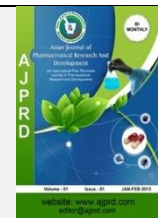


Available online on 15.08.2023 at <http://ajprd.com>

Asian Journal of Pharmaceutical Research and Development

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Review Article

A Detailed Review on Diabetic Wound Healing Activity

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ABSTRACT

Skin damage is known as a wound. Hemostasis, inflammatory, proliferative, and tissue remodelling or resolution are the four perfectly timed and highly planned phases that make up the normal biological process of wound healing in the human body. There are two basic categories of wounds: acute wounds and chronic wounds. Long-term negative effects on one's health are caused by the chronic metabolic condition known as diabetes mellitus, which is becoming more common. 25 percent of those with diabetes mellitus are thought to have poor wound healing due to their diabetes. Oxygenation, infection, hormones related to ageing and sex, stress, diabetes, and obesity, drugs, alcoholism, smoking, and diet are among the factors that affect wound healing. To address their basic medical needs, According to estimates, 80% of people who live in underdeveloped nations need traditional medicines, which are typically made from medicinal plants. Numerous individuals in Africa and other poor nations employ using medicinal herbs to cure diabetic wounds and associated issues due to the abundant supply With therapeutic herbs and enough conventional wisdom regarding wounds healing. Recent developments in functional genomics, nanotechnology, wound healing in diabetics, along with a better knowing the pathophysiology of chronic wounds. In the following review, detailed information about healing of diabetic wounds with mechanism, factors affecting, impairment of wound healing with its pathophysiology, herbal treatments and current advances when treating diabetic wounds are examined.

Keywords: Wound healing, diabetes, impairment, pathophysiology, medicinal plants, current advances.

ARTICLE INFO: Received 2023; Review Complete 2023; Accepted 2023; Available online 15 August 2023



Cite this article as:

Bhopale RS, Jangam RD, Dhekale HM, Aiwale PP, Chaware VJ, Redasani VK, A Detailed Review on Diabetic Wound Healing Activity, Asian Journal of Pharmaceutical Research and Development. 2023; 11(4):95-105. DOI: <http://dx.doi.org/10.22270/ajprd.v11i4.1293>

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INTRODUCTION

Wounded living tissue is damaged due to cutor break. According to how long they take to heal, wounds are categorised into two groups as acute wounds (which heal quickly) and chronic wounds (which heal slowly). Hemostasis, inflammatory, proliferative, and tissue remodelling or resolution are the four closely coupled and overlapping phases that make up the normal biological process of wound healing in the human body.^[1] By definition, those wounds are chronic that have not healed completely and have instead entered a period of pathologic inflammation. As a result, the procedure of healing is slowed down, rendered ineffective, and does not go forward in a coordinated fashion, leading to a subpar anatomical and functional outcome.^[2] These wounds are chronic, frequently

recur, and result in a significant handicap. The underlying causes of non-healing wounds have a wide range of differential diagnoses, although ischemia, which is linked to hyperglycemia (diabetes), venous stasis, and pressure, accounts for the majority of ulcers (70%).^[4] Diabetes mellitus (DM), which affects close to 500 million people worldwide, is expected to rise dramatically in the future years. Over \$300 billion is spent yearly in the US alone on Expenses for medical care and lost productivity due to DM. Diabetic wound or diabetic foot ulcer is one example of a chronic, non-healing wound that is estimated to affect one in three to one in five patients with diabetes over the course of their lifetime. Alarming frequency of DFUs (40 percent within one year & 65 percent in five years), and there are no reliable ways to predict their development. Diabetes has a complicated pathophysiology that includes vascular,

neuropathic, immunological, and metabolic elements that leads to impaired recovery.^[3] Blood vessels that are stiffer in hyperglycemia have slower blood flow and microvascular dysfunction, which results in less oxygen reaching the tissues. Diabetes-related blood vessel changes are also responsible for decreased leukocyte migration into the wound, which makes it more susceptible to infections.^[4] The presence of hyperglycemia itself can impair leucocyte activity. Peripheral neuropathy can also cause numbness and a decreased capacity for pain, which can result in the chronicization of wounds that are not promptly identified and well treated.^[4] Impaired wound healing can be caused by a variety of things. In general, there are two categories of elements that affect repair: local and systemic. Local variables are those that have an immediate impact on the wound's physical characteristics, whereas systemic factors are those that have an overall negative impact on a person's health or ability to recover from a condition. Many of these

elements are interconnected, and the systemic factors influence wound healing by way of the local impacts. In folkloric cultures, many herbs are used to treat burns, wounds, and cuts. Numerous plant and herb species with wound-healing properties have been found notably in Africa & other poor nations as a result of ethnobotanical research. Utilising medicinal herbs for wound treatment and care include cleaning, debriding, and creating a favourable environment for the body's own healing process.^[5,20]

Wound & Types of Wounds:

Wound is destruction of living tissue produced by cut, blow, or break. Wound is an anatomical and functional disruption of the skin following an injury. In general, wounds are categorised based on the underlying factor that led to their development.^[19]

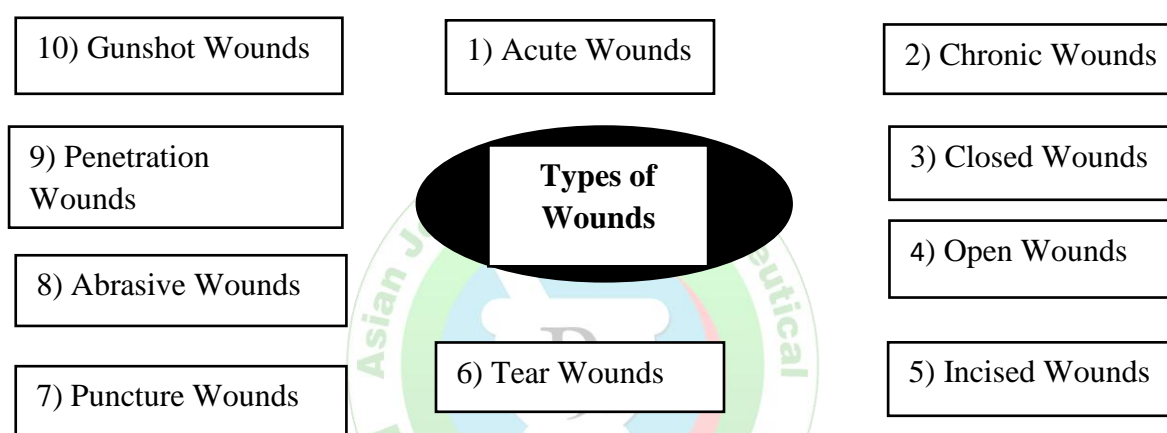


Figure 1 : Types of Wounds

1. Acute wounds :

The anatomical and functional integrity is typically sustainably recovered in acute wounds after tissue damage/injury occurs through an ordered and time-reparative phase. Typically, cuts or surgical incisions result in acute wounds.

2. Chronic wounds :

an inflammatory condition that is develops in chronic wounds because they have not experienced the normal healing phases. They require extra time for healing.^[6]

3. Closed wounds :

Closed wounds cause blood to leak from the circulatory system, but the blood remains inside the body. Bumps on the body make it obvious.

4. Open wounds :

An open wound causes the body to lose blood, which is readily apparent. According to the source that caused the wound, these wound may be further classified into subtypes.

5. Incised wounds :

This type of wound results in just modest tissue injury and no tissue loss. Sharp objects like a scalpel or knife are the main culprits for this condition.

6. Tear or laceration wounds :

This non-surgical injury occurs when other trauma types are present and causes tissue loss and damage.

7. Puncture wounds :

These injuries are brought on by something poking the skin, such as a nail or needle. Infection risks are high in them because dirt may enter deeply into the wound.

8. Cuts that are abrasive or superficial :

There is abrasion when you slide across a rough surface. The skin's outermost layer, or epidermis, is scraped off during this process, exposing nerve endings and causing a painful injury.

9. Penetration wounds:

A knife, for example, frequently penetrates and exits the skin to form a penetration wound.

10. Gunshot wounds:

These injuries are often caused by an object like a projectile or bullet that enters the body.^[19]

Wound Healing Process:

Hemostasis, inflammatory, proliferative, and tissue remodelling or resolution are the four closely related and overlapping phases of the process wound healing.^[1] These

phases and associated biophysiological processes must occur inside the right order, at the right time, and with the right amount of intensity. The four main, interconnected mechanisms that contribute to wound healing are briefly discussed below.^[20]

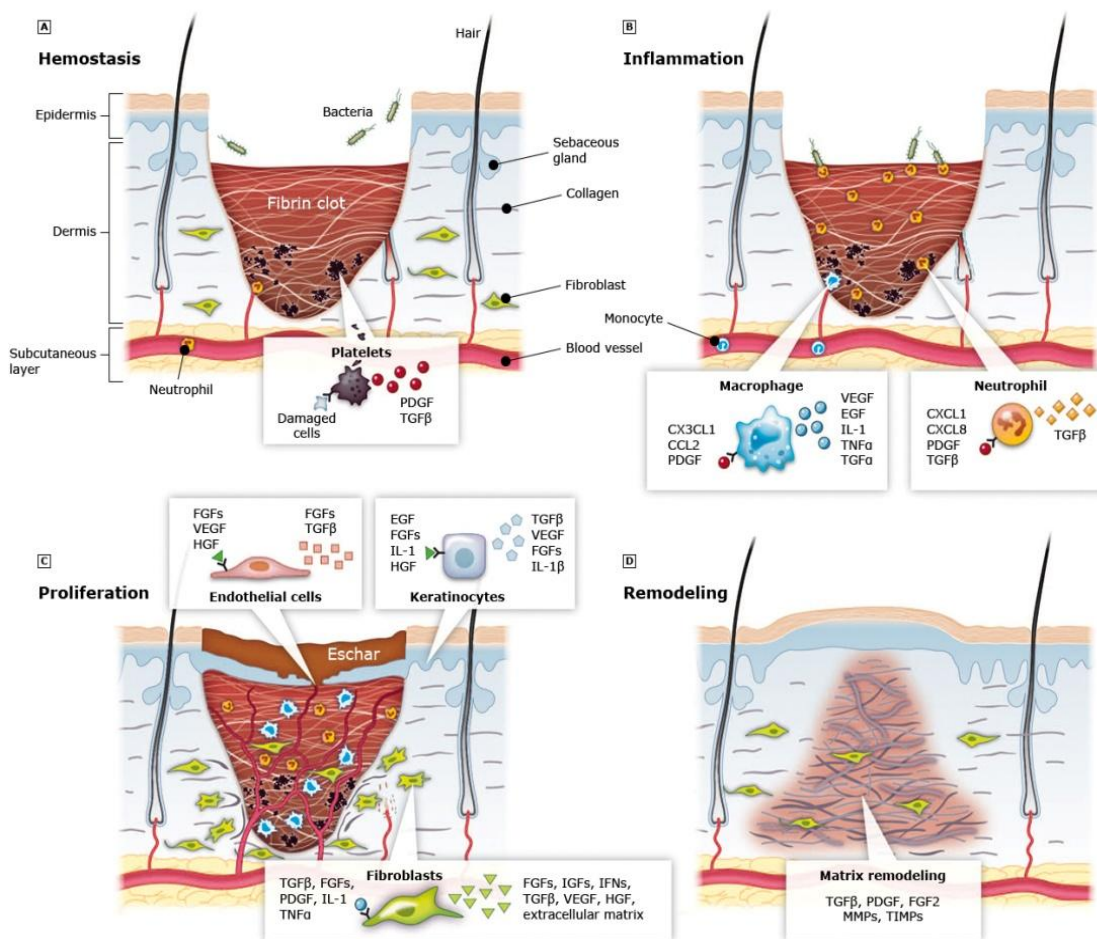


Figure 2 :Wound Healing Process

1. Hemostasis phase :

Activated platelets that have been exposed by an injury attach to it and secrete glycoproteins that cause platelet aggregation. Through the generation of thrombin, the complex secretes substances that work in concert to trigger the intrinsic clotting cascade, which in turn triggers the development of fibrin from fibrinogen. The platelet and fibrin mesh combine to form a durable hemostatic stopper. It is well known that blood vessels constrict minutes after injury, limiting the extent of haemorrhage through many phases that enable hemostasis to be established.

2. Inflammation phase :

The hemostatic phase and the inflammatory phase play overlapping roles. The hemostatic mechanisms appear to be activated during the inflammatory phase in an effort to prevent bleeding from the wound or damage site immediately. Up to two weeks could pass during this phase. Vasoconstriction and platelet aggregation to cause blood clotting are indicative of the inflammatory phase, which is

followed by vasodilation and phagocytosis to cause inflammation at the wound site.^[7]

3. Proliferative phase :

This phase, which comes after the inflammatory phase and lasts for two to three weeks, includes the critical processes of granulation, contraction, and epithelialization. With the growth of fresh capillaries, fibroblasts create a bed of collagen during granulation. In the previous two processes, the wound site's margins contracted to minimise flaws (contraction) and epithelialized to cover the wound site (epithelialization).^[8]

4. Remodelling phase :

New collagen is produced during this phase, which is also characterised by an increase in tissue tensile strength brought on by the intermolecular cross-linking of collagen caused by Vitamin C-dependent hydroxylation. This phase is thought to last anywhere from three weeks to two years.^[9]

Time	Phases	Cellular and Bio-physiological Events
↓	Hemostasis	1)Vascular constriction 2)Aggregation of platelets, degranulation, and thrombus formation
Hours ↓	Inflammation	1)Neutrophil infiltration 2)Monocyte infiltration and differentiation to Macrophage, 3)Lymphocyte infiltration
Days ↓	Proliferation	1)Re-epithelialization 2)Angiogenesis 3)Collagen synthesis 4)ECM formation
Weeks to Months	Remodeling	1)Collagen remodelling 2)Vascular maturation and regression

Figure 3: Time, Phases of Wound Healing, Events Associated with Cells and Biophysiology involved in each Phase.

Factors Affecting Wound Healing :

Impaired wound healing can be caused by a variety of things. In general, There are two categories of elements that affect repair: local and systemic. Local factors are those that directly impact the wound's features, whereas systemic factors are those that affect a person's overall health or illness status and impair their capacity to heal. We'll talk about some elements that influence wound healing below.^[14,18]

1. Wound site :

The location of the wound is crucial to how quickly it heals since wound infection is frequently the cause of delayed wound healing. A few of the microorganisms can result in wound infections are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. According to research, *S. aureus* is the predominant pathogen linked to diabetic foot infections.

2. Immune state :

Patients with diabetes experience various immune system impairments. Leukocyte adhesion, chemotaxis, and phagocytosis may all be negatively impacted in a diabetic condition, which would delay wound healing. Polymorphonuclear leukocyte activity has also been discovered to be impaired, especially in the presence of acidosis. Hyperglycemia (DM) may decrease anti-oxidant systems that take part in bactericidal activity, leaving diabetes patients' wounds more prone to infection. Diabetes is associated with a higher death rate and a risk factor for bacteria in individuals with pneumococcal pneumonia.

3. Age :

The age of an individual and the wound healing rate appear to be related. In senior age, wound healing seems to take longer. This may be because fibroblast activity and growth slow down with age, and older people who have been damaged also produce less collagen and have slower wound contraction.

4. Disease state:

In the early stages of diabetic foot infections, beta-hemolytic streptococci and *S. aureus* are treated as pathogens. According to studies, diabetic women experience more bacterial infections than women without diabetes. Diabetes patients appear to be more prone to wound infection. Diabetes patients had a greater rate of wound infection (11%) than the general patient population, according to Greenhalgh.

5. Reactive oxygen species (ROS) :

A high ROS concentration could cause significant tissue damage that could progress to neoplastic transformation and hinder the healing process by damaging cells, DNA, proteins, and lipids.

6. Diet :

Diet has reportedly been linked to wound healing. It was found that sufficient wound healing requires level of serum albumin of at least 3.5 g/dl. Reduced protein levels may have a deleterious impact on collagen synthesis and wound healing.

7. Stress :

The effects of stress on one's physical and social behaviours are significant. A relationship between stress and number of ailments, including diabetes, cancer, weakened wound healing, and cardiovascular disease. Studies on both animals and human being have shown that psychological stress significantly slows the healing of wounds. Patients with Alzheimer's disease and students who were under academic pressure during exams showed delayed wound healing.

8. Sex Hormones in Aged Male and Female Individuals:

Age-related deficiencies in wound healing are related to sex hormones. Aged males have been found to heal acute wounds less rapidly than aged females. The fact that male androgens testosterone and 5-

dihydrotestosterone (DHT) and their steroid precursor dehydroepiandrosterone (DHEA) appear to have considerable influence on the wound-healing process may help to explain this in part.

9. Obesity :

Obese people typically experience wound complications include pressure ulcers, venous ulcers, hematoma and seroma development, skin wound infection, and dehiscence. Obese individuals receiving bariatric and non-bariatric procedures have been demonstrated to experience more wound problems.

10. Alcohol Consumption :

Clinical research and animal studies have demonstrated that consumption of alcohol hinders wound healing and raises the risk of infection. Alcohol use reduces host resistance, and being intoxicated when injured increases the likelihood of developing an infection in the wound.^[10]

11. Smoking :

Smoking is known to raise the risk of heart and vascular disease, stroke, COPD (chronic obstructive pulmonary disease) as well as other malignancies. Similar to this, smoking has long been recognised to have detrimental impacts on how well wounds heal. Smokers exhibit a delayed wound healing process after operations(surgery), as well as an increase in a number of problems, including infections, wound rupture, anastomotic leaking, wound and flap necrosis, epidermolysis, and a reduction in the tensile strength of wounds.

12. Medications :

Numerous drugs have the potential to alter how well wounds heal, including those that interfere with platelet function, clot formation, inflamed reactions, as well as cell proliferation. Glucocorticosteroids, NSAIDs (non-steroidal anti-inflammatory drugs), and chemotherapeutic agents are just a few of the regularly prescribed drugs we cover here since they have a substantial impact on healing.

i. Glucocorticoid Steroids :

Systemic glucocorticoids (GC), which are often used as anti-inflammatory medications, are well known for preventing the healing of wounds by suppressing cellular wound responses such as fibroblast growth and collagen synthesis as well as overall anti-inflammatory actions. Systemic steroids lead to incomplete granulation tissue formation and diminished wound contraction during the healing process. Hypoxia-inducible factor-1 (HIF-1), a crucial transcriptional factor in wound healing, is likewise inhibited by glucocorticoids.

ii. Non-steroidal Anti-inflammatory Drugs (NSAIDs) :

There is little evidence that using short-term NSAIDs has a detrimental effect on healing. The issue of whether long-time NSAIDs (non-steroidal anti-inflammatory drugs) use impairs healing of wounds is still up for debate. Ibuprofen has been shown to have an anti-proliferative effect on healing of wound into animal models, resulting in a reduction in the number of fibroblasts, diminished breaking strength, decreased wound contraction, postponed epithelialization, and impaired angiogenesis.

iii. Chemotherapeutic Drugs :

The majority of chemotherapeutic medications aim to block angiogenesis, fast cell division, and cellular metabolism, hence blocking many of the processes necessary for effective wound healing. These drugs prevent the synthesis of DNA, RNA, or proteins, which reduces fibroplasia and promotes neovascularization in wounds. Chemotherapeutic agents slow down the entry of cells into the wound, lessen the generation of collagen, slow down fibroblast proliferation, and prevent wound contraction.^[14,18]

Impaired Wound Healing in Diabetes :

Diabetes has a complicated pathophysiology that includes vascular, neuropathic, immunological, and metabolic elements that leads to impaired recovery.^[3] Stiffer blood arteries associated with hyperglycemia result in slower blood flow and microvascular dysfunction, which results in less tissue oxygenation. Diabetes patients' blood vessel changes also explain why fewer leukocytes migrate to the site, making it more susceptible to infection.^[4] Even the presence of high blood glucose level can impair leucocyte performance. Peripheral neuropathy can also cause numbness and a decreased capacity for pain, which can result in the chronicization of wounds that are not promptly identified and well treated.^[4] As a result of atherosclerosis, compromised function of different skin cells, and peripheral neuropathy, hyperglycemia in DM patients might lead to defective healing of wound as well as the formation of DFUs. Although diabetes' vascular problems have also been linked to hypoglycemia. Hyperglycemia promotes atherosclerosis, which prevents circulating nutrients from getting to wounds and slows healing. Furthermore, it has been discovered that hyperglycemia in DM patients may contribute to endothelial cell dysfunction, which is essential for the repair of DFUs. Along with endothelial cells, hyperglycemia also impairs keratinocyte and fibroblast migration, proliferation, and protein synthesis, all of which are essential for re-epithelialization. Due to diminished enzyme action of the antioxidants, glutathione peroxidase and superoxide dismutase, free radical damage is another way that hyperglycemia hinders the healing of wounds. ROS (Reactive oxygen species) can also be produced by hyperglycemia via the protein kinase C, polyol, hexosamine, and AGE pathways. Although it is known that ROS are necessary

for the early (initial) phases of wound healing, it has been demonstrated that later wound healing stages are negatively impacted by an imbalance in the generation of ROS. Increased ROS concentrations can specifically harm peripheral neurons' metabolism, blood flow, and

structural integrity. This can cause autonomic, motor or sensory dysfunction in the nerves that are damaged, and each impairment increases the chance of developing a DFU in a different way.^[11,15,16]

Pathophysiology Associated with Diabetic Wound:

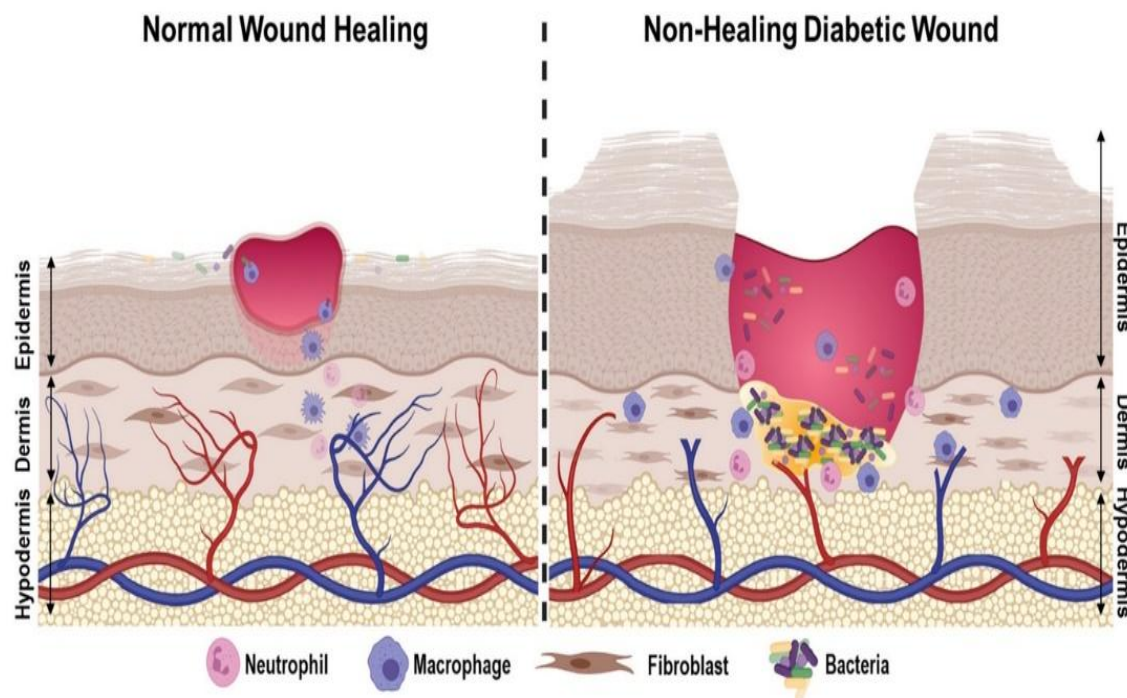


Figure 4: Pathophysiology of diabetic wounds.

1. Neuropathy :

Sensory, motor, and/or autonomic neuropathies can all individually contribute to impeded DFU healing in addition to raising the likelihood of DFU formation. For instance, autonomic neuropathy causes sweat gland activity to diminish, resulting in dry, cracked skin that is more susceptible to pruritus and infection, both of which slow the healing of wounds. Diabetes neuropathy is related with pruritus for unknown reasons, along with dry skin and impaired circulation. The pressure on the foot's plantar surface is increased by motor neuropathy, which causes tissue ischemia and death. Neuropathic skin has generally a lower neuronal density and shows slower skin regeneration.

2. Microvascular Complications :

Peripheral Arterial Disease: Patients with DFU frequently have peripheral artery disease (PAD), which worsens outcomes and raises the likelihood of limb amputation. In a cross-sectional research, 43% of DFU cases had PAD. Comparing Charcot foot patients retrospectively revealed a high prevalence of PAD, which was anticipated by the existence of DFUs.

Hypoxia: DFUs naturally lead to hypoxic conditions as a result of DM patients' impaired circulation. Different skin cell populations exhibit variable gene expression in a

hypoxic environment. Endothelial cells and differentiated macrophages encode genes for angiogenesis, cytokines, and growth factors, while keratinocytes and dermal fibroblasts exhibit altered gene expression for cell metabolism proteins, according to research by Alessandro et al. making use of a cell culture model. A recent study using a cell-culture-based model to assess skin hypoxia discovered that reduces levels in DFUs were associated with problems and a worse prognosis for healing.

Anemia: Anaemia has been found to be common in individuals with DM, particularly when DFUs are present, according to recent investigations. On the relationship between anaemia and the prognosis for DFU, however, there are contradicting results. According to a meta-analysis, increasing anaemia severity was linked to DFU severity and may be a predictor of mortality and amputation. Anaemia was discovered to be significantly linked to deeper, larger ulcers, more serious infections, a higher risk of amputation, and higher mortality rates in retrospective cohort studies, while observational studies in Nigeria found anaemia to be linked to poor wound healing, amputation, and higher mortality. The scenario in which anaemia may be a predictive factor for DFU (Diabetic Foot Ulcer) wound healing is still disputed and needs additional clarification because other research found anaemia to be a non-

significant predictor of clinical outcome for patients with DFUs.^[10]

3. Barrier Disruption and Infection :

TEWL (Transepidermal Water Loss) : Age-related changes in the skin include a decrease in lamellar body secretions, lipid depletion, a slower rate of barrier repair, and an increase in TEWL. Despite the fact that the stratum corneum's water content declines with ageing, the lipid content, stratum corneum hydration, and AGE levels of diabetic skin reported to be strikingly similar to those of old skin. However, while some studies revealed no significant changes in TEWL (Transepidermal Water Loss), others found an increase. Horikawa et al.'s recent mouse model study comparing dryness of skin in type 1 and type 2 diabetes mellitus (DM) discovered that type 1 diabetes increased AGEs and matrix metalloproteinase-9 (MMP-9), which resulted in a decrease in collagen IV, whereas type 2 diabetes decreased hyaluronic acid levels and increased inflammatory cytokines levels. Skin moisture was discovered to be a significant predictor of wound healing when tested before therapies like recanalization and appeared to be connected with microcirculation. Additionally, by altering tight junction protein 1's distribution, altering the histology of the epidermis, and altering the ultrastructure of the basal cells, which all interfere with the normal operation of the skin barrier, hyperglycemia raises the possibility of infection.

Antimicrobial Peptides: Dermal fibroblasts can develop into adipocytes in response to *Staphylococcus aureus* infection in healthy skin, producing cathelicidin (LL-37), which has also been shown to speed up wound healing by promoting keratinocyte migration and angiogenesis. However, DFUs produce very little to no cathelicidin, which results in the phenotype of impaired wound healing. Human defensin expression has been shown to be increased in DFUs, but it has been suggested that subsequent AMP synthesis is insufficient for microbial regulation. To make matters even more difficult, it has been demonstrated that common diabetes medications, including metformin, which has been found to downregulate RNase 7, can affect AMP synthesis. Diabetes creates a milieu that is less favourable for wound healing due to low AMP synthesis, indications of elevated AGEs, poor lamellar body generation, and decreased stratum corneum lipid content.

Bacterial Diversity: The characterisation of the diabetic skin and microbiome has increased with the introduction of high-throughput technologies including 16S rRNA sequencing, microarrays, and whole-genome sequencing. There is mounting evidence of microbiome dysbiosis in diabetics' gut as well as skin, which may aid in the progression and consequences of diabetes. *S. aureus* as well as *S. epidermidis* have both been found to colonise the skin more heavily in diabetic individuals. The most frequent

bacterial colonisers were discovered to be *Staphylococcus*, *Pseudomonas*, and *Enterobacteriaceae* in a recent study of German patients with DFUs.

pH and Microbiome : While there has often been no discernible difference in the pH of intact skin between diabetics and controls, one study found a somewhat higher skin pH in the intertriginous regions of diabetics. The intricate host-microbiome interaction is facilitated by the substantially more alkaline wound environment of DFUs compared to acute wounds. Alkaline pH conditions boosted biofilm development in a test of various bacterial strains, including *Pseudomonas*, with pH also showing variable effects on bacterial resistance to drugs.^[12]

4. Inflammation and Immune System Deficiency in Chronic Wounds :

Hemostasis, inflammatory proliferative & remodelling are the four overlapping stages of the healing dynamics in acute wounds. Chronic wounds like non-healing DFUs, which result from disruption of each stage of wound healing, can develop in diabetics among other issues. First, unlike acute wounds, DFUs are characterised by the non-resolving inflammation phase, where a large number of neutrophils and macrophages are found in the wound bed, as well as the chronic release of proinflammatory cytokines including interleukin (IL)-1, IL-6, tumour necrosis factor (TNF)- α , and plasma C reactive protein, and bacterial proliferation being the most explored factors that contribute to the impaired healing process. Another characteristic of DFUs is a condition of chronic hypoxia brought on by insufficient angiogenesis. This state is exacerbated by ongoing inflammation, which leads to an increase in ROS and a defective healing process.^[17]

The Function of Medicinal Plants in Diabetic Wound Healing :

Numerous plant and herb species with wound-healing properties have been discovered in Africa and other emerging countries as a result of ethnobotanical research. Cleaning, debridement, and creating an atmosphere that is conducive to a natural healing process are all part of the management and care of wounds using medicinal plants.^[5] The increased and renewed interest in the use and application of medicinal (herbal) plants in the process of wound healing, both in diabetic and non-diabetic conditions, is due to the assumption that ingredients from medicinal plants are less toxic and have fewer side effects compared with orthodox therapeutic agents. Health professionals around the world view the impairment of diabetic wound healing as a serious health challenge, and in some cases, this is linked to the non-specific aetiology. As a result, one therapeutic approach to treatment is the application of medicinal plants, especially in settings with limited resources.^[13,18,19]



Figure 5 :Medicinal plants used in diabetic wound healing.

1. Carica papaya :

There have been claims that *C. papaya* extract exhibits antibacterial, antioxidant, and anti-inflammatory properties. Nayak et al. examined *C. papaya*'s ability to treat wounds in an animal model of diabetes.

2. Rosmarinus officinalis :

This plant is well-known for its antibacterial and antioxidant properties. AbulAl-Basal used an animal model to investigate the healing potential of a plant extract on full-thickness excision cutaneous wounds in mice with alloxan-induced diabetes. When topically applied to the wound of diabetic mice, the essential oil from the aerial parts of the plant demonstrated superior significant healing effect over the aqueous extract, and the wound healing potential of the plant could be linked to the strong antimicrobial, anti-inflammatory, and antioxidant activities of the plant.^[5]

3. Radix Rehmanniae :

In traditional Chinese medicine, *Radix Rehmanniae* is said to aid in the treatment of foot ulcers. In order to examine the *Radix Rehmanniae*'s effects on wound healing in a diabetic foot ulcer animal model.

4. Annona squamosa :

Custard apple is another name for *Annona squamosa*. It is grown in India, where locals treat diabetes and other illnesses like fever and ulcers with the leaves and seeds. The effectiveness of the plant's ethanolic/alcoholic extract of leaf

on wound healing in streptozotocin (STZ)-induced diabetic rats was evaluated by Ponrasu and Suguna.

5. Catharanthus roseus:

C. roseus, sometimes known as *Vinca rosea*, is a shrub native to Madagascar with distinctive purple or white flowers. Numerous phytochemicals dispersed throughout the plant have been related to the plants' hypoglycemic properties. Nayak examined how the ethanol extract of *C. roseus* affected the rate of wound healing in diabetic rats.

6. Centella asiatica :

Ayurvedic, traditional African, and traditional Chinese medicine all use *C. asiatica* as a common medicinal herb. It has been shown to enhance collagen production and fibroblast proliferation. On the third day following the creation(induction) of diabetes, excision wounds were produced by Nganlasom et al. In the experimental rats, the skin of the dorsal flank was sliced on the left side. Following anaesthesia, excision wounds were created by removing a 15 mm by 15 mm square of skin from the area that had been shaved. The study found that *C. asiatica* could speed up wound healing in an animal model of diabetes, but more research is needed to pinpoint the precise components that are responsible for the healing effects.

7. Acalypha langiana :

The leaves of the herb *Acalypha langiana*, which grows in the wild, have been employed in traditional medicine to treat wounds and bacterial infections. The healing process in diabetic rats was significantly and dose-dependently

affected by the topical administration of the aqueous leaves extract of *A. langiana*. Particularly, using the extract, the tensile strength was greatly increased. of incision wounds. Additionally, the findings show that in comparison to control wounds, tissue regeneration occurred substantially more quickly in granulation tissue sections in the extract-treated group.

8. *Hylocereus undatus* :

The huge, fragrant blossoms on this plant, which is widely dispersed throughout Brazil and only blooms at night, are thought to have significant culinary and traditional medicinal uses. Its leaves and blossoms, specifically, are utilised as a hypoglycemic agent. to evaluate the plant's capacity for wound healing. The research proved that topical application of both aqueous leaf and floral extracts resulted in considerable wound healing activity.

9. *Punica granatum* :

The flowers of *P. granatum*, a significant Middle Eastern medicinal plant, are used extensively to treat wounds and function as antibacterial, antifungal, and antiviral agents. *P. granatum*'s impact on diabetic animals' wound healing.

10. *Aloe vera* :

Different civilizations all over the world have recognised and employed *A. vera* in traditional medicine to treat a variety of illness conditions. It has been demonstrated to have antibacterial, anti-inflammatory, and anti-diabetic effects. *A. vera* extract has been shown to speed up wound healing in diabetic patients, which shows that *A. vera* treatment may have positive effects on the different stages of wound healing like fibroplasia, collagen production, and contraction.

11. *Martynia annua* :

This annual herb with glandular hairs is mostly used to treat epilepsy and TB. Additionally, it is used to treat wounds, inflammation, and sore throats. After STZ injection-induced diabetes was produced in Wistar rats, an excision wound was formed. When compared to the wounds in the control group, the extract-treated wounds were seen to significantly contract. Additionally, it was discovered that the hydroxyproline concentration of animals given plant extract was much higher than that of control animals. In mice given *M. annua* extract, histological analysis exhibited a rise in fibroblast cells and well-organized collagen fibres.^[18,19]

Current Advances in Diabetic Wound Healing :

DFUs continue to be a clinical issue because of the complicated pathophysiology of diabetic wounds. Standard of care treatments for wounds include debridement, offloading, glycemic control, and infection control, whereas advanced treatments include hyperbaric oxygen therapy (HBOT), wound dressings, negative pressure wound therapy (NPWT), and growth factor therapies such as platelet-rich plasma, stem cells, and cell- and tissue-based products. Given the clinical requirement, stimuli-responsive and

multifunctional therapeutic approaches that might hasten the healing of diabetic wounds are anticipated to play a significant role in diabetic wound management in the future.^[22]

1. Debridement :

Debridement of the wound bed is a common procedure that, among other things, improves the efficiency of the immune system and lowers bacterial burden, including biofilm. While bacterial biofilms in acute wounds serve as a mechanical barrier and an inherent step in the healing process, unchecked biofilm production in DFUs can lead to multidrug resistance and hinder the healing process. The standard of care for DFUs includes surgical debridement of wounds, which is believed to enhance healing by eliminating non-viable tissue and may combine synergistically with other concurrent treatments.

2. Hyperbaric Oxygen Therapy :

Recent research has highlighted that HBOT can be effective for treating patients with Wagner grade 3 and 4 ulcers, showing a concurrent improvement in HbA1c, leukocyte levels, and serum creatinine. This is true despite the lack of numerous high-quality trials in the use of HBOT. Accelerated wound healing and a considerable drop in MMP-9 levels were discovered in a study utilising a diabetic mouse model. Long-term hyperbaric oxygen therapy has also been demonstrated to lessen neutrophil recruitment and adhesion, boost oxygen delivery to injured tissues, lessen inflammation, and speed healing in diabetic ulcer patients. Topical oxygen therapy, as opposed to HBOT, has recently been proven in studies to promote an aerobic wound microbiota and healing in DFUs.

3. Negative Pressure Therapy and Off-Loading :

Results from recent randomised controlled trials evaluating the efficacy of NPWT in the management of DFUs have been conflicting. In more challenging surgically treated DFUs, landmark studies revealed that using NPWT before a wound closure therapy improved overall healing. However, a recent study demonstrated no appreciable distinction between NPWT and conventional moist wound care in terms of wound closure. Leukocyte count, discomfort, and systemic inflammatory response were all considerably reduced during therapy with NPWT; discharge criteria and granulation tissue also appeared noticeably sooner. The standard treatment for patients with DFUs that has been the most thoroughly researched and tested is off-loading. Reducing high plantar foot pressure in particular as part of the treatment may assist to avoid the development of ulcers. Because walking with elevated plantar pressures has been linked to the occurrence of ulcers, this is crucial for patients with neuropathy. According to several research, surgical off-loading considerably improves the healing and amputation rates for patients with DFUs as compared to non-surgical treatment.

4. Growth Factor-Based Therapies :

Growth factors, such as keratinocyte growth factor (KGF)-2, platelet-derived growth factor (PDGF), basic fibroblast growth factor (FGF), epidermal growth factor (EGF), and others, have long been thought of as potential strategies in diabetic wound healing and have shown promise in small animal models of diabetic wound healing. This is because they are involved in practically every stage of wound healing and are generally dysregulated in chronic wounds. After 5–14 weeks of therapy, NGF supplementation has also shown some promise in promoting recovery; however, the data were from a relatively limited sample size. Becaplermin (0.01% Regranex® gel), a topical growth-factor (GF)-based treatment, is the only one with FDA approval that effectively promotes DFU healing. Despite showing encouraging outcomes in small animal models and in vitro, all but one growth factor therapy ultimately failed to be effective in speeding diabetic wound closure for a variety of reasons.

5. Hydrogels/Matrices/Dressings and Skin Substitutes :

Using dressings together with a variety of subsequent treatments is a typical protocol for treating DFUs. Various forms of hydrogels made from adipose-derived stem cells, MSCs (mesenchymal stem cells) from bone marrow, and human adipose stem cells containing hyaluronic acid have been used recently. Studies utilising both mouse models and human subjects have shown that the combination of extracellular matrix and stromal vascular fraction gels increased collagen formation and neoangiogenesis in addition to improving healing. In the United States, there are 76 skin substitute products now on the market, the majority of which are acellular and manufactured of decellularized cutaneous, placental, or animal tissue, according to a recent study by the Agency for Healthcare Research and Quality. For bioengineered skin substitutes with live cells, the best, highest quality clinical data are available. When compared to standard of care, meta-analyses have shown that skin substitute therapy of DFUs resulted in a quicker time to wound healing and a lower amputation rate.

6. Platelet Gels and PRPs :

For more than 30 years, it has been documented that using autologous platelet-rich plasma (PRP) and platelet gel products can hasten the healing of chronic wounds. This is caused by a number of growth factors, such as PDGF, TGF- β 1, and EGF, as well as antimicrobial actions that promote tissue regeneration, cell proliferation and differentiation, degranulation, and chemotaxis. Even though allogeneic-PRP is an efficient and secure treatment for diabetic chronic wounds, it has received substantially less research than autologous-PRP. PRP is currently mixed with various activators and used as gels or injection therapies, such as when platelet-enriched fibrin is coupled with collagen-based dressings.

7. Stem Cells Therapy:

Recently, there has been a lot of interest in the use of stem cells in the treatment of DFUs. Adipose, umbilical, bone-marrow and smooth-muscle derived stem cells, as well as combination therapies with MSCs, have all been demonstrated to hasten wound healing in murine diabetes models. In randomised controlled studies of autologous stem cell therapy, decreased amputation rates and improved wound healing were seen. Stem cells may be the next generation of treatments for DFU wound healing given their recent rapid progress.^[22]

CONCLUSION:

Hemostasis, inflammatory, proliferative, and remodelling are all components of the intricate biological process of wound healing. This process involves numerous cell types, including as neutrophils, macrophages, lymphocytes, keratinocytes, fibroblasts, and endothelial cells. One or more stages of the process can be impacted by a variety of variables, which can result in impaired wound healing. Although there has been a tremendous advancement in our understanding of the mechanisms behind diabetic wound healing, there are still unmet demands in the therapeutic management of diabetic wounds. Diagnoses could be made more quickly, more easily, and more affordably if the variations in wound status were better understood. Smart wound dressings, hydrogels, and other technologies can enable personalised care and treatment of diabetic wounds. Due to the fact that patients frequently underestimate the severity of their wounds, close monitoring and prompt therapies based on these technologies may be able to stop non-healing wounds from getting worse. There is an increasing demand for management of chronic wounds as the number of diabetic patients rises, and more study is required to learn how to speed up the healing of diabetic wounds and enhance patients' quality of life. This research reports on the notable efficacy of medicinal plants' wound-healing properties in diabetic patients. The effectiveness and safety of various medicinal (herbal) plants and their mechanisms of action (MOA) on diabetic wound healing call for more investigation and clinical trials.

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