

Systematic developments of evidence-based Chinese herb-drug interaction monographs for a clinical decision-support database

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ABSTRACT

Introduction The global use of Chinese herbal medicines (CHMs) alongside pharmaceutical drugs has increased the need for systematic assessment of herb-drug interactions (HDIs) to support safe integrative practice. However, existing databases show limited CHM coverage, inconsistent evidence grading, and poor clinical interpretability. This review describes the systematic development of evidence-based Chinese HDI monographs for IMgateway (<https://www.imgateway.net>), using dual-language English and Chinese evidence, predefined evidence-level classification, causality assessment, and interaction likelihood grading to support clinically interpretable decision-making. **Methods** A structured three-phase methodology was applied to evaluate 200 commonly used Chinese herbs. Comprehensive searches were conducted across English- and Chinese-language databases. Standardized criteria were developed to assess interaction likelihood, strength of evidence, mechanistic plausibility, causality, and potential clinical relevance across different levels of available evidence. **Results** A total of 497 peer-reviewed articles were included, from which 595 HDI monographs were developed. The included evidence comprised clinical studies, including randomized controlled trials (RCTs) and human case reports, and preclinical studies, including *in vitro* and *in vivo* investigations. Based on monograph classification, 241 monographs were derived from RCTs, 27 from human case reports, and 327 from preclinical studies. Interactions were categorized according to evidence level and assigned likelihood classifications. Seven HDIs were categorized as “avoid combination,” and 114 as “caution,” highlighting clinically significant safety concerns. In addition, 295 HDIs were classified as potentially beneficial, 73 as unlikely, and 106 as unresolved. Evidence strength was further classified as well-established ($n = 28$), good ($n = 76$), limited ($n = 395$), and unknown ($n = 96$). **Conclusion** By integrating dual-language evidence and standardized grading criteria, the database enhances prescribing safety, supports patient counselling, and strengthens pharmacovigilance in integrative healthcare settings. Continuous updates and prospective validation will further improve its clinical applicability.

KEYWORDS

Chinese herbal medicines, pharmaceutical drugs, herb-drug interactions, monographs, evidence synthesis

CITE THIS ARTICLE

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1. Introduction

Herbal medicines (HMs) have been used worldwide for centuries as therapeutic agents for the prevention and management of various chronic disorders.¹ The World Health Organization (WHO) reports that HMs are recognized in more than 170 countries and are used by approximately 80% of the global population.² Traditional and Complementary Medicine (T&CM) is highly institutionalized in many regions, particularly in Asian, Pacific, and African countries, and is increasingly being integrated into Western healthcare systems.³ Among T&CM modalities, Chinese herbal medicines (CHMs) are widely used for conditions such as chronic inflammatory disorders, metabolic diseases, cancer supportive care, and immune-related illnesses, often alongside prescription medications.^{4–6} This concurrent use creates a complex therapeutic landscape in which clinicians must evaluate both the efficacy and safety of combined therapies. Herb-drug interactions (HDIs) are clinically important because they may alter drug exposure, therapeutic efficacy, or toxicity through pharmacokinetic and pharmacodynamic mechanisms.⁷ These risks are particularly relevant in patients using multiple medicines, old-

er adults, individuals with chronic diseases, and patients receiving drugs with narrow therapeutic indices, such as anticoagulants, immunosuppressants, antidiabetic agents, and anticancer therapies.^{8,9} Inadequate documentation or disclosure of T&CM use may further increase the risk of unrecognized interactions and compromise prescribing safety.¹⁰ As integrative healthcare continues to expand, the need for structured, evidence-based tools to support safe and informed clinical decision-making has become increasingly evident.

Chinese HDIs are clinically significant and supported by diverse evidence demonstrating both synergistic and antagonistic effects. Several studies have reported synergistic interactions, with evidence suggesting improved therapeutic outcomes and reduced drug-related toxicity. For example, a systematic review reported that *Astragalus membranaceus* Fisch. (*A. membranaceus*, Huang Qi) improved immune function, enhanced tumour response, and reduced chemotherapy-induced myelosuppression when used in combination with platinum-based chemotherapy.¹¹ Similarly, a review of the therapeutic potential of curcumin reported that it enhances the anti-inflammatory effects of non-steroidal anti-inflammatory drugs through modulation of key inflammatory pathways, including cyclooxygenase-2, 5-lipoxygenase, interleukin-6 (IL-6), and nuclear factor-kappa B.¹² In contrast, antagonistic interactions may arise through pharmacokinetic and pharmacodynamic mechanisms, potentially leading to reduced drug exposure, therapeutic failure, or increased adverse effects. For instance, ginsenosides derived from *Panax ginseng* L. (*P. ginseng*, Ren Shen) were shown to alter the pharmacokinetics of

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aspirin by affecting the time to peak plasma concentration (T_{max}) in Sprague–Dawley rats.¹³ Similarly, another study reported that the concurrent use of *Salvia miltiorrhiza* Bge. (*S. miltiorrhiza*, Dan Shen) with warfarin may enhance anticoagulant effects, increasing the risk of bleeding and excessive international normalized ratio elevations.¹⁴ The coexistence of these divergent outcomes highlights the limitations of individual reports and underscores the need for systematic evaluation of HDI evidence.

Chinese HDIs directly influence clinical decision-making by affecting prescribing practices and strategies for assessing patient risk.¹⁵ Inadequate documentation of CHM use may compromise patient safety, particularly in the context of polypharmacy and among vulnerable patient populations. Although several HDI databases are currently available, many are limited by incomplete coverage of CHMs, variable evidence quality, inconsistent terminology, and limited clinically interpretable information, which reduces their practical value for healthcare professionals (HCPs).^{16–19} Existing HDI resources often rely predominantly on English-language evidence and may not fully capture Chinese-language studies where much traditional Chinese medicine (TCM) research is published. In addition, differences in evidence grading, causality assessment, and clinical recommendation formats may make it difficult for HCPs to interpret the certainty, relevance, and practical implications of reported interactions. Therefore, a structured, transparent, and evidence-based Chinese HDI database is needed to support safer decision-making in integrative healthcare.

Consequently, access to rigorously evaluated, transparent, and clinically relevant interaction data remains limited. Furthermore, the absence of standardized, evidence-based, and clinically interpretable resources on Chinese HDIs continues to present a major barrier to the safe integration of CHMs into modern healthcare systems. To address these challenges, the systematic development of evidence-based Chinese HDI monographs is needed to translate available evidence into structured and transparent assessments suitable for clinical decision-support systems. The aim of this review is to describe the systematic methodology used to develop evidence-based Chinese HDI monographs and to demonstrate their application within a clinical decision-support database, with the goal of improving prescribing safety, consistency, and patient outcomes in integrative medicine. These monographs were developed for integration into IMgateway (<https://www.imgateway.net>, accessed January 11, 2026), an online clinical decision-support database designed to provide HCPs with structured, evidence-based information on HDIs.

2. Methods

2.1. Selection of single Chinese herbs

Two hundred commonly used Chinese herbs were selected from the *Guidelines for Safe Practice of Chinese Herbal Medicine*, published by the Chinese Medicine Board of Australia.²⁰ The research was conducted in three phases. Phase I included 10 Chinese herbs and served as a pilot study to evaluate the HDI assessment criteria. Phase II expanded the analysis to 100 Chinese herbs, and Phase III included an additional 90 herbs. Herbs commonly used by TCM practitioners in Australia but associated with restrictions or safety concerns under the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) were prioritized. Herbs not listed in the SUSMP and therefore freely used in Australia were included next, followed by a small number of herbs that are not permitted for use in Australia but remain available in Asian markets. Additionally, herbs were selected based on clinical relevance, frequency of use, and the availability of evidence related to potential HDIs.

2.2. Literature search and strategy

The literature search and study selection process was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist, where applicable. The completed PRISMA checklist and the full database-specific search strategies, including search terms, screening methods, and eligibility criteria, are provided in Appendix 1.

An extensive literature search was conducted across English-language databases, including PubMed, Scopus, and ScienceDirect, as well as the Chinese database China National Knowledge Infrastructure (CNKI), to identify studies reporting potential Chinese HDIs. Search strategies were adapted for each database according to its indexing structure and search functions. Search terms were developed to capture herb-related, drug-related, and interaction-related concepts. These included the common English name, scientific name, pharmaceutical name, pinyin name, and Chinese name of each herb, combined with drug names, drug classes, and interaction-related terms such as “herb-drug interaction,” “combination,” “synergistic effect,” “antagonistic effect,” “pharmacokinetic,” “pharmacodynamic,” “toxicity,” “adverse reaction,” and “clinical efficacy.” The complete search strategy is provided in Appendix 2.

Grey literature searches were also conducted to identify additional relevant evidence and minimize publication bias. Grey literature sources included Google Scholar, regulatory websites, conference abstracts, and reference lists of included studies. Grey literature searches used simplified combinations of herb names, drug names, and interaction-related terms. The records from each grey literature search were screened for relevance. Reference lists of included articles and relevant reviews were also manually checked to identify additional studies. Grey literature records were included only when they provided sufficient methodological and outcome details relevant to HDIs. Non-scientific webpages, editorials opinions, and records without adequate methodological information were excluded.

The initial search was conducted manually and was subsequently supplemented using SciSpace to maximize coverage and identify potentially relevant studies not captured during manual searching. Chinese-language studies were translated into English using DeepL (version 26.8.1; DeepL SE, Cologne, Germany), ChatGPT (GPT-5.6 Sol; OpenAI OpCo, LLC, San Francisco, CA), and Google Translate. Translations were then verified by a senior TCM practitioner (BHY) to minimize potential translation errors.

2.3. Inclusion and exclusion criteria

The detailed inclusion and exclusion criteria are provided in Appendix 3. The included studies provided strong evidence for HDIs to facilitate informed decisions for clinical practitioners and consumers, comprising both clinical studies and well-documented human case reports and preclinical studies (*in vitro* and *in vivo*). Studies involving single herbs in combination with multiple pharmaceutical drugs, as well as complex HDI, were included. Additionally, dietary supplements derived from herbs were included to address potential HDIs. Herbs and herbal products were included regardless of the route of administration. To ensure a comprehensive representation of Chinese-language studies, studies involving parenteral administration were also included, despite the difference in administration routes between China and Australia. Studies involving herbs combined with multiple drugs were also included. Studies with poor methodological quality, lacking adequate control groups including single-arm studies, improper or flawed statistical analysis, were generally excluded. Methodological quality was assessed by our research team in collaboration with industry partner, UnityHealth Pty Ltd. (Kew, Victoria, Australia) and researchers from the University of Sydney to ensure consistency and rigor in study selection.

2.4. Data extraction for Chinese herbal monograph development

Each monograph summarized key study information, including the herb (common English name, scientific name, and pharmaceutical name), drug name and class, and the full-text citation formatted in PubMed style. Additional details included study type (*in vitro*, *in vivo*, or human study), study aims, subjects, experimental or treatment duration, methods, outcome variables, key results, conclusions, and researcher comments regarding study quality and potential bias. Monographs were assessed for relevance and categorized according to the level of evidence. The findings were organized into a comprehensive tabular format that summarized study references and conclusions. Studies referring to the same HDI were grouped within the same table.

Each HDI entry also included tailored practitioner guidance based on the evidence level, clinical outcomes, and likelihood of interaction. The commentary section summarized key findings and highlighted potential implications for healthcare providers, along with precautionary considerations for patients. To avoid overlap with the quality assessment process, this section focused on the extraction and organization of study-level information required for monograph development, while evidence grading, causality assessment, and likelihood classification were addressed separately in the quality assessment section.

2.5. Review of flowchart and grading system

A decision-making flowchart was developed by the National Institute of Complementary Medicine (NICM) Health Research team to guide the development of Chinese HDI monographs and the formulation of recommendations for HDIs (Figure 1). The flowchart was designed to classify and grade evidence based on relevant studies, providing a clear pathway from evidence identification to recommendation. In collaboration with Prof. Dr. Bo-hua Yan, a senior TCM practitioner from the Adverse Drug Reaction Monitoring Center, Hospital of Chengdu University of TCM (Chengdu, China), the NICM research team also established a grading system and defined criteria for the systematic assessment of HDI evidence.

2.6. Quality assessment

Methodological quality was assessed using a predefined HDI-specific appraisal framework developed to support monograph preparation. Because the aim of this study was to develop evidence-based Chinese HDI monographs rather than conduct a conventional meta-analysis, a single standard risk-of-bias tool was not considered suitable for all included evidence types, which comprised RCTs, human case reports, *in vivo* studies, and *in vitro* studies. The appraisal framework assessed whether each study provided sufficient and reliable evidence for HDI evaluation, including study design, appropriateness of control or comparator groups, clarity of herb and drug identification, relevance of herb-drug co-administration, reporting of pharmacokinetic, pharmacodynamic, clinical or safety outcomes, adequacy of statistical analysis, and relevance to evidence grading and likelihood classification. Study eligibility and methodological quality were assessed according to the predefined inclusion and exclusion criteria and the HDI evidence framework. Studies considered to have poor methodological quality were excluded when they lacked appropriate controls, did not clearly assess concurrent herb-drug use, reported insufficient interaction-specific outcomes, had unclear or flawed statistical analysis, or provided inadequate methodological detail for evidence grading. Disagreements during assessment were resolved through discussion and consensus. Where required, uncertain cases were further reviewed by the expert panel.

The level of evidence for each study was evaluated using a quality assessment scale that considered study design, evidence strength, the number of relevant studies available, clinical outcomes, and causality. Evidence levels were categorized as “well-established/very good” (i.e., supported by at least two clinical trials with identified pharmacological mechanisms), “good” (i.e.,

supported by at least one clinical trial with pharmacological mechanisms), “limited” (i.e., supported primarily by pharmacological or mechanistic evidence), and “not established” (i.e., no available studies or contradictory evidence). These categories helped determine the strength of evidence supporting each identified interaction and distinguish robust findings from those with limited support. Based on the level of evidence, each interaction was assigned a likelihood classification: “avoid combination,” “caution,” “unresolved,” “unlikely,” or “potentially beneficial.” For HDIs classified as “avoid combination,” practitioners were advised not to co-administer the herb and drug due to the potential for clinically significant adverse outcomes. A “caution” classification indicated that the combination should be used carefully with close clinical supervision, possible dose adjustment, and monitoring for adverse or altered therapeutic effects. “Unlikely” interactions suggested that clinically significant effects were not expected based on current evidence, although clinical vigilance was still recommended. “Potentially beneficial” interactions indicated possible enhancement of therapeutic efficacy or reduction of toxicity, with guidance to weigh potential benefits against risks and monitor for variability in patient responses. “Unresolved” interactions reflected inconclusive or contradictory evidence, and practitioners were advised to consider patient-specific factors and maintain careful monitoring.

Causality assessment for case reports followed the WHO guidelines, which classify interactions as “certain,” “probable,” “possible,” or “unlikely.”²¹ A “certain” classification indicates that the interaction is associated with a clinical event or laboratory abnormality, demonstrates a clear temporal relationship, shows recovery after drug withdrawal (dechallenge), is supported by a plausible pharmacological mechanism, cannot be explained by underlying disease or other drugs, and may include evidence from rechallenge if available. A “probable” classification indicates a similar clinical and temporal association with improvement upon dechallenge, where alternative explanations such as disease or other drugs are unlikely, although rechallenge evidence is not required. A “possible” classification refers to interactions associated with a clinical event and temporal relationship, but where information on withdrawal may be unclear or alternative explanations such as disease or other medications cannot be excluded. An “unlikely” classification indicates that the temporal relationship makes a causal association improbable and that the observed clinical event is more plausibly explained by disease, drugs, or other factors (Figure 2).

2.7. Review process and publication of monographs

The review process for drafted monographs followed a structured, multi-step workflow to ensure accuracy, consistency, and clinical relevance. First, a comprehensive literature search was conducted to identify relevant studies published in both English and Chinese for each included Chinese herb. These studies were then used by the NICM research team to draft detailed HDI monographs in accordance with the established evaluation methodology. The initial drafts underwent panel review by a committee comprising a senior pharmacologist, a senior toxicologist, and a TCM practitioner (physician), who assessed the interpretation of evidence, interaction classification, and clinical relevance. Following panel review, the monographs were proofread and finalized by a native English speaker. Once approved, the monographs

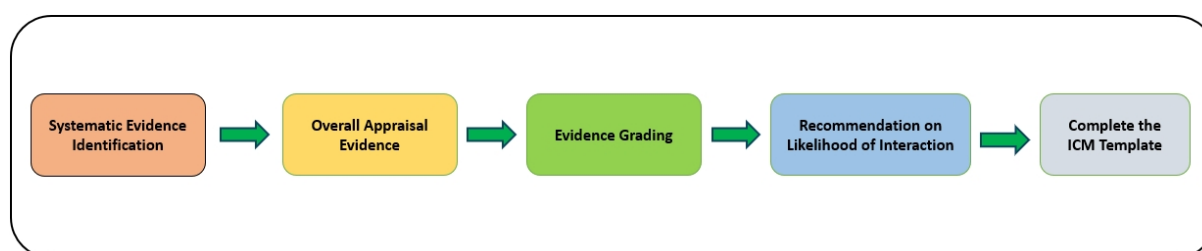


Figure 1 Workflow for the systematic development and evaluation of Chinese herb-drug interaction HDI monographs

Notes: ICM: integrative and complementary medicine. This figure summarizes the key steps used to identify evidence, extract data, assess evidence level and causality, assign interaction likelihood, conduct expert review, and integrate finalised monographs into the IMgateway database.

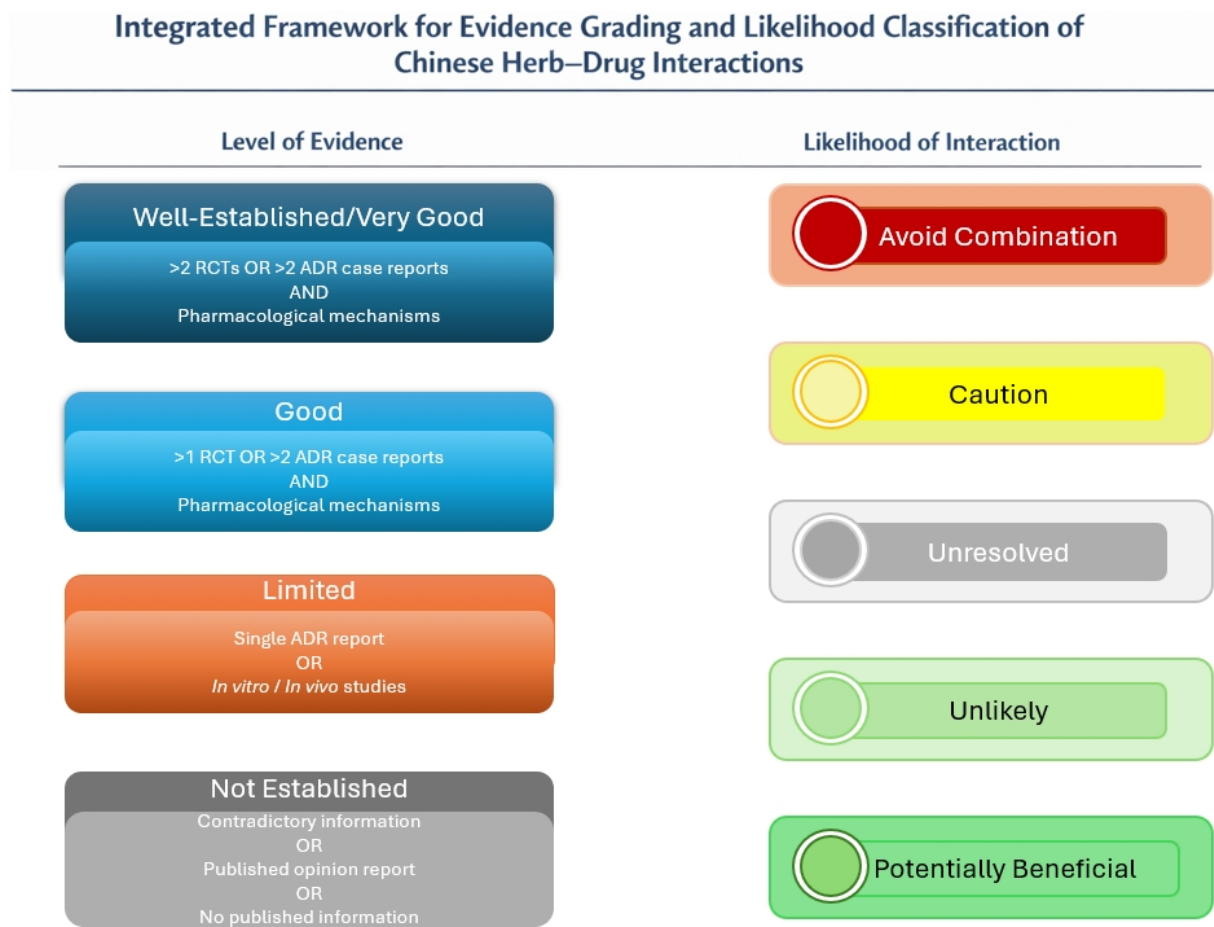


Figure 2 Evidence grading and interaction likelihood classification framework

Notes: ADR: adverse case report; RCT: randomized controlled trial. Evidence was graded into four levels: well-established/very good, good, limited, or not established. Well-established/very good evidence required support from at least two clinical trials or ADRs with identified pharmacological mechanisms. Good evidence referred to interactions supported by at least one clinical trial or two ADRs with pharmacological mechanisms. Limited evidence referred to interactions supported mainly by one ADR or preclinical studies (*in vitro* and *in vivo*). Not established evidence referred to interactions for which no relevant studies were available, evidence was contradictory, or available information was insufficient to support a clear conclusion. Based on the evidence level, clinical relevance, and potential risk–benefit profile, each interaction was assigned a likelihood category: avoid combination, caution, unresolved, unlikely, or potentially beneficial. Avoid combination indicated that co-administration was not recommended due to potential clinically significant adverse outcomes. Caution indicated that the combination may be used only with close clinical supervision, possible dose adjustment, and monitoring for adverse or altered therapeutic effects. Unresolved indicated that evidence was inconclusive, contradictory, or insufficient to provide a definitive clinical recommendation. Unlikely indicated that clinically significant interaction effects were not expected based on current evidence. Potentially beneficial indicated evidence suggesting possible enhancement of therapeutic efficacy or reduction of toxicity.

were incorporated into the IMgateway clinical decision-support database to enhance prescribing safety, support evidence-based integrative practice, and improve patient outcomes.

3. Results

3.1. Chinese herb list and study selection

A total of 200 Chinese herbs were included and systematically assessed for potential HDIs using a predefined search strategy. In Phase I, 10 Chinese herbs were evaluated, and 72 studies were identified from English and Chinese databases. After removing 11 duplicates, 61 studies were screened, with 20 excluded at the title and abstract stage. Of the remaining 41 full-text articles assessed, 10 were excluded due to poor methodological quality, insufficient HDI data, inappropriate study design, or lack of relevance. Ultimately, 31 studies were included in the final analysis. In Phase II, the assessment expanded to an additional 100 Chinese herbs, identifying 1221 studies. After removing 52 duplicates, 1169 studies were screened, and 421 were excluded at

the title and abstract stage. This left 748 full-text articles for detailed evaluation. Of these, 384 studies were excluded, resulting in 364 studies included in the final analysis. The excluded studies did not meet the predefined inclusion criteria, primarily due to poor methodological quality, absence of appropriate control groups (e.g., single-arm designs), inadequate or unclear statistical analysis, or lack of relevance to HDIs, such as studies not involving concurrent herb–drug use or focusing solely on herbal or pharmaceutical interventions. In Phase III, a further 90 Chinese herbs were assessed, identifying 882 studies. After removing 70 duplicates, 812 studies underwent title and abstract screening, with 364 excluded at this stage. Of the remaining 448 full-text articles reviewed, 346 were excluded and 102 were included in the final analysis. Full-text exclusions were based on similar criteria, including insufficient evidence to support HDIs, unclear or indirect interaction outcomes, inappropriate study design, or lack of clinically meaningful data. Overall, 497 studies were included in the database, comprising both clinical and preclinical (*in vitro* and *in vivo*) research (Figure 3). Clinical studies ($n = 268$) provided evidence for specific Chinese herb–drug interactions, while preclinical studies ($n = 229$) contributed pharmacokinetic and pharmacodynamic data relevant to interaction assessment.

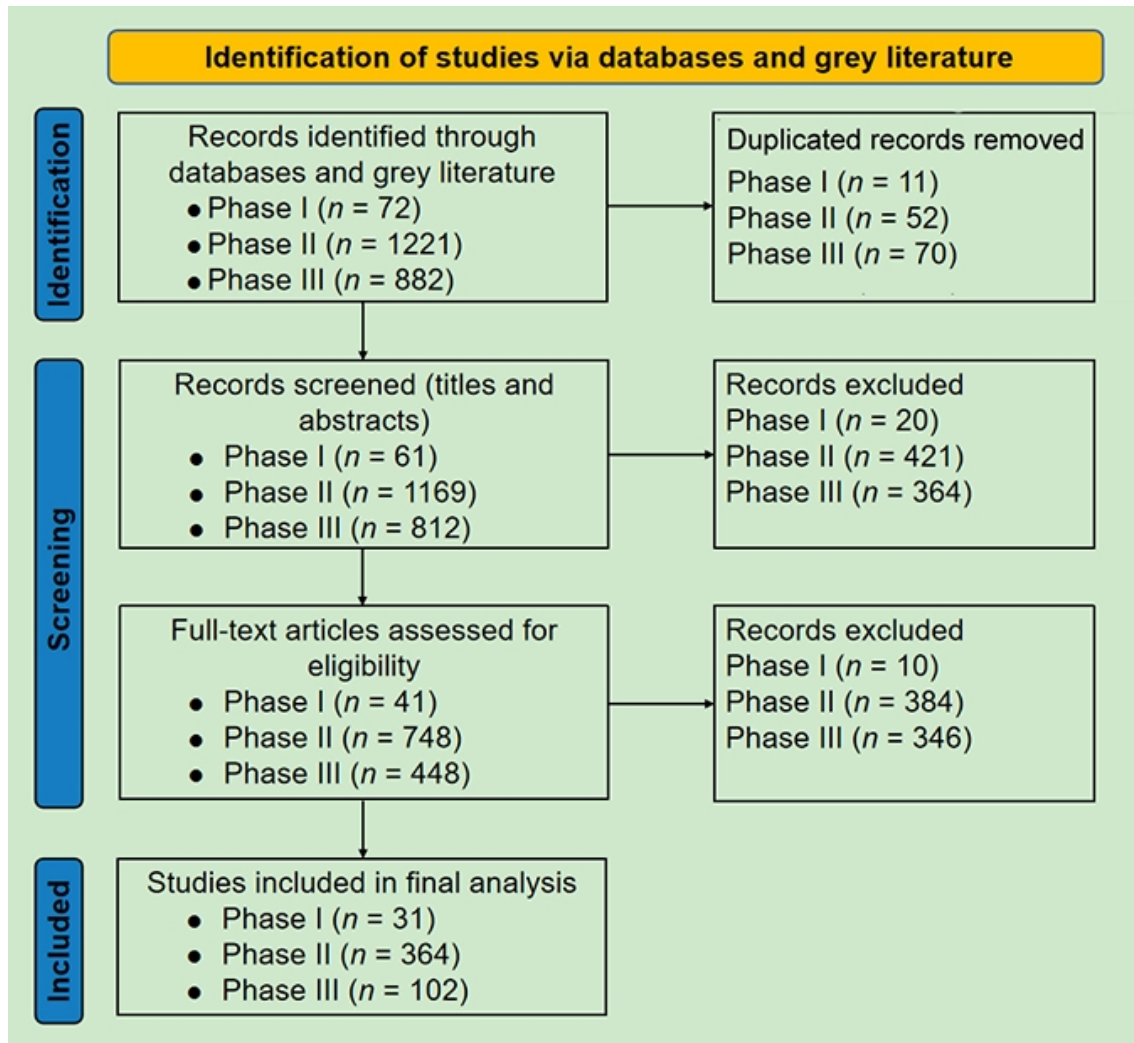


Figure 3 Flowchart of study identification, screening, and inclusion across the three review phases

3.2. Characteristics of included studies

Following the literature search and study selection process, a total of 497 studies published in English and Chinese were included as the evidence base for developing the Chinese HDI monographs. From these studies, 595 HDI monographs were developed for the database. The difference between the number of included studies and the number of monographs occurred because some studies investigated multiple HDIs, resulting in more than one monograph, with each HDI extracted and presented separately. Conversely, multiple studies investigating the same HDI were consolidated into a single monograph.

The number of monographs varied across the included herbs. For example, *Astragalus membranaceus* Fisch. (*A. membranaceus*, Huang Qi) was associated with more than 40 monographs. Two herbs, *Apis mellifera* L. (*A. mellifera*, Feng Mi), and *Coptis chinensis* Franch. (*C. chinensis*, Huang Lian), were linked to more than 20 monographs each. Thirteen herbs, including commonly used Chinese herbs such as *Salvia miltiorrhiza* Bge (*S. miltiorrhiza*, Dan Shen), and *Ginkgo biloba* L. (*G. biloba*, Yin Xing), were supported by more than 10 monographs each, while the remaining herbs were associated with fewer than 10 monographs each. This distribution reflects variability in the number of reported HDIs for each herb within the compiled database.

Of the 595 HDI monographs developed from the 497 included studies, 241 were based on RCTs, 27 on human case reports, and 327 on preclinical studies. Among the preclinical monographs, 183 reported *in vitro* findings

and 144 reported *in vivo* findings.

3.3. Determination of interaction likelihood and evidence level

Implementation of the established evaluation framework across the 595 Chinese HDI monographs revealed variability in the strength of supporting evidence. Twenty-eight interactions were classified as well-established, supported by consistent and high-quality clinical trials or case reports. Seventy-six interactions were categorized as having good evidence, based on supportive clinical findings accompanied by mechanistic insights. The majority of interactions ($n = 395$) were supported by limited evidence, primarily derived from clinical and preclinical studies. A further 96 interactions were classified as unknown due to insufficient or conflicting evidence. Overall, interactions supported by strong clinical evidence represented only a small proportion compared with those supported by limited or preclinical evidence. Based on the assigned evidence levels, an interaction likelihood classification was generated for all monographs. Seven interactions were categorized as “avoid combination,” indicating a high probability of clinically significant interactions. One hundred and fourteen interactions were classified as “caution,” reflecting a moderate probability based on the available evidence. Seventy-three interactions were considered “unlikely,” suggesting a low probability of clinically significant interaction. Two hundred and ninety-five interactions were categorized as “potentially beneficial,” where available evidence suggest-

ed enhanced drug efficacy or reduced toxicity without an increased safety risk. The remaining 106 interactions were classified as “unresolved” due to insufficient or inconsistent evidence.

Figure 4 illustrates the distribution of monographs, evidence levels, and interaction likelihood classifications across the 595 Chinese HDI monographs included in the database.

3.4. Clinical relevance and implications for decision-making

The predefined classification of the 595 Chinese HDI monographs into specific evidence and likelihood categories provides a clinically practical framework to support prescribing decisions in integrative healthcare settings. Interactions categorized as “avoid combination” ($n = 7$) represent herb-drug combinations with a high probability of clinically significant adverse outcomes and therefore warrant avoidance, substitution, or close therapeutic monitoring. For example, a clinical case report documented that co-administration of *Curcuma longa* L. (*C. longa*, Jiang Huang) with tacrolimus potentiated toxicity and resulted in acute nephrotoxicity in a transplant recipient.²² Interactions classified as “caution” ($n = 114$) indicate a moderate probability of interaction and highlight the need for individualized risk-benefit assessment, potential dose adjustment, or enhanced monitoring. For instance, a study reported that the co-administration of *Gastrodia elata* Bl. (*G. elata*, Tian Ma) with valproic acid altered the pharmacokinetic profile of valproic acid by increasing drug exposure and enhancing blood–brain barrier penetration.²³ Interactions categorized as “unlikely” ($n = 73$) provide reassurance where available data suggest minimal interaction risk, thereby reducing unnecessary discontinuation of CHM. For example, co-administration of *Morus alba* L. (*M. alba*, Sang Bai Pi) with ciprofloxacin did not demonstrate clinically significant beneficial or harmful effects.²⁴ Potentially beneficial HDIs ($n = 295$) highlight combinations where co-administration may enhance therapeutic efficacy or reduce drug-related toxicity, particularly when supported

by clinical evidence. For example, a RCT reported that *Ziziphus jujuba* Mill. (*Z. jujuba*, Da Zao), when used with cetirizine, improved urticaria outcomes. Preclinical studies have also demonstrated synergistic anticancer effects of *Crocus sativus* L. (*C. sativus*, Xi Hong Hua) in combination with temozolomide in glioma cell lines.^{25,26} Meanwhile, interactions classified as “unresolved” ($n = 106$) indicate combinations that require clinical vigilance and further investigation due to insufficient or inconsistent evidence. For instance, evidence regarding the interaction between *Panax ginseng* C. A. Mey. (*P. ginseng*, Ren Shen) and warfarin remains unresolved. One case report has suggested a potential adverse interaction, whereas one RCT and one animal study did not demonstrate significant effects on the pharmacokinetic or pharmacodynamic of warfarin.^{27–29} Overall, this evidence-based classification translates heterogeneous clinical and preclinical findings into standardized recommendations that can inform risk assessment, guide patient counselling, support pharmacovigilance practices, and facilitate the safe integration of CHMs with conventional therapeutic regimens.

In clinical practice, the database may assist HCPs by providing rapid access to structured information on the likelihood, evidence strength, mechanism, and clinical relevance of Chinese HDIs. This can support risk–benefit assessment, guide decisions on whether to avoid a combination, use it with caution, monitor therapy more closely, or consider a potentially beneficial interaction. The database may also support patient counselling, documentation of CHM use, and pharmacovigilance by helping clinicians identify interactions that require monitoring or further reporting.

4. Discussion

This study addresses a significant knowledge gap in the field of Chinese HDIs by systematically integrating clinical, pharmacological, and traditional evidence into standardized, evidence-graded monographs and incorporating them into an online database accessible to TCM practitioners and other HCPs. Although HMs are widely used worldwide, interaction data from

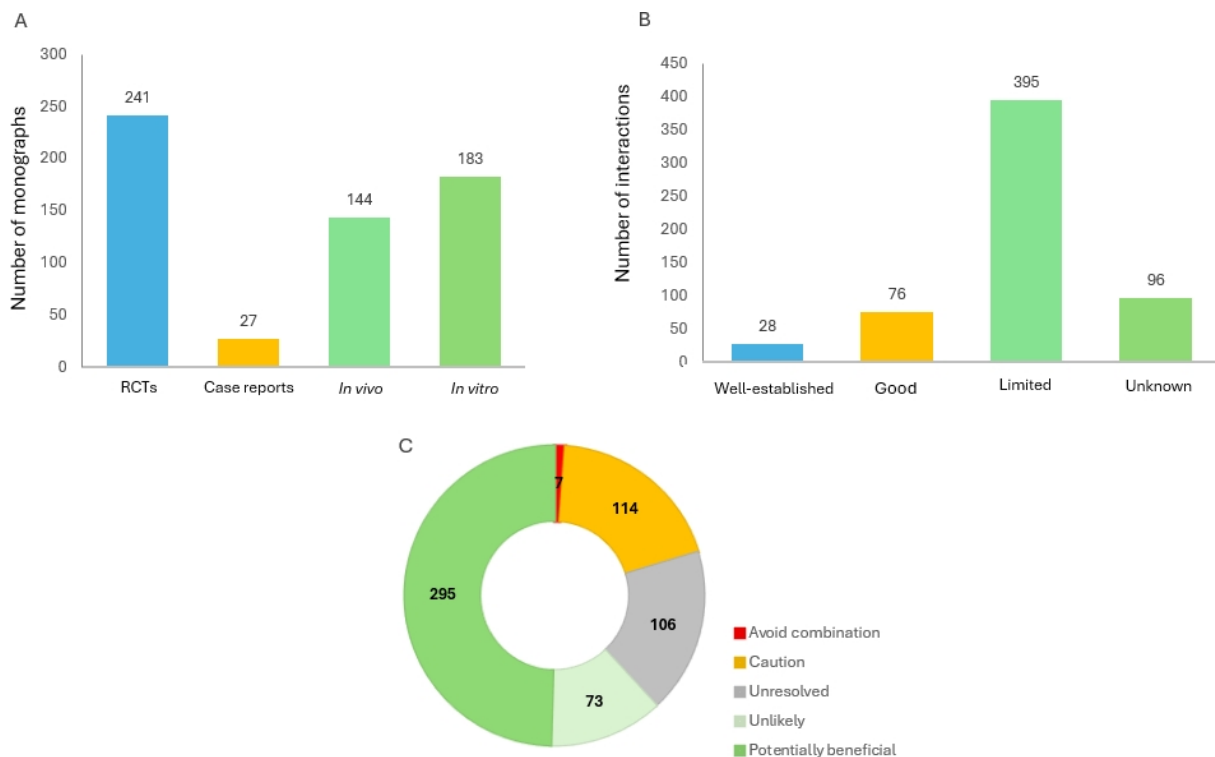


Figure 4 Distribution of HDI monographs by evidence source, evidence level, and likelihood classification. (A) Monographs classified by evidence source. (B) Evidence-level classification. (C) Interaction likelihood classification.

Notes: HDI: herb-drug interaction; RCTs: randomized controlled trials.

RCTs, human case reports, pharmacokinetic studies, and mechanistic laboratory research are often fragmented and frequently lack harmonized causality assessment or transparent grading criteria. Recent evaluations have highlighted the increasing global reliance on HMs alongside conventional pharmacotherapy and the growing need for robust pharmacovigilance systems.³⁰ Similarly, previous reviews have identified persistent inconsistencies in HDI documentation, underreporting of HM use in clinical settings, and variability in causality assessment methods.³¹ By incorporating both English- and Chinese-language literature and applying predefined evidence-level classifications aligned with WHO pharmacovigilance principles, the IMgateway database provides a transparent and reproducible framework that moves beyond narrative reporting toward standardized clinical interpretation.³² This approach helps bridge the gap between mechanistic research, clinical observations, and practical decision-support applications.

This study describes the systematic development of evidence-based Chinese HDI monographs for integration into the IMgateway clinical decision-support database. A total of 497 studies published in English and Chinese were included, from which 595 HDI monographs were developed. The findings demonstrate that Chinese HDI evidence is broad but heterogeneous, with substantial variation in study design, evidence strength, clinical relevance, and interaction likelihood. Only a small proportion of interactions were supported by well-established or good-quality clinical evidence, whereas many were supported primarily by limited or preclinical evidence. This highlights the need for cautious interpretation of HDI evidence and supports the value of a structured framework that links evidence level, causality assessment, mechanism, and clinical recommendation. The predominance of limited evidence highlights the need for cautious clinical interpretation. While preclinical and mechanistic studies provide useful signals for potential HDIs, further well-designed human pharmacokinetic studies, controlled clinical trials, and real-world observational studies are required to confirm the clinical significance of many reported interactions. This pattern is consistent with findings from recent evaluations of herbal safety literature, which indicate that much of the current evidence base remains dominated by *in vitro* and animal studies rather than robust clinical trials.³³ However, the structured linkage between graded evidence levels and defined likelihood categories in this study enables clearer differentiation between high-risk combinations (“avoid combination”), moderate-risk scenarios (“caution”), minimal-risk pairings (“unlikely”), and potentially beneficial interactions. The identification of potentially beneficial interactions is particularly relevant in areas such as oncology, cardiology, and chronic inflammatory disorders. Several included Chinese herbs have demonstrated synergistic effects, including reduced chemotherapy-related toxicity and improved symptom control.³⁴

At the same time, interactions classified as “unlikely” also provide important safety insights. Although these studies did not demonstrate clinically meaningful beneficial or harmful effects, they contribute valuable evidence supporting the safe integrative use of TCM alongside conventional medications. The absence of significant interaction signals in these cases may offer reassurance for commonly co-administered herb-drug combinations in clinical practice. Together, findings related to both potentially beneficial and unlikely interactions highlight the importance of balanced evaluation recognising therapeutic opportunities while maintaining careful safety considerations in integrative medicine. In this context, evidence-level classification not only helps quantify interaction risk but also reflects the therapeutic complexity inherent in integrative healthcare.

Several established resources provide useful herb, supplement, and drug-interaction information, including Natural Medicines, Memorial Sloan Kettering Cancer Center’s About Herbs database, PHYtotherapy DruG Interaction (PHYDGI) and Lexicomp.^{16,35–37} The Memorial Sloan Kettering About Herbs database is designed for both the public and HCPs and includes information on uses, mechanisms, adverse effects, and potential interactions.³⁵ Natural Medicines provides evidence-based monographs and an interaction checker for natural medicines and prescription or over-the-counter medicines.³⁶ PHYDGI is another structured HDI resource that, as of 2022, included 58 plants and 114 medical substances, with emphasis on pharmacokinetic interaction evidence.¹⁶

Compared with these resources, the IMgateway Chinese HDI monograph framework provides several complementary features. First, it specifically focuses on CHMs and incorporates both English- and Chinese-language evidence, which is important because most of TCM research is published in Chinese-language databases. Second, the framework applies predefined criteria for evidence level, causality, and interaction likelihood, allowing users to distinguish between well-supported clinical interactions, preliminary preclinical signals, unlikely interactions, and potentially beneficial combinations. Third, the database translates heterogeneous evidence into practitioner guidance, which may be more directly applicable to clinical decision-making in integrative healthcare settings.

In clinical settings, the IMgateway Chinese HDI database may support clinical decision-making by providing HCPs with rapid access to structured and evidence-graded information on the likelihood, mechanism, clinical relevance, and recommended management of Chinese HDIs. At the point of care, practitioners could use the database when reviewing a patient’s medication and CHM history to identify whether a specific herb-drug combination should be avoided, used with caution, monitored more closely, considered unlikely to cause clinically meaningful interaction, or recognised as potentially beneficial. This may support individualized risk–benefit assessment, particularly for patients using multiple medicines, older adults, patients with chronic diseases, and those receiving drugs with narrow therapeutic indices. The database may also guide practical prescribing decisions, such as whether to discontinue or substitute a CHM, adjust monitoring frequency, check relevant clinical or laboratory parameters, counsel patients about possible interaction symptoms, or document and report suspected adverse events. In this way, the database is intended not only as an evidence repository, but as a clinically interpretable decision-support tool that can help translate heterogeneous HDI evidence into safer prescribing, improved communication between HCPs and patients, and strengthened pharmacovigilance in integrative healthcare.

Despite its strengths, this study has several limitations. Although 200 individual Chinese herbs were systematically assessed, the database does not yet comprehensively address multi-herb formulations, proprietary Chinese medicines or complex prescriptions commonly used in real-world TCM practice. This may limit direct clinical applicability, as interactions in multi-herb formulas may differ from those of single herbs due to herb–herb interactions, dose variation, preparation methods, product standardization, and manufacturing variability. In addition, the predominance of preclinical data for many interactions underscores the continued need for well-designed human pharmacokinetic and clinical outcome studies. Although the database provides a structured and evidence-based framework for classifying Chinese HDIs, its clinical impact has not yet been prospectively validated in healthcare settings. This is partly because the database has been newly developed and recently launched; therefore, real-world user feedback, clinical usability data, and prescribing outcome data are still being collected. Moreover, formal inter-rater agreement, such as Cohen’s kappa, was not calculated. However, this reflects the consensus-based nature of the monograph development process, in which studies were assessed using predefined HDI-specific criteria.

Future development and validation should follow a stepwise approach. First, the database can be expanded to include commonly used multi-herb formulas and proprietary Chinese medicines to better reflect real-world TCM practice. However, the inclusion of multi-herb formulas presents several methodological challenges, including the limited availability of clinical interaction studies, difficulty in identifying and explaining the mechanisms of HDIs, variation in herb composition and dosage, and lack of standardization across formulations, preparation methods, and commercial products. These factors may complicate evidence grading and clinical interpretation, and should therefore be addressed through transparent documentation of formulation details, quality standards, and the strength of available evidence. Second, selected monographs should undergo multidisciplinary expert review by TCM practitioners, pharmacists, pharmacologists, toxicologists, and medical practitioners to confirm clinical relevance, clarity, and practical usability. Third, usability testing should be conducted with HCPs to assess whether the

database is easy to navigate, clinically interpretable, and useful during patient consultation or medication review. Fourth, pilot implementation in clinical settings should evaluate how the database is used in real-world decision-making, including its role in identifying potential interactions, supporting monitoring decisions, improving documentation of CHM use, and guiding patient counselling. Finally, prospective studies should assess whether use of the database improves prescribing decisions, enhances adverse-event detection and reporting, supports safer patient counselling, and contributes to improved clinical outcomes in integrative healthcare practice.

5. Conclusion

This study presents a systematic, evidence-based framework for evaluating Chinese HDIs and reports 595 structured HDI monographs developed from 497 included studies across three phases. By incorporating both English- and Chinese-language literature and applying predefined evidence grading and likelihood classification criteria, the database translates heterogeneous clinical and preclinical findings into standardized, clinically interpretable recommendations. This classification provides practical guidance for HCPs managing the concurrent use of herbal and pharmaceutical therapies. The findings reflect the growing body of literature on HDIs while also demonstrating that many reported interactions remain supported primarily by limited or preclinical evidence, highlighting the need for systematic appraisal and cautious clinical interpretation. Organising fragmented evidence within a transparent and standardized decision-support framework helps address this challenge. The database facilitates safer prescribing, enhances patient counselling, and strengthens pharmacovigilance within integrative healthcare practice. Continued expansion, regular updating, and clinical validation of the database will further strengthen its role as a reliable tool for optimising therapeutic safety and efficacy in settings where CHM and pharmaceutical drugs are co-administered.

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Data Availability

Additional data related to this paper may be obtained from the corresponding author upon reasonable request.

Author Contribution Statement

Faiza Azhar: Data curation, formal analysis, methodology, visualization, and writing – original draft. **Belinda Huor:** Investigation, visualization, software, and writing – review & editing. **Bo-hua Yan:** Data curation, methodology, and writing – reviewing & editing. **Chun Guang Li:** Formal analysis, supervision, and writing – review & editing. **Gerald Münch:** Supervision and writing – review & editing. **Xian Zhou:** Supervision, methodology, validation, project administration, funding acquisition, and writing – review & editing.

Use of AI Statement

The authors used ChatGPT (GPT-5.6 Sol; OpenAI OpCo, LLC, San Francisco, CA) to assist with language polishing and grammar improvement. The authors take full responsibility for the accuracy and integrity of the content.

Declaration of Competing Interest

No potential conflict of interest was reported by the authors.

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Electronic Supplementary Material

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