INPLASY

Traditional Polyherbal Formulations for Diabetic Wound Healing: A Systematic Review of In Vivo Studies

Corresponding author:
Samuel Abiodun Kehinde

samuelkehinde0707@gmail.com

Author Affiliation:
School of Health Science, Mae Fah Luang University, Chiang Rai. Thailand.

Kehinde, SA; Awaeloh, N; Na-Phatthalung, P; Kantisin, S; Chusri,S.

ADMINISTRATIVE INFORMATION

Support - Not applicable.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202630068

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 March 2026 and was last updated on 18 March 2026.

INTRODUCTION

*R*eview question / Objective To systematically synthesize preclinical in vivo evidence on the efficacy and mechanisms of traditional polyherbal formulations in diabetic wound healing and evaluate methodological quality and risk of bias.

Rationale Diabetic wounds, particularly diabetic foot ulcers, represent a major global health burden characterized by chronic inflammation, impaired angiogenesis, oxidative stress, and delayed tissue repair. Current standard care remains suboptimal, especially in low- and middle-income settings, due to high costs, antimicrobial resistance, and limited accessibility to advanced therapies.

Traditional polyherbal formulations offer a mechanistically plausible alternative due to their multi-target pharmacological actions, including antioxidant, anti-inflammatory, antimicrobial, and pro-angiogenic effects. While numerous in vivo studies have explored these formulations, the evidence remains fragmented, heterogeneous, and methodologically inconsistent.

This systematic review addresses a critical gap by synthesizing available preclinical evidence, evaluating consistency of therapeutic effects, and assessing methodological rigor. The findings aim to inform translational research and guide future clinical investigations.

Condition being studied The condition of interest is diabetic wound healing impairment, particularly diabetic foot ulcers. This condition arises from chronic hyperglycemia leading to excessive reactive oxygen species, advanced glycation end-products, impaired angiogenesis, persistent inflammation, and defective extracellular matrix remodeling.

These pathological disruptions affect all phases of wound healing (hemostasis, inflammation, proliferation, remodeling), resulting in chronic, non-healing wounds. Complications include infection,

tissue necrosis, and high risk of amputation, with substantial morbidity and mortality.

METHODS

Search strategy A comprehensive search will be conducted across PubMed, SCOPUS, ScienceDirect, and AMED (EBSCO) from inception to March 2026.

Search terms will combine three domains using Boolean operators:

Diabetes domain: "diabetes mellitus", "hyperglycemia", "streptozotocin", "alloxan", "diabetic model"

Wound healing domain: "wound healing", "wound closure", "epithelialization", "granulation tissue", "diabetic wound", "skin ulcer"

Polyherbal domain: "polyherbal formulation", "herbal medicine", "plant extract", "traditional medicine", "phytotherapy", "ethnopharmacology"

Controlled vocabulary (e.g., MeSH) and free-text terms will be combined. Truncation and phrase searching will be applied. No study design filters will be used during search; screening will apply PICOS criteria.

Participant or population
In vivo animal models of diabetes, including:

Chemically induced (streptozotocin, alloxan)

Diet-induced (high-fat diet + STZ)

Genetic models (e.g., Goto-Kakizaki rats)

All rodent species, strains, sexes, and ages are eligible, provided diabetes is confirmed (≥200 mg/dL glucose).

Intervention Traditional polyherbal formulations containing two or more medicinal plants, administered via:

Topical routes (ointments, creams, gels)

Systemic routes (oral administration)

No restriction on dosage, preparation method, or traditional system.

Comparator Untreated diabetic wound control

Vehicle/excipient control

Standard wound-care agents (e.g., silver sulfadiazine, povidone-iodine)

Single-herb comparators.

Study designs to be included Controlled in vivo experimental animal studies with at least one polyherbal intervention group and one diabetic wound control group.

Eligibility criteria
Inclusion:
In vivo diabetic wound models
Polyherbal formulations (≥2 plants)
Quantitative wound-healing outcomes
Peer-reviewed articles in English

Exclusion:
In vitro or ex vivo studies
Clinical trials or observational studies
Single-herb or synthetic interventions
Studies without control groups
Non-English publications.

Information sources
Electronic databases: PubMed, SCOPUS, ScienceDirect, AMED.
Additional sources:
Reference list screening
Contacting corresponding authors.

Main outcome(s)
Wound closure rate (%)
Epithelialization period (days)
Effect measures: mean differences, percentage change, or narrative comparison depending on data availability.

Additional outcome(s)
Collagen content (hydroxyproline, histology)
Angiogenesis markers (VEGF, CD31, α-SMA)
Inflammatory cytokines (TNF-α, IL-1β, IL-6)
Oxidative stress markers (MDA, SOD, GSH, catalase)
Histopathological scores.

Data management Data will be extracted using standardized forms by multiple independent reviewers. Extracted variables include study design, animal characteristics, intervention details, and outcomes.
Discrepancies will be resolved through consensus or third-reviewer adjudication. Data will be stored in structured databases and cross-verified.

Quality assessment / Risk of bias analysis
SYRCLE Risk of Bias tool for animal studies
CAMARADES checklist for methodological quality

Domains include selection, performance, detection, attrition, and reporting bias. Each study will be rated as low, high, or unclear risk.

Strategy of data synthesis Narrative synthesis will be conducted due to heterogeneity in study designs, interventions, and outcomes.
Meta-analysis will only be performed if ≥3 studies report comparable outcomes with sufficient statistical data. Otherwise, results will be descriptively summarized.

Subgroup analysis
Where data permit:
Type of diabetes model (STZ vs genetic vs HFD)
Route of administration (topical vs oral)
Number of herbal components
Treatment duration.

Sensitivity analysis
Sensitivity analyses will assess robustness by:
Excluding high-risk-of-bias studies
Comparing results across methodological quality tiers
Evaluating influence of sample size and study design.

Language restriction English-language studies only.

Country(ies) involved Thailand.

Other relevant information The review follows PRISMA 2020 and SYRCLE guidelines and is prospectively registered on INPLASY. It focuses exclusively on preclinical evidence to bridge translational gaps toward clinical application

Keywords Polyherbal formulations; diabetic wound healing; in vivo; oxidative stress; angiogenesis; traditional medicine.

Dissemination plans Findings will be disseminated through:
Peer-reviewed journal publication
Conference presentations
Integration into translational research frameworks
The review aims to inform clinical trial design and evidence-based use of traditional polyherbal therapies.

Contributions of each author
Author 1 - Samuel Abiodun Kehinde - Samuel Abiodun Kehinde drafted the manuscript, conducted a literature search, independently screened the potential studies and extracted the data and edited the manuscript.
Email: samuelkehinde0707@gmail.com

Author 2 - Nurulhusna Awaeloh - Nurulhusna Awaeloh conducted a literature search and independently screened the potential studies and extracted the data.
Email: nurulhusna@nmc.ac.th
Author 3 - Pinanong Na-Phatthalung - Pinanong Na-Phatthalung arbitrated any disagreements and Edit the Manuscript.
Email: pinanong.naphatthalung@mssm.edu
Author 4 - Siriwan Kantisin - Siriwan Kantisin conducted a literature search.
Email: siriwan.kan@mfu.ac.th
Author 5 - Sasitorn Chusri - Sasitorn Chusri arbitrated any disagreements and edited the manuscript.
Email: sasitorn.chu@mfu.ac.th