



THE EVOLUTION AND THERAPEUTIC POTENTIAL OF POLYHERBAL GELS AND KEY BOTANICAL EXTRACTS IN DIABETIC FOOT ULCER MANAGEMENT: A COMPREHENSIVE NARRATIVE REVIEW

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ABSTRACT

Background: Diabetic foot ulcers (DFUs) are a devastating, multifactorial complication of diabetes mellitus characterized by neuropathy, ischemia, and chronic infection. Conventional wound care often fails to address these compounding factors, leading to high amputation rates and increasing antibiotic resistance. **Objective:** To systematically explore the evolution of polyherbal gels as topical interventions for DFUs (2015–2025) and comprehensively review the pharmacological evidence supporting the use of key botanical extracts: *Commiphora molmol*, *Curcuma longa*, Dragon's Blood resin, and Propolis. **Methods:** A detailed literature review was conducted analyzing the transition from empirical herbal ointments to advanced polyherbal hydrogels, alongside the pharmacognosy, *in vitro*, *in vivo*, and clinical efficacy of selected natural components. **Discussion:** The management of DFUs has evolved toward sophisticated delivery systems, including nano-enhanced and bioinspired hydrogels. Literature confirms that extracts such as *Commiphora molmol* and Propolis exhibit potent antimicrobial, anti-inflammatory, and hypoglycemic properties. *Curcuma longa* provides significant tissue-regenerative benefits, while Dragon's Blood resin accelerates epithelialization via targeted molecular pathways (e.g., Wnt/β-catenin, Nrf2). The integration of these botanicals offers synergistic effects that simultaneously target infection, oxidative stress, and impaired angiogenesis. **Conclusion:** Polyherbal gels represent a holistic, cost-effective, and resistance-minimizing paradigm in DFU management. Utilizing these synergistic natural compounds offers an evidence-based alternative to conventional treatments, particularly in resource-constrained healthcare settings.

KEYWORDS: Diabetic Foot Ulcer; Polyherbal Gels; *Commiphora molmol*; *Curcuma longa*; Dragon's Blood; Propolis; Wound Healing.

1. INTRODUCTION

Diabetic foot ulcers (DFUs) are a severe and prevalent complication of diabetes mellitus, manifesting as chronic, non-healing wounds driven by a combination of neuropathy, peripheral ischemia, infection, and an impaired immune response.^[1] Traditional treatments,

such as surgical debridement and antibiotic dressings, frequently fall short due to the rising incidence of multidrug-resistant organisms and their inability to simultaneously address the multifactorial pathophysiology of diabetic wounds. Early pilot studies demonstrated the potential of polyherbal formulation

creams in accelerating the healing of DFUs.^[2] Consequently, polyherbal gels—topical formulations combining extracts from multiple medicinal plants in semi-solid matrices—have emerged as highly promising, multi-target alternatives.

2. Polyherbal Gel Formulations and Their Evolution (2015–2025)

Over the past decade, polyherbal wound care has evolved significantly from basic empirical ointments to highly sophisticated delivery systems. In 2016, Amin and Doupis underscored the antibacterial potential of polyherbal topical preparations, including those containing herbal analogs of neomycin and mupirocin, for managing DFU infections.^[1]

By 2018, Kuai et al. evaluated the Sheng-Ji Hua-Yu formula (a blend including *Astragalus membranaceus* and *Salvia miltiorrhiza*) in ointment form, demonstrating the promotion of granulation and re-epithelialization via cAMP/PKA/CREB signaling and Activin/Follistatin regulation in diabetic rat models.^[3]

In 2020, research by Zhang et al. confirmed that Huangbai liniment accelerated wound healing by activating Nrf2 signaling, thereby reducing oxidative stress.^[4] Concurrently, a multicenter clinical trial by Liu et al. reported a 96.48% efficacy rate for Fufang Huangbai Fluid (FHBF) in treating DFUs, proving superior to conventional controls.^[5]

Molecular understanding deepened in 2021 when Xiang et al. utilized transcriptional profiling to identify circRNA-miRNA-mRNA networks in Sheng-Ji Hua-Yu-treated DFUs, revealing distinct mechanisms that inhibited inflammation.^[6]

The year 2022 marked the rise of advanced gel matrices. Chumpolphant et al. designed a Carbopol 940-based polyherbal gel that achieved 90% wound contraction in diabetic rats by day 15, driven by potent DPPH scavenging.^[7]

Wu et al. demonstrated that Ruyi Jinhuang Powder in gel form accelerated DFU healing by regulating the Wnt/ β -catenin signaling pathway in fibroblasts.^[8] Additionally, Zhang et al. showed that combining Huangbai liniment with berberine promoted healing via the Nrf2/HO-1/eNOS pathways.^[9]

In 2023, Rayate et al. highlighted the success of polyherbal hydrogels (e.g., *Aloe vera* with polyvinylpyrrolidone), which achieved significant tensile strength improvements and over 80% wound closure.^[10] Li et al. advanced this by loading *Panax ginseng* and *Astragalus* into carboxymethyl chitosan-sodium alginate hydrogels, which enhanced healing by reducing TNF- α /IL-6 and supporting PI3K/Akt-mediated angiogenesis.^[11] The integration of nanotechnology also emerged, with Geng et al. developing ultra-small copper

nanoparticle-loaded self-healing hydrogels possessing antibacterial and angiogenesis-enhancing properties.^[12]

Recent applications in 2024 include findings by Yang et al., who demonstrated the pharmacoeconomic advantages and superior clinical efficacy of FHBF hydropathic compresses compared to antimicrobial calcium alginate dressings.^[13]

Looking toward recent innovations, Manhas and Malairaman evaluated a polyherbal gel (PGF4) showing 86% *in vitro* scratch closure and superior DFU healing via α -amylase inhibition.^[14] Shelar et al. successfully integrated bioinspired silver nanoparticles into a polyherbal gel to achieve 85% wound closure by day 16 through PI3K/Akt activation.^[15] A comprehensive 2025 review by Feng et al. emphasizes that these novel delivery systems—including nano-enhanced hydrogels—represent the future of DFU management.^[16]

3. Advantages and Significance of Polyherbal Gels

Polyherbal gels offer profound advantages over conventional single-compound synthetic drugs. Bio-based materials naturally address the complex etiology of chronic diabetic wounds without inducing antibiotic resistance.^[17]

This alternative therapeutic approach relies on synergistic phytochemical interactions that provide potent anti-inflammatory, antioxidant, and regenerative properties.^[18] By utilizing multiple medicinal plant components, these gels scavenge reactive oxygen species, downregulate pro-inflammatory cytokines, and promote angiogenesis, offering an accessible, cost-effective paradigm for diverse patient populations globally.^[19]

4. Pharmacognosy and Evidence of Selected Botanical Components

The therapeutic efficacy of these gels is rooted in their constituent extracts. Four key natural substances—*Commiphora molmol*, *Curcuma longa*, Dragon's Blood resin, and Propolis—demonstrate robust, complementary mechanisms for diabetic wound healing.

4.1 *Commiphora molmol* (Myrrh)

Commiphora molmol has an established role in traditional medicine, particularly in the treatment and management of periodontal diseases and inflamed skin lesions.^[20] Native to the Arabian Peninsula, including Yemen, bark and resin preparations have been culturally significant for wound healing and blood purification.^[21] Pharmacologically, it is recognized for its complex phytochemical profile, rich in bioactive oleo-gum-resins.^[22,23]

Extensive pharmacological studies validate its efficacy. Haffor demonstrated that myrrh elevates leukocyte proliferation, significantly enhancing the immune response during the healing of skin injuries and gastric ulcers.^[24]

AL-Yahya confirmed its antiulcer and tissue-healing effects through detailed histological studies.^[25] In diabetic models, Sotoudeh et al. found that combinations containing *Commiphora* extracts acted as potent anti-diabetic and antioxidant agents, significantly improving plasma glucose and hepatic antioxidant markers.^[26] Hassanzadeh-Taheri et al. investigated its ethanolic extracts on hepatorenal injury, noting amelioration of pathological changes.^[27] Furthermore, Al-Romaiyan et al. discovered that *Commiphora myrrha* stimulates insulin secretion from pancreatic β -cells by activating atypical protein kinase C.^[28] Shahin et al. reported that myrrh modulates hepatic insulin signaling in skeletal muscle, reducing total antioxidant capacity and ameliorating oxidative stress.^[29] Comprehensive preclinical studies by Mansouri et al. further confirmed the profound antidiabetic, antioxidant, and antimicrobial efficacies of *Commiphora myrrha* resin.^[30]

4.2 Curcuma longa (Turmeric)

The rhizome of *Curcuma longa* is a cornerstone of traditional plant medicine.^[31] It has been utilized extensively in alternative approaches to wound healing, particularly for persistent diabetic lesions.^[32] Its primary biological activities are attributed to its rich chemical composition of essential oils and curcuminoids.^[33]

A systematic review by Zhang et al. highlighted curcumin's protective effects against diabetes via anti-inflammatory and glucose-regulating properties.^[34] An umbrella review by Pathomwichaiwat et al. confirmed that turmeric supplementation significantly improves glucose metabolism in patients with diabetes and metabolic syndrome.^[35] Zeng et al. corroborated these findings, presenting clinical evidence of curcumin's therapeutic effects on metabolic diseases.^[36] Research by Islam et al. demonstrated the wound healing and anti-diabetic effects of pure active compounds derived from specific *Curcuma* varieties.^[37] Kamran outlined the future perspectives of curcumin in comprehensively managing diabetes complications, including foot infections.^[38] Clinically, a pilot study by Ruke et al. proved the effectiveness and tolerability of topical curcumin for managing DFUs.^[39] Molecularly, Cao et al. identified that curcumin promotes DFU healing by inhibiting miR-152-3p and activating the FBN1/TGF- β pathway.^[40] Recent innovations reviewed by Deng et al. focus on curcumin-loaded drug delivery systems (hydrogels and nanoparticles) to maximize bioavailability.^[41] A 2025 case report by Mustafa et al. further documented that a glycerol-based turmeric extract formulation successfully achieved complete diabetic wound closure.^[42]

4.3 Dragon's Blood Resin

Dragon's Blood, derived from species like *Dracaena cinnabari* and *Daemonorops draco*, is renowned in botany and ethnopharmacology for its therapeutic uses.^[43] It has a long history in traditional medicine as a

treatment for inflammation, viral infections, and chronic wounds.^[44] and its clinical safety profile is well-documented.^[45]

Pharmacological investigations by Gu et al. confirmed the antidiabetic effects of active fractions extracted from Dragon's blood.^[46] A randomized, double-blind, placebo-controlled clinical trial by Namjoyan et al. demonstrated that Dragon's blood cream significantly accelerated wound closure compared to controls.^[47] Mohammed and Khanum specifically highlighted the anti-diabetic activity of *Dracaena cinnabari* extracts from Socotra Island, Yemen.^[48] Lu et al. found that dracorhodin perchlorate (an active derivative) enhances wound healing by activating β -catenin, ERK/p38, and AKT signaling in human keratinocytes.^[49] Chen et al. demonstrated novel therapeutic activities of palm tree *Daemonorops draco* blood in treating chronic diabetic wounds through enhanced angiogenesis.^[50] Ching et al. confirmed the significant hypoglycemic effects of these extracts in animal models.^[51] Tang et al. elucidated the underlying mechanism, proving through network pharmacology and experimental validation that dracorhodin accelerates DFU healing via the Nrf2 pathway.^[52]

4.4 Propolis Extract

Propolis, a resinous bee product, is a highly versatile material with expansive applications in wound healing.^[53] Historical and modern research underscores its long-standing efficacy in medicine.^[54] supported by a highly complex chemistry of polyphenols.^[55] that provide vast biological actions and health benefits.^[56] Its composition and functional properties make it an exceptional antimicrobial and regenerative agent.^[57]

Al-Hariri established the direct and indirect hypoglycemic effects of propolis in diabetic models.^[58] Al-Waili demonstrated that mixing different propolis samples potentiates their antimicrobial activity, presenting a novel approach to infected wounds.^[59] Clinically, Mujica et al. confirmed that propolis serves as a highly effective adjuvant in healing human diabetic foot wounds in hospital settings.^[60] *In vivo* and *in vitro* studies by El Adaouia Taleb et al. further validated its anti-diabetic activity.^[61] Alassaf et al. found that bee propolis improves fasting blood glucose, HbA1c, and insulin resistance in healthy human volunteers.^[62] A recent update by Zuhendri et al. detailed the powerful anti-inflammatory activities of propolis.^[63] Canales-Alvarez et al. demonstrated its positive effect on wound healing in a murine model of diabetes mellitus.^[64] A literature review by Sukmana emphasized its consistent potential for diabetic wound healing.^[65] while Alsarayrah et al. provided a comprehensive review of stingless bee propolis, confirming its versatile health efficacy.^[66]

Formulating natural sources and herbal extracts as advanced drug delivery systems that have been developed and formulated in different pharmaceutical

dosage forms and therapeutic doses appropriate to the type of diseases such as acute, chronic, or emergency cases and the principles and strategies of treating them, whether direct, auxiliary, or preventive treatment. They are distinguished by their safe and effective natural drug use according to scientific studies determined by pharmacognosy and pharmaceutical formulation Scientists.^[67,79]

5. CONCLUSION

The evolution of polyherbal gels from traditional ointments to bioengineered hydrogels represents a critical advancement in the management of diabetic foot ulcers. By integrating scientifically validated botanical extracts such as *Commiphora molmol*, *Curcuma longa*, Dragon's Blood, and Propolis, clinicians can leverage synergistic anti-inflammatory, antimicrobial, and regenerative mechanisms. This holistic approach successfully addresses the multifactorial pathophysiology of DFUs, mitigating the risks of antibiotic resistance and offering a highly effective, accessible therapeutic strategy for global diabetes care.

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