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Systematic review and meta-analysis of Jueyin disease theory in the treatment of gangrene with traditional Chinese medicine formulations

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Abstract

Objective This review aims to systematically evaluate the application of Jueyin disease theory in the diagnosis and treatment of gangrene within the framework of traditional Chinese medicine (TCM). Through systematic review and meta-analysis, the efficacy of commonly used TCM formulations, including Wumei pill, Pulsatilla decoction, and Dang-Gui-Si-Ni decoction, is explored.

Methods A systematic search of PubMed, Web of Science, and CNKI was conducted, integrating meta-analysis and systematic review. Clinical trials and case reports based on Jueyin disease theory for gangrene treatment were included. Data extraction, quality assessment, and statistical analyses were performed.

Results A total of nine studies met the inclusion criteria. The meta-analysis indicated that TCM formulations significantly improved clinical outcomes, particularly in enhancing the ankle-brachial index (ABI) and maximum walking distance, with mean differences of 0.17 (95% CI, 0.11, 0.24; $p < 0.01$) and 293.22 (95% CI, 174.85, 411.60; $p < 0.01$), respectively. Sensitivity analysis and tests for publication bias confirmed the robustness and consistency of the findings. Sensitivity analysis and publication bias assessment confirmed the robustness and reliability of the results.

Conclusion Jueyin disease theory and its related formulas (Wumei pill, Pulsatilla decoction, and Dang-Gui-Si-Ni decoction) demonstrate significant clinical value in traditional Chinese medicine (TCM) treatment of gangrene, effectively improving clinical symptoms and blood circulation. The findings provide scientific evidence for the modern application of Jueyin disease theory in TCM while acknowledging limitations such as small sample sizes and study heterogeneity, offering valuable insights for future research and clinical practice.

Keywords Jueyin disease, Gangrene, Traditional Chinese medicine formulations, Wumei pill, Pulsatilla decoction, Dang-Gui-Si-Ni decoction, Systematic review and meta-analysis

Introduction

Gangrene is a pathological condition in traditional Chinese medicine (TCM), characterized by necrosis at the extremities due to impaired blood circulation. In modern medicine, similar conditions are referred to as gangrene or tissue necrosis, often caused by vascular occlusion or hypoxia due to arteriosclerosis, diabetes, and other underlying diseases [1–3]. While advancements in modern diagnostics and treatments, such as imaging and

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vascular surgery, have improved management [4–6], therapeutic outcomes remain limited, particularly in enhancing blood circulation and addressing local lesions. Gangrene significantly impacts patients' quality of life and can lead to severe complications, including infections, necrosis, and even limb amputation [7], posing life-threatening risks in severe cases. Thus, effective treatment strategies for gangrene remain a critical medical challenge.

In recent years, the role of TCM in gangrene treatment has gained increasing attention [8]. TCM attributes gangrene to cold coagulation, blood stasis, and Yang deficiency, typically employing therapies that promote blood circulation and warm Yang [9, 10]. Western medicine has made progress in gangrene treatment through vascular reconstruction and antithrombotic therapies, yet challenges remain, especially in improving blood flow and preventing amputation [11–13]. Integrating TCM, particularly Jueyin disease theory, may offer new therapeutic perspectives. This theory provides a unique understanding of the interplay between cold, heat, deficiency, and excess, offering a novel framework for gangrene treatment. Recent studies have highlighted the effectiveness of TCM formulas such as Wumei pill, Pulsatilla decoction, and Dang-Gui-Si-Ni decoction [14–17] in alleviating gangrene symptoms and promoting blood circulation.

Although Jueyin disease theory is promising for treating gangrene, current research is limited to case reports and small-scale clinical observations, lacking comprehensive meta-analyses and systematic reviews. Hence, it is imperative to employ rigorous scientific methods to thoroughly evaluate the application of Jueyin disease theory in treating gangrene.

The primary aim of this research is to systematically evaluate the therapeutic value of Jueyin disease theory in gangrene treatment, mainly focusing on the clinical effects of formulations such as Wumei pill, Pulsatilla decoction, and Dang-Gui-Si-Ni decoction. By performing a meta-analysis of existing literature, we can quantify the effectiveness of these formulations in improving key indicators such as the ankle-brachial index (ABI) and maximum walking distance. The findings will provide scientific evidence for applying Jueyin disease theory in modern TCM, offering essential references for future clinical practice and research and further advancing the application of Jueyin disease theory in TCM diagnostics and treatment.

Materials and methods

Search and selection strategy

A detailed literature search was conducted to assess the application of Jueyin disease theory in TCM treatment of gangrene. Searches were performed in PubMed, Web of Science, CNKI, and Wan Fang Data, covering all relevant literature up to August 2024. Keywords included "Jueyin Disease," "Jueyin Disease theory," "Jueyin pathomechanism," "gangrene," "Traditional Chinese Medicine," and key formulations such as "Wumei Pill," "Dang-Gui-Si-Ni Decoction," and "Pulsatilla Decoction." According to the MeSH database, these terms do not have corresponding MeSH entries. Therefore, they were used as keywords for retrieval to ensure comprehensive literature coverage.

To enhance completeness, real-world clinical cases were reviewed, and treatment outcomes were analyzed. Search strategies were dynamically adjusted based on database characteristics. Manual searches were also conducted, including reference list reviews and proceedings from major TCM conferences, such as the International Conference on Traditional Chinese Medicine and the National TCM Conference. Additionally, classical TCM texts, including the Treatise on Cold Damage (Shang Han Lun), were referenced to explore historical formulations.

The initial screening was conducted independently by two researchers based on titles and abstracts, using predefined inclusion and exclusion criteria to determine eligibility for the next stage. Full-text articles of potentially relevant studies were then assessed independently by the same two researchers. Discrepancies were resolved through discussion or, if necessary, adjudicated by a third expert.

Inclusion and exclusion criteria

The quality and specificity of this review were ensured by meticulously screening literature based on specific criteria, focusing on TCM treatments for gangrene. Inclusion criteria consisted of studies based on Jueyin disease theory, clinical trials, and case reports using specific TCM formulations such as Wumei pill, Dang-Gui-Si-Ni decoction, and Pulsatilla decoction, with no restrictions on age or gender. Studies also had to include clear evaluation metrics, such as symptom improvement, blood circulation, and regression of local lesions.

Exclusion criteria involved eliminating studies that did not meet these conditions, such as those not based on Jueyin disease theory, using other TCM formulations or Western medicine, non-clinical trials, case reports, or studies with incomplete data. Duplicate publications, reviews, and expert opinion articles were excluded to avoid redundancy and bias.

This review focused on TCM treatments guided by Jueyin disease theory while also considering the integration of other therapeutic approaches in clinical practice. Studies using other TCM formulations or adjunctive therapies (e.g., electroacupuncture) were included, with

control groups receiving Western medicine or other TCM formulations.

Quality assessment

The quality of the included studies was assessed using the Cochrane Risk of Bias tool (ROB 2 version) [18], evaluating aspects such as study design, randomization methods, blinding procedures, data completeness, and outcome reporting to ensure the reliability and validity of the results [19].

Data extraction

Key information extracted from each study included author, publication year, sample size, and data relevant to the treatment of gangrene based on the Jueyin disease theory. This encompassed the TCM formulas used, symptom improvement, blood circulation status, and regression of local lesions. All data were systematically organized and recorded using Excel for traceability.

Further data extraction focused on detailed treatment information, including specific TCM formulas such as Wumei Wan, Danggui Sini Tang, and Baitouweng Tang. Recorded variables included symptom changes, improvements in blood circulation, and lesion regression. Assessment of the scientific validity and effectiveness of the treatments was supported by the collection of statistical data, including sample size, experimental group setup, p-values, and confidence intervals (CIs).

Statistical methods

This review conducted a meta-analysis using RevMan 5.4 and R software, with effect size and 95% CI as the primary evaluation metrics. Cochran's Q test and I^2 statistics were applied to assess heterogeneity among studies. An I^2 value of 0–40% indicated no significant heterogeneity, 30–60% indicated moderate heterogeneity, 50–90% indicated significant heterogeneity, and 75–100% indicated very high heterogeneity. For studies with high heterogeneity, a random-effects model was used for analysis. Additionally, sensitivity analysis was performed to evaluate the stability of the results. Publication bias was assessed through funnel plots and Egger's test. The significance level for all statistical tests was set at $P<0.05$.

Results

Literature screening summary and quality assessment of included studies

During the literature search, 2436 articles were identified from PubMed, Web of Science, CNKI, and Wan Fang Data databases (Fig. 1A). After removing duplicates, 1645 articles were further screened. Based on the initial screening of titles and abstracts, 1283 studies were excluded, including non-randomized, non-human, and studies with inconsistent research objectives. Subsequently, 362 articles underwent full-text review, and 353 were excluded due to incomplete data, missing full text, or inconsistent research standards. Finally, 9 studies were included in the quantitative meta-analysis. The basic characteristics of the included studies, such as the first author, publication year, sample size, and treatment methods, are summarized in Tables 1 and 2.

The quality of the included studies was assessed based on the Cochrane Risk of Bias Tool (Fig. 1B). Potential biases in each study, including random sequence generation, allocation concealment, blinding implementation, and outcome assessment, were classified into low, high, or unclear risk categories. Studies with inadequate randomization or allocation concealment were rated as high risk for selection bias, those with missing information or unclear bias risk were rated as unclear, and studies meeting the criteria were rated as low risk. The results showed that most studies were rated low risk for random sequence generation, allocation concealment, blinding of participants and researchers, and blinding of outcome data indicating high quality in review design and implementation (Fig. 1B). Only studies with low risk of bias and those with unclear bias risk but still having potential research value were included in the final analysis to ensure the stability and reliability of the results.

Meta-analysis of TCM formulations on ABI improvement

This meta-analysis evaluated the impact of TCM formulations on ABI in patients with gangrene (Fig. 2). The results demonstrated a statistically significant difference in ABI between the experimental group (treated with TCM formulations) and the control group, with a mean difference (MD) of 0.17, a 95% CI of [0.11, 0.24], and a p-value of less than 0.01 (Fig. 2A). This indicates a significant advantage of TCM formulations in improving ABI. Furthermore, by improving hemodynamics, TCM treatment significantly enhanced the patients' quality of life, reducing activity limitations and other related treatment needs caused by the disease.

However, the heterogeneity test revealed high variability among the included studies ($I^2=90\%$), suggesting significant differences in the results, which could be attributed to variations in study design, TCM formulations, or patient baseline characteristics. Despite this, the majority of studies, including those by GuoPP (2023), ZhangQian1 (2014), and HuanN (2018), reported improvements in ABI with MD values ranging from 0.12 to 0.48, clearly reflecting their contributions to the overall effect and illustrating both the weight and consistency or variability of the results across the studies.

In the sensitivity analysis for the ABI, each study was individually excluded to assess its impact on the overall

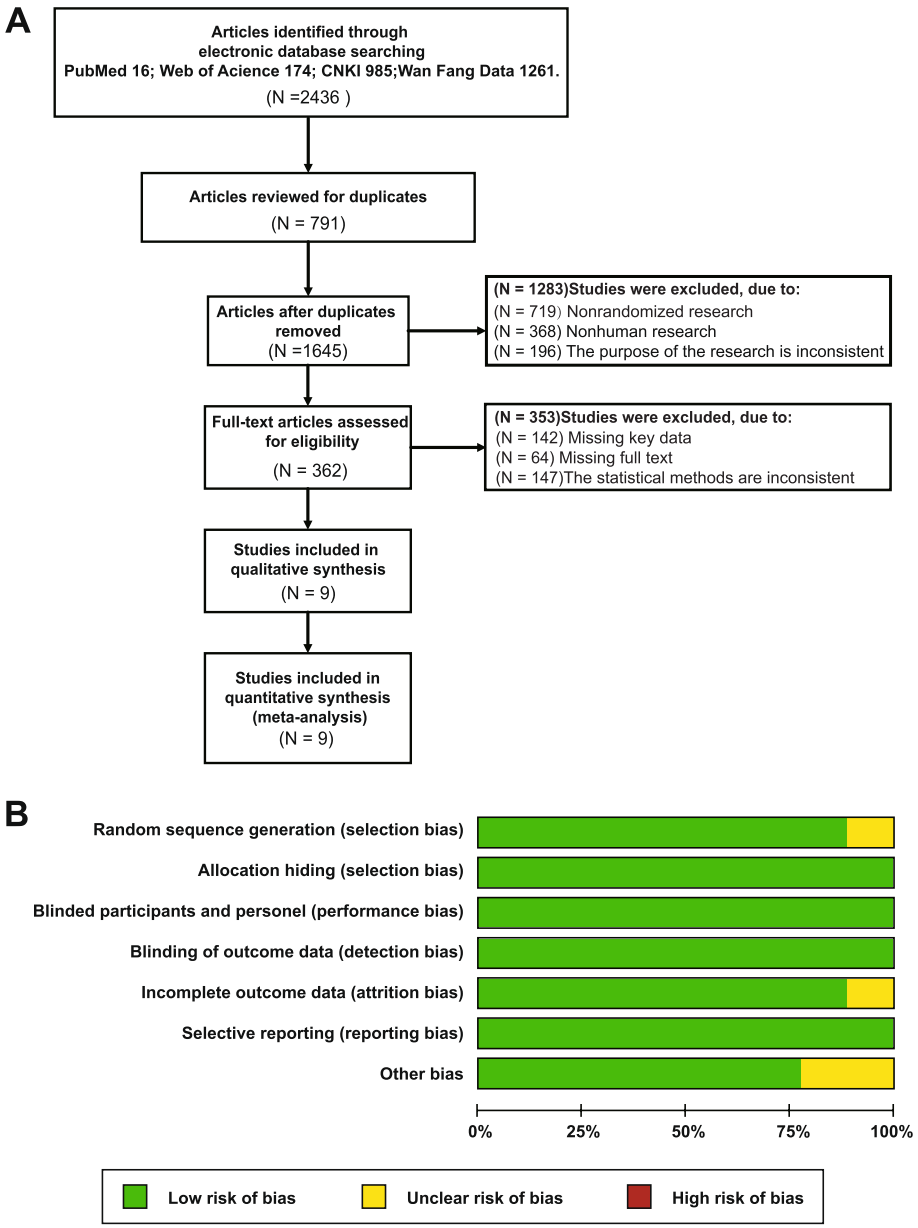

Fig. 1 Literature screening process and quality assessment results. **A** Flowchart of the literature inclusion process. **B** Summary of the risk of bias assessment for included studies. Green indicates low risk, yellow indicates unclear risk, and red indicates high risk. The biases assessed include random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome data (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases

effect size. The results indicated that excluding any single study did not lead to substantial changes in the MD or the 95% CIs, and the I^2 value remained high at 90% (Fig. 2B, Table 3). It demonstrates the high stability and reliability of the results. Further tests for publication bias involved visual inspection of funnel plots, where data points were generally symmetrically distributed, indicating no significant publication bias (Fig. 2C). This supports the credibility and robustness of the meta-analysis findings.

Meta-Analysis Shows TCM Formulations Significantly Extend Maximum Walking Distance

The meta-analysis also assessed the impact of TCM formulations on the maximum walking distance in patients with gangrene (Fig. 3). The results indicated a statistically significant difference in maximum walking distance between the experimental group (treated with TCM formulations) and the control group, with a MD of 293.22, a 95% CI of [174.85, 411.60], and a p-value less than

Table 1 Information about the literature that met the inclusion criteria

Authors	Review design	Year	Research topic
Guo Xian [20]	Randomized controlled trial	2023	Study on the clinical efficacy of using Yanghe decoction with fumigation method for pre-ulcer stage gangrene
Cui Haiyan [21]	Randomized controlled trial	2020	Clinical study on the treatment of stage I thromboangiitis obliterans with arterial no.1
Wei Dongdong [22]	Randomized controlled trial	2022	Effect of Chinese medicine fumigation combined with individualized pain management on patients with thromboangiitis obliterans
Zhang Qian [23]	Randomized controlled trial	2021	Clinical study of electroacupuncture at Jiaji points in the treatment of stage I thromboangiitis obliterans
Zhang Qi [24]	Randomized controlled trial	2021	Clinical study on modified Simiao Yong'an decoction combined with femoral artery perfusion in the treatment of stage I thromboangiitis obliterans (damp-heat downward flow type)
Huang Nan [25]	Randomized controlled trial	2018	Clinical observation on the treatment of thromboangiitis obliterans with Tongyang Huoxue decoction fumigation in 32 cases
Guo Panpan [26]	Randomized controlled trial	2023	Effect of modified Taohong Siwu decoction on hemodynamics and lower limb motor function in patients with early and middle-stage thromboangiitis obliterans
Huang Qian [27]	Randomized controlled trial	2021	Clinical observation on the efficacy of Simiao Tongmai decoction in treating thromboangiitis obliterans
Xun Xiaoyu [28]	Prospective intervention review	2021	Study on the mechanism of ginkgo leaf regulating thromboangiitis obliterans based on network pharmacology

Table 2 Baseline data of the literature that met the inclusion criteria

Authors	Sample size	Diagnosis	Treatment	Outcome
Guo Xian [20]	70	Pre-ulcer stage gangrene	Yanghe decoction with fumigation method	Significantly improve limb function in patients with pre-ulcer stage gangrene, significant efficacy
Cui Haiyan [21]	68	Stage I thromboangiitis obliterans (cold coagulation meridian type)	Arterial no.1 and Yanghe decoction	The overall clinical efficacy of the arterial no.1 group is better than that of the Yanghe decoction group
Wei Dongdong [22]	97	Thromboangiitis obliterans	Chinese medicine fumigation combined with individualized pain management	Significant improvement in ABI, reduction in inflammation and pain, improved clinical symptoms
Zhang Qian [23]	40	Stage I thromboangiitis obliterans	Electroacupuncture at Jiaji points	Improved overall symptoms, higher effective rate
Zhang Qi [24]	60	Stage I thromboangiitis obliterans (damp-heat downward flow type)	Modified Simiao Yong'an decoction combined with femoral artery perfusion	Effective in reducing symptoms and improving blood flow
Huang Nan [25]	64	Thromboangiitis obliterans	Tongyang Huoxue decoction fumigation	Significant improvement in ABI, reduction in inflammation and pain, improved clinical symptoms
Guo Panpan [26]	120	Early and middle-stage thromboangiitis obliterans	Modified Taohong Siwu decoction	Improved hemodynamics, reduced blood viscosity, enhanced lower limb motor function
Huang Qian [27]	50	Thromboangiitis obliterans	Simiao Tongmai decoction	Effective in reducing symptoms and improving blood flow
Xun Xiaoyu [28]	17	Thromboangiitis obliterans	Ginkgo leaf	Regulates related mechanisms and improves symptoms

0.01 (Fig. 3A). This suggests that TCM formulations significantly enhance patients' mobility, thereby improving their quality of life and potentially reducing the need for other assistive devices or treatments.

However, the heterogeneity test showed high variability among the included studies ($I^2 = 99\%$), indicating significant differences in effect sizes across studies, which may be influenced by factors such as review design, TCM formulations, or patient characteristics. Despite this heterogeneity, most studies still demonstrated improvements in maximum walking distance with TCM treatment, with MD values ranging from

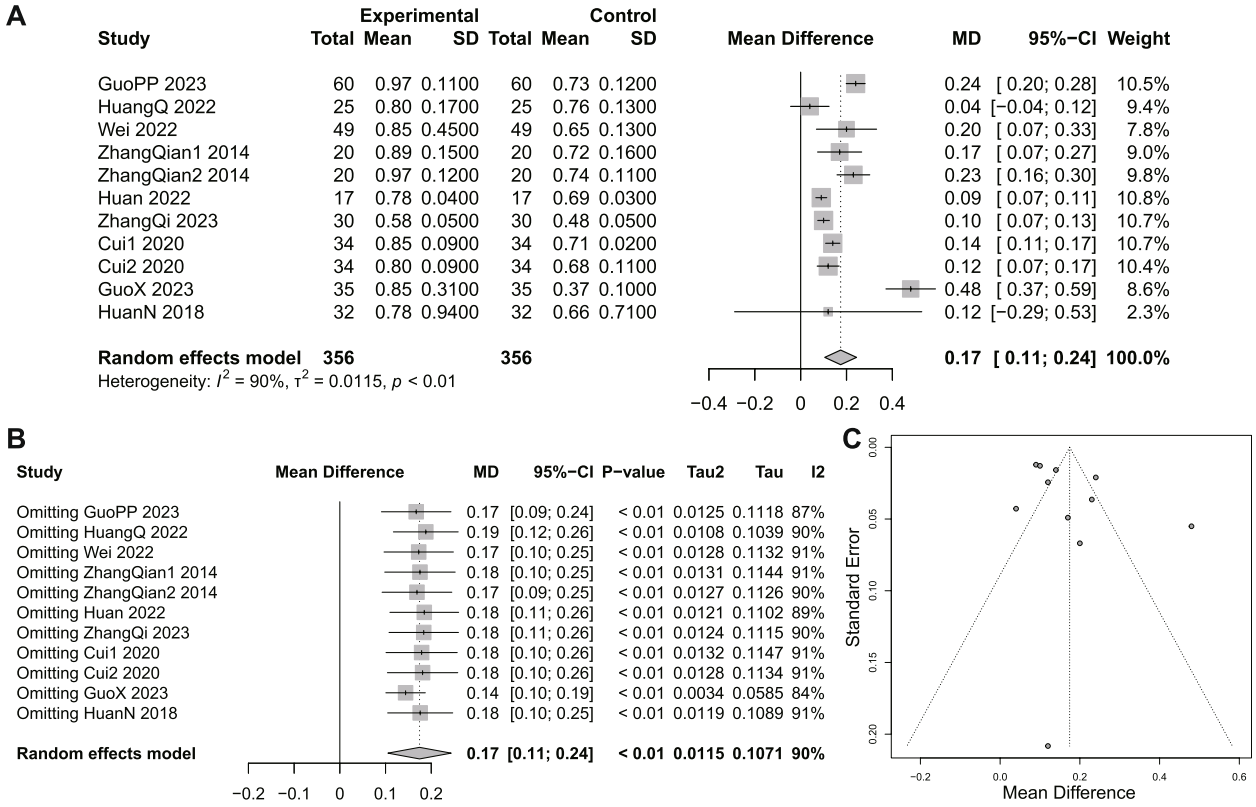

Fig. 2 Meta-analysis of the impact of TCM formulations on ABI in gangrene treatment. **A** Forest plot of the impact of TCM formulations ABI: This plot shows in results and weights in each study, with a pooled mean difference (MD (ot 0.17 and a 95% confidence interval (CI) of [0.11, 0.24], indicating high heterogeneity (I^2 = 90%)), which suggests significant variation between of study results. **B** Sensitivity analysis plot of TCM formulations on ABI in the treatment of gangrene: This plot evaluates the impact of each individual study on the overall effect size by sequentially excluding studies. **C** Funnel plot assessing the impact of TCM formulations on ABI in gangrene treatment. The symmetrical distribution of data points suggests a low risk of publication bias

Table 3 Sensitivity analysis of the influence of Chinese medicine on ankle-brachial index (ABI) in the diagnosis and treatment of gangrene

Deleted document	Pooled effect size of remaining literature (Pooled MD)	95% confidence intervals (CI) for the remaining literature
Guo PP 2023	0.18	[0.09; 0.24]
Huang Q 2022	0.19	[0.12; 0.26]
Wei 2022	0.17	[0.10; 0.25]
ZhangQian1 2014	0.18	[0.10; 0.25]
ZhangQian2 2014	0.17	[0.09; 0.25]
Huan 2022	0.18	[0.11; 0.26]
ZhangQi 2023	0.18	[0.1076; 0.26]
Cui1 2020	0.18	[0.10; 0.26]
Cui2 2020	0.18	[0.10; 0.26]
GuoX 2023	0.14	[0.10; 0.19]
HuanN 2018	0.18	[0.10; 0.25]

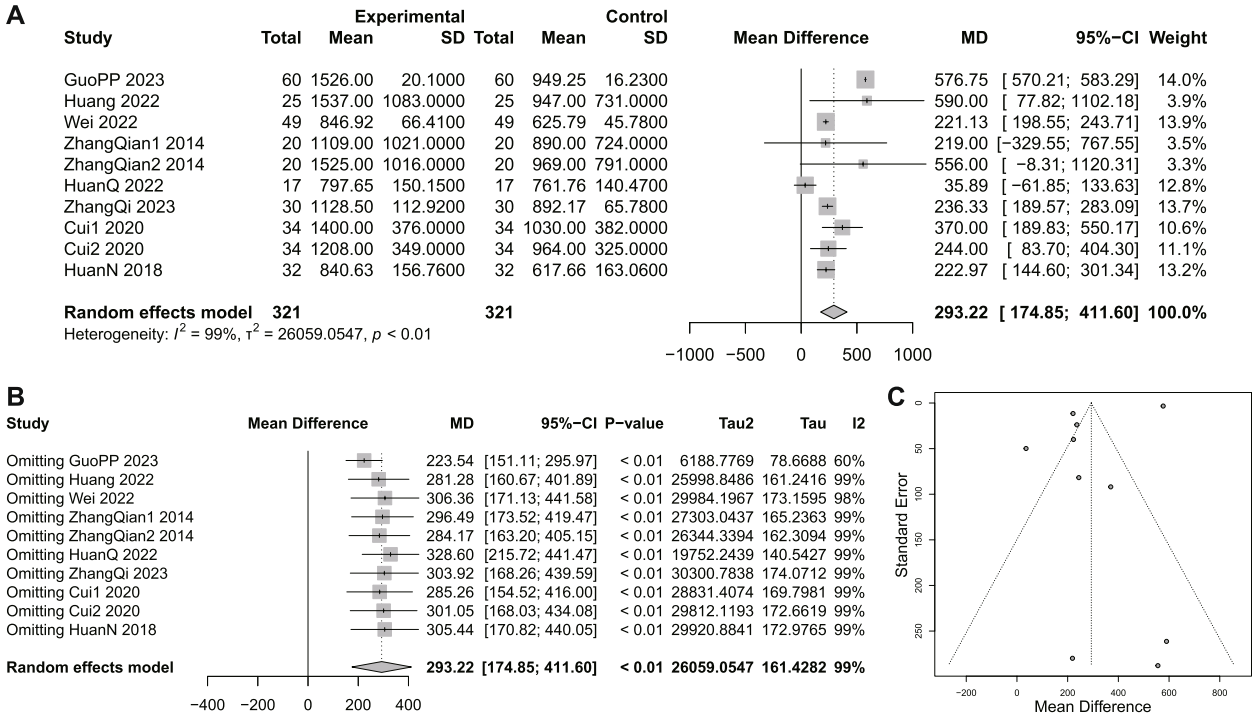

Fig. 3 Meta-analysis of the impact of TCM formulations on maximum walking distance in gangrene treatment. N:e: **A** Forest plot ng the impact of TCM formulations on maximum walking distance in the TCM treatment of gangrene: The pooled mean difference (MD) is 293.22, with a 95% confidence interval (CI) of [174.85, 411.60], and extremely high heterogeneity (I^2 = 99%). (Sensitivity analysis forest plot of TCM formulations on maximum walking distance in the TCM treatment of gang: **B** This plot evaluates the effect of each individual study on the overall effect size by sequentially excluding studies. **C** Funnel plot assessing the impact of TCM formulations on maximum walking distance in the TCM treatment of gangrene: The symmetrical distribution of data points indicates no significant publication bias

221.13 to 590.00 in studies such as GuoPP 2023, Huang 2022, and Cui1 2020.

In the sensitivity analysis for maximum walking distance, we individually excluded each study to assess its impact on the overall effect size. The results showed that excluding any single study did not lead to substantive changes in the pooled MD or the 95% CI, with the I^2 value consistently remaining at 99% (Fig. 3B, Table 4). This indicates a high level of stability and reliability in the results. The test for publication bias, illustrated through

Table 4 Sensitivity analysis of the influence of Chinese medicine prescription on the maximum walking distance in the diagnosis and treatment of gangrene

Deleted document	Pooled effect size of remaining literature (Pooled MD)	95% confidence intervals (CI) for the remaining literature
GuoPP 2023	223.54	[151.11; 295.97]
HuangQ 2022	281.28	[160.67; 401.89]
Wei 2022	306.36	[171.13; 441.58]
ZhangQian1 2014	296.49	[173.52; 419.47]
ZhangQian2 2014	284.17	[163.20; 405.15]
Huan 2022	328.60	[215.72; 441.47]
ZhangQi 2023	303.92	[168.26; 439.59]
Cui1 2020	285.26	[154.52; 416.00]
Cui2 2020	301.05	[168.03; 434.08]
GuoX 2023	305.44	[170.82; 440.05]

funnel plots, revealed a generally symmetrical distribution of data points, suggesting an absence of significant publication bias (Fig. 3C). This further supports the credibility and robustness of the meta-analysis findings.

In this meta-analysis, the sensitivity analysis involved systematically excluding each study to evaluate the influence of individual articles on the overall effect size. This method allowed us to examine the impact on the overall meta-analysis results when a particular study was removed. We focused on whether a specific study's removal caused significant changes in the pooled MD and the corresponding 95% CI. A significant change upon removal would indicate that the study had a substantial influence, potentially identifying it as a sensitivity study.

Sources of Heterogeneity and Subgroup Analysis of Different TCM Interventions for Gangrene

This study conducted subgroup analyses to evaluate the effects of different TCM interventions on the ankle-brachial index (ABI) and maximum walking distance in patients with gangrene, and explored potential sources of heterogeneity (Fig. 4). Results showed significant differences among subgroups (ABI heterogeneity test: $\chi^2 = 28.61$, $p < 0.0001$), indicating that intervention type is a major source of heterogeneity.

In terms of ABI improvement (Fig. 4A), high heterogeneity was observed in TCM compound formulas ($I^2 = 66.9\%$) and integrated TCM-Western interventions ($I^2 = 53.6\%$), likely due to variations in herbal combinations (e.g., formulas for activating blood vs. warming yang) and lack of standardization in Western adjunct therapies (e.g., femoral artery perfusion, pain management). In contrast, acupuncture showed high consistency ($I^2 = 0\%$), possibly attributed to standardized procedures such as electroacupuncture at Jiaji points. The TCM fumigation subgroup showed moderate heterogeneity ($I^2 = 64.2\%$) due to variability in duration and drug concentration.

For maximum walking distance (Fig. 4B), the integrated TCM-Western subgroup demonstrated stable effects ($I^2 = 0\%$), while the TCM compound subgroup exhibited substantial heterogeneity ($I^2 = 80.2\%$), possibly linked to differences in treatment duration (4–12 weeks) and patient characteristics (e.g., disease stage). In the single-herb subgroup, the study by Huang et al. (2022) had a small sample size ($n = 25$) and wide confidence interval (CI: 77.82–1102.18), with a weight of only 3.9%, suggesting that small trials may overestimate effect sizes and increase heterogeneity. Additionally, some studies lacked clear TCM syndrome differentiation (e.g., cold-induced blood stasis vs. damp-heat patterns), potentially contributing to outcome bias and further heterogeneity. Overall, TCM compound formulas and integrated interventions show clinical potential in improving ABI and walking capacity. However, high heterogeneity highlights the need for standardized herbal formulations, consistent use of adjunctive Western therapies, and clearer reporting of syndrome differentiation. While acupuncture demonstrated consistent effects, the limited sample size and wide confidence intervals (e.g., MD = 382.73, 95% CI [−10.61, 776.06]) underscore the need for larger RCTs.

Discussion

Interpretation and pathogenesis of Jueyin disease

Jueyin disease, as discussed in the "Treatise on Cold Pathogenic Diseases," is one of the most debated sections due to its concise yet profound text. Lu Yuanlei once called it "an eternal conundrum," suggesting that

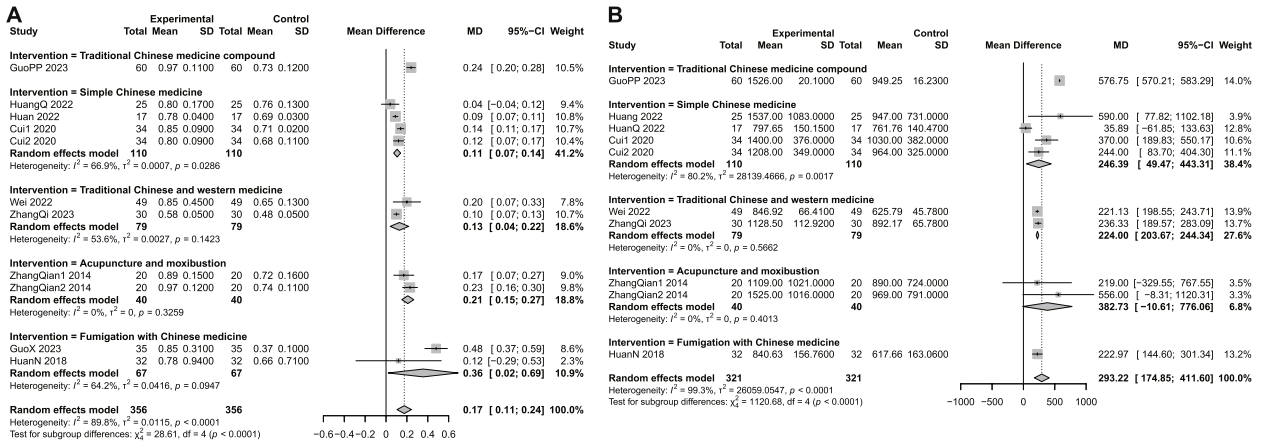

Fig. 4 Subgroup analysis of the effects of Chinese herbal formulas on maximum walking distance in patients with gangrene. Note: **A** Subgroup analysis of the effects of Chinese herbal formulas on ankle-brachial index (ABI) in gangrene. **B** Subgroup analysis of the effects of Chinese herbal formulas on maximum walking distance in gangrene

Jueyin disease might merely be a component of Shaoyin and Taiyin diseases [29]. However, a thorough analysis of the text and its correlation with clinical practice have validated the relevance of the Jueyin disease chapter, proving it indispensable for guiding differential diagnosis and treatment in TCM. The essence of Jueyin disease lies in the alternation of Yin and Yang and the intermingling of cold and heat, making the condition complex and variable. This disease involves multiple meridians, presenting both cold and heat symptoms, with the progression dependent on restoring Yang Qi within the body [30]. Jueyin disease primarily affects the lower part of the body and is closely related to the liver and gallbladder, often manifesting symptoms such as icy extremities, vomiting, and diarrhea.

According to the characteristics of Jueyin disease, its pathological mechanisms can be categorized into three types (Fig. 5). The first type is characterized by the "upper body heat and lower body cold" phenomenon. Ancient texts describe this condition as heat in the upper body and cold in the lower body, disrupting the Yin-Yang balance within the body [31]. After the pathogen enters the Jueyin meridian, the heat pathogen ascends, causing symptoms such as thirst and chest pain, while the lower body experiences coldness and diarrhea due to the heat pathogen obstructing the normal flow of Qi and blood [32]. The core issue here involves disrupting Yin and Yang Qi flow within the body [33].

The second pathological mechanism is "accumulation of toxic heat," where heat directly invades the Jueyin, leading to inflammation in the lower abdomen. In this scenario, liver heat forces the toxic heat downward, affecting colon function and causing symptoms like diarrhea. Due to the intense activity of the liver, the heat quickly causes Qi stagnation and toxin accumulation [29].

The third type is "blood deficiency and cold coagulation," characterized by poor blood circulation that leads to icy limbs. This condition typically occurs in individuals with weak constitutions, particularly when Yang Qi is deficient, allowing pathogenic factors to further impair blood circulation. The main symptoms include icy extremities and a preference for warmth while exhibiting a fear of cold.

Jueyin disease is the final stage of illness described in the "Treatise on Cold Pathogenic Diseases," its pathological features reflect the essence of the six meridian diseases. However, the critical texts on Jueyin disease struggle to fully encapsulate their intricate pathological mechanisms, which explain the diversity of interpretations among scholars through the ages. Jueyin disease involves multiple meridian systems, including the liver and pericardium, and its pathology is both complex and varied [34].

Overview and classification of syndromes in gangrene

Gangrene has been documented since ancient times, with the earliest references dating back to the Spring and Autumn and Warring States periods in the "Ling Shu·Ying Ju," which describes a condition starting in the toes, referred to as "detached sore." It states, "It begins in the toes, called detached sore, appears red–black, death is inevitable if untreated, if not red–black, it does not lead to death, cut it off promptly, or else death ensues." The term "gangrene" was officially introduced during the late Jin Dynasty in "Liu Juanzi Gui Yi Fang·Ju Lun," describing the primary characteristics of the disease as starting in the toes with a reddish-black color and noting that, if not

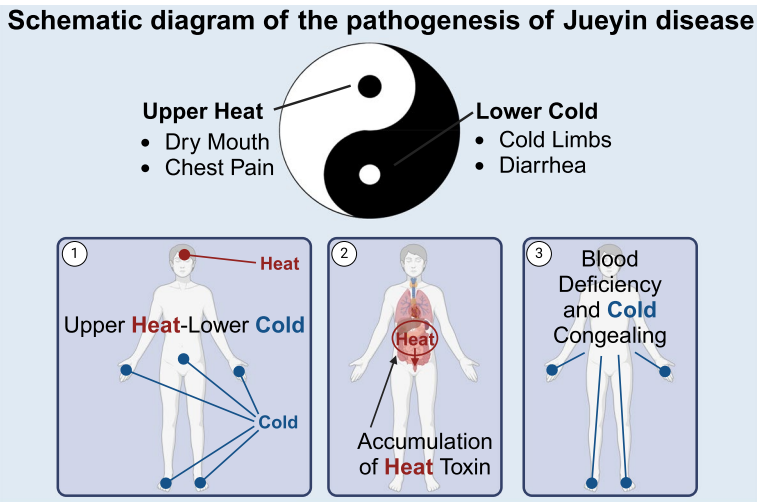

Fig. 5 Schematic diagram of the pathogenesis of Jueyin disease

managed promptly in severe cases, it could be fatal [35]. The fundamental pathological mechanism of gangrene involves impaired blood circulation, and its etiology is complex, potentially caused by a combination of factors, including constitutional weakness, robustness, cold, and heat. This complexity makes the disease relatively easy to diagnose but challenging to treat.

Gangrene, according to its causes and pathological mechanisms, can be divided into several types, as illustrated in Fig. 6. The first type is damp-heat gangrene [36], which is often caused by poor dietary habits, such as excessive consumption of high-fat foods, leading to the accumulation of internal damp heat. This damp heat attacks the blood vessels, impairing blood circulation and causing local inflammation and tissue damage. Symptoms commonly include limb pain, particularly intensifying at night, accompanied by swelling and dark purple skin.

The second type is cold coagulation gangrene, which is more prevalent in individuals with deficient Yang Qi. This makes them susceptible to cold pathogenic invasion that obstructs blood circulation. The cold causes the blood to thicken and flow poorly within the vessels, ultimately leading to symptoms such as pain, icy limbs, and pale skin.

The last type is upper body heat and lower body cold gangrene [37, 38], which can occur independently or as a complication of diabetes. The pathological mechanism involves an imbalance of Yin and Yang within the body, with dry heat in the upper and cold in the lower parts. Patients typically exhibit symptoms such as dry mouth, thirst, coldness in the lower limbs, and pain.

TCM posits that long-term illness often leads to impaired blood circulation and general physical debility. Gangrene is one of the late-stage complications of diabetes. It is frequently associated with internal weakness, typically manifested as yin, qi, and blood deficiencies. The condition is often triggered by internal heat, blood stasis, and toxins[39]. This scenario is commonly called a "mixture of deficiency and excess," where internal weakness coexists with substantive external problems.

The pathological mechanism of gangrene in TCM primarily includes both qi and blood deficiency, obstructed blood circulation, accumulation of damp-heat toxins, and heat toxins damaging the body fluids. The use of several herbal components in Si Miao Yong An Tang, such as honeysuckle (Jin Yin Hua), Scrophularia (Xuan Shen), Dong Quai (Dang Gui), and licorice (Gan Cao), collaboratively work to clear heat, detoxify, activate blood circulation, and alleviate pain. Modern pharmacological studies have found that these ingredients possess anti-inflammatory, antioxidant, and antiviral properties [40].

Topical TCM exhibits unique advantages in treating chronic skin ulcers [41]. These medications act directly on the lesion sites through differentiated treatment stages, accelerating wound growth and healing. Ruyi Jinhua San has shown significant therapeutic effects in treating damp-heat type diabetic foot. Studies indicate that patients treated with Ruyi Jinhua San experience better symptom improvement, control of blood sugar, and overall effectiveness than the control group, without significant side effects.

In TCM, ischemic lower limb diseases are considered a manifestation of gangrene, commonly resulting from blood vessel obstruction due to insufficient Yang Qi. Professor Li Jun advocates for using a "warming Yang and promoting circulation" method with hot compresses, which, by warming the spleen and kidneys and unblocking blood vessels, effectively improves blood circulation and significantly enhances quality of life. Zhang Keren

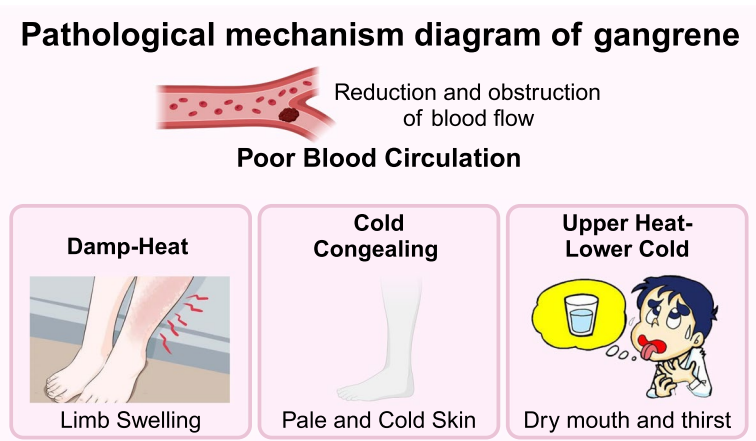

Fig. 6 Pathological mechanism diagram of gangrene

suggests that the occurrence of diabetic foot is closely related to the dysfunction of the five organs. Therefore, treatment should start with the liver, heart, spleen, lungs, and kidneys, aiming to regulate the function of these organs comprehensively for therapeutic effects [42].

Compatibility of Jueyin disease theory with gangrene treatment

Since ancient times, TCM has utilized Jueyin disease theory to treat gangrene, frequently employing Dang-Gui-Si-Ni decoction as the treatment of choice. TCM surgical expert Ai Rudi has achieved significant clinical success in treating gangrene by adjusting the formula of Dang-Gui-Si-Ni decoction [43]. Similarly, Huang Genhua treated 30 patients with cold coagulation and blood stasis type gangrene using Dang-Gui-Si-Ni decoction, and after 1–3 treatment courses, all patients experienced significant pain relief, with an overall effectiveness rate of 100% [44]. However, while these treatment experiences effectively combine Jueyin disease theory with gangrene management, they primarily focus on symptom relief and do not deeply explore the profound compatibility of the two in terms of pathological mechanisms.

From the perspective of pathological mechanisms, Jueyin Disease and gangrene exhibit a high degree of consistency in many aspects, involving the complex interplay of cold and heat, the deficiency and excess of Yin and Yang energies, and damage to Qi and blood (Fig. 7). Jueyin disease typically involves lesions in the lower abdomen, while the primary focus of gangrene is in the liver, with potential long-term impacts on spleen and kidney functions, aligning with the locational attributes of Jueyin disease. Both conditions also share clinical manifestations, such as icy extremities. The "Yi Zong Jin Jian" (Golden Mirror of the Medical Tradition) notes, "In Jueyin Disease, regardless of cold or heat, the limbs will feel icy." It highlights that alternating symptoms of cold and heat are common in both Jueyin Disease and gangrene, with the disease progression typically moving from external to internal, from the surface to the core.

Although the primary pathological mechanism of gangrene is impaired blood circulation, the "Huangdi Neijing" emphasizes that "to treat disease, one must seek the root cause" [45], meaning that treatment should fundamentally restore the balance of Yin and Yang within the body. The occurrence of gangrene is closely related to internal imbalances of Yin and Yang, alternating cold and heat, and the accumulation of phlegm dampness and blood stasis. Therefore, treatment requires not only the activation of blood circulation and the resolution of stasis but also the regulation of the internal balance between cold and heat. By clearing heat from the upper body, warming cold in the lower body, and simultaneously promoting blood circulation and unblocking meridians, the underlying pathogenic factors can be effectively eliminated, leading to significant therapeutic outcomes.

In summary, applying Jueyin disease theory not only aligns deeply with the pathological mechanisms of gangrene but also offers a more comprehensive and practical treatment approach, improving clinical symptoms and enhancing patients' quality of life.

Analysis of the correlation between Jueyin disease formulas and gangrene treatment

In recent years, applying Jueyin disease formulas to treat gangrene has garnered significant attention, particularly with formulations like Wumei pill, Pulsatilla decoction, and Dang-Gui-Si-Ni decoction. These formulas have demonstrated remarkable therapeutic effects in clinical practice and provided modern medicine with new approaches and insights.

Wumei pill, originally from the Jueyin disease section of the "Treatise on Cold Pathogenic Diseases," is specifically used to treat conditions of alternating cold and heat, characterized by upper body heat and lower body cold. The pill addresses a complex state of mixed deficiency

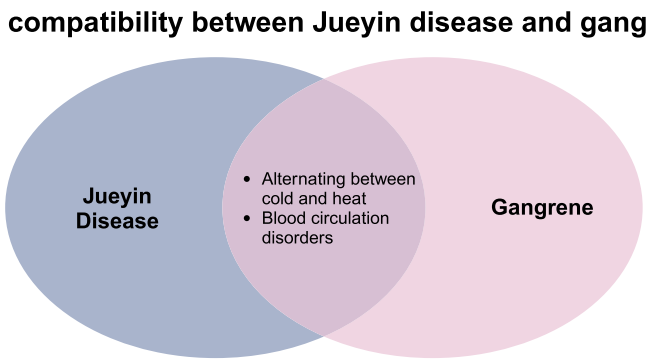

Fig. 7 The compatibility between Jueyin disease and gangrene

and excess, with a predominance of cold over heat and deficiency over excess, which aligns with the pathogenesis of Jueyin disease [30]. Modern pharmacological research has shown that the Wumei pill is also effective in treating diabetic gastroparesis and gastroesophageal reflux disease [46]. Liu Xiaorui and colleagues further explored the application of the Wumei pill in treating diabetic macrovascular complications by linking its pathogenesis with that of diabetes-induced extensive vessel disease [47]. The ingredients of Wumei pill, including Coptis and Phellodendron to clear heat and consolidate Yin, Asarum, and Aconite to warm the cold in the lower burner, Cinnamon Twig to promote the flow of Yang Qi, Ginseng to tonify Qi, and Angelica to nourish blood and harmonize the Ying Qi, work synergistically to achieve a balanced effect of clearing heat above and warming cold below. This complex state of mixed cold and heat, deficiency, and excess is characteristic of Jueyin Disease.

Pulsatilla decoction is primarily indicated for Jueyin syndrome, characterized by heat toxin-induced diarrhea, particularly suitable for conditions where liver heat descends into the large intestine, leading to obstruction by damp heat and turbid toxins. Chen Weili's research highlights the significant efficacy of Pulsatilla decoction in treating syndromes involving the interconnection of liver fire, damp-toxin, and Qi stagnation [48]. The formula's ingredients—Pulsatilla and Cortex Fraxini—are bitter and cold, clearing heat toxins and cooling the blood, while Coptis and Phellodendron clear damp heat from the lower burner by consolidating Yin—the synergistic effect of these four herbs results in a potent treatment for heat toxin-induced diarrhea. However, due to the formula's bitter and cold nature, it is essential to cease its use once the desired therapeutic effect is achieved to avoid cold stagnation in the blood vessels and depletion of vital Qi.

Dang-Gui-Si-Ni decoction, derived from Gui Zhi Tang, is modified with Asarum, Rice Paper Plant Pith, and Dong Quai while omitting Fresh Ginger and Prepared Aconite. It is particularly suited for conditions of blood deficiency leading to cold convulsions. This formula nourishes the blood, disperses cold, and warms the meridians, making it especially effective in treating cold-induced blood stasis gangrene. Research by Li Wenwen, Liu Zhe, and Fang Yudong has demonstrated that Dang-Gui-Si-Ni decoction significantly improves the lipid profiles of gangrene patients, prevents the formation of atherosclerotic plaques, reduces the risk of postoperative restenosis, and exhibits marked efficacy in pain management [49]. By nourishing the blood, dispersing cold, and warming the meridians, this formula harmonizes Qi and blood, unblocks the meridians, and significantly improves clinical symptoms in patients.

The application of Dang-Gui-Si-Ni decoction in the treatment of gangrene has become well-established. Research by Li Wenwen, Liu Zhe, and Fang Yudong has shown that Dang-Gui-Si-Ni decoction significantly improves the lipid profiles of gangrene patients, prevents the formation of atherosclerotic plaques, and reduces the risk of restenosis following vascular interventions. Additionally, the formula has demonstrated remarkable efficacy in pain management for these patients [49].

Based on the "Jueyin Latent Pathogen" theory, Jiawei Lianli decoction has significantly inhibited the proliferation and invasion of liver cancer cells and promoted apoptosis. The research revealed that this decoction exerts its anti-angiogenic effects by regulating the DEPTOR protein and the PDCD4/e-Jun (AP-1) signaling axis [50]. Wu Zhu Yu decoction has shown high clinical efficacy and safety in treating Jueyin-type headaches. By warming the stomach, dispersing cold, and harmonizing the stomach to counteract reversal, Wu Zhu Yu decoction effectively alleviated clinical symptoms and improved the quality of life for patients [51].

Modern pharmacological studies have shown that TCM extracts and their active components possess unique chemical structures and precise therapeutic effects. These compounds promote internal balance through multiple pathways and targets, offering personalized treatment options at different stages of sepsis [52]. Professor Zhu Jiangu believes that the primary pathological mechanism of diabetic foot stems from Qi and Yin deficiencies, which, over time, lead to a decline in Yang Qi and impaired blood circulation. The combination of cold-induced blood stasis and damp heat is the leading cause of local vascular obstruction and tissue necrosis. Treatment should focus on warming the body and promoting blood circulation [38]. Research indicates that topical application of licorice oil significantly improves wound healing after skin grafting in diabetic foot patients by effectively reducing inflammatory factors and promoting wound repair [53].

Professor Zhang Chunyu has pointed out that elderly individuals, due to insufficient Yang Qi and poor blood circulation, are particularly susceptible to cold stimuli, which can lead to gangrene. Therefore, methods that warm and tonify Yang Qi while promoting blood circulation effectively treat gangrene in the elderly [54]. The "warming meridians and tonifying Yang" method has also shown significant efficacy in treating thromboangiitis obliterans, improving patients' quality of life by warming and nourishing the spleen and kidneys and unblocking blood vessels [55]. Professor Liu Guobin emphasized that the primary pathological mechanism of thromboangiitis obliterans is cold-induced meridian obstruction and impaired blood circulation. Treatment should prioritize warming the meridians and

promoting blood circulation, which has yielded favorable clinical outcomes [10]. These research findings not only enrich the modern application of traditional formulas but also lay a foundation for further exploration of the potential of TCM in modern medical practices.

This review conducted a systematic meta-analysis and comprehensive systematic review to deeply explore the application value of Jueyin disease theory in the TCM treatment of gangrene. The results demonstrated a high degree of compatibility between the pathogenesis of Jueyin disease and gangrene, with both conditions characterized by a complex interplay of cold and heat, deficiency and excess, and disruptions in Yin, Yang, Qi, and blood. By applying theories such as upper body heat and lower body cold, toxic heat accumulation, and blood deficiency leading to cold convulsions from Jueyin Disease, and utilizing formulas like Wumei pill, Pulsatilla decoction, and Dang-Gui-Si-Ni decoction, significant improvements were observed in the clinical symptoms of gangrene patients. These treatments effectively enhanced blood circulation and promoted the regression of local lesions, achieving favorable clinical outcomes.

The meta-analysis further confirmed the significant advantages of TCM formulations in improving the ABI and maximum walking distance, indicating their clinical efficacy and safety in the treatment of gangrene. Sensitivity analysis and publication bias tests showed that the results were highly stable. However, some heterogeneity was observed across the studies, which may be attributed to differences in TCM formulations, diversity in patient populations, and inconsistencies in treatment protocols. Factors such as variations in herbal ingredients, disease progression, and treatment duration may also have influenced the therapeutic effects. Nevertheless, TCM formulations still demonstrate significant benefits. Future research should focus on standardizing formulations, improving patient selection, and ensuring consistency in treatment protocols to enhance the reproducibility of studies and the generalizability of clinical applications, thereby ensuring broader applicability and practical value. Overall, despite the heterogeneity, the review consistently shows that TCM formulations significantly improve clinical symptoms in patients with gangrene.

However, gangrene remains a severe condition within the realm of TCM surgery, characterized by severe clinical symptoms and low quality of life for patients, with treatment often focusing on symptom relief. As lifestyle changes and population aging continue to increase the incidence of this disease, the need to develop new diagnostic and therapeutic frameworks becomes increasingly urgent. Despite being over 2000 years old, Jueyin disease theory remains relevant, offering fresh perspectives and methods for the modern TCM treatment of gangrene.

While Jueyin disease and gangrene share similarities, it is essential to note that they also exhibit distinct characteristics. Jueyin disease may involve transitions to Shaoyang conditions or stagnation of Yang Qi, whereas gangrene is primarily concerned with blood stasis and vascular obstruction. Therefore, when applying the theory of Jueyin disease to the treatment of gangrene, it is essential to both explore the connections and acknowledge the differences between the two. Moreover, the application of Jueyin disease theory is not limited to gangrene. Its potential in managing chronic conditions such as hypertension, diabetes, and cardiovascular diseases is gradually emerging. With its holistic view of cold-heat, deficiency-excess, and the principles of balancing Yin, Yang, Qi, and blood, Jueyin disease theory offers new insights for TCM treatment of these conditions, particularly in regulating blood circulation, improving microcirculation, and exerting anti-inflammatory effects. When combined with modern medical treatments, Jueyin disease theory can provide patients a more comprehensive therapeutic approach.

In the future, integrating Jueyin disease theory with modern medicine, especially in the interdisciplinary research fields of molecular biology, pharmacology, and immunology, will be key to improving treatment outcomes. Through interdisciplinary collaboration, Jueyin disease theory is expected to become an important foundation for integrated TCM and Western medicine, promoting the development of personalized treatment and improving therapeutic effects for chronic disease patients. Particularly in the combined treatment of gangrene and other related conditions, further research and the establishment of standardized treatment protocols will be necessary to ensure uniformity and individualization in treatment. Future studies should focus on combining Jueyin disease theory with modern Western medicine's personalized treatment approaches, developing individualized treatment plans based on patients' pathological characteristics and genetic profiles to enhance efficacy and reduce adverse reactions.

However, current integrated TCM and Western medicine treatment plans still exhibit differences, and the specific treatment pathways have not yet been unified. Future research should address issues in clinical implementation, such as drug interactions, inconsistent efficacy evaluation standards, and patient compliance. Therefore, large-scale, multi-center clinical trials are essential to assess different treatment regimens' efficacy, safety, and potential in improving therapeutic outcomes, reducing side effects, and enhancing patients' quality of life. Advancing these research directions will enable the integrated TCM and Western medicine treatment model to provide more personalized and comprehensive treatment options, promoting its widespread clinical application.

This study systematically evaluated the application of Jueyin disease theory in the traditional Chinese medicine (TCM) treatment of gangrene, combining a comprehensive literature review with meta-analysis to provide both scientific validity and clinical relevance. Strengths include a broad inclusion of studies, standardized methodology, and the use of the Cochrane Risk of Bias tool and PRISMA framework, which enhanced the transparency and reliability of the results. Sensitivity analyses and assessments for publication bias further confirmed the robustness of the findings. However, several limitations should be noted. Most included studies had relatively small sample sizes and were single-center in design, limiting the generalizability of the conclusions. There was considerable heterogeneity across studies in terms of herbal formulations, treatment duration, and outcome measures. Additionally, the predominance of Chinese-language publications may introduce regional and language bias. Some studies also failed to report the relationship between TCM syndrome differentiation and clinical efficacy, potentially masking significant benefits in specific subgroups (e.g., "cold coagulation and blood stasis type"). Future research should adopt "disease-syndrome combination" models, integrating modern techniques such as metabolomics to explore the link between pathophysiological mechanisms (e.g., "upper heat and lower cold") and local disease microenvironments (e.g., inflammatory cytokine levels) to guide precise herbal interventions. Moreover, multi-center, standardized clinical trials comparing Jueyin-based formulas with classical approaches such as Xuefu Zhuyu decoction are needed to further clarify their unique therapeutic advantages.

Conclusion

In summary, through systematic literature review and rigorous meta-analysis, we have demonstrated the significant clinical efficacy of TCM formulations guided by Jueyin disease theory in treating gangrene. This study provides scientific support for applying Jueyin disease theory in modern TCM and offers valuable insights for future research and clinical practice. As research and practice continue to advance, Jueyin disease theory is expected to play an increasingly important role in the TCM treatment of gangrene and other related conditions, offering more significant benefits to patients.

Abbreviations

ABI	Ankle-brachial index
CI	Confidence interval
MD	Mean differences
TCM	Traditional Chinese medicine

Supplementary Information

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Supplementary Material 1.

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None.

Authors' contributions

Youzhi Zhang: Conceptualization, methodology, and investigation; conducted data extraction and quality assessment; contributed to the drafting and revision of the manuscript. Bochuan Lv: Supervision and project administration; contributed to study design and critical review of the manuscript; corresponded with editors and reviewers. Yue Teng: Formal analysis and statistical evaluation; contributed to data interpretation and visualization; assisted with manuscript drafting. Jintao Xu: Literature search and resources management; participated in the writing and proofreading of the manuscript; provided technical and theoretical expertise in Jueyin disease theory. All authors have read and approved the final manuscript.

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Data availability

The data that support the findings of the study are available from the corresponding author upon reasonable request. In accordance with the FAIR data principles, the data will be made findable, accessible, interoperable, and reusable for researchers, subject to ethical and privacy considerations.

Declarations

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Competing interests

The authors declare no competing interests.

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