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Review Paper

Formulation and Pharmacological Evaluation of a Polyherbal Hydrogel Containing Aloe vera, Curcumin, and Centella asiatica for Diabetic Wound Healing Activity: A Comprehensive Review and Methodological Framework

Sanskruti Pandekar*, Ulka Mote, Dr. Pravin Uttekar, Sagar Daitkar

Late Laxmibai Phadtare College of Pharmacy A/P-Kalamb-Walchandnagar,Tal : Indapur Dist : Pune.

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ABSTRACT

Background: Diabetic wound healing is a complex and challenging clinical problem, characterized by a self-perpetuating cycle of oxidative stress, chronic inflammation, impaired angiogenesis, and defective extracellular matrix (ECM) remodeling. Conventional wound dressings often provide passive care and fail to address this multifactorial pathophysiology.Objective: This review outlines the scientific rationale, formulation design, and comprehensive evaluation strategy for a polyherbal hydrogel containing standardized extracts of Aloe vera, curcumin (Curcuma longa), and Centella asiatica. The objective is to create a bioactive dressing that synergistically targets multiple pathways to accelerate diabetic wound repair.Methods: We review the pathophysiology of diabetic wounds and the pharmacological actions of the selected herbs. A detailed experimental methodology is provided, covering pre-formulation studies, hydrogel development using modern polymer science (e.g., Carbopol/HPMC), Quality-by-Design (QbD) principles, and advanced evaluation techniques. This includes physicochemical characterization (rheology, bio-adhesion), in vitro release kinetics, and biological assays (antioxidant, antimicrobial, cell migration). A robust in vivo protocol using a streptozotocin (STZ)-induced diabetic rat excision wound model is detailed, with endpoints including wound contraction rate, histopathology (collagen, angiogenesis via CD31/VEGF), and biochemical markers (hydroxyproline, MDA, TNF-α). Expected Outcomes: The proposed polyherbal hydrogel is expected to maintain a moist wound environment while actively promoting healing. Aloe vera will provide hydration and support re-epithelialization; curcumin will offer potent antioxidant and anti-inflammatory effects; and Centella asiatica will stimulate fibroblast proliferation and collagen synthesis. This multi-pronged approach is hypothesized to lead to faster

***Corresponding Author:** Sanskruti Pandekar
Address: *Late Laxmibai Phadtare College of Pharmacy A/P-Kalamb-Walchandnagar,Tal : Indapur Dist : Pune..*
Email ✉ : sanskrutipandekar@gmail.com

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wound closure, enhanced tissue quality, and reduced infection risk compared to untreated or single-agent controls. Conclusion: A well-formulated and rigorously evaluated polyherbal hydrogel represents a promising, next-generation therapeutic strategy for managing chronic diabetic wounds. This manuscript provides a complete framework to guide its development from concept to preclinical validation

INTRODUCTION

Diabetes mellitus has reached pandemic proportions, and its complications represent a significant global health burden. Among the most debilitating of these is the diabetic foot ulcer (DFU), a chronic, non-healing wound that is a leading cause of non-traumatic lower-limb amputations [1]. The pathophysiology of diabetic wounds is notoriously complex, involving a vicious cycle of hyperglycemia, peripheral neuropathy, vascular insufficiency, oxidative stress, and a persistent, non-resolving inflammatory state [2]. This hostile microenvironment impairs all phases of the normal wound healing cascade, from cell proliferation and migration to angiogenesis and matrix remodeling [3].

Conventional wound dressings, such as gauze or films, primarily offer a passive protective barrier. While advanced dressings (e.g., foams, alginates) provide better moisture management, they do not actively intervene in the underlying biological defects of the diabetic wound [4]. There is a critical unmet need for "active" or "bioactive" dressings that can modulate the wound environment to promote healing.

Hydrogels—three-dimensional, hydrophilic polymer networks—are exceptional platforms for modern wound care. They can donate moisture to dry wounds, absorb excess exudate, are biocompatible, and can be designed to provide sustained, localized delivery of therapeutic agents [5]. This makes them ideal vehicles for delivering phytochemicals with known wound-healing properties.

This review focuses on the development of a sophisticated polyherbal hydrogel combining three powerhouse botanicals: *Aloe vera*, curcumin (*from Curcuma longa*), and *Centella asiatica* (*Gotu Kola*).

- ***Aloe vera*** is renowned for its hydrating and soothing properties, primarily driven by the polysaccharide acemannan, which stimulates fibroblast growth and epithelialization [6, 7].
- **Curcumin** is a potent antioxidant and anti-inflammatory agent that can quench reactive oxygen species (ROS) and downregulate pro-inflammatory cytokines like TNF-α and IL-6, which are chronically elevated in diabetic wounds [8, 9].
- ***Centella asiatica*** contains bioactive triterpenes (asiaticoside, madecassoside) that are proven to enhance collagen synthesis, improve tensile strength of newly formed skin, and promote angiogenesis [10, 11].

By combining these three agents in a single hydrogel formulation, we hypothesize a synergistic effect that addresses multiple facets of diabetic wound pathology simultaneously (Figure 1). This manuscript provides a comprehensive scientific framework for the formulation, characterization, and pharmacological evaluation of this novel polyherbal therapeutic system.

FIGURE 1: DUAL MECHANISM OF DIABETIC WOUNDS AND HYDROGEL THERAPY

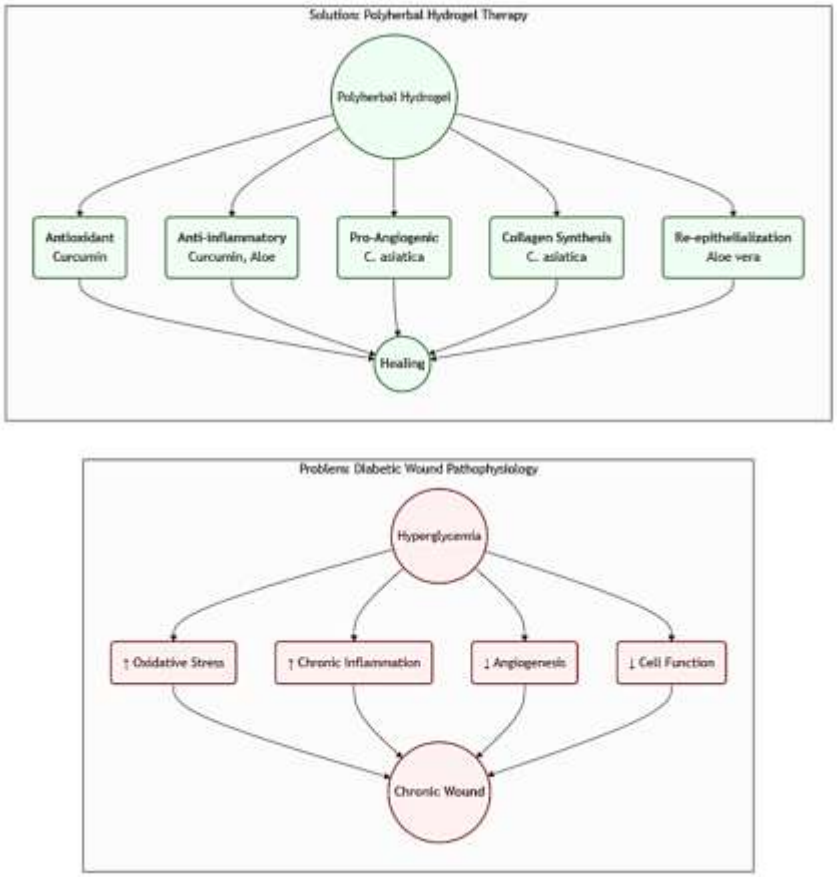

Figure 1: Pathophysiology vs. Therapeutic Action

This diagram illustrates how the polyherbal hydrogel is designed to counteract the key pathological defects present in a chronic diabetic wound.

2. RATIONALE FOR THE POLYHERBAL APPROACH

A single-agent therapy is often insufficient to overcome the multifaceted barriers in diabetic wound healing. A polyherbal approach, as summarized in Table 1, allows for a synergistic, multi-pronged attack on the wound's pathophysiology.

TABLE 1: PATHOPHYSIOLOGY OF DIABETIC WOUNDS AND CORRESPONDING HERBAL ACTIONS

Pathological Feature in Diabetic Wound	Pharmacological Action of Herbal Component
↑ Oxidative Stress & ROS Damage	Curcumin: Potent ROS scavenger, upregulates antioxidant enzymes (e.g., Nrf2 pathway).
↑ Chronic Inflammation (High TNF-α, IL-6)	Curcumin & Aloe vera: Inhibit NF-κB signaling, reducing pro-inflammatory cytokine production.
↓ Impaired Angiogenesis	Centella asiatica & Curcumin: Stimulate Vascular Endothelial Growth Factor (VEGF) production, promoting new blood vessel formation.

↓ Defective Collagen Synthesis & ECM	Centella asiatica: Triterpenes (asiaticoside) directly stimulate fibroblast proliferation and Type I collagen synthesis.
↓ Impaired Re-epithelialization	Aloe vera: Acemannan stimulates keratinocyte migration and proliferation.
High Risk of Microbial Colonization	Hydrogel Barrier, Curcumin, & Aloe vera: Provide a physical barrier and possess intrinsic antimicrobial properties.
Wound Dehydration / Excessive Exudate	Hydrogel Base: Maintains optimal moisture balance by donating or absorbing water.

3. FORMULATION DESIGN AND METHODOLOGY

The successful development of the hydrogel relies on rational selection of excipients and a carefully controlled manufacturing process (Figure 2).

FIGURE 2: FORMULATION AND EVALUATION WORKFLOW

Figure 2: Comprehensive Development Workflow

This workflow diagram outlines the systematic steps from raw material selection to final preclinical evaluation, incorporating modern pharmaceutical development principles like Quality-by-Design (QbD) and Design of Experiments (DoE).

3.1. MATERIALS AND METHODS

3.1.1. Materials

Standardized extracts of *Aloe vera* (≥10% acemannan), *Curcuma longa* (≥95% curcuminoids), and *Centella asiatica* (≥40% triterpenes) will be procured. Pharmaceutical-grade polymers (Carbopol 940, HPMC K100M), humectants (propylene glycol), neutralizers (triethanolamine), and solubilizers for curcumin (e.g., Polysorbate 80, HP-β-Cyclodextrin) will be used.

3.1.2. Pre-formulation Studies

Solubility of extracts in various solvents will be determined. Drug-excipient compatibility will be assessed using Fourier-Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) to detect any potential interactions.

3.1.3. Formulation of the Hydrogel

A detailed breakdown of components is provided in Table 2. The hydrogel will be prepared by dispersing the gelling agent (e.g., Carbopol 940) in purified water, followed by the addition of other polymers and humectants. The herbal extracts and solubilized curcumin will be incorporated with gentle mixing. Finally, the pH will be adjusted to ~6.0 using triethanolamine to induce gelation.

4. PHARMACOLOGICAL EVALUATION (IN VIVO)

4.1. Experimental Animals

Healthy adult Wistar rats (180–220 g) of either sex will be used. The study protocol will be approved by the Institutional Animal Ethics Committee (IAEC).

4.2. Induction of Diabetes

Diabetes will be induced by a single intraperitoneal (i.p.) injection of Streptozotocin (STZ) at a dose of 55 mg/kg, dissolved in cold citrate buffer (pH 4.5). Animals with fasting blood glucose levels >250 mg/dL after 72 hours will be considered diabetic and selected for the study.

4.3. Excision Wound Model

The diabetic rats will be anesthetized, and the dorsal thoracic region will be shaved. A circular, full-thickness excision wound of approximately 200 mm² will be created using a sterile biopsy punch.

TABLE 2: COMPONENTS AND RATIONALE FOR THE POLYHERBAL HYDROGEL FORMULATION

Component	Example	Concentration (% w/w)	Rationale / Function
Gelling Agent	Carbopol® 940	0.5 – 1.5	Creates the primary hydrogel network; provides viscosity.
Viscosity Modifier	HPMC K100M	0.5 – 2.0	Modulates viscosity, improves bio-adhesion and controls release.
Humectant	Propylene Glycol	5 – 10	Prevents the dressing from drying out; acts as a co-solvent.
Curcumin Solubilizer	HP-β-Cyclodextrin or Polysorbate 80	1:2 molar ratio or 1-5%	Enhances solubility and stability of poorly soluble curcumin.
Active 1	*Aloe vera* extract	1 – 5	Provides healing polysaccharides (acemannan) and hydration.
Active 2	Curcumin	0.1 – 0.5	Serves as the primary antioxidant and anti-inflammatory agent.
Active 3	*Centella asiatica* extract	0.5 – 2	Delivers triterpenes to stimulate collagen and angiogenesis.
Neutralizing Agent	Triethanolamine (TEA)	q.s. to pH 6.0	Neutralizes Carbopol to form the viscous gel structure.
Vehicle	Purified Water	q.s. to 100	The primary solvent and hydrating medium.

3.2. Evaluation of the Polyherbal Hydrogel

A comprehensive set of evaluation parameters (Table 3) will be used to ensure the quality, safety, and efficacy of the final formulation.

TABLE 3: COMPREHENSIVE EVALUATION PARAMETERS FOR THE HYDROGEL

Category	Parameter	Method / Instrument	Acceptance Criteria
Physicochemical	Appearance & Homogeneity	Visual Inspection	Homogeneous, smooth, free of lumps
	pH	pH meter	5.5 – 6.5 (skin compatible)
	Viscosity & Rheology	Brookfield Viscometer / Rheometer	Appropriate viscosity for topical application (e.g., 20,000-50,000 cP)
	Spreadability	Parallel Plate Method	Good spreadability circle diameter
	Bio-adhesion	Texture Analyzer	Adequate force of detachment
Performance	Drug Content Uniformity	HPLC	90% – 110% of label claim
	In Vitro Release Test	Franz Diffusion Cell	Sustained release over 8-12 hours
Biological	In Vitro Antioxidant Activity	DPPH/ABTS Assay	Significant radical scavenging activity
	In Vitro Antimicrobial Activity	Agar Well Diffusion	Zone of inhibition against *S. aureus*, *P. aeruginosa*
In Vivo Efficacy	Wound Contraction Rate	Digital Planimetry	Significantly faster closure vs. control
	Histopathology	H&E and Masson's Trichrome Staining	Enhanced collagen deposition, re-epithelialization, angiogenesis
	Biochemical Markers	ELISA / Colorimetric Assays	↑ Hydroxyproline, ↓ MDA, ↓ TNF-α
Safety	Dermal Irritation Test	OECD Guideline 404 (Rabbit model)	Non-irritant
Stability	ICH Stability Studies	Stability Chamber	Stable for at least 6 months under accelerated conditions

4.4. Experimental Groups

The animals will be divided into the following groups (n=6 per group):

- **Group I:** Normal Control (non-diabetic, untreated wound)
- **Group II:** Diabetic Control (untreated wound)
- **Group III:** Diabetic + Placebo Hydrogel (hydrogel base without herbal extracts)
- **Group IV:** Diabetic + Standard Drug (e.g., Povidone-Iodine ointment)
- **Group V:** Diabetic + Polyherbal Hydrogel

4.5. Treatment and Evaluation

The formulations will be applied topically to the wound area once daily for 21 days. Wound contraction will be measured every 3rd day by tracing the wound boundary on a transparent sheet and calculating the area. The period of epithelialization will be noted as the number of days required for the scar to fall off completely.

On day 21, animals will be euthanized, and wound tissue will be collected for:

- **Histopathological Analysis:** Tissue sections stained with Hematoxylin & Eosin (H&E) and Masson's Trichrome will be evaluated for collagen deposition, re-epithelialization,

inflammatory cell infiltration, and angiogenesis.

- **Biochemical Analysis:** Tissue homogenates will be analyzed for hydroxyproline content (a marker of collagen), malondialdehyde (MDA, a marker of oxidative stress), and levels of inflammatory cytokines (TNF-α, IL-6).

FIGURE 3: PROPOSED MECHANISM OF ACTION OF INDIVIDUAL HERBAL COMPONENTS

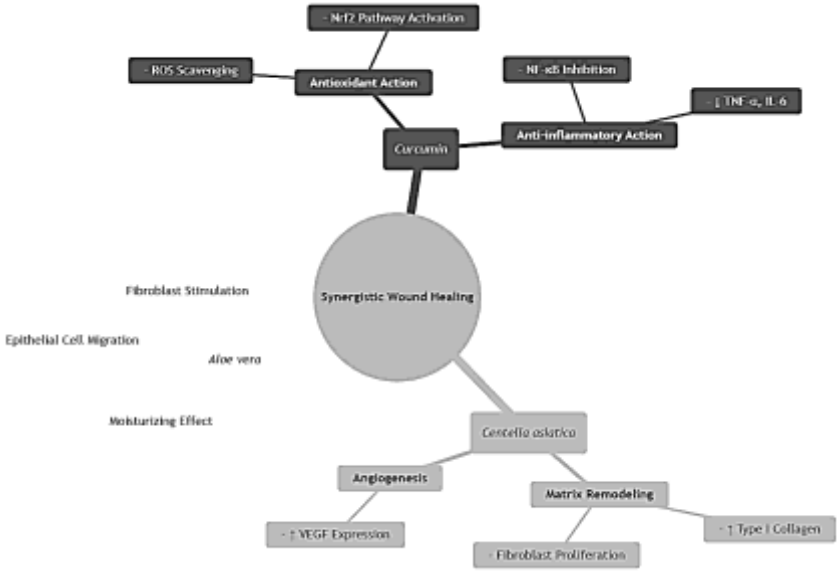

Figure 3: Multi-Target Action of Herbal Components

This mind map illustrates how the three herbal actives work on distinct yet complementary pathways to promote holistic wound repair.

CONCLUSION

The development of a polyherbal hydrogel containing *Aloe vera*, curcumin, and *Centella asiatica* presents a scientifically robust and highly promising strategy for the management of chronic diabetic wounds. By combining the hydrating and sustained-release benefits of a hydrogel vehicle with the synergistic, multi-target pharmacological actions of the selected botanicals, this formulation is poised to address the core pathological defects that hinder healing in diabetic patients. The comprehensive methodological framework outlined in this review, from QbD-based formulation to rigorous in vivo evaluation, provides a clear roadmap for translating this concept from the laboratory bench to a potential clinical application. Successful validation would mark a significant advancement in active wound care, offering a safer, more effective, and plant-based alternative for this major unmet medical need.

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