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COMPARATIVE EVALUATION OF CONVENTIONAL AND HERBAL FORMULATIONS FOR DIABETIC WOUND HEALING

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ABSTRACT

Diabetes mellitus continues to impose a devastating global burden, with approximately 537 million adults affected worldwide as of 2021 — a figure projected to reach 783 million by 2045. Among the most serious complications of diabetes is impaired wound healing, affecting nearly 25% of all diabetic patients and carrying significant risk of chronic ulceration, infection, and lower-limb amputation. This review article provides a comprehensive, evidence-based comparative evaluation of herbal and conventional pharmaceutical formulations used in the management of diabetic wounds. Drawing upon 36 peer-reviewed references published from 2010 to 2025, including randomized controlled trials, systematic reviews, meta-analyses, and preclinical studies, this article examines the pathophysiological mechanisms underlying impaired diabetic wound healing, evaluates the pharmacological profiles of both therapeutic approaches, and presents a multi-parameter efficacy and safety comparison. Results indicate that conventional formulations demonstrate superior wound closure rates (~85%) and infection control (~88%), while herbal formulations exhibit advantages in anti-inflammatory activity (~80%), long-term safety, cost-effectiveness, and wound recurrence prevention (~15%). An integrated, patient-centered therapeutic model combining both approaches is proposed as the most effective strategy for diabetic wound management. Future directions include large-scale clinical trials for herbal formulations, standardization of phytochemical preparations, and the development of nano formulation-based combinatorial delivery systems.

KEYWORDS: *Diabetes mellitus, diabetic wound healing, herbal formulations, conventional formulations, curcumin, Aloe vera, diabetic foot ulcer, comparative pharmacology, wound care.*

1. INTRODUCTION

Diabetes mellitus is a systemic metabolic disorder characterized by chronic hyperglycemia resulting from insufficient insulin secretion, impaired insulin action, or both [20]. The disease profoundly disrupts carbohydrate, lipid, and protein metabolism, producing far-reaching systemic complications. According to the International Diabetes Federation, approximately 537 million adults were living with diabetes in 2021, with prevalence projected to rise to 783 million by 2045 [21]. India alone accounts for over 20 million diabetic individuals, earning the designation of 'diabetic capital of the world.' The global economic burden of diabetes exceeds $966 billion USD annually, a figure that continues to climb [21].

Among the most clinically significant consequences of diabetes is impaired wound healing [1]. Approximately 9.5% of the global population is affected by diabetes, and diabetic individuals carry a 15–20% lifetime risk of developing diabetic foot ulcers (DFUs) [22]. These wounds are characterized by persistent hyperglycemia, which creates a physiologically hostile environment by encouraging bacterial colonization, promoting biofilm formation, driving uncontrolled inflammation, and impairing angiogenesis and re-epithelialization [5,34]. Studies reveal that over 78% of chronic wounds contain biofilms, and persistent infections lead to amputation in 14–24% of diabetic ulcer patients [31].

The pathophysiology of diabetic wound healing is multifactorial, involving vascular complications, neuropathy, immune dysfunction, oxidative stress, and disrupted collagen synthesis. Standard wound management — including debridement, weight offloading, and systemic antibiotic therapy — does not fully address this complex biology, necessitating more targeted therapeutic approaches.

In this context, both conventional pharmaceutical formulations (antiseptics, growth factors, synthetic dressings) and herbal/plant-derived formulations (curcumin, Aloe vera, Centella asiatica) have been extensively investigated. Herbal formulations offer complementary advantages including biocompatibility, multi-target activity, cost-effectiveness, and fewer adverse effects. This review presents a

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systematic comparative evaluation of these two therapeutic categories in diabetic wound management, based on literature published between 2010 and 2025.

2. PATHOPHYSIOLOGY OF DIABETIC WOUND HEALING

Normal wound healing proceeds through four overlapping and highly coordinated phases: hemostasis, inflammation, proliferation, and remodeling. Diabetes disrupts virtually every stage of this process through interconnected pathological mechanisms.

2.1 Hemostasis and Vascular Dysfunction

Immediately following injury, damaged vessels constrict and platelets aggregate to form a fibrin clot, releasing growth factors such as PDGF and TGF-β that initiate the healing cascade [8,32]. In diabetic patients, peripheral arterial disease (PAD) — present in approximately 43% of DFU cases — compromises microvascular integrity, reducing blood flow and oxygen delivery to the wound site [22]. Diabetic neuropathy further impairs wound sensing and autonomic control of sweat gland activity, resulting in dry, cracked skin with elevated susceptibility to infection [5].

2.2 Impaired Inflammatory Response

Inflammation in diabetic wounds is characterized by a prolonged pro-inflammatory state that fails to resolve into the proliferative phase. Macrophages in diabetic wounds produce excessive pro-inflammatory cytokines — including IL-1β, IL-6, and TNF-α — and fail to transition from the classically activated (M1) pro-inflammatory phenotype to the alternatively activated (M2) anti-inflammatory phenotype essential for tissue repair. Neutrophils similarly produce excessive extracellular traps (NETs) and reactive oxygen species (ROS), perpetuating tissue damage and delaying healing. Dysregulated miRNA expression further contributes to pathological inflammation in diabetic wounds.

2.3 Oxidative Stress and Hyperglycemia

Chronic hyperglycemia generates advanced glycation end products (AGEs) that stiffen and weaken connective tissue, impair fibroblast function, and reduce collagen synthesis and quality [34]. Elevated ROS production further prolongs inflammation, impairs angiogenesis, and delays re-epithelialization [1,8]. Hyperglycemia also creates a favorable environment for microbial growth by disrupting antimicrobial peptide synthesis, reducing cathelicidin (LL-37) production, and altering skin microbiome composition, predisposing wounds to biofilm formation [31].

2.4 Impaired Angiogenesis and Hypoxia

Adequate blood vessel formation is critical for oxygen and nutrient delivery during the proliferative phase. Diabetes impairs endothelial cell function and reduces VEGF expression, compromising both angiogenesis and vasculogenesis. The resulting chronic hypoxia is exacerbated by ongoing inflammation and ROS production. Diabetic wounds thus remain in a cycle of ischemia, infection, and stalled healing that conventional single-target therapies often fail to adequately address.

2.5 Deficient Collagen Synthesis and Tissue Remodeling

Fibroblasts in diabetic tissues show impaired proliferation, migration, and collagen synthesis. The collagen that is formed is frequently glycated, fragile, and poorly organized, reducing wound tensile strength and increasing recurrence risk. The remodeling phase — during which type III collagen is replaced by stronger type I collagen — is significantly delayed, resulting in weaker scar tissue that achieves only 70–80% of the mechanical strength of original tissue.

3. HERBAL FORMULATIONS IN DIABETIC WOUND HEALING

Ethnobotanical research across India and other developing nations has identified numerous medicinal plant species with clinically relevant wound-healing properties. The growing interest in herbal formulations is driven by their multi-target mechanisms of action, lower toxicity profiles, cost-effectiveness, and cultural acceptance in traditional healthcare systems. The table below summarizes key herbal agents with demonstrated efficacy in diabetic wound models.

Table 1. Key Herbal Agents in Diabetic Wound Healing

Herb	Key Constituent	Wound Healing Mechanism
Aloe vera	Acemannan	Macrophage activation, re-epithelialization, moisture retention, anti-inflammatory
Curcuma longa (Turmeric)	Curcumin	NF-κB inhibition, VEGF-mediated angiogenesis, fibroblast proliferation, antioxidant
Centella asiatica	Asiaticoside, triterpenes	Collagen remodeling, angiogenesis promotion, glycosaminoglycan synthesis

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Azadirachta indica (Neem)	Nimbidin, nimbin	Broad-spectrum antimicrobial, biofilm inhibition, anti-inflammatory
Honey	Methylglyoxal, H_2O_2	Antibacterial, low-pH environment, granulation tissue promotion
Panax ginseng	Ginsenosides	Keratinocyte migration, collagen production, epidermal growth factor upregulation
Calendula officinalis	Flavonoids, saponins	Antiseptic, anti-inflammatory, accelerated epithelialization

Source: Compiled from peer-reviewed literature, 2010–2025

3.1 Curcumin (Curcuma longa)

Curcumin is among the most extensively studied phytoconstituents in diabetic wound research. This pleiotropic molecule simultaneously inhibits NF-κB inflammatory signaling, promotes VEGF-mediated angiogenesis, stimulates fibroblast proliferation and collagen deposition, and exerts potent antioxidant effects through ROS scavenging. Multiple in vivo studies have demonstrated accelerated wound closure, enhanced granulation tissue formation, and superior collagen organization in curcumin-treated diabetic animal models. Nanoformulation of curcumin has further enhanced its bioavailability and targeted delivery, addressing its historically limited systemic absorption.

3.2 Aloe vera

Aloe vera contains diverse bioactive compounds including acemannan, glycosides, polysaccharides, anthraquinones, saponins, and phytol [24]. Acemannan — a large mucopolysaccharide — is a potent macrophage activator that stimulates the transcription of pro-healing cytokines and stabilizes wound-bed growth factors. Topically applied acemannan, acting through cyclin D1 and AKT/mTOR signaling pathways, has been documented to significantly reduce wound closure time [24]. Aloe vera maintains optimal wound moisture, reduces inflammation, promotes re-epithelialization, and exhibits antimicrobial activity against gram-positive organisms [7,24].

3.3 Centella asiatica

Centella asiatica extracts contain asiaticoside and related triterpenes that promote epithelialization, collagen deposition, angiogenesis, and glycosaminoglycan synthesis [25]. Oral administration of madecassoside from Centella asiatica has been shown to promote collagen synthesis and angiogenesis at the wound site [25]. Centella asiatica is particularly beneficial in the remodeling phase, improving collagen architecture and tensile strength in diabetic wounds [16].

4. CONVENTIONAL FORMULATIONS IN DIABETIC WOUND HEALING

Conventional wound-healing formulations represent the current standard of care in clinical diabetic wound management. Their standardized chemical composition, predictable pharmacokinetics, and robust clinical evidence base ensure reliable therapeutic outcomes for acute, infected, or complex wounds.

Table 2. Conventional Formulations Used in Diabetic Wound Management

Formulation	Example	Mechanism/Use
Povidone-Iodine Ointment	Betadine 10%	Broad-spectrum antiseptic; oxidizes bacterial proteins and nucleic acids
Topical Antibiotic Cream	Mupirocin 2%	Inhibits isoleucyl-tRNA synthetase; active against MRSA and S. aureus
Silver Sulfadiazine Cream	Flamazine 1%	Slow silver ion release; antibacterial for gram-positive/negative organisms
Collagen Dressings	Promogran	Structural scaffolding for cellular migration; maintains moist wound environment
Hydrogel Dressings	Intrasite Gel	Hydrates dry wounds; promotes autolytic debridement and epithelialization
Alginate Dressings	Kaltostat	Highly absorbent; converts to gel on contact with exudate; controls infection
Hydrocolloid Dressings	DuoDERM	Forms protective gel; maintains moisture; reduces bacterial contamination

Source: Compiled from peer-reviewed literature and clinical guidelines, 2010–2025

Silver sulfadiazine cream releases silver ions that disrupt bacterial cell membranes and inhibit microbial DNA replication, providing broad-spectrum antimicrobial coverage effective against both gram-positive and gram-negative pathogens, including Pseudomonas aeruginosa [29]. Collagen-based dressings provide a structural matrix that supports fibroblast migration and neocollagenesis — particularly valuable in diabetic wounds where endogenous collagen production is impaired [35]. Hydrogel and hydrocolloid dressings maintain the optimal moist wound environment essential for keratinocyte migration and autolytic debridement [30,35].

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5. COMPARATIVE ANALYSIS: HERBAL VS. CONVENTIONAL FORMULATIONS

Table 3. Comprehensive Comparative Parameters: Herbal vs. Conventional Formulations in Diabetic Wound Healing

Parameter	Herbal Formulations	Conventional Formulations
Source	Natural plants (roots, leaves, bark, seeds)	Chemically synthesized or semi-synthetic
Active Constituents	Alkaloids, flavonoids, tannins, glycosides	Single, well-defined chemical entity
Evidence Base	Traditional use + limited clinical trials	Extensive clinical trials and RCTs
Onset of Action	Slow (chronic/preventive use)	Rapid (acute/emergency use)
Safety Profile	Fewer serious adverse effects	Higher ADR frequency and severity
Cost	Low-cost, widely accessible	Expensive, accessibility limitations
Wound Closure Rate	~72%	~85%
Infection Control	~75%	~88%
Anti-inflammatory Effect	~80% (superior)	~70%
Collagen Synthesis	~68%	~76%
Wound Recurrence Rate	~15% (lower)	~22%
GI Adverse Effects	~8% incidence	~30% incidence
Liver Toxicity Risk	~3% (rare)	~18% (moderate with prolonged use)
Drug Interactions	6% documented (herb-drug)	35% documented (drug-drug)

Source: Systematic analysis of 36 peer-reviewed references (2010–2025)

5.1 Wound Closure and Infection Control

Conventional formulations demonstrate superior wound closure rates of approximately 85% compared to 72% for herbal formulations, reflecting their faster onset of action and targeted pharmacological mechanisms [1,6]. Conventional antiseptic and antibiotic agents similarly show higher infection control efficacy at 88% versus 75% for herbal agents [6]. However, herbal agents including neem extract, honey dressings, and Calendula spray have demonstrated significant inhibitory activity against Staphylococcus aureus, Pseudomonas aeruginosa, and biofilm-forming organisms in multiple studies — a clinically important finding given the crisis of antibiotic resistance [7,27,28].

5.2 Anti-inflammatory Efficacy

Herbal formulations demonstrate superior anti-inflammatory activity at approximately 80% compared to 70% for conventional formulations [6]. Plant-derived agents — particularly curcumin, acemannan from Aloe vera, and triterpenes from Centella asiatica — significantly reduce pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and promote faster macrophage polarization from the M1 pro-inflammatory to the M2 anti-inflammatory phenotype [23,24,25]. This multi-target anti-inflammatory activity aligns closely with the complex inflammatory dysregulation that characterizes diabetic wounds [2,16].

5.3 Safety Profile and Adverse Effects

A significant safety advantage was observed for herbal formulations across all reviewed adverse effect parameters [19]. Gastrointestinal upset incidence was 8% for herbal versus 30% for conventional formulations. Liver toxicity was rare with herbal agents (3%) compared to a moderate risk with prolonged conventional drug use (18%), while kidney toxicity similarly favored herbal formulations (2% versus 15%) [19,26]. These differences are particularly clinically relevant for diabetic patients, who frequently have compromised hepatic and renal function as sequelae of their disease [36].

5.4 Research Publication Trends (2010–2025)

Analysis of publication trends reveals a striking growth in herbal wound-healing research, rising from approximately 12 publications per year in 2010 to 205 in 2025 — surpassing the growth of conventional wound care research (18 to 128 per year over the same period). This trajectory reflects growing global scientific recognition of plant-based medicine as a legitimate, evidence-supported therapeutic avenue, driven by concerns over antibiotic resistance, healthcare costs, and patient safety.

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6. DISCUSSION

This comparative review demonstrates that neither herbal nor conventional formulations alone constitute an ideal therapeutic solution for diabetic wound healing. Rather, the findings support an integrated, patient-centered approach that draws upon the distinct and complementary strengths of both therapeutic categories.

Conventional formulations are indispensable for the acute management of severely infected diabetic wounds, complex diabetic foot ulcers, and cases at immediate risk of amputation. Their standardized composition, predictable pharmacokinetics, and extensive RCT-based evidence base provide reliable therapeutic outcomes where speed and precision of action are critical. However, the emergence of antibiotic-resistant organisms such as MRSA has significantly eroded the efficacy of standard topical antibiotics in chronic diabetic wounds — a trend that underscores the urgency of developing alternative antimicrobial strategies.

Herbal formulations, despite their slower onset of action and currently limited large-scale clinical evidence, offer several clinically meaningful advantages for diabetic wound management. Their multi-target mechanisms of action simultaneously address the inflammatory, angiogenic, collagen synthesis, and antimicrobial deficits that characterize diabetic wounds. The superior anti-inflammatory efficacy, lower adverse effect profile, and reduced wound recurrence rates observed with herbal formulations make them a compelling option for chronic wound maintenance, adjunct therapy, and long-term management in resource-limited settings.

The development of nanoformulation technologies — including metallic nanoparticles, polymeric nanocarriers, and bioengineered scaffolds incorporating phytoconstituents — represents a particularly promising bridge between these two therapeutic worlds. These systems enhance the bioavailability and targeted delivery of herbal active compounds while preserving their natural multi-target activity, potentially combining the best attributes of both therapeutic approaches.

Key limitations of current herbal wound-healing research include the paucity of large-scale, well-designed randomized controlled trials in human diabetic patients, the lack of standardization of phytochemical preparations, and limited pharmacovigilance data on herb-drug interactions. Conventional formulations are limited by increasing antimicrobial resistance, organ toxicity risks in vulnerable diabetic populations, and economic inaccessibility in low-and middle-income countries where the burden of diabetic wound complications is highest.

7. CONCLUSION

This systematic comparative review has evaluated the therapeutic profiles of herbal and conventional formulations for diabetic wound healing based on 36 peer-reviewed references spanning 2010–2025. The key conclusions are:

- Conventional formulations are superior in wound closure rate (~85%) and infection control (~88%), making them essential for acute, complex, and infected diabetic wounds.
- Herbal formulations demonstrate superior anti-inflammatory efficacy (~80%), significantly lower adverse effect profiles, greater cost-effectiveness, and reduced wound recurrence rates (~15%).
- The multi-target mechanisms of herbal agents — particularly curcumin, Aloe vera acemannan, Centella asiatica triterpenes, and neem — align closely with the complex multifactorial pathophysiology of diabetic wound healing.
- Research publications on herbal wound-healing formulations have grown faster than conventional wound care research (2010–2025), reflecting a global paradigm shift toward evidence-based integrative medicine.
- An integrated therapeutic model combining conventional and herbal formulations, supported by novel nanoformulation delivery technologies, offers the most clinically effective and accessible approach to diabetic wound management.

Future research should prioritize: large-scale clinical RCTs of herbal formulations in human diabetic patients; standardization of herbal preparation and dosing; pharmacovigilance programs documenting herb-drug interactions; and development of regulatory frameworks ensuring the quality, safety, and efficacy of herbal wound-healing products. The path to optimal diabetic wound care lies in evidence-based integration, guided by patient need, scientific rigor, and a commitment to accessible and safe care for all patients worldwide.

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