

Integrated evidence chain (Eff-iEC) based effectiveness evaluation of a multifunctional traditional Chinese medicine formula: Taking Xiaoyao San as an example

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Abstract

The study focuses on the concept of multifunctional traditional Chinese medicine (TCM) formulas and aims to evaluate the efficacy of the classical formula Xiaoyao San (逍遥散). Study employs the integrated evidence chain (Eff-iEC) method to organize, integrate, and evaluate its therapeutic efficacy in treating different diseases with the same therapy, and to investigate the feasibility of using Eff-iEC to evaluate the multifunctionality of TCM formulas. The evaluation covered Xiaoyao San's therapeutic effects on depression, premenstrual syndrome, chronic hepatitis, irritable bowel syndrome, dyspepsia, and menopausal syndrome. Concurrently, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system was used for evaluation, and authoritative medical documents were incorporated to corroborate the recognition of Xiaoyao San within the medical community. Depression and menopausal syndrome received higher ratings than other conditions in the Eff-iEC, GRADE, and Medical Community Recognition assessments. The Eff-iEC evidence grade for Xiaoyao San was rated as "High" or above for chronic hepatitis, irritable bowel syndrome, dyspepsia, and menopausal syndrome. Premenstrual syndrome received a "Moderate+" rating. The GRADE evidence level was "Low-○○⊕⊕" for depression, premenstrual syndrome, and chronic hepatitis; "Moderate-○○⊕⊕" for dyspepsia and menopausal syndrome; and "Very Low-○○○⊕" for irritable bowel syndrome. Depression and menopausal syndrome had the highest inclusion frequency, appearing in all 4 categories. Premenstrual syndrome, chronic hepatitis, and dyspepsia are not recommended in Western medical guidelines, but they are included in TCM guidelines, the China National Basic Medical Insurance Drug List, and the China National Essential Drug List. Irritable bowel syndrome appears only in the China National Basic Medical Insurance Drug List and China National Essential Drug List. The evaluation results obtained using the Eff-iEC method align with Medical Community Recognition, providing an objective and comprehensive assessment of Xiaoyao San's efficacy. The findings suggest that Xiaoyao San has strong evidence for treating depression and menopausal syndrome. However, further experimental and clinical trials are needed to assess its efficacy in treating premenstrual syndrome, chronic hepatitis, irritable bowel syndrome, and dyspepsia. These results support the clinical efficacy and rational use of Xiaoyao San, expand the application scope of the Eff-iEC method, and offer valuable insights and methodological references for the comparative evaluation of multifunctional TCM formulas.

Key words: GRADE; Integrated evidence chain; TCM effectiveness evaluation; Xiaoyao San

1. Introduction

In the context of globalization, traditional Chinese medicine (TCM) has entered an era of unprecedented development opportunities. As the international community increasingly

recognizes the value of traditional medicine, the influence of TCM continues to expand. With its characteristics of "multiple components, multiple targets, and multiple functions," TCM offers a more holistic regulatory advantage compared with chemical drugs, which typically consist of single

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components and functions, for treating complex diseases (also known as the principle of treating different diseases with the same therapy). This principle is a key strength of TCM. However, the absence of high-quality evidence-based medical support has made it difficult for TCM's efficacy to gain widespread recognition. Some have misinterpreted the advantage of treating different diseases with the same formula in TCM as a "cure-all."

The root of this issue lies in the systemic incompatibility between the current randomized controlled trial (RCT) evaluation framework and the unique characteristics of TCM diagnosis and treatment. This contradiction has been previously discussed^[1] and addressed through the development of the integrated evidence chain (Eff-iEC) methodology. However, no evaluations have yet specifically addressed the TCM principle of treating different diseases with the same method.

This study aims to assess the efficacy of the classical TCM formula, Xiaoyao San (逍遥散), using the Eff-iEC method and to investigate the feasibility of using Eff-iEC to evaluate the multiple effects of TCM. Xiaoyao San consists of 8 Chinese herbal medicines, including Bupleuri Radix, Angelicae Sinensis Radix, Paeoniae Radix Alba, Atractylodis Rhizoma, Poria, Glycyrrhizae Radix et Rhizoma Praeparata cum Melle, Menthae Haplocalycis Herba, and Zingiberis Rhizoma Recens. It was first recorded in the official medical text *Formulary of the Bureau of Taiping People's Welfare Pharmacy* (*Taiping Huimin Heji Bureau*, 太平惠民和剂局方). According to the text, Xiaoyao San is used to treat blood deficiency and relieve liver depression. In clinical practice, Xiaoyao San is widely used across various fields, including the treatment of neurological disorders,^[2] gynecological disorders,^[3] internal medicine disorders,^[4] and digestive system disorders.^[5] It is most frequently used to treat depression, breast hyperplasia, irritable bowel syndrome, chronic hepatitis B, and functional dyspepsia.^[6] However, it remains unclear which diseases have high-quality evidence supporting its use and which still lack such evidence. A comprehensive collection and quality assessment of evidence for its use in various diseases is therefore necessary. This study systematically evaluates the therapeutic evidence for Xiaoyao San in treating depression, premenstrual syndrome, chronic hepatitis, irritable bowel syndrome, dyspepsia, and menopausal syndrome using the Eff-iEC method. This study aims to provide support for the clinical efficacy and rational use of Xiaoyao San and offer insights and methodological references for the comparative evaluation of multifunctional TCM formulas.

2. Materials and methods

2.1. Summary of clinical evidence of Xiaoyao San

Information on the composition, functions, and uses is provided in Supplemental File 1, <https://links.lww.com/STCM/A80>. The evaluation of clinical evidence focuses on the original records of Xiaoyao San, the first documented use of Xiaoyao San for various diseases, its market introduction, and the duration of continuous use. Searches were conducted in databases such as PubMed, Excerpta Medica Database (EMBASE), Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Data, VIP Chinese Science and Technology Periodical Database (VIP), China Biology Medicine disc (CBM), as well as specialized ancient literature databases (e.g., Airusheng) and drug registration databases (e.g., Yaozhiwang). Each database was searched from its inception to March 31, 2025.

Keywords for the search included "depression," "premenstrual syndrome," "chronic hepatitis," "irritable bowel syndrome," "dyspepsia," "menopausal syndrome," and "Xiaoyao."

2.2. Experimental research evidence of Xiaoyao San

2.2.1. Search strategy

The evaluation of experimental evidence focused on the efficacy of Xiaoyao San as confirmed by multimodal and multiteam pharmacological and pharmacodynamic experiments. Animal experimental data provide evidence for the validity of the drug but do not directly infer equivalence to clinical efficacy. Searches were conducted in 8 databases, including PubMed, EMBASE, Cochrane Library, Web of Science, CNKI, Wanfang Data, VIP, and CBM. Each database was searched from its inception to March 31, 2025, using keywords such as "depression," "premenstrual syndrome," "chronic hepatitis," "irritable bowel syndrome," "dyspepsia," "menopausal syndrome," and "Xiaoyao." The full literature search strategy is provided in Supplemental File 2, <https://links.lww.com/STCM/A80>.

2.2.2. Study selection

The inclusion criteria were as follows: (1) The research object was Xiaoyao San; (2) The research type was an *in vivo* experimental study; (3) The research content was directly related to the pharmacodynamics and pharmacological mechanisms of Xiaoyao San in treating the 6 diseases mentioned above.

The exclusion criteria were as follows: (1) Experimental models or data sources were not clearly described; (2) Studies with outcome metrics unrelated to the disease; (3) Abstracts only; (4) Clinical studies; (5) Studies with no full text or available results; (6) duplicate publications.

2.2.3. Data analysis and induction

Two reviewers independently searched for and extracted the data, screening studies based on the inclusion and exclusion criteria. For studies meeting the inclusion criteria, the 2 reviewers independently extracted the data. Any disagreements were resolved through discussion with a third party, and the final data were reviewed by the corresponding author.

2.3. Clinical trial evidence of Xiaoyao San

2.3.1. Search strategy

The methodology for searching, selecting, and extracting clinical trial evidence followed a systematic review and meta-analysis protocol. A total of 8 databases were searched, including PubMed, EMBASE, Cochrane Library, Web of Science, CNKI, Wanfang Data, VIP, and CBM. Each database was searched from its inception to March 31, 2025. A combination of subject terms and free terms was used in the literature search, including subject terms such as "depression," "premenstrual syndrome," "chronic hepatitis," "irritable bowel syndrome," "dyspepsia," "menopausal syndrome," "Xiaoyao," and "randomized controlled trials." The full literature search strategy is provided in Supplemental File 3, <https://links.lww.com/STCM/A80>.

2.3.2. Study selection

The inclusion criteria were as follows: (1) The original data were clinical RCTs published in Chinese or English, with the randomization method clearly described or the term "randomized" mentioned; (2) The study participants were patients diagnosed with the above diseases according to specific diagnostic criteria, with no restrictions on gender or ethnicity; (3) The interventions in the experimental group involved either Xiaoyao San alone or Xiaoyao San combined with adjustments (adjustments were made based on additions and subtractions to the core components, belonging to the "same category of efficacy" of the original formula, rather than cross-category

Table 1**Clinical evidence levels.**

Indication	Provenance	Earliest modern literature	Continuous use*	Grade
Depression	<i>Formulary of the Bureau of Taiping People's Welfare Pharmacy</i> (太平惠民和剂局方)	Chinese Journal of Integrated Traditional and Western Medicine, 2006	Yes	A ⁺
Premenstrual syndrome	<i>Formulary of the Bureau of Taiping People's Welfare Pharmacy</i>	Shanxi Traditional Chinese Medicine, 1997	Yes	A
Chronic hepatitis	<i>Formulary of the Bureau of Taiping People's Welfare Pharmacy</i>	Guangxi Traditional Chinese Medicine, 1979	Yes	A
Irritable bowel syndrome	<i>Collection of Prescriptions with Notes</i> (医方集解)	Sichuan Traditional Chinese Medicine, 2000	Yes	A
Dyspepsia	<i>Formulary of the Bureau of Taiping People's Welfare Pharmacy</i>	Shanxi Traditional Chinese Medicine, 1999	Yes	A
Menopausal syndrome	<i>Formulary of the Bureau of Taiping People's Welfare Pharmacy</i>	Journal of International Obstetrics and Gynecology 1981	Yes	A ⁺

*"Continuous use" reflects the stability of historical experience, but its value requires validation through modern research.

replacement, so as to ensure that the core medicinal ingredients in the formula are not changed). The experimental group could use the same combination of Western medicines as the control group. Unless otherwise specified, Xiaoyao San refers to the prepared formulation of Xiaoyao San; (4) The control group received conventional treatment, placebo, or no treatment, with no limitations on the type of drug or dosage. If the experimental group was treated with combination therapy, the control drugs should be the same as the experimental group, except for the Xiaoyao San treatment; (5) The data in the original article were complete and extractable.

The exclusion criteria were as follows: (1) duplicate or previously published studies; (2) Experimental group interventions that included treatment combinations not specified in the criteria; (3) Studies with no full text or unavailable results.

2.3.3. Data analysis and induction

The protocol was developed in accordance with the Program for Systematic Evaluation and Meta-Analysis 2015 guidelines. Literature search, selection, and data extraction followed the Eff-iEC process for clinical research.

2.3.4. Data analysis and generalization

Two reviewers independently searched and extracted data, screening against the inclusion and exclusion criteria. For studies meeting the inclusion criteria, data were independently extracted by both reviewers. The retrieved data included title, authors, publication date, sample size, diagnostic

criteria, baseline data, interventions, treatment course, duration of follow-up, outcome measures, results, and adverse events. Any disagreements were resolved through discussion with a third reviewer, and the final data were reviewed by the corresponding author. For ambiguous data, the corresponding author was contacted for clarification or additional information. If no response was received, only the available data were included, with potential downgrading in the results. The information on outcome indicators for the 6 diseases is provided in Supplemental File 4, <https://links.lww.com/STCM/A80>.

2.4. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)

The quality of evidence for treating the 6 diseases with Xiaoyao San was evaluated using the standard GRADE evaluation process. The outcome indicators for each disease were independently evaluated by 2 reviewers. The risk of bias for each study was assessed using the Cochrane Collaboration tool. Meta-analysis was conducted with Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration Review Manager [RevMan]. Copenhagen, Denmark, 2014.), and the level of evidence was determined using the GRADE online guide (<https://gdt.gradeapro.org/app/>). Key findings were presented in a transparent and simple format using the "Summary of Findings" table.

The inclusion of the GRADE system alongside Eff-iEC serves 2 complementary purposes: first, as a comparative benchmark to highlight Eff-iEC's methodological distinctiveness; second, as a lens to contextualize Eff-iEC's suitability for TCM research.

2.5. Medical community recognition

This study refers to several authoritative medical documents, including the China National Basic Medical Insurance Drug List (CNBMIDL), the China National Essential Drug List (CNEDL), and relevant guidelines and consensus statements issued by national professional associations, such as the Chinese Association of Integrative Medicine, the China Association of Chinese Medicine, and the Chinese Medical Association. By counting the frequency of Xiaoyao San's inclusion in these documents, we can infer the degree of recognition of its clinical application value within the medical community. A higher frequency of inclusion indicates that Xiaoyao San is more widely accepted and respected in clinical practice. The inclusion of

Table 2**Experimental evidence levels.**

Indication	Multiple models	Multiple teams	Additional criterion*	Grade
Depression	Yes	Yes	① ②	A ⁺
Premenstrual syndrome	None	Yes	① ②	B ⁺
Chronic hepatitis	Yes	Yes	②	A ⁺
Irritable bowel syndrome	Yes	Yes	None	A
Dyspepsia	Yes	Yes	②	A ⁺
Menopausal syndrome	Yes	Yes	②	A ⁺

*The experimental evidence for each disease was further validated through 2 additional criteria: ① validation with clinical samples, and ② bioinformatics analysis.

Table 3
Clinical trial levels.

Indication	Interventional study		Observational study				Grade
	RCT/PCT	Limited RCT/PCT	OS with very large effect	OS with large effect	Other studies	Additional criterion	
Depression	None	Yes	None	None	None	None	B
Premenstrual syndrome	None	Yes	None	None	None	None	B
Chronic hepatitis	None	Yes	None	None	None	None	B
Irritable bowel syndrome	None	Yes	None	None	None	None	B
Dyspepsia	None	Yes	None	None	None	None	B
Menopausal syndrome	Yes	None	None	None	Yes	None	A

Xiaoyao San in these lists reflects not only clinical evidence but also economic, historical, and policy factors.

3. Results

3.1. Clinical evidence levels

The historical use of Xiaoyao San for the treatment of these diseases, as well as its continued application over time, is substantiated by clear and verifiable medical literature. The summarized results are presented in Table 1, with the earliest modern literature included in Supplemental File 5, <https://links.lww.com/STCM/A80>.

3.2. Experimental evidence levels

The extraction and evaluation of the included literature were conducted, with the results summarized in Table 2. A total of 49 experimental studies (e.g., Su et al.^[7]) on depression were included in the analysis. These studies not only met the experimental design criteria of “multi-model, multi-team” but also passed additional assessments, including clinical sample validation and network pharmacological analysis, resulting in a high evidence level of grade A*.

Relatively few animal model studies (e.g., Xu et al.^[8]) have been conducted on premenstrual syndrome. However, multiple research teams have validated clinical samples and performed bioinformatics analyses, leading to an evidence grade of B*.

In the field of chronic hepatitis, the therapeutic efficacy of Xiaoyao San was supported by an A* level of evidence. This high grade was based on a robust research base, including animal models, cellular experiments, and multi-institutional studies. Additionally, its mechanism of action has been validated through 3 network pharmacology studies and 1 multiomics study (e.g., Yang et al.^[9]).

The grade of evidence for experimental studies on irritable bowel syndrome was A. These studies (e.g., Shi et al.^[10]) were rigorously validated by multiple research teams and models, all of which were published in Chinese core journals.

Dyspepsia was included in 2 experimental studies and 1 study focusing on diversity analyses (e.g., Jin et al.^[11]). Menopausal syndrome was included in 4 experimental studies, as well as 1 proteomics study (e.g., Hu et al.^[12]). These high-quality studies earned them an A* rating.

The detailed experimental studies included for each disease are listed in Supplemental File 6, <https://links.lww.com/STCM/A80>.

3.3. Clinical trial evidence levels

A total of 14 (e.g., Wang et al.^[13]), 18 (e.g., Liu^[14]), 46 (e.g., Wang^[15]), 20 (e.g., Guo et al.^[16]), and 6 (e.g., Xu^[17]) RCTs on depression, premenstrual syndrome, chronic hepatitis, irritable bowel syndrome, and dyspepsia, respectively, were included in the analysis. All of these studies were RCTs; however, some did not specify the randomization methods used, exhibited selective reporting of results, or showed significant heterogeneity in their findings. After applying the downgrading criteria, the overall quality of evidence for these studies was rated as B.

A total of 11 RCTs and 1 retrospective cohort study (e.g., Zhou^[18]) on menopausal syndrome were included. No serious downgrading factors were observed, resulting in an evidence level of A.

The clinical trial evidence levels and outcome information are summarized in Tables 3 and 4. Figures 1 and 2 present the risk of bias graphs. The clinical trial studies included for each disease, along with the forest plots of meta-analysis and funnel plots for bias analysis, are provided in Supplemental Files 7–10, <https://links.lww.com/STCM/A80>.

Table 4
Information on outcome indicators for 6 diseases.

Indication	Primary outcome	Secondary outcomes
Depression	Efficacy rate	Hamilton Anxiety Rating Scale score, Pittsburgh Sleep Quality Index score, adverse event rate, TESS score
Premenstrual syndrome	Efficacy rate	Adverse reaction incidence, luteinizing hormone, follicle-stimulating hormone (FSH)
Chronic hepatitis	Efficacy rate	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), hepatitis B virus deoxyribonucleic acid (HBV-DNA), hepatitis B e antigen (HBeAg), total cholesterol (TC), triglyceride (TG)
Irritable bowel syndrome	Efficacy rate	Degree of abdominal pain, degree of abdominal distension, Irritable Bowel Syndrome Quality of Life, Irritable Bowel Syndrome Symptom Severity Score
Dyspepsia	Efficacy rate	Abdominal distension, epigastric pain, belch, early satiety, score of symptoms related to indigestion, adverse reaction incidence
Menopausal syndrome	Efficacy rate	Adverse reaction incidence

3.4. Results of Eff-iEC comprehensive evaluation

The quality of evidence for the treatment of 6 diseases by Xiaoyao San was synthesized and evaluated according to the Eff-iEC criteria. Menopausal syndrome and depression were evaluated across 3 dimensions, earning respective ratings of A+A and A+A. According to the Eff-iEC standard, both conditions were classified as “High+,” the highest level among the 6 diseases. Chronic hepatitis and dyspepsia received AA+B ratings, corresponding to the “High+” level under the Eff-iEC standards. Irritable bowel syndrome received an AAB rating, classified as “High,” but it lacks large-scale data mining, bioinformatics analysis, and high-quality RCTs compared with other conditions. Premenstrual syndrome received an AB+B rating, classified as “Moderate+.” The detailed results are shown in Table 5.

3.5. Analysis of medical community recognition

Xiaoyao San is widely recognized for its effectiveness in treating depression, as evidenced by its inclusion in both TCM guidelines and Western medical (WM) guidelines, as well as the CNBMIDL and CNEDL. While conditions such as premenstrual syndrome, dyspepsia, and menopausal syndrome are not recommended in WM guidelines, they are included in TCM guidelines and both CNBMIDL and CNEDL. This underscores the recognized value of Xiaoyao San in the treatment of gynecological and digestive system disorders.

For chronic hepatitis, Xiaoyao San is recommended due to its significant role in TCM syndrome differentiation and is also included in both the CNBMIDL and CNEDL.

In contrast, irritable bowel syndrome has a relatively lower inclusion frequency, appearing only in CNBMIDL and CNEDL. The detailed results are shown in Table 6, with additional references and the Consensus Statement provided in Table 7.

3.6. Comprehensive analysis of Eff-iEC, GRADE, and recognition in the medical field

Both menopausal syndrome and dyspepsia received higher ratings than the other conditions in the Eff-iEC and GRADE evaluations. These conditions have been included in multiple guidelines and expert consensus statements issued by national academic societies. They are also listed in the CNBMIDL and CNEDL, reflecting a high level of consensus within the medical community regarding the use of Xiaoyao San for treating menopausal syndrome and dyspepsia. Although depression is rated as “Low-○○○○” in the GRADE evaluation, its high Eff-iEC evidence grade, along with significant medical

community attention, suggests promising research prospects. Premenstrual syndrome and chronic hepatitis are rated as “High+” in the Eff-iEC evaluation and “Low-○○○○” in GRADE. These are classic treatments derived from traditional formulas. While they are not recommended in WM guidelines, they are included in TCM guidelines, CNBMIDL, and CNEDL to meet basic healthcare needs, making them common clinical options with strong medical community recognition. Irritable bowel syndrome is rated as “Very Low-○○○○” in GRADE, but it has solid Eff-iEC evidence, supported by a strong foundation of human experience and high-level experimental research. It is widely used in clinical practice. The low level of consensus may stem from the failure to update guidelines and consensus documents in a timely manner. Overall, the Eff-iEC evaluation results align with the actual value and role of the drugs. This indicates that Eff-iEC is an effective evaluation tool and will provide valuable guidance for the rational use of drugs in clinical practice. The Eff-iEC, GRADE, and Medical Community Recognition analysis results are presented in Table 8.

4. Discussion

The 6 diseases treated by Xiaoyao San were evaluated using Eff-iEC, GRADE, and Medical Community Recognition. The results show that depression and menopausal syndrome received higher ratings compared with the other conditions. The Eff-iEC evidence grade for Xiaoyao San was rated “High” or above for chronic hepatitis, irritable bowel syndrome, dyspepsia, and menopausal syndrome, while premenstrual syndrome received a “Moderate+” rating. The GRADE evidence levels were as follows: “Low-○○○○” for depression, premenstrual syndrome, and chronic hepatitis; “Moderate-○○○○” for dyspepsia and menopausal syndrome; and “Very Low-○○○○” for irritable bowel syndrome. Depression and menopausal syndrome had the highest inclusion frequency, appearing in all 4 categories of documents. While premenstrual syndrome, chronic hepatitis, and dyspepsia are not recommended in WM guidelines, they are included in TCM guidelines, CNBMIDL, and CNEDL. Irritable bowel syndrome had a relatively lower inclusion frequency, appearing only in CNBMIDL and CNEDL.

The Eff-iEC and GRADE frameworks generally align in their assessment of evidence levels but differ in their evaluation of irritable bowel syndrome. This disparity stems from the fact that Eff-iEC incorporates both clinical experience and experimental research, which elevates the overall evidence level. The credibility of a drug's effectiveness is strengthened by its

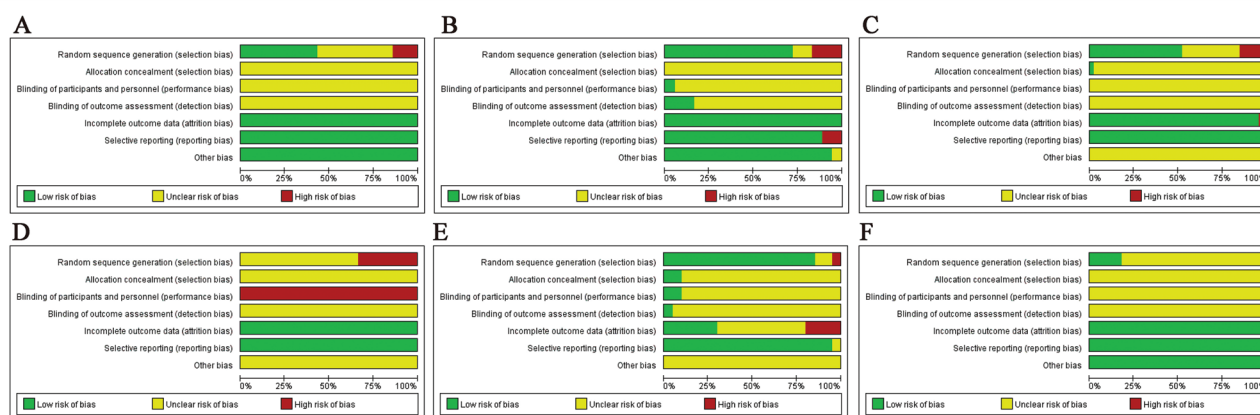


Figure 1. Review authors' judgements regarding each risk of bias item, presented as percentages across all included studies. (A) Depression. (B) Premenstrual syndrome. (C) Chronic hepatitis. (D) Irritable bowel syndrome. (E) Dyspepsia. (F) Menopausal syndrome.

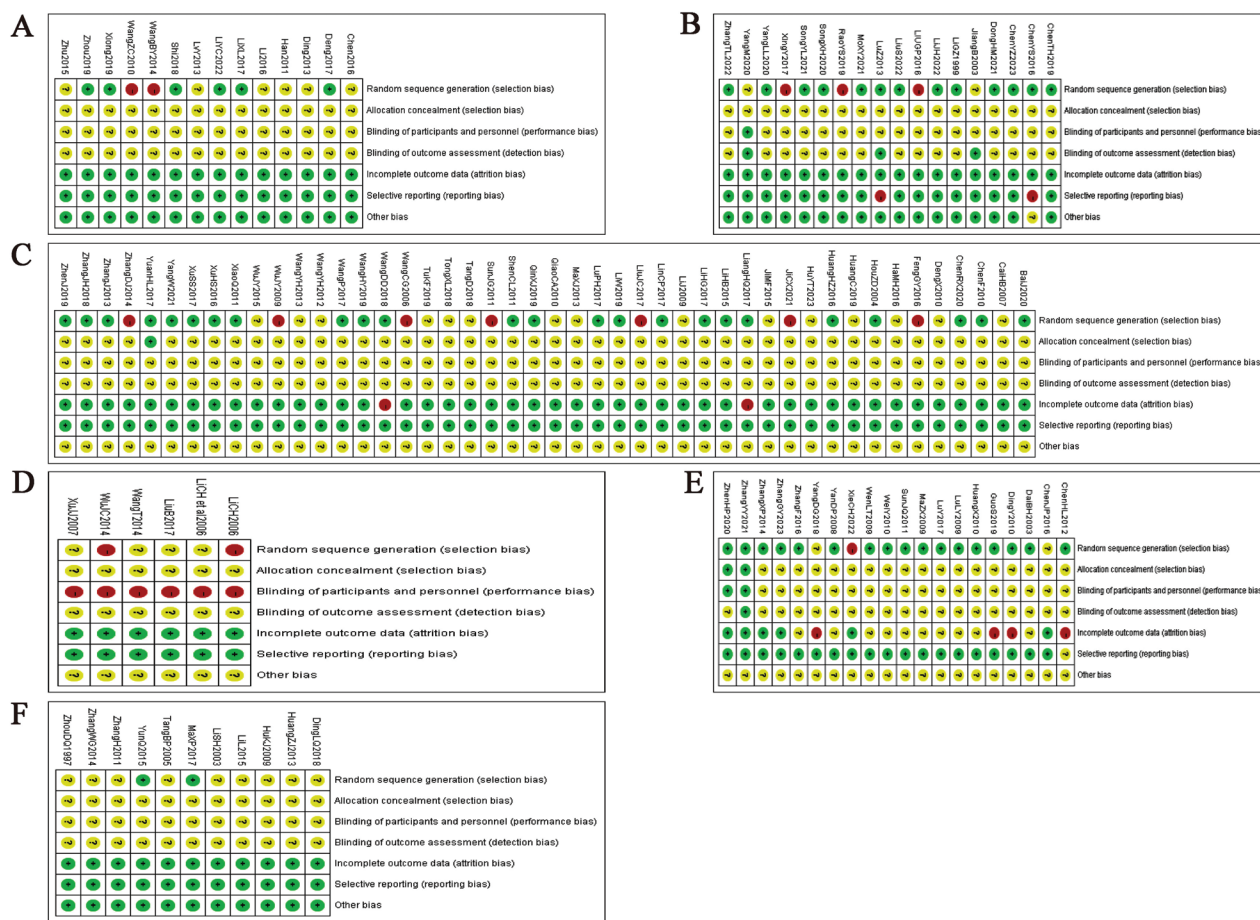


Figure 2. Risk of bias summary: review authors' judgements regarding each risk of bias item for each included study. (A) Depression. (B) Premenstrual syndrome. (C) Chronic hepatitis. (D) Irritable bowel syndrome. (E) Dyspepsia. (F) Menopausal syndrome.

long-standing use and the historical accumulation of clinical experience. When the biological mechanisms of therapies documented in ancient texts are validated by modern research, including animal experiments, the credibility of these historical records is significantly enhanced, which in turn improves the evidence of drug efficacy. Evaluating TCM formulas for conditions like irritable bowel syndrome requires more than just relying on RCTs. A more appropriate framework involves: (1) emphasizing individualization and humanization, treating each patient as a unique individual and tailoring treatment plans

based on their specific condition, while emphasizing the theory of differentiation; (2) Integrating traditional experience with modern research; (3) Focusing on the macro perspective and the whole, seeking balance between mind, body, and environment; (4) Prioritizing patient outcomes and patient-perceived indicators; and (5) Bridging TCM theory with Western biology, allowing for a more integrated approach to healthcare. By adopting this approach, we move beyond the binary debate of "high" versus "low" evidence, toward a more nuanced and holistic understanding of what makes Xiaoyao San clinically valuable.

GRADE is widely recognized as the gold standard for evidence grading in mainstream evidence-based medicine, with a well-established emphasis on prioritizing RCTs and systematically downgrading evidence based on limitations such as risk of bias, inconsistency, or imprecision. By comparing GRADE with Eff-iEC, we aim to highlight the unique features of Eff-iEC—specifically, its structured integration of non-RCT evidence (including clinical experimental studies, experimental mechanistic research, and medical community consensus), which is often crucial in TCM. In TCM, RCTs may be limited by complex interventions, long-term outcomes, or ethical constraints. By providing this comparison, GRADE serves as a familiar reference point to validate the reasonableness of Eff-iEC. If Eff-iEC ratings align with GRADE in cases where RCT evidence is strong, this supports the reliability of Eff-iEC. However, when the 2 frameworks diverge, it underscores Eff-iEC's ability to capture value from evidence types that are underemphasized by GRADE.

Table 5

Analysis of Eff-iEC comprehensive evaluation results.

Indication	Clinical experience	Experimental research	Clinical trial	Result	Eff-iEC
Depression	A ⁺	A ⁺	B	A ⁺ A ⁺ B	High ⁺⁺
Premenstrual syndrome	A	B ⁺	B	AB ⁺ B	Moderate ⁺
Chronic hepatitis	A	A ⁺	B	AA ⁺ B	High ⁺
Irritable bowel syndrome	A	A	B	AAB	High
Dyspepsia	A	A ⁺	B	AA ⁺ B	High ⁺
Menopausal syndrome	A ⁺	A ⁺	A	A ⁺ A ⁺ A	High ⁺⁺

Table 6**Analysis of medical recognition.**

Indication	Guidelines/consensus by NPAs (WM)	Guidelines/consensus by NPAs (TCM)	China National Basic Medical Insurance Drug List (CNBMIDL) ^[19]	China National Essential Drug List (CNEDL) ^[20]	Total*
Depression	Yes	Yes	Yes	Yes	⊙⊙⊙⊙
Premenstrual syndrome	None	Yes	Yes	Yes	⊙⊙⊙⊙
Chronic hepatitis	None	Yes	Yes	Yes	⊙⊙⊙⊙
Irritable bowel syndrome	None	None	Yes	Yes	⊙⊙⊙⊙
Dyspepsia	None	Yes	Yes	Yes	⊙⊙⊙⊙
Menopausal syndrome	None	Yes	Yes	Yes	⊙⊙⊙⊙

*The term "Total" denotes the inclusion status of the drugs in medical documents, with the symbols "⊙" indicating inclusion and "○" indicating exclusion, respectively. Animal experimental data provide evidence for the validity, rather than the equivalence of the model to human disease, and do not directly infer clinical efficacy. NPA, national professional associations.

The multifunctional TCM formula is a foundational concept in TCM, offering a unique approach to diagnosing and treating diseases. For conditions with the same TCM syndrome pattern, a standardized treatment method can be applied, allowing for personalized care while also supporting the multitarget, multipathway therapeutic effects of herbal medicines. The Eff-iEC aligns well with the current medical community consensus on evaluating the multifunctional TCM formula, accurately reflecting the practical value and clinical relevance of Xiaoyao San. The evaluation results indicate that Xiaoyao San has sufficient evidence supporting its effectiveness in treating depression and menopausal syndrome. However, for premenstrual syndrome and irritable bowel syndrome, further experiential and clinical research is needed. Additionally, for chronic hepatitis and dyspepsia, large-scale, multicenter RCTs and observational studies with strong efficacy outcomes are required to further enhance the recognition of their therapeutic value in modern medical practice.

5. Conclusions

The core concept of TCM is treatment based on syndrome differentiation, which posits that different diseases with the same syndrome pattern can be treated using the same herbal formula. This principle forms the theoretical foundation for the multifunctional TCM formula approach in Chinese herbal medicine. In this study, we evaluated the evidence supporting the use of Xiaoyao San for treating multiple conditions and found sufficient evidence of its efficacy in managing depression and menopausal syndrome.

Table 7**Inclusion of Xiaoyao San in treatment guidelines and expert consensus of depression, premenstrual syndrome, chronic hepatitis, irritable bowel syndrome, dyspepsia, and menopausal syndrome.**

National Professional Associations	Chinese Association of Integrative Medicine	China Association of Chinese Medicine	Chinese Medical Association	China Press of Chinese Medicine
Depression	Yes ^[21,22]	Yes ^[23]	Yes ^[24]	None
Premenstrual syndrome	None	Yes ^[25]	None	None
Chronic hepatitis	Yes ^[26,27]	None	None	None
Irritable bowel syndrome	None	None	None	None
Dyspepsia	None	Yes ^[28]	None	Yes ^[29]
Menopausal syndrome	Yes ^[30]	Yes ^[31]	None	None

Table 8**Comprehensive analysis of Eff-iEC, GRADE, and medical community recognition.**

Indication	GRADE*	Eff-iEC	Medical community recognition
Depression	Low-⊙⊙⊕⊕	High ⁺⁺	⊙⊙⊙⊙
Premenstrual syndrome	Low-⊙⊙⊕⊕	Moderate ⁺	⊙⊙⊙⊙
Chronic hepatitis	Low-⊙⊙⊕⊕	High ⁺	⊙⊙⊙⊙
Irritable bowel syndrome	Very low-⊙⊙⊙⊕	High	⊙⊙⊙⊙
Dyspepsia	Moderate-⊙⊕⊕⊕	High ⁺	⊙⊙⊙⊙
Menopausal syndrome	Moderate-⊙⊕⊕⊕	High ⁺⁺	⊙⊙⊙⊙

*The term "GRADE" denotes the inclusion status of the GRADE, with the symbols "⊕" indicating inclusion and "○" indicating exclusion, respectively.

However, more research is needed to further explore its effectiveness in treating premenstrual syndrome, chronic hepatitis, irritable bowel syndrome, and dyspepsia. This can be achieved through enhanced experimental and clinical studies. Our findings also demonstrate that Eff-iEC offers a scientific, objective, and comprehensive evaluation of Xiaoyao San's efficacy. These results not only support the clinical application and value positioning of Xiaoyao San across various disease types but also expand the scope of the Eff-iEC method. Furthermore, they provide valuable insights and methodological references for the comparative evaluation of multifunctional TCM formulas.

Statement of ethics

Not applicable.

Conflicts of Interest statement

Xiaohe Xiao is the editorial board member of the Science of Traditional Chinese Medicine. The article was subject to the journal's standard procedures, with peer review handled independently of this Editorial Board member and their research groups. The remaining authors have no conflicts of interest with regard to the content of this report.

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Data availability statement

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Author contributions

Caiping He: Conceptualization, methodology, and validation; Data curation, writing—original draft. Ye Luo: Writing—review and editing. Zhiqi Li: Writing—review and editing. Haocheng Yang: Formal analysis; Software. Lu Liu: Methodology; Visualization. Yingjie Xu: Methodology and visualization. Xiaoyan Chen, Siqi Huang, and Jincai Wen: Investigation. Xiaoyan Zhan: Methodology. Xu Zhao: Writing—review and editing, project administration. Zhao Fang Bai: Project administration and funding acquisition. Xiaohe Xiao: Conceptualization, validation, and supervision; funding acquisition. All authors have read and agreed to the published version of the manuscript.

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