Formulation and Evaluation of an Herbal-Based Self-Healing Hydrogel for Chronic Wound Dressings such as Diabetic Ulcers: A Review

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***Abstract*---Chronic wounds, particularly diabetic foot ulcers (DFUs), represent a significant global health burden due to their high prevalence, prolonged healing times, susceptibility to infection, and substantial socioeconomic impact. Traditional wound dressings often fall short in managing the complex microenvironment of diabetic ulcers. Recently, self-healing hydrogels have emerged as a promising class of biomaterials due to their ability to autonomously repair mechanical damage, maintain structural integrity, and provide a moist wound-healing environment. Incorporating herbal extracts—known for their anti-inflammatory, antimicrobial, antioxidant, and tissue-regenerative properties—into these hydrogels offers a synergistic strategy for enhancing wound repair. This review comprehensively synthesizes current research on the formulation and evaluation of herbal-based self-healing hydrogels for diabetic wound management. It discusses the therapeutic potential of key phytoconstituents, design principles for self-healing and stimuli-responsive hydrogels, fabrication techniques, characterization methodologies, and preclinical evidence of efficacy. Additionally, challenges in standardization, scalability, stability, and regulatory approval are addressed. The integration of natural herbal extracts within advanced hydrogel matrices presents a sustainable, biocompatible, and multifunctional approach with significant promise in accelerating the healing of chronic diabetic ulcers.**

***Index Terms*—Self-healing hydrogel, herbal extracts, diabetic ulcers, chronic wound healing, wound dressing, natural polymers, biocompatibility.**

I. INTRODUCTION

Diabetic foot ulcers (DFUs) are a devastating complication of diabetes mellitus, affecting approximately 15–25% of diabetic patients during their lifetime.[1] These ulcers arise due to a combination of neuropathy, peripheral vascular disease, cellular dysfunction, and prolonged inflammatory states, leading to impaired wound healing processes. Once formed, DFUs frequently become chronic, persisting for weeks to months, and are prone to infection, with a high risk of amputation if left untreated.[2]

Current wound care strategies—including gauze dressings, alginates, foams, and advanced biologics—often fail to address the persistent inflammation, oxidative stress, microbial colonization, and poor angiogenesis characteristic of DFUs.[3] Moreover, most conventional dressings do not dynamically respond to changes in the wound microenvironment, nor do they actively contribute to tissue regeneration. Thus, there is an urgent need for innovative, multifunctional wound dressings that can accelerate healing, reduce infection rates, and improve patient outcomes.

In recent years, hydrogels have garnered extensive attention in wound care due to their high water content, biocompatibility, oxygen permeability, and ability to mimic the natural extracellular matrix (ECM).[4] Among these, self-healing hydrogels represent a revolutionary advancement. These materials possess the intrinsic ability to repair mechanical damage through reversible physical or chemical crosslinking mechanisms, thereby maintaining structural integrity during movement and application, which is particularly advantageous for wounds on mobile body parts (e.g., feet and ankles).[5]

The integration of herbal medicines into these hydrogel systems offers a powerful synergy. Herbs

such as *Curcuma longa* (turmeric), *Aloe vera*, *Centella asiatica*, *Calendula officinalis*, and *Azadirachta indica* (neem) have centuries-old anecdotal and scientific support for their wound-healing properties. These plants contain bioactive compounds (e.g., curcuminoids, flavonoids, polysaccharides, tannins) with documented anti-inflammatory, antioxidant, antimicrobial, and pro-angiogenic effects[6]. By incorporating these phytochemicals into self-healing hydrogels, one can simultaneously provide sustained therapeutic delivery and a durable, responsive scaffold conducive to tissue regeneration.

This review presents a comprehensive analysis of the formulation and evaluation of herbal-based self-healing hydrogels for the management of chronic diabetic ulcers. It examines the rationale behind combining herbal actives with smart hydrogels, elucidates the mechanisms of self-healing, outlines formulation strategies, and evaluates current preclinical evidence. Furthermore, critical challenges and future directions are discussed to guide the development of clinically viable herbal hydrogel dressings.

II. PATHOPHYSIOLOGY OF DIABETIC ULCERS

To appreciate the rationale for using herbal-based self-healing hydrogels in diabetic ulcer management, it is essential to understand the pathophysiological challenges associated with DFUs. The wound-healing process typically progresses through four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. In diabetic patients, this cascade is profoundly disrupted.

Persistent hyperglycemia leads to the accumulation of advanced glycation end-products (AGEs), which impair fibroblast and keratinocyte function, reduce collagen synthesis, and hinder ECM remodeling.[7] Microvascular complications—such as endothelial dysfunction, reduced capillary density, and impaired angiogenesis—further limit oxygen and nutrient delivery to the wound site. Neuropathy diminishes protective sensation, increasing the risk of unnoticed trauma and mechanical stress, which can exacerbate tissue breakdown.

The inflammatory phase in DFUs is often prolonged due to dysregulated cytokine signaling. Elevated levels of tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and matrix metalloproteinases (MMPs) prolong inflammation, degrade newly formed ECM, and delay re-epithelialization.[8] Additionally, the high glucose environment promotes bacterial colonization and biofilm formation, commonly by *Staphylococcus aureus* and *Pseudomonas aeruginosa*, leading to chronic infection and further tissue damage.

Concurrently, impaired macrophage polarization and reduced production of growth factors like vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β) compromise the proliferative and remodeling phases.[9] The wound environment becomes dominated by oxidative stress, with excessive reactive oxygen species (ROS) causing cellular damage and apoptosis.

Given this multifactorial dysfunction, effective wound dressings must simultaneously address infection, inflammation, oxidative stress, and tissue regeneration. Ideal biomaterials should provide sustained release of therapeutic agents, maintain a moist microenvironment, and dynamically adapt to wound exudate and mechanical strain. Self-healing hydrogels loaded with herbal actives emerge as a highly suitable platform to meet these criteria.

III. HYDROGEL-BASED WOUND DRESSINGS: FUNDAMENTALS AND ADVANCEMENTS

Hydrogels are three-dimensional polymeric networks capable of absorbing large quantities of water or biological fluids without dissolving. They are composed of natural (e.g., chitosan, alginate, hyaluronic acid, collagen) or synthetic (e.g., poly(ethylene glycol), poly(vinyl alcohol)) polymers crosslinked via physical or chemical bonds.[10]

Key advantages of hydrogels in wound care include:

- High water content (70–90%), which maintains a moist wound environment conducive to cell migration and autolytic debridement.
- Permeability to oxygen and nutrients, supporting fibroblast proliferation and angiogenesis.
- Elasticity and flexibility, allowing conformation to wound topography and minimizing mechanical damage.

- Biocompatibility and low immunogenicity, reducing adverse reactions.
- Controlled release of embedded therapeutic agents.[11]

Over the past decade, intelligent hydrogels that respond to stimuli such as pH, temperature, moisture, and enzymes have gained attention. These "smart" hydrogels can adapt their properties to the changing wound microenvironment. For instance, DFUs often exhibit an acidic pH (5.0–6.5) due to bacterial metabolism and inflammation. pH-responsive hydrogels can be designed to release drugs preferentially at lower pH, thereby targeting the wound site more effectively.[12]

Among recent innovations, self-healing hydrogels represent a significant leap forward. These materials can autonomously repair cracks or cuts, restoring their mechanical integrity and functionality. This self-repair capability is crucial in wound dressings, as movement during daily activities can cause mechanical failure and compromise barrier function.[13]

IV. MECHANISMS OF SELF-HEALING IN HYDROGELS

Self-healing in hydrogels is primarily mediated through dynamic, reversible bonds that can reform after disruption. These include:

A. Supramolecular Interactions

Non-covalent interactions such as hydrogen bonding, hydrophobic interactions, π–π stacking, and metal-ligand coordination can enable self-healing. For example, hydrogels based on poly(acrylic acid) and poly (vinyl alcohol) can form intermolecular hydrogen bonds that break under stress but re-form upon relaxation, conferring self-healing ability.[14]

B. Dynamic Covalent Bonds

These include imine, disulfide, boronate ester, and Diels-Alder bonds. Diels-Alder adducts, for instance, are thermally reversible, allowing the hydrogel to "heal" when mildly heated. Boronate ester bonds, formed between boronic acid and diols (e.g., in PVA), are pH-responsive and can reform under physiological conditions, offering both self-healing and glucose-sensing capability—particularly beneficial in diabetic wound care.[15]

C. Host-Guest Interactions

Macrocyclic hosts like cyclodextrin (CD) and crown ethers can form inclusion complexes with guest molecules (e.g., adamantane). These interactions are reversible and facilitate self-healing. Cyclodextrin-adamantane pairs are widely used in hydrogel systems due to their high binding affinity and biocompatibility.[16]

D. Ionic Interactions

Polymers with charged groups (e.g., chitosan and alginate) can form polyelectrolyte complexes. The dynamic ionic interactions enable healing after mechanical damage, as demonstrated in chitosan/alginate-based hydrogels.[17]

The choice of self-healing mechanism influences the hydrogel's mechanical strength, healing rate, biocompatibility, and responsiveness. In diabetic wound applications, the ideal system should balance robustness with flexibility, exhibit rapid healing at body temperature, and respond favorably to the wound microenvironment.

V. HERBAL EXTRACTS IN WOUND HEALING: THERAPEUTIC RATIONALE

The integration of herbal extracts into hydrogels provides multiple therapeutic benefits. Key herbs and their active constituents are summarized below:

A. Curcuma longa (Turmeric)

Active compound: Curcumin Curcumin is a polyphenolic compound with potent anti-inflammatory, antioxidant, and antimicrobial properties. It downregulates NF-κB signaling, reduces TNF-α and IL-6 expression, scavenges ROS, and promotes collagen deposition and fibroblast proliferation. However, curcumin has low water solubility and poor bioavailability. Encapsulation in hydrogels enhances its stability and allows for sustained release at the wound site.[18]

B. Aloe vera

Bioactive components: Acemannan, glycoproteins, polysaccharides Aloe vera gel stimulates fibroblast proliferation, enhances collagen synthesis, and exhibits anti-inflammatory effects. Acemannan, a mannose-rich polysaccharide, activates macrophages and promotes granulation tissue formation.[19]

C. Centella asiatica

Active constituents: Asiaticoside, madecassoside Centella extracts promote angiogenesis, collagen synthesis, and re-epithelialization. Asiaticoside accelerates wound contraction and increases hydroxyproline content, a key component of collagen. Its inclusion in hydrogels has been shown to improve healing in diabetic rats.[20]

D. Calendula officinalis

Flavonoids, triterpenoids, and carotenoids in Calendula exhibit anti-inflammatory, antioxidant, and tissue-regenerative activities. It enhances wound closure rates and reduces oxidative stress.[21]

E. Azadirachta indica (Neem)

Neem contains azadirachtin, nimbolide, and quercetin, which possess broad-spectrum antimicrobial and anti-inflammatory properties. It is particularly effective against common wound pathogens, including methicillin-resistant *S. aureus* (MRSA).[22]

These botanicals are not only therapeutically potent but are also generally regarded as safe (GRAS), reducing the risk of adverse reactions. Their multifunctionality aligns well with the needs of chronic wound management.

VI. FORMULATION STRATEGIES FOR HERBAL-BASED SELF-HEALING HYDROGELS

Designing effective herbal-based self-healing hydrogels requires careful selection of polymer matrices, crosslinking agents, herbal loading methods, and fabrication techniques.

A. Selection of Base Polymers

Natural polymers are preferred due to their biocompatibility, biodegradability, and inherent bioactivity.

- Chitosan: A cationic polysaccharide derived from chitin. It promotes hemostasis, has inherent antimicrobial activity, and enhances cell adhesion. It can form polyelectrolyte complexes with anionic polymers (e.g., alginate, hyaluronic acid) for self-healing.
- Alginate: Extracted from brown seaweed. It forms ionically crosslinked hydrogels with divalent cations (e.g., Ca^{2+}), which can be reversible under certain conditions.
- Hyaluronic Acid (HA): A major component of ECM. It supports cell migration and tissue hydration. HA-based hydrogels are often modified with boronic acid or host-guest systems to enable self-healing.
- Collagen and Gelatin: Denatured collagen provides natural adhesion sites for cells and promotes re-epithelialization.

Synthetic polymers like PVA or PEG are often blended with natural polymers to enhance mechanical stability and tailor degradation rates.

B. Integration of Herbal Extracts

Herbal actives can be incorporated via:

- Direct mixing: Simple dispersion of powdered extract or crude extract into the polymer solution before gelation.
- Encapsulation: Use of liposomes, nanoparticles, or micelles to encapsulate hydrophobic compounds (e.g., curcumin) and enhance bioavailability.
- Covalent conjugation: Binding of herbal molecules (e.g., curcumin) to polymer chains via ester or amide linkages for controlled release.

For example, curcumin-loaded chitosan nanoparticles embedded in an alginate hydrogel matrix showed sustained release over 7 days and enhanced healing in diabetic mice.[23]

C. Inducing Self-Healing Properties

Common strategies include:

- Borate crosslinking: PVA and borax form reversible boronate ester bonds. Addition of chitosan or herb-loaded nanoparticles into this system yields self-healing, antimicrobial hydrogels.
- Host-guest chemistry: β-cyclodextrin-functionalized PEG and adamantane-tagged alginate create supramolecular networks with rapid self-healing.
- Schiff base formation: Chitosan and oxidized alginate react via amino-aldehyde condensation to form imine bonds, which are pH-responsive and self-healable.

D. Fabrication Techniques

- Sol-gel transition: Mixing of two polymer solutions (e.g., chitosan and oxidized alginate) at room temperature.
- Freeze-thaw cycling: Used for PVA-based hydrogels, where repeated freezing and thawing induce physical crosslinking.
- In situ gelation: Injectable formulations that gel upon contact with physiological fluids, conforming to irregular wound shapes.

Recent advances include 3D printing of herbal hydrogel scaffolds with controlled porosity and spatial distribution of bioactive agents.[24]

VII. EVALUATION OF HERBAL-BASED SELF-HEALING HYDROGELS

A comprehensive evaluation of hydrogel performance involves physical, chemical, biological, and preclinical assessments.

A. Physical and Chemical Characterization

- Swelling ratio: Determines fluid absorption capacity. Optimal hydrogels swell to retain exudate without disintegration.
- Mechanical properties: Assessed via rheometry and tensile testing. Self-healing efficiency is calculated using recovery tests after damage.
- Morphology: Scanning electron microscopy (SEM) reveals pore structure and homogeneity.
- FTIR and NMR spectroscopy: Confirm chemical structure and interaction between polymers and herbal components.
- Thermal analysis (TGA/DSC): Evaluates thermal stability and degradation behavior.

B. Self-Healing Assessment

- Visual inspection of cut surfaces rejoining over time.
- Rheological recovery tests: Oscillatory strain sweeps to measure recovery of storage (G') and loss (G") moduli.
- Cyclic tensile tests: Demonstrate healing over multiple damage-repair cycles.[25]

C. *In-Vitro* Drug Release Studies

- Conducted in simulated wound fluid (pH 5.5–7.4) using Franz diffusion cells.
- Release kinetics are modeled using Higuchi, Korsmeyer-Peppas, or zero-order models to understand release mechanisms.
- pH-responsive systems show accelerated release under acidic conditions.[26]

D. Biological Evaluations

- Cytotoxicity (MTT assay): Tested on fibroblasts (e.g., L929 or NIH-3T3) to ensure biocompatibility.
- Antimicrobial activity: Disc diffusion or broth dilution assays against *S. aureus*, *P. aeruginosa*, and *E. coli*.
- Antioxidant capacity: DPPH and ABTS radical scavenging assays.
- Cell migration and proliferation: Scratch assays and live/dead staining to assess wound closure potential.[27]

E. *In-Vivo* Wound Healing Studies

- Typically conducted in streptozotocin (STZ)-induced diabetic rodent models.
- Parameters measured:
  - Wound closure rate (% area reduction over time)
  - Histopathological analysis (H&E, Masson's trichrome for collagen)
  - Immunohistochemistry for markers of inflammation (CD68), angiogenesis (CD31), and proliferation (Ki67)
  - ELISA for cytokine levels (TNF-α, IL-10, VEGF)

For instance, a curcumin-chitosan/alginate self-healing hydrogel demonstrated 92% wound closure in diabetic rats by day 14, compared to 65% in controls.

VIII. CHALLENGES AND LIMITATIONS

Despite their promise, several challenges must be overcome before clinical translation:

A. Standardization of Herbal Extracts

Variability in phytochemical content due to plant source, extraction method, and storage conditions can affect consistency and reproducibility. Standardized extraction protocols and HPLC-based quality control are essential.

B. Stability and Shelf Life

Herbal compounds like curcumin are photosensitive and prone to degradation. Encapsulation and storage in inert conditions are needed to ensure long-term stability.

C. Scalability and Manufacturing Costs

Complex fabrication processes (e.g., nanoparticle synthesis, 3D printing) may hinder large-scale production. Simplified, cost-effective methods must be developed.

D. Regulatory Hurdles

Combination products (drug + device) face rigorous FDA/EMA requirements. Demonstrating safety, efficacy, and quality control across multiple batches is challenging.

E. Biocompatibility and Long-Term Effects

While natural polymers are generally safe, some patients may exhibit allergic reactions (e.g., to chitosan). Long-term in vivo biodegradation and immune responses require thorough investigation.

IX. FUTURE PERSPECTIVES

The field of herbal-based self-healing hydrogels is poised for rapid advancement. Future directions include:

- Multifunctional Smart Systems: Integration of glucose-responsive elements (e.g., phenylboronic acid) to enable real-time monitoring and feedback-controlled drug release.
- Gene-Activated Hydrogels: Delivery of plasmid DNA or siRNA encoding growth factors or anti-inflammatory cytokines.
- Microbiome-Responsive Hydrogels: Materials that sense and respond to specific microbial metabolites.
- Personalized Wound Dressings: 3D bioprinting using patient-specific wound scans and autologous cells.
- Clinical Trials: Translational studies to validate safety and efficacy in human diabetic patients.

Additionally, sustainable sourcing of herbal materials and green synthesis methods align with global trends toward eco-friendly healthcare solutions.

X. CONCLUSION

Herbal-based self-healing hydrogels represent a cutting-edge, multidisciplinary approach to managing chronic diabetic ulcers. By combining the regenerative and therapeutic properties of medicinal plants with the mechanical resilience and adaptability of self-healing hydrogels, these biomaterials offer unprecedented potential to address the complex pathophysiology of diabetic wounds. The formulation of such hydrogels involves judicious selection of natural polymers, dynamic crosslinking mechanisms, and optimized delivery systems for herbal bioactives. Preclinical evidence consistently demonstrates enhanced wound closure, reduced inflammation, and improved tissue regeneration. However, challenges related to standardization, scalability, and regulatory approval must be addressed to facilitate clinical adoption. With continued innovation and rigorous evaluation, herbal-based self-healing hydrogels may revolutionize chronic wound care, offering safer, more effective, and accessible treatment options for millions of diabetic patients worldwide.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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