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REVIEW ARTICLE

A Review on Potential Treatment of Diabetic Foot Ulcers Using Herbal Formulations

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Abstract: Diabetes mellitus represents a rapidly escalating metabolic challenge globally, characterized by chronic hyperglycemia and profound systemic complications. Among these, Diabetic Foot Ulcers (DFUs) emerge as a debilitating microvascular and macrovascular pathology, contributing significantly to patient morbidity, amputation rates, and healthcare expenditures. The pathophysiology of DFUs is multifactorial, involving peripheral neuropathy, ischemia, immune dysfunction, and persistent oxidative stress, which collectively impair tissue regeneration and promote chronic infection. Conventional therapeutic strategies, including glycemic control, surgical debridement, and infection management, often face limitations such as antibiotic resistance, high recurrence rates, and suboptimal healing outcomes. Consequently, there is a critical need for alternative therapeutic paradigms. Phytochemicals and herbal formulations have garnered scientific interest for their pleiotropic effects, offering antioxidant, anti-inflammatory, and antimicrobial benefits that address the complex wound microenvironment. However, the clinical efficacy of crude herbal extracts is frequently hindered by poor bioavailability and instability. Recent advancements in novel drug delivery systems, particularly nanotechnology-based carriers like transferosomes, solid lipid nanoparticles, and hydrogels, present a viable solution to these pharmacokinetic challenges. These advanced systems enhance the solubility, stability, and targeted delivery of bioactive plant compounds, thereby amplifying their therapeutic potential. This review describes the underlying mechanisms of DFU pathogenesis, evaluates the limitations of current standard-of-care treatments, and assesses the role of herbal therapeutics and bioengineered delivery systems in accelerating wound closure and tissue regeneration.

Keywords: Diabetic foot ulcers; Phytotherapeutics; Wound healing; Nanomedicine, Tissue regeneration

1. Introduction

Chronic metabolic disorders have firmly established themselves as a predominant burden on the global health infrastructure, with Diabetes Mellitus (DM) standing out as the central driver of this non-communicable disease epidemic. Clinically, DM is not merely a disorder of sugar regulation but a complex syndrome characterized by persistent hyperglycemia resulting from fundamental defects in insulin secretion, impaired insulin action, or a pathogenic combination of both mechanisms. This chronic hyperglycemic state precipitates widespread metabolic chaos, severely disrupting the homeostasis of carbohydrate, lipid, and protein metabolism. Over time, these metabolic derangements induce cellular dysfunction and tissue damage, laying the groundwork for life-threatening systemic complications [1, 2].

The sheer scale of this health crisis is vividly captured in recent epidemiological surveillance. Data indicates that in 2021, approximately 537 million adults aged 20-79 years were living with diabetes globally, representing a prevalence of roughly 10.5%. The trajectory of this pandemic is alarming; projections suggest that if current trends persist, the number of affected individuals will rise to 643 million by 2030 and could reach a staggering 783 million by 2045 [3, 4]. While this is a global phenomenon, the burden is unequally distributed. Low- and middle-income nations bear a disproportionately high share of this impact, where systemic challenges such as delayed diagnosis, inadequate monitoring, and constrained healthcare access significantly exacerbate morbidity and mortality rates. India, specifically, is at the epicenter of this crisis, facing a severe diabetic burden that has led to it being ranked second globally, with an estimated 77 million affected individuals [5]. The internal epidemiology of diabetes in India reflects the country's rapid socioeconomic transition. Prevalence rates exhibit significant variance, ranging from 8–12% in urban centers where sedentary lifestyles and high-calorie diets are prevalent to 4-7% in rural areas. A particularly concerning trend is the "age shift" in incidence; there is a rising prevalence among younger age groups and the working-age population, which threatens the nation's economic productivity [6].

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Compounding the issue is the insidious nature of the disease. A significant proportion of diabetic cases remain undiagnosed for extended periods, often only coming to light upon the clinical presentation of irreversible chronic complications. Prolonged exposure to unmanaged hyperglycemia inflicts progressive damage across multiple organ systems. This systemic toxicity manifests as severe microvascular and macrovascular complications, including neuropathy, nephropathy, retinopathy, and cardiovascular diseases. Among these sequelae, diabetic foot disorders and peripheral vascular disease represent some of the most debilitating outcomes. They are leading causes of prolonged hospitalization, infection, and long-term disability, including lower-limb amputation. These challenges highlight the critical and urgent necessity for developing more effective, accessible preventive measures and improved therapeutic strategies to mitigate the devastating toll of this disease [7].

2. Diabetes Mellitus: Etiology and Clinical Manifestations

2.1. Classification and Etiopathogenesis

The etiology of diabetes is complex, involving an interplay of genetic susceptibility and environmental factors. The condition is broadly categorized based on pathogenic processes. Type 1 Diabetes Mellitus (T1DM) is predominantly autoimmune, characterized by the destruction of pancreatic β-cells leading to absolute insulin deficiency [1]. In contrast, Type 2 Diabetes Mellitus (T2DM) accounts for the majority of cases and is driven by insulin resistance coupled with relative insulin deficiency. T2DM shows a strong association with lifestyle factors such as obesity, physical inactivity, and aging, alongside chronic inflammation and oxidative stress [5, 8]. Gestational Diabetes Mellitus (GDM) arises from glucose intolerance first recognized during pregnancy, which typically resolves postpartum but increases the risk of future T2DM [2]. Other specific types include defects due to genetic mutations, pancreatic exocrine diseases, or drug-induced hyperglycemia [8].

Table 1. Etiological Classification and Characteristics of Diabetes Mellitus

Type	Primary Etiology	Clinical Characteristics
Type 1 Diabetes Mellitus (T1DM)	Autoimmune destruction of pancreatic β-cells.	Absolute insulin deficiency; typically early onset; requires exogenous insulin for survival; prone to ketoacidosis.
Type 2 Diabetes Mellitus (T2DM)	Insulin resistance combined with relative insulin deficiency.	Strong association with obesity, aging, and sedentary lifestyle; often asymptomatic in early stages; associated with metabolic syndrome.
Gestational Diabetes Mellitus (GDM)	Glucose intolerance with onset or first recognition during pregnancy.	Hormonal changes induce insulin resistance; usually resolves postpartum but increases risk of future T2DM for both mother and child.
Specific Types	Genetic defects (MODY), pancreatic exocrine disease (pancreatitis), or drug-induced (corticosteroids).	Heterogeneous presentation depending on the underlying cause; often requires specific targeted management.

2.2. Clinical Presentation and Systemic Complications

The clinical symptomatology of uncontrolled diabetes is directly linked to hyperglycemic states. Patients frequently present with polyuria due to osmotic diuresis, which subsequently drives polydipsia as a compensatory mechanism for fluid loss. Cellular energy deprivation results in polyphagia and profound fatigue, while impaired vascular function and immune responses lead to delayed wound healing [9, 10].

Long-term hyperglycemia inflicts damage on blood vessels and nerves, leading to distinct microvascular and macrovascular complications. Neuropathy affects the peripheral and autonomic nervous systems, reducing sensation and altering hemodynamic regulation. Peripheral vascular disease restricts blood flow to the extremities, while nephropathy and retinopathy threaten kidney function and vision, respectively. These systemic failures create a physiological environment highly susceptible to the development of chronic wounds, specifically diabetic foot ulcers [11, 12].

3. Diabetic Foot Ulcers: Pathophysiology and Clinical Challenges

3.1. Definition and Epidemiology

A Diabetic Foot Ulcer (DFU) is defined as a full-thickness wound penetrating through the dermis, located below the ankle in a person with diabetes. It represents one of the most severe and costly complications of the disease, often serving as a precursor to lower-limb amputation [13]. The global prevalence of DFUs is estimated at 6.3%, with a higher incidence observed in males and patients with Type 2 diabetes compared to Type 1 [14]. The lifetime risk of developing a foot ulcer for a person with diabetes can be as high as 25%, with annual incidence rates ranging between 5.3% and 10.5% [13].

Regional disparities are evident, with prevalence rates in Africa reaching up to 30%, compared to approximately 13% in North America and 14.8% in Latin America [15]. A critical challenge in DFU management is the high rate of recurrence, which can reach 65% within three to five years of healing. Furthermore, the mortality rate associated with DFUs is alarmingly high, approaching 50% within five years of ulcer onset, a statistic comparable to many aggressive cancers [16, 17].

3.2. Pathogenesis and Risk Factors

The development of DFUs is rarely due to a single cause but rather arises from a confluence of metabolic, neurological, vascular, and mechanical factors. Chronic hyperglycemia acts as the central driver, inducing oxidative stress that damages DNA, proteins, and lipids, thereby impairing cellular function and tissue integrity [18].

3.2.1. Neuropathy

Diabetic peripheral neuropathy is the most prominent risk factor, affecting over 60% of patients. It manifests as a loss of protective sensation, meaning patients are often unaware of minor trauma, thermal injury, or pressure. Motor neuropathy leads to the atrophy of intrinsic foot muscles, causing structural deformities like hammertoes or Charcot foot, which create new areas of high plantar pressure. Concurrently, autonomic neuropathy results in anhydrosis (dry skin), increasing susceptibility to cracking and subsequent infection [19, 20].

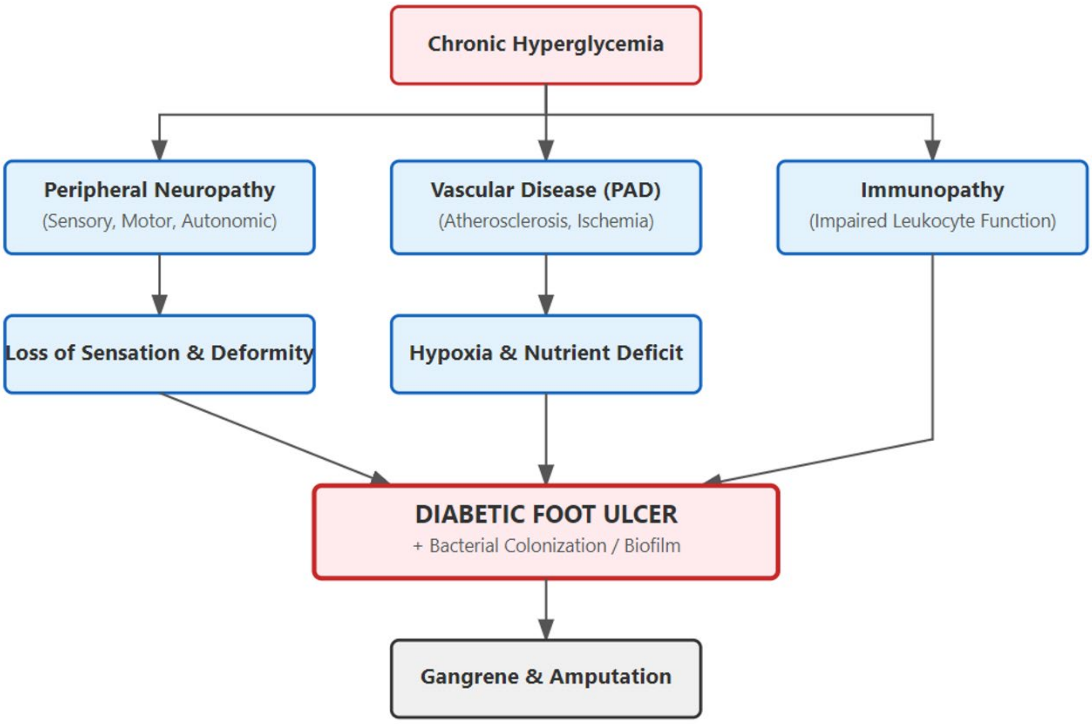

Figure 1. Schematic representation of the multifactorial pathogenesis of Diabetic Foot Ulcers (DFU).

3.2.2. Vascular Insufficiency

Peripheral Arterial Disease (PAD) complicates the healing process by restricting blood flow. Hyperglycemia accelerates atherosclerosis, leading to stenosis and occlusion of lower-extremity vessels. This macrovascular impairment results in tissue ischemia, depriving the wound of oxygen, nutrients, and antibiotics required for healing [21].

3.2.3. Immunopathy and Infection

Diabetes compromises the immune system by impairing leukocyte chemotaxis, phagocytosis, and intracellular killing. This immune dysfunction renders the diabetic foot highly susceptible to polymicrobial infections involving pathogens such as *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. The presence of biofilm-forming bacteria further complicates treatment by creating resistance to standard antimicrobial therapies [22].

3.3. Classification and Diagnosis

Effective management relies on accurate classification of the ulcer. Based on the underlying etiology, ulcers are categorized into three main types. Neuropathic ulcers are typically painless and situated on weight-bearing areas, surrounded by callus. Ischemic ulcers, resulting from poor perfusion, are often painful, pale, and located on the toes or lateral foot margins. Neuro-ischemic ulcers present a mixed etiology with a high risk of gangrene and amputation [23, 24].

Table 2. Wagner-Meggitt Classification System for Diabetic Foot Ulcers

Grade	Clinical Description	Tissue Involvement	Risk Profile
Grade 0	Pre-ulcerative lesion; intact skin.	Healed ulcers, presence of deformities (Charcot foot), or callus.	High risk for ulceration.
Grade 1	Superficial ulcer.	Involves full skin thickness but no underlying deep tissue infection.	Low amputation risk if managed early.
Grade 2	Deep ulcer.	Penetrates to ligament, tendon, joint capsule, or deep fascia; no abscess or osteomyelitis.	Moderate risk; requires off-loading and debridement.
Grade 3	Deep ulcer with infection.	Presence of abscess, osteomyelitis, or septic arthritis.	High risk; often requires hospitalization and intravenous antibiotics.
Grade 4	Localized gangrene.	Gangrene limited to toes or forefoot.	Very high risk; likely requires minor amputation (toes/ray).
Grade 5	Extensive gangrene.	Gangrene involving the whole foot.	Critical; usually necessitates major amputation (below/above knee).

Clinicians frequently employ the Wagner-Meggitt classification system to grade ulcer severity. Grade 0 indicates intact skin at risk, while Grades 1 through 3 describe ulcers of increasing depth, extending to tendon, bone, or abscess formation. Grades 4 and 5 indicate localized and extensive gangrene, respectively. Higher Wagner grades correlate strongly with poor prognosis and increased amputation risk [25, 26].

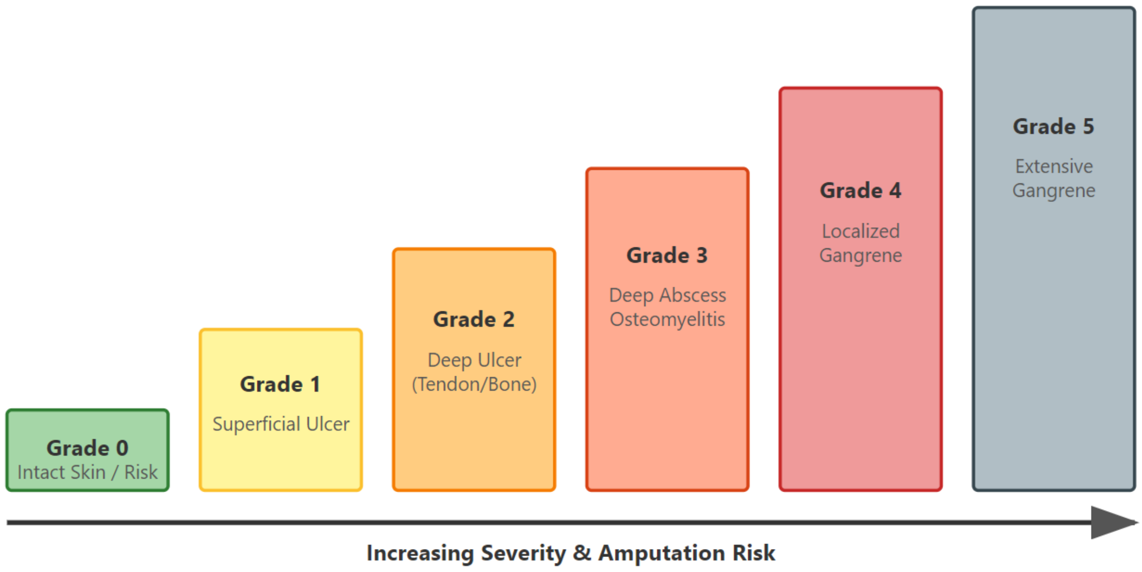

Figure 2. Progression of Wagner-Meggitt Classification

3.4. Limitations of Conventional Management

Standard care for DFUs involves a multifaceted approach comprising glycemic control, surgical debridement of necrotic tissue, infection management with systemic antibiotics, and mechanical off-loading using casts or specialized footwear [27]. Revascularization procedures are employed for ischemic limbs to restore perfusion.

Despite these interventions, clinical outcomes remain suboptimal for many patients. The widespread use of antibiotics has accelerated the emergence of multidrug-resistant organisms, complicating infection control [28]. Furthermore, conventional therapies often fail to address the molecular intricacies of the chronic wound environment, such as persistent inflammation and deficient growth factor activity. The economic burden is also substantial, with high costs associated with long-term hospitalization and repeated surgical interventions. These limitations underscore the urgent necessity for adjunctive therapies that can target multiple pathological pathways simultaneously [29, 30].

Table 3. Comparison of Conventional Standard of Care vs. Polyherbal Strategies

Feature	Conventional Management	Polyherbal & Adjunctive Therapy
Primary Mechanism	Single-target interventions (e.g., bacterial killing, glycemic control).	Multi-target approach (synergistic action on inflammation, oxidation, and infection).
Antibiotic Sensitivity	High risk of developing multidrug-resistant (MDR) strains over time.	Broad-spectrum antimicrobial activity; efficacy against biofilms; lower resistance potential.
Wound Environment	Focuses on debridement and moisture balance; often passive.	Actively modulates the microenvironment (upregulates growth factors like VEGF, TGF-β).
Cost Implications	High recurring costs due to long-term hospitalization and expensive biological dressings.	Generally cost-effective; utilizes locally available resources (ethnomedicine).
Side Effects	Systemic toxicity from antibiotics; risk of surgical complications.	Favorable safety profile; typically low toxicity when topically applied.

4. Phytotherapeutic Interventions in Wound Management

Herbal medicine has emerged as a potent adjunctive strategy in the management of diabetic wounds. Unlike synthetic drugs that typically target a single pathway, phytochemicals possess a multitargeted mechanism of action. They modulate complex physiological processes including inflammation, angiogenesis, collagen synthesis, and oxidative stress. The following section details key medicinal plants and their specific contributions to DFU healing.

4.1. Medicinal Plants and Mechanisms

4.1.1. Turmeric (Curcuma longa)

The rhizome of turmeric contains curcumin, a bioactive compound renowned for its potent anti-inflammatory and antioxidant properties. In the context of diabetic wounds, curcumin modulates the nuclear factor-kappa B (NF-κB) pathway and inhibits Cyclooxygenase-2 (COX-2), thereby reducing excessive inflammation. Additionally, it accelerates wound contraction by upregulating Transforming Growth Factor-beta (TGF-β) and Vascular Endothelial Growth Factor (VEGF), which are critical for angiogenesis and tissue remodeling [31].

4.1.2. Neem (Azadirachta indica)

Neem leaves and oil are rich in azadirachtin and nimbin. These constituents exhibit strong antimicrobial activity by disrupting bacterial cell membranes, a crucial feature for combating polymicrobial DFU infections. Furthermore, neem reduces oxidative stress in the wound microenvironment, protecting regenerating tissue from free radical damage [32].

4.1.3. Aloe Vera (Aloe barbadensis)

Known for its soothing properties, Aloe vera contains aloin and acemannan. These polysaccharides stimulate the synthesis of glycosaminoglycans, which are essential components of the extracellular matrix. Aloe vera maintains a moist wound environment, accelerates epithelialization, and reduces inflammation, making it highly effective for chronic ulcers [33].

Table 4. Therapeutic Profile of Medicinal Plants in the Management of DFU

Common Name	Scientific Name	Active Constituents	Primary Mechanism of Action in DFU
Turmeric	*Curcuma longa*	Curcumin	Downregulates NF-κB/COX-2 (Anti-inflammatory); enhances angiogenesis (VEGF/TGF-β).
Neem	*Azadirachta indica*	Azadirachtin, Nimbin	Disrupts bacterial cell membranes (Antimicrobial); scavenges free radicals.
Aloe Vera	*Aloe barbadensis*	Acemannan, Aloin	Increases glycosaminoglycans; maintains moist wound bed; accelerates epithelialization.
Ginger	*Zingiber officinale*	Gingerols, Shogaols	Analgesic; improves microcirculation to ischemic wounds; reduces inflammation.
Holy Basil	*Ocimum sanctum*	Eugenol, Rosmarinic acid	Wound sterilization; broad-spectrum antimicrobial; immunomodulation.
Garlic	*Allium sativum*	Allicin	Inhibits biofilm formation; potent natural antibiotic; immunostimulant.
Gotu Kola	*Centella asiatica*	Asiaticoside, Madecassoside	Stimulates fibroblast proliferation; promotes synthesis of Type I & III collagen.
Licorice	*Glycyrrhiza glabra*	Glycyrrhizin, Glabridin	Anti-inflammatory (inhibits prostaglandins); protects skin cells from oxidative damage.
Marigold	*Tagetes erecta / Calendula officinalis*	Lutein, Flavonoids	Stimulates granulation tissue formation; promotes re-epithelialization; antiseptic.
Purslane	*Portulaca oleracea*	Omega-3 fatty acids, Vitamins	Accelerates keratinocyte migration; reduces oxidative stress.
Black Pepper	*Piper nigrum*	Piperine	Bioavailability enhancer; potentiates absorption and effect of other herbal actives.
Banana	*Musa sapientum*	Polyphenols, Alkaloids	Astringent action; precipitates proteins to form protective layer; reduces exudate.
Rehmannia	*Rehmannia glutinosa*	Catalpol	Neuroprotective (addresses neuropathy); reduces inflammatory cytokines.
Chinese Angelica	*Angelica sinensis*	Ferulic acid	Invigorates blood circulation; improves microcirculation in ischemic tissues.
Scutellaria	*Scutellaria baicalensis*	Baicalin, Wogonin	Potent antimicrobial against wound pathogens; reduces tissue edema.
Areca Nut	*Areca catechu*	Tannins, Alkaloids	Astringent; aids in wound contraction; infection control.
Astragalus	*Astragalus membranaceus*	Astragalosides, Polysaccharides	Immunomodulator; enhances VEGF expression to promote angiogenesis.

4.1.4. Ginger (Zingiber officinale)

The bioactive components gingerol and shogaol provide analgesic and anti-inflammatory benefits. Ginger extract has been shown to improve local microcirculation, thereby enhancing oxygen and nutrient delivery to ischemic wound beds. It also reduces inflammatory markers, facilitating the transition from the inflammatory to the proliferative phase of healing [34].

4.1.5. Holy Basil (Ocimum sanctum)

Also known as Tulsi, this herb contains eugenol, linoleic acid, and rosmarinic acid. It possesses immunomodulatory and broad-spectrum antimicrobial properties. Topical application aids in wound sterilization and reduces inflammation, while its antioxidant capacity mitigates tissue damage caused by hyperglycemia-induced oxidative stress [35].

4.1.6. Garlic (Allium sativum)

Rich in sulfur-containing compounds like allicin, garlic acts as a powerful natural antibiotic and immunostimulant. It effectively reduces microbial burden in infected ulcers and inhibits biofilm formation. Its antioxidant profile further aids in neutralizing reactive oxygen species (ROS) at the wound site [36].

4.1.7. Gotu Kola (Centella asiatica)

This plant is a cornerstone of wound care, containing triterpenoids such as asiaticoside and madecassoside. These compounds specifically stimulate fibroblast proliferation and increase the synthesis of Type I and Type III collagen. This action strengthens the tensile strength of the newly formed tissue and promotes rapid wound closure [37].

4.1.8. Licorice (Glycyrrhiza glabra)

The active constituents glycyrrhizin and glabridin offer significant anti-inflammatory benefits by inhibiting prostaglandin synthesis. Licorice extracts also demonstrate antimicrobial activity and protect skin cells from oxidative damage, supporting the preservation of viable tissue around the ulcer margin [38].

4.1.9. Marigold (Tagetes erecta / Calendula officinalis)

Marigold flowers are rich in lutein and flavonoids. These extracts are widely used to stimulate granulation tissue formation and re-epithelialization. They possess antiseptic properties that help prevent secondary infections in open wounds [39].

4.1.10. Purslane (Portulaca oleracea)

High in Omega-3 fatty acids and vitamins, purslane accelerates the migration of keratinocytes and reduces oxidative stress. Its anti-inflammatory nature helps in resolving chronic inflammation, a hallmark of non-healing diabetic wounds [39].

4.1.11. Black Pepper (Piper nigrum)

Piperine, the alkaloid in black pepper, is primarily utilized as a bioavailability enhancer. When co-administered with other herbal extracts, it increases their absorption and intracellular concentration, thereby potentiating the overall therapeutic effect [34].

4.1.12. Banana (Musa sapientum)

Extracts from various parts of the banana plant contain polyphenols and alkaloids with astringent and antimicrobial properties. These compounds can precipitate proteins to form a protective layer over the wound, reducing exudate and preventing bacterial invasion [38].

4.1.13. Rehmannia (Rehmannia glutinosa)

Used extensively in Traditional Chinese Medicine, this herb contains catalpol. It exhibits neuroprotective effects, which are particularly beneficial for addressing the neuropathic component of DFUs. It also reduces inflammatory cytokines and supports tissue regeneration [40].

4.1.14. Chinese Angelica (Angelica sinensis)

Known for its ability to invigorate blood circulation, this herb contains ferulic acid. It improves microcirculation in ischemic tissues, thereby addressing one of the fundamental causes of delayed healing in diabetic patients [40].

4.1.15. Scutellaria (Scutellaria baicalensis)

The roots contain baicalin and wogonin, which offer potent antimicrobial and anti-inflammatory effects. They are particularly effective in inhibiting the growth of common wound pathogens and reducing tissue edema [40].

4.1.16. Areca Nut (Areca catechu)

Rich in tannins and alkaloids, areca nut extracts provide astringent and antimicrobial benefits, aiding in wound contraction and infection control [34].

4.1.17. Astragalus (Astragalus membranaceus)

This herb contains astragalosides and polysaccharides that function as immunomodulators. Importantly, Astragalus promotes angiogenesis by enhancing VEGF expression, helping to restore blood supply to the wound bed [41].

5. Polyherbal Formulations

While single herbal extracts offer therapeutic value, their efficacy can be limited when used in isolation. Polyherbal formulations capitalize on the concept of synergy, where the combined effect of multiple constituents exceeds the sum of their individual effects. This approach allows for simultaneous targeting of infection, inflammation, ischemia, and neuropathy.

Several polyherbal compositions have demonstrated efficacy in DFU management. For instance, formulations combining *Cassia fistula*, *Azadirachta indica*, and *Curcuma longa* have been developed specifically to treat DFUs complicated by osteomyelitis, effectively reducing deep-tissue inflammation. Similarly, the Thai traditional foot bath (F3), comprising turmeric, ginger, and *Centella asiatica*, has been shown to enhance keratinocyte migration and upregulate growth factors like VEGF and TGF-β. Traditional Chinese decoctions, such as "Gubu," modulate macrophage polarization from the pro-inflammatory M1 phenotype to the reparative M2 phenotype, promoting tissue resolution [42, 43].

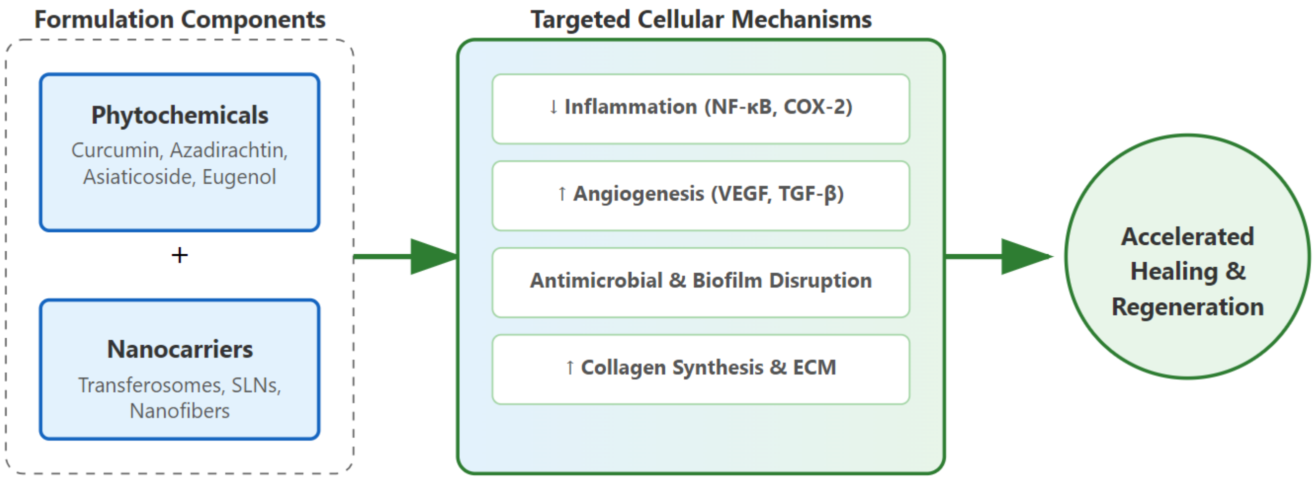

Figure 3. Synergistic Mechanism of Herbal Nanomedicine

Topical gels combining *Calendula officinalis*, garlic, and honey utilize a multimodal intervention strategy; garlic and honey combat infection, while calendula stimulates tissue regeneration. Other formulations incorporating clove oil provide local analgesic effects and enhance microcirculation, while pastes containing *Gymnema sylvestre* help reduce matrix metalloproteinase (MMP) levels, preventing the degradation of the extracellular matrix in chronic ulcers [44, 45].

6. Nanotechnology-Based Delivery Systems

Despite the promise of herbal therapeutics, their clinical translation is often hindered by low solubility, poor stability, and limited skin permeability. Nanotechnology offers a sophisticated solution to these barriers, enabling the development of advanced delivery systems that ensure controlled release and deep tissue penetration.

6.1. Vesicular Systems: Transferosomes and Ethosomes

Transferosomes are ultra-deformable vesicular carriers capable of squeezing through the tight junctions of the stratum corneum. This elasticity allows them to deliver hydrophilic and lipophilic herbal actives such as *Centella asiatica* triterpenoids or neem polyphenols deep into the dermal layers. This results in enhanced bioavailability and prolonged retention of the therapeutic agents at the wound site, significantly superior to conventional creams [46].

6.2. Solid Lipid Nanoparticles (SLNs)

SLNs encapsulate lipophilic compounds like curcumin or tea tree oil within a lipid matrix. This structure protects sensitive phytochemicals from oxidative and enzymatic degradation. SLNs facilitate a sustained release profile over 24 to 48 hours, maintaining therapeutic concentrations within the wound bed and reducing the frequency of dressing changes required [47].

6.3. Nano-Hydrogels and Scaffolds

Nano-hydrogels incorporating extracts of *Ocimum sanctum* or *Aloe vera* provide a dual function: they maintain the critical moist environment needed for healing while the nano-sized network allows for deep penetration of antimicrobial agents into necrotic tissue. Furthermore, nanofibrous scaffolds made of polymers like PCL or PLGA, embedded with herbal extracts, mimic the architecture of the natural extracellular matrix. These scaffolds support fibroblast adhesion, guide collagen deposition, and provide mechanical stability for the developing granulation tissue [48, 49].

Table 5. Advanced Nanotechnology-Based Delivery Systems for Herbal Actives

Delivery System	Encapsulated Phytochemical	Technological Advantage
Transferosomes	*Centella asiatica* triterpenoids	Ultra-deformable vesicles penetrate the stratum corneum to deliver drugs to deep dermal layers.
Solid Lipid Nanoparticles (SLNs)	Curcumin, Tea Tree Oil	Protects lipophilic compounds from degradation; provides controlled, sustained release (24–48h).
Nano-Hydrogels	*Aloe vera*, *Ocimum sanctum*	Maintains moisture balance while ensuring deep penetration of antimicrobial agents into necrotic tissue.
Nanofibrous Scaffolds	PCL/PLGA + Herbal Extracts	Mimics the extracellular matrix (ECM) architecture to support cell adhesion and organized tissue growth.
Green AgNPs	*Camellia sinensis* (Green Tea) + Ag	Synergistic antibacterial effect; silver acts as a potent sterilizer while polyphenols reduce oxidative stress.

6.4. Green-Synthesized Silver Nanocomposites

The integration of herbal extracts with metallic nanoparticles represents a green chemistry approach. For example, silver nanoparticles synthesized using *Camellia sinensis* (green tea) utilize the plant polyphenols as reducing and stabilizing agents. These nanocomposites exhibit potent synergistic antibacterial activity, effectively sterilizing the wound while promoting rapid healing through the biological activity of the plant extract [50].

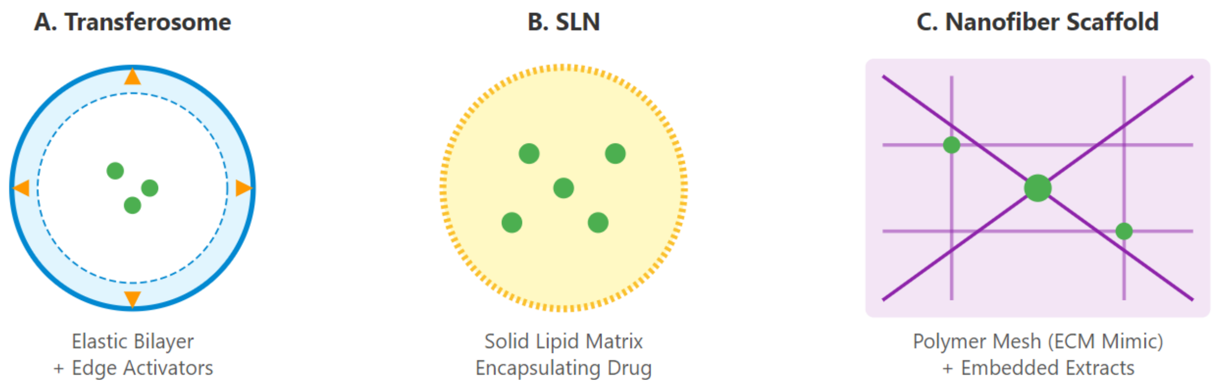

Figure 4. Structure of advanced herbal delivery systems. (A) Transferosomes feature an elastic lipid bilayer modified with edge activators for skin penetration. (B) Solid Lipid Nanoparticles (SLN) consist of a solid lipid core stabilizing the drug. (C) Nanofibrous Scaffolds create a mesh-like structure mimicking the extracellular matrix (ECM) to support tissue regeneration. Green circles represent the bioactive herbal compounds.

7. Conclusion

Diabetic foot ulcers are difficult to manage due to various factors like neuropathy, vascular insufficiency, and immune dysregulation. Conventional therapies, while essential, are increasingly constrained by antibiotic resistance and their inability to comprehensively address the multifactorial pathology of diabetic wounds. This review shows the potential of herbal and polyherbal strategies as superior adjunctive therapies. By leveraging the synergistic properties of diverse phytochemicals, these interventions actively promote tissue regeneration, combat resistant pathogens, and ameliorate oxidative stress. Moreover, the convergence of traditional herbal medicine with modern nanotechnology marks a paradigm shift in DFU management. Advanced delivery systems such as transferosomes, SLNs, and bioactive scaffolds overcome the pharmacokinetic limitations of crude extracts, ensuring deep penetration and sustained therapeutic action. Future research should prioritize the standardization of these polyherbal nanomedicines and the conduct of rigorous clinical trials to validate their efficacy, paving the way for cost-effective, accessible, and highly effective wound care solutions.

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