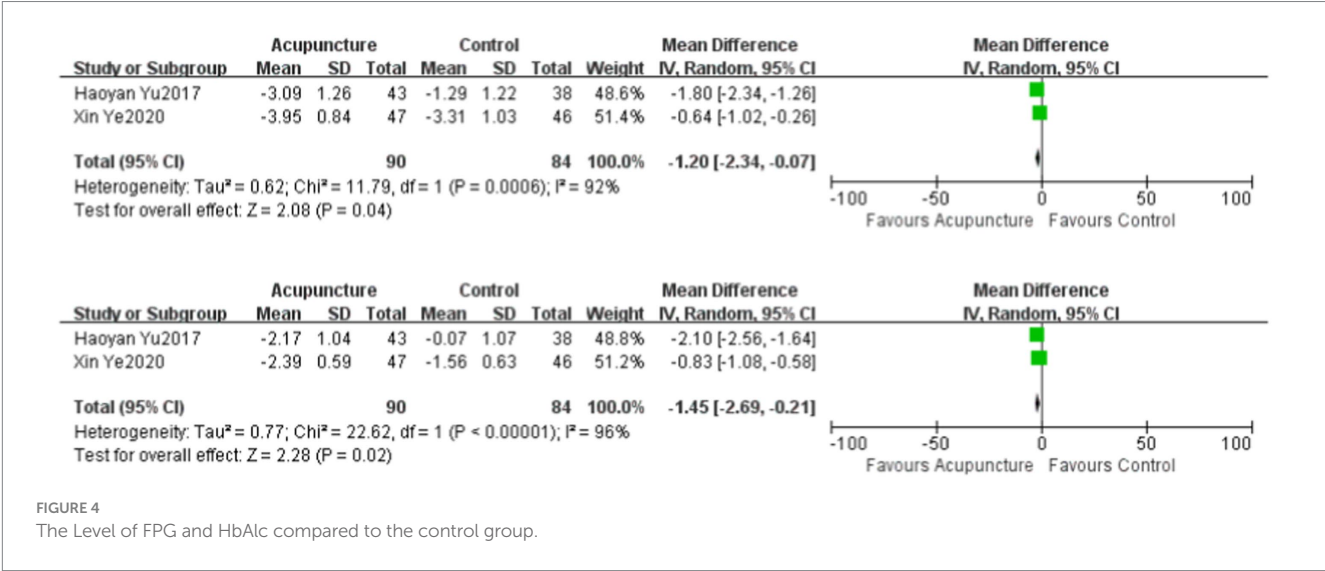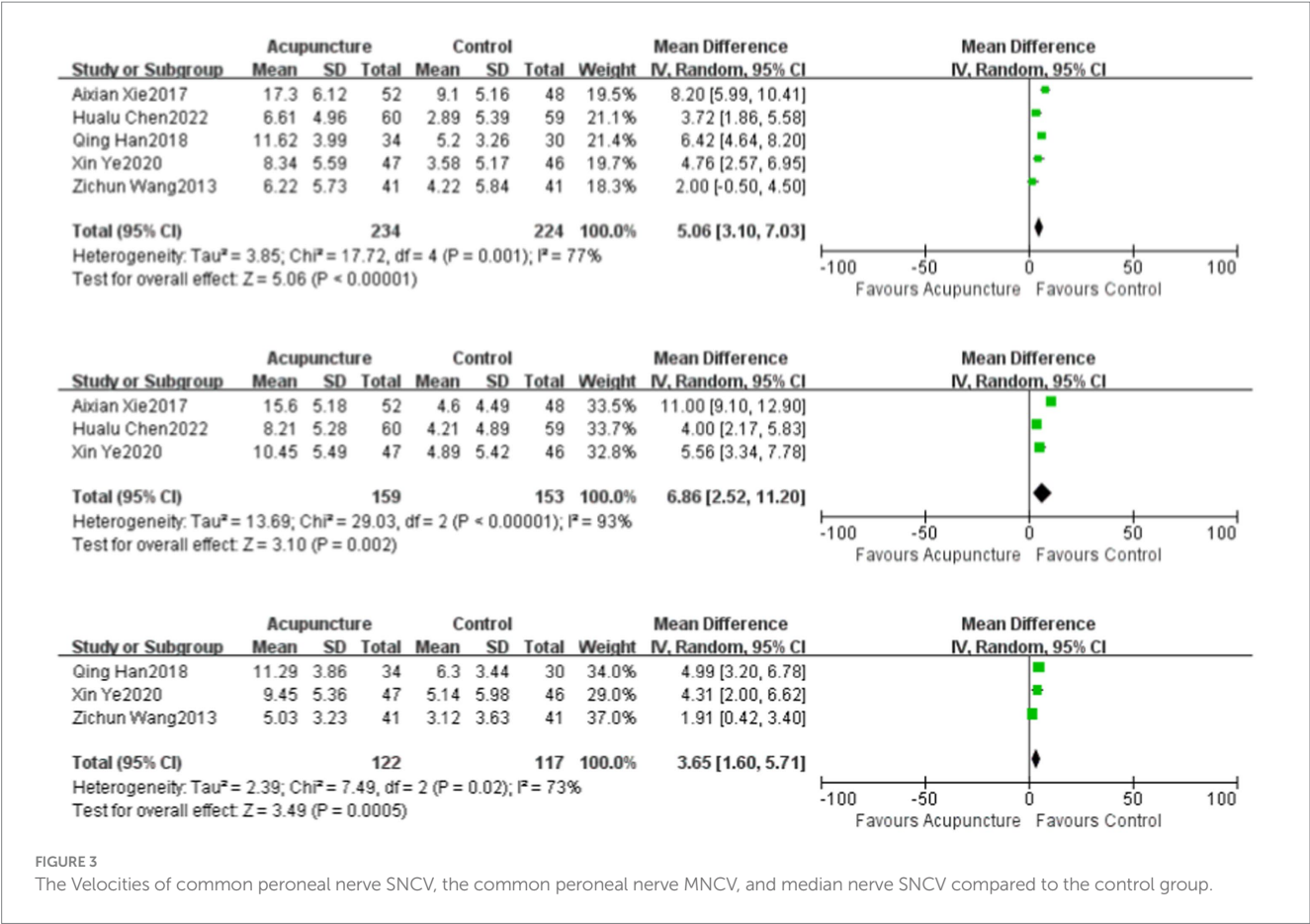

FIGURE 2
The Score of the TCSS compared to the control group in four studies.

4 Conclusion

We managed to minimize the risk of bias and draw as objective conclusions as possible by formulating a detailed protocol in advance, conducting a comprehensive search for published trials, using clear findings, data extraction, and data analysis methods, and rigorously performing literature quality assessments. In conclusion, acupuncture treatment is significantly better than regular treatment and can effectively alleviate the symptoms of DPN patients, reduce their blood glucose levels, and improve their NCVs. The results of this study have a certain degree of reliability; however, due to the above shortcomings and limitations, more large-sample, high-quality, and low-bias studies are needed to prove it.

FIGURE 3
The Velocities of common peroneal nerve SNCV, the common peroneal nerve MNCV, and median nerve SNCV compared to the control group.

FIGURE 4
The Level of FPG and HbAlc compared to the control group.

5 Discussion

This review focuses on assessing the efficacy of acupuncture in treating elderly patients with DPN. A total of nine randomized controlled trials were included, with acupuncture, specimen matching acupuncture, and warm acupuncture as the intervention group and methylcobalamin, vitamin B, diabetes education, and walking step training as the control group.

Nine studies with a total of 751 randomized participants were eligible for inclusion in this review. For the main outcome indicators, acupuncture alleviated the symptoms of DPN in the elderly compared to conventional Western medical treatment.

Four studies evaluated the efficacy of acupuncture in treating DPN using the TCSS, with significant differences. The results of this meta-analysis showed a significant increase in the response rate and a significant decrease in the TCSS scores of patients with acupuncture intervention. The response rate and TCSS can be assessed comprehensively in DPN patients and can show visually that acupuncture relieves the clinical symptoms of the patients. During the pathogenesis of elderly patients with DPN, hyperglycemia activates the glucose polyol pathway and generates a large number of free radicals that damage nerves, leading to a decrease in MNCV and SNCV (21). Three studies evaluated median nerve SNCV, three studies evaluated common peroneal nerve MNCV, and five studies reported common peroneal nerve SNCV with statistically significant changes in NCVs. The NCVs are an important outcome indicator of neurologic function, but they cannot be used as direct evidence of the clinical efficacy of DPN. The study also showed that acupuncture can improve NCV and control blood glucose concentration in patients. Therefore, acupuncture can not only alleviate clinical symptoms in DPN patients but also control blood glucose and repair nerves, improving clinical efficacy.

We found that the acupuncture group had a lower incidence of adverse events and dropout rates. As a non-pharmacological treatment, acupuncture therapy will be a safe complementary approach to treating elderly patients with DPN. However, the evidence has a low level of certainty because of the small number of included studies and the fact that some of the studies did not report the incidence of adverse events or dropout rates. None of the literature included in this study followed up with patients to compare the long-term efficacy of acupuncture in the treatment of DPN in the elderly.

DPN patients' blood is mainly hypercoagulable, which can easily lead to tissue ischemia and hypoxia (22). In addition, in patients with long-term high glucose levels, coagulation and anticoagulation factors are expressed abnormally, resulting in dyslipidemia and accelerated vascular lesions, both of which are associated with DPN disease progression (23). In addition, Tang et al. (24) found that the possible mechanism of alleviating the symptoms of DPN by acupuncture is related to the regulation of P2X4 expression and inflammatory response in rat spinal microglia. An RCT (20) shows that acupuncture can effectively reduce lipid concentration and improve inflammatory cytokines. Hualu Chen et al. (19) show that acupuncture can effectively reduce whole blood viscosity, plasma-specific viscosity, and fibrinogen levels while also improving blood condition, thereby accelerating blood microcirculation, improving local nutritional status, and alleviating patients' clinical symptoms. This suggests that acupuncture may improve the symptoms of elderly patients with DPN by improving blood rheology, inhibiting inflammatory factors, and increasing nerve conduction speed, which will provide some inspiration for future exploration of the DPN mechanism. To some extent, this study showed that acupuncture could improve the symptoms of patients by reducing blood glucose and increasing NCV, but the discussion of blood rheology, lipid concentration, and inflammatory factors was not involved. Some studies have shown that the decline in inflammatory factors and lipid markers can delay the progression of DPN disease, providing new treatment ideas for DPN patients.

The meta-analysis showed that except for the homogeneity of the total effective rate, the heterogeneity of the other indicators was high, which may be due to the following reasons: ① none of the included studies mentioned DPN caused by type I or type II DM, and their specific pathogenesis may be different; ② the disease duration of the patients with DPN included in the study was different, and some of the studies did not describe it in detail, which resulted in the difference in therapeutic efficacy; ③the regular treatment of Western medicines used was not the same, and the dosage also varied, which may cause different therapeutic effects; and ④ the acupoints, manipulation, and period of treatment used in the nine studies are not the same, thus affecting the therapeutic effects.

There are several potential limitations to the current study. First, only nine randomized controlled trials were included in this study, which is a small sample size. The low quality of the literature included in this paper and the small sample size reduce the credibility of the evidence, second, although a comprehensive search was conducted, publication and language bias may be present. Third, the effects of acupuncture on DPN at different acupoints and stimulation volume pairs have not been demonstrated, and nine of the nine randomized controlled trials followed up, so the long-term efficacy of acupuncture for DPN is unclear. Fourth, none of the included literature mentioned blinding, resulting in a low overall quality of the literature. In addition, some of the included studies did not indicate the duration and staging of the patients, thus affecting the accuracy of the baseline. Because there is no standardized protocol for the treatment of DPN, there are no specific standards for the acupoints selection, manipulation, and duration of treatment used in clinical practice, and the methods of measurement are inconsistent. Future studies should aim to address these limitations, increase the number of sample sizes, improve the quality of clinical evidence, and explore the optimal dose and duration of acupuncture for DPN.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1339747/full#supplementary-material

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Bergenin mitigates neuroinflammatory damage induced by high glucose: insights from Zebrafish, murine microbial cell line, and rat models

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Background: The escalating global burden of diabetes and its associated cognitive impairment underscores the urgency for effective interventions. Bergenin shows promise in regulating glucose metabolism, mitigating inflammation, and improving cognitive function. Zebrafish models offer a unique platform for assessing drug efficacy and exploring pharmacological mechanisms, complemented by subsequent investigations in cell and rat models.

Methods: The experimental subjects included zebrafish larvae (CZ98:*Tg (mpeg1: EGFP)*$^{ihb20Tg/+}$), adult zebrafish (immersed in 2% glucose), BV2 cell line (50 mM glucose + 10 μm Aβ$_{1-42}$), and a streptozotocin (STZ) bilateral intracerebroventricular injection rat model. Bergenin's effects on the toxicity, behavior, and cognitive function of zebrafish larvae and adults were evaluated. The Morris water maze assessed cognitive function in rats. Neuronal histopathological changes were evaluated using HE and Nissl staining. qPCR and Western blot detected the expression of glycolysis enzymes, inflammatory factors, and Bergenin's regulation of PPAR/NF-κB pathway in these three models.

Results: 1) In zebrafish larvae, Bergenin interventions significantly reduced glucose levels and increased survival rates while decreasing teratogenicity rates. Microglial cell fluorescence in the brain notably decreased, and altered swimming behavior tended to normalize. 2) In adult zebrafish, Bergenin administration reduced BMI and blood glucose levels, altered swimming behavior to slower speeds and more regular trajectories, enhanced recognition ability, decreased brain glucose and lactate levels, weakened glycolytic enzyme activities, improved pathological changes in the

telencephalon and gills, reduced expression of pro-inflammatory cytokines, decreased *ins* expression and increased expression of *irs1*, *irs2a*, and *irs2b*, suggesting a reduction in insulin resistance. It also altered the expression of *pparg* and *rela*. 3) In BV2 cell line, Bergenin significantly reduced the protein expression of glycolytic enzymes (GLUT1, HK2, PKFKB3, and PKM2), lowered IL-1β, IL-6, and TNF-α mRNA expression, elevated PPAR-γ protein expression, and decreased P-NF-κB-p65 protein expression. 4) In the rat model, Bergenin improves learning and memory abilities in STZ-induced rats, mitigates neuronal damage in the hippocampal region, and reduces the expression of inflammatory factors IL-1β, IL-6, and TNF-α. Bergenin decreases brain glucose and lactate levels, as well as glycolytic enzyme activity. Furthermore, Bergenin increases PPARγ expression and decreases p-NF-κB p65/NF-κB p65 expression in the hippocampus.

Conclusion: Bergenin intervenes through the PPAR-γ/NF-κB pathway, redirecting glucose metabolism, alleviating inflammation, and preventing high glucose-induced neuronal damage.

1 Introduction

According to a report from the International Diabetes Federation (IDF), in 2019, the global count of adult diabetes patients reached 463 million. Projections suggest this number will rise to 578 million by 2030 and surge to 700 million by 2045 (Sun et al., 2022). Diabetes-Associated Cognitive Impairment (DACI) emerges as a chronic complication of type 2 diabetes (T2DM), manifesting in diminished memory, comprehension, and spatial orientation abilities, significantly impacting patients' self-care and quality of life. DACI has now surpassed cardiovascular complications, becoming the second leading cause of death among diabetic patients (Bellia et al., 2022; Li et al., 2023). Meanwhile, epidemiological studies indicate that T2DM can elevate the risk of Alzheimer's disease (AD) by 1.5–2.5 times (Xue et al., 2019). The primary pathogenic mechanism of DACI involves disrupted cerebral glucose metabolism, leading to overactivation of microglial cells, resulting in neuroinflammation and subsequent cognitive impairment (Dove et al., 2021; Leng and Edison, 2021). Despite this understanding, the precise mechanism linking cognitive decline and T2DM remains incompletely elucidated, with no available drugs to effectively halt disease progression. Given the crucial role of neuroinflammation induced by activated microglial cells in DACI pathogenesis, regulating glucose metabolism to prevent excessive microglial cell activation represents a novel approach for early DACI intervention.

Compared to synthetic drugs, natural products have increasingly attracted attention as therapeutic agents due to their lower cytotoxicity and reduced side effects (Zhu et al., 2022), some natural products have demonstrated significant efficacy in improving diabetes and its complications, as well as in reducing inflammatory responses (Sharma et al., 2020). *Bergenia purpurascens* (Hook. f. et Thoms.) Engl., a plant belonging to Saxifragaceae, Bergenia Moench, is used in traditional Chinese medicine. Its primary active component, bergenin, a C-glycoside of 4-O-methylgallic acid, exhibits diverse pharmacological effects, including the regulation of glucose and lipid metabolism, anti-inflammatory properties, and mitigation of oxidative stress (Barai et al.,

2019; Villarreal et al., 2020; Zhang et al., 2023). Numerous studies have demonstrated bergenin's role in regulating glucose metabolism and improving diabetes and its complications (Barai et al., 2019; Qiao et al., 2019; Villarreal et al., 2020; Yin et al., 2023; Zhang et al., 2023). Recent research has identified bergenin as a promising therapeutic agent for inhibiting glycolysis by downregulating Hexokinase 2 (HK2), the first glycolytic rate-limiting enzyme (Li et al., 2023). Furthermore, bergenin modulates the production of pro- and anti-inflammatory cytokines, reducing the expression of IL-1β, IL-6, and TNF-α proinflammatory cytokines, thereby ameliorating inflammatory responses (Yin et al., 2023). Additionally, bergenin exerts neuroprotective effects, improving cognitive dysfunction (Ji et al., 2019; Singla et al., 2022).

Zebrafish offer distinct advantages in studying mechanisms of glucose metabolism, sharing biological mechanisms with humans in regulating glucose homeostasis (Zang et al., 2017). Key metabolic organs and genes are conserved in zebrafish (Cox et al., 2018), which exhibit hyperglycemic symptoms and impaired glucose metabolism when fed a glucose-rich diet (Kleinert et al., 2018). The zebrafish model of type II diabetes mellitus responds positively to antidiabetic drugs like metformin and glimepiride, making them valuable models for investigating human diabetes and metabolic disorders (Mohammadi et al., 2020). Furthermore, the skin or gills of zebrafish provide a gateway for non-invasive administration of biologically active compounds, allowing precise delivery into the water surrounding hundreds of zebrafish embryos, larvae, or adults (Angom and Nakka, 2024). This feature makes zebrafish an independent system for screening antidiabetic drugs, validating their effects on type 2 diabetes mellitus (T2DM) complications, and studying pharmacokinetics (Wang et al., 2023).

The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor superfamily. PPARγ, a ligand-dependent nuclear transcription factor, translocates into the nucleus and binds to PPAR response elements (PPREs) upon ligand binding, thereby regulating the transcription and translation of downstream target genes involved in lipid and glucose metabolism as well as inflammation (Chen et al., 2023). This renders PPARγ an attractive pharmacological target for treating metabolic diseases such as

insulin resistance, type 2 diabetes (Shehnaz et al., 2023), chronic inflammation, and degenerative disorders (Geng et al., 2018). NF-κB serves as a pivotal transcription factor in inflammation regulation. The nuclear translocation of NF-κB heterodimers plays a crucial role in microglial cell activation, induced by pro-inflammatory stimuli such as IL-1β, IL-6, and TNF-α (Poma, 2020; Peng et al., 2022). It is noteworthy that multiple experiments have demonstrated Bergenin's role as a natural PPARγ agonist. The activation of PPARγ inhibits IκBα degradation, p65 nuclear translocation, DNA-binding activity, and phosphorylation, or indirectly inhibits NF-κB activation by competitively binding to p65, thereby reducing the production of pro-inflammatory cytokines and chemokines (Wang et al., 2017; Yang et al., 2022).

Given the pivotal roles of glucose metabolism disorder and neuroinflammation in diabetic neuropathy, this study aims to confirm bergenin's potential protective effects against high glucose-induced glycolysis enhancement and neuroinflammatory responses, while preliminarily exploring its pharmacological mechanisms. This study employs the zebrafish model for rapid assessment of drug safety and validation of pathological mechanism hypotheses. Subsequently, a comprehensive investigation into the molecular mechanisms was conducted using rat and cell models (Supplementary Figures S1, 2).

2 Materials and methods

2.1 Experimental animals and cells

Wild-type zebrafish (AB line, *Danio rerio*) and transgenic zebrafish (CZ98:*Tg (mpeg1:EGFP)$^{ihb20Tg/+}$*) were obtained from the China Zebrafish Resource Center and bred at the Zebrafish Breeding Platform of the Hunan Key Laboratory for Integrative Prevention and Treatment of Cardio-Cerebral Diseases, Hunan University of Chinese Medicine. Zebrafish were maintained in tanks with a water temperature of 28°C ± 0.5°C, pH 7.0–7.3, dissolved oxygen 7.3 ± 0.2 mg/L, conductivity 460 ± 50 μS/cm, water hardness 128 ± 25 mg/L, and salinity of 0.3 ng/L (Shang et al., 2024), under a light-dark cycle of 14 h: 10 h with eight fish reared in each 1-L tank. They were fed twice daily at 08:30 and 17:30 with newly hatched *Artemia salina*. Embryos were obtained through natural breeding. Fertilized eggs were collected and incubated at 28°C in an incubator. All research protocols were approved by the Experimental Animal Ethics Committee of Hunan University of Chinese Medicine (Changsha, China), Approval number: LLBH-202205030001.

The BV2 cell line was purchased from Wuhan PuNuoSai Biotechnology Co., Ltd. and cultured in RPMI 1640 medium containing 10% fetal bovine serum and 1% penicillin-streptomycin at 37°C under 5% CO_2 (He et al., 2024).

SPF-grade male SD rats (n = 50), weighing (150 ± 20) g, were purchased from Hunan Slaike Jingda Experimental Animals Co., Ltd. (License No.: SCXK(Hunan)2021–0004). The rats were housed in the SPF-grade animal barrier system at the Animal Experimental Center of Hunan University of Chinese Medicine, with three rats per cage. They were fed standard animal feed and water, maintained at a constant temperature of (25 ± 2)°C, and subjected to a 12-h light-dark cycle. The experimental procedures complied with ethical standards for animal research (LLBH202205100001).

2.2 Drugs and reagents

Bergenin (MedChemExpress, HY-N0017); Metformin Hydrochloride, Hexokinase (HK), Phosphofructokinase (PFK), Pyruvate Kinase (PK) Activity Assay Kit (Beijing Solarbio Science & Technology Co., Ltd., SM9400, BC0745, BC0535, BC0545); Glucose, Lactic Acid assay kit (Nanjing Jiancheng Biotech Co., Ltd., A154-1-1, A019-2-1); β-amyloid peptides (Shanghai Aladdin Bio-Chem Technology Co., Ltd., B111464); 2-DG, DADA, DMSO (Sigma-Aldrich, D8375-1G, D135665, D2650-100 ML); Fetal bovine serum, RPMI 1640 medium (Gibc, 10099-141, 11875093); D-glucose solution, Penicillin-Streptomycin Solution (Wuhan Pricella Biotechnology Co.,Ltd., PB180418, PB180120); Serum-free freezing medium, β-actin, IL-1β, IL-6, TNF-α primers (Shanghai BioWork Biotech Co., Ltd., 05-065-1B); TRIzol Reagent (Thermo Fisher Scientific, 15596018); Isopropyl alcohol (Macklin, I811925); Reverse transcription kit (Suzhou Jinkang Protein Technology Co., Ltd., 0521751); SYBR Green Premix (Shanghai MoNa Biotechnology Co., Ltd., MQ00401); DEPC-treated Water (Beyotime, R0022); PPAR gamma Antibody, NF-κB p65 Polyclonal Antibody (Bioss, BS-0530R, RRID:AB_10860216, BS-0465R, RRID:AB_10855447); Anti-RELA (Phospho-Ser276) rabbit polyclonal antibody (Sangon Biotech, D155005); β-actin (Affinity Biosciences, AF7018, RRID:AB_2839420); Goat anti-rabbit secondary antibody (Sigma-Aldrich, AP132P); RIPA Lysis Buffer (Cwbio, CW233S); BCA Protein Quantification Kit (Multi Sciences, PQ0012); Streptozotocin (STZ, Sigma-Aldrich, S0130).

2.3 Experimental instruments

ZebHigh-throughput Observation Chamber for Zebrafish Embryo Larvae, Automated Zebrafish Analysis System for Adult Fish Observation Tower (Viewpoint, France); Conventional Brightfield Microscope (Leica, S9i); BioTek Cytation™ 5 Cell Imaging Multi-Mode Reader (Agilent Technologies Co., Ltd., China); DW-2000D Brain Locating Instrument (Chengdu Techman Software Co., Ltd.); Smart 3.0-Video Tracking System (Panlab, RRID:SCR_002852); Tri-Gas Incubator (Thermo Fisher Scientific, United States); Inverted Fluorescence Microscope (Zeiss, Germany); SorvallTM LegendTM Micro 17R Microcentrifuge (Thermo Fisher, United States); Cytation3 Multimode Reader (Bio-Tek, United States); T100TM Thermal Cycle, CFX96 Touch Real-Time PCR Detection System (Bio-Rad, United States); Mini-PROTEAN Tetra Electrophoresis System, Mini Trans-Blot Transfer System (Bio-Rad, United States); ChemiDoc XRS + Chemiluminescence Gel Imaging System (Bio-Rad, United States of America); HM 325 Paraffin microtome (Thermo Fisher, United States); Tissue-FAXS Plus Panoramic Tissue Scanning Imaging System (Tissue Gnostics GmbH, Austria).

2.4 Zebrafish experiment

2.4.1 Embryo-Larvae rearing and experimental grouping

The macrophage-specific GFP transgenic zebrafish (CZ98: *Tg(mpeg1:EGFP)$^{ihb20Tg/+}$*) were selected for the experiment. Healthy zebrafish embryos at 9 h post-fertilization (hpf) were

randomly allocated to 6-well plates, with 30 embryos per well. Based on preliminary findings on glucose, bergenin, and metformin concentrations, the embryos were divided into four groups: Control (0.1% DMSO), Model (1% glucose + 0.1% DMSO), Bergenin (1% glucose + 2.5 mg/L bergenin), and Metformin (1% glucose + 3 mg/L metformin). Bergenin and metformin were dissolved in 0.1% DMSO for administration. Each group had three replicate wells. The plates were incubated in a constant temperature light incubator at 28°C ± 0.5°C, under a light-dark cycle of 14 h:10 h, with the solution changed every 24 h.

2.4.2 Hatchability, survival rate, and teratogenicity analysis

The hatching rate was calculated on day 5 post-fertilization (dpf). Zebrafish embryos were examined for abnormalities such as organ edema and spinal curvature. Survival rate was determined on day 8 post-fertilization after larval rearing. (Li et al., 2022).Tissues were phosphate-buffered saline (PBS)-washed, homogenized at 0.1 g per sample with 1 mL extraction buffer on ice, then centrifuged at 8000 g for 10 min at 4°C. The resulting supernatant was collected and stored on ice for subsequent analysis. Glucose content in the supernatant was assessed following assay kit instructions. Prompt removal of detached embryo membranes and dead larvae was ensured.

2.4.3 Zebrafish Larval brain fluorescence signal recording

Microglial cell activation in the brain was assessed by directly detecting fluorescence in the macrophage-specific GFP transgenic zebrafish (96hpf) using a fluorescence microscope (Bruzzone et al., 2021). The intensity and aggregation of green fluorescent signals within the brain can directly reflect the degree of microglial cell activation, thereby indirectly indicating the extent of inflammation response in the brain.

2.4.4 Zebrafish Larval behavioral experiment

The locomotion patterns of zebrafish larvae were observed on the 5 th day post modeling administration. Zebrafish were grouped and placed in a 12-well plate containing 1 mL of embryo medium before being transferred to the Zebrafish High-throughput Observation Chamber. Videos and images capturing locomotion trajectories were recorded to quantify the distance (mm) and speed of movement for each fish. Movement was categorized into high-speed (>10 mm/s), medium-speed (2–10 mm/s), and low-speed (<2 mm/s) to determine their states. Zebrafish locomotion distance and trajectories were recorded and analyzed for 60 s in this experiment (Benvenutti et al., 2021).

2.4.5 The grouping and treatment of adult zebrafish experiments

A total of 240 adult zebrafish (6–8 months old) were randomly assigned to control, model, and three bergenin dose groups (1.25 mg/L, 2.5 mg/L, and 5 mg/L), as well as a metformin group (3 mg/L), with each group containing 40 fish. The control group remained in standard water conditions, while the model, bergenin, and metformin groups were immersed in a 2% glucose solution (10 fish per 1500 mL) for 28 days. (Chen and Liu, 2022). Fish were fed three times the standard amount of Artemia daily to induce

hyperglycemia. Starting from day 21, the low, medium, and high-dose bergenin groups, along with the metformin group, received continuous administration for 7 days. Measurements of body length, weight, body mass index (BMI), and blood glucose levels were obtained via tail clipping. Half of the solution volume in each tank was replaced daily.

2.4.6 Zebrafish vitality and T-maze behavioral testing experiment

Following drug administration, behavioral and T-maze experiments were conducted on zebrafish to observe changes and assess the efficacy of the model and medication. Zebrafish behavioral tests were conducted in a square tank, with each fish observed for 180 s per trial over three consecutive days. This method serves to assess zebrafish vitality and anxiety levels (Wang et al., 2023). Furthermore, the T-maze was used to evaluate zebrafish learning and memory. The T-maze consisted of horizontally equal-length left and right arms and a vertical channel. Specifically, the left arm was designated as the Enriched Chamber (EC) area, where specific enrichment was provided. The starting point was located at one end of the vertical channel, which corresponds to the end of the non-equal length left and right arms. The testing period spanned 5 days.

Formal testing began promptly at 09:00 each morning. Prior to the start, a single zebrafish designated for testing was placed in the starting zone. It was allowed 1 min to acclimate to the T-maze environment, including water quality and temperature, with the starting zone closed during this period. Following adaptation, the barrier in the starting zone was opened. The zebrafish was then allowed to freely explore the T-maze, aiming to find and remain in the Enriched Chamber (EC) area for 30 s. Zebrafish successfully entering the EC area were rewarded with food after the 6-min test. If a zebrafish failed to find the EC area within the allotted time, a correction procedure was initiated after 6 min. In this procedure, the barrier on the non-EC side of the T-maze was closed, and the experiment was repeated, guiding the zebrafish from the starting zone to the EC area and encouraging it to stay for 3 min, followed by a food reward.

During formal testing, zebrafish initiated from the starting zone and staying in the Enriched Chamber (EC) area for 30 s were considered as having entered the EC area. The testing duration was set at 6 min. Zebrafish swimming trajectories were recorded and represented by different colored lines based on their speed: white lines indicated slow movement (<2 cm/s), green lines indicated moderate movement (2–5 cm/s), and red lines indicated high-speed movement (>5 cm/s). Swimming trajectories were documented, and parameters such as total swimming distance, average swimming speed, latency to enter the EC area, and cumulative time spent in the EC area were quantified. A longer swimming distance and faster swimming speed within the designated time frame indicated higher vitality. A shorter latency to enter the EC area and longer cumulative time spent in the EC area indicated stronger recognition of the EC area, implying enhanced learning and memory capabilities (Benvenutti et al., 2021).

2.4.7 Sample collection of adult zebrafish experiments

After completing the T-maze behavioral test, brain tissue samples were collected. Thirty zebrafish were randomly selected

from each group and anesthetized in ice water. Their brains were dissected and placed in cryovials on ice. Liver and muscle samples were also obtained, rapidly frozen in liquid nitrogen, and stored at −80°C. Additionally, 10 zebrafish from each group were anesthetized in ice water, and their heads were swiftly removed on ice. The excised heads were then placed in 1.5 mL tubes and immersed in Bouin's solution for 24 h for fixation. Subsequently, brain tissue was dissected to prepare for subsequent H&E staining experiments, and gill samples were also collected (Luo et al., 2024).

2.4.8 Detection of glucose consumption, lactate production and the activities of Hexokinase (HK), Phosphofructokinase (PFK), pyruvate Kinase (PK)

15 zebrafish brain tissues were randomly selected from each group, divided into three portions of 0.1 g tissue each. Each portion was homogenized in 1 mL of extraction buffer on ice. The homogenate was then centrifuged at 8000 g for 10 min at 4°C. The supernatant was collected and used for analysis. Glucose content, lactate production, and the activity levels of hexokinase (HK), phosphofructokinase (PFK), and pyruvate kinase (PK) were determined using commercially available assay kits following the manufacturer's instructions (Li et al., 2022).

2.4.9 Tissue pathological analysis

After fixation in Bouin's solution for 24 h, brain and gills tissues were sliced in the sagittal plane using a paraffin microtome. Following deparaffinization, 1% methylene blue was applied for 25 min at 37°C, followed by 95% ethanol differentiation for 30 s. The tissues were then subjected to gradient dehydration, xylene transparency, covered with coverslips, and sealed with neutral resin. Hematoxylin and eosin (HE) staining was utilized to observe morphological pathological changes in the zebrafish brain and gills tissues (Luo et al., 2024).

2.5 Cell experiments

When BV2 cells reached the logarithmic growth phase, they were harvested and plated at a density of 3×10^5 cells per well in 6-well plates (He et al., 2024). The experimental groups comprised control, model, bergenin, glycolysis inhibitor 2-deoxy-D-glucose (2-DG), and pyruvate dehydrogenase activator diisopropylamine dichloroacetate (DADA), each with 3 replicate wells. The control group received RPMI 1640 medium, while the model, bergenin, 2-DG, and DADA groups were treated with 50 mM glucose and 10 μM Aβ1-42 oligomers for 24 h to establish a BV2 model of glucose metabolism disorder and inflammation activation. After establishing the High-glucose-induced BV2 model, the bergenin group received continuous administration of 40 μg/mL bergenin, the 2-DG group received 0.2 mM 2-DG, and the DADA group received 1 mM DADA for an additional 24 h. Bergenin was dissolved in DMSO, while 2-DG and DADA were dissolved in sterile water.

2.6 Rat experiment

2.6.1 Animal modeling and grouping

After 1 week of acclimation feeding, fifty rats were randomly assigned to five groups: Control (sham surgery), Model, Low-dose

(20 mg/kg/d) Bergenin, High-dose (80 mg/kg/d) Bergenin, and Metformin (150 mg/kg/d), each comprising 10 rats. Prior to modeling, rats underwent a 12-h fast, followed by anesthesia with 3% pentobarbital sodium. Using the sixth edition of the "Rat Brain Stereotaxic Atlas" as a guide, their heads were secured in a brain fixation device, with needle insertion coordinates determined relative to the anterior fontanelle: 0.8 mm posteriorly, 1.5 mm laterally to the left and right of the skull midline, and a depth of 3.7 mm from the skull surface (He et al., 2023). In groups other than the sham surgery group, rats received controlled injections of 5 μL STZ (2.4 mg/kg) into each side of the lateral ventricle at a rate of 1 μL/min (Jin et al., 2023). The sham surgery group received 5 μL of normal saline. After injection, the needle remained in place for 5 min before wound closure, and the animals were returned to their cages for observation, awaiting natural awakening. After 2 days post-modeling, intragastric administration was carried out twice daily at 9:00 a.m. and 6:00 p.m. for 14 consecutive days (Sharma et al., 2020). Both the control and model groups received equivalent volumes of normal saline.

2.6.2 Morris water maze

After 14 days of drug intervention, the Morris water maze was conducted. A constant-temperature swimming pool (1.6 m in diameter) was used, and rats were placed into the maze 1 day prior for a 120-s free swim for acclimatization. The maze was divided into four quadrants, and a 12 cm-diameter platform was placed at the center of the first quadrant (platform quadrant) with water added to a depth of 1 cm. Smart 3.0 software recorded the rats' movement trajectories and time-distance data. Over the first 5 days, rats were placed facing the wall of each of the four quadrants at a fixed time each day, and the software set a 1 min search time for the platform (escape latency). If the rat remained on the platform for more than 2 s within 1 min, the test was terminated, and the time recorded. If not, the escape latency was recorded as 60 s, and the rat was guided to the platform for a 20-s stay for learning and memory. On the 6th day, the platform was removed, and rats were placed into the water from the opposite quadrant of the platform quadrant. The number of times the rats crossed the original platform area within 60 s and the time spent in the platform quadrant were recorded (He et al., 2023).

2.6.3 Sample collection and preservation

The rats were anesthetized with intraperitoneal injections of 3% pentobarbital sodium based on their body weight. Subsequently, their limbs were secured, and a U-shaped incision was made in the abdominal cavity. The right atrium was opened, and 50 mL of pre-cooled physiological saline was injected into the left ventricle until the visceral organs became pale, indicating successful cardiac perfusion (Jin et al., 2023). The head was then severed, and the left brain was fixed in 4% paraformaldehyde. The right brain was divided into the cortex and hippocampus, snap-frozen in liquid nitrogen, and then stored in a −80°C freezer.

2.6.4 Hematoxylin and eosin (HE) staining and Nissl staining

After fixing the left hemisphere, alcohol gradient dehydration, xylene clearing, paraffin embedding, and sectioning using a microtome at a thickness of 3 μm in the coronal plane were

TABLE 1 Primer sequences of PCR.

Gene (zebrafish)	Forward primer (5′-3′)	Reverse primer (5′-3′)
il1b	GCTGCTGTTCTTCAGGAAGGAGAC	TCCACCATCTGCGAATCTTCATACG
il6	GTCTGCTACACTGGCTACACTCTTC	CGTCCACATCCTGAACTTCGTCTC
tnfa	CCATAAGACCCAGGGCAATC	GATTCAGAGTTGTATCCACCTG
ins	GGTCGTGTCCAGTGTAAGCA	CAGGTGTTTCTGGCATTGGC
irs1	GGTGTCTTTTCAACACCGCC	TCAAAACAAGCGCAGTCAGC
irs2a	AAGAGTGCTTCAGTCAGCCC	CCTGCTCAATCTTGTACAGTGG
irs2b	TATGAGAATGGCGAGTCCGC	GAAAAAGCGCTTGTGTCCGT
pparg	CTCTCCGCTGATATGGTGGAC	GGCAGATCTGGACTGGTAGC
rela	CCTGGACTCGTGGGAGAGTA	GGTCTGATCCGTGACAATGTG
actb1	ACCACGGCCGAAAGAGAAAT	ATGTCCACGTCGCACTTCAT
Gene (Cell)	Forward primer(5′-3′)	Reverse primer(5′-3′)
IL-1β	TCGCAGCAGCACATCAACAAGAG	TGCTCATGTCCTCATCCTGGAAGG
IL-6	CTCCCAACAGACCTGTCTATAC	CCATTGCACAACTCTTTTCTCA
TNF-α	GTCTCAGCCTCTTCTCATTCC	CTACAGGCTTGTCACTCGAA
β-actin	AAGTGTGACGTTGACATCCG	TCTGCATCCTGTCAGCAATG
Gene (Rat)	Forward primer(5′-3′)	Reverse primer(5′-3′)
IL-1β	GTGTAAAACGCAGCTCAGTAACA	TCAGCAAGCAGGAGTACGATG
IL-6	CAGAATTGCCATTGCACAATAGCA	GACAGCCACTGCCTTCCCTACTT
TNF-α	CCGCTTGGTGGTTTGCTACGAC	GGTCCCAACAAGGAGGAGAAGTTC
β-actin	GTGTAAAACGCAGCTCAGTAACA	TCAGCAAGCAGGCGTACGATG

performed. Following deparaffinization in xylene and rehydration through a graded series of alcohols, one portion of the sections underwent 5 min staining with hematoxylin, followed by rinsing in running water and differentiation in 0.5% hydrochloric acid ethanol for 1 min, with termination of differentiation by rinsing in running water, immersion in PBS for counterstaining, and final staining with eosin for 1 min. The other portion of the sections underwent 25-min staining with 1% cresyl violet at 37℃, followed by differentiation in 95% ethanol for 30 s and termination of differentiation by rinsing in running water (He et al., 2023). Dehydration was then performed in a gradient of 70%–90% ethanol for 10 min each, followed by absolute ethanol dehydration, xylene clearing, application of neutral resin, covering with coverslips, and air-drying at room temperature. The dorsal hippocampal area was observed under an optical microscope, and photomicrographs were taken for histological analysis.

2.6.5 Detection of glucose consumption, lactate production and the activities of Hexokinase (HK), Phosphofructokinase (PFK), pyruvate Kinase (PK)

Brain tissue samples from nine rats were randomly selected from each group, divided into three portions of 0.1 g tissue each. Each portion was homogenized in 1 mL of extraction buffer on ice. The homogenate was then centrifuged at 8000 g for 10 min at 4℃. The supernatant was collected and used for analysis. Glucose content, lactate production, and the activity levels of hexokinase (HK), phosphofructokinase (PFK), and pyruvate kinase (PK) were

determined using commercially available assay kits following the manufacturer's instructions (Pancera et al., 2006).

2.7 Quantitative real-time PCR (RT-qPCR)

Total RNA was extracted using the TRIzol method, followed by reverse transcription into cDNA. SYBR Green dye method was utilized with the Bio-Rad CFX96 real-time PCR system for amplification. The PCR program entailed an initial denaturation at 95℃ for 10 min, followed by 40 cycles of denaturation at 95℃ for 5 s and annealing/extension at 58℃ for 30 s (Jin et al., 2023). Melting curve analysis was performed from 65℃ to 95℃ with 0.5℃ increments to detect fluorescence signals. β-actin served as an internal reference, and relative expression levels of target genes were analyzed using the $2^{-\Delta\Delta Ct}$ method. Primer sequences are provided in Table 1.

2.8 Western blot

Total cellular proteins were extracted and quantified using the BCA assay. Protein concentrations were adjusted to 2 μg/μL for sample buffer preparation. Electrophoresis was conducted at 80 V for 30 min, followed by an adjustment to 100 V for 90 min. Wet transfer to a membrane was performed at 200 mA for 90 min. The
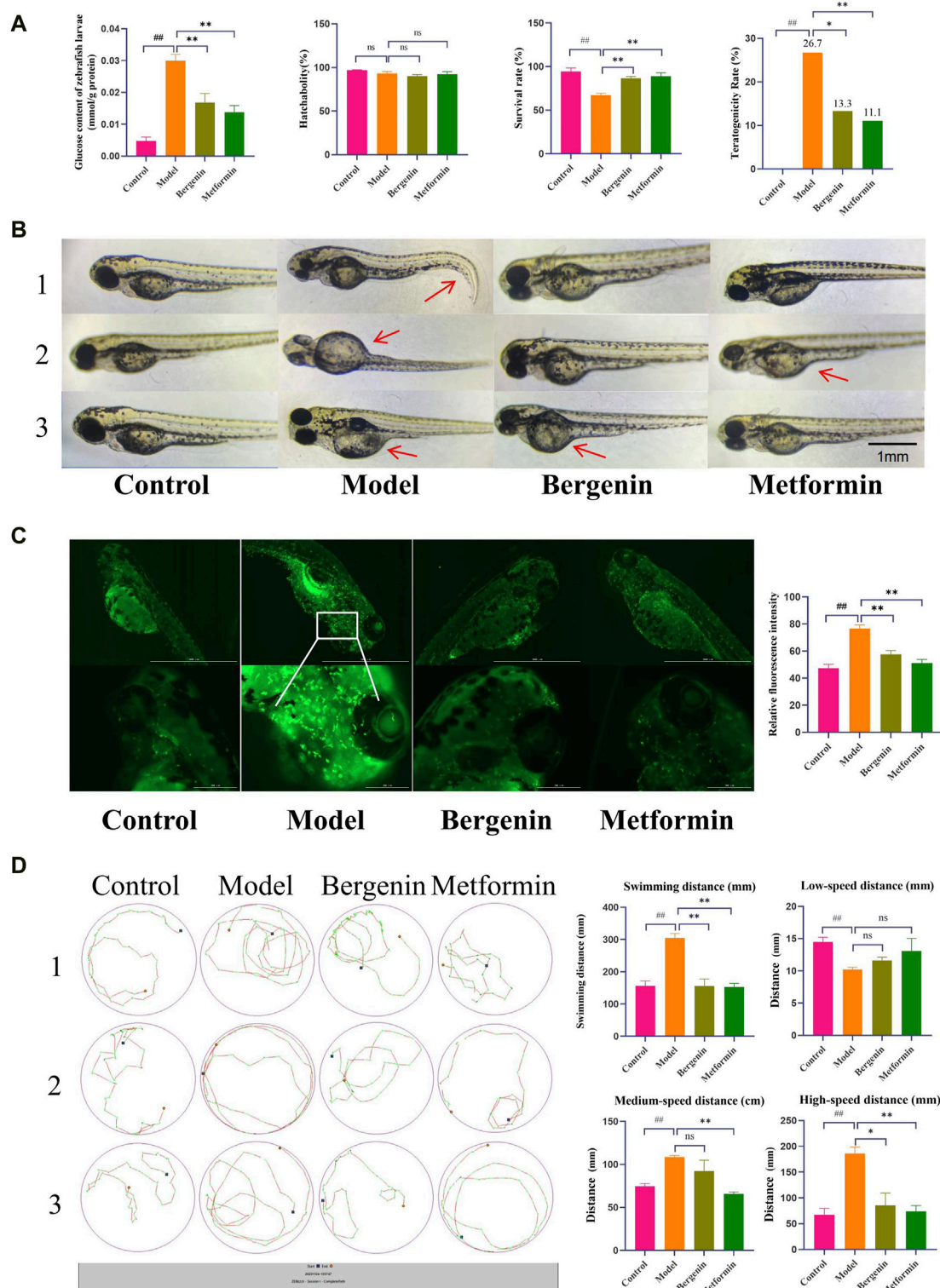
FIGURE 1
Effects of Bergenin on High-Glucose-Induced Zebrafish Larvae. **(A)** Glucose Content in Zebrafish Larvae; Hatchability, Survival Rate, Teratogenicity Rate of Zebrafish Larvae; **(B)** Teratogenicity in zebrafish larvae; The arrow points to teratogenic effects, such as organ edema or tail malformation; **(C)** Fluorescence Expression in the Brains of Zebrafish Larvae and Relative Fluorescence Intensity; **(D)** Behavioral Trajectory Plot of Zebrafish Larvae and Statistical Analysis of Zebrafish Larval Behavior Data: Total Swimming Distance; Low-Speed Distance (<2 mm/s); Medium-Speed Distance (2–10 mm/s); High-Speed Distance (>10 mm/s). "ns" indicates no statistical significance; $^{##}P < 0.01$ indicates significance compared to the control group; $*P < 0.05$, $**P < 0.01$ indicates significance compared to the model group. (One-way ANOVA and Pearson Chi-square test, Mean $\pm$ SD, N = 30).

membrane was then incubated with 5% non-fat milk (prepared in TBST) at room temperature for 1 h. Primary antibodies against GLUT1 (1:1000), HK2 (1:1000), PFKFB3 (1:2000), PKM2 (1:2000), PPARγ (1:1000), NF-κB (1:1000), P-NF-κB (1:1000) and β-actin (1: 10000) were applied overnight at 4°C, followed by three washes with TBST for 10 min each. Subsequently, the membrane was incubated with goat anti-rabbit secondary antibody (1:8000) at 37°C for 1 h with shaking, followed by three washes with TBST for 10 min each (He et al., 2023). Chemiluminescence imaging was performed using a gel imaging system, and grayscale analysis was conducted using ImageJ software.

2.9 Statistical analysis

The statistical analysis was performed using GraphPad Prism 8.0. The differences between groups were analyzed using One-way analysis of variance (One Way ANOVA) and Pearson Chi-square test. All data are expressed as the mean ± SD. A probability value of $P < 0.05$ was considered to indicate a statistically significant difference.

3 Results

3.1 The effect of bergenin on high-glucose-induced Zebrafish

3.1.1 The effect of bergenin on High-Glucose-Induced Zebrafish Larvae

Using a glucose assay kit, the glucose content in each group of zebrafish was measured to investigate the effect of bergenin on glucose levels in zebrafish larvae induced by high glucose. As shown in Figure 1A, the glucose content in zebrafish larvae in the model group was significantly elevated compared to the control group ($P < 0.01$), with a mean of 0.029 mmol/g protein, which was 6–7 times higher than that of the control group (0.004 mmol/g protein). After administration of bergenin ($P < 0.01$) and metformin ($P < 0.01$), the blood glucose levels significantly decreased. This indicates that the high-glucose-induced zebrafish larval model was established, and bergenin has potential hypoglycemic effects. Next, we evaluated the impact of bergenin on the development of zebrafish larvae induced by high glucose. As shown in Figure 1A, the hatching rates of zebrafish larvae in each group were minimally affected. In Figure 1A, exposure to high glucose resulted in a significant decrease in the survival rate of zebrafish larvae ($P < 0.01$). Conversely, the bergenin ($P < 0.01$) and metformin ($P < 0.01$) treatment groups exhibited significantly increased survival rates. Additionally, the model group displayed developmental teratogenicity such as organ edema and spinal curvature, with a teratogenicity rate of 26.7%. However, the teratogenicity rates decreased to 13.3% and 11.1% in the bergenin and metformin groups, respectively (Figures 1A,B) (Table 2).

Bergenin significantly affects the activation of zebrafish larval microglial cells induced by high glucose. The transgenic zebrafish line CZ98:Tg(mpeg1:EGFP)$^{ihb20Tg/+}$ expresses green fluorescent protein driven by the mpeg1 promoter, specifically labeling macrophages. Activated macrophages exhibit strong green fluorescence. As shown in Figure 1C, high glucose induces

increased systemic macrophage activation in zebrafish, with significantly elevated microglial activation in the brain, as indicated by the relative fluorescence intensity ($P < 0.01$). Subsequent treatment with bergenin ($P < 0.01$) and metformin ($P < 0.01$) results in a marked decrease in microglial fluorescence expression in the brain.

Additionally, we also observed the effects of bergenin on the behavior of zebrafish larvae induced by high glucose. Elevated blood glucose levels may lead to increased intracellular oxygen pressure through pathways such as mitochondrial dysfunction, reactive oxygen species production, and blood flow alterations (Kashihara et al., 2022). As illustrated in Figure 1D, zebrafish larvae in the model group exhibited significantly enhanced locomotor activity, with total distance traveled and swimming speed notably higher compared to other groups ($P < 0.01$). High-speed swimming (>10 mm/s) was increased ($P < 0.01$), accompanied by abnormal behaviors such as circling near the edge of the well, known as wall-hugging behavior. Following administration of bergenin ($P < 0.01$) and metformin ($P < 0.01$), swimming speed slowed down, primarily manifesting as medium to low-speed movements (2–10 mm/s, <2 mm/s), and swimming trajectories tended towards normalcy.

3.1.2 The Effects of Bergenin on High glucose-induced Zebrafish Adults

We first evaluated the effect of bergenin on zebrafish BMI and blood glucose induced by high glucose. As shown in Figures 2A–C, zebrafish in the model group exhibited greater abdominal fat deposition compared to other groups, with a mean BMI of 38.5 mg/cm² and a mean blood glucose level of 5.82 mmol/L, both significantly higher than the control group ($P < 0.05$ and $P < 0.01$). The mean BMI values in the bergenin groups and the metformin group were significantly lower than those in the model group ($P < 0.01$), accompanied by a significant reduction in blood glucose levels compared to the model group ($P < 0.01$). Furthermore, we assessed the impact of bergenin on the behavior of zebrafish induced by high glucose using the adult zebrafish behavioral observation system. As observed in the behavioral swimming trajectories and statistical data presented in Figures 2D,E, zebrafish in the model group predominantly exhibited red-colored swimming trajectories, with significantly higher total distance traveled and swimming speed compared to other groups, along with an increase in high-speed swimming (>5 cm/s) ($P < 0.01$). In contrast, zebrafish treated with varying doses of bergenin and the metformin group showed reduced swimming speed, trending towards more green-colored trajectories, primarily characterized by medium to low-speed movements (2–5 cm/s, <2 cm/s) ($P < 0.01$), indicating a tendency towards normalized swimming trajectories. Finally, we evaluated the effect of bergenin on the learning and memory abilities of zebrafish induced by high glucose through the T-maze experiment. As shown in Figures 2F–H, zebrafish with normal learning and memory abilities can identify food rewards in the EC area through learning. As formal training progresses, the latency to enter the EC area decreases, while the time spent and distance traveled in the EC area increase. Compared to the control group, zebrafish in the model group exhibit higher total distance traveled and average speed, but weaker recognition ability towards the EC area. Interestingly, as learning progresses, the distance and time spent in the EC area decrease. Zebrafish

TABLE 2 Deformities in zebrafish larvae.

Developmental toxicity	Teratogenic effects	Control	Model	Bergenin	Metformin	Σt	%
Teratogenic effects	Cardiac edema	0	12	7	4	23	6.4
	Tail malformation[a]	0	8	4	5	17	4.7
	Scoliosis	0	6	0	1	7	1.9
	Yolk edema	0	15	8	6	29	8.1
	Growth retardation[b]	0	10	4	2	16	4.4
	Σ Teratogenic embryos	0	24	12	10	41	—
	% Teratogenic embryos	0	26.7[##]	13.3[*]	11.1[**]	—	—

[a]Tail malformation occurred when an embryo had a curved, twisted, or hook-like tail.
[b]Growth retardation was evaluated by comparing treated embryos with control ones (size, development stage). At 72 and 96 hpf, growth retardation was considered when embryos' size was less than 2.9 and 3.3 mm, respectively.
[##]$P < 0.01$ compared with Control group; [*]$P < 0.05$, [**]$P < 0.01$ compared with Model group (Pearson Chi-square test).

treated with bergenin and metformin show enhanced recognition ability towards the EC area, with significant increases in the time spent and distance traveled in the EC area as training progresses.

3.1.3 The effect of bergenin on inflammatory in high glucose-induced zebrafish

HE staining revealed an increase in activated microglia, indicating enhanced inflammatory response in the telencephalic region of the model group ($P < 0.01$) (Figure 3A). Gill tissues observations included dilatation of capillaries, capillary disarrangement, vascular congestion, and hyperplasia of epithelial cells on secondary lamellae of the model group ($P < 0.01$) (Figure 3B). After treatment with bergenin and metformin, pathological changes in the telencephalon and gills were partially alleviated, leading to reduced congestion and associated inflammatory alterations ($P < 0.01$).

The impact of bergenin on the expression of inflammatory factors in the brains of high glucose-induced zebrafish was investigated using RT-qPCR. As shown in Figure 3C, compared to the control group, the mRNA levels of inflammatory factors *il1b* ($P < 0.01$), *il6* ($P < 0.01$), and *tnfa* ($P < 0.01$) were significantly increased in the model group. However, the mRNA expression levels of *il1b* ($P < 0.01$), *il6* ($P < 0.01$), and *tnfa* ($P < 0.01$) were significantly decreased in the bergenin and metformin groups compared to the model group, indicating an amelioration in brain inflammation levels.

We investigated bergenin's impact on the expression of insulin resistance-related genes in the brains of zebrafish induced with high glucose using RT-qPCR. As shown in Figure 3C, compared to the control group, the insulin gene (*ins*) expression was upregulated in the model group, while the expression of insulin receptor substrate genes (*irs1, irs2a, and irs2b*) decreased significantly ($P < 0.01$). However, in both the bergenin and metformin groups ($P < 0.01$), ins expression decreased while *irs1, irs2a, and irs2b* expression increased, indicating bergenin's effectiveness in alleviating insulin resistance.

3.1.4 The effect of bergenin on glucose, Lactic Acid, and Glycolytic Key Enzymes in High Glucose-Induced zebrafish

As depicted in Figures 4A–E, zebrafish induced with high glucose exhibited elevated brain glucose levels ($P < 0.05$),

increased lactate production ($P < 0.01$), and enhanced activity of glycolytic key enzymes HK and PFK ($P < 0.05$). Subsequent administration of bergenin and metformin resulted in a decrease in brain glucose levels ($P < 0.05$), lactate production ($P < 0.05$), and activity of glycolytic enzymes HK and PFK ($P < 0.01$). These findings indicate disrupted brain glucose metabolism and enhanced glycolysis in zebrafish induced with high glucose. Bergenin and metformin demonstrate the ability to reduce brain glycolysis levels, thereby improving brain glucose metabolism.
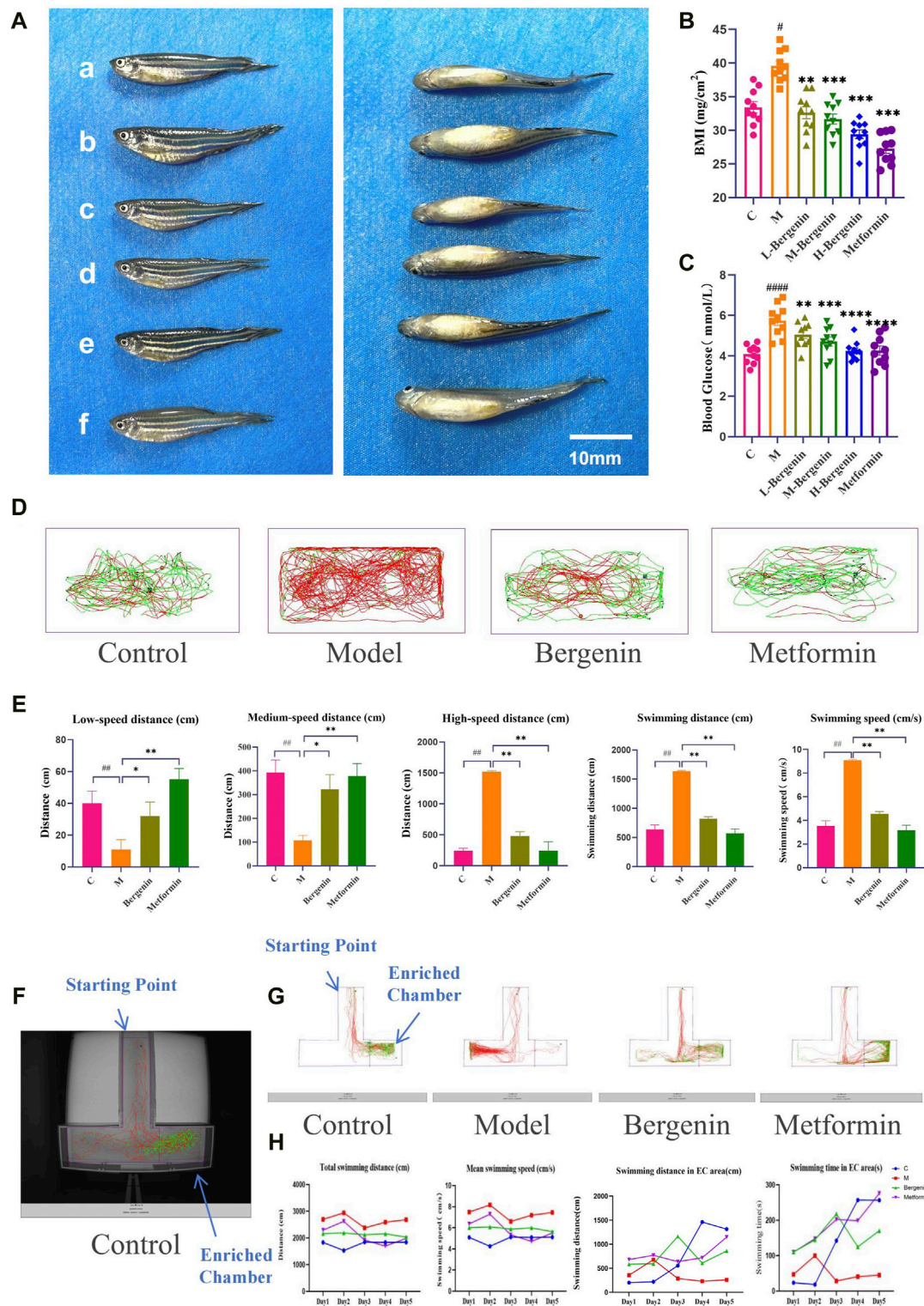
3.1.5 The effect of bergenin on PPAR-γ/NF-κB pathway mRNA in high glucose-induced zebrafish

Tissue samples from the brains, livers, and muscles of zebrafish were collected to investigate the impact of bergenin on PPAR-γ/NF-κB pathway-related gene expression induced by high glucose, using RT-qPCR. As depicted in Figures 4F–K, compared to the control group, PPAR-γ expression decreased while NF-κB expression increased in the brains, livers, and muscles of zebrafish in the model group ($P < 0.01$). Conversely, in the bergenin group ($P < 0.05$) and the metformin group ($P < 0.05$), PPAR-γ expression increased while NF-κB expression decreased, suggesting that high glucose induction and bergenin treatment affect multiple tissues in zebrafish. Furthermore, bergenin exerts its neuroprotective effects by activating PPAR-γ and inhibiting NF-κB.
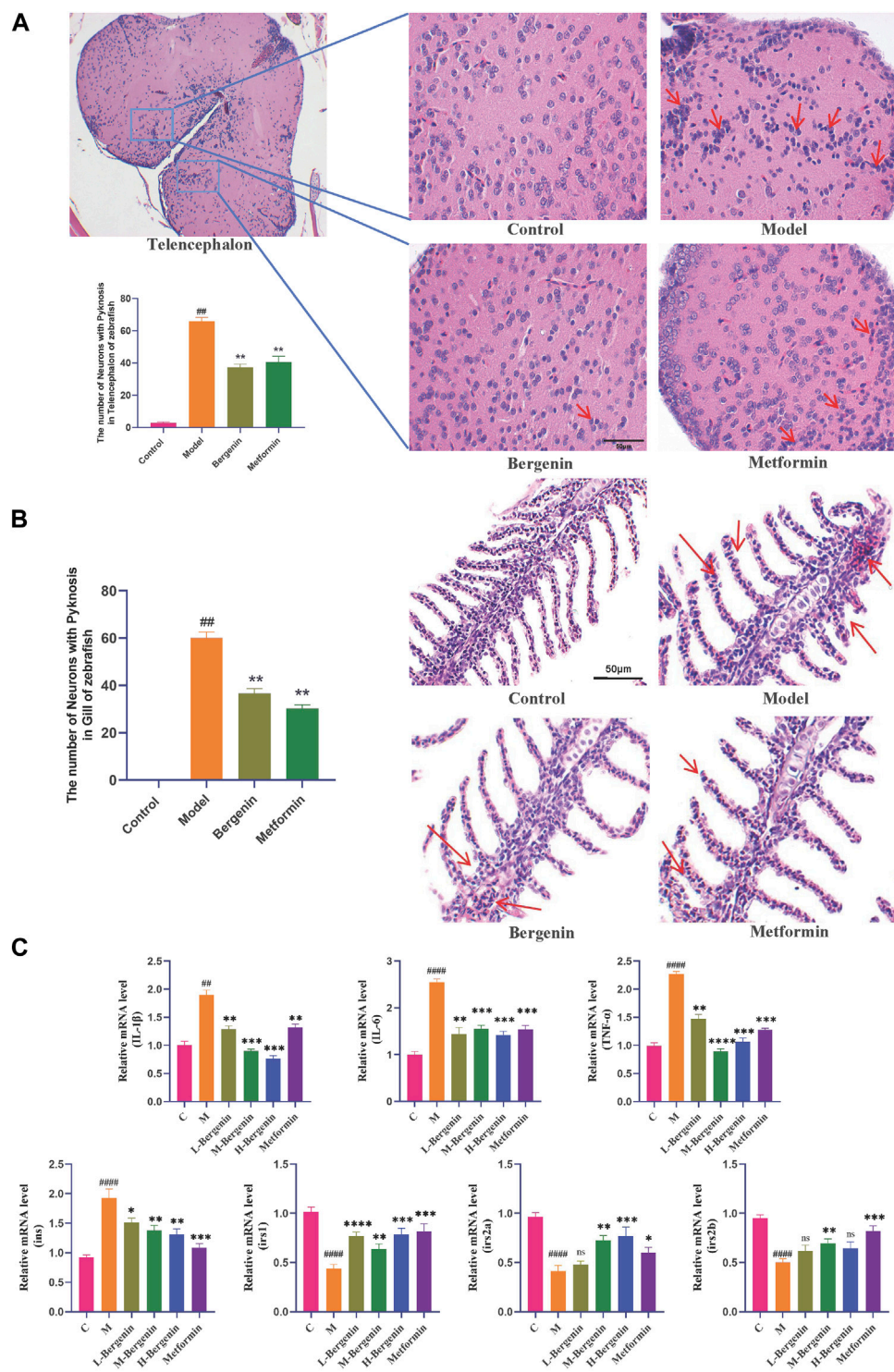
3.2 The effect of bergenin on high glucose-induced BV2 cells

3.2.1 The effect of bergenin on inflammatory factors in high glucose-induced BV2 cells

Under bright-field microscopy, changes in cell morphology were observed: BV2 cells in the control group exhibited a regular distribution, without cell aggregation, mostly in a quiescent state, appearing round or spindle-shaped. In comparison, the model group showed a significant increase in amoeboid-like cell clusters. After treatment with Bergenin, 2DG, and DADA on modeled BV2 cells, all three groups exhibited reduced numbers of amoeboid-like cells and fewer clusters compared to the model group. The impact of bergenin on the expression of inflammatory factors in BV2 cell models was studied using RT-qPCR. As shown in

FIGURE 2
Effects of Bergenin on High-Glucose-Induced Zebrafish Adults. **(A)** Imaging of Adult Zebrafish After Modeling and Drug Administration; **(B)** Body Mass Index (BMI) of Zebrafish Adults; **(C)** Blood Glucose of Zebrafish Adults; **(D)** Zebrafish Behavioral Trajectories; **(E)** Statistical Analysis of Zebrafish Behavior Data: Low-Speed Distance (<2 cm/s); Medium-Speed Distance (2–5 cm/s); High-Speed Distance (>5 cm/s); Total Swimming Distance; Swimming Speed; **(F)** Actual Scene of T-Maze; **(G)** Zebrafish Behavioral Trajectories in the T-maze. **(H)** Statistical Analysis of Zebrafish T-Maze Data: Total Swimming Distance; Mean Swimming Speed; Swimming Distance in EC area; Swimming Time in EC area. [#]$P < 0.05$, [##]$P < 0.01$, [####]$P < 0.001$ indicates significance compared to the control group; [*]$P < 0.05$, [**]$P < 0.01$, [***]$P < 0.001$, [****]$P < 0.0001$ indicates significance compared to the model group. (One-way ANOVA, Mean $\pm$ SD, N = 20).

FIGURE 3
Effects of Bergenin on Inflammation and Insulin Resistance in High-Glucose-Induced Zebrafish Adults. **(A)** Pathological Changes in the Telencephalon Region of High-Glucose-Induced Zebrafish Adults: The arrow indicates activated and aggregated microglial cells (HE staining); **(B)** Pathological Changes in Gill Tissues: The arrow indicates inflammation response in the gill, characterized by capillary disorder, dilation, and congestion (HE staining); **(C)** The Effect of Bergenin on Inflammatory Factors and Insulin Resistance in High Glucose-Induced Zebrafish: Relative mRNA level of *il1b, il6, tnfa, ins, irs1, irs2a,* and *irs2b.* "ns" indicates no statistical significance; $^{\#\#}P < 0.01$, $^{\#\#\#\#}P < 0.0001$ indicates significance compared to the control group; $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, $****P < 0.0001$ indicates significance compared to the model group. (One-way ANOVA, Mean $\pm$ SD, N = 15).
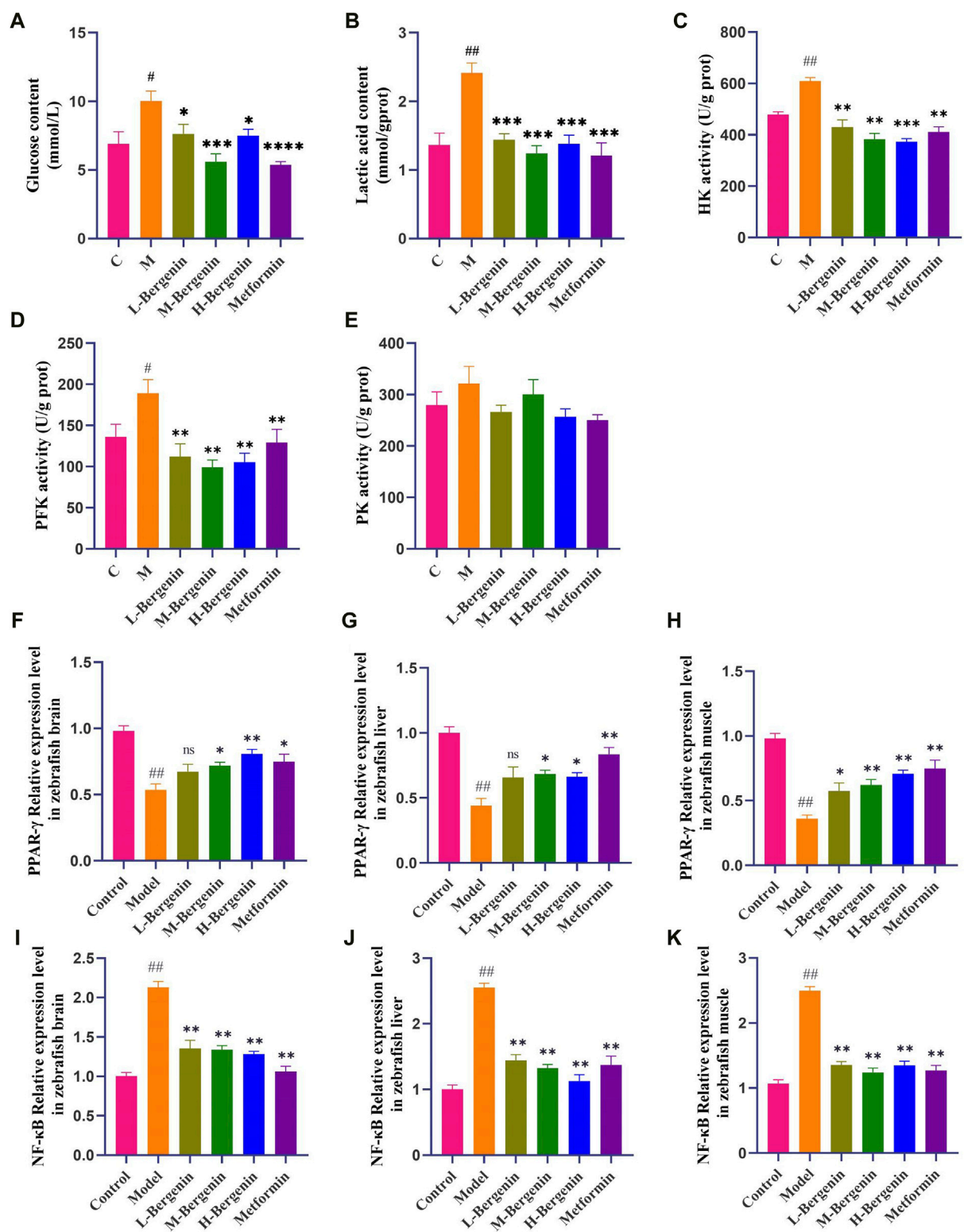
FIGURE 4
Effects of Bergenin on Glycolysis and PPAR-γ/NF-κB pathway in High-Glucose-Induced Zebrafish Adults. **(A–E)**: The Effect of Bergenin on Glucose, Lactic Acid, and Glycolytic Key Enzymes in High Glucose-Induced Zebrafish: **(A)** Glucose content; **(B)** Lactic acid content; **(C)** HK activity; **(D)** PFK activity; **(E)** PK activity; **(F–K)**: The Effect of Bergenin on PPAR-γ/NF-κB pathway mRNA in High Glucose-Induced Zebrafish: **(F–H)** Relative mRNA levels of *pparg* in the brain, liver, and muscle of zebrafish; **(I–K)** Relative mRNA level of *rela* in the brain, liver and muscle of zebrafish. "ns" indicates no statistical significance; #$P < 0.05$, ##$P < 0.01$ indicates significance compared to the control group; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$ indicates significance compared to the model group. (One-way ANOVA, Mean ± SD, N = 15).
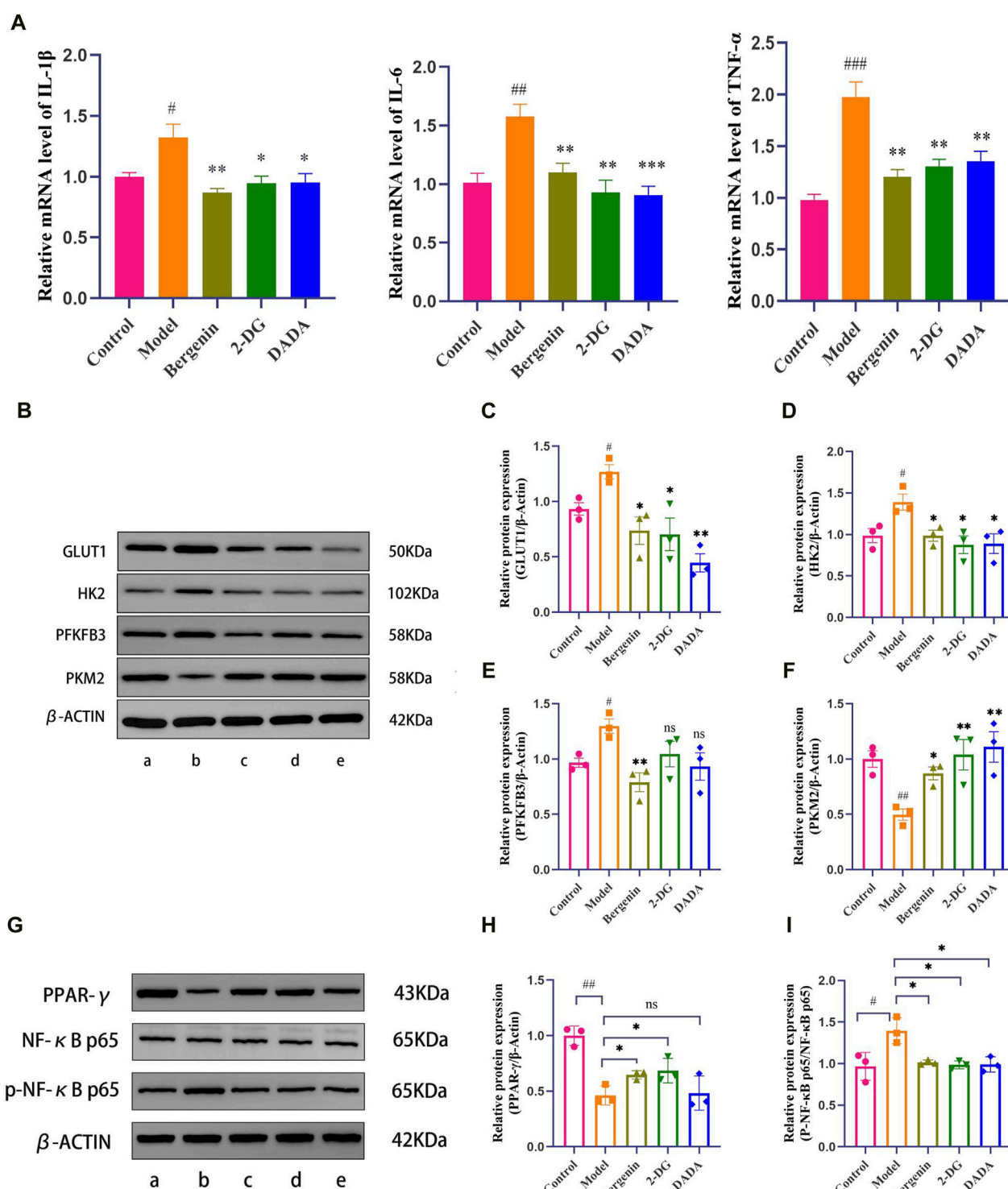
FIGURE 5
Effects of Bergenin in High Glucose-Induced BV2 Cells. **(A)** The Effect of Bergenin on Inflammatory Factors in High Glucose-Induced BV2 Cells: Relative mRNA level of IL-1β, IL-6, TNF-α; B−F: The Effect of Bergenin on Glycolytic Key Enzymes in High Glucose-Induced BV2 Cells: The Western blot images of glycolysis-related enzymes **(B)**. Data are represented as GLUT1/β-actin **(C)**, HK2/β-actin **(D)**, PFKFB3/β-actin **(E)** and PKM2/β-actin **(F)**. **(G−I)**: The Effect of Bergenin on the PPAR-γ/NF-κB Pathway in High Glucose-Induced BV2 Cells: The Western blot images of PPAR-γ/NF-κB Pathway **(G)**. Data are represented as PPAR-γ/β-actin **(H)** and p-p65/p65 **(I)**. "ns" indicates no statistical significance; $^{#}P < 0.05$, $^{##}P < 0.01$, $^{###}P < 0.001$ indicates significance compared to the control group; $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ indicates significance compared to the model group. (One-way ANOVA, Mean ± SD, N = 3).

Figure 5A, compared to the control group, the model group exhibited increased mRNA expression of inflammatory factors IL-1β ($P < 0.05$), IL-6 ($P < 0.01$), and TNF-α ($P < 0.01$). Following intervention with bergenin, 2DG, and DADA, the mRNA expression of IL-1β ($P < 0.05$), IL-6 ($P < 0.01$), and TNF-α ($P < 0.01$) decreased. This indicates that bergenin, 2DG, and DADA can exert a certain inhibitory effect on inflammation induced in BV2 cells by high glucose through the regulation of the glycolytic pathway.

3.2.2 The effect of bergenin on glycolytic key enzymes in high glucose-induced BV2 cells

High glucose induces metabolic reprogramming, shifting the primary mode of intracellular glucose metabolism from oxidative phosphorylation to aerobic glycolysis. The expression of key enzyme proteins Glucose Transporter Type 1 (GLUT1), HK2, 6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 3 (PFKFB3), and PKM2 (Pyruvate Kinase M2) during glycolysis was further assessed using Western Blot analysis. As depicted in Figures 5B–F, compared to the control group, the model group showed significantly increased expression of GLUT1, HK2, and PFKFB3 ($P < 0.05$). However, following intervention with bergenin, 2DG, and DADA, the protein expression of GLUT1, HK2, and PFKFB3 in BV2 cells significantly decreased ($P < 0.05$) compared to the model group, indicating that bergenin can exert a glycolysis inhibitory effect similar to that of 2DG, regulating metabolic reprogramming. Additionally, compared to the control group, the expression of PKM2 decreased in the model group. However, following intervention with bergenin, 2DG, and DADA, the expression of PKM2 increased, although the underlying mechanism requires further elucidation.

3.2.3 Bergenin activates PPAR-γ and reduces NF-κB p65 phosphorylation in high glucose-treated BV2 cells

To investigate the protective mechanism of bergenin against high glucose-induced neurotoxicity, we measured the protein levels of PPAR-γ. The results showed a significant decrease in PPAR-γ expression induced by high glucose (Figures 5G,H). This decrease was reversed by bergenin ($P < 0.05$). Concurrently, we assessed the phosphorylation of NF-κB protein, closely associated with cellular inflammatory response. The results indicated a significant increase in p-p65 levels induced by high glucose, which was markedly inhibited by bergenin treatment ($P < 0.05$) (Figures 5G,I). Therefore, we propose that bergenin's improvement of high glucose-induced glycolysis and increased inflammation is associated with the activation of PPAR-γ and deactivation of its downstream NF-κB pathway.

3.3 The effect of bergenin on STZ-Induced rat models

3.3.1 The effect of bergenin on the learning and memory abilities in STZ-induced rat models

Compared to the control group, the model group exhibited a decline in learning and memory abilities, with a significantly prolonged time to find the platform ($P < 0.01$). When compared

to the model group, the Bergenin low-dose ($P < 0.05$), high-dose ($P < 0.01$), and Metformin ($P < 0.01$) groups showed a reduction in the time to find the platform. After removing the platform, compared to the control group, the model group significantly reduced the time spent in the target platform quadrant ($P < 0.01$) and the number of crossings through the platform ($P < 0.01$). In comparison to the model group, the Bergenin groups exhibited a significant increase in the time spent in the target platform quadrant and an increase in the number of crossings. Bergenin improved the learning and memory abilities in STZ-Induced Rat Model (Figures 6A,B).

HE results showed (Figures 6C,E) that the number of neurons in the CA2 and CA3 regions of rats in the model group decreased, with disordered cell arrangement, nuclear condensation, darkening color, and neuronal damage ($P < 0.01$). Bergenin and Metformin groups showed improved neuronal damage, with normal cell morphology and orderly arrangement. In the low-dose group, there were fewer cells with deepened nuclear staining and pyknosis ($P < 0.01$). Nissl staining results (Figures 6D,F) revealed that in the model group, neurons in the hippocampal region of rats were loosely arranged, with a decrease in Nissl bodies, lightened staining, and cells appearing vacuolated or shrunken, with a reduced number ($P < 0.01$). In the Bergenin and Metformin groups, the number of Nissl bodies inside hippocampal neurons increased, cells were arranged orderly, and cell morphology was normal, with an increased number ($P < 0.01$, $P < 0.01$). Bergenin can reduce abnormal neurons in the hippocampal region of AD rats.

3.3.2 The effect of bergenin on the inflammatory and glycolytic process and in the hippocampus in STZ-induced rat models

Using RT-qPCR to detect the mRNA expression levels of inflammatory factors in the rat hippocampal region, compared with the control group, the model group showed a significant increase in TNF-α, IL-6, and IL-1β mRNA expression levels ($P < 0.01$). Compared with the model group, the expression levels were significantly reduced in the low-dose, high-dose Bergenin, and Metformin groups ($P < 0.05$, $P < 0.01$) (Figure 6G).

As shown in Figures 7A–E, the model group exhibited elevated brain glucose levels ($P < 0.01$), increased lactate production ($P < 0.01$), and enhanced activity of glycolytic key enzymes HK, PFK, and PK ($P < 0.01$). Following administration of bergenin and metformin, there was a significant decrease in brain glucose levels ($P < 0.05$), lactate production ($P < 0.05$), and activity of glycolytic enzymes HK, PFK, and PK ($P < 0.05$). These findings suggest enhanced glycolysis in STZ-induced rat models. Bergenin and metformin demonstrate the ability to reduce brain glycolysis levels, thereby improving brain glucose metabolism.

3.3.3 The effect of bergenin on the PPARγ/NF-κB signaling pathway in the hippocampus in STZ-Induced rat models

WB detection of PPARγ and p-NF-κB p65 protein expression in the hippocampal of rats in each group (Figures 7F–H), the expression of PPARγ in the hippocampus of rats in the model group significantly decreased ($P < 0.001$), while the expression level of p-NF-κB p65/NF-κB p65 significantly increased ($P < 0.05$). In comparison to the model group, the high-dose Bergenin and Metformin groups showed a significant increase in the expression
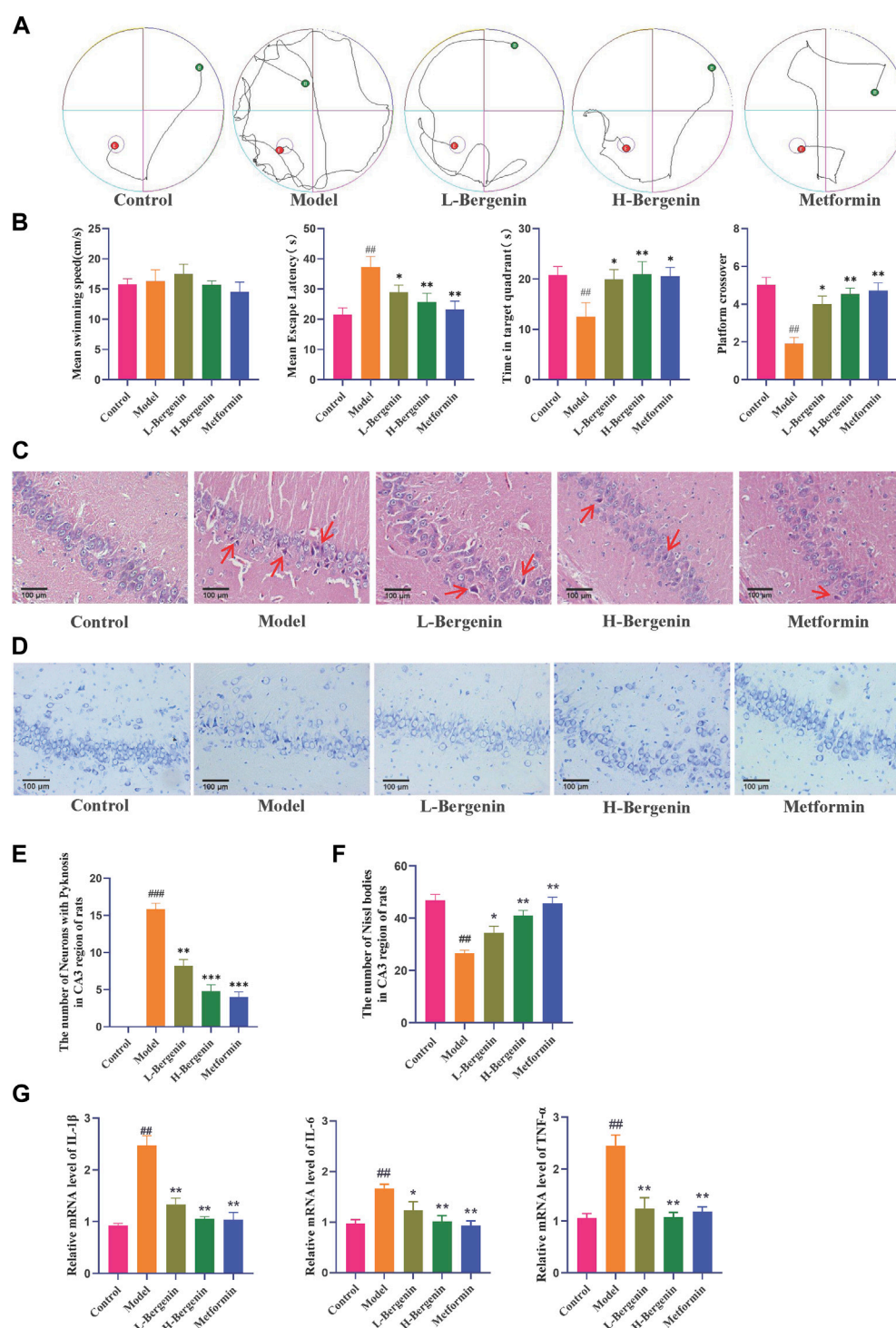
FIGURE 6
Effects of Bergenin in STZ-Induced Intracerebral Injection Rat Model. **(A)** The Morris Water Maze Trajectory Map evaluated the neurological functions, as well as the learning and memory abilities of rats. **(B)** Statistical data from the Morris Water Maze included the mean swimming speed, latency time to discover the platform, residence time in the quadrant, and frequency of crossing the target platform. **(C–F)**: Effects of Bergenin on the Morphology of Hippocampal Neurons in the STZ-induced Intracerebral Injection Rat Model Detected by HE Staining **(C, E)** and Nissl Staining **(D, F)**, The arrows respectively indicate pyknosis **(C)**; **(G)** The Effect of Bergenin on Inflammatory Factors in STZ-Induced Intracerebral Injection Rat Model: Relative mRNA level of IL-1β, IL-6, TNF-α. #P < 0.05, ##P < 0.01 indicates significance compared to the control group; *P< 0.05, **P< 0.01 indicates significance compared to the model group. (One-way ANOVA, Mean ± SD, N = 3).
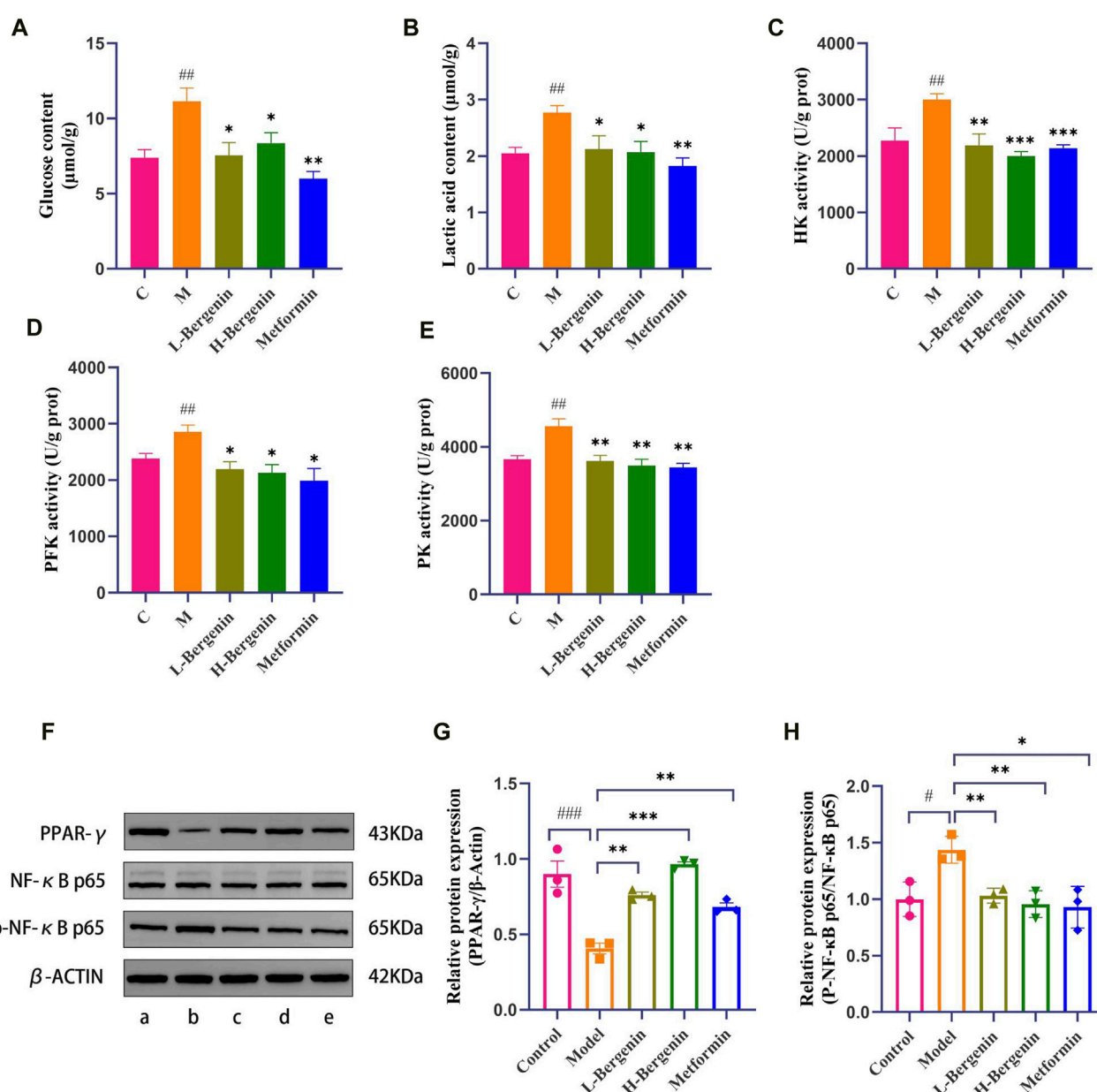
FIGURE 7
Effects of Bergenin on Glycolysis and PPAR-γ/NF-κB Pathway in STZ-Induced Intracerebral Injection Rat Model. A–E: The Effect of Bergenin on Glucose, Lactic Acid, and Glycolytic Key Enzymes in STZ-Induced Intracerebral Injection Rat Model: **(A)** Glucose content; **(B)** Lactic acid content; **(C)** HK activity; **(D)** PFK activity; **(E)** PK activity; **(F–H)**: The Effect of Bergenin on the PPAR-γ/NF-κB Pathway in STZ-Induced Intracerebral Injection Rat Model: The Western blot images of PPAR-γ/NF-κB Pathway **(F)**. Data are represented as PPAR-γ/β-actin **(G)** and p-p65/p65 **(H)**. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ indicates significance compared to the control group; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ indicates significance compared to the model group. (One-way ANOVA, Mean $\pm$ SD, N = 3).

of PPARγ and a significant decrease in the expression of p-NF-κB p65/NF-κB p65 in the hippocampal region.

4 Discussion

Diabetes mellitus (DM), a metabolic disorder resulting from lifelong hyperglycemia, is multifactorial. Prolonged hyperglycemia in diabetic patients often leads to widespread chronic damage and dysfunction in various tissues, notably affecting the eyes, kidneys,

heart, blood vessels, and nerves, significantly impacting human health (Cloete, 2022). In recent years, there has been increasing attention to DACI. The risk of dementia is reported to be 2.8 times higher in the T2DM population compared to non-T2DM individuals, with an estimated prevalence of mild cognitive impairment (MCI) ranging from 20% to 30% and a dementia incidence of approximately 17.3% among T2DM patients (Zheng et al., 2018; Liang et al., 2023). Clinical studies have shown that T2DM patients commonly exhibit widespread brain atrophy and cerebral microvascular damage, which is age-dependent. Moreover,

T2DM-induced reduction in brain volume is three times greater than that of normal aging (Rachdaoui, 2020; Steinbrenner et al., 2022; Miao et al., 2023). High glucose levels have also been identified as a primary cause of excessive phosphorylation of tau protein in hippocampal neurons, contributing to DACI (Chow et al., 2019).

The pathophysiological mechanisms of DACI remain elusive. Evidence suggests that aberrations in brain cell metabolism and heightened levels of inflammatory mediators play significant roles in the onset of DACI (Grandl and Wolfrum, 2018; Shen et al., 2022). Extensive experimental data support the involvement of activated microglial cells in neuronal damage and cognitive impairment in T2DM models (Li et al., 2023). Furthermore, several hypotheses, including insulin resistance, insulin deficiency, disrupted insulin signaling pathways, alterations in brain tissue architecture, changes in cerebral blood flow, immune dysregulation, and mitochondrial dysfunction, have been proposed. These pathophysiological changes further contribute to structural and functional damage to nerve cells, thus affecting cognitive function. Abnormal brain glucose metabolism is closely linked to microglial cell activation, which undergoes metabolic reprogramming from oxidative phosphorylation to glycolysis (Jasleen et al., 2023). Given the significant role of neuroinflammation induced by activated microglial cells in DACI pathogenesis, regulating glucose metabolism to prevent excessive microglial cell activation has emerged as a novel early intervention approach for DACI.

The Traditional Chinese Medicine (TCM) *B. purpurascens* (Hook. f. et Thoms.) Engl., commonly used in China, India, Nepal, and other countries, has been recorded in the "Classification of Herbal Medicines" in China for over a century. Its main active component, bergenin, is recognized for its significant antitussive effect and is included in the *Chinese Pharmacopoeia* as an antitussive and expectorant drug. Modern pharmacological studies have shown that bergenin exerts anti-inflammatory effects by downregulating pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α(Barai et al., 2018). Furthermore, bergenin exhibits anti-diabetic activity and demonstrates neuroregulatory, acetylcholinesterase inhibitory, antioxidant, and reduction of Aβ$_{1-42}$ and p-*tau* expression levels, supporting its overall neuroprotective effects (Barai et al., 2019; Singla et al., 2022). Our study results indicate that bergenin administration significantly reduces glucose levels, inflammatory pathological manifestations, and levels of inflammatory factors induced by high glucose in zebrafish larvae, adult zebrafish models, and rats injected with STZ into the lateral ventricle. It also improves behavioral abnormalities induced by high glucose and enhances learning and memory abilities. This confirms the dose-dependent hypoglycemic effect and its significant protective effect against inflammation-induced neuronal damage induced by high glucose. The performance characteristics of bergenin highlight its potential as a natural compound for the development of drugs targeting neuronal damage induced by high glucose.
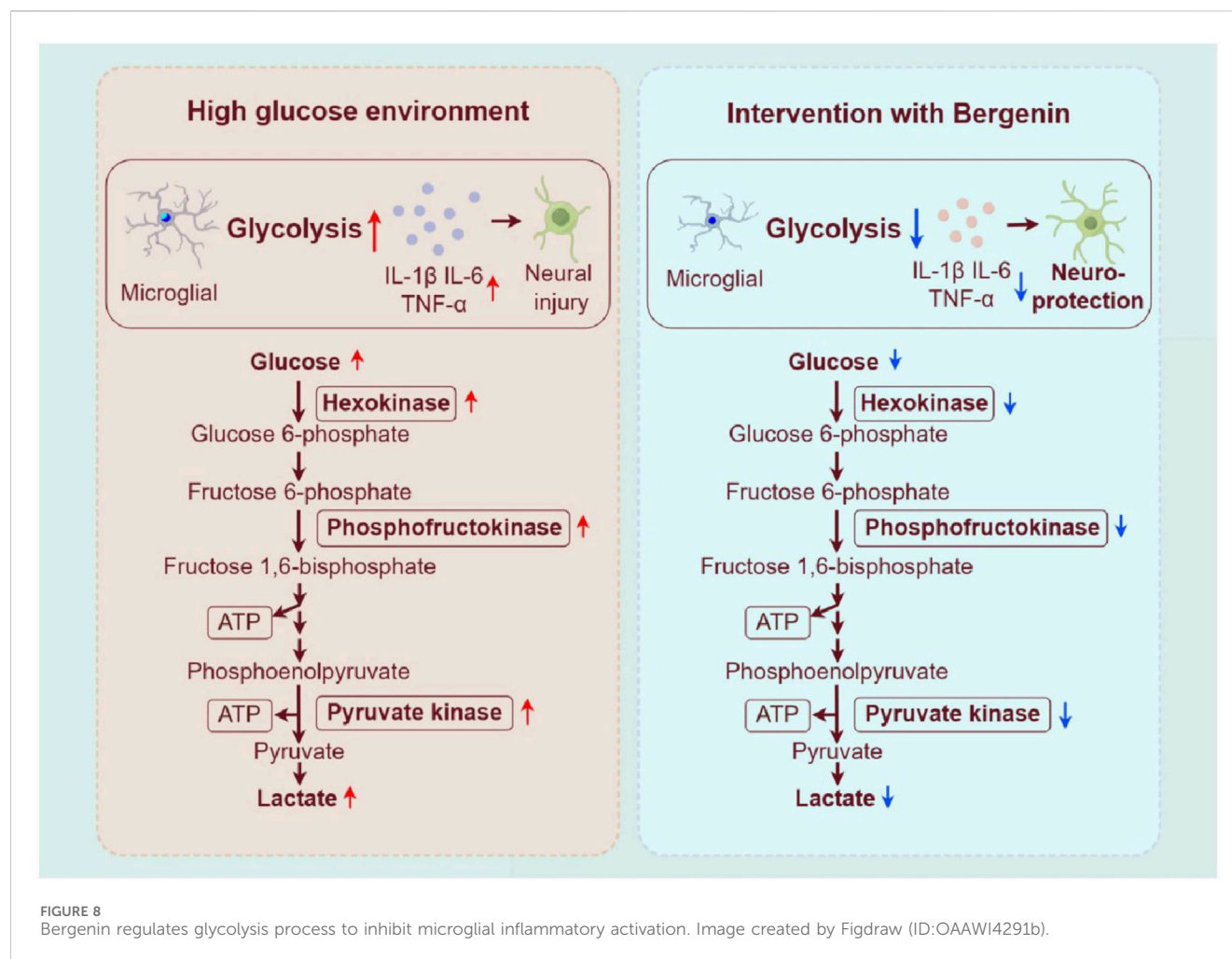
Research suggests that peripheral hyperglycemia can enter the brain through active transport, and chronic cerebral hyperglycemia can lead to cerebral hyperinsulinemia, inducing insulin resistance in neurons and increasing the risk of diseases such as DACI and AD (Kellar and Craft, 2020). However, the mechanism by which cerebral hyperglycemia induces neuronal damage remains to be elucidated; some studies suggest that upon developing insulin resistance, a compensatory response may occur, increasing glucose metabolic pathways to meet cellular energy demands, manifested as enhanced glycolysis (Cardoso et al., 2017). Glucose metabolism is a crucial component of energy metabolism, involving oxidative phosphorylation and glycolysis pathways. ATP is generated from glucose breakdown to sustain normal physiological functions. Normally, cerebral glucose metabolism relies on oxidative phosphorylation. However, under pathological conditions, when there's a sudden demand for ATP, cerebral metabolism shifts to glycolysis due to its faster ATP production rate, despite aerobic conditions (Dienel, 2019). This study reveals that in high-glucose-induced zebrafish and STZ lateral ventricle injection rat models, glucose uptake increases, key glycolytic enzymes are upregulated, and lactate release rises. Similarly, in the high-glucose-induced BV2 cell model, expressions of GLUT-1, HK2, PFKFB3, PKM2 are elevated, but bergenin can modulate glucose metabolism and curb excessive glycolysis (Figure 8).

In the pathological process of neurodegenerative diseases, neuroinflammation mediated by microglia plays a crucial role. Elevated levels of glycolysis may trigger microglial activation, leading to the release of a large number of inflammatory mediators, which adversely affect surrounding neurons (Wu et al., 2023; Yang et al., 2024). Moreover, research suggests that the inflammatory response of microglia can stimulate glycolytic pathway activity while inhibiting oxidative phosphorylation processes (Li et al., 2016). Furthermore, blocking glycolytic metabolism can effectively reduce the immune effects triggered by microglial activation (Lu et al., 2021; Miao et al., 2023). The characteristics of AD and DACI include reduced neuronal glucose uptake, decreased tricarboxylic acid cycle activity, mitochondrial dysfunction, and the interruption of astrocytic energy support to neurons. Additionally, neuroinflammation promotes the competition for glucose by microglia and astrocytes, further exacerbating neuronal glucose hypometabolism. In our study, we observed an increase in glycolytic enzyme activity and expression of inflammatory factors under high glucose conditions in various *in vitro* and *in vivo* models, including zebrafish, cells, and rats. Additionally, increased activation of microglia in the brains of zebrafish and rats was observed. Bergenin was observed to alleviate inflammatory pathological changes induced by high glucose in zebrafish and rats, while also significantly reducing the elevated expression of IL-1β, IL-6, and TNF-α induced by high glucose in zebrafish, BV2 cells, and rats.

PPARγ, a key nuclear receptor, inhibits the nuclear translocation and DNA-binding activity of NF-κB-p65, thereby reducing the expression of pro-inflammatory cytokines (Luo et al., 2020). Bergenin, an isocoumarin, shows potential as a PPARγ activator. Numerous studies have confirmed Bergenin's role as a natural PPARγ agonist, inhibiting inflammatory cell aggregation, and being widely used clinically to treat inflammatory-related diseases. NF-κB acts as a key transcription factor in inflammation regulation. Upon activation, NF-κB translocates from the cytosol to the nucleus, where it binds to the promoters of inflammation-related genes, such as IL1-β, IL-6, and TNF-α (Barnabei et al., 2021). Our study demonstrated that bergenin can attenuate the inflammatory stress response of microglial cells by inhibiting glycolytic enzyme activity, thereby exerting

FIGURE 8
Bergenin regulates glycolysis process to inhibit microglial inflammatory activation. Image created by Figdraw (ID:OAAWI4291b).

neuroprotective effects. Mechanistic investigations revealed that bergenin suppressed the enhancement of glycolysis by activating the PPAR-γ signaling pathway in high-glucose-induced microglial cells. Additionally, bergenin inhibited the NF-κB signaling pathway, reducing the inflammatory response of microglial cells (Figure 9).

The use of multiple models in drug development expands the options available and enables a thorough assessment of drug efficacy. Zebrafish, as a model organism, possess advantages such as small size, large egg production, transparent embryos, and short experimental cycles. In recent years, zebrafish have been increasingly utilized for research on metabolic disorders, brain function mechanisms, and high-throughput drug screening (Gore and Pillay, 2018). The cell model provides more direct cellular-level information, facilitating molecular mechanism studies. Meanwhile, rodent models are more akin to the human physiological environment, capable of simulating complex biological processes and drug metabolism pathways, thus offering crucial insights for clinical translation of drugs. Integrating these models in drug development allows us to capitalize on their respective strengths, enhancing the reliability and effectiveness of research while reducing errors and shortcomings (Gore and Pillay, 2018; Muhammed and Aki-Yalcin, 2019; Barrett et al., 2022). Our study employs a combined approach involving zebrafish, cell, and animal models, providing
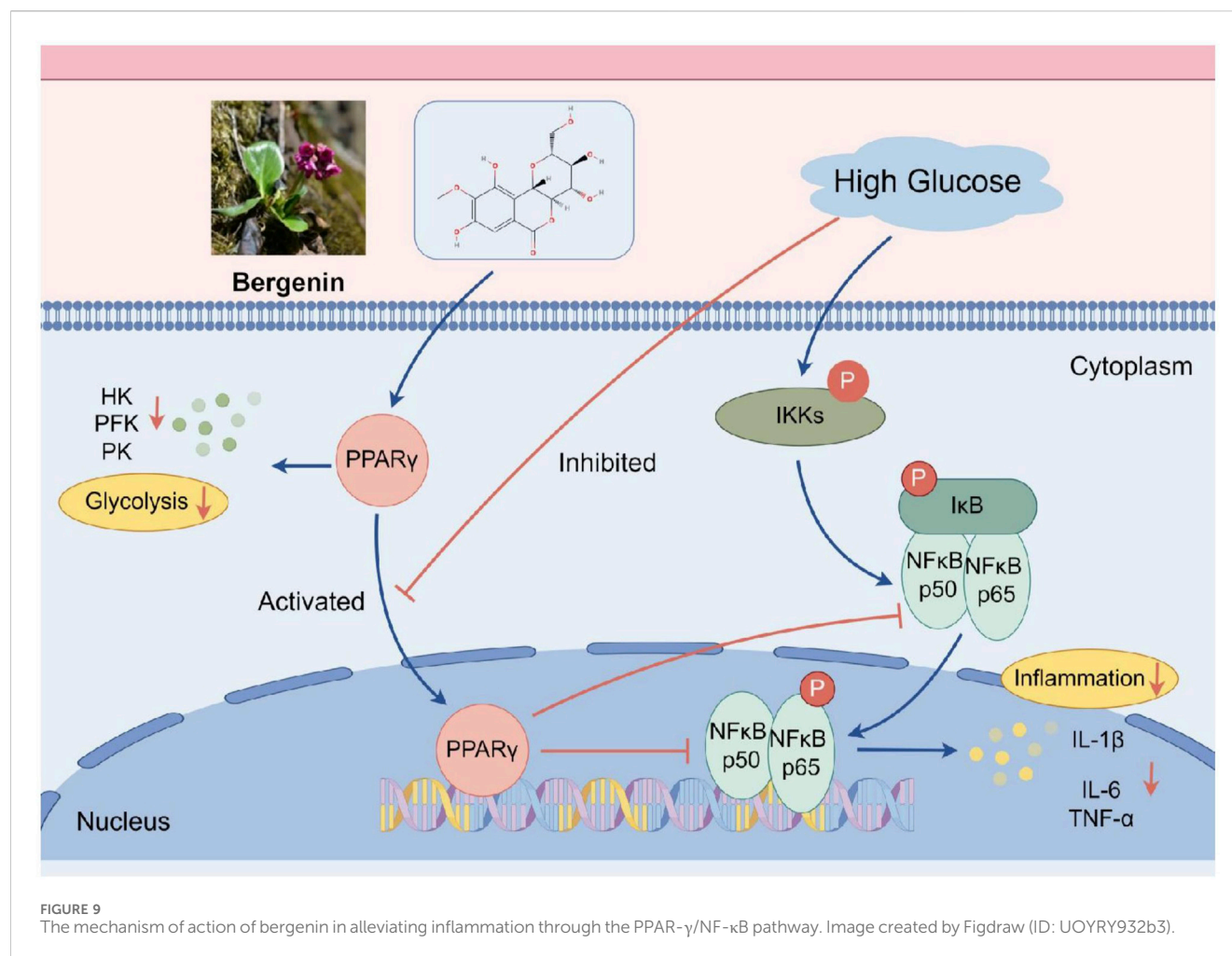
a fresh perspective and a more thorough evaluation method for drug screening. This approach serves as a significant reference and guide for discovering novel drugs to address diabetes and its related diseases.

While this study provides valuable insights into the protective effects of bergenin against neural damage induced by high glucose, there are several limitations that need to be addressed. Firstly, the experimental models used in this study may not fully recapitulate the complex pathophysiology of neural damage induced by high glucose in humans. Zebrafish, cell, and rat models have their own inherent differences from human physiology, and the findings from these models may not directly translate to clinical applications. Additionally, the mechanisms underlying bergenin's effects on glucose metabolism and inflammation need further elucidation. Future studies should explore the long-term effects of bergenin treatment, as well as its potential side effects and safety profile.

5 Conclusion

This study utilizes zebrafish, cell, and rat models to experimentally demonstrate that high glucose disrupts brain glucose metabolism, triggering inflammatory polarization of

FIGURE 9
The mechanism of action of bergenin in alleviating inflammation through the PPAR-γ/NF-κB pathway. Image created by Figdraw (ID: UOYRY932b3).

microglial cells and subsequent neuronal damage. Bergenin activates PPAR-γ, inhibiting glycolysis enzymes and shifting glucose metabolism from aerobic glycolysis to oxidative phosphorylation. Furthermore, bergenin inhibits IκB phosphorylation and NF-κB activation, reduces the expression of inflammatory factors, and regulates microglial cell activity, thereby alleviating inflammation. In conclusion, bergenin shows potential in mitigating compensatory glycolysis enhancement through the PPAR-γ/NF-κB pathway, alleviate inflammation, and protecting against neural damage induced by high glucose.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was approved by the Experimental animal Ethics Committee, Hunan University of Chinese Medicine. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

WY: Writing–original draft. RL: Writing–original draft. CH: Writing–review and editing, Investigation. ZL: Writing–review and editing, Data curation. MY: Writing–review and editing, Methodology. JZ: Writing–review and editing, Data curation. JH: Writing–review and editing, Formal Analysis. QC: Writing–review and editing, Project administration. ZS: Writing–review and editing, Validation. SC: Writing–original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1339178/full#supplementary-material

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