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ORIGINAL ARTICLE

Integrated evidence chain-based effectiveness evaluation of traditional Chinese medicines (Eff-iEC): A demonstration study

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TCM effectiveness evaluation;
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Abstract Addressing the enduring challenge of evaluating traditional Chinese medicines (TCMs), the integrated evidence chain-based effectiveness evaluation of TCMs (Eff-iEC) has emerged. This paper explored its capacity through a demonstration study that evaluated the effectiveness evidence of six commonly used anti-hepatic fibrosis Chinese patent medicines (CPMs), including Biejiajian Pill (BP), Dahuang Zhechong Pill (DZP), Biejia Ruangan Compound (BRC), Fuzheng Huayu Capsule (FHC),

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Integrated evidence chain;
Demonstration study;
Anti-hepatic fibrosis;
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Anluo Huaxian Pill (AHP), and Heluo Shugan Capsule (HSC), using both Eff-iEC and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. The recognition of these CPMs within the TCM academic community was also assessed through their inclusion in relevant medical documents. Results showed that the evidence of BRC and FHC received higher assessments in both Eff-iEC and GRADE system, while the assessments for others varied. Analysis of community recognition revealed that Eff-iEC more accurately reflects the clinical value of these CPMs, exhibiting superior evaluative capabilities. By breaking through the conventional pattern of TCMs effectiveness evaluation, Eff-iEC offers a novel epistemology that better aligns with the clinical realities and reasoning of TCMs, providing a coherent methodology for clinical decision-making, new drug evaluations, and health policy formulation.

1. Introduction

Traditional Chinese medicine (TCM) has made substantial contributions to healthcare and its international application is steadily expanding. In 2019, the World Health Organization (WHO) added a chapter on TCM to the International Classification of Diseases-11 (ICD-11)[1], marking a significant milestone for its growing recognition within the global medical community. However, this decision has faced criticism. The European Academies Science Advisory Council (EASAC), the Federation of European Academies of Medicine (FEAM) and other institutions have expressed concerns regarding the efficacy and safety of traditional Chinese medicines (TCMs)[2,3].

These concerns revolve around the need for rigorous scientific research to further substantiate the efficacy of TCMs, as highlighted by WHO and National Institutes of Health (NIH) documents since the 1990s[4,5]. Currently, the evidence hierarchy for TCM primarily adheres to evidence-based medicine (EBM) methodologies, emphasizing randomized controlled trials (RCTs) as the "gold standard" for evaluating efficacy. Yet, despite TCM's long history of use, continued widespread application, and recognition of its efficacy in practice, the existing body of evidence is often graded as low or very low, failing to fully capture its therapeutic value.

This contradiction indicates the limitations of applying a single-hierarchy EBM model to assess TCMs comprehensively. As Laura E. Bothwell stated, while RCTs are crucial, they are not the only means of generating medical knowledge and face challenges when evaluating highly individualized interventions[6]. The NIH similarly acknowledged that RCTs are not the sole method for evaluating efficacy, and their appropriateness for TCMs evaluation remains debated[4]. The WHO further emphasized the need to respect the knowledge and experience derived from TCM's long-established practices, noting that the assessment criteria may differ substantially from those of Western Medicine (WM)[5]. Despite this recognition, a formal framework that fully accommodates TCM knowledge and experience has yet to be developed.

Therefore, it is necessary to break through the conventional EBM paradigm and explore methodologies that balance TCM realities with the established conventions and rigor of biomedicine-based research protocols. In 2019, the *Guiding Opinions of the Central Committee of the Communist Party of China and the State Council on Promoting the Inheritance and Innovation of Traditional Chinese Medicine* introduced a "three-in-one" system for TCMs evidence evaluation, integrating TCM theory, clinical experience, and clinical trials[7]. This directive emphasizes clinical experience, setting a clear and widely endorsed direction within the TCM community. However, no systematic operational protocol has been developed yet at the implementation level, particularly regarding the constitution and utilization of clinical experience. Furthermore, the contributions of experimental research and cutting-edge technologies, such as bioinformatics and big data analysis, in corroborating effectiveness assessments of TCMs remains underrecognized.

Addressing these challenges, Xiaohe Xiao and his team[8] have pioneered the integrated evidence chain-based effectiveness evaluation of TCMs (Eff-iEC, Fig. 1). This novel model synthesizes clinical experience, experimental research, and clinical trials, incorporating advanced tools such as bioinformatics and big data analytics. A comprehensive overview of the background and grading standards of Eff-iEC is presented in the Supporting Information Appendix 1. To enhance global understanding, the implementation steps of the model are illustrated through this demonstration study on TCMs treatment for liver fibrosis, evaluating and comparing the effectiveness evidence of six commonly used Chinese patent medicines (CPMs). This case study aims to provide innovative strategies for assessing effectiveness of CPMs, and also offers an important reference for future TCMs evaluations.

2. Demonstrative study of Eff-iEC: TCMs for liver fibrosis

Liver fibrosis (LF) is a critical pathological condition that significantly impacts long-term outcomes such as cirrhosis, liver cancer, liver failure and mortality[9,10]. Discovering anti-hepatic fibrosis strategies is crucial to preventing these severe consequences. Nonetheless, there remains no approved biological or chemical antifibrotic drug to date[11–13].

The term "liver fibrosis" does not appear in ancient TCM literature. However, based on its pathological changes and clinical manifestations, LF may be classified under TCM concepts such as "aggregation-accumulation (Ji Ju, AA)" or "hypochondriac pain (Xie Tong, HP)", reflecting conditions secondary to weakened qi, blood, and meridian blockages[14]. TCM has a long-standing accumulation of knowledge in this area, offering significant advantages and a rich resource for developing anti-fibrotic drug candidates[15]. In China, the National Medical Products Administration has approved a range of medications for LF, including classic TCM formulas and novel CPMs derived from experienced and collaborative prescriptions[16,17]. Clinical experience,

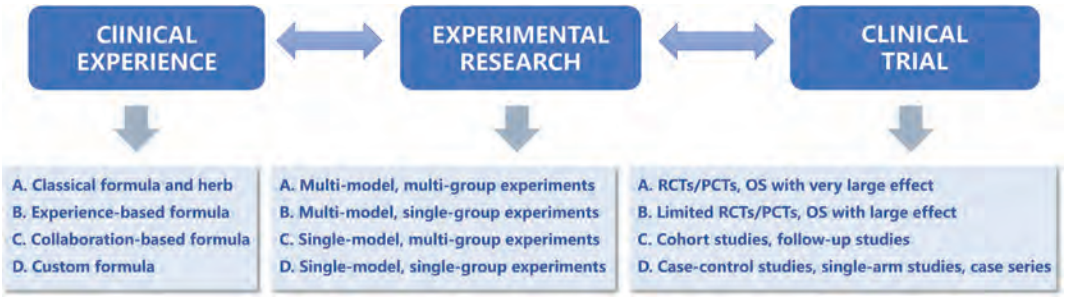

Figure 1 The integrated evidence chain-based effectiveness evaluation of TCMs (Eff-iEC)[8]. RCTs, randomized controlled studies; PCTs, pragmatic clinical trials; OS, observational studies.

experimental research, and clinical studies provide both direct and indirect evidence supporting the effectiveness of these drugs. However, a comprehensive collection and quality evaluation of this evidence is still needed.

To aid clinical decision-making, this paper conducts a systematic evaluation of six CPMs, including Biejiajian Pill (BP), Dahuang Zhechong Pill (DZP), Biejia Ruangan Compound (BRC), Fuzheng Huayu Capsule (FHC), Anluo Huaxian Pill (AHP), and Heluo Shugan Capsule (HSC). These CPMs are commonly used clinically[18–22], and recommended by multiple guidelines[14,23–28]. The information on their ingredients, functions and indications are detailed in Supporting Information Appendix 2. This evaluation employs Eff-iEC and GRADE, with an analysis focused on the recognition of these CPMs within the medical community, as indicated by their inclusion in authoritative medical documents.

2.1. Evaluation methods and outcomes of clinical experience evidence

The evaluation of clinical experience evidence focuses on the medicine's original records, initial application timing for LF treatment, market introduction, and the duration of continuous use. Searches were conducted in databases such as PubMed, EMbase, the Cochrane Library, the Web of Science, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), WanFang DATA, VIP, and specialized TCM literature databases like Airusheng, along with drug registration databases such as Yaozhi Network. Grey literature sources, including reviews, editorials, and online content, were also examined.

Keywords for the search included "Biejiajian Pill," "Dahuang Zhechong Pill," "Biejia Ruangan Compound," "Fuzheng Huayu Capsule," "Anluo Huaxian Pill," "Heluo Shugan Capsule," and "liver fibrosis". The historical application of these drugs for LF and the duration of their continuous use were confirmed through clear, verifiable medical literature. The results are summarized in Table 1 [29-38] with detailed references provided in Supporting Information Appendix 3.

Following a thorough literature review, it has been found that BP and DZP possess the longest history of application, traceable to Zhang Zhongjing's *Synopsis of Prescription of the Golden Chamber* (*Jin Kui Yao Lve*, *SPGC*) from the Eastern Han Dynasty[29]. Traditionally, these formulations have been commonly used to treat aggregation-accumulation, a condition analogous to LF. The earliest modern reports recognizing their use for LF were both published in 1995[30,31], and they remain in clinical use today. Given their historical significance and prolonged application, they are rated Grade A (classical formula).

BRC[32,33], FHC[34], AHP[35,36], and HSC[37,38] are rated Grade B (experience-based formula), supported by a well-documented clinical and research history in the treatment of LF spanning over 15 years.

2.2. Evaluation methods and outcomes of experimental evidence

The evaluation of experimental evidence centers on the effectiveness of drugs as substantiated by multi-model, multi-source animal experiments. A search was conducted across various databases, including PubMed, Embase, the Cochrane Library, the Web of Science, CNKI, CBM, WanFang DATA, and VIP, using keywords like "Biejiajian Pill," "Dahuang Zhechong Pill," "Biejia Ruangan Compound," "Fuzheng Huayu Capsule," "Anluo Huaxian Pill," "Heluo Shugan Capsule," and "liver fibrosis." Detailed search strategies are available in Supporting Information Appendix 4.

Inclusion criteria for literature: *In vivo* experimental research; animal models related to LF; the intervention must involve one of the six CPMs.

Exclusion criteria for literature: Given the maturity of animal models for LF, *in vitro* and other alternative models; studies with outcome indicators unrelated to LF; abstracts only; clinical

Table 1 Summary of clinical experience evidence of six CPMs in LF.

CPMs	Provenance	Earliest modern literature of LF	Continuous use	Grade
BP	*Synopsis of Prescription of the Golden Chamber*, Eastern Han Dynasty[29]	1995[30]	Yes	A
DZP	*Synopsis of Prescription of the Golden Chamber*, Eastern Han Dynasty[29]	1995[31]	Yes	A
BRC	Derived from a folk formula, collected by PLA 302 hospital in 1972[32], marketed in 1999	1991[33]	Yes	B
FHC	Derived from "Tao Hong Yin", developed by Shanghai University of traditional Chinese medicine in 1992[34], marketed in 2002	1992[34]	Yes	B
AHP	Derived from a folk formula[35], marketed in 2002	1999[36]	Yes	B
HSC	Derived from a collaboration formula[37], marketed in 2000	2001[38]	Yes	B

studies; incomplete or erroneous information; and duplicates. The included literature underwent information extraction and evaluation, with results summarized in Table 2[39−99].

A total of 23 experimental studies on FHC were included[69−91], the highest among the evaluated CPMs[69−91], with 14 published in SCI-indexed journals[69−72,74,78−81,83,84,86,87,90], and remaining studies in either English[73,77,82,89,91] or Chinese core journals[75,76,85,88]. Noteworthy studies included clinical sample validation[69] and bioinformatics analysis[70], resulting in an evidence rating of Grade A^{++} (multi-model, multi-group experiments).

For the BRC, 10 studies were included[59−68], with 4 published in SCI-indexed journals[65−68]. Three studies explored the mechanisms through network pharmacology[59,60,67], earning it a Grade A^{+} rating.

Nine studies on BP were included[39−47], including one published in an SCI-indexed journal[46] and another involving network pharmacology analysis[45], earning a Grade A^{+}.

Eleven studies on DZP were included[48−58], with four published in SCI-indexed journals[54−56,58], including one study focused on metabolomics[54], also rated as Grade A^{+}.

For AHP and HSC, five[92−96] and three[97−99] studies were included, respectively, all published in Chinese core journals, each earning a Grade A rating.

2.3. Evaluation methods and outcomes of clinical trial evidence

The methodology for retrieving, selecting, and extracting clinical trial evidence follows systematic review and meta-analysis protocols. The search keywords and databases are similar to those used for experimental evidence, and detailed search strategies can be found in Supporting Information Appendix 5.

Inclusion criteria: Clinical studies; participants diagnosed with LF; interventions involving the six CPMs combined with regular WM treatment; RCTs with a Jadad scale (0−5)[100] >2; outcomes include Ishak fibrosis stages, serological markers, or liver stiffness measurement (LSM).

Exclusion criteria: Participants with decompensated cirrhosis; meta-analyses or systematic reviews; abstracts or protocols only; experimental research; incomplete or erroneous information; duplicates.

Primary outcome focuses on the Ishak fibrosis stages, with secondary outcomes including serological indicators and/or LSM. Included studies undergo information extraction and quality assessment, with downgraded evaluations for flawed RCTs. Results are detailed in Table 3[101-147].

Ten RCTs on BRC were included[114−123], with no downgraded factors observed. Notably, a pivotal multicenter RCT published in *The Journal of Infectious Diseases* showed that, after 72 weeks, patients receiving BRC in combination with entecavir exhibited a higher LF regression rate compared to those on entecavir alone (40% *vs*. 31.8%, $P = 0.0069$)[114]. Given it as the official publication of the Infectious Diseases Society of America, the findings carry substantial international impact. Follow-up findings published in the *Journal of Hepatology* further confirmed BRC's antifibrotic efficacy, showing a 51.1% reduction in hepatocellular carcinoma incidence among patients with hepatitis B-related LF who received the combined therapy[148]. This influential trial has substantiated the efficacy of BRC for LF treatment. Consequently, the evidence of BRC is rated as Grade A^{+}.

Six RCTs on FHC were included[124−129], with two studies employing the Ishak system as an outcome measure[126,127]. No downgraded factors were observed. Additionally, its efficacy was supported by one retrospective cohort study[130] and two single-arm studies[131,132]. Overall, the evidence of FHC is rated as Grade A.

Thirteen RCTs on AHP were included[133−145], with two studies utilizing the Ishak system for outcome measures[142,143]. After applying downgraded criteria, several limits, including bias risk were identified. One RCT that used LSM as an outcome measure was published in the *Journal of Ethnopharmacology*, a journal with significant influence in the field of traditional medicine[144], earning it an additional "$^{+}$". Overall, the evidence of AHP is graded as B^{+}.

Four[101−103,105], eight[106−113] and two[146,147] RCTs on BP, DZP, and HSC were included, respectively, focusing on outcomes like Ishak system, LSM, or serum biomarkers. After a thorough assessment, limits including bias risk were identified. Overall, the evidence for these 3 formulations is all rated Grade B.

Table 2 Summary of experimental evidence for six CPMs in LF.

CPM	Multi-model	Multi-source	Additional criterion[a]	Grade
BP[39−47]	Yes	Yes	①[45]	A^{+}
DZP[48−58]	Yes	Yes	②[54]	A^{+}
BRC[59−68]	Yes	Yes	②[59,60,67]	A^{+}
FHC[69−91]	Yes	Yes	①[69]②[70]	A^{++}
AHP[92−96]	Yes	Yes	None	A
HSC[97−99]	Yes	Yes	None	A

[a]Additional criteria: ①Validation with clinical samples; ②Bioinformatics analysis.

2.4. Evaluation methods and outcomes of Eff-iEC synthesis and GRADE criteria

The results were integrated comprehensively. Meanwhile, the evidence quality of LF treatments using the six CPMs was evaluated by GRADE criteria. Literature retrieval, selection, and data extraction followed the Eff-iEC process for clinical research, with Ishak fibrosis stage as the primary outcome. The risk of bias for each study was evaluated using the Cochrane Collaboration tool[149], and the evidence levels were assessed *via* the GRADE online guideline (https://gdt.gradepro.org/app/). The detailed results and their comparison with the Eff-iEC are presented in Table 4.

2.5. Analysis of TCM academic community recognition

To gauge the TCM academic community's recognition of the six CPMs' efficacy, this paper references several medical documents: The China National Basic Medical Insurance Drug List, the China National Essential Drug List, and guidelines and consensus statements on LF by National Professional Associations (NPAs), such as the Chinese Medical Association, China Association of Chinese Medicine, and China Association for Integrative Medicine. The referenced guidelines and consensus statements are detailed in Supporting Information Appendix 6. The inclusion frequency of these CPMs in these documents was recorded. A higher frequency of inclusion reflects a greater level of clinical efficacy recognition within TCM academia. The results are presented in Table 5[14,23-28,150,151].

FHC has the highest inclusion frequency, appearing in all four categories of documents, underscoring its significant recognition

Table 3 Summary of clinical trial evidence for six CPMs in LF.

CPM	Interventional study		Observational study			Additional criterion[a]	Grade
	RCT/PCT	Limited RCT/PCT	OS with very large effect	OS with large effect	Other studies		
BP	None	Yes[101−105]	None	None	None	None	B
DZP	None	Yes[106−113]	None	None	Yes[113]	None	B
BRC	Yes[114−123]	None	None	None	None	①[114]	A^+
FHC	Yes[124−129]	None	None	None	Yes[130−132]	None	A
AHP	None	Yes[133−145]	None	None	None	①[144]	B^+
HSC	None	Yes[146,147]	None	None	None	None	B

[a]Additional criteria: ①Published in high-impact journals.

within the TCM community. BP, DZP, BRC, and AHP are included in three categories each. Notably, classical formulas like BP and DZP differ in inclusion compared to modern CPMs such as BRC and AHP; the China National Essential Drug List includes the classical formulas, whereas guidelines with a WM background favor the modern formulations. HSC has the lowest inclusion frequency, appearing only in TCM guidelines.

In general, documents with a TCM cognitive background, such as TCM guidelines, tend to favor classical formulas like BP and DZP. Conversely, documents reflecting a WM perspective show a preference for modern CPMs like FHC, BRC, and AHP.

2.6. Discussion

2.6.1. Analysis of Eff-iEC, GRADE and medical community recognition

The Eff-iEC assessment of the six CPMs for LF treatment shows that BP, DZP, BRC, and FHC were all rated as High, while AHP and HSC received a Moderate rating. Compared with the GRADE results, it is clear that the evaluations for FHC and BRC align more closely across both methodologies. However, discrepancies exist for the other CPMs, largely because Eff-iEC incorporates clinical experience, which elevates the integrated evidence level.

Table 4 Eff-iEC and GRADE outcomes for six CPMs in LF.

CPM	Eff-iEC		GRADE	
	Result	Evidence level	Result	Evidence level
BP	AA^+B	$High^+$	D	Very low
DZP	AA^+B	$High^+$	D	Very low
BRC	BA^+A^+	$High^{++}$	B	Moderate
FHC	$BA^{++}A$	$High^{++}$	B	Moderate
AHP	BAB^+	$Moderate^+$	C	Low
HSC	BAB	Moderate	D	Very low

A comprehensive analysis indicates that the Eff-iEC results align well with the inclusion of these CPMs in relevant medical documents. FHC and BRC, highly rated by both Eff-iEC and GRADE, are included in multiple guidelines, consensus statements, and the China National Basic Medical Insurance Drug List, indicating strong recognition of their effectiveness within the community. BP and DZP are classical formulas that are rated High in Eff-iEC but Very Low in GRADE. Despite their absence in WM guidelines, they are included in several authoritative documents, particularly the China National Essential Drug List, highlighting their widespread clinical use and community recognition as essential treatments for basic health needs. AHP, despite being rated as moderate in Eff-iEC, its additional "$^+$" still indicates higher academic interest and promising research potential. Overall, Eff-iEC effectively reflects the clinical understanding and value of CPMs, suggesting strong evaluative capability and promising to serve as a useful guide for decision-making in TCM.

2.6.2. Direction of evidence body enhancement

The evaluation results of the CPMs at different stages of Eff-iEC also highlight key areas where the evidence body requires enhancement. BRC and FHC, with solid foundations in clinical application—nearly 50 years for the former and over 30 years for the latter—are bolstered by extensive experimental and clinical research, including multiple additional factors. Their evaluation results align closely with GRADE, identifying them as optimal treatments for LF. Future research should focus on gathering long-term, large-scale real-world data to confirm their efficacy and elevate their clinical experience evidence grade to A, while exploring syndrome-differentiated models and clinical applicability to showcase the advantages of TCM.

BP and DZP, while backed by substantial clinical experience, face downgrades in clinical trial evidence due to limitations in existing RCTs, resulting in inconsistencies with GRADE evaluation. To address this, rigorous RCTs and large-effect OS are

Table 5 Analysis of medical community recognition for six CPMs in the treatment of LF.

CPM	Guidelines/consensus by NPAs (WM)[23−25]	Guidelines/consensus by NPAs (TCM)[14,26−28]	China National Basic Medical Insurance Drug List[150]	China National Essential Drug List[151]	Total[a]
BP	None	Yes	Yes	Yes	○⊕⊕⊕
DZP	None	Yes	Yes	Yes	○⊕⊕⊕
BRC	Yes	Yes	Yes	None	⊕⊕⊕○
FHC	Yes	Yes	Yes	Yes	⊕⊕⊕⊕
AHP	Yes	Yes	Yes	None	⊕⊕⊕○
HSC	None	Yes	None	None	○⊕○○

[a]The term "Total" denotes the inclusion status of the drugs in medical documents, with the symbols "⊕" indicating inclusion and "○" indicating exclusion, respectively.

needed to strengthen their efficacy within the framework of modern medicine.

The Eff-iEC results for AHP and HSC were rated as Moderate, based on over 15 years of clinical application and research. Enhancing the traceability and organization of clinical data could elevate their grade of experience evidence. AHP has laboratory and clinical evidence with additional factors, but faces methodological flaws in clinical trials, necessitating rigorous RCTs to generate high-level evidence. HSC meets basic efficacy criteria but presents weaker evidence in both laboratory and clinical research, highlighting the need for updated studies to provide fresh evidence of its effectiveness.

2.6.3. The advantages and limitations of Eff-iEC

By evaluating the evidence of CPMs for liver fibrosis, the operational protocol of the Eff-iEC are demonstrated. The analysis above suggests that Eff-iEC adjusts the single-hierarchy model of relying solely on modern research for clinical decision-making, facilitating a more comprehensive, objective, and authentic synthesis and assessment of evidence. This approach aligns more closely with current medical community recognition and reflects the actual application value and status of medicines, providing essential knowledge and support for clinical decision-making. In terms of methodology, Eff-iEC serves as an integrated evaluation of evidence from the three stages of research. The strongest evidence is composed of Grade A evidence from all three stages, along with additional factors, forming a complete evidence chain.

The Eff-iEC offers several advantages over the single-hierarchy model currently in use: (1) It recognizes the value of clinical experience in TCM practice, incorporating it into the evidence system with qualitative grading. These experiential evidences embody knowledge gained from TCM practice and offer clues for further research. (2) It positions experimental evidence as a bridge between classical experience and modern medicine, aiming to clarify the mechanisms of TCM efficacy. (3) By integrating evidence through a meta-meta-analysis and emphasizing the importance of clinical trials, the method enhances rigor and minimizes bias. (4) The comprehensive evaluation results also indicate directions for improving and upgrading evidence, providing guidance for strengthening the evidence base of TCM efficacy.

However, challenges remain in implementation. Variations in contribution and methodological rigor of clinical experience, experimental research, and clinical trials complicate direct comparisons, raising questions about whether equivalent grades indicate equal significance or require statistical weighting. This question may be complex, as these stages are distinct and non-competitive parts of effectiveness assessment. Besides, the distinctions and connections in TCM's understanding of diseases (or symptoms) from ancient to modern times should be considered. Ongoing refinement and validation through extensive research are crucial to addressing these challenges.

3. Conclusions and future perspectives

The Eff-iEC breakthroughs the conventional pattern of TCMs effectiveness evaluation, expanding the range of evidence types, thus broadening the boundaries and increasing the volume of available evidence. Each type of evidence, including clinical experience, experimentation, and clinical trials, plays a vital role in providing an objective, comprehensive, and authentic evaluation of TCMs' effectiveness. The Eff-iEC does not aim to replace RCTs and their associated rigor with other types of evidence, nor to undermine RCTs' significance as the "gold" standard in efficacy evaluation, but rather to create a more balanced "alloy" based on EBM theories and TCM realities.

With its innovative epistemology and methodology, Eff-iEC aligns closely with the needs of medical decision-making, bridging the gap between TCM practices and biomedicine's systematic review outcomes. As such, this tool, which truly reflects the characteristics of TCM, holds promise for international recognition. It provides essential support for the "three-in-one" evidence evaluation system for TCM, particularly in integrating and transforming human-used experience. In future studies, Eff-iEC can be applied to assess the efficacy of TCM formulas, new drugs, natural medicines, hospital prescriptions, post-marketing products, and health-related products. It also offers technical support for clinical guidelines and the inclusion of TCMs in national basic medical insurance and essential drug lists. Through these applications, Eff-iEC establishes a coherent theoretical and methodological framework for clinical decision-making, new drug assessments, and health policy formulation in TCM, enhancing its position within the mainstream healthcare system.

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Author contributions

Xiaohe Xiao, Xiangmei Chen, Aiguo Dai, Jiabo Wang, Zhaofang Bai, Ye Luo, Xu Zhao, Ruilin Wang conceived and designed the project. Ye Luo performed data processing, drafted the tables and manuscript. Tianyi Zhang, Tingting He, Jing Jing provided new ideas. Jianyu Li, Fengyi Li, Ping Zhang, Junling Cao, Jinfa Tang, Zhijie Ma, Tingming Shen, Shuanglin Qin, Ming Yang, Jun Zhao participated in the study design and coordination. Xiaoyan Zhan drew the illustration. Xiaohe Xiao, Xu Zhao, Ruilin Wang polished the manuscript. All the authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supporting information

Supporting information to this article can be found online at https://doi.org/10.1016/j.apsb.2024.12.024.

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