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Natural compounds derived from Chinese materia medica for post-myocardial infarction cardiac remodeling: a preclinical systematic review and meta-analysis protocol

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ADMINISTRATIVE INFORMATION

Support - This review has received no specific financial support. The work will be conducted using institutional academic resources of the authors' affiliated institutions.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - The corresponding author holds an intellectual patent related to a self-developed Chinese herbal formula, Danshen Tongluo Jiedu Decoction. This formula is not an eligible intervention in the present review, because the review will exclude Chinese herbal formulas, decoctions, proprietary Chinese medicines, injections, and other undefined compound preparations according to the predefined eligibility criteria. The present review focuses on natural compounds derived from Chinese materia medica and chemically defined extracts in animal models of post-myocardial infarction cardiac remodeling. This intellectual property interest will not influence the review question, eligibility criteria, study selection, data extraction, risk-of-bias assessment, statistical analysis, interpretation, or publication. All procedures will follow the prospectively registered protocol and will be conducted by at least two independent reviewers.

INPLASY registration number: INPLASY202650174

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 May 2026 and was last updated on 31 May 2026.

INTRODUCTION

Review question / Objective This review aims to systematically evaluate the efficacy and mechanistic evidence of natural compounds derived from Chinese materia medica and defined extracts in animal models of post-myocardial infarction cardiac remodeling.

Using a PICOS framework, the population will include in vivo animal models of myocardial infarction-induced cardiac remodeling or myocardial fibrosis, primarily models established by permanent left anterior descending coronary artery or coronary artery ligation. Ischemia/reperfusion models will only be considered when the follow-up duration and outcomes clearly reflect ventricular remodeling, myocardial fibrosis, or long-term cardiac functional changes. The interventions will include Chinese materia medica-derived bioactive compounds, isolated natural compounds, and chemically defined extract fractions, such as saponins, flavonoids, polyphenols, phenolic acids, alkaloids, terpenoids, polysaccharides, and glycosides. Comparators will include model controls, vehicle controls, saline

controls, placebo controls, or identical background treatment controls.

The primary outcomes will include left ventricular ejection fraction, left ventricular fractional shortening, left ventricular end-diastolic diameter or dimension, and left ventricular end-systolic diameter or dimension. Secondary outcomes will include myocardial fibrosis, infarct size, ventricular structural indices, myocardial injury markers, and hemodynamic parameters. Mechanistic outcomes will include markers related to anti-fibrotic, anti-inflammatory, antioxidant, anti-apoptotic, mitochondrial, autophagy, and ferroptosis-related pathways.

This review is designed to clarify whether these interventions improve cardiac function, structural remodeling, and myocardial fibrosis in post-myocardial infarction animal models, and to identify candidate compounds or extract categories that may warrant further confirmatory preclinical and translational investigation.

Rationale Myocardial infarction-induced cardiac remodeling is a major pathological process leading to progressive left ventricular dysfunction, myocardial fibrosis, heart failure and adverse prognosis. Numerous animal studies have reported potentially beneficial effects of natural compounds, particularly Chinese materia medica-derived bioactive compounds and chemically defined extracts, on post-infarction cardiac remodeling. However, the available evidence is fragmented across different compounds, extract categories, animal species, infarction models, treatment windows, doses and outcome measures.

Existing related reviews are mainly focused on clinical Chinese herbal formulas, proprietary Chinese medicines or broad cardiovascular interventions, whereas the preclinical evidence for individual natural compounds and defined extracts in post-myocardial infarction remodeling has not been systematically synthesized with a clear translational framework. A rigorous preclinical systematic review and meta-analysis is therefore needed to estimate the magnitude and robustness of organ-level benefits, assess risk of bias in animal studies, identify sources of heterogeneity, and summarize mechanistic evidence involving fibrosis, inflammation, oxidative stress, apoptosis, mitochondrial function, autophagy and ferroptosis-related pathways.

This review is not intended to provide direct clinical treatment recommendations. Instead, it aims to identify candidate compounds or extract categories with relatively reproducible effects and translational plausibility, thereby informing confirmatory animal experiments, pharmacological development and future clinical research.

Condition being studied The condition being studied is post-myocardial infarction cardiac remodeling in animal models. Following myocardial infarction, the injured heart undergoes progressive structural and functional changes, including left ventricular dilation, impaired systolic function, myocardial fibrosis, collagen deposition, inflammatory activation, oxidative stress, cardiomyocyte apoptosis, mitochondrial dysfunction and changes in extracellular matrix turnover. These processes contribute to the development of heart failure and poor long-term outcomes after myocardial infarction.

This review will focus on in vivo animal models of myocardial infarction-induced ventricular remodeling or post-myocardial infarction myocardial fibrosis, primarily models established by permanent left anterior descending coronary artery or coronary artery ligation. Ischemia/reperfusion models will only be considered when the follow-up duration and reported outcomes clearly reflect ventricular remodeling, myocardial fibrosis, collagen deposition or long-term cardiac functional and structural changes rather than acute ischemia/reperfusion injury alone.

The review will not focus on non-myocardial infarction models such as pressure overload, isoproterenol-induced myocardial injury, doxorubicin cardiomyopathy, diabetic cardiomyopathy, hypertensive heart disease or sepsis-induced myocardial injury.

METHODS

Search strategy We will search PubMed, Embase, Web of Science Core Collection, Cochrane Library, CNKI, WanFang, SinoMed and VIP from database inception to the date of the final database search. No restriction on publication year will be applied. English and Chinese databases will be searched. Scopus will not be included as a main database because of substantial coverage overlap with Web of Science and Embase and database access/export limitations; this will be compensated for by backward and forward citation searching.

The search strategy will combine four core concepts: myocardial infarction/post-infarction animal models, ventricular remodeling or fibrosis-related outcomes, natural compounds or defined extracts, and animal studies. Search terms for the

disease/model concept will include "myocardial infarction", "acute myocardial infarction", "post-myocardial infarction", "post-MI", "post-infarction", "infarcted heart", "coronary artery ligation", "left anterior descending", "LAD ligation", and corresponding Chinese terms. Search terms for remodeling and outcome concepts will include "cardiac remodeling", "ventricular remodeling", "left ventricular remodeling", "myocardial fibrosis", "cardiac fibrosis", "collagen deposition", "cardiac function", "left ventricular dysfunction", "echocardiography", "ejection fraction", "LVEF", "LVFS", "LVEDD", "LVESD", "LVIDd" and "LVIDs".

Intervention terms will include "natural product", "phytochemical", "bioactive compound", "active constituent", "isolated compound", "plant extract", "defined extract", "extract fraction", "Chinese materia medica", "traditional Chinese medicine", "Chinese herbal medicine", "medicinal plant", "flavonoid", "polyphenol", "alkaloid", "saponin", "phenolic acid", "terpenoid", "polysaccharide", "glycoside", and representative compound names such as ginsenoside, notoginsenoside, tanshinone, salvianolic acid, puerarin, paeonol, curcumin, resveratrol, astragaloside, baicalin, berberine, quercetin, icariin, ligustrazine and salidroside. Animal terms will include "animal", "rat", "mouse", "mice", "murine", "rodent", "rabbit", "swine", "pig", "dog" and "in vivo", with database-specific animal filters applied where appropriate.

The search will not use broad NOT terms to exclude formulas, decoctions, capsules, injections or compound preparations, in order to avoid incorrectly excluding eligible records containing terms such as "active compound". These exclusions will be applied during full-text screening according to predefined eligibility criteria. Reference lists of included studies and relevant reviews will also be screened, and additional records will be documented separately in the PRISMA flow diagram.

Participant or population This review will include in vivo animal models of myocardial infarction-induced cardiac remodeling or post-myocardial infarction myocardial fibrosis. Eligible animal species will include rats, mice and other mammalian species such as rabbits, dogs, pigs or swine, if relevant data are available. Models will primarily include permanent left anterior descending coronary artery ligation or coronary artery ligation-induced myocardial infarction.

Ischemia/reperfusion models will only be included when the follow-up duration and reported outcomes clearly reflect ventricular remodeling, myocardial fibrosis, collagen deposition, or long-term cardiac functional and structural changes rather than acute ischemia/reperfusion injury alone. Studies with a follow-up duration of at least 7 days after myocardial infarction will be prioritized. Studies with shorter follow-up may only be considered if they clearly report structural remodeling or fibrosis-related outcomes and will be examined in sensitivity analyses.

Non-myocardial infarction models, including pressure overload, isoproterenol-induced myocardial injury, doxorubicin cardiomyopathy, diabetic cardiomyopathy, hypertensive heart disease, sepsis-induced myocardial injury, or isolated heart failure models without myocardial infarction, will be excluded.

Intervention Eligible interventions will include natural compounds derived from Chinese materia medica, isolated bioactive compounds, and chemically defined extract fractions used in animal models of post-myocardial infarction cardiac remodeling. Examples include, but are not limited to, ginsenosides, notoginsenosides, tanshinones, salvianolic acids, puerarin, paeonol, curcumin, resveratrol, astragaloside, baicalin, berberine, quercetin, icariin, ligustrazine, salidroside, and chemically defined categories such as total saponins, total flavonoids, polyphenols, phenolic acids, alkaloids, terpenoids, polysaccharides and glycosides.

To be eligible, the intervention should be reported as a single compound, a defined active constituent, or a chemically characterized extract or fraction. The source, chemical category, dose, route of administration, timing of administration and treatment duration will be extracted whenever available.

Chinese herbal formulas, decoctions, proprietary Chinese medicines, injections, capsules, pills, granules, medicated serum, crude extracts without clear composition, undefined compound preparations, synthetic drugs, gene therapy, cell therapy, exosomes, biomaterials and interventions combined with other therapies in a way that prevents isolation of the compound-specific effect will be excluded.

Comparator Eligible comparators will include myocardial infarction model controls, vehicle controls, saline controls, placebo controls, or groups receiving the same background treatment without the target natural compound or defined extract. For multi-arm dose-response studies, each eligible intervention dose may be compared

with the corresponding model or vehicle control according to the predefined data extraction and statistical rules.

Positive control drugs may be recorded as supplementary information, but studies will not be eligible if the only comparison is between the natural compound or defined extract and a positive drug without a model, vehicle, saline or placebo control group. If all experimental groups receive the same background treatment, the study may be included provided that the independent effect of the target intervention can be extracted.

Study designs to be included In vivo controlled animal intervention studies will be included. Eligible records may include peer-reviewed full-text articles and dissertations with extractable quantitative data. Clinical studies, in vitro-only studies, reviews, systematic reviews, meta-analyses, conference abstracts, protocols, comments, letters, network pharmacology-only studies and bioinformatics-only studies will be excluded.

Eligibility criteria Studies will be eligible if they meet the predefined PICOS criteria and report at least one relevant quantitative outcome related to cardiac function, ventricular remodeling, myocardial fibrosis, infarct size, myocardial injury or hemodynamics. Eligible studies must provide mean, standard deviation or standard error, and sample size, or present data that can be extracted from figures. If standard deviation is not directly reported, it will be converted from standard error or other available data when appropriate.

Studies will be excluded if the full text is unavailable, if the intervention effect cannot be separated from co-interventions, if there is no eligible model or vehicle control group, or if the outcomes are limited to pharmacokinetics, toxicity, descriptive morphology or isolated molecular markers without phenotypic cardiac outcomes. Duplicate publications or overlapping datasets will be assessed carefully; when multiple reports use the same animals or dataset, the most complete or most original report will be retained. Studies using Chinese herbal formulas, decoctions, proprietary Chinese medicines, injections, pills, capsules, granules, medicated serum or undefined crude extracts will be excluded.

Information sources The following electronic databases will be searched from inception to the final search date: PubMed, Embase, Web of Science Core Collection, Cochrane Library, China National Knowledge Infrastructure, WanFang, SinoMed and VIP. English and Chinese databases will be searched without restriction on publication year. Search strategies will be adapted for each database using controlled vocabulary and free-text terms related to myocardial infarction, post-infarction remodeling, ventricular remodeling, myocardial fibrosis, natural compounds, Chinese materia medica-derived bioactive compounds, defined extracts and animal studies.

Scopus will not be included as a main database because of substantial coverage overlap with Web of Science and Embase and database access/export limitations. To reduce the risk of missing eligible studies, we will screen the reference lists of all included studies and relevant reviews. Forward citation searching may be performed in Web of Science and PubMed when necessary. Additional records identified through citation searching or other sources will be documented separately in the PRISMA flow diagram. When key data are missing or unclear, study authors may be contacted for further information.

Main outcome(s) The main outcomes will be cardiac function and left ventricular remodeling indices in post-myocardial infarction animal models. Primary outcomes will include left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS), left ventricular end-diastolic diameter or dimension (LVEDD/LVIDd), and left ventricular end-systolic diameter or dimension (LVESD/LVIDs), mainly measured by echocardiography or comparable cardiac functional assessment methods.

Outcomes will be extracted at the latest relevant follow-up time point after myocardial infarction or intervention, provided that the timing reflects ventricular remodeling rather than acute myocardial injury alone. Studies with follow-up of at least 7 days after myocardial infarction will be prioritized. If multiple time points, doses or intervention arms are reported, predefined extraction rules will be applied to avoid inappropriate double-counting of shared control groups. Mean differences will be used when outcome units are consistent; standardized mean differences will be used when measurement methods or units differ.

Additional outcome(s) Additional outcomes will include myocardial fibrosis, infarct size, ventricular structural indices, myocardial injury markers, hemodynamic parameters and mechanistic biomarkers.

Fibrosis-related outcomes will include Masson staining, collagen volume fraction, collagen I/III, α-SMA and other extracellular matrix-related indices. Infarct size will include TTC staining or other quantitative infarct area measurements. Ventricular structural and hemodynamic outcomes will include heart weight/body weight, left ventricular weight/body weight, left ventricular mass, LVEDP and ±dp/dtmax. Myocardial injury markers will include CK-MB, LDH, cTnI and cTnT where available.

Mechanistic outcomes will be summarized as exploratory evidence and may include anti-fibrotic pathways such as TGF-β/Smad, inflammatory markers such as TNF-α, IL-6, IL-1β and NF-κB, oxidative stress markers such as MDA, SOD, GSH, ROS and Nrf2/HO-1, apoptosis-related markers such as Bax, Bcl-2, caspase-3 and TUNEL, as well as mitochondrial function, autophagy and ferroptosis-related markers including LC3, Beclin-1, p62, GPX4, SLC7A11, ACSL4, 4-HNE and Fe^{2+}.

Data management All records retrieved from electronic databases and supplementary searches will be imported into reference management software such as EndNote, Zotero or NoteExpress, and then transferred to Rayyan, Covidence or an equivalent platform for screening. Duplicates will be removed using DOI, PMID, title, author, year and manual verification, including manual checking of possible Chinese-English duplicate reports.

Two reviewers will independently screen titles/abstracts and full texts according to the predefined eligibility criteria. Disagreements will be resolved through discussion or consultation with a third reviewer. Reasons for full-text exclusion will be recorded and summarized in the PRISMA flow diagram.

Data will be extracted independently by two reviewers using a standardized extraction form. Extracted information will include bibliographic details, animal characteristics, model characteristics, intervention details, comparator, outcome data, time points, sample sizes, data source, and risk-of-bias information. Numerical data will be extracted from text, tables, supplementary materials or figures; figure data may be digitized using validated software when necessary. Missing or unclear data may be requested from study authors.

All data files, screening decisions, extraction sheets, risk-of-bias assessments and analysis files will be stored with version control and regular backup. Any protocol deviations will be dated, documented and justified.

Quality assessment / Risk of bias analysis Risk of bias in included animal studies will be assessed independently by two reviewers using the SYRCLE risk of bias tool. The assessment will cover sequence generation, baseline characteristics, allocation concealment, random housing, blinding of caregivers or investigators, random outcome assessment, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other potential sources of bias. Each domain will be judged as low, high or unclear risk of bias according to the information reported in the original study.

Disagreements between reviewers will be resolved by discussion or consultation with a third reviewer. Risk-of-bias results will be summarized in tables and figures and considered in sensitivity analyses. Studies will not be excluded solely based on risk-of-bias assessment, but the influence of high or unclear risk of bias will be explored. Key ARRIVE-related reporting items, including animal characteristics, sample size calculation, randomization, blinding, ethical approval and housing conditions, will also be recorded as supplementary information on reporting quality.

Strategy of data synthesis A quantitative meta-analysis will be performed when at least two studies report comparable outcomes. Continuous outcomes will be summarized using mean difference when units and measurement methods are sufficiently consistent, and standardized mean difference when different scales, methods or units are used. Random-effects models will be used as the default approach because methodological and biological heterogeneity is expected across animal species, infarction models, interventions, doses and follow-up durations.

For each study, means, standard deviations and sample sizes will be extracted. Standard errors will be converted to standard deviations when necessary. If data are presented only in figures, numerical values may be extracted using digital image extraction software. When multiple doses, time points or intervention arms are reported, predefined rules will be applied to avoid inappropriate double-counting of shared control groups. The latest relevant follow-up time point reflecting ventricular remodeling will be prioritized for primary analyses.

Heterogeneity will be assessed using I^2 statistics and chi-square tests. Potential sources of

heterogeneity will be explored by subgroup analyses and sensitivity analyses. Publication bias will be assessed using funnel plots and Egger's test when at least 10 studies are available for a given outcome. If quantitative synthesis is not appropriate, findings will be summarized narratively according to intervention category, model characteristics, outcome type and risk of bias.

Subgroup analysis If sufficient data are available, predefined subgroup analyses will be performed according to animal species, infarction model, intervention type, chemical category, treatment timing, treatment duration, follow-up duration, route of administration, dose level and risk of bias.

Planned subgroup variables include species such as rat, mouse or other mammalian species; model type such as permanent coronary or LAD ligation versus ischemia/reperfusion models with remodeling follow-up; intervention type such as isolated single compounds versus chemically defined extracts or fractions; chemical category such as saponins, flavonoids, polyphenols, phenolic acids, alkaloids, terpenoids, polysaccharides or glycosides; treatment timing such as pre-treatment, early post-treatment or delayed post-treatment; treatment duration such as ≤2 weeks versus >2 weeks; and follow-up duration.

Additional subgroup analyses may include sex of animals, route of administration, presence or absence of positive control drugs, and whether randomization or blinding was reported. Subgroup analyses will be interpreted cautiously and regarded as exploratory when the number of studies is limited.

If data are insufficient for a prespecified subgroup, the subgroup analysis may be omitted, combined into broader clinically or pharmacologically meaningful categories, or summarized narratively. Any additional subgroup analyses not specified in this protocol will be clearly labelled as post hoc exploratory analyses in the final review.

Sensitivity analysis Sensitivity analyses will be performed to assess the robustness of the main findings. Planned sensitivity analyses will include excluding studies with high risk of bias, excluding studies without reported randomization or blinding, excluding dissertations or non-peer-reviewed full-text sources, excluding data extracted only from figures, excluding studies with very small sample sizes, and excluding studies with borderline eligibility such as follow-up shorter than 7 days but reporting remodeling-related outcomes.

If multiple reports appear to use overlapping animals, datasets or highly similar experiments from the same research group, sensitivity analyses will be conducted by retaining only the most complete or most original dataset. Leave-one-out analyses may be performed for outcomes with sufficient numbers of studies to identify whether the pooled effect is driven by a single study. Sensitivity analyses may also examine the influence of model type, such as excluding ischemia/reperfusion studies if they are judged to be insufficiently representative of chronic post-myocardial infarction remodeling.

Where appropriate, sensitivity analyses will compare results using different statistical assumptions, such as mean difference versus standardized mean difference when applicable, or alternative handling of multi-arm studies with shared control groups. If the direction, magnitude or statistical significance of pooled effects changes substantially after sensitivity analyses, the certainty and interpretation of the findings will be downgraded accordingly. All sensitivity analyses will be reported transparently, and any additional sensitivity analyses not specified in this protocol will be labelled as post hoc exploratory analyses.

Language restriction Studies published in English or Chinese will be included. No other language restrictions will be applied at the search stage where database interfaces allow.

Country(ies) involved China.

Other relevant information The full protocol, database-specific search strategies, data extraction form, risk-of-bias assessment template and statistical analysis plan may be archived in an open repository such as OSF before formal data extraction. Any deviations from this registered protocol will be dated, documented and justified in the final manuscript.

This review will focus on natural compounds derived from Chinese materia medica and chemically defined extracts. Chinese herbal formulas, decoctions, proprietary Chinese medicines, injections and undefined compound preparations will be excluded according to the predefined eligibility criteria. Any intellectual property related to excluded herbal formulas will not be evaluated as an intervention in this review.

Scopus will not be used as a main database because of overlap with Web of Science and Embase and database access/export limitations. Citation searching will be used to reduce potential omission of eligible studies.

Keywords myocardial infarction; cardiac remodeling; natural compounds; Chinese materia medica; preclinical meta-analysis; animal studies.

Dissemination plans The results of this systematic review and meta-analysis will be submitted for publication in a peer-reviewed pharmacology, cardiovascular or translational medicine journal. Findings may also be presented at academic conferences or seminars. Where appropriate, the protocol, search strategies, extracted datasets, risk-of-bias assessments and statistical code may be made available through an open repository to improve transparency and reproducibility.

Contributions of each author

Author 1 - Hang Qi - Hang Qi contributed to the conception and design of the review, developed the eligibility criteria and search strategy, drafted the protocol, and will coordinate literature screening, data extraction, risk-of-bias assessment, data analysis, interpretation of findings and manuscript preparation.
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Author 2 - Xinhui Li - Xinhui Li conceived and supervised the review, provided methodological and academic guidance, reviewed and revised the protocol, and will oversee the integrity, accuracy and transparency of the review process.
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Author 3 - Xiao Jiang - Xiao Jiang Will participate in literature screening, full-text assessment, data extraction and verification of extracted data.
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Author 6 - Dan Ouyang - Dan Ouyang Will contribute to pharmacological interpretation, classification of natural compounds and mechanistic outcome interpretation.
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Author 7 - Mali Xu - Mali Xu Will contribute to cardiovascular disease expertise, interpretation of post-myocardial infarction remodeling outcomes and translational relevance.
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