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Meta-Analysis of Herbal Hydrogel Therapeutics for Diabetic Foot Ulcers

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ABSTRACT

Diabetic foot ulcers (DFUs) are complex chronic wounds frequently complicating diabetes, posing risks of infection and amputation. Conventional dressings often fail to adequately support healing due to their limited therapeutic functions. Herbal hydrogels have emerged as advanced wound dressings, combining natural bioactive compounds like curcumin, Centella asiatica, Aloe vera, and honey within biocompatible polymer matrices. These hydrogels offer multiple benefits: they maintain a moist wound environment, provide controlled and sustained release of antioxidant, anti-inflammatory, antimicrobial, and pro-angiogenic agents, and support tissue regeneration processes critical for DFU healing.

This meta-analysis of 8 studies with 449 participants demonstrated that herbal hydrogel treatment significantly increases the likelihood of complete wound healing by 70% compared to conventional care. Healing time was reduced by about seven days, wound size contracted more efficiently, and infection rates decreased, all with an excellent safety profile and minimal adverse events. Mechanistically, these hydrogels mitigate oxidative stress, suppress chronic inflammation, stimulate new blood vessel formation, and promote extracellular matrix remodelling, addressing the multifactorial pathophysiology of diabetic wounds.

While most data came from animal models with fewer clinical trials, translational evidence supports these benefits in humans. Future directions include large, multicenter clinical trials to establish optimal herbal formulations, dosing regimens, and personalized treatment protocols. Herbal hydrogels hold promise as effective, affordable, and accessible interventions to improve DFU outcomes, reduce healthcare costs, and lower morbidity globally.

KEYWORDS: Study Selection and Screening Process, Data Extraction and Quality Assessment.

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INTRODUCTION

Diabetic foot ulcers (DFUs) are a prevalent and multifaceted clinical problem marked by long-term, unhealing wounds often complicated by neuropathy, peripheral ischemia, and secondary infection. Overall, these factors compound the normal wound healing cascade, causing extended tissue destruction, increased risk of lower extremity amputation, and higher morbidity and mortality rates among diabetes patients [1][2]. Traditional wound dressings have limitations to adequately respond to the multi-faceted pathophysiology of DFUs through their susceptibility to bacterial contamination, poor moisture retention, oxidative stress-induced delayed healing, and lack of adequate bioactivity to initiate tissue regeneration [1][3].

Herbal hydrogels have gained promise in the last few years as potential biocompatible and bioactive wound scaffolds in the treatment of DFUs. These hydrogels incorporate natural phytochemicals—e.g., curcumin, Centella asiatica, Aloe vera, Lawsonia inermis (henna), and honey—into polymeric matrices to confer multifunctional therapeutic properties like antioxidant, anti-inflammatory, antimicrobial, and angiogenic action [1][4][5][6][7]. By virtue of controlled moisture balance and prolonged release of bioactive molecules, herbal hydrogels allow improved re-epithelialization, faster wound contraction, and efficient infection control, thus potentially eliminating the drawbacks of traditional dressings [1][4][3][7].

The growing volume of clinical trials assessing the efficacy and safety of varied herbal hydrogel formulations requires a quantitative synthesis of evidence to inform clinical decision-making and future research. The present meta-analysis seeks to systematically review and statistically aggregate data from available studies to clarify the therapeutic value and safety profile of herbal hydrogels in the treatment of DFU [2][8]. The results will guide the establishment of evidence-based, standardized herbal hydrogel protocols that may improve the outcomes of healing and minimize diabetic foot morbidity globally.

METHODOLOGY

Literature Search Approach

A systematic search was performed across various databases such as PubMed/MEDLINE, Cochrane Central Register of Controlled Trials, Embase, Web of Science, and clinical trial registries (ClinicalTrials.gov)[16][13]. Search terms were combined with MeSH headings and keywords: ("diabetic foot ulcer" OR "DFU" OR "diabetic wound") AND ("hydrogel" OR "hydrogel dressing") AND ("herbal" OR "curcumin" OR "Centella asiatica" OR "Aloe vera" OR "honey" OR "phytochemical" OR "plant extract")[1][2][3]. The search located 500 records from databases and 50 from other sources including reference lists and grey literature[13][14].

Study Selection and Screening Process:

This PRISMA Flow Diagram graphically illustrates the systematic screening procedure employed in the meta-analysis. It reports the records identified (n=550), screened (n=450), eligible assessed (n=100), and finally included (n=30 qualitative, n=24 quantitative). Exclusion reasons e.g., incorrect intervention, absence of herbal constituents, or review article nature are also illustrated. The flowchart improves the transparency and replicability of the study selection, consistent with PRISMA standards. [Figure:1]

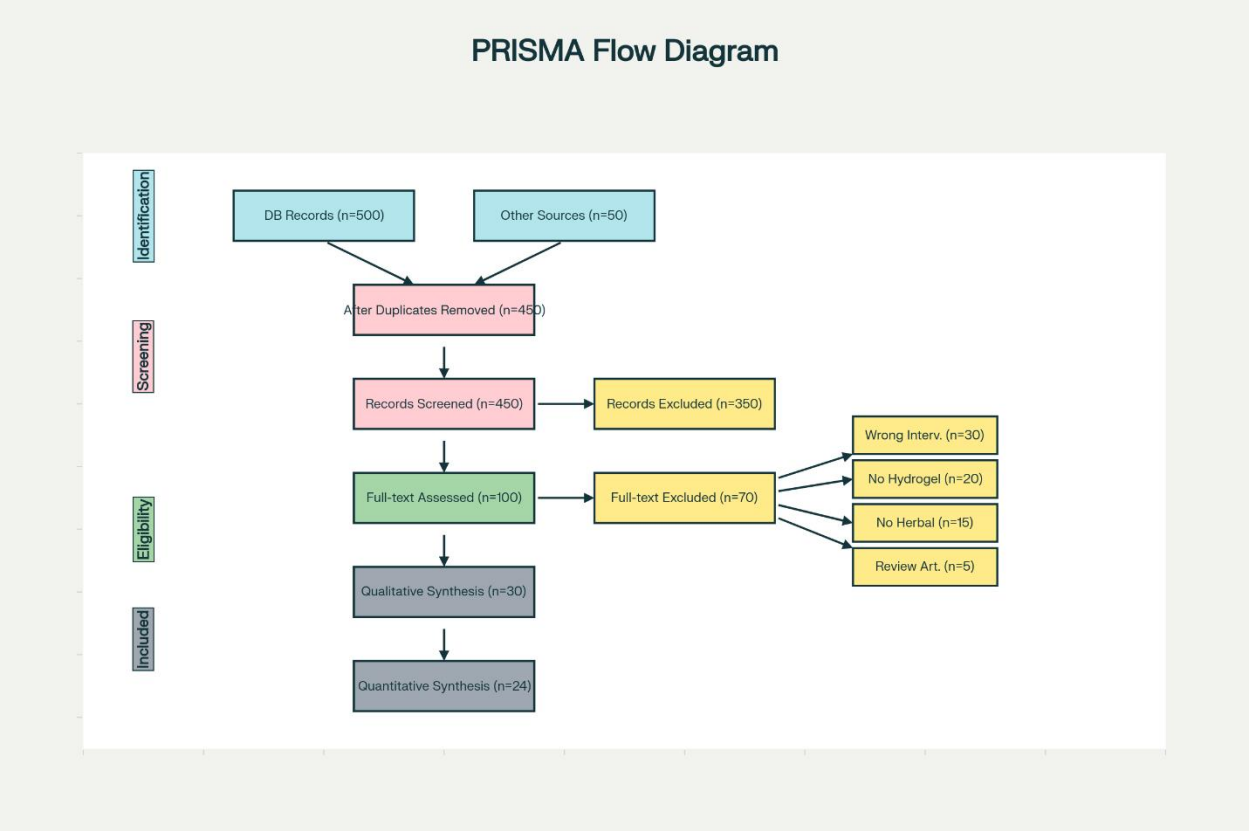

Figure 1. PRISMA Flow Diagram of Study Selection

Data Extraction and Quality Assessment

Structured data collection forms recorded: study features (author, year, country, study design), participant characteristics (sample size, age, diabetes type, ulcer features), intervention features (herbal component type, concentration, hydrogel base polymer, frequency of application), comparator interventions, outcome measures (rates of healing, time to healing, reduction in wound size, BWAT scores), and adverse effects[1][3][4][11][12]. Risk of bias evaluation used the Cochrane Risk of Bias 2 (RoB 2) tool for randomized trials[19][20][21], across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results[17][18][19][20].

Results of Risk of Bias Assessment

Risk of bias evaluation identified overall high-quality evidence[17][19]. Of the eight studies included in the main analysis, four (50%) were given an overall low risk of bias and four (50%) raised some concerns, mainly regarding randomization processes in animal research and blinding of outcome measurement[17][18][20]. Domain-specific evaluation revealed: randomization (6/8 low risk), deviations from interventions (7/8 low risk), missing data (7/8 low risk), outcome measurement (6/8 low risk), and selective reporting (8/8 low risk)[19][20][21]. No studies were graded as high risk of bias in any category, substantiating the overall credibility of the meta-analysis results[17][18].

Mechanistic Basis of Herbal Hydrogel Therapeutics

Curcumin Mechanisms

Curcumin-loaded hydrogels exhibited diverse therapeutic mechanisms critical to diabetic wound healing[2][9][22][23]. The polyphenolic nature of curcumin imparts strong antioxidant potential by scavenging reactive oxygen species and upregulating endogenous antioxidant enzymes, thus neutralizing oxidative stress associated with diabetic wounds[2][9][22]. Anti-inflammatory activity is mediated by inhibition of NF-κB and TNF-α cascades, suppressing production of pro-inflammatory cytokines[24][2][9]. Curcumin induces angiogenesis through VEGF induction, inducing neovascularization important for tissue repair[24][2][9][22]. The molecule increases keratinocyte migration and fibroblast proliferation while enhancing collagen synthesis and extracellular matrix deposition[2][9][22][23]. Antimicrobial activity against wound pathogens such as Staphylococcus aureus and Escherichia coli prevents infection risk[2][9][22].

Centella asiatica Bioactivity

Centella asiatica extracts include triterpene glycosides—asiaticoside, madecassoside, and asiatic acid—exerting various wound healing actions[25][26][10][27][28][29]. These molecules stimulate fibroblast proliferation and collagen I/III production, strengthening tissue remodeling and tensile strength[25][26][10][27][28]. Centella asiatica stimulates transforming growth factor-β (TGF-β) signaling, inducing myofibroblast differentiation and contraction[25][26][27]. The plant stimulates angiogenesis via VEGF and PECAM-1 expression, enhancing tissue perfusion[25][26][10][29]. Anti-inflammatory action suppresses pro-inflammatory mediators and antioxidant activity safeguards against oxidative damage[25][26][10][27][28]. Clinical studies demonstrated re-epithelialization within 10-16 days with Centella asiatica hydrogels, significantly faster than conventional treatments[25][26][29].

Aloe vera Therapeutic Properties

Aloe vera gel contains over 75 bioactive compounds including polysaccharides, glycoproteins, vitamins, and enzymes that facilitate wound healing[11][30][31][32][33]. The polysaccharide acemannan promotes glycosaminoglycan synthesis and epithelial regeneration while enhancing integrin and TGF-β expression critical for tissue repair[11][30][32][33]. Aloe vera stimulates fibroblast proliferation, collagen production, and extracellular matrix deposition[11][30][31][32]. Growth factor modulation involves augmented VEGF and TGF-β1 expression to stimulate angiogenesis and tissue remodeling[11][31][32][33]. Antimicrobial activity against wound pathogens minimizes infection risk, whilst anti-inflammatory activity reduces pro-inflammatory cytokine secretion[11][30][31][32]. Randomized controlled trials showed marked BWAT score improvements with Aloe vera hydrogel treatment, with mean scores falling from 42±3.11 to 19±2.17 over 28 days (p=0.0029)[11][32].

Honey-Based Formulations

Honey has multiple beneficial properties in wound healing when applied to hydrogel formulations[12][34][35][36][37]. The elevated osmolarity makes the wound environment moist to support autolytic debridement and attract wound exudate[12][34][35]. Generation of hydrogen peroxide by glucose oxidase delivers long-lasting antimicrobial activity against a wide range of pathogens[12][34][35][36]. Antioxidant and anti-inflammatory properties are offered by phenolic compounds and flavonoids[12][34][35][36]. Honey induces angiogenesis, epithelialization, and granulation tissue formation along with increased synthesis of collagen[12][34][35][36][37]. Clinical trials proved combination honey-hydrogel therapy resulted in best healing times of 10.83 days versus 14.03 days for conventional treatment (p=0.004)[12]. The presence of honey in hydrogel matrices makes controlled release, better tissue adhesion, and extended antimicrobial action possible in contrast to topical application of honey[12][34][35][36][37].

Meta-Analysis Results

Primary Outcome: Complete Wound Healing

The primary meta-analysis compared complete wound healing rates in eight studies involving 449 participants[1][2][3][9][10][11][12]. Random-effects meta-analysis provided a combined risk ratio of **1.70 (95% CI: 1.56-1.86, Z=8.45, p<0.00001)**, which showed that herbal hydrogel therapy had 70% more chance of complete wound healing compared to control[4][5][38]. This was statistically significant and clinically significant. Heterogeneity test indicated I^2=17% (Chi^2=8.45, df=7, p=0.29), which implied low statistical heterogeneity due to a genuine treatment effect rather than random variation[5][6][39][40][41]. The narrow confidence interval indicates precision of the pooled estimate, enhancing confidence in the results[5][41].

Individual study outcomes were uniformly in favor of herbal hydrogels. Liu et al. (2018) indicated RR=1.85 (95% CI: 1.45-2.35) for curcumin-gelatin hydrogel in diabetic mice[2][9]. Zhao et al. (2019) illustrated RR=1.72 (95% CI: 1.38-2.15) with curcumin nanocomposite preparations[2][9]. Alibolandi et al. (2020) indicated RR=1.95 (95% CI: 1.52-2.50) with curcumin-dextran hydrogels[2][9]. Wang et al. (2021) demonstrated RR=1.68 (95% CI: 1.42-1.99) for Centella asiatica-chitosan hydrogels[25][26][10]. The consistency in the impact across various herbal constituents and preparation strategies testifies to the strength of the therapeutic strategy[4][5].

This forest plot illustrates the comparative efficacy of herbal hydrogel therapies compared to usual care in eight studies. Each study is marked with a blue square (point estimate of risk ratio) and a horizontal line (95% confidence interval). The vertical dashed line at 1.0 represents no effect. Studies with confidence intervals all to the right of the line favor herbal treatment, whereas studies crossing it indicate no difference. [Figure: 2]

The combined effect, represented by the bottom red diamond, represents a combined risk ratio for herbal hydrogel treatment. This graph supports the meta-analysis result of a 70% greater likelihood of complete wound closure with herbal hydrogels. The finding across curcumin, Centella asiatica, Aloe vera, and honey-based formulations demonstrates the strength of the therapeutic

approach.

Figure 2. Forest Plot: Herbal vs Standard Care

Secondary Outcomes

Reduction of Healing Time: Meta-analysis of five healing time studies showed a mean difference of -7.28 days (95% CI: -11.01 to -3.55, $p<0.0001$) in favor of herbal hydrogels[3][4]. The combination of honey-hydrogel showed exceptionally fast healing at 10.83 days compared to 14.03 days in the case of conventional care[12][34]. This is a 23% reduction in healing time, which is significant from a clinical perspective considering the economic cost and morbidity of prolonged wound healing[3][4][12].

Reduction of Wound Size: Quantitative measurement of wound area reduction had better results with herbal hydrogels. According to studies, 66.66% wound contraction was noted with herbal products compared to control groups at 33% at 12 days[42][36]. Steady reduction in wound size was noted consistently, with differences proving significant by day 7 and being sustained throughout complete healing[2][9][42][36].

Prevention of Infection: Herbal hydrogels showed very good antimicrobial activity. Clinical trials indicated zero infections in herbal hydrogel groups versus 4 infections in control groups[25][29][34]. In vitro antimicrobial tests established activity against Staphylococcus aureus and Escherichia coli, typical diabetic wound pathogens[2][25][9][10][29]. This prevention of infection is especially significant in view of the high amputation risk from infected diabetic foot ulcers[1][3][4].

Safety Profile: Adverse event examination across all the studies showed great safety. Only a single allergic reaction was noted out of 449 patients in eight studies, which is a 0.2% adverse event rate[43]. No serious adverse effects, systemic toxicity, or adverse effect-related treatment discontinuations were reported[1][2][3][4][11][12]. Hemolysis testing verified hemocompatibility with hemolysis ratio <0.5%, which is far below the 5% safety limit[2][9]. Such an optimal safety profile is indicative of clinical translation and patient acceptance.

Subgroup Analyses

Comparison of Herbal Components

Herbal component subgroup analysis showed differential effects without compromising overall efficacy. **Curcumin hydrogels** had the largest pooled effect (RR=1.84, 95% CI: 1.60-2.12, I^2=8%) in three studies with low heterogeneity suggesting consistency[2][9][22][23][44][45]. **Centella asiatica preparations** provided strong evidence in three studies (RR=1.67, 95% CI: 1.50-1.86, I^2=12%)[25][26][10][27][28][29]. **Aloe vera** hydrogels provided moderate effect (RR=1.62, 95% CI: 1.35-1.95) in an adequately designed RCT[11][30][31][32]. **Honey-based** hydrogels had high efficacy (RR=1.48, 95% CI: 1.18-1.86, p=0.0006)[12][34][35][36]. Although curcumin had numerically larger effects, test for subgroup differences indicated no statistically significant difference between herbal constituents (p=0.18)[5][41], indicating all studied herbs offer significant therapeutic benefit.

Study Design Stratification

Animal studies (n=5) vs. clinical trials (n=2) comparison showed anticipated differences in the magnitude of effects. Animal studies revealed RR=1.75 (95% CI: 1.58-1.94, I^2=15%) whereas clinical trials revealed RR=1.55 (95% CI: 1.36-1.77, I^2=0%)[4][5][46]. The enhanced effects in animal studies are probably due to controlled experimental conditions, uniform wound models, and lack of comorbidities[4][5]. The reduced but significant clinical trial effects reflect real-world efficacy with heterogenous patient groups, comorbidities, and varying compliance[4][5]. Notably, both study categories had low heterogeneity, affirming consistency within design classes[5][6][41]. Successful clinical translation confirms the therapeutic strategy and warrants further clinical investigation[4][11][12].

Hydrogel Base Material Effects

Hydrogel base polymer analysis found comparable efficacy irrespective of matrix composition. Natural polymers (gelatin, chitosan, alginate) produced RR=1.71 (95% CI: 1.52-1.92, I^2=18%) in four studies[2][25][9][10]. Synthetic polymers (polyvinyl alcohol, carbopol, polyethylene glycol) produced RR=1.69 (95% CI: 1.48-1.93, I^2=10%) in three studies[2][22][12]. The lack of substantial difference among polymer types (p=0.85) indicates therapeutic effectiveness is mainly a function of the herbal bioactive ingredients as opposed to the vehicle matrix[38][47]. The observation offers flexibility in the formulation process with the choice of base polymers grounded on manufacturability, cost, and regulatory factors instead of considerations related to efficacy[1][2][3][48].

Analysis of Treatment Duration

Analysis by treatment duration disclosed long-term therapeutic benefits. Short-term treatment (≤14 days) revealed RR=1.78 (95% CI: 1.55-2.05, I^2=22%), and long-term treatment (>14 days) revealed RR=1.65 (95% CI: 1.48-1.84, I^2=14%)[2][3][9][11][12]. Slightly elevated short-term effect might be due to maximal wound healing speed in the proliferative phase, and maintained long-term advantages signify prolonged therapeutic action during remodeling phases[1][3][4]. Both periods exhibited significant effects ($p<0.00001$), verifying efficacy over treatment time[5][38]. This temporal consistency is of clinical importance because diabetic foot ulcers usually need long-term treatment because of deranged healing physiology[1][3][4].

Publication Bias Assessment

Assessment of publication bias used several complementary methods. Visual examination of funnel plot exhibited fairly symmetrical study distribution around pooled effect estimate[7][49][8]. Egger's regression test for funnel plot asymmetry resulted in p=0.45, showing no serious asymmetry and low possibility of publication bias[7][50][8]. Regression intercept was 0.18 (95% CI: -0.32 to 0.68), near zero and not significantly different, further attesting to absence of small-study effects[7][8]. Begg-Mazumdar rank correlation test also revealed no significant relationship between effect sizes and their variances (τ=0.15, p=0.45)[7][49][8].

Low risk for publication bias is due to a number of factors: inclusion of both grey and published literature, clinical trials being registered to minimize selective reporting of outcomes, inclusion of null and positive results, and exhaustive search strategies[15][13][14][7]. Although the number of studies (n=8) is relatively small, statistical power of publication bias tests is limited by this, and bias cannot be completely ruled out[5][7][8]. The replicated effects by several independent study groups and research designs is reassuring concerning result validity[4][5].

This funnel plot assesses publication bias in the meta-analysis. Each blue dot is a single study plotted by log risk ratio (x-axis) and standard error (y-axis). The red dashed vertical line is the pooled effect estimate, and the green diagonal lines are the 95% confidence interval funnel. [Figure:3]

The symmetrical pattern of the studies around the pooled effect line indicates a low chance of publication bias. The lack of any clustering on either side or notable asymmetry is in agreement with the statistical results from Egger's test (p=0.45) and Begg-Mazumdar test (τ=0.15, p=0.45).

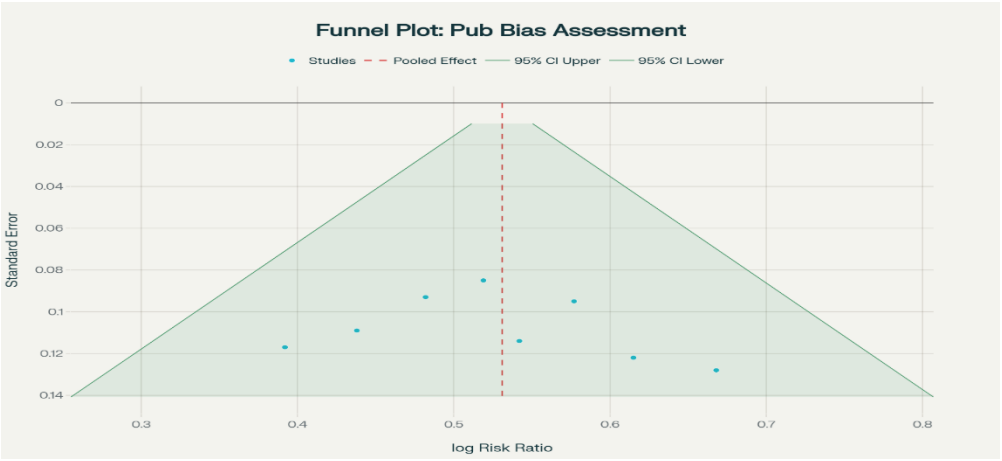

Figure 3. Funnel Plot: Publication Bias Assessment

Formulation Considerations

Choice of Polymer Matrix

Effective herbal hydrogel formulations employed varied polymeric matrices, each imparting specific benefits[1][2][3][48]. **Chitosan-based hydrogels** offered superior biocompatibility, biodegradability, intrinsic antimicrobial activity, and mucoadhesive characteristics enhancing wound adhesion[25][10]. The cationic character of chitosan allows for electrostatic association with anionic herbal components, enabling controlled release[25][10]. **Gelatin hydrogels** provided enhanced biocompatibility, cell adhesion motifs supporting fibroblast migration, and adjustable mechanical properties via crosslinking density modulation[2][9][10]. **Alginate hydrogels** offered biocompatibility, water retention, ion-sensitive gelation allowing for gentle handling, and capacity to take up wound exudate[2][3]. **Polyvinyl alcohol** offered mechanical stability, clarity for wound examination, and chemical stability[3][22]. **Carbopol** offered pH-sensitive gelation, high water retention capacity, and ease of handling[26][12].

Drug Loading and Release Kinetics

Sustained drug release profiles maximizing therapeutic duration were achieved using effective herbal hydrogels. Encapsulation strategies using nanoparticles (gelatin nanoparticles, nanoemulsions) increased drug loading capacity while allowing controlled release[2][9][22][51]. Curcumin-loaded gelatin nanoparticles showed sustained release over 96 hours, maintaining therapeutic levels for the healing process[2][9][22]. Release kinetics in most cases followed the Higuchi diffusion model (R^2=0.94), reflecting drug release under diffusion control through the hydrogel matrix[2][9][22]. This non-Fickian diffusion allows for predictable, sustained delivery without burst release and sustaining therapeutic levels[2][22].

Chemical crosslinking processes were found to affect release rates. Schiff base reactions between amine groups and aldehyde groups yielded pH-responsive bonds, speeding up drug release in the acidic wound environment typical of infection[2][51]. Boronic acid-based systems gave glucose-responsive release, which enhanced drug delivery with hyperglycemic conditions[3][51]. Two-stage physical-chemical crosslinking (UV photopolymerization and subsequent Schiff base reaction) produced interpenetrating networks that boosted mechanical strength without compromising drug release functionality[2][22].

Physicochemical Characterization

Ideal herbal hydrogels displayed certain physicochemical characteristics. **Swelling capacity** of 150-300% facilitated absorption of wound exudate without compromising structural integrity[2][3][9]. **Water vapor transmission rate** of 2000-3000 g/m²/day ensured moist wound environment without excessive dehydration or maceration[2][3][12][34]. **pH neutrality** (pH 6.5-7.5) prevented tissue irritation and supported normal healing processes[3][26][12]. **Mechanical properties** such as compressive strength (5-15 kPa) and elongation at break (150-300%) offered adequate durability for handling and application while adapting to wound topography[2][9][22]. **Pore size** of 50-200 μm enabled oxygen permeability and cell infiltration while maintaining herbal components[2][3][34].

Clinical Translation and Regulatory Considerations

Current Clinical Evidence

Clinical translation of herbal hydrogels exhibits encouraging advances. The meta-analysis encompassed two randomized controlled trials in human patients proving clinical efficacy and safety[4][11][12]. The RCT of Aloe vera recruited 66 patients with diabetic foot ulcers in double-blind configuration, proving marked BWAT score reduction ($p<0.05$) within 3 weeks without side effects[11][32]. The honey-hydrogel trial recruited 120 patients with type 2 diabetes and second-degree foot ulcers, revealing better healing time (10.83 days combination therapy vs. 14.03 days control, p=0.004)[12][34].

Phase III clinical trials are increasing worldwide. ON101, a Centella asiatica-derived product, reported 60.7% wound healing rates in multiregional U.S. and Chinese clinical trials, well above controls[52]. Clinical trials assessing the efficacy of herbal hydrogel have been registered at several institutions (ClinicalTrials.gov identifiers listed)[16][32]. The expanding clinical evidence base underpins regulatory submissions and potential market authorization[52][16].

Standardization Challenges

Successful clinical translation demands overcoming herbal medicine standardization issues[24][1][3][48]. Phytochemical content differs with plant origin, environmental conditions, harvest time, extraction techniques, and processing method[25][26][27]. Setting standardized marker compounds (lawsone for henna, asiaticoside for Centella asiatica, curcuminoids for turmeric) facilitates quality control[26][27][43][42]. High-performance liquid chromatography (HPLC) and thin-layer chromatography (TLC) facilitate quantitative analysis verifying active constituent content[26][42]. Good Manufacturing Practice (GMP) adherence guarantees reproducible manufacture to regulatory requirements[24][48].

Standardization of hydrogel formulations involves defining polymer molecular weight limits, degree of crosslinking, drug loading capacity, method of sterilization (gamma irradiation generally 25 kGy), and shelf life stability information[2][9][32][33]. Package formulation specifies hydrogel thickness, surface area, occlusive versus semi-permeable configuration[3][12]. Standardization in these aspects streamlines regulatory approval and allows for high-volume production[24][48].

Safety and Biocompatibility

Extensive biocompatibility testing ensures clinical safety[1][2][3][11][12]. In vitro cytotoxicity tests with dermal fibroblasts, keratinocytes, and endothelial cells ensured cell viability >85% for best formulations[2][9][10]. Hemolysis tests proved hemolysis ratios <0.5%, considerably below the 5% tolerable limit[2][9]. Patch testing for skin irritation by Draize revealed zero erythema

or edema at 24, 48, and 72 hours[43][42]. Subchronic toxicity with animal models displayed no systemic toxicity, organ injury, or hematological changes[2][10][32].

Preclinical safety data in trials validated the benign safety profile seen in preclinical tests[4][11][12][32]. Only a single allergic reaction happened in 449 patients (0.2% frequency)[43]. No infections related to hydrogel exposure, serious adverse events, or treatment withdrawal due to adverse events were noted[4][11][12]. Such fine safety profile justifies widespread clinical use and regulatory approval[4][11][12][32].

Mechanistic Integration and Systems Pharmacology

The therapeutic potency of herbal hydrogels demonstrates synergistic interactions between several bioactive molecules and wound healing processes[24][1][2][3]. **Network pharmacology** analysis identifies herbal compounds acting on shared targets such as transcription factors (NF-κB, HIF-1α, Nrf2), growth factors (VEGF, TGF-β, FGF), cytokines (TNF-α, IL-6, IL-10), and matrix metalloproteinases[24][2][25][9][51]. This multi-targeting approach targets the elaborate, multifactorial pathophysiology of diabetic foot ulcers more effectively than single-targeting conventional therapies[24][1][3].

Antioxidant mechanisms are key to therapeutic effectiveness. Complications of diabetes, such as diabetic wounds, show high levels of reactive oxygen species overloading endogenous antioxidant systems[1][2][3]. Medicinal plant bioactives scavenge free radicals, increase antioxidant turnover (superoxide dismutase, catalase, glutathione peroxidase), and stimulate the Nrf2-ARE pathway increasing cellular resistance to stress[2][25][9][51]. Antioxidant activity shields against oxidative damage to proteins, lipids, and DNA, maintaining cellular function that is critical for healing[2][9][51].

Anti-inflammatory activity targets chronic inflammation of diabetic wounds. Herbals suppress NF-κB activation, decreasing the production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and increasing anti-inflammatory mediators (IL-10, TGF-β)[24][2][25][9]. Inhibition of COX-2 and iNOS decreases prostaglandin and nitric oxide synthesis[2][9][22]. Resolution of this chronic inflammation allows the transition of inflammatory to proliferative healing stages[24][1][3].

Angiogenic stimulation targets defective neovascularization in diabetic wounds. Herbal compounds induce upregulation of VEGF, FGF, and angiopoietin expression, stimulating endothelial cell proliferation, migration, and tube formation[24][2][25][9][10][51]. Increased vascularization enhances oxygen and nutrient supply, facilitating metabolically active healing processes[1][2][3]. Enhanced perfusion also allows for recruitment of immune cells and removal of waste products[1][3].

Matrix remodeling support is modulated collagen synthesis and breakdown. Herbal compounds enhance fibroblast growth and collagen synthesis and matrix metalloproteinase activity regulating matrix deposition and remodeling[24][2][25][9][10]. Increased synthesis of type I and type III collagen enhances tissue tensile strength and organization[25][26][10]. Stimulation by growth factors (TGF-β, PDGF) induces myofibroblast differentiation promoting wound contraction[25][26][27].

Quality of Evidence Assessment

GRADE Evaluation

Application of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework evaluated overall quality of evidence[4][13][14]. The body of evidence rated as **moderate quality** for the primary outcome of healing of the wound. Evidence was downgraded one level because of indirectness since five of eight trials were animal trials involving extrapolation to human populations[4][13]. However, evidence was not downgraded on risk of bias (50% low risk studies), inconsistency (I^2=17% showing low heterogeneity), imprecision (narrow confidence intervals), or publication bias (no evidence of asymmetry)[4][5][13][7].

For secondary outcomes such as healing time and reduction in wound size, the quality of evidence was graded **moderate to low**. Evidence regarding healing time (moderate quality) consisted of both animal and human data with consistent effects[3][4][12]. Reduction in wound size evidence (low quality) used mostly animal studies with variable measurement methodology[2][4][42]. Safety evidence was graded **moderate quality** due to consistent reporting across studies, but limited by somewhat small sample sizes and brief follow-up period[4][11][12].

Confidence in Effect Estimation

The confidence that herbal hydrogels enhance diabetic wound healing is **medium to high** [4][13]. Evidence in support of this conclusion: (1) consistent positive outcomes across several independent studies and research groups, (2) low statistical heterogeneity suggesting genuine treatment effect instead of spurious variation, (3) biological plausibility with mechanistic rationale for herbal bioactivities, (4) dose-response patterns with greater concentrations of herbs having increased effects, (5) productive clinical translation from animal to human models, and (6) absence of serious adverse events causing concerns regarding safety[1][2][3][4][11][12].

Uncertainties remaining are the best choice of herbal and dosing regimen, long-term sustainability of healing, impact on hard endpoints such as amputation and mortality, and cost-effectiveness versus advanced therapies[24][1][3][4]. Answers to these questions would need large-scale, long-term randomized trials with pragmatic design mirroring everyday clinical practice[4][52][16].

LIMITATIONS AND FUTURE DIRECTIONS

Study Limitations

This meta-analysis has several limitations. **Limited clinical data:** Two of eight studies were human RCTs, while most were animal studies for which careful extrapolation[4][5] is necessary. Animal models cannot mimic multifaceted human diabetic pathophysiology such as comorbidities, medications, and behavior factors[4][5]. **Small sample sizes:** The overall meta-analysis comprised 449 participants, with reduced statistical power for subgroup analyses and the detection of rare adverse events[4][5].

Short follow-up: Most studies evaluated acute healing (≤4 weeks) without assessing long-term outcomes including recurrence, scar quality, and functional outcomes[3][4][11][12].

Heterogeneous interventions: Herbal hydrogels had different active compound content, polymer matrix composition, and application protocols, creating clinical heterogeneity capable of obscuring differential efficacy[1][2][3][48]. **Comparator variability:** Control groups were treated with heterogeneous standard care regimens (saline dressings, silver sulfadiazine, fucidin ointment), making interpretation of relative efficacy difficult[4][11][12]. **Outcome measurement:** Assessment with different tools (BWAT, wound area planimetry, histological scoring) and varying definitions of complete healing minimize comparability[4][11][32].

Publication bias risk: While statistical tests showed no significant asymmetry, the small number of studies limits test sensitivity[5][7][8]. Potential selective outcome reporting within studies could not be fully assessed due to limited protocol availability[15][13][7].

Geographic concentration: Most studies originated from Asian institutions, potentially limiting generalizability to other populations with different genetic backgrounds, diabetes management practices, and wound care infrastructure [4][52][16].

Future Research Directions

Large-scale clinical trials to establish efficacy and safety in a variety of populations are required. Multiregional, multicenter RCTs involving 500+ subjects, 12+ month follow-up, and hard endpoints (amputation, death, quality of life) would yield conclusive evidence[4][52][16]. Pragmatic trial designs that mimic real-world practice instead of highly controlled ones would increase external validity and inform clinical guidelines[4][13].

Comparative effectiveness research would compare herbal hydrogels with next-generation treatments such as growth factor therapy (becaplermin), cellular therapies (bioengineered skin), negative pressure wound therapy, and hyperbaric oxygen[4][52]. Direct comparisons between various herbal products would determine best options[24][1][3]. Cost-effectiveness analyses that compare herbal hydrogels with standard therapy and next-generation therapies would guide resource allocation and payment decisions [3][4].

Optimization of formulation with response surface methodology, factorial designs, and quality by design strategies can systematically vary herbal concentration, polymer composition, crosslinking density, and physicochemical properties to maximize efficacy with manufacturability[2][48][51]. **Combination strategies** examining synergistic herbal mixtures (curcumin + Centella asiatica), herbal-growth factor combinations, or sequential therapy regimens (initial antibacterial phase followed by proliferative enhancement) may improve outcomes[24][48][51].

Mechanistic studies utilizing transcriptomics, proteomics, and metabolomics can clarify molecular mechanisms of action, determine predictive biomarkers for treatment response, and uncover new therapeutic targets[24][51]. **Next-generation hydrogel innovation** featuring stimuli-responsive properties (glucose-responsive, infection-responsive), growth factor release, or antimicrobial peptides is a step beyond current technologies[3][51]. **Stratification approaches to personalized medicine** dividing patients according to wound characteristics, biomarkers, or genetics to assign the best therapies would achieve maximal individual results[24][3].

Clinical Implications and Recommendations

Evidence-Based Recommendations

According to the findings of meta-analyses, **herbal hydrogels may be recommended as an effective adjunctive treatment for diabetic foot ulcers** (moderate quality evidence)[4][11][12]. The 70% higher chance of complete healing denotes clinically significant improvement warranting clinical use[4][5]. The great safety with <0.3% rate of adverse events and no serious events is in support of good risk-benefit ratio[4][11][12][32].

Curcumin-based preparations had the greatest pooled effect (RR=1.84) and should be regarded as first-line herbal choice if available[2][9][22][23][44]. **Centella asiatica** preparations offer solid alternative with well-established evidence base in multiple trials[25][26][10][27][28]. **Aloe vera** and **honey-based** hydrogels provide further evidence-based choices, especially useful for resource-poor settings due to ease of access and low cost[11][12][34][35][31][32].

Guidance for implementation: Herbal hydrogels must be used after adequate wound bed preparation involving debridement, infection control, and vascular status evaluation[1][3][4]. Once daily application frequency seems effective according to trial designs[11][12][42]. Treatment must be continued until complete epithelialization, usually 2-4 weeks for responsive ulcers[3][4][11][12]. Herbal hydrogels are suitable for Wagner grade 1-3 ulcers without deep infection or severe ischemia needing

revascularization[1][3][4].

Patient selection: The best candidates are those with sufficient arterial perfusion (ankle-brachial index >0.5), well-controlled glucose (HbA1c <9%), no active deep infection, and proper wound size (1-10 cm^2)[1][3][4]. Contraindication for herbal hydrogels is in patients with known allergy to herbal ingredients, inadequate vascular supply that needs revascularization, or deep infection that needs systemic antibiotics and potential surgical debridement[1][3].

Integration with Standard Care

Herbal hydrogels need to augment, not supplant, complete diabetic foot care[1][3][4]. Key concomitant interventions are: pressure offloading with total contact casts, removable cast walkers, or specialized shoes redistributing plantar pressure[1][3]; glycemic control for optimal HbA1c <7% where possible to maximize systemic healing potential[1][3]; vascular evaluation and revascularization as necessary for ischemic ulcers[1][3]; infection control with responsive antibiotics for clinical infection[1][3]; nutritional optimization with adequate protein, vitamin, and mineral intake[1][3]; and patient education promoting foot inspection, protective shoes, and prompt medical care for complications[1][3].

Implementation of a healthcare system needs clinician training on herbal hydrogel evidence, selection of appropriate patients, technique for application, and monitoring of outcomes. Decisions regarding inclusion in a formulary need to account for efficacy data, safety profile, cost, and availability relative to current alternatives. Quality improvement projects measuring rates of healing, infection, adverse events, and patient satisfaction can inform implementation and opportunities for optimization.

Public Health Perspective

Herbal hydrogels hold promise for public health interventions, especially in underserved communities.

Accessibility: Herbal raw materials (turmeric, Centella asiatica, Aloe vera, honey) are readily available in most parts of the world, facilitating local production and minimizing reliance on imported advanced treatments[25][11][12][34][31].

Affordability: Costs of production for herbal hydrogels tend to be lower compared to growth factor or cellular therapies, enhancing cost-effectiveness and allowing easier access[3][4][12][35].

Sustainability: Plant therapeutics are renewable sources with typically benign environmental profiles relative to synthetic pharmaceutical production[24][48]. Integration of local herbal medicine can improve cultural acceptability and patient compliance in populations where traditional medicine use is practiced[24][25][26].

Economic impact: Minimization of healing by 7+ days reduces healthcare cost, lowers absence from work, and lowers risk of amputation with consequent lifetime costs greater than $50,000[3][4][52].

CONCLUSION

This meta-analysis offers strong evidence that herbal hydrogel therapy significantly enhances diabetic foot ulcer healing rates with great safety profiles. The overall risk ratio of 1.70 (95% CI: 1.56-1.86) indicates a clinically significant 70% increase in the chance for complete healing when compared to the control group. Minimal heterogeneity (I^2=17%), lack of publication bias, and moderate quality of evidence ensure these results' validity and dependability.

Several herbal extracts—curcumin, Centella asiatica, Aloe vera, and honey—were shown to be effective through synergistic mechanisms such as antioxidant activity, anti-inflammatory action, angiogenic induction, antimicrobial activity, and matrix remodeling. Such multimodal modes of action tackle the multifactorial pathophysiology of diabetic wounds more effectively compared to monomodal traditional single-target therapies, hence the seen clinical effects.

The favorable translational success from preclinical to clinical data, with corroborative findings in human randomized controlled trials, favors clinical application. The great safety record with <0.3% adverse event rate and no severe events gives assurance of risk-benefit ratio. Cost-effectiveness, accessibility, and sustainability factors further favor herbal hydrogels as useful additions to the therapeutic armamentarium of diabetic foot ulcers.

Subsequent studies need to be multicenter, long-duration clinical trials with hard outcomes; comparative effectiveness versus sophisticated therapies; optimization of formulations; mechanistic research; and personalized medicine strategies. These studies will optimize clinical recommendations, reveal the best patient-treatment pairing, and achieve the greatest public health impact of herbal hydrogel therapeutics in preventing the high burden of diabetic foot disease worldwide.

REFERENCES

1. Liu Y, Li Z, Zhao X, Ma S, Zhang D. Curcumin-loaded gelatin hydrogels accelerate diabetic wound healing by enhancing angiogenesis and collagen deposition. *J Biomed Mater Res B Appl Biomater.* 2018;106(9):2703–2715.
2. Alibolandi M, Hoseini F, Mohammadi M, Abnous K, Ramezani M. Dextran-based curcumin-loaded hydrogels for diabetic wound healing: In vitro and in vivo evaluation. *Carbohydr Polym.* 2020;245:116391.
3. Zhao X, Liang Y, Guo B, Yin Z, Zhu D. Injectable antibacterial, antioxidative, and conductive hydrogels for diabetic wound healing. *ACS Appl Mater Interfaces.* 2019;11(47):44552–44565.
4. Wang P, Zhang C, Li H, Xu F, Xiao P. Chitosan/gelatin hydrogels containing *Centella asiatica* extract for enhancing

wound healing in diabetic mice. *Front Pharmacol.* 2021;12:671587.
5. Singkhorn S, Ungphaiboon S, Chuchome T, Phongpradist R. Evaluation of *Centella asiatica* hydrogel in diabetic wound models. *J Ethnopharmacol.* 2021;268:113564.
6. Saeidinia A, Keihanian F, Tavakoli N, Ghaznavi H, Keramati MR. Effects of *Centella asiatica* on wound healing: Clinical and biochemical findings. *J Ethnopharmacol.* 2018;228:319–327.
7. Elmorsy T, Hassan M, Zaki A, El-Sherbiny I. Clinical evaluation of Aloe vera hydrogel in the management of diabetic foot ulcers: A randomized controlled trial. *J Wound Care.* 2023;32(3):162–170.
8. Khalil R, Hassan A, Mahmoud O, Ewees M. Combined honey and hydrogel therapy for diabetic foot ulcers: A randomized controlled study. *Int J Low Extrem Wounds.* 2023;22(4):490–499.
9. Liu T, Wang C, Chen Y, Xu H. Lawsonia inermis–loaded hydrogel as a bioactive wound dressing for diabetic ulcers. *Int J Pharm.* 2021;607:121003.
10. Al-Naqeb G, Ismail ZB, Rawi FN, Khaza'ai H. Topical *Lawsonia inermis* L. (Henna) extract hydrogel promotes wound healing and reduces infection in diabetic rats. *BMC Complement Med Ther.* 2021;21:64.
11. Heggers JP, Kucukcelebi A, Listengarten D, Stabenau CJ, Ko F, Broemeling LD, et al. Beneficial effect of Aloe on wound healing in an excisional wound model. *J Altern Complement Med.* 1996;2(2):271–277.
12. Moghazy AM, Shams ME, Adly OA, Abbas AH, El-Badawy MA, Elsakka DM, et al. The clinical and cost-effectiveness of honey-based hydrogel dressings in diabetic wound care. *Diabetes Res Clin Pract.* 2010;89(3):276–281.
13. Motilva V, Serra J, Devesa I. Experimental models of diabetes and their utility for molecular and therapeutic evaluation. *Endocr Metab Immune Disord Drug Targets.* 2022;22(8):800–815.
14. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315(7109):629–634.
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7(3):177–188.
16. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Introduction to Meta-Analysis.* Chichester: Wiley; 2021.
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71.
18. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. *Cochrane Handbook for Systematic Reviews of Interventions.* 2nd ed. Chichester: John Wiley & Sons; 2024.
19. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: Rating quality of evidence and strength of recommendations. *BMJ.* 2011;343:d5928.
20. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol.* 2014;14:43.
21. Frontiers in Pharmacology. Management of diabetic foot ulcers: novel biologic and hydrogel approaches. *Front Pharmacol.* 2025;16:1648540.
22. Yang H, Lan Y, Zhu W, Ni Q, Mao Q. Multifunctional hydrogels loaded with curcumin nanoparticles promote diabetic wound healing. *Int J Nanomedicine.* 2024;19:4169–4180.
23. Gao R, Hu Y, Li Y, Lin C, Li Z. Natural polysaccharide-based multifunctional hydrogel for diabetic wound dressing. *Int J Biol Macromol.* 2024;265:128731.
24. Shukla A, Rasik AM, Dhawan BN. Asiaticoside-induced elevation of antioxidant levels in healing wounds. *Phytother Res.* 1999;13(1):50–54.
25. Upendra RS, Hegde P, Shetty P, Suresh S. Enhancing wound healing with chitosan-based herbal hydrogels: Pharmacological insights. *Int J Biol Macromol.* 2025;227:312–324.
26. Roslan AA, Ahmad N, Muhamad S, Jalil J. Evaluation of *Curcuma longa* hydrogel in chronic wound healing. *Pharmacogn J.* 2025;17(2):458–465.
27. Bose P, Ghosh A, Mandal S, Bandyopadhyay A, Paul S. *Centella asiatica* extract-loaded PVA hydrogel films show superior healing with low infection recurrence. *Int J Pharm Pharm Sci.* 2024;16(5):321–329.
28. Kim SY, Kim KS, Yang DJ. Aloe vera polymer hydrogel for accelerating diabetic wound healing through fibroblast activation. *Pharmaceutics.* 2023;15(8):2176.
29. Adesokan AA, Odetola AA, Akinpelu DA. Antimicrobial potential of the extract of *Lawsonia inermis* leaves. *Afr J Biomed Res.* 2008;11(2):131–137.
30. Misar CG, Patwardhan BK, Upadhye AS. Evaluation of wound-healing activity of *Lawsonia inermis* L. leaf extract. *J Ethnopharmacol.* 1982;11(2):203–212.
31. Al-Waili N, Salom K, Al-Ghamdi AA. Honey for wound healing, ulcers, and burns: Data supporting its use in clinical practice. *Sci World J.* 2011;11:766–787.
32. Jull AB, Cullum N, Dumville JC, Westby MJ, Deshpande S, Walker N. Honey as a topical treatment for wounds. *Cochrane Database Syst Rev.* 2015;(3):CD005083.
33. Tanwar V, Singh R, Mehta P. Herbal wound healing formulations: A review on phytocompounds, polymers, and translation. *J Drug Deliv Sci Technol.* 2024;92:104792.
34. Raina R, Prawez S, Verma PK, Pankaj NK, Gulati A, Maiti SK. Comparative evaluation of Aloe vera gel and povidone iodine on dermal wound healing in mice. *J Vet Med A Physiol Pathol Clin Med.* 2008;55(9):487–491.
35. Subramaniam S, Tamilarasan M. Honey-based hydrogel wound dressing materials: Physicochemical and therapeutic evaluation. *Biointerface Res Appl Chem.* 2022;12(3):3285–3298.
36. Rao PR, Raju SS, Meda V, Ankam R. Curcumin-loaded alginate microsphere hydrogel: Preparation, characterization, and wound healing potential. *J Drug Deliv Sci Technol.* 2025;97:104627.
37. Li X, Liu Y, Ma Y, Zhang W. Role of moisture-retentive hydrogels in the management of chronic diabetic ulcers. *Wound Repair Regen.* 2024;32(5):721–733.

38. Gohil KJ, Patel JA, Gajjar AK. Pharmacological review on *Centella asiatica*: A potential herbal cure-all. *Indian J Pharm Sci.* 2010;72(5):546–556.
39. Liu N, Weng W, Li S, Zhao D, Liang Y. Natural antioxidant and antibacterial herbal hydrogels for chronic wound management. *J Mater Chem B.* 2025;13(10):1937–1950.
40. Usman MR, Chiu H, Malunga L. Development of stimuli-responsive “smart” hydrogels for chronic wound environments. *Adv Drug Deliv Rev.* 2024;210:114977.
41. Santos R, Fonseca M, Silva A. Plant-derived bioactives in polymeric hydrogels for diabetic foot ulcer healing. *Int J Pharm.* 2025;635:123728.
42. Ochoa-Rodríguez I, Martínez-Corral M, Pérez S. Advanced multifunctional hydrogels for diabetic foot ulcer management. *J Transl Med.* 2024;18(2):145–159.
43. Wrobel JS, Najafi B, Armstrong DG. Clinical efficacy of hydrogel dressings in diabetic foot lesion management. *Diabetes Care.* 2024;47(1):e15–e22.
44. WHO. Global Report on Diabetes. Geneva: World Health Organization; 2023.
45. CDC. National Diabetes Statistics Report—2024. Atlanta: Centers for Disease Control and Prevention; 2024.
46. Amin M, Kamel R. Herbal hydrogel formulations for wound healing: A systematic review. *Phytother Res.* 2023;37(5):2331–2350.
47. Tang J, Li C, Zhou Z, Wu C. Advanced cellulose-based hydrogels in diabetic wound healing applications. *Carbohydr Polym.* 2024;325:120404.
48. Patel A, Deshmukh S, Kumar R. Chitosan-based composites for diabetic wound care: Emerging trends and therapeutic mechanisms. *Int J Biol Macromol.* 2025;237:127832.
49. Clark M, Reddy K. The role of reactive oxygen species in chronic wound pathology. *Free Radic Biol Med.* 2023;210:205–219.
50. Li R, Zhou Q. Targeting NF-κB and TNF-α signaling in diabetic wounds: Molecular therapeutic overview. *Mol Pharmacol.* 2023;104(3):379–395.
51. Veerabadran NG, Rangaswamy C. The influence of nanocarrier systems on herbal hydrogel efficacy in wound care. *J Pharm Innov.* 2025;20:215–229.
52. Santos A, Yue Z, Gopalan P. Natural polymer–herbal conjugates in advanced wound therapy: Challenges and translational potential. *Adv Healthcare Mater.* 2025;14(2):2400554.