



EXPLORING THERAPEUTIC POTENTIAL OF MEDICINAL PLANTS FOR CHRONIC WOUND MANAGEMENT: A SYSTEMATIC REVIEW OF ETHNOBOTANICAL, PHYTOCHEMICAL, AND PHARMACOLOGICAL STUDIES

Anuja Mishra¹, Kashinath Mahato^{*2}

¹Bilaspur (C.G.) 495006.

²Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, 495009, C.G., India.



***Corresponding Author: Kashinath Mahato**

Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, 495009, C.G., India. DOI: <https://doi.org/10.5281/zenodo.23035471>



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ABSTRACT

Diabetic wounds (DWs) pose a life-threatening global health problem because they are associated with impaired angiogenesis, chronic inflammation, oxidative stress, and defective tissue regeneration. These nonhealing chronic ulcers, which affect approximately 15-25% of diabetic patients during their lifetime, significantly increase the risk of infection and amputation. This review highlights the role of major phytochemical classes, including flavonoids (e.g., quercetin, apigenin), terpenoids, and alkaloids, in balancing redox homeostasis and enhancing vascularization. These are observed through the modulation of key signalling pathways, such as nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGF-β). This systematic review was conducted for evidence-based synthesis and critical analysis of plant-based interventions for DW management. Although strong preclinical evidence has indicated that these botanicals promote the proliferation and collagen deposition of fibroblasts, this study indicates that there is a major translational gap between laboratory results and standard clinical validation.

KEYWORDS: Diabetic wound, Ethnobotany, Chronic inflammation.

1. INTRODUCTION

Diabetic wounds (DWs) represent one of the most severe and chronic complications of diabetes mellitus and are highly responsible for morbidity and health spending worldwide. It is estimated that 15-25% of diabetic patients experience nonhealing wounds in their lifetime, which are associated with a markedly increased risk of infection, lower-limb amputation, and mortality (Armstrong et al., 2017). DWs are an ever-growing global problem, particularly in China and India, where diabetic cases are rapidly increasing due to the rise in urbanization, dietary changes, and sedentary lifestyles (IDF, 2025). In addition to physical complications, chronic wounds impose serious psychological trauma and financial burdens, thereby reducing patients quality of life (Lin et al., 2024).

The pathophysiology of DWs is complex and characterized by persistent hyperglycemia, impaired

angiogenesis, neuropathy, oxidative stress, and an unregulated inflammatory response. All these pathological changes disrupt the stages of the wound healing process, namely, hemostasis, inflammation, proliferation, and remodelling, thereby delaying wound healing and leading to relapse (Okonkwo & Dipietro, 2017). Several therapies used for the management of DWs have been proposed, ranging from basic wound dressings and debridement surgeries to highly advanced pharmacological and cellular therapies. Among such agents, growth factors, negative-pressure wound therapy, and bioengineered skin substitutes have shown clinical promise, but their clinical application is limited because of their high costs, instability, or unpredictable outcomes in diabetic patients (Y. Sharma et al., 2024). The use of smaller molecules that can inhibit key signalling pathways, such as VEGF, TGF-β, and Nrf2, has gained interest in recent years as a strategy to control the oxidative and inflammatory microenvironments, which

are major contributors to the pathology of chronic wounds (Cai et al., 2023).

Although studies have investigated the use of natural compounds in the management of DWs, the majority have focused on well-known medicinal plants, with limited exploration at the molecular, experimental, and translational levels. Therefore, the present review aims to address this gap by providing details of medicinal plant with molecular pathways and targets involved in DW healing. The present analytical review aims to bridge the phytochemical diversity to functional outcome by integrating comparative mechanistic tabular representations, pathway-specific disease schematics, and bibliometric representations, hence providing a translational framework on which safer, multiple-target natural therapies of DWs can be developed.

2. Medicinal plants utilized in DW management

A thorough literature review was done to find research studies on which medicinal plants, plant-derived compounds, and different formulations were used as therapeutic mechanisms in the management of DWs wound care. The literature survey covers studies reported encompassing a decade of research that demonstrates the progressive evolution of scientific knowledge and research trends in the field of plant-based DW management. The evolution of the knowledge modulating the state of oxidative stress and angiogenic signalling pathways (VEGF, eNOS, and HIF-1), matrix remodelling, and the integration of novel formulation-based delivery systems in wound care are considered in this review. A decade-long study period was selected to ensure a regular evaluation of mechanistic and translational advancements and uniformity in reporting standards and experimental methodologies.

This review comprises two complementary sections. The introduction section provides a comprehensive overview of current trends in research in the phytochemical and herbal therapy of DWs, and the most common plant species, as well as the most common classes of bioactive compounds. It also discusses the traditional ethnomedical basis of wound cures and its evolution into scientifically-validated pharmacological studies.

The second part of the article explores the pathophysiology and the molecular environment of DWs and outlines the biological events that take place during the various stages of wound repair. This observation also explains the way hyperglycemia affects the wound healing mechanism. Along with this, this section explains the modulation of key signalling pathways by bioactive compounds found in plants that promote tissue regeneration and alleviate oxidative stress. All this together forms an integrative effort that combines conventional phytomedicine and current molecular insights and eventually leads to the creation of safer and efficient therapeutic factors in the management of DWs.

2.1 Research trends

Despite the growing volume of literature, studies employing rigorously designed and independently validated designs are relatively limited, although they are generally of high quality. This underscores the importance of being careful but selective in giving emphasis on strong evidence in this area of research. This progressive trend in well-standardized and mechanistically-characterized studies indicates that a number of long-standing issues are yet to be solved, such as inconsistencies with phytochemical profiling and standardization of extracts, absence of harmonisation of diabetic animal models, and large-scale multicentre clinical trials to directly transfer promising preclinical results into clinical practice. Moreover, leanings suggest a new interdisciplinary focus which incorporates the pharmacognosy, advanced biomaterials (i.e., hydrogels, and microneedle systems), and systems biology to enhance the efficacy, stability, and targeted delivery of plant-derived bioactive compounds in DW management.

In general, these tendencies are indicative of a more general paradigm change of natural and multi-target-oriented therapeutic approaches in DW care and highlight the therapeutic potential of understudied medicinal plants and their secondary metabolites.

Importantly, the transition of laboratory findings towards commercial viability and the clinical implementation of herbal formulations requires rigorous standardization and validation. Consequently, the advancement of plant-based therapies for DWs from the preclinical stage to evidence-based clinical practice is contingent upon the performance of extensive, well-designed, and adequately powered clinical trials.

Such ecological plasticity of some plant species, especially those species that are adapted to arid or other environmental stressful environments, can lead to an augmentation in the creation of protective secondary metabolites. This property facilitates the sustainable entry and scalable generation of phytochemicals to be used in the management of wounds. The results are in line with the rising worldwide focus towards sustainable and ethical production of phytopharmaceuticals in which conservation-oriented farming strategies and fair-trade guidelines become more a priority in the study of natural products.

2.2 Etiological factors associated with DW management

Metabolic, vascular, and immune dysregulation play a major role in the multifaceted cascade of biological events in DWs and is expressed as nonhealing chronic lesions. These injuries are chronic complications that are mainly caused by neuropathy, microvascular impairment and biomechanical stress (Armstrong et al., 2017). The complex interplay between persistent hyperglycemia and impaired tissue repair, characterized by the accumulation of advanced glycation end products (AGEs), oxidative stress, and chronic low-grade inflammation, constitutes a

major disruption of the normal wound-healing process in diabetic conditions.

The healing of DWs involves a highly regulated wound-healing cascade consisting of four sequential and overlapping phases: hemostasis, inflammation, proliferation, and maturation or remodelling (**Fig. 1**) (Okonkwo & Dipietro, 2017). During hemostasis, platelets aggregate to form a fibrin clot that prevents

blood loss, while the inflammatory phase involves the recruitment of neutrophils and macrophages to eliminate debris and invading pathogens. In the proliferative phase, fibroblasts deposit extracellular matrix (ECM) components, keratinocytes re-epithelialize the wound surface, and angiogenesis supports neovascularization (Okonkwo & Dipietro, 2017). The final remodelling phase includes collagen maturation and scar formation.

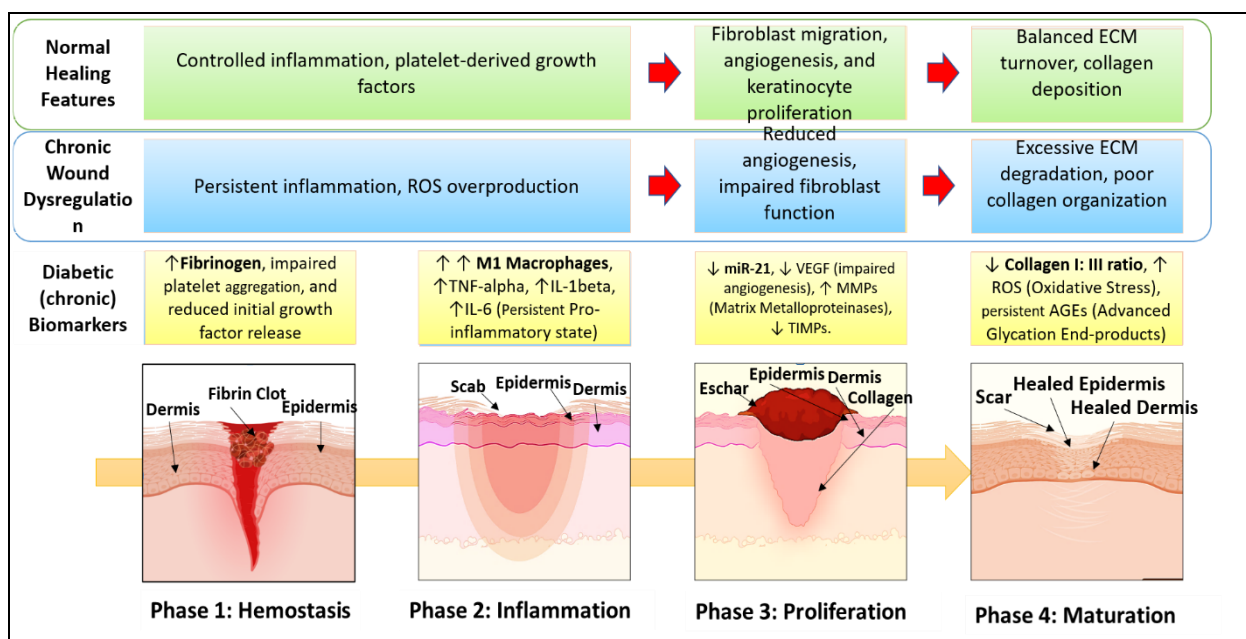


Fig. 1: Schematic representation of normal wound-healing phases overlaid with chronic wound dysregulation.

In diabetes, this tightly regulated cascade is disrupted at multiple levels, resulting in persistent inflammation, impaired angiogenesis, reduced fibroblast and keratinocyte activity, and excessive degradation of the ECM due to increased matrix metalloproteinase (MMP) activity. There are significant psychological and socioeconomic implications of chronic DWs, which cannot be undervalued because they often result in pain, disability, anxiety, and poor quality of life and also contribute to recurring infections and limb amputation (Lin et al., 2024). Moreover, the impairment in wound-healing is further aggravated by nutritional deficiencies, especially protein, zinc, vitamin C and vitamin D deficiencies. Therefore, a healthy and well-balanced diet that is balanced in nutrients is the key to tissue recovery and immune response in diabetes patients.

DW pathology is a complicated and multidimensional interaction of metabolic dysregulation, vascular dysfunction, immune dysfunction, and nutritional imbalance. They are essential pathological pathways that have important implications to the design of effective treating plans and are instrumental in reducing the physical and psychological burden of the chronic wounds (Okonkwo & Dipietro, 2017). The molecular pathway of DW healing especially the pathways that interact with the oxidative stress, growth factor signalling and

microbiome interactions are still being studied to clarify the mechanism of the disease and can be used to develop specific and more efficient interventions to improve wound healing.

3. Aetiological Concepts and Ethnobotanical Practices in Traditional Indian DW Management

India's traditional system of medicine, Ayurveda, Homeopathy, Siddha, and Unani, is grounded in empirical knowledge derived from systemic observation and centuries of accumulated clinical experience (Patwardhan et al., 2005). More than 1,200 diseases are mentioned in various classical Ayurvedic texts, with therapeutic interventions involving more than 1,000 medicinal plants (89.93%), 58 minerals, metals, or ores (5.24%), and 54 animal and marine products (4.86%) used in various forms for disease management (T. K. Biswas & Mukherjee, 2003).

One of the most extensively documented and clinically significant areas of Ayurveda is wound healing, which is described under the concept of *Vranaropaka* (**Fig. 2**) (V. Kumar et al., 2021). The medical understanding of wounds was first mentioned by Maharshi Agnibesha in the *Agnibesha Sambita* (later called *Charaka Samhita*). Maharshi Sushruta further elaborated on this subject in the *Sushruta Samhita*, providing detailed descriptions of

wound classification and therapeutic approaches (V. Kumar et al., 2021). In Ayurveda, a wound (*Vrana*) is a discontinuity of the skin or underlying tissue that, on healing, usually results in permanent scarring an interpretation that is very similar to the contemporary clinical meaning (T. K. Biswas & Mukherjee, 2003). Inflammation is regarded as a first and important step in developing pathogenesis of wounds and is referred as *Vranashotha* (V. Kumar et al., 2021).

According to Ayurvedic principles, wounds may arise from endogenous causes, including *Vata* (nerve impulses), *Pitta* (enzymes and hormones), and *Kapha* (body fluids), or from exogenous factors, such as *Chinna* (incised wounds), *Bhinna* (perforated wounds), *Viddha* (punctured wounds), *Kshata* (lacerated wounds), *Picchita* (contusions) and *Ghrista* (abrasions) (T. K. Biswas & Mukherjee, 2003). These categories have striking similarities with the wound types in modern medical practice (Thakur et al., 2011).

The classical wound care methods outlined in *Sushruta Samhita* have a total of about 60 therapeutic measures, which are initiated by antiseptic wound cleansing and therapeutic wound care is achieved by full restoration of structure and function (V. Kumar et al., 2021). These treatments were aimed at improving the quality of tissues and providing the best possible aesthetics besides speeding up the healing process. It is estimated that almost 70 percent of the Ayurvedic wound-healing formulations are of plant origin, 20 percent of these are mineral based and the rest 10 percent are of animal origin (T. K. Biswas & Mukherjee, 2003). Such formulae are widely reported in authoritative Ayurvedic books, such as *Charaka Samhita* (ca. 5000 B.C.), *Sushruta Samhita* (ca. 1000 B.C.), *Astanga Hridaya* (ca. A.D. 600), *Bhavaprakash Nighantu* (ca. A.D. 1500), *Dhanwantari Nighantu* (ca. A.D. 1800), and *Ayurveda Siksha* (20th century A.D.) (Patwardhan et al., 2005).

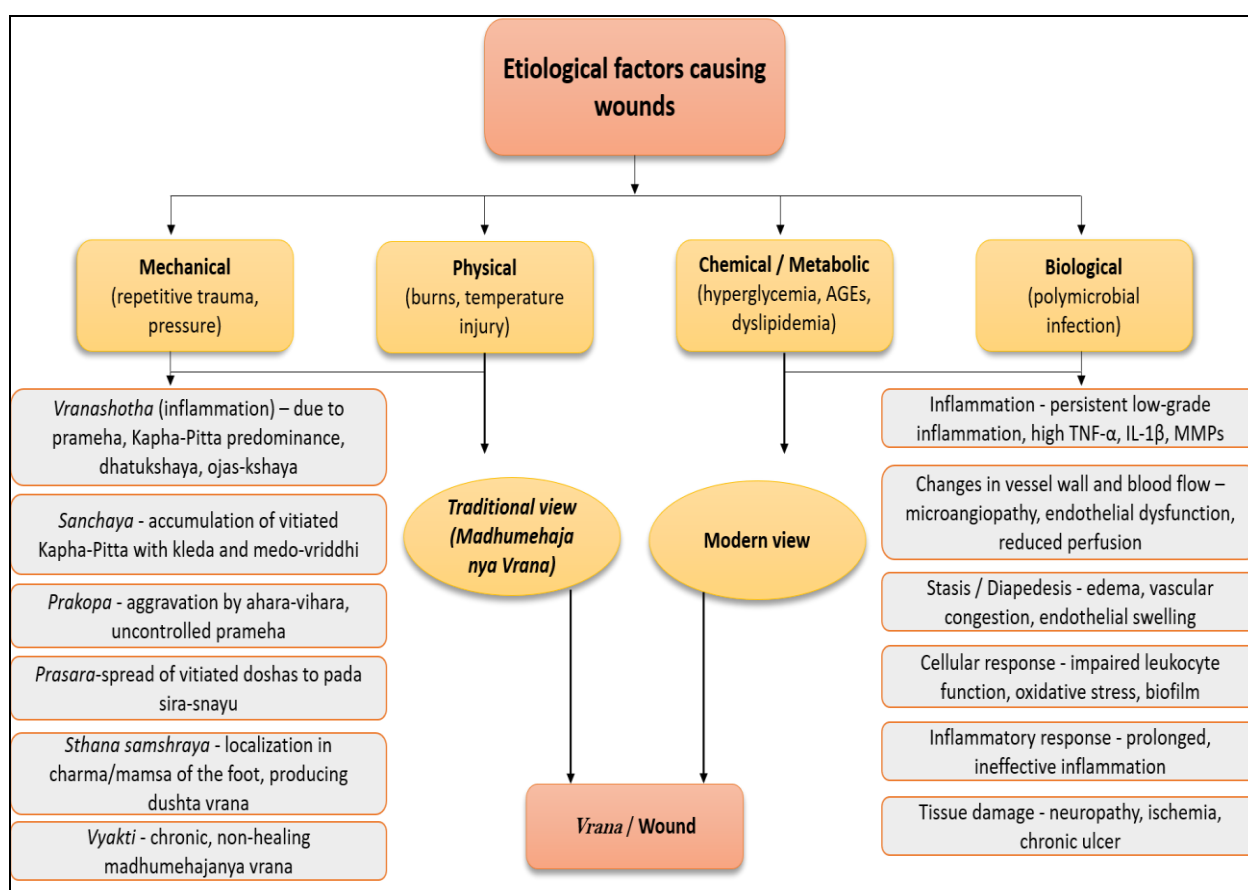


Fig. 2. Etiopathogenesis of Wounds: A Comparison between Traditional and Modern Medical Systems

These medications have been reported to be efficient in the management of various disorders, including *Vrana* (wounds or ulcers), *Nadivrana* (sinuses), *Vidradhi* (abscess), *Visarpa* (erysipelas), *Upadamsha* (syphilitic ulcers), *Vranajakrimi* (maggots in wounds), *Dus-tavrana* (septic wounds), *Vranashotha* (inflammatory changes in wounds), *Vranavisha* (cellulitis), *Ugravrana* (purulent ulcers), and *Netravrana* (hordeolum or styne sepsis) (T. K.

Biswas & Mukherjee, 2003). Several of these formulations have been subjected to scientific investigations to evaluate their wound-healing potential (B. Kumar et al., 2007).

There is a wide dispersion of botanical information on plants traditionally used in India for the treatment of cuts, wounds, and burns in leading journals specializing

in ethnobotany and traditional medicine (J. Sharma et al., 2014). Ethnic applications of plants in studies of skin disease have been reported, especially with respect to cuts, wounds, and burns (Ayyanar M, n.d.). In the present review, we described such plants that are widely employed in traditional and folk medicine in India; reported in ethnobotanical literature; used in the healing of wounds; and categorized these plants in terms of their application in cuts, wounds, or burns (Dudhamal, 2023).

A few medicinal plants possess distinct bioactive profiles (**Table 1**) that may exert beneficial effects on DW repair. For example, *Butea monosperma* flower extract, a rich source of flavonoids and phenolic compounds, has been reported to significantly increase wound contraction and

reduce blood glucose levels in diabetic animal models. These findings support its traditional application of this compound in wound healing and indicates the existence of antioxidant-mediated processes that promote tissue healing in hyperglycemic environments (Parveen & Siddiqui, n.d.). Equally, the methanolic extract of the *Ixora coccinea* has been reported to have good antioxidant and antimicrobial properties and has been reported to increase fibroblast proliferation and collagen production in cutaneous wound models (Selvaraj et al., 2011). All these characteristics suggest that it can help activate oxidative stress relief and the development of the extracellular matrix, which are essential in DW healing.

Table 1: Potential Medicinal Plants used in DW Care.

Plant Name	Major Bioactive Class(reported/predominant)	Nrf2/Antioxidant Potential	NF-κB/Anti-inflammatory Potential	VEGF/Angiogenesis Potential	Evidence Status	Representative Reference(s)
<i>Abutilon indicum</i>	Flavonoids, phenolic acids, mucilage polysaccharides, sterols	Moderate	Moderate	Low	Granulation studies (non-DM)	Ethnomedical wound reports
<i>Alysicarpus vaginalis</i>	Flavonoids, phenolic acids, tannins, glycosides	Low-moderate	Low	Low	Ethnomedicinal only	Traditional use surveys
<i>Argyrea nervosa</i>	Alkaloids, flavonoids, phenolic acids, glycosides	Moderate	Moderate	Moderate	Very limited	Preliminary phytochemical studies
<i>Barleria cristata</i>	Flavonoids, phenolic acids, iridoids, glycosides	Low	Moderate	Low	Antimicrobial focus	Herbal pharmacopeia
<i>Butea monosperma</i>	Chalcones, flavonoids, tannins, glycosides	High	Moderate	Moderate	Preclinical wound models	Experimental wound-healing studies
<i>Cassia occidentalis</i>	Anthraquinones, flavonoids, phenolic acids, glycosides	Moderate	Moderate	Low	Preclinical only	Toxicology-focused studies
<i>Celosia argentea</i>	Flavonoids, saponins, polysaccharides, phenolic acids	Moderate	Low	Moderate	Non-DM wound hints	Angiogenesis-related reports
<i>Cissampelos pareira</i>	Alkaloids, flavonoids, lignans, phenolic acids	Moderate	Moderate	Low	Immunomodulatory	Pharmacological screenings
<i>Cleome viscosa</i>	Glucosinolates, flavonoids, terpenoids, phenolic acids	Moderate	Moderate	Low	Wound contraction	In vivo wound models
<i>Cocculus hirsutus</i>	Alkaloids, flavonoids, glycosides, phenolic acids	Moderate	Moderate	Low	Sparse data	Regional medicinal plant surveys
<i>Cordia macleodii</i>	Flavonoids, phenolic acids, tannins, triterpenoids	High	Moderate	Moderate	Non-DW models	In vivo wound-healing studies
<i>Costus speciosus</i>	Steroidal saponins, flavonoids, terpenoids, phenolic acids	Moderate	Moderate	Moderate	Metabolic studies	Antidiabetic plant reviews
<i>Desmodium gangeticum</i>	Flavonoids, alkaloids, saponins, phenolic acids	Moderate	Moderate	Low	Limited wound work	Ayurvedic pharmacology texts
<i>Ehretia laevis</i>	Phenolic acids, flavonoids, tannins, triterpenoids	Moderate	Low	Low	Traditional use	Ethnobotanical records
<i>Enydra fluctuans</i>	Flavonoids, phenolic acids, sesquiterpene lactones, sterols	High	High	Moderate	Preliminary pharmacology	Anti-inflammatory plant studies
<i>Erythrina variegata</i>	Isoflavones, alkaloids, flavonoids, phenolic acids	Moderate	High	Low	Anti-TNF data	Cytokine modulation studies
<i>Ficus racemosa</i>	Polyphenols, flavonoids, tannins, triterpenoids	High	Moderate	Moderate	Wound contraction	Experimental wound models
<i>Flacourtia indica</i>	Tannins, flavonoids, phenolic acids, triterpenoids	Moderate	Low	Low	Non-DM wound	Traditional wound remedies
<i>Gardenia gummifera</i>	Resins, iridoids, flavonoids, phenolic acids	Low-moderate	Moderate	Low	Limited evidence	Pharmacognosy monographs
<i>Grewia asiatica</i>	Polyphenols, flavonoids, anthocyanins, tannins	High	Low	Low	Antioxidant rich	Oxidative stress studies
<i>Hemidesmus indicus</i>	Phenolic acids, flavonoids, saponins, coumarins	High	Moderate	Low	Anti-glycation	Diabetic complication reviews
<i>Hygrophila auriculata</i>	Sterols, flavonoids, alkaloids, phenolic acids	Moderate	Low	Moderate	Circulatory benefit	Vascular activity reports
<i>Hygrophila spinosa</i>	Sterols, flavonoids, alkaloids, phenolic acids	Low-moderate	Low	Moderate	Vascular hints	Traditional medicine texts

<i>Ixora coccinea</i>	Anthocyanins, flavonoids, tannins, phenolic acids	Moderate	Moderate	High	Non-DM wound	Angiogenesis-linked studies
<i>Lannea coromandelica</i>	Tannins, flavonoids, phenolic acids, triterpenoids	Moderate	Moderate	Low	Bark studies	Anti-inflammatory reports
<i>Leucas aspera</i>	Terpenoids, flavonoids, sterols, phenolic acids	Low	Moderate	Low	Anti-inflammatory	Folk medicine sources
<i>Mimosa pudica</i>	Tannins, flavonoids, alkaloids, phenolic acids	Moderate	Moderate	Low	Traditional use	Ethnopharmacology reviews
<i>Mollugo pentaphylla</i>	Polysaccharides, flavonoids, sterols, phenolic acids	Moderate	Low	Low	Poorly explored	Limited phytochemical data
<i>Nyctanthes arbor-tristis</i>	Iridoids, flavonoids, glycosides, phenolic acids	Moderate	Moderate	Low	Immunomodulatory	Experimental inflammation models
<i>Pavetta indica</i>	Phenolic acids, flavonoids, tannins, glycosides	Low-moderate	Moderate	Low	Antimicrobial	Ethnomedicine reports
<i>Pergularia daemia</i>	Cardiac glycosides, flavonoids, terpenoids, phenolic acids	Low	Moderate	Low	Sparse data	Preliminary screenings
<i>Phyllanthus amarus</i>	Lignans, flavonoids, tannins, phenolic acids	High	Moderate	Low	Antioxidant rich	Hepato-protective studies
<i>Pluchea lanceolata</i>	Terpenoids, flavonoids, sterols, phenolic acids	Low-moderate	High	Low	Anti-edematous	Anti-inflammatory studies
<i>Rotula aquatica</i>	Phenolic acids, flavonoids, tannins, triterpenoids	Low	Low	Low	Ethnomedicine only	Traditional renal remedies
<i>Salacia reticulata</i>	Polyphenols, flavonoids, xanthenes, glycosides	High	Low	Low	Glycemic control	Antidiabetic clinical reviews
<i>Scoparia dulcis</i>	Flavonoids, diterpenes, alkaloids, phenolic acids	High	Moderate	Low	Insulin signalling	Metabolic pathway studies
<i>Sida cordifolia</i>	Alkaloids, flavonoids, phenolic acids, glycosides	Moderate	High	Low-moderate	Preclinical	Anti-inflammatory studies
<i>Sphaeranthus indicus</i>	Sesquiterpene lactones, flavonoids, sterols, phenolic acids	Moderate	High	Low	Cytokine studies	NF-κB-focused reports
<i>Tectona grandis</i>	Quinones, flavonoids, phenolic acids, terpenoids	Moderate	Low	Moderate	Fibroblast data	Cell-based wound assays
<i>Tephrosia purpurea</i>	Isoflavones, flavonoids, sterols, phenolic acids	High	Moderate	Moderate	Sparse models	Antioxidant plant reviews
<i>Trianthema portulacastrum</i>	Flavonoids, phenolic acids, sterols, alkaloids	Moderate	Low	Low	Antioxidant	Experimental screenings
<i>Tragia involucrata</i>	Terpenoids, flavonoids, sterols, phenolic acids	Low	Moderate	Low	Sparse	Folk medicinal use
<i>Vitex negundo</i>	Flavonoids, iridoids, terpenoids, phenolic acids	Moderate	High	Low	Anti-inflammatory	COX/NF-κB studies
<i>Vitex trifolia</i>	Flavonoids, terpenoids, iridoids, phenolic acids	Moderate	Moderate	Moderate	Angiogenic hints	Coastal medicinal plant reports
<i>Zehneria scabra</i>	Saponins, flavonoids, triterpenoids, phenolic acids	Moderate	Low	Low	Very limited	Preliminary phytochemistry
<i>Ziziphus nummularia</i>	Flavonoids, saponins, tannins, phenolic acids	Moderate	Low	Low	Antioxidant	Desert plant studies

Leaf extracts of *Rhus coriaria*, *Globularia arabica* and *Malva sylvestris* have not been massively tested in DW models, but have demonstrated considerable effectiveness in promoting wound contraction and fibroblast migration in diabetic rats (Alsarayreh et al., 2022). These findings underscore the applicability of their phytochemicals in regulating cell and pathway dysregulations in diabetic repair. Additionally, there are other plants like *Barleria cristata*, *Celosia argentea*, *Cissampelos pareira*, *Costus speciosus* and *Tephrosia purpurea* that have been found to be abundant sources of flavonoids, phenolic acids, and other antioxidant components on the basis of ethnobotanical evidence and pharmacological studies (Ansari et al., 2021; El-Far et al., 2018; Sharma et al., 2025; Thim-uam et al., 2025; Pandey et al., 2016). These compounds play a mechanistic role in the regulation of oxidative stress and inflammation using the Nrf2 signalling pathway and the NF-κB pathway are both central pathological features of impaired wound healing in diabetes.

Similarly, other species like *Ficus racemosa*, *Enydra fluctuans*, and *Erythrina variegata* have been reported to have a significant antioxidant or anti-inflammatory activity and moderate angiogenic capacity which could impact VEGF-mediated neovascularization and extracellular matrix remodelling (Article et al., n.d.; Gaurav Kumar et al., 2023a; Pahari et al., 2022). There is however no direct evidence that these processes occur in DW models.

Also, the ethnomedicinal relevance and antimicrobial activity of *Abutilon indicum*, *Cleome viscosa*, and *Cocculus hirsutus* have been documented, which is why they should be the subject of focused research in the context of oxidative imbalance and immune dysregulation peculiarities of DW pathology (Abat et al., 2017; Chambhare, 2025). All of these medicinal plants are valid prospective candidate targets in mechanistic research of DW models to confirm their antioxidant, anti-inflammatory, and proangiogenic activities, which

are needed to carry out a successful tissue repair in the diabetic environment.

3.1. Compounds from marine and microbial sources for antidiabetic wound healing

The use of marine organisms and microbial metabolites has not yet received as much attention as higher plants do, but they are potential sources of bioactive compounds to heal DWs. For example, extracts of the brown algae *Halodule pinifolia* and *Padina tetrastrum* have been demonstrated to induce the expression of major growth factors, including VEGF and IGF-1, and they are as effective as traditional angiogenic interventions in preclinical DW models (Kannan et al., 2013; Naveen et al., 2021). The isolated sulfated polysaccharides and fucoxanthin derivatives of these seaweeds stimulate angiogenesis, fibroblast proliferation, and antioxidant responses, which help increase wound repair and tissue remodelling.

Similarly, microbial metabolites, such as some bacterial exopolysaccharides and fungal secondary metabolites, have been shown to potentially affect inflammation, collagen production, and antimicrobial protection in DWs (Arslan et al., 2024). For example, bacterial cellulose produced by *Gluconacetobacter xylinus* can be used as a wound dressing material, which can preserve the balance of moisture and support the continuous release of therapeutic substances (Kończowska et al., 2019). Marine-derived peptides and enzymes also have anti-inflammatory and antimicrobial effects, which are useful in preventing the risk of developing infection in diabetic ulcers in the chronic stage.

Although research on marine and microbial natural products as wound healing agents in diabetic patients is relatively limited, the available evidence shows that these materials have great potential for treatment. The sources offer distinct chemical scaffolds and processes that supplement earth-based vegetal treatments and should be given greater systematic research attention. An investigation of this unexploited marine and microbial biodiversity has the potential to identify novel, multitargeted bioactive compounds, furthering the creation of new and efficient DWs.

3.2. Geographical origins and their impact on the metabolite profile

In this section, we discuss the medicinal plants used for DW healing across different geographical regions, with particular emphasis on the impact of geographical and cultural peculiarities on the implementation and metabolite profiles of DW. Climate, altitude, soil composition and traditional knowledge have a great influence on the biosynthesis and accumulation of bioactive secondary metabolites and thus regulate wound-healing efficacy.

As an illustration, *Centella asiatica* and *Eclipta alba* are common plants in tropical Asia, particularly in India and

Southeast Asia; the two have a long tradition of use in traditional medicines to heal wounds (D. Biswas et al., 2021; Chung et al., 2017). The plants *Curcuma longa* and *Azadirachta indica* are native to the Indian subcontinent and *Ficus racemosa* and *Hygrophila auriculata* to South and Southeast Asia (D. Kumar, 2022).

Some of the endemic ones, such as *Alstonia scholaris*, are found in the locality of South Asia and the tropical part of Africa, and *Calendula officinalis* is found mainly in the Mediterranean region and European countries (Chhajed et al., 2023; Vella et al., 2024). It has been reported that marine bio-diversity of the East Asian coasts has therapeutic potential of DWs since marine algae like *Saccharina japonica* and *Undaria pinnatifida* are growing along coasts (Kahwa et al., 2025).

The geographic origin of these plants is a significant point of influence of the quality and concentration of secondary metabolites that lead to their wound-healing activities. Phytochemical biosynthesis is controlled by temperature, rainfall, altitude, type of soil, water nutrients and other environmental influences resulting in large variation even within the same species of different places. It is dependent on the varying soil compositions and climatic conditions across populations in the Indian and Southeast Asian subcontinents to vary the concentration of asiaticoside in *Centella asiatica* in relation to different effects of asiaticoside on collagen production and angiogenesis (Hein et al., 2025). In a similar way, the amount of curcuminoids in *Curcuma longa* grown in various parts of India differs and influences the antioxidant and anti-inflammatory effects of the spice, which is necessary in curing DWs (Fuloria et al., 2022). *Saccharina japonica* also displays a seasonal variability of the concentrations of fucoxanthin and polysaccharides as well as by the temperature of the water and nutrient flux influencing the bioactivity patterns of marine algae (Bogdan et al., 2025).

This geographical and environmental diversity highlights the importance of the integration of metabolomic and phytochemical profiling within the diverse plant populations to guarantee consistency, fidelity, as well as repeatability of the botanical extracts to be used in DW management. This would enhance the validity of pharmacological evaluations, as well as the formulation of evidence-based herbal payments with universal potential.

Furthermore, systematic metabolomic characterization of various ecoregions needs to be the priority of future research to optimize the extraction procedure, define quality control parameters, and design formulations based on ecoregional phytochemical profiles to achieve maximum therapeutic value. This approach will facilitate uniformity and validity in transferring conventional botanical knowledge to contemporary DW-care practices worldwide (Raza et al., 2024).

3.3. Comparative analysis of therapeutic efficacy

To elucidate the molecular mechanisms underlying plant-based interventions for DW healing, we classified the evidence regarding the main plant-derived secondary metabolites into three levels of investigation: in vitro, in vivo, and clinical trials. These data are summarized in

Fig. 3, illustrating the effects of bioactive compounds on key pathways, including angiogenesis (VEGF, HIF-1 α), anti-inflammatory signalling (NF- κ B inhibition), the antioxidant response (Nrf2 activation), and extracellular matrix remodelling (TGF- β 1, PDGF, and MMP regulation).

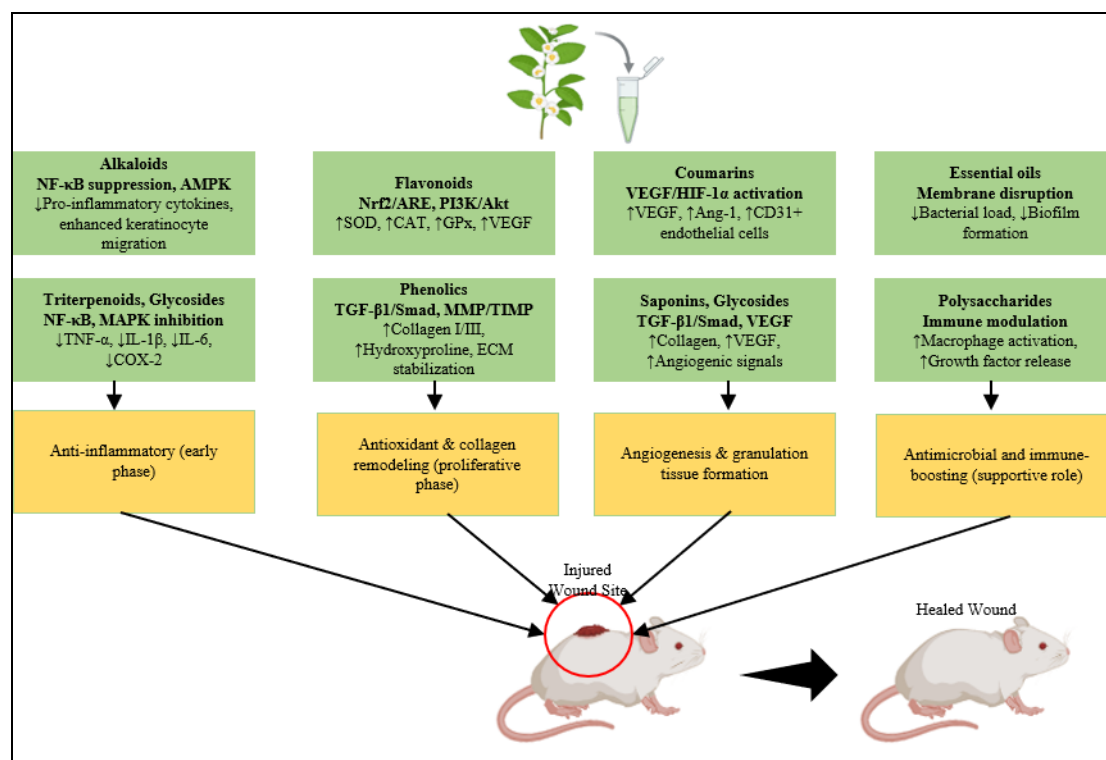


Fig. 3: Schematic illustration showing how major phytoconstituent classes from medicinal plants coordinate multiple signalling pathways to promote the orderly progression of wound healing from inflammation to complete tissue repair.

Numerous phytochemicals derived from medicinal plants have demonstrated significant therapeutic effects in laboratory assays and animal models. These effects include enhanced vascularization, regulation of inflammatory cytokines, increased re-epithelialization and greater collagen deposition, which are all essential factors in making wounds healed.

Nevertheless, the translation of these findings into human clinical trials remains limited. Only a few botanicals, including *Centella asiatica*, *Curcuma longa*, *Azadirachta indica*, and *Ficus racemosa*, have shown safety and initial efficacy in diabetic foot ulcer patients (S. Kumar et al., 2023; Narzary et al., 2023). The majority of evidence is still beyond the preclinical stage, highlighting a lack of relatedness between encouraging preclinical research and solid clinical trials. This underlines the necessity of well-crafted randomized controlled trials, characterization of extracts, and pharmacokinetic and dose-response research to establish therapeutic potential and safety (Golledge & Thanigaimani, 2021).

Comparative analysis suggests that *Centella asiatica*, *Curcuma longa*, *Ficus racemosa* and *Azadirachta indica*

can be considered candidates for translation in the near future because of their combined ability to stimulate angiogenesis, regulate inflammation, enhance collagen deposition, and trigger wound contraction, combined with emerging human data. Other promising plants, e.g., *Enhydra fluctuans* and *Cordia macleoidii*, demonstrate promising mechanistic effects but still need additional clinical safety and efficacy research before being used extensively (Gaurav Kumar et al., 2023b; Giles-Rivas et al., 2020).

An integrated assessment of the plants reviewed reveals substantial variability in mechanistic knowledge and translational readiness. For example, the Nrf2 activation, growth factor upregulation, and matrix remodelling effects of *Centella asiatica* and *Curcuma longa* have been confirmed in various wound models and clinical trials (Shahcheraghi et al., 2022; Shedeova et al., 2019). On the other hand, some species, such as *Ficus racemosa*, exhibit high levels of antioxidant and anti-inflammatory effects, but more detailed evidence from humans is needed.

Some marine vegetative extracts like *Saccharina japonica* have demonstrated unmatched, dual,

mechanistic (i.e., angiogenesis and inhibition of inflammatory mediators) potential, but are in clinical use (Collins *et al.*, 2016).

To conclude, molecular mechanistic facts show that different species of plants hold high prospects of incision in designing standardized therapeutics in curing DW. However, a lot of clinical assessment, which is aimed at extract standardization, dosage, safety, and pharmacodynamics is necessary before the extensive application of clinical testing. Systems biology, computational modelling, and clinical trials will play vital roles in integrating these phytochemicals as scientific research agents into effective and dependable therapies for DWs.

4. Key Findings of the Review

This systematic review provides a total synthesis of plant-based therapeutic strategies used to manage DWs in the last decade. One of the key observations of this review is that phytochemicals, especially flavonoids, terpenoids, phenolic acids, alkaloids and polysaccharides, play a central role in regulating various pathological hallmarks of DWs (Miraj *et al.*, 2023). These compounds have pleiotropic effects, which include the restoration of redox balance; the inhibition of chronic inflammation; angiogenesis; and the stimulation of fibroblast and keratinocyte proliferation (Riaz *et al.*, 2024). Mechanistically, their actions focus on major signalling axes, such as the Nrf2/HO-1, NF- κ B, VEGF, TGF- β , HIF-1 α , PI3K/Akt and Wnt/ β -catenin pathways, which collectively regulate oxidative stress, immune regulation, vascular remodelling, and deposition of the extracellular matrix (Landge, 2024).

There is solid preclinical support for the capacity of plant-derived preparations to accelerate wound contraction, intensify collagen deposition, and augment neovascularization as well as tensile power in diabetic animals (Kaparekar & Anandasadagopan, 2022). However, the review also states that there is a large translational gap since most of the studies are restricted to in vitro and small-scale in vivo models and few well-designed clinical trials. Moreover, there is a high level of research bias on a limited number of popular medicinal plants, and many ethnobotanically significant but under researched plants have not received scientific attention, even though they have potentially valuable bioactive profiles.

5. Outlook and Future Research Avenues

Future studies on plant-based DW management should shift their focus to investigations that are motivated by mechanisms and translational and clinical research. The systematic study of underused medicinal plants, especially those that have been singled out on the basis of ethnobotanical evidence and initial antioxidant or anti-inflammatory effects, should be prioritized. These species constitute a relatively untapped source of new

bioactive compounds that can target DW-specific molecular pathways.

The plant extracts and formulations used are standardized. Rigorous phytochemical profiling, batch-to-batch consistency and quantification via marker-based standardization should be performed in future studies, and reproducibility and adherence to regulatory requirements should be achieved. It will be necessary to combine multiomics (transcriptomics, proteomics, and metabolomics) with new sophisticated molecular tests to understand interactions at the level of pathways and predictive biomarkers of therapeutic response.

The second issue of significance is the addition of phytochemicals, including hydrogel scaffolds, nanofibres, MNs and bioresponsive scaffolds, to better delivery vehicle to enhance their stability, bioavailability, and local function in hostile DW microenvironment. These new hybrid strategies can bridge the gap between traditional medicine and the emerging technologies in wound-care.

More importantly, the field needs to develop in the direction of designed, efficiently powered, multicentred clinical trials supported by standardized animal models and outcome measures. Similar regulatory-based toxicological and pharmacokinetic experiments are also necessary to enable clinical translation. Finally, enhancing international and interdisciplinary cooperation that will help speed up the innovation process and make promising laboratory findings develop into evidence-based therapeutic options for clinical practice is essential.

6. CONCLUSION

The present review offers an evidence-based and comprehensive overview of the therapeutic potential of plant-derived interventions in DW healing by combining systematic literature analysis and bibliometric mapping with phytochemical profiling and molecular pathway integration. The results revealed that the multilevel regulatory effects of botanical bioactives on oxidative stress, inflammation, angiogenesis, and tissue regeneration are more comprehensive and multifactorial than the complex and multifactorial pathology of DWs in response to simple and single-target therapies.

Although there is good preclinical evidence, these findings are still not fully translated into clinical practice owing to poor standardization, lack of mechanistic depth, and a dearth of good quality clinical evidence. These limitations need to be addressed by means of strict experimental design, sophisticated formulation approaches, and clinical research in translational studies, which will increase the therapeutic potential of plant-based wound-healing agents.

In summary, plant-based therapeutics are scientifically plausible, mechanically sound, and clinically effective

for DW management. The combination of strategic investment in untapped medical plants and modern technologies involving molecules and biomaterials can provide the possibility of safer and more cost effective as well as multitargeted therapy, which can provide patients with chronic DWs with a significant portion of improvement.

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