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# Ethnobotanical Perspective and Pharmacological Insights of North East Indian Medicinal Plants Ameliorating Diabetic Wound: A Comprehensive Review

**Soubhik Bhattacharyya[1,2], Snigdha Rani Behera[3], Kunal Datta[4], Moumita Kundu[5], Dhanya B. Sen[6] and Dhrubajyoti Sarkar[1*]**

[1]Faculty of Pharmaceutical Science, Assam Down Town University, Gandhinagar, Panikhaiti, Guwahati – 781026, Assam, India; dhrub.s@gmail.com

[2]School of Pharmacy, The Neotia University, Sarisha, Diamond Harbour – 743368, West Bengal, India

[3]School of Pharmacy, ARKA JAIN University, Gamharia, Jamshedpur – 832108, Jharkhand, India

[4]Netaji Subhas Chandra Bose Institute of Pharmacy, Tatla, Roypara, Chakdaha, Nadia – 741222, West Bengal, India

[5]Department of Pharmacy, JIS University, Kolkata – 700109, West Bengal, India

[6]Sumandeep Vidyapeeth Deemed to be University, Piparia, Waghodia, Vadodara – 391760, Gujarat, India

## Abstract

The escalating global health crisis of diabetes mellitus, projected to affect 783 million individuals by 2045, is frequently complicated by impaired wound healing, imposing substantial economic burdens. This study addresses the critical need for innovative therapeutic interventions by investigating the potential of the North East Indian flora to mitigate the chronicity of diabetic wounds. By integrating ethnobotanical knowledge with rigorous scientific inquiry, we aim to identify and validate indigenous herbs that possess significant wound-healing properties relevant to the diabetic milieu. Our review focuses on elucidating the phytoconstituent profiles and pharmacological mechanisms of selected herbs, specifically targeting pathways involved in impaired angiogenesis, inflammation dysregulation, and compromised tissue regeneration characteristic of diabetic wounds. This review employed a comprehensive literature search across PubMed, Google Scholar, and ScienceDirect databases. Keywords included "Northeast India plants", "diabetic wound", and "phytoconstituents for wound healing". This study summarised 26 bioactive phytochemicals and 24 medicinal plants that have been shown to impact diabetic wound healing. The outcomes of this investigation hold promise for developing evidence-based herbal formulations, offering accessible and culturally congruent therapeutic strategies to enhance diabetic wound repair and alleviate the associated healthcare burden.

**Major Findings:** This review explores traditional Northeast Indian herbs that enhance angiogenesis, reduce inflammation, and promote tissue regeneration. Numerous plants exhibit potent antioxidant, anti-inflammatory, antimicrobial, and pro-angiogenic properties. The identified phytochemicals and medicinal plants have considerable potential to inform culturally relevant, evidence-based strategies for managing diabetic wounds.

**Keywords:** Diabetes Mellitus, North East India, Pharmacology, Phytochemistry, Wound Healing

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## 1. Introduction

In 2021, the International Diabetes Federation reported that there were 537 million individuals diagnosed with diabetes and an additional 88 million individuals with prediabetes, which is predicted to increase dramatically to 643 million worldwide by 2030, and 783 million by 2045[1]. These conditions resulted in a significant yearly

*Author for correspondence

medical expenditure of $237 billion[2]. Diabetic sores, such as foot ulcers, impact around 25% of individuals with diabetes[3]. The management of these wounds incurs significant expenses, accounting for at least one-third of the overall expenditure associated with the treatment of diabetes and its consequences[4].

Diabetes is linked to various pathological alterations that hinder wound healing. A chronic rise in blood glucose injures arteries and disrupts normal blood circulation. Patients who have diabetes frequently experience peripheral vascular neuropathy, which complicates the diagnosis and healing of wounds. Diabetic wounds are characterised by persistent inflammation, decreased angiogenesis, reduced fibroblast proliferation, and impaired keratinocyte motility[5]. Collectively, these modifications lead to heightened wound problems in individuals with diabetes, such as infections, wound separation, and persistent non-healing wounds that develop into chronic conditions[6]. If a wound is not treated, it can become infected, potentially spreading to nearby muscles and bones. Failure to treat an infection in the wound might lead to the advancement of gangrene. Gangrene frequently leads to amputations in individuals who have limb loss due to diabetes[7]. Individuals with unmanaged infections may develop sepsis, which occurs when an infection spreads through the bloodstream. Sepsis has the potential to be fatal[8].

Effective management of diabetic foot ulcers (DFUs) involves a multifaceted approach that combines wound care techniques, infection control, and strategies to promote tissue regeneration. One of the key components of this approach is debridement, the removal of foreign material, clots, and nonviable tissue to improve wound healing, using surgical, enzymatic, or wet-to-dry methods[9]. Sharp debridement, which is especially effective for diabetic ulcers, can remove callus and reduce pressure by as much as 30%; however, it carries a risk of additional tissue damage and can be extremely uncomfortable[10]. Wound dressings, consisting of natural or synthetic materials, are crucial in diabetic wound care, but they must be customised to the various types of wounds. The ideal dressing maintains a moist environment to facilitate tissue regeneration, cell migration, and angiogenesis[11]. Many modern dressings still have issues like toxicity, allergic responses, restricted angiogenesis, and rejection, even with advancements in bioengineering[12]. Pressure off-loading is a widely used treatment for diabetic foot ulcers (DFUs), categorised into non-removable, removable, and surgical methods, with non-removable casts shown to be the most effective[13]. Revascularisation, commonly used to treat Peripheral Arterial Disease (PAD), a condition affecting 40% of DFU patients, involves restoring blood flow through pharmacological or surgical methods such as angioplasty or bypass[14]. Topical antiseptics and antimicrobials are also frequently used in DFU management due to their low toxicity to host cells[15]. Among these, 10% povidone-iodine is effective at disrupting bacterial biofilms and accelerating healing; it is typically used temporarily and reassessed every 2–4 weeks. Acetic acid targets *Pseudomonas* and other Gram-negative bacteria but may inhibit fibroblast growth and cause tissue damage[16]. Similarly, hydrogen peroxide is active against Gram-positive bacteria but is linked to blister formation.

The recovery from diabetic wounds is a significant health challenge for healthcare professionals worldwide, as unknown factors often cause it. Despite the availability of traditional therapy choices, they are insufficient to rectify underlying difficulties such as inadequate circulation, chronic inflammation, compromised angiogenesis, and neuropathy, highlighting the clinical necessity for alternative therapeutic strategies[17]. Therefore, one potential treatment approach is the use of medicinal plants, especially in resource-scarce areas[18]. Several studies have demonstrated that phytoconstituents such as flavonoids, tannins, saponins, and essential oils can enhance wound healing through antioxidant, anti-inflammatory, antimicrobial, and pro-angiogenic mechanisms. Being one of the centres of biodiversity, the Eastern Himalaya, geographically known as North East India, is rich in natural resources[19]. Approximately 70%–80% of the population in northeastern India utilises herbal medications for primary healthcare due to their perceived lack of adverse effects, affordability, and local accessibility. This traditional use of medicinal plants shows that this region could be an ideal source of bioactive compounds for treating wounds in people with diabetes. Insights from this region may help identify novel bioactive compounds with potential therapeutic applications worldwide.

Previous reviews and ethnobotanical surveys on the wound-healing activity of Northeast Indian Plants

have documented the traditional use of medicinal plants from Northeast India for wound management. Talukdar *et al.,* reported the antimicrobial potential of several regional species active against diabetic wound pathogens, supporting their ethnomedicinal relevance in infection control[20]. Bordoloi focused specifically on members of the *Asteraceae* family traditionally employed for wound healing, underscoring the phytochemical richness of this group but providing limited pharmacological validation beyond descriptive ethnobotany[21]. Adhikary *et al.,* reviewed the bioactive compounds and molecular mechanisms underlying wound-healing activity, providing useful information for phytochemical-based therapeutic development[22]. Although these advancements have been made, most research remains at the preclinical stage. Only a limited number of research studies have progressed to systematic pharmacological evaluation or clinical validation. Additionally, most studies fail to integrate mechanistic pathways, phytochemical correlations, and modern formulation methodologies, underscoring the need for a comprehensive synthesis linking ethnobotanical knowledge with pharmacological and translational evidence from the flora of Northeast India.

This review attempts to address the gap by systematically accumulating and critically assessing the existing literature on Northeast Indian medicinal plants with potential for managing diabetic wounds. It uniquely integrates ethnobotanical insights, phytochemical characterisation, pharmacological validation, and mapping of molecular mechanisms to provide a comprehensive understanding of the medicinal benefits of these plants.

This review followed a methodical approach to identify and synthesise relevant literature on North East Indian medicinal plants with potential for diabetic wound healing. An extensive search was conducted in electronic databases, including PubMed, Google Scholar, and ScienceDirect, covering the period from 2012 to 2024. The search strategy utilised a combination of keywords, including "Northeast India plants", "diabetic wound", "traditional medicine", "phytoconstituents", and "wound healing properties".

Studies were selected based on inclusion criteria such as:

- Reporting on the ethnobotanical use of North East Indian herbs.
- Preclinical/clinical pharmacological validation of wound healing or antidiabetic potential.

From the search result, a total of 178 research articles were initially selected based on keywords like ("Northeast India plants", "diabetic wound", "traditional medicine", "phytoconstituents", and "wound healing properties"). From those 178 articles, after removing duplicates and screening for relevance, 124 articles were excluded for not meeting the inclusion criteria, including a lack of ethnobotanical linkage, insufficient pharmacological evidence, unavailability of full-text articles, or irrelevance to diabetic wound healing. Finally, after sorting, 82 articles were included in the review, comprising ethnobotanical surveys, preclinical animal studies, and clinical investigations that provided validated evidence of the wound-healing or antidiabetic potential of North East Indian medicinal plants.

## 2. Pathways Involved in Wound Formation

The formation and healing of wounds are dynamic processes involving several cellular signalling pathways that regulate inflammation, oxidative stress, angiogenesis, immune responses, and extracellular matrix (ECM) remodelling. Infection, ischaemia, hyperglycemia, or oxidative imbalance can throw these pathways out of whack, which leads to wounds that won't heal. These molecular pathways are involved in the initiation and progression of wound formation. Their normal activation promotes tissue repair, whereas their dysregulation leads to chronic or diabetic wounds.

### 2.1 Inflammatory Pathways

Immediately after tissue injury, inflammatory pathways are activated to prevent microbial invasion and contain tissue damage. However, prolonged or excessive inflammation impairs healing and leads to chronic wound formation.

#### *2.1.1 NF-κB Pathway (Nuclear Factor-kappa B)*

The NF-κB (Nuclear Factor-kappa B) signalling pathway is crucial for initiating inflammatory responses during wound healing. It is also very important for coordinating immunological defence, cytokine synthesis, and inflammatory amplification during early wound formation. In normal circumstances,

NF-κB dimers such as p65/p50 remain inactive in the cytoplasm, where they are held in place by proteins called IκBs[23]. When tissue is hurt, damaged cells emit damage-associated molecular patterns (DAMPs), and invading pathogens release pathogen-associated molecular patterns (PAMPs). These activate pattern recognition receptors (PRRs), especially Toll-like receptors (TLRs), on immunological and epithelial cells. This brings in adaptor molecules like MyD88 and TRAF6, which turn on TAK1 (Transforming Growth Factor-β Activated Kinase 1), which adds a phosphate group to the IKK complex (IKKα/β/γ). IKKβ phosphorylates IκBα upon activation, targeting it for ubiquitination and proteasomal degradation. This frees the NF-κB complex to translocate into the nucleus[24]. Nuclear NF-κB binds to κB elements in target genes, which causes the transcription of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines (MCP-1, CXCL8), adhesion molecules (ICAM-1, VCAM-1), and matrix metalloproteinases (MMPs) that control the involvement of immune cells, inflammation, and remodelling of the extracellular matrix. While short-term NF-κB activation helps clear bacteria and heal tissue, long-term activation, as in diabetic or chronic wounds, sustains inflammation, elevates ROS and protease levels, degrades granulation tissue, and impedes re-epithelialisation[25]. NF-κB also interacts with other signalling pathways such as MAPK, Nrf2, PI3K/Akt, and HIF-1α, amplifying inflammatory and oxidative responses. Chronic hyperglycemia, oxidative stress, and advanced glycation end products (AGEs) maintain NF-κB activation in diabetic wounds, driving ongoing inflammation and impaired tissue integrity[26].

#### 2.1.2 MAPK Pathway (Mitogen-Activated Protein Kinase)

The Mitogen-Activated Protein Kinase (MAPK) pathway controls inflammation and stress responses associated with wound formation. MAP3Ks and MAP2Ks sequentially phosphorylate three main subfamilies: ERK, JNK, and p38 MAPK. This occurs in response to extracellular signals, including growth factors, cytokines, oxidative stress, and bacterial components[27]. Pro-inflammatory cytokines (IL-1β, TNF-α) and reactive oxygen species (ROS) activate ASK1 and MEKK1, which then phosphorylate MKK3/6 (p38), MKK4/7 (JNK), and MEK1/2 (ERK). This activates transcription factors such as AP-1, Elk-1, and ATF2 after injury, leading to the production of inflammatory mediators[28]. However, prolonged or excessive activation, particularly of p38 MAPK, in diabetic, ischaemic, or infected wounds results in MMP overproduction, collagen degradation, fibroblast senescence, and inadequate granulation tissue formation, contributing to chronic wound formation. The MAPK pathway also works with NF-κB, PI3K/Akt, and TGF-β/Smad signalling to control both inflammatory and reparative activities. MAPK-Nrf2 signalling alters redox homeostasis by suppressing the expression of antioxidant genes under oxidative stress[29]. This pathway is a therapeutic target for chronic and diabetic wound repair because dysregulation, particularly prolonged activation of p38 and JNK, converts acute healing into chronic inflammation[30].

### 2.2 Oxidative Stress Pathway

After tissue damage, neutrophils and macrophages release reactive oxygen species (ROS) during the respiratory burst. Controlled levels of ROS are beneficial for killing microbes and signalling, but excessive ROS can cause lipid peroxidation, protein oxidation, and DNA damage, worsening wounds.

#### 2.2.1 Nrf2/Keap1 Pathway (Nuclear Factor Erythroid 2–Related Factor 2)

The Nrf2/Keap1 pathway is a main regulator of the cellular antioxidant defence system. Under oxidative stress, Nrf2 separates from its cytoplasmic repressor Keap1 and relocates to the nucleus. There, it binds to the Antioxidant Response Element (ARE) to increase the activity of antioxidant enzymes like HO-1, SOD, and glutathione peroxidase. Not activating or suppressing Nrf2 signalling enough, which is common in diabetes wounds, causes antioxidant responses to be weaker, oxidative stress to last longer, and tissue to break down over time. This imbalance sustains inflammation and necrosis, which are two important steps in wound healing[31].

### 2.3 Hypoxia and Angiogenesis Pathway

Wound sites are initially hypoxic due to vascular disruption. Controlled hypoxia induces angiogenesis, but persistent hypoxia can delay healing.

#### 2.3.1 HIF-1α (Hypoxia-Inducible Factor-1alpha) Pathway

Under hypoxic conditions, HIF-1α stabilises and binds with HIF-1β to activate genes regulating angiogenesis and metabolism, such as VEGF and GLUT1. However, in diabetic or ischemic wounds, impaired HIF-1α stabilisation reduces VEGF expression and angiogenic response, resulting in poor vascularisation, ischemic necrosis, and tissue breakdown. These deficiencies in oxygen sensing and angiogenic signalling are major contributors to wound formation and the persistence of chronic ulcers[32].

### 2.4 Growth Factor Signalling Pathways

Growth factors coordinate the proliferation and migration of keratinocytes, fibroblasts, and endothelial cells during tissue repair.

#### 2.4.1 TGF-β/Smad Pathway (Transforming Growth Factor-beta)

Macrophages and platelets release TGF-β, which binds to TGF-β receptors and phosphorylates Smad2/3 proteins. These proteins then bind to Smad4 to control gene expression. Normally regulates fibroblast activity, collagen synthesis, and ECM remodelling. Too much TGF-β signalling causes fibrotic scarring or the formation of keloids, while too little TGF-β signalling causes weak granulation tissue[33]. These disrupt the wound healing process.

### 2.5 Immune Modulatory Pathways

The balance between pro-inflammatory (M1) and anti-inflammatory (M2) macrophage phenotypes is critical.

#### 2.5.1 JAK/STAT Pathway (Janus Kinase/Signal Transducer and Activator of Transcription)

The JAK/STAT pathway regulates inflammation, immune responses, cell proliferation, and tissue regeneration. It sends signals from outside the cell, such as cytokines and growth factors, directly into the nucleus to control gene transcription. In the event of tissue damage, cytokines (IL-6, IL-10, IL-22, and IFN-γ) and growth factors (EGF and VEGF) interact with Janus kinases (JAK1, JAK2, JAK3, and TYK2) through cell-surface receptors. This contact between a ligand and a receptor causes JAKs to autophosphorylate and become active. JAKs then phosphorylate the tyrosine residues in the receptor's cytoplasmic domain. These phosphotyrosine motifs attach to STAT proteins, notably STAT1, STAT3, and STAT5. JAKs then phosphorylate these proteins, causing them to dimerise and translocate to the nucleus[34,35]. Dysregulation of the JAK/STAT system, characterised by chronic or excessive activation, can lead to pathological conditions. IL-6/JAK/STAT3 signalling sustains low-grade inflammation, accelerates fibroblast senescence, and inhibits collagen synthesis in chronic or diabetic wounds, making them harder to heal. But insufficient STAT3 activation slows epithelial cell migration and granulation tissue growth. JAK/STAT works with other signalling pathways, such as NF-κB, PI3K/Akt, and MAPK, to regulate immune cell recruitment, angiogenesis, and cellular responses to oxidative stress[36]. JAK2/STAT3 and NF-κB work together to control the expression of IL-6 and TNF-α. This creates a positive feedback loop that can worsen inflammation if not appropriately handled[36].

## 3. Current Approaches in Wound Healing

Conventional approaches to wound management include basic wound care such as cleansing, debridement, and infection control, as well as the application of modern dressings, antimicrobial therapy, advanced physical modalities, biologics, and tissue replacements. Standard wound care aims to maintain a moist yet protected environment and remove infected tissue, while topical or systemic antimicrobials are used to prevent infection. Negative-pressure wound therapy (NPWT) is used to remove excess debris, reduce oedema, and promote granulation tissue generation. In hypoxic or poorly perfused wounds, adjunctive oxygen therapies such as hyperbaric oxygen therapy (HBOT) may increase tissue oxygenation. Advanced techniques encompass the utilisation of growth factors, stem/progenitor cell therapies, and designed skin substitutes or grafts to stimulate angiogenesis, re-epithelialisation, and matrix remodelling actively[37].

### 3.1 Antibiotic Therapy

Topical and systemic antibiotics, like mupirocin, neomycin, and silver-based formulations, are widely

used to control wound infections by targeting bacterial cell wall synthesis, protein synthesis, or nucleic acid replication. Mupirocin, a tropical antibiotic, inhibits protein synthesis by suppressing the bacterial enzyme isoleucyl-tRNA synthetase[38]. Neomycin, an aminoglycoside that binds to the 30S ribosomal subunit and causes misreading of mRNA, preventing bacteria from generating proteins[39]. Silver ions ($Ag^+$), which are found in silver sulfadiazine or nanocrystalline dressings, destroy bacteria through a wide range of mechanisms, including binding to their DNA and proteins, generating reactive oxygen species (ROS), and disrupting membranes[40]. Antibiotics are effective for short-term infections, but they face significant challenges in treating long-term wounds. Biofilms are structured groups of microbes that are enclosed by extracellular polymeric substances. They make it more challenging for antibiotics to penetrate the film and protect bacteria from immune responses, resulting in chronic infections[41]. Overuse or inappropriate use of antibiotics leads to antimicrobial resistance (AMR), which results in the emergence of pathogens resistant to multiple drugs, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Additionally, high concentrations of antibiotics can cause cytotoxicity in fibroblasts and keratinocytes, thereby slowing the healing process and re-epithelialization[42].

## 3.2 Growth Factor Therapy

Growth factor therapy relies on recombinant or naturally sourced biomolecules, which include Platelet-Derived Growth Factor (PDGF), Epidermal Growth Factor (EGF), Fibroblast Growth Factor (FGF), and Vascular Endothelial Growth Factor (VEGF), to facilitate cellular proliferation, migration, angiogenesis, and Extracellular Matrix (ECM) remodelling during the wound healing process[43]. PDGF binds to tyrosine kinase receptors on fibroblasts and smooth muscle cells, thereby inducing chemotaxis and collagen deposition. EGF, on the other hand, acts through the EGFR pathway to accelerate keratinocyte migration and re-epithelialisation. VEGF primarily affects endothelial cells by activating VEGFR-2–mediated signalling, which promotes angiogenesis and increases vascular permeability. These processes are important for delivering oxygen and nutrients to the healing tissue[44]. Although strong molecular evidence exists, the therapeutic use of growth factors is constrained by their short biological half-life, rapid proteolytic degradation in the chronic wound environment, and inactivation by oxidative stress. Moreover, achieving regulated, prolonged administration at the wound site is difficult due to their elevated molecular weight and susceptibility to denaturation[45]. Additionally, excessive or uncontrolled expression of growth factors may lead to aberrant fibrosis, scarring, or tumorigenic risks, emphasising the need for safe, cost-effective, and natural alternatives, such as phytochemical-based formulations that can modulate endogenous growth factor signalling and accelerate tissue repair[46].

## 3.3 Negative Pressure Wound Therapy

Negative Pressure Wound Therapy (NPWT) is an emerging technique for wound care that uses a vacuum pump to create subatmospheric pressure on the wound bed. This is done with a sealed foam or gauze dressing. This regulated suction eliminates unnecessary skin debris and infectious agents, mitigates tissue oedema, and improves local microcirculation and oxygenation, collectively promoting granulation tissue development and angiogenesis[47]. The mechanical forces generated by NPWT cause cells to change shape and transmit mechanical signals, promoting fibroblast growth and migration while keeping the wound moist, which is beneficial for healing[48].

Although NPWT is beneficial, its limitations make it difficult to use in all situations. It costs a substantial amount of money and requires specialised equipment and trained staff, so it's less practical in outpatient or low-resource settings. Changing dressings can often cause pain, bleeding, or tissue damage, especially in delicate wounds or ischaemic ulcers[49]. Additionally, maceration of peri-wound skin, the risk of infection from inadequate sealing, and device-related complications are prevalent concerns. Its effectiveness varies with wound aetiology, with minimal success in extensively necrotic or inadequately perfused wounds. Also, the exact reasons why it works are not yet fully understood, and the evidence that it is more effective than standard care for chronic wounds remains mixed[50]. Thus, although NPWT is beneficial for the management of complex and exudative wounds, it should be incorporated thoughtfully into a multimodal therapeutic framework that may encompass biologically

active agents or phytochemical-based formulations to enhance healing outcomes[51].

### 3.4 Hyperbaric Oxygen Therapy

Hyperbaric Oxygen Therapy (HBOT) involves breathing 100% oxygen at pressures exceeding atmospheric levels (often 2–3 ATA) inside a pressurised chamber. This treatment significantly increases the oxygen content of the plasma, making it easier for oxygen to reach hypoxic or ischaemic tissues[52]. Higher oxygen levels promote fibroblast proliferation, collagen production, and the formation of new blood vessels. They also help leukocytes destroy pathogens and reduce swelling in the area. HBOT has shown clinical advantages in the treatment of diabetic foot ulcers, radiation-induced necrosis, and chronic refractory wounds by enhancing tissue oxygenation and facilitating cellular healing processes[53].

However, the regular application of HBOT is limited by various restrictions. It requires specialised tools and skilled staff, which makes it expensive to run and hard to access, especially in resource-poor areas. Long-term or repetitive exposure to hyperoxia can lead to oxygen toxicity, which can produce barotrauma, lung injury, or effects on the central nervous system, including seizures[54]. Furthermore, evidence on its long-term efficacy and cost-effectiveness remains inconclusive, with meta-analyses showing inconsistent outcomes across wound types and patient demographics. Consequently, although HBOT may serve as a supplementary treatment for specific ischaemic or infected wounds, its limitations underscore the necessity for alternative therapeutic approaches, such as phytochemical-based oxygenating agents or natural antioxidants, to improve tissue oxygenation and healing in a safer, more cost-effective manner[55].

### 3.5 Stem Cell and Tissue Engineering Approaches

Stem cell-based therapies represent a novel advancement in regenerative wound therapy, primarily employing mesenchymal stem cells sourced from bone marrow, adipose tissue, or umbilical cord, alongside bioengineered scaffolds that replicate the extracellular matrix[56]. These cells can differentiate into various cell types and exert paracrine effects by releasing growth factors such as VEGF, TGF-β, and HGF, which together promote angiogenesis, fibroblast proliferation, and collagen deposition. Additionally, MSCs alter the inflammatory microenvironment by decreasing pro-inflammatory cytokines (e.g., TNF-α, IL-6) and increasing anti-inflammatory mediators, thereby facilitating the transition of wound healing from the inflammatory phase to the proliferative phase. When used with biomaterial scaffolds like collagen, chitosan, or hydrogel matrices, MSCs have better survival, retention, and functional integration at the wound site[57].

Even while these results are promising, there are still some problems that make it hard to use them in real life. It is still hard and expensive to isolate, expand, and preserve viable stem cells, and the diversity between batches makes it hard to reproduce results[58]. Ethical issues with some sources of stem cells (including embryonic stem cells), the absence of standardised clinical methods, and regulatory hurdles make it even harder to use stem cells widely. Furthermore, concerns about immunological rejection, unregulated differentiation, and tumorigenic potential heighten safety concerns, particularly with prolonged use. Current clinical data are limited to small-scale trials, necessitating comprehensive, multicenter investigations to validate the efficacy, safety, and standardisation of stem cell-based therapies for chronic and diabetic wound healing[59].

## 4. Traditional Use of Herbs of the Northeast for Treating Wound Healing

The ethnomedicinal practices of the Ahom community in Assam state are largely obscure. The Ahoms are one of the major Mongoloid populations in Assam and also part of the Tai or Shan family, and migrated to Assam from Myanmar through the Patkai Mountains in 1228 AD[60]. The Ahom incorporated many wild vegetables into their everyday diet, utilising them both as sustenance and for medicinal purposes; for example, neem (*Azadirachta indica)* is used to treat smallpox. The Indigenous inhabitants of Darrang District have consistently utilised the rich flora to address numerous diseases and sustain their overall well-being[61]. Assam possesses the most abundant plant diversity, encompassing both terrestrial and

aquatic flora. *Nelumbo nucifera* is a plant used by the indigenous tribes residing in Kamrup. These tribes use rhizomes, leaf petioles, and fruits as vegetables, while the flowers are used as sacred offerings in Hindu rites and rituals. The roots are also used to treat smallpox and dysentery[62].

Manipur, a northeastern state, is recognised as a biodiversity hotspot. The state exhibits a notable and unique diversity of flora and fauna, with a plethora of plant species evident in their use by indigenous cultures[63]. The Zeliangrong, comprising the Zeme, Liangmai, and Rongmei tribes, constitute a significant and well-established indigenous Naga community that largely inhabits the highlands of the Tamenglong region of the state. These tribes use several plants for medicinal purposes; for instance, Aloe vera is used to treat burns and blisters. *Mimosa pudica* is used to treat various ailments, including nephrolithiasis, odontalgia, and jaundice[64]. Table 1 summarises the ethnomedical uses of herbs traditionally used for wound-healing activities.

India's North-Eastern Hill (NEH) region is a notable biodiversity hotspot within the Indian gene centre, distinguished by its abundant ethnic and traditional variety. The tribes in this region employ *Emblica officinalis* to treat cancer, diarrhoea, dysentery, epistaxis, gingival haemorrhage, stomatitis, ophthalmic disorders, and liver cirrhosis, among other maladies[65]. *Aegle marmelos* is a herbal remedy employed in the treatment of diarrhoea, dysentery, indigestion, ophthalmia, hearing impairment, inflammation, diabetes, and asthma, and as an antidysenteric[66]. Table 2 summarises the ethnomedical uses of herbal products for wound healing activity.

## 5. Ethnopharmacological Evidence of the Use of Specific Herbs of Northeast India For Treating Diabetic Wound Healing

Ethnobotanical research has revealed various plant and herb species with wound-healing properties in *Ayurveda* and other ancient texts. Utilising medicinal plants in wound management and care encompasses cleaning, debridement, and creating an optimal environment to facilitate the natural healing process[104]. Medicinal plants are believed to be less toxic and have fewer side effects than conventional therapeutic agents. This has resulted in increased interest in the utilisation of plants for medicinal purposes in wound healing in both diabetic and non-diabetic scenarios. The management of diabetic wound healing presents a considerable health challenge for healthcare providers globally. This challenge frequently arises from an ambiguous cause. Consequently, one possible therapeutic strategy is the utilisation of medicinal flora, particularly in resource-constrained regions[18]. Table 3 presents data on significant Northeast India plants utilised to heal diabetic wounds.

## 6. Phytochemical Compounds Found in Selected North East Indian Herbs with Potential Diabetic Wound Healing Properties Based on Their Mechanistic Pathways

In an effort to study medicinal plants used to treat diabetic wounds, a comprehensive review of 32 plant species utilised by various tribes in Northeast India was conducted. Among these, 24 plants were specifically reported for their role in diabetic wound management. Phytochemical investigations of these species identified 26 different bioactive compounds (Figure 1). Notably, most of these plants contain polyphenolic constituents such as flavonoids and tannins, along with saponins, coumarins, terpenoids, and essential oils, which collectively contribute to their anti-inflammatory, antioxidant, antimicrobial, and tissue-regenerative activities related to diabetic wound healing.

### 6.1 Effects of Phytochemicals in Diabetic Wound Healing

Research has indicated that aloesin, a compound found in *Aloe vera*, enhances leukocyte extravasation and the release of cytokines and growth factors during the early phases of wound healing. Aloesin appears to influence the motility of fibroblasts and leukocytes[128]. Aloesin is believed to affect leukocyte migration through the phosphorylation of Cdc42 and Rac1, two signalling proteins that orchestrate and regulate actin dynamics and cellular polarisation[129]. Aloesin stimulates the expression of pro-inflammatory markers, including TNF-alpha, Interleukin 1 beta (IL-1beta), Interleukin 6 (IL-6), and TGF-1, which are involved in leukocyte signalling, migration, and phagocytosis[130]. Along with aleosin, other bioactive compounds that show a significant effect

**Table 1.** Different medicinal plants from North East India have wound healing properties

| Sr. No. | Plant Name and Family | Vernacular Name | Parts Used | Use | References |
|---|---|---|---|---|---|
| 1 | *Bambusa* sp. *Poaceae* | *Bash* | Internode | The inner skin of the internodes is applied directly to fresh wounds and wrapped in cloth to stop bleeding. | [21] |
| 2 | *Blechnum orientae* L. *Blechnaceae* | *Bonoria dhekia* | Fruit | Fruits are macerated and put on the injuries. | [21] |
| 3 | *Clitonia ternatea Papilonaceae* | *Aparajita* | Root | Root paste is administered to the injuries. | [21] |
| 4 | *Cynodon dactylon Poaceae* | *Phaitualhlo* | Leaf | Leaves are pulverised, and the juice that is extracted is administered to halt haemorrhage. | [21] |
| 5 | *Delonix regia Fabaceae* | *Krishnochura* | Leaf | Pulverised leaves are placed on the wounds. | [21] |
| 6 | *Dillenia indica* L. *Dilleniaceae* | *Otenga* | Bark | Bark is soaked in water overnight, then crushed into a paste and applied to the wounds. | [21] |
| 7 | *Euphorbia hirta Euphorbiaceae* | *Paal chedi* | whole plant | The plant is pulverised into a smooth paste, slightly heated, and then applied to the sores. | [21] |
| 8 | *Melocanna baccifera Poaceae* | *Mautak* | Stem | The exterior surface of the stem or cortex is applied for the treatment of wounds. | [21] |
| 9 | *Nicotiana tabacum Solanaceae* | *Vaihlo* | Leaf | The leaf is pulverised, and the extract is administered to injuries and lacerations. | [21] |
| 10 | *Adhatoda zeylanica Acanthaceae* | *Kawl-dai* | Leaf | The leaves are used to treat normal wounds and cuts. | [67] |
| 11 | *Aegle marmelos Rutaceae* | Bel | Leaf | Leaves are pulverised into a paste with black pepper, gently warmed, and then rubbed onto the ulcers. | [68] |
| 12 | *Ageratum conyzoides* L. *Asteraceae* | *Ghondva Bon* | Leaf, young shoot | The paste is put onto the affected area of injuries and cuts. | [69] |
| 13 | *Alocasia indica Araceae* | *Kochu* | Stem | Stems are cut, and their juice is applied to the wounds. | [70] |
| 14 | *Argemone mexicana Papaveraceae* | *Siyal kata* | Root | Root paste is applied to the wounds. | [70] |
| 15 | *Alstonia scholaris Apocynaceae* | *Thum-riat* | Latex | The latex is utilised for wounds and boils for faster healing. | [71] |
| 16 | *Amaranthus tricolour* L. *Amaranthaceae* | *Bishalyakarani* | Leaf | A paste made from leaves is mixed with saliva and applied to lacerations and abrasions to expedite healing. | [72] |
| 17 | *Azadirachta indica Meliaceae* | *Neem pat* | Leaf | Steamed leaves are utilised for cleansing wounds. A paste of leaves mixed with mustard oil is used for wound healing. | [73] |
| 18 | *Centella asiatica* L. *Apiaceae* | *Bor manimuni* | Leaf | Paste made from leaves is employed for wound treatment. | [74] |
| 19 | *Clerodendrum infortunatum* Linn. *Verbenaceae* | *Phuihnam chia* | Leaf | Leaf juice is taken to treat skin disorders. | [75] |
| 20 | *Curcuma longa* L. *Zingiberaceae* | *Haladhi* | Rhizome | The rhizome is pulverised into a paste, blended with mustard oil, and applied to the incisions. | [76] |
| 21 | *Drymaria cordata* L. *Caryophyllaceae* | *Lai Jabor* | Leaf | Leaves are macerated in saliva and applied to the injuries. | [77] |
| 22 | *Eclipta prostrata* L. *Asteraceae* | *Keheraj* | Root | Roots are pulverised into a paste, mixed with coconut oil, and applied to injuries. | [78] |

**Table 1.** Continued...

| Sr. No. | Plant Name and Family | Vernacular Name | Parts Used | Use | References |
|---|---|---|---|---|---|
| 23 | *Emblica officinalis* *Euphorbiaceae* | *Sun-hlu* | Bark | The crushed bark is applied to wounds and cuts. | [79] |
| 24 | *Eupatorium odoratum* *Astraceae* | *Jarmani bon* | Leaf, young shoot | Leaf paste is mixed with drool and applied to injuries to promote accelerated healing. | [80] |
| 25 | *Gelsemium elegans* *Loganiaceae* | *Hnam-tur* | Leaf | The leaves are applied to wounds. | [81] |
| 26 | *Hydrocotyle sibthorpioides Apiaceae* | *Khoru manimuni* | Leaf | The leaves were pulverised into a paste, mixed with coconut oil, and applied to wounds before bedtime. | [82] |
| 27 | *Kalanchoe pinnata* (Lam.) Pers. *Crassulaceae* | | Leaf | The leaf paste is applied to wounds and burns. | [83] |
| 28 | *Melastoma malabathricum* *Melastomataceae* | *Builukham-pa* | Bark, root | The bark and roots are utilised for the treatment of wounds and various dermatological conditions. | [84] |
| 29 | *Mikania micrantha* *Asteraceae* | *Japan-also* | Leaf | The leaf sap is utilised for haemostasis in cuts and wounds as a form of first aid. | [85] |
| 30 | *Mimosa pudica* *Mimosaceae* | *nilaj bon* | Leaf | Leaves are crushed along with *Eupatorium odoratum* and applied to the wounds. | [86] |
| 31 | *Parkia roxburghii* *Mimosaceae* | *Zawng-tah* | Fruit | The green component of the fruit is combined with a small amount of water and used to treat wounds and infestations. | [87] |
| 32 | *Schima wallichii* *Theaceae* | *Khiang* | Stem | The stem's fluid is used to stop bleeding from lacerations and acts as an antiseptic. | [88] |

**Table 2.** Different medicinal formulations used by tribes from North East India for wound healing activity

| Sr. No. | Community/ Tribe | State | Formulation Name | Ingredients | Preparation Method | Application | References |
|---|---|---|---|---|---|---|---|
| 1 | Khasi Tribe | Meghalaya | Traditional wound healing paste | *Centella asiatica* (Leaves), *Plantago major* (Leaves), *Mikania micrantha* (Leaves) | Fresh leaves are crushed and made into a paste with water or rice water | Topical application to wounds, cuts, and burns. | [89] |
| 2 | Garo Tribe | Meghalaya | *Achik* medicine for wounds | *Azadirachta indica* (Leaves), *Curcuma longa* (Rhizome), *Aloe vera* (Gel) | Leaves ground with turmeric powder and aloe gel to form a healing paste | Direct application to wounds and infected areas. | [90] |
| 3 | Rongmei Tribe | Manipur | Polyherbal wound healing compound | *Homalomena aromatica* (Rhizome), *Zingiber officinale* (Rhizome), *Ocimum sanctum* (Leaves) | Rhizomes crushed with holy basil leaves, mixed with mustard oil | Applied as a poultice on wounds and injured areas. | [91] |
| 4 | Chakpa Community | Manipur | Folk medicine wound treatment | *Centella asiatica* (Whole plant), *Terminalia chebula* (Fruits), *Ficus hispida* (Leaves) | Plants boiled in water to make a decoction, cooled and applied | Wound washing and topical application. | [92] |
| 5 | Mishing Community | Assam | Traditional healing paste | *Acampe rigida* (Leaves), *Blechnum orientale* (Fronds), *Schima wallichii* (Leaves) | Fresh plant parts are crushed together and applied as a paste | Direct topical application to wounds and cuts. | [93] |

**Table 2.** Continued...

| Sr. No. | Community/ Tribe | State | Formulation Name | Ingredients | Preparation Method | Application | References |
|---|---|---|---|---|---|---|---|
| 6 | Deori Community | Assam | Herbal wound healing mixture | *Mikania micrantha* (Leaves), *Zingiber officinale* (Rhizome), *Allium sativum* (Bulbs) | Leaves and rhizome are crushed with garlic, made into a paste with water | Applied to wounds, cuts, and infected areas. | 94 |
| 7 | Jaintia Tribe | Meghalaya | Traditional wound care formula | *Plantago major* (Leaves), *Ocimum sanctum* (Leaves), *Curcuma longa* (Rhizome) | Leaves crushed with turmeric powder, mixed with sesame oil | Applied as an ointment on wounds and burns. | 95 |
| 8 | Bodo Community | Assam | Ethnoveterinary wound paste | *Azadirachta indica* (Leaves), *Curcuma longa* (Rhizome), *Piper nigrum* (Fruits) | Neem leaves ground with turmeric and black pepper, made into a paste | Applied to wounds of livestock and humans. | 96 |
| 9 | Tripuri Tribe | Tripura | Medicinal plant compound | *Argyreia speciosa* (Leaves), *Hibiscus rosa-sinensis* (Leaves), *Psidium guajava* (Leaves) | Fresh leaves are crushed together and applied as a poultice | Topical application to wounds and skin conditions. | 97 |
| 10 | Khamti Tribe | Arunachal Pradesh | Anti-inflammatory wound treatment | *Coptis teeta* (Rhizome), *Stemona tuberosa* (Roots), *Zingiber officinale* (Rhizome) | Dried rhizomes are powdered and mixed with ginger juice | Applied as a paste on wounds and inflamed areas. | 98 |
| 11 | Tagin Tribe | Arunachal Pradesh | Traditional wound healing formula | *Homalomena aromatica* (Rhizome), *Curcuma longa* (Rhizome), Local medicinal herbs | Rhizomes are boiled and ground into a paste with local herbs | Applied to wounds and used for post-injury care. | 99 |
| 12 | Assamese Community | Assam | Multi-herb wound healing paste | *Centella asiatica* (Leaves), *Azadirachta indica* (Leaves), *Moringa oleifera* (Leaves) | Equal parts of leaves ground together with rice water | Applied to wounds, cuts, and skin infections. | 100 |
| 13 | Kaibarta Community | Assam | Traditional healing compound | *Mikania micrantha* (Leaves), *Brassica campestris* (Oil), *Allium sativum* (Bulbs) | Leaves crushed and mixed with mustard oil and garlic paste | Applied as an ointment on wounds and infected areas. | 101 |
| 14 | Ethnic Groups of Mizoram | Mizoram | Polyherbal wound treatment | *Tridax procumbens* (Whole plant), *Euphorbia hirta* (Leaves), *Carica papaya* (Leaves) | Plants were crushed together and made into a paste with water | Direct application to wounds and bleeding cuts. | 102 |
| 15 | Various Tribal Communities | Tinsukia, Assam | Regional wound healing preparation | *Centella asiatica* (Leaves), *Plantago major* (Leaves), *Terminalia chebula* (Fruits) | Leaves and fruits are processed into a decoction and a concentrated paste | Topical application and wound washing. | 103 |

**Table 3.** Different medicinal plants from Northeast India have diabetic wound healing properties

| Sr. No. | Plant Name (Family) | Ethnobotanical Knowledge (Local/Tribal Use) | Animal/Clinical Model | Type of Study | Pharmacological Key Findings | References |
|---|---|---|---|---|---|---|
| 1 | *Acalypha langiana* (*Euphorbiaceae)* | Leaves are applied as a poultice for cuts and skin sores. | STZ-induced diabetic rats | Excision and incision wounds | Bi-daily application of the aqueous extract significantly improved healing within 7 days. | 105 |
| 2 | *Aloe vera* (*Liliaceae*) | Gel is applied directly to burns and wounds by rural/ tribal healers. | STZ-induced diabetic rats | Incision and excision wounds | Improved fibroplasia, collagen synthesis, maturation, and contraction, aided by the hypoglycemic effect. | 106 |
| 3 | *Amaranthus tricolor* L. (*Amaranthaceae*) | Red spinach leaves are used in folk medicine as a poultice for burns and wounds. | Alloxan-induced diabetic rats | Excision wounds | Methanol extract increased wound contraction on day 12; moderate effect on epithelialisation. | 107 |
| 4 | *Annona squamosa* (*Annonaceae*) | Seeds and leaves are applied traditionally to boils and ulcers. | STZ-nicotinamide-induced diabetic rats | Open excision wounds | Enhanced cellular proliferation, collagen synthesis, wound contraction, and epithelialisation. | 108 |
| 5 | *Berberis aristata* (*Berberidacea*) | Tribal communities use root bark paste to treat boils, ulcers, and wounds. | Alloxan-induced diabetic rats | Incision and excision wounds | Herbal cream B was more effective than framycetin cream for diabetic wounds. | 109 |
| 6 | *Caesalpinia bonducella* (*Fabaceae*) | Seeds are traditionally ground and applied to skin sores and chronic ulcers. | STZ-induced diabetic rats | Excision wounds | Significant wound contraction (98% *vs* 90% in control) correlated with improved glucose levels. | 110 |
| 7 | *Carica papaya* (*Caricaceae*) | Tribal healers use latex/pulp for wound cleaning, pus removal, and ulcer healing. | STZ-induced diabetic rats | Excision and dead space wounds | Extract-treated wounds showed reduced wound area and faster epithelialisation compared with controls. | 111 |
| 8 | *Catharanthus roseus* (*Apocynaceae*) | Leaves are used in traditional remedies for diabetes and minor cuts. | STZ-induced diabetic rats | Excision wound model | Wound size was reduced more than in the mupirocin and diabetic controls. | 112 |
| 9 | *Centella asiatica* L. (*Apiaceae*) | Fresh leaf juice/paste applied by the Khasi and Mizo tribes to wounds, ulcers, and diabetic sores. | Diabetic patients and animal models | Excision wounds | Promoted wound healing, angiogenesis, and prevented scarring in diabetic wounds. | 113 |

**Table 3.** Continued...

| Sr. No. | Plant Name (Family) | Ethnobotanical Knowledge (Local/Tribal Use) | Animal/Clinical Model | Type of Study | Pharmacological Key Findings | References |
|---|---|---|---|---|---|---|
| 10 | *Cinnamomum verum* (*Lauraceae*) | Bark is used traditionally in poultices for skin infections and as a spice for diabetes. | Diabetic experimental animals | Excision wound | Cinnamon extract increased fibroblast proliferation, collagen and keratin levels, contraction, and antioxidant effects. | 114 |
| 11 | *Curculigo orchioides* (*Hypoxidaceae*) | Folk practitioners use root tubers for ulcers and inflammatory wounds. | STZ-induced diabetic rats | Normal wound | Extract enhanced angiogenesis and antioxidant enzyme activity, accelerating wound healing. | 115 |
| 12 | *Curcuma longa* L. (*Zingiberaceae*) | Rhizome paste applied to wounds, ulcers, and infected skin by NE Indian tribes. | Alloxan-induced diabetic mice | Excision wound | Improved wound healing by enhancing glucose sensitivity and collagen deposition. | 116 |
| 13 | *Emblica officinalis* (*Phyllanthaceae*) | Fruit paste/juice is used by rural healers to treat skin infections and wounds. | STZ-induced diabetic mice | Excision wound | PE cream promoted dose-dependent wound healing via angiogenic activity. | 117 |
| 14 | *Euphorbia hirta* (*Euphorbiaceae*) | Decoction/paste used by local healers to clean wounds and stop bleeding. | Alloxan-induced diabetic rats | Excision of skin wounds | Whole plant extract enhanced wound recovery compared with diabetic control rats, which exhibited delayed healing. | 118 |
| 15 | *Gymnema sylvestre* (*Apocynaceae*) | Leaves are chewed in traditional practice to treat diabetes and ulcers. | STZ-induced diabetic mice | Systemic study | Lowered glucose and lipids; regenerated pancreatic β-cells; indirectly improved wound healing. | 119 |
| 16 | *Hylocereus undatus* (*Cactaceae*) | Floral paste and leaf extracts are used in folk remedies for burns and wounds. | STZ-induced diabetic rats | Excision wound | Extracts enhance collagen deposition and granulation tissue formation. | 120 |
| 17 | *Martynia annua* (*Martyniaceae*) | Tribes use leaf paste for boils, ulcers, and chronic wounds. | STZ-induced diabetic rats | Excision wound | MAF fraction and luteolin improved wound contraction; histology showed mature collagen, fibroblasts, and angiogenesis. | 121 |
| 18 | *Ocimum sanctum* (*Lamiaceae*) | *Tulsi* leaf paste/decoction is used for diabetic ulcers and infected wounds. | STZ-induced diabetic mice | Dead space wound | Increased connective tissue, antioxidants, lowered glucose, free radicals, and MPO. | 122 |

**Table 3.** Continued...

| Sr. No. | Plant Name (Family) | Ethnobotanical Knowledge (Local/Tribal Use) | Animal/Clinical Model | Type of Study | Pharmacological Key Findings | References |
|---|---|---|---|---|---|---|
| 19 | *Punica granatum* (*Lythraceae*) | Fruit rind/extract has traditionally been used for ulcers, wounds, and infections. | Alloxan-induced diabetic rats | Normal wound | Superior tissue regeneration observed on day 9 with the extract ointment. | 122 |
| 20 | *Radix Rehmanniae* (*Scrophulariaceae*) | Root is used in Chinese traditional medicine for ulcers and inflamed wounds. | STZ-induced diabetic rats | Standard wound | The treated group showed a smaller lesion extent than the water-treated control. | 123 |
| 21 | *Rosmarinus officinalis* (*Lamiaceae*) | Infusion has traditionally been applied to cuts and ulcers for its antimicrobial and healing properties. | Alloxan-induced diabetic BALB/c mice | Excision wounds | Reduced inflammation; improved contraction, re-epithelialisation, granulation tissue regeneration, angiogenesis, and collagen deposition. | 124 |
| 22 | *Tinospora cordifolia* (*Menispermaceae*) | Tribal healers use stem juice to treat chronic wounds and ulcers. | Diabetic experimental animals | Excision wound | Octacosanol increased wound strength, granuloma mass, and cell infiltration. | 125 |
| 23 | *Withania somnifera* (*Solanaceae*) | Root paste used in *Ayurveda* for ulcers, cuts, and diabetic wounds. | Diabetic experimental animals | Excision wound | Increased collagen, protein, SOD, and CAT; decreased hexosamine levels. | 126 |
| 24 | *Zingiber officinale* (*Zingiberaceae*) | In tribal medicine, ginger paste is used on infected wounds, and a decoction is used for diabetes. | STZ-induced diabetic mice | Excision wound | Gingerol promoted vascularisation and fibrin deposition, and reduced BP, triglycerides, and cholesterol. | 127 |

on diabetic wound healing are summarised in Table 4. The structure of the phytoconstituents involved in diabetic wound healing is shown in Figure 2.

## 7. Elucidation of the Molecular Mechanisms that Govern the Therapeutic Actions of North East Indian Herbs in Diabetic Wound Healing

### 7.1 Free Radicals and Oxidative Stress

Oxidative stress results from elevated levels of free radicals, Reactive Oxygen Species (ROS), and Reactive Nitrogen Species (RNS) in the body. This imbalance interferes with the regular metabolic activities of cells, affecting the redox status[158]. The antioxidant system includes essential enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH), which efficiently neutralise reactive oxygen species (ROS) and alleviate the harmful effects of oxidative stress[159]. An abundance of free radicals and a lack of antioxidants in the body lead to an overproduction of Reactive Oxygen Species (ROS), causing cellular and tissue damage, inflammation, neuropathy, ischaemic lesions, and superficial infections. This consequently impedes the healing of diabetic lesions[160]. Consequently, reducing

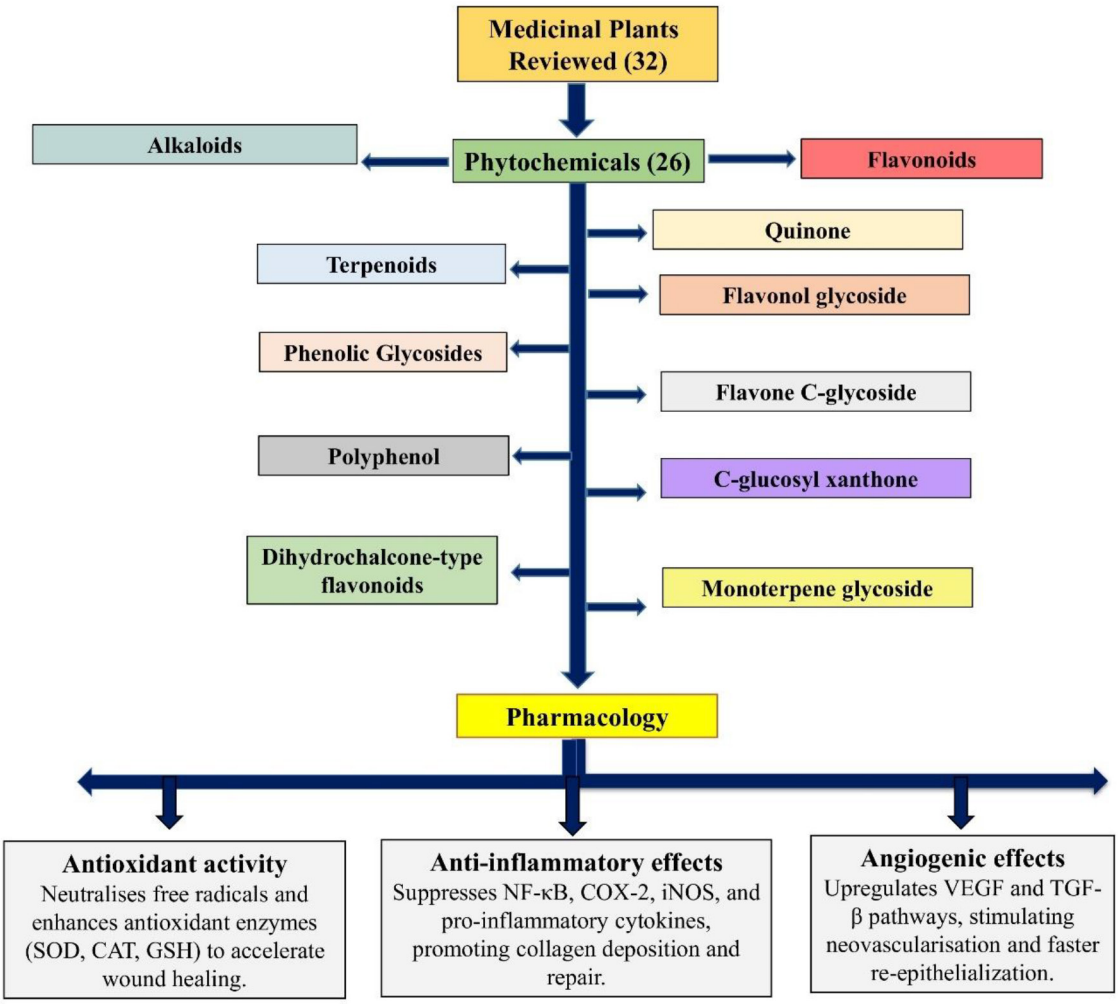



**Figure 1.** Schematic diagram of phytochemicals used in the treatment of diabetic wound healing.

Reactive Oxygen Species (ROS) levels through antioxidant pathways may improve wound healing in individuals with diabetes.

A topical cream containing luteolin and a flavonoid fraction derived from *Martynia annua*, along with a solution of resveratrol, resveratrol-loaded microparticles, and resveratrol-loaded microparticles incorporated in a dermal matrix, has demonstrated efficacy in enhancing the healing of diabetic wounds through the effective neutralisation of harmful free radicals[138]. The use of *Piper betel* paste led to a significant decrease in oxidative stress markers, namely Superoxide Dismutase (SOD) and 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1) expression, in diabetic wounds relative to untreated diabetic wounds[161]. Phytoconstituents like curcumin from *Curcuma longa*[162], Gallic acid and emblicanin A/B from *Emblica officinalis*, rosmarinic and carnosic acids from *Rosmarinus officinalis*, and punicalagins from *Punica granatum* promote high free-radical scavenging activity and enhance the expression of endogenous antioxidants like superoxide dismutase (SOD) and catalase[163].

## 7.2 Impaired Inflammatory Cell Response

Elevated glucose levels and free fatty acids stimulate macrophage-mediated inflammation in diabetes, leading to increased production of pro-inflammatory cytokines[164]. M1-like macrophages, which exhibit pro-inflammatory properties, secrete cytokines such as IL-12, IL-1β, IL-6, TNFα, and iNOS. On the other hand, M2-like macrophages, which have anti-inflammatory characteristics, are more prevalent during the proliferative stage of wound healing in individuals with

**Table 4.** Summary of bioactive compounds in North East Indian herbs and their reported effects on diabetic wound healing

| Sr. No. | Herbal Products | Plant Name | Methodology | Mechanism of Action | Key Findings | References |
|---|---|---|---|---|---|---|
| 1 | Hesperidin | *Citrus aurantium L.* | Wistar rats with STZ-induced diabetes; excision wound model. | | Treatment with hesperidin accelerates angiogenesis and vasculogenesisby upregulating VEGF-c, Ang-1/Tie-2, TGF-β, and Smad-2/3 mRNA expression, thereby enhancing wound healing in chronic diabetic foot ulcers. | 131 |
| 2 | Neferine | *Nelumbo nucifera* (lotus) | Streptozotocin-induced diabetic incision wound models in rats | Anti-inflammatory | Operates by diminishing inflammatory mediators (NF-κB, iNOS, IL-1β, IL-8, TNF-α, and C1OX-2) while enhancing growth factors. | 132 |
| 3 | 20(S)-protopanaxadiol | *Panax notoginseng* | Leptin receptor-deficient mice; excision wound model | Angiogenic activity | PD accelerated wound closure and epithelial gap repair, enhanced VEGF expression, and facilitated capillary formation; PPD stimulated angiogenesis-mediated HIF-1α-mediated VEGF expression via stimulating p70S6K through the PI3K/Akt/mTOR and Raf/MEK/ERK signalling networks. | 133 |
| 4 | arnebin-1 | *Arnebia euchroma (Zicao)* | AM-induced diabetic rats; punch wound model | Angiogenic activity | Substantially enhanced wound closure rate; reduced macrophage count, elevated fibroblast count, notable extent of neovascularisation and epithelialisation; synergistic impact with VEGF. | 134 |
| 5 | Kaempferol | | STZ-induced diabetic Wistar rats; incision and excision wound model | Antioxidant activity; anti-inflammatory activity | 1% KM ointment demonstrates optimal wound healing performance, increased hydroxyproline and collagen levels, improved tensile strength, accelerated wound closure, and fast re-epithelialization. | 135 |
| 6 | Kirenol | *Siegesbeckia orientalis* | STZ-induced diabetic Wistar rats; excision wound model | Anti-inflammatory activity; angiogenic activity | Closure of wounds, augmented granulation tissue with significant fibroblast proliferation, increased angiogenesis, and deposition of collagen fibres; reduced levels of NF-κB, COX-2, iNOS, MMP-2, and MMP-9. | 136 |
| 7 | Luteolin | | STZ-induced diabetic Wistar rats; incision and excision wound models | | The most effective wound healing activity was noted in incision and excision wounds treated with luteolin ointment. | 137 |

**Table 4.** Continued...

| Sr. No. | Herbal Products | Plant Name | Methodology | Mechanism of Action | Key Findings | References |
|---|---|---|---|---|---|---|
| 8 | Luteolin; flavonoids | fraction from *Martynia annua* | STZ-induced diabetic Wistar rats; excision wound model | Antioxidant activity | Improved wound healing via free radical-scavenging activities. | 138 |
| 9 | Pongamol | flavonoid-rich fraction from *Tephrosia purpurea* | STZ-induced diabetic rats, excision wound model | Antioxidant activity, angiogenic activity | Complete wound contraction; elevated levels of hydroxyproline and enzymes (SOD, CAT, and GSH), along with matured collagen fibres and fibroblasts, demonstrating enhanced angiogenesis. | 139 |
| 10 | Quercetin | | STZ-induced diabetic rats, excision wound model | Antioxidant activity | Quercetin modulates macrophage polarisation, shifting from M1 to M2 phenotype, which inhibits inflammatory reactions and accelerates diabetic wound repair. | 140 |
| 11 | Quercetin | | STZ-induced diabetic Wistar rats; excision wound model | Antioxidant activity | Increased wound healing. | 141 |
| 12 | Kirenol | *Siegesbeckia orientalis* | STZ-induced diabetic rats, excision wound model | Anti-inflammatory activity | Influence wound closure by reducing levels of NF-κB, COX-2, iNOS, MMP-2, and MMP-9. | 142 |
| 13 | Curcumin | *Curcuma* species | Standardised skin wounds in streptozotocin-induced diabetic mice. | Anti-inflammatory activity | Reduce oxidative stress through the scavenging of free radicals and effectively regulate oxidative stress by enhancing the expression of the superoxide dismutase enzyme. | 143 |
| 14 | Oleuropein | *Olea europaea* | Standardised skin wounds in streptozotocin-induced diabetic mice. | | The results indicate that OLE wound dressing is more effective than traditional wound dressing methods for wound healing in both diabetic and non-diabetic wounds, as evidenced by success ratios. | 144 |
| 15 | Rutin | *Fagopyrum esculentum* | Full-thickness incision wound in streptozotocin-induced diabetic mice. | | The results indicate faster wound healing by accelerating re-epithelialization. | 145 |
| 16 | Vicenin-2 | *Ocimum sanctum* | Full-thickness excision wound in streptozotocin-induced diabetic rats | | Enhance wound healing by increasing IL-1β, IL-6, and TNF-α levels and accelerating angiogenesis. | 146 |
| 17 | Gamma-tocopherol | Walnuts, pecans, pistachios and sesame | Full-thickness excision wound in alloxan-induced diabetic mice | Anti-inflammatory activity | Promotes wound healing by increasing collagen deposition and inhibiting inflammatory markers. | 147 |

**Table 4.** Continued...

| Sr. No. | Herbal Products | Plant Name | Methodology | Mechanism of Action | Key Findings | References |
|---|---|---|---|---|---|---|
| 18 | Icariin | *Epimedium* spp. | Full-thickness excision wound in streptozotocin-induced diabetic mice. | Anti-inflammatory activity | Promotes wound healing by increasing IL-10 levels and inhibiting inflammatory markers. | [148] |
| 19 | Resveratrol | *Veratrum grandiflorum* | Full-thickness excision wound in streptozotocin-induced diabetic mice. | Anti-inflammatory activity | Enhance wound healing by decreasing NF-κB levels and inhibiting the actions of inflammatory markers. And accelerating the angiogenesis process. | [149] |
| 20 | Mangiferin | *Mangifera indica* | Full-thickness excision wound in streptozotocin-nicotinamide induced diabetic mice. | | Increased levels of EGF, FGF, TGF-β, and VEGF lead to faster wound healing. | [150] |
| 21 | Betulinic acid | *Betula alba* | Full-thickness burn wound in streptozotocin-induced diabetic mice. | Angiogenic activity | Enhance wound healing by inhibiting the actions of inflammatory markers. | [151] |
| 22 | Berberine | *Berberis aristata* | Full-thickness excision wound in streptozotocin-induced diabetic mice. | | Enhance wound healing by increasing the re-epithelialisation and faster wound closure. | [152] |
| 23 | Gallocatechin | *Camellia sinesis* | Full-thickness excision wound in streptozotocin-induced diabetic mice. | Angiogenic activity | The results concluded that the extract shows faster wound healing. | [153] |
| 24 | Loureirin-A and Loureirin-B | *Dracaena cochinchin ensis* | Full-thickness excision wound in streptozotocin-induced diabetic rats. | | The result shows decreased NF-kB, p50 levels and faster wound closure. | [154] |
| 25 | Paeoniflorin | *Paeonia lactiflora* | Full-thickness excision wound in streptozotocin-induced diabetic rats. | Angiogenic activity | A decrease in IL-1β, IL-18, TNF-α, NF-κB, CXCR2, and p-IκB (Ser36) levels leads to faster wound closure. | [155] |
| 26 | Puerarin | *Pueraria lobata* | Full-thickness excision wound in streptozotocin-induced diabetic mice. | Angiogenic activity | Faster wound closure and inhibiting the actions of inflammatory markers. | [156] |
| 27 | Lupeol | *Bowdichia virgilioides* | Full-thickness excision wound in streptozotocin-induced hyperglycemic rats | | Faster wound closure and inhibiting the actions of inflammatory markers. | [157] |

diabetes[165]. Those engaged macrophages and immune cells are essential for the effective healing of diabetic wounds[166]. Research has demonstrated that the dysregulation of macrophages and the production of IL-1β by macrophages result in a prolonged inflammatory phase and hinder the healing of diabetic wounds.

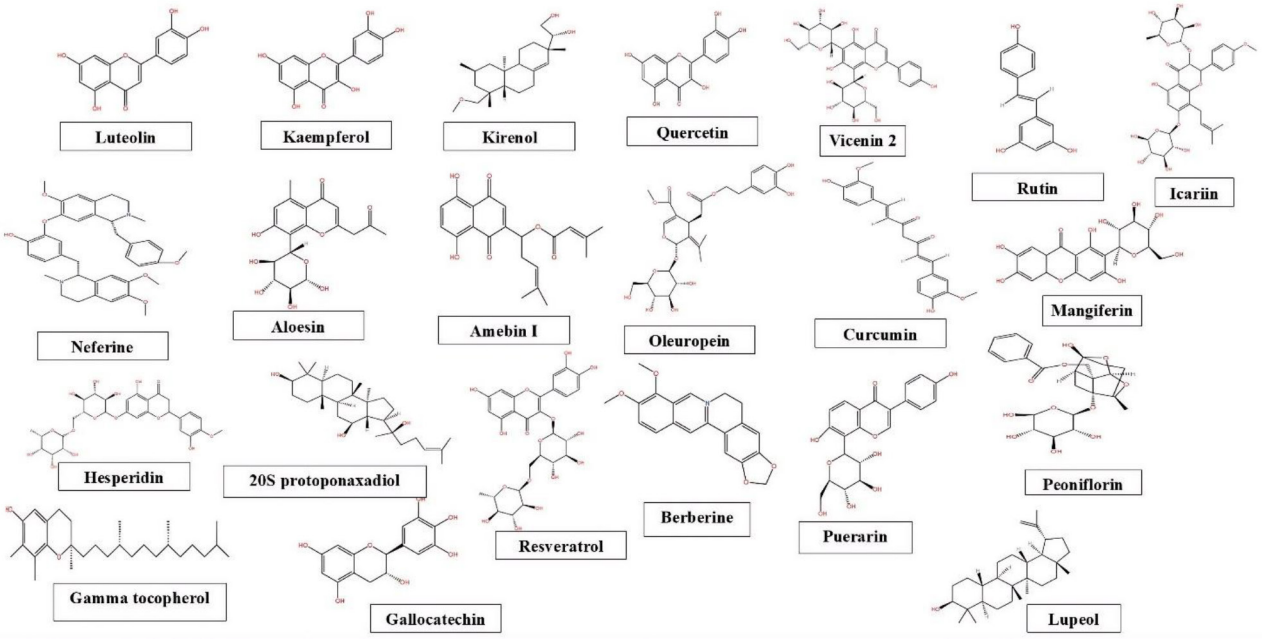



**Figure 2.** Chemical structure of phytoconstituents found in northeast Indian plants involved in diabetic wound healing.

Herbal medicines and the substances they contain are widely recognised for their anti-inflammatory properties, which can be beneficial in treating diabetic wound healing and its associated problems[167]. An ointment comprising *Aloe vera* gel and *Teucrium polium* hydroethanolic extract demonstrated a reduction in the duration of the inflammatory phase and a decrease in tissue malondialdehyde (MDA), TNF-α, and IL-1β levels in contrast to the mupirocin control group[106]. *Moringa oleifera* enhanced the healing process by reducing the expression of inflammatory mediators, including TNF-α, IL-1β, IL-6, iNOS synthase, and COX-2, while facilitating the generation of VEGF[168]. In STZ-induced diabetic rats, the chemical Kirenol promotes wound healing by increasing collagen formation in the wound and decreasing the production of inflammatory factors[169]. Phytochemicals such as berberine from *B. aristata*, withaferin A from *W. somnifera*, ursolic acid and eugenol from *O. sanctum*, and rosmarinic acid from *R. officinalis* suppress NF-κB activation and inhibit pro-inflammatory cytokine release[170]. Acemannan from *Aloe vera* and tinosporaside from *T. cordifolia* exhibit immunomodulatory effects by promoting M2 macrophage polarisation and enhancing the secretion of anti-inflammatory mediators such as IL-10 and TGF-β[171].

## 7.3 Impaired Growth Factors

Manufacturing Growth factors are crucial for initiating and sustaining the different phases of wound healing[168]. Numerous growth factors, such as transforming growth factor (TGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF), keratinocyte growth factor (KGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), are considered crucial for wound healing[172]. Patients suffering from diabetes exhibit slower healing of wounds due to a decrease in growth factor receptors, as well as the accelerated breakdown of growth factors[172]. TGF-β enlists and enhances the activation of inflammatory cells, such as keratinocytes, lymphocytes, neutrophils, fibroblasts, and macrophages. It also stimulates the production of growth factors. Diabetic wounds exhibit a reduced concentration of TGF-β[173]. Furthermore, EGF promotes re-epithelialization, collagen production, and fibroblast proliferation, enhancing the healing of diabetic wounds[174]. Cell proliferation was impeded, and diabetic wound healing was postponed due to the lack of FGF-7 and KGF[175]. Specific herbal medications and their active constituents enhance growth factors, resulting in increased cell proliferation, migration, and contraction of diabetic wounds. The use of an ointment

comprising *Aloe vera* gel and *T. polium* extract led to a significant increase in the levels of VEGF, IGF-1, GLUT-1, and FGF-2[106]. Using *M. indica* extract resulted in increased levels of EGF, FGF, TGF-β, and VEGF, leading to faster wound healing[150].

### 7.4 Impaired Angiogenesis

Angiogenesis, also known as neovascularisation, is a crucial component of the wound-healing process. It involves the creation of a new network of small blood vessels (microvasculature) in response to low oxygen levels or other triggers[176]. In diabetes, the lack of oxygen (hypoxic circumstances) stimulates macrophages to release growth factors, including FGF, VEGF, and PDGF, which promote the formation of new blood vessels. Additionally, cytokines such as TGF-β and IL-1 are also secreted by macrophages and have a role in regulating several aspects of angiogenesis[177]. EGF is a crucial element in the formation of new blood vessels in wounds, and its production is influenced by low oxygen levels and high blood sugar levels. Following an injury, the lack of oxygen (hypoxia) triggers the activation of a protein called hypoxia-inducible factor-1 (HIF-1). HIF-1 is a molecule that enhances the production of new blood vessels (angiogenesis) by increasing the expression of specific genes, such as VEGF-A. On the other hand, high blood sugar levels (hyperglycaemia) indirectly cause excessive production of VEGF through a process controlled by another molecule called TGF-β. Furthermore, the increased expression of FGF and PDGF is linked to the formation of new blood vessels in diabetes and promotes the process of wound rehabilitation in diabetic mice[178]. Chronic, non-healing diabetes lesions are commonly associated with inadequate vascular networks. Herbal products and the active components they contain are a valuable reservoir of new substances that might influence the process of angiogenesis in the healing of wounds in individuals with diabetes[178]. The extract of *C. sinensis* stimulates the process of angiogenesis and vascular remodelling by regulating the circulation of hypoxia-responsive microRNAs, specifically miR-424, miR-210, miR-199a, and miR-21, in both diabetic and non-diabetic wounds[179]. The application of the water-based portion of *M. oleifera* to the skin improved the healing of wounds in diabetic rats by increasing the expression of VEGF and speeding up the process of angiogenesis[168]. Using *P. indica* extract improved wound healing by speeding up re-epithelialization and boosting angiogenesis[180]. The use of Vicenin-2 in *O. sanctum* extract promoted wound healing by raising IL-1β, IL-6, and TNF-α levels and accelerating the angiogenesis process[146].

### 7.5 Impaired Keratinocyte and Fibroblast Proliferation and Migration

In the course of the proliferative phase of wound healing, keratinocytes, endothelial cells, and fibroblasts undergo cell division, movement, and specialisation. This process allows for the development of granulation tissue, reconstruction of the dermal matrix, repair of the skin's surface, and facilitation of wound closure[181]. These processes can be enhanced by herbal products and the bioactive compounds they contain. The application of curcumin extracted from *C. longa* in electro-spun nanofibers promoted wound healing by inducing the production of well-developed granulation tissue areas characterised by increased fibroblast proliferation, collagen deposition, fast regeneration of the epithelial layer, and the development of sweat glands and hair follicle tissues[182]. By boosting collagen deposition, re-epithelialisation, and the development of new blood vessels, the substance luteolin, which is derived from *M. annua*, aids in wound healing[183]. The molecular mechanism adopted by various Northeast Indian plants in curing diabetic wound healing is shown in Figure 3.

## 8. Challenges and Considerations in Translating Preclinical Findings to Clinical Practice

Animal models are essential for evaluating the anti-diabetic and wound-healing potential of medicinal plants, with streptozotocin (STZ) and alloxan monohydrate commonly used to induce diabetes. These agents selectively damage pancreatic β-cells via the GLUT2 transporter, leading to insulin deficiency and hyperglycemia. STZ is used to model both type 1 and type 2 diabetes, while alloxan primarily induces type 1 by inhibiting the glucokinase enzyme[184]. Genetic and dietary models, such as STZ combined with a high-fat diet or leptin receptor-deficient (db/db) mice, are also employed to simulate type 2 diabetes[185]. Despite the prevalence of animal studies on herbal remedies for diabetic wound healing, clinical trials are scarce due

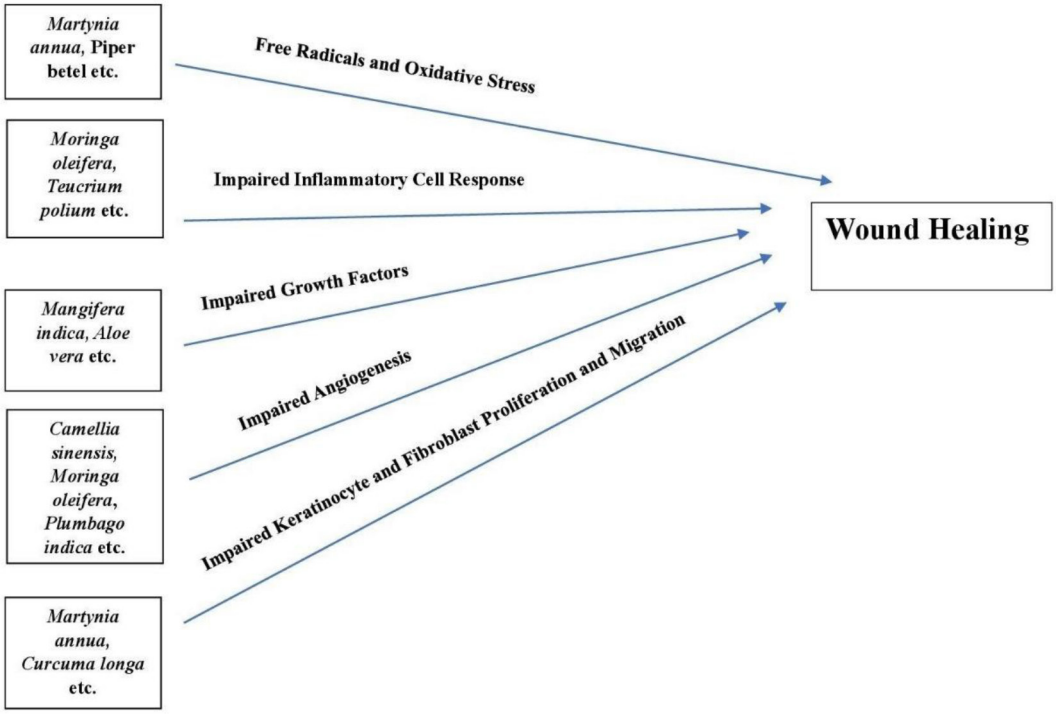



**Figure 3.** Molecular mechanism adopted by various Northeast Indian plants in curing diabetic wound healing.

to regulatory, financial, and logistical challenges. The worldwide advancement of herbal medicine encounters numerous obstacles, especially in wealthy nations, despite its extensive acknowledgement and thoroughly recorded historical application. Before the global dissemination of traditional herbal knowledge can take place, several obstacles must be addressed[186,187].

## 8.1 Quality Issues

The principal factors that undermine the effectiveness of herbal preparations and substantially affect the quality and purity of herbal medications are adulteration, plant misidentification, inadequate collecting and preparation techniques, and improper formulation processes[188].

## 8.2 Processing and Harvesting Issues

The substandard quality of herbal medications is chiefly attributed to indiscriminate harvesting, inadequate agricultural and propagation techniques, insufficient pre- and post-harvest practices, and a deficiency in processing expertise[188].

## 8.3 Quality Control-related Issues

The biggest obstacle to maintaining the quality of herbal pharmaceuticals is the absence of standardised procedures, inadequate quality control measures, and a lack of adherence to Good Manufacturing Practices (GMP). Insufficient knowledge about the guidelines among growers and manufacturers, as well as inadequate enforcement and regulation of the guidelines, are common issues in small and medium-scale enterprises[189].

## 8.4 Administrative Issues

Insufficient regulation and oversight in the herbal industry, as well as a lack of effective monitoring and control, are crucial for ensuring the quality of pharmaceuticals. The main challenges in infrastructure include the absence of advanced processing techniques, a shortage of trained personnel, a lack of sophisticated instruments, limited utilisation of contemporary techniques, and the absence of local instrument fabrication facilities[190].

## 8.5 Pharmacovigilance

Pharmacovigilance is crucial in the herbal sector to gather toxicological data and identify adverse medication reactions associated with herbal drugs. It is essential to carefully monitor adverse responses, contraindications, and combinations with other drugs,

**Table 5.** Herbs and herbal formulations from North East India used in clinical trials

| Sr. No. | Herbs (s) Used | Study Title | Methodology | Key Findings | References |
|---|---|---|---|---|---|
| 1 | *Curcuma Longa* | Clinical | 60 patients. Participants were randomly allocated into two groups (30 participants in each group) | Nano curcumin intake in patients with DFU resulted in a significant improvement in glycemic control, total- and LDL-cholesterol, TAC, and GSH, but did not affect the indicators of ulcer size. | 195 |
| 2 | *Azadirachta indica* | Clinical | Random allocation of 100 participants to each group was performed using the simple random sampling technique. | The results indicate that treatment with Neem leaf extract for foot ulcers is deemed very safe, as it did not result in any systemic problems during the trial. Neem leaf extract solution may serve as an alternative to conventional saline solution. | 196 |
| 3 | *Actindia deliciosa* | Clinical | Randomised clinical investigation involving 37 patients with neuropathic diabetic foot ulcers; 20 patients in the control group; 17 patients in the experimental group. | Decrease in foot ulcer surface area; markedly elevated levels of collagen and granulation tissue; substantially elevated levels of angiogenesis; absence of notable antibacterial action. | 197 |
| 4 | *Aloe vera* | Clinical | Sixty people were diagnosed with type 2 diabetes mellitus: Thirty patients in the positive control group, and thirty patients underwent intervention. | Accelerated wound healing. | 198 |
| 5 | *Centella Asiatica* | Clinical | Randomised, controlled, open-label trial; Twenty-four patients with diabetic foot ulcers: twelve received treatment with WH-1 cream, and twelve were treated with hydrocolloid fibre dressings. | No statistically significant variations in wound size following the use of WH-1 cream. | 199 |
| 6 | *Coffea canephora* | Clinical | A total of 130 patients | The use of coffee powder as a wound dressing has a strong influence on the emergence of a new paradigm in the management of wounds. | 200 |
| 7 | *Calendula officinalis* | Clinical | 41 patients (17 women, average age 62 years) completed the study. | The study found that 54% of patients achieved complete wound closure by the $11^{th}$ week, 68% by the $20^{th}$ week, and 78% by the $30^{th}$ week, with a mean healing time of 15.5 weeks. The treatment significantly lowered wound size, exudate, fibrin slough, necrotic tissue, and odour. The number of colonised wounds decreased from 29 to 5, without any adverse events. | |
| 8 | Polyherbal formulations (*Glycyrrhiza glabra, Musa paradisiaca, Curcuma longa,* and *Pandanus odoratissimus*) | Clinical | Forty patients with type 2 diabetes were randomly assigned, in a 1:1 ratio, to two groups. | A similar reduction in ulcer size; average healing time was 43 days for both treatments. | 201 |

**Table 5.** Continued...

| Sr. No. | Herbs (s) Used | Study Title | Methodology | Key Findings | References |
|---|---|---|---|---|---|
| 9 | *Ageratina pichinchensis* extract | Clinical | Randomised, placebo-controlled clinical study with 20 patients. | 77.5% healing process; average healing time 65.47 days. | 202 |
| 10 | Oral Polyherbal formulation (*Rehmannia glutinosa, Dioscorea oppositifolia, Paeonia suffruticosa, Alisma orientale, Smilax glabra, Astragalus membranaceus,* and *Schisandra chinensis*) | Clinical | Randomised, placebo-controlled clinical study with 80 patients to evaluate an oral polyherbal formulation | The results concluded a 42% decrease in TNF-α levels, improved surface oxygen tension (P = 0.005), and rapid wound healing. | 203 |

food, and existing orthodox medications. Clinical trials are essential for assessing the safety and effectiveness of herbal treatments before they are put into the worldwide market, due to ongoing concerns about their safety[191].

### 8.6 IPR and Biopiracy

Intellectual property rights (IPR) and biopiracy pose a significant challenge to the advancement of traditional herbal medicine. Documenting traditional knowledge is crucial for our future[192].

### 8.7 Irrational Utilisation

There is a prevailing belief that herbal products are devoid of any adverse effects or interactions; however, regrettably, this notion is incorrect. Therefore, the inappropriate use of these pharmaceuticals can result in a multitude of issues that can impede the advancement of such medications[192].

### 8.8 Research and Development

Research and development (R and D) is crucial for any drug, as it focuses on dose, processing, and procedures. However, in the herbal business, R and D is somewhat limited compared to allopathic medicine. However, the tendency has been shifting in recent years. Investigation is necessary to understand the mechanisms of action and pharmacokinetic processes, as well as to improve or create monographs and reference standards for marker-based analysis. A severe deficiency in research within ethnopharmacology and contemporary medicinal plants obstructs the sustainable, socio-culturally equitable, and safe provision of herbal remedies[191].

### 8.9 Other Issues

The global promotion of herbal medicine is hindered by unethical practices, a shortage of qualified physicians, the dissemination of incorrect and misleading information, inadequate funding, a lack of targeted marketing and branding, and limited knowledge exchange. The absence of measures to safeguard biodiversity and preserve traditional medicinal plants poses a significant obstacle[193].

## 9. Clinical Trials Studies

Existing human studies mainly focus on diabetic foot ulcers (DFUs), which are linked to poor vascularisation, neuropathy, and chronic non-healing wounds, often requiring multidisciplinary treatment[194]. A summary of clinical research evaluating the efficacy of Northeast Indian herbs in diabetic wound-healing models is presented in Table 5.

## 10. Discussion

Diabetic wounds remain a significant clinical challenge worldwide, frequently leading to chronic ulcers, infections, and, in extreme cases, amputations. Impaired wound healing in diabetes is complex, comprising persistent hyperglycemia, oxidative stress, chronic inflammation, neuropathy, and faulty extracellular matrix remodelling[204]. These pathophysiological factors disrupt the normal wound-healing process and reduce the efficacy of standard treatments, including dressings, antibiotics, and growth factor therapy. As a result, people are showing interest in safer, more

effective, and more affordable options, such as plant-derived medications[205].

Northeast India, which is part of the Eastern Himalaya and known for its biodiversity, is home to a wide variety of medicinal plants. The conventional wisdom in the area says that 70% to 80% of people use herbal treatments for their main health care since they are easy to get, cheap, and thought to be safe. This ethnobotanical legacy offers a distinctive opportunity to investigate bioactive substances that may target the intricate pathogenesis of diabetic wounds[191].

Phytochemicals have become a potential possibility because of their multi-targeted actions. These substances affect oxidative stress, inflammatory pathways, angiogenesis, and collagen formation, all of which are important steps in wound healing. This review examined 32 medicinal plants from Northeast India, emphasising 13 principal categories of phytochemicals, such as flavonoids, phenolic acids, terpenoids, alkaloids, saponins, and polysaccharides. These substances work together to accelerate wound healing, improve epithelialisation, and reduce infections[204].

Despite satisfactory preclinical outcomes, challenges to clinical translation remain. The therapeutic efficacy of some phytochemicals, including quercetin and curcumin, is diminished when taken by mouth or applied to the skin as medicines. Crude plant extracts may contain impurities, and differences in dosing, extract preparation, and animal models make it difficult to consistently reproduce the same results. Also, there isn't sufficient long-term safety data, and patient-specific characteristics such as comorbidities and wound severity may affect treatment effectiveness[206].

Future research should prioritise meticulously designed clinical studies to assess efficacy, optimal dose, and safety. Standardised extraction procedures and improved delivery technologies, including nanoparticles and targeted-release formulations, may enhance bioavailability and therapeutic outcomes. Combination therapies that use more than one phytochemical or combine them with standard treatments may take advantage of synergistic effects and reduce required doses. Translational research should focus on bioactive substances with robust preclinical evidence, such as curcumin, quercetin, and mangiferin.

## 11. Conclusion

Integrating Northeast Indian herbs into the mechanisms of diabetic wound healing presents a promising approach to improving treatment outcomes. The unique phytochemical profiles of these herbs offer potential anti-inflammatory, antioxidant, and antimicrobial properties that can significantly aid in wound management. By leveraging traditional knowledge alongside modern research, we can develop effective, sustainable, and culturally relevant therapies. Significantly, 26 phytoconstituents found primarily between 2012 and 2024 have demonstrated participation in diabetic wound healing, highlighting the medicinal potential of these natural substances. Future studies should focus on rigorous clinical trials to validate these herbal applications and explore their mechanisms of action further, ensuring safe and effective integration into standard diabetic care practices. This holistic approach not only supports wound healing but also promotes a deeper appreciation of biodiversity and traditional medicine in modern healthcare.

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## Author Contribution

Conceptualisation: DJS, SB; Methodology: KD; Data Curation: SRB, MK; Writing and Editing: SB; Supervision: DBS, DJS. All the authors have read and agreed to publish the manuscript. All authors have read and agreed to the published version of the manuscript.