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Effectiveness of Herbal Extraction for Wound Healing on Diabetic Foot Ulcer

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Abstract:- A serious consequence of diabetes mellitus, diabetic foot ulcers (DFUs) may result in chronic, non-healing sores and increased morbidity. As a result of their resistance to traditional wound healing therapy, DFUs provide a substantial management problem in the healthcare industry. Diabetic foot ulcers (DFUs) pose a significant clinical challenge due to their slow healing and potential for severe complications. Untreated diabetic foot ulcers can result in serious side effects such osteomyelitis, and, in extreme situations, gangrene, which might need amputation. Cleaning the wound, debridement (the removal of dead tissue), infection control, relieving pressure from the affected area, and other measures are frequently used to treat diabetic foot ulcers. Recent years have seen a rise in interest in herbal-based formulations as potential replacements for DFU wound healing. As the wound heals, several herbal ingredients may help to decrease scarring. The purpose of this review is to determine if a unique herbal extraction can effectively promote wound healing in individuals with diabetic foot ulcers. It's essential for wound healing to maintain the proper amount of moisture around the area. Herbal extracts can assist in controlling moisture and maintaining a healing-friendly environment around the area. Many herbal extracts with anti-inflammatory, antibacterial, and tissue-regenerating effects have been exposed as components in wound healing gels and cream form.

Keywords:- *Diabetic foot ulcers (DFUs), DFU wound healing, debridement, anti-inflammatory, antibacterial.*

I. INTRODUCTION

A typical chronic condition is diabetes mellitus. One of the most harmful effects of diabetes is diabetic foot ulceration (DFU). The three main factors that contribute to foot and lower leg ulcers are poorly controlled diabetes, distal circulation issues, and neurological impairment. Amputations of the toes, a portion of the foot, or the lower leg may be necessary in severe situations [1]. There are 422 million people with diabetes mellitus globally, and it is thought to be the cause of 2 million fatalities per year [2]. Amputation of the ulcerated foot is necessary in 14%–24% of diabetics who develop one of these ulcers over time due to complications such bone infection or other ulcer-related issues. Around 15% of people with diabetes will eventually develop one of these ulcers [3]. Neuropathy, which includes distal symmetrical polyneuropathy (DSPN), mono-neuropathies, and a number of autonomic neuropathies that include erectile dysfunction, urine incontinence, gastroparesis, and nocturnal diarrhoea, affects more than 60% of diabetes patients.

Diabetes mellitus accounts for about 50% of all non-traumatic amputations worldwide due to accelerated lower extremity vascular disease and neuropathy. In people with diabetes, the risk of cardiovascular problems is elevated by a factor of two to six. Because of the higher mortality from diabetic complications, the life expectancy is often 7 to 10 years shorter than for persons without diabetes mellitus. In both type 1 diabetes and type 2 diabetes, many prospective clinical investigations demonstrate a high correlation between glycemia and diabetic microvascular problems [4] [5]. When localized foot issues such as swelling, skin discoloration, discomfort, drainage, or ulceration initially emerge, DFUs should be considered [6] [7].Cellulitis, myositis, abscesses, necrotizing fasciitis, septic arthritis, tendinitis, and osteomyelitis are among the several infection forms. All diabetic patients should expect thorough foot assessment and examination as a standard aspect of their care. More than half of patients with insensitive feet have no prior history of neuropathic symptoms, thus the clinician should never only depend on the emergence of symptoms to identify high-risk individuals [8].

Most diabetic foot infection (DFI) have a neuropathic DFU as their primary etiology. Therefore, the development of a DFU is frequently one of the first stages in the pathogenesis of DFI. The most important risk factor for DFU production is neuropathy (autonomic, sensory, and/or motor), which is brought on by long-term, poorly managed hyperglycemia [9].

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II. PATHOLOGY OF DIABETES MELLITUS

A. World Scenario

According to estimates from the World Health Organization (WHO), type 1 and type 2 diabetes, but not gestational diabetes, affected around 3% of the world's population in 2000[10].The Gulf States have prevalence rates comparable to Saudi Arabia's, while 20 of the 22 countries in the Earthquake Model of the Middle East (EMME) region have rates that are higher than the global prevalence rate of 6.4% from 2010. Most diabetics in underdeveloped nations are between the ages of 45 and 64 [11].

In comparison, it was >64 years old in wealthy nations. In developing countries, there will be over 82 million diabetics over the age of 64 by 2030, compared to over 48 million in industrialized nations. According to the most recent estimates, which are based on the advice of local experts, the prevalence of diabetes in rural areas of Bangladesh, Bhutan, India, the Maldives, Nepal, and Sri Lanka is considered to be one-quarter that of urban areas [12].

B. Indian scenario

Between 1989 and 1991, the country's rural populations participated in the National Rural Diabetes Survey, which revealed a prevalence of diabetes of 2.8%.[13].A cross-sectional population survey was conducted in Kashmir Valley in 2000, and the prevalence of "known diabetes" was 1.9% among persons over the age of 40 [14].In the National Urban Diabetes Survey (NUDS), 11,216 individuals representing all socioeconomic strata who were at least 20 years old and living in six major Indian cities (Delhi, Mumbai, Kolkata, Chennai, Hyderabad, and Bangalore) were recruited [15].

An extremely high prevalence of 19.5% was found in the Amrita Diabetes and Endocrine Population Survey (ADEPS), a community-based cross-sectional survey conducted in urban areas of Kerala's Ernakulum district. Diabetes Prevalence in India Study (PODIS). In 77 centers (40 urban and 37 rural) across India, a multicentric cross-sectional population survey was conducted to ascertain the prevalence of diabetes mellitus and impaired glucose tolerance in subjects aged 25 years and above. There were 18363 patients in all (905 females and 9008 men). Urban regions contributed 10617 (5379 men and 5238 women), whereas rural areas contributed 7746 (3629 men and 4117 women). In the entire Indian population, urban and rural, the prevalence rates for DM were 4.3 and 5.9, respectively.

The corresponding IGT rates were 5.2, 6.3, and 3.7% in the three populations, respectively. In this study, the prevalence of DM and IGT was considerably higher in the urban population than in the rural population (P 0.001 in both cases). In both rural and urban groups, the prevalence of DM was substantially higher than that of IGT (P 0.001) [16]

C. Pathology Diabetic Foot Ulcer (DFU) in People with Diabetes

Compared to other long-term consequences of diabetes, foot issues in diabetic individuals are the leading cause of hospital admissions and are associated with rising morbidity and death.A multitude of illnesses are included in the diabetic foot syndrome, such as diabetic neuropathy, peripheral vascular disease, Charcot neuroarthropathy, foot ulceration, osteomyelitis, and the possibly avoidable end point amputation. Patients who have diabetes might have many diabetic complications, and their care may involve paying attention to a variety of different things. According to the Centers for Disease Control and Prevention (CDCP) in 2003, the prevalence rate of foot ulcers in the United States was as high as 11.6%. In the USA, a population-based study revealed a prevalence rate of DFU of 10.6% and an incidence rate of 2.2% annually [17]

III. PATHOGENESIS OF DIABETIC FOOT ULCER

The complex pathology of DFU is caused by a number of causes, namely diabetic microangiopathy and neuropathy [18][19]. Due to decreased tissue perfusion brought on by diabetic microangiopathy, the foot is more vulnerable to infection, weakened local defenses, and delayed healing.

As a result of diabetic neuropathy, particularly sensory loss, the foot is more vulnerable to frequent trauma and improper foot care. Infected tissue is prone to glycaemic metabolic disturbance. Type 2 diabetics are more likely to develop diabetic ulcers in the lower extremities, neuropathy, and long-term problems of vasculopathy as a result of peripheral insulin resistance [18][20]. Key molecular regulators that control wound healing, including as growth factors, chemokines, and cytokines, are produced by the wound on its own.[21]. Chronic wounds are unable to go through the remodelling phase of the wound healing continuum because they are locked in the proliferative stage.

Chronic wounds have strong inflammatory cells, high protease and cytokine activity, and low mitotic activity [21][22].Senescent cells within these wounds are unresponsive to signals intended to remove inflammation and promote epithelization [21][23].

Extracellular matrix (ECM) synthesis is hampered by the exudate's antiproliferative nature [22].Additionally indicative of infection in chronic wounds and contributing to non-responsiveness are undermining of the edges, friable granulation tissue, bad Odor, or exudative floor [21].Similar to acute healing wounds, bed preparation for chronic wounds should concentrate on enhancing the molecular and cellular surroundings to promote the natural healing process [21][24].A complex protective matrix called a biofilm is made up of bacterial colonies and different extracellular polymeric materials, such as sugars, lipids, and glycocalyx. It has properties that are both sticky and protective to the environment and the immune system [25][26].The development of bioburden is facilitated by biofilm, which in turn enables the biofilm to further stabilize, adhere, and advance. Additionally, biofilms (which abnormally infiltrate neutrophils and produce large amounts of proteases and reactive oxygen species as a result) help chronic

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inflammation persist [27][28].Additionally, it makes it easier for antimicrobial resistance to spread horizontally. Additionally feeding the biofilm is wound exudate [27].In addition to the conventional definition, biofilm presents a challenge for detection and clearance assessment. Clinical evaluation can validate these problems. Physically removing biofilm from the skin reduces bioburden and localized chronic inflammation, transforms the chronicity into a supportive environment for active healing, and enhances the effectiveness of antimicrobials.

Due to the varying effects of topical medications like silver, cadexomer, polyhexamethylene biguanide, etc., medicines or phytochemicals with hygroscopic or surfactant action are being evaluated [25][27].Controlling hyperglycaemia and concomitant nephropathy and vasculopathy typically requires systemic therapy. With the primary goal of reestablishing the balance of important molecular regulators, wound management in DFU is specifically adjusted based on the TIME (Tissue control, Infection/inflammation, Moisture balance, Edge of the wound) concept. TIME is an acronym for tissue regulator, infection/inflammation complicated, moisture-exudate balancing, epithelial growth, and wound surgical operation and scrubbing [21][25].

Numerous studies have been conducted on various facets of DFU (microbiota, hazards, protection, control, burden, result, newer trials, etc.), and there is an abundant supply of both traditional and cutting-edge wound-care items. Regardless of the dressing material selected, the primary purpose will always be to reduce the bioburden. The effectiveness of one dressing material over others in aiding wound healing has not yet been established [28][29].

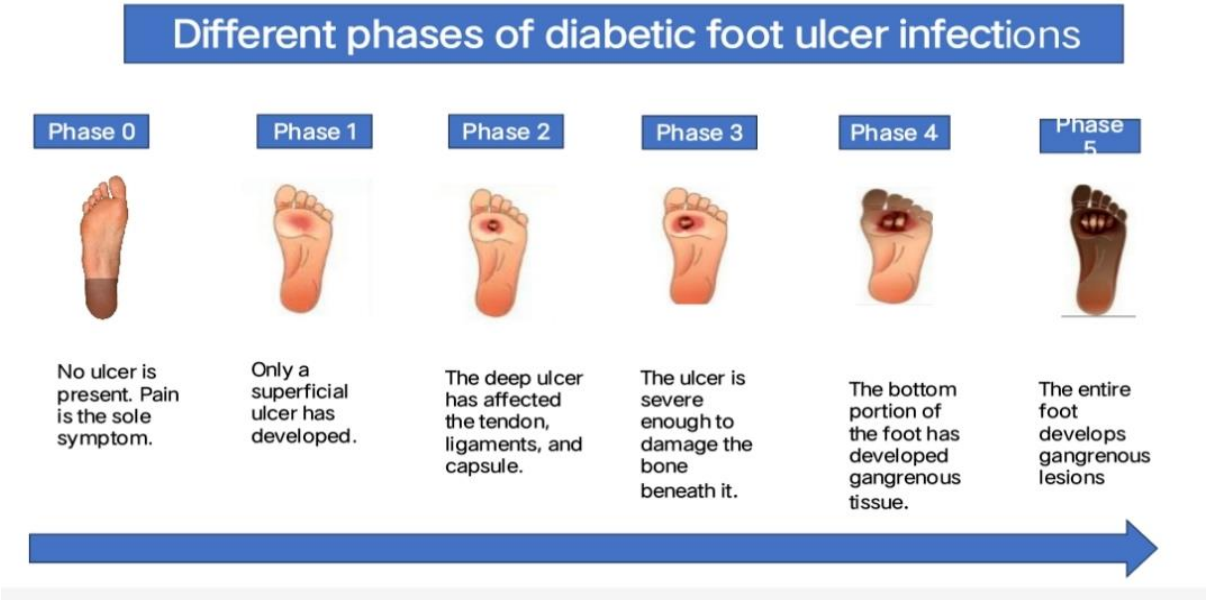

Fig. 1: Different phases of diabetic foot ulcer infections

IV. TREATMENT OF DIABETIC FOOT ULCER

The three main issues that must be handled in the therapy of DFUs are

- Surgical debridement
- Wound off loading and
- Infection control [30][31][32]

A. Surgical debridement

Debridement of a wound entails the removal of all necrotic and devitalized tissue, as well as the callus that has formed around it.

This procedure lowers plantar pressures in callused sites and promotes the production of granulation tissue and re-epithelialization [31]. Debridement is crucial for infection prevention as well since devitalized tissues operate as a breeding ground for bacteria, a physical barrier to antibiotics, and a restriction on the immune system's ability to combat infection [33].

B. Wound off loading

Using a wheelchair or crutches to completely reduce weight bearing on the affected foot is the most efficient way to unload when treating a foot ulcer. Total contact casts are challenging and time-consuming to apply, yet they have been shown to considerably reduce wound pressure and heal 73–100% of all wounds.

C. Infection control

In limb-threatening diabetic foot infections, polymicrobial infections are frequent. resistant bacteria to the drug methicillin There are several prevalent infections, including *Staphylococcus aureus*, -hemolytic streptococci, Enterobacteriaceae, *Pseudomonas aeruginosa*, and Enterococci. In mixed infections with aerobes, anaerobes such bacteroides, Pepto coccus, and Pepto streptococcus are rarely the only pathogens. Even though they can be seen in illnesses that also have aerobes. Infections are treated with antibiotics, which are antibiotics.

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V. HERBAL REMEDY FOR THE TREATMENT OF DFUs

Numerous herbs and plants have been found to have wound-healing properties, with both known and unidentified chemical compositions and processes [34].Debridement, disinfection, and the establishment of an environment supportive of natural healing are all included in the use of medicinal herbs in ulcer heal therapy and care. The growing interest in using medicinal plants and their use in wound healing, both in diabetic and non-diabetic conditions, is likely due to the fact that they are thought to be less toxic and to have less side effects than usual therapeutic medications [35]. Medical professionals from all around the world consider impaired wound healing in diabetes to be a serious health concern, and it is occasionally linked to an unidentified etiology. As a result, using medicinal plants for therapy is one of the therapeutic possibilities, especially in communities with limited resources. Here are a few plants with natural wound-healing abilities.

Fig. 2: Herbal remedy for the treatment of DFUs

A. *Azadirachta indica*

Azadirachta indica, a member of the Meliaceae family tree, has long been used in India to cure a variety of illnesses in both medicine and dentistry. Neem leaf had therapeutic qualities, according to phytochemical analysis. Nearly all components of the neem plant are used medicinally to treat diabetes, fever, infections, inflammation, and other conditions like skin illnesses and dental issues.Alkaloids, steroids, saponins, flavonoids, and tannic acids are all present in neem extract [36].Neem has been shown to have numerous pharmaceutical benefits, including antibacterial, anti-allergic, antifungal, and medical treatment [37].Neem extract's antibacterial activity has been proven in several tests, which were conducted on rats and other animals, to speed up the healing of DFU wounds [38].It also decreases inflammation and aids in the healing process [39].

B. *Actinidia deliciosa*

Actinidia deliciosa is a member of the Actinidiaceae family and consists of fruits. It has been proven that kiwifruit (*A. deliciosa*) has antibacterial and proangiogenic characteristics. Proteolytic enzymes (actinidin) and ascorbic acid are also present. In this study, the effects of kiwifruit on the recovery of neuropathic DFUs in clinical settings were examined. The ulcers were examined and rated based on their macroscopic, microscopic, and microbiological state. Before and after the treatments, biopsies of the ulcers were taken in order to perform histological and microbiological tests. It has been proven that kiwifruit (*A. deliciosa*) has antibacterial and proangiogenic characteristics. Ascorbic acid and additional proteolytic enzymes (actinidin) are also present [40]. Researchers looked into the effects of kiwifruit on the recovery of neuropathic DFUs in clinical settings. Actinidin and other naturally occurring compounds in kiwifruit, which contain protein-dissolving enzymes, enhanced several aspects of wound healing. Based on these benefits and safety considerations, we draw the conclusion that using kiwifruit to treat neuropathic DFUs is a simple,

flexible, and efficient strategy. To speed up the DFU healing process, numerous biological studies have been carried out and a variety of treatments have been investigated.

Over the past century, different herbal ulcer-healing remedies have been developed in Africa and Asia. The kiwifruit is a fruit that was first discovered in China, where it has been consumed for over 700 years. This fruit is thought to contain strong protein-dissolving enzymes that is actinidin, ascorbic acid (scavenging agent), antibacterial compounds, and hence can aid in the healing of ulcers. The kiwifruit has been shown to have established properties in ulcer debridement, angiogenesis, and disinfection in several in vitro and animal investigations [41].

C. Cotinus coggygria

One species of Cotinus coggygria Scop, an Anacardiaceae member, is found in Turkey [42]. The leaves of this plant have been employed in traditional Balkan and Anatolian medicine for antipyretic, antiseptic, antihemorrhagic, diarrhoea therapy, and wound healing [43][44]. It has been shown to have numerous pharmaceutical benefits, including antioxidant activity and anti-inflammatory activity [45]. By minimizing oxidative cell damage at the wound site, it might accelerate wound healing. The presence of phenolic components such as flavonoids, phenolic acids, and tannins in *Cotinus coggygria* may be the cause of the plant's wound-healing properties in diabetic rats. [46][47].

By scavenging free radicals created during the inflammatory phase, phenols can promote wound healing. Tannins promote wound healing by chelating free radicals, promoting wound contraction, increasing capillary vessel and fibroblast production, and boosting keratinocyte proliferation [48]. Flavonoids are typically recognized for their anti-inflammatory, antioxidant, and capacity to reduce lipid peroxidation properties [49].

D. Annona squamosa

All over India, Annona squamosa L. (Annonaceae), often known as custard apple, is grown primarily for its tasty fruit. The young leaves of A. squamosa and the seeds of Piper nigrum are traditionally used by tribes and locals in the Aligarh district and Chotanagpur districts of India to treat diabetes [50]. Additionally, it has antitumor, antifertility, and abortifacient effects. [51][52].Several flavonoids and a tetrahydroisoquinoline alkaloid with cardiotonic action were isolated from the leaves of A. squamosa [53].Aqueous *A. squamosa* leaf extract's partially purified flavonoids have antibacterial, insecticidal, and antioxidant properties [54].Cold aqueous extract has been shown to have anti-diabetic effects in type 2 diabetic mice treated with streptozotocin (STZ) and nicotinamide. The twigs of *A. squamosa* also have antiulcer properties [55].

Thangavel Ponrasu et al [56] observed that the effectiveness of an ethanolic extract from *A. squamosa* leaves on wound healing in diabetic rats caused by streptozotocin and nicotinamide. As a result of this study, he macroscopic examination of the wounds revealed that the *A. squamosa* treated groups required a total of 17 days (for non-diabetics) and 22 days (for diabetics) respectively for complete healing, whereas the control groups required a total of 23 days (for non-diabetics) and 28 days (for diabetics).

E. Aloe barbadensis

Lupeol, salicylic acid, urea nitrogen, cinnamomic acid, phenols, sulfur, vitamins, enzymes, minerals, lignin, and amino acids, as well as anthraquinones, dihydroxyanthraquinones, saponins, and aloin emodin, are clinical metabolites that provide to antibacterial, anti-inflammatory, and antioxidant actions [57][58].By using disc diffusion techniques, Nejatzadeh-Barandozi et al [57] and Danish et al [59] investigated the antibacterial impact against different Gram-positive and Gram-negative microorganisms.

Aloe vera acetone extracts were shown to be superior than ethanol or aqueous extracts, according to Nejatzadeh-Barandozi et al [57]. The zones of inhibition for acetone and ethanol extracts against Pseudomonas were 19 0.57 mm and 14 0.53 mm, respectively.With a zone of inhibition of > 13 mm at a dosage of 30 mg, ethanol extracts of aloe vera root and leaf showed strong antibacterial activity [59].Aloe vera distillate proved efficient against Gram-negative bacteria such *K. pneumoniae and P. aeruginosa* as well as methicillin-resistant MRSA and *Staphylococci* [60].Vancomycin only exhibited a 72.2% in vitro activity against *Pseudomonas*, but aloe vera had a higher in vitro activity against *Staphylococci* and *Streptococci* (75.3% vs. 80.5% of vancomycin) [61].According to Takzaree et al [62]., increased TGF- gene expression in the *aloe vera* gel-treated group caused fast angiogenesis, epithelialization, and granulation tissue development in rats.By the ninth day (P 0.0001), Daburkar et al [63] noticed that aloe-treated DFU had significantly larger amounts of glycosaminoglycans, quick wound closure, and improved breaking (tensile) strength.

F. Calendula officinalis

It is a flower from the Asteraceae (*C. officinalis*) family. A homoeopathic treatment for DFUs that has several benefits is calendula [64].This homoeopathic remedy is created from a flowering plant called "Pot Marigold." For treating DFUs, calendula works best when applied topically. Direct application of calendula gels or sprays to a DFU results in great results and accelerates wound healing [65].Calendula extract has advantageous anti-inflammatory, antioxidant, and anti-microbial effects. Because of this, the homeopathic medication aids in the treatment and prevention of infections in DFUs. Calendula helps the foot ulcer heal more quickly by reducing its unpleasant smell and encouraging the growth of new tissues. Natural substances include triterpene sapiens, triterpene alcohols (amyrins and faradiol), and flavonoids (quercetin and isorhamnetin) are found in calendula flowers [65].

Topical formulations' ability to block ultraviolet light is assumed to be a result of increased collagen formation in the subepidermal connective tissue. Calendula contains substances that promote the growth of new tissue and reduce inflammation in the healing process of wounds. Early research suggests that using a calendula spray in addition to

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standard care and hygiene can assist people with DFUs prevent infection and decreases Odor [66].In addition to fungi like Candida and Aspergillus, calendula has a broad antibacterial impact on a variety of Gram-positive and Gram-negative bacteria [67].

For the purpose of reducing ulcer size in diabetic individuals with leg ulcers, Carvalho et al [68] conducted a four-arm randomized control experiment. Calendula extract oil group, low-level laser therapy group, a combination of both, and a control group receiving normal medical care were the four groups, each with eight patients. The calendula group did not exhibit any discernible reduction in baseline wound size (pre- vs. post-treatment) at the end of 3 weeks. Both the laser group and the laser group alone produced statistically superior outcomes.

G. Persea americana

The avocado fruit, or *Persea americana* (P. americana), is a member of the Lauraceae family. Lutein (70% of the measured carotenoids) had the highest concentration of monounsaturated fatty acids in the fruit pulp [69][70]. Additionally, it is a good source of phospholipids, glycolipids, vitamin E, and A. Vitamin E is the main lipid-soluble antioxidant in the skin, and vitamin A is necessary for immune system function, cell differentiation, and epithelial development. Wound healing is aided by topical, oral, and systemic carotenoids as well as vitamin E. Additionally discovered to have wound-healing capabilities are phospholipid and glycolipid derivatives [71].

Methanolic leaf extracts of P. americana were tested against clinical strains of Pseudomonas aeruginosa and Escherichia coli by Ajayi et al. [72]. The research revealed that the extracts have strong antibacterial properties. According to the research by Ajayi et al. [72], secondary plant metabolites were responsible for the antibacterial effects seen.

H. Ageratina pichinchensis

The Asteraceae family member *Ageratina pichinchensis* is a crucial therapeutic plant in Mexican traditional medicine. Numerous in vitro and in vivo experiments have shown that the aqueous extract of *A. pichinchensis* has wound healing activities and protects skin damage against fungus infections [73].The primary processes underlying this plant's capacity to promote wound healing are its anti-inflammatory characteristics and impact on cell proliferation [74].Additionally, 7-O-(-D-glucopyranosyl)-galactin, a flavonoid derivative, is primarily responsible for the extract's pro-proliferative effects, suggesting that flavonoid structures are crucial for wound healing [75].A. pichinchensis was tested on 30 patients with DFUs in a randomized, double-blind, controlled, pilot research by Romero-Cerecero et al [76] to determine its effectiveness and safety as a topical wound healing agent.

Patients in the experimental group got the n-hexane/ethyl acetate extract of A. pichinchensis topically as a 5% cream formulation, while patients in the control group received 1% micronized silver sulfadiazine once per week. Compared to 69.8% of patients in the control group, 77.5% of patients in the intervention group had healed their wounds after 6 weeks. For the intervention group and the control group, the average time to wound healing was roughly 65 days and 77 days, respectively. All of these results were therapeutically useful even if none of them were statistically significant (P >.05).Clinically, they may be useful. An 11-day reduction in the time needed for wound healing would be advantageous for patients given the incapacitating effects of a DFU [76].

I. Rosmarinus officinalis

R. officinalis, a member of the Lamiaceae family, is used as medicinal plant. The antioxidant and antibacterial effects of this plant are widely known. 1, 8-cineol, camphor, -pinene, linalool, camphene, and limonene are the chemical components of the medicinal plant with potent anti-inflammatory effect [77].Terpenoids and polyphenols like carnosol, carnosic acid, and rosmarinic acid are the main bioactive compounds that have been isolated from both aqueous and organic extracts of the aerial parts of Rosemary with potential effect on inhibiting pathogenic growth, reducing inflammatory response, and preserving viable tissue [78][79][80][81].

By injecting alloxan intraperitoneally, male BALB/c mice were given diabetes. The mice were given 4 mm-diameter incisions on their backs when the presence of hyperglycaemia was confirmed, and they were then given one of four treatments: control, vehicle, aqueous extract, and essential oil.In comparison to the male BALB/c mice in the aqueous extract group, the essential oil group's mice shown healing, angiogenesis, and advancements in granulation tissue at various stages. [77]. Using R. officinalis oil topically applied to diabetic rats, another study found that both diabetic and non-diabetic animals increase in wound healing [82]. According to certain studies, *R. officinalis* aqueous extract applied topically accelerated the healing of DFU in rats' wounds [83][84].

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Table 1: Herbal remedy and their mechanism for treating DFUs

S.no	Family name	Common name	Scientific name of the plant and fruit	Significant components	Mechanism of action
1	Meliaceae	Neem	*Azadirachta indica*	nimbolinin azadirachtin, quercetin, sodium nimbinate, nimbidin, nimbidol.	Due to its antimicrobial properties, accelerates DFU wound healing. It also lessens inflammation and aids in the healing process.
2	Actinidiaceae	Kiwifruit	*Actinidia deliciosa*	lutein, beta-carotene, fisetin, ascorbic acid.	antibacterial and a characteristic that dissolves proteins (Debridement activity).
3	Anacardiaceae	Smoke plant	*Cotinus coggygria*	phenols, flavonoids and tannins	antioxidative, antibacterial, antifungal, antiviral, anticancer, antigenotoxic, hepatoprotective and anti-inflammatory
4	Annonaceae	Custard apple	*Annona squamosa*	Annotemoyin	Annotemoyin speeds up epithelialization, cellular growth, and collagen production**.**
5	Xanthorrhoeaceae	Aloe vera	*Aloe barbadensis*	Saponons, naftoquinones, anthroquinones, sterols and triterpenoids.	Aloe vera decreases swelling and pain while increasing blood flow to the site**.**
6	Asteraceae	Pot marigold	*Calendula officinalis*	Flavonoids, triterpenoids, essential oil and polysaccharides	It can be used to treat minor wounds, skin irritation reduce swelling, and inflammation.
7	Lauraceae	avocado fruit	*Persea americana*	Monosaturated fatty acid, leutin, Vitamin A and E, phospho and glycolipids.	The Persea Americana encourages collagen production during the proliferative stage of wound healing. Proteins, beta-carotene, lecithin, fatty acids, vitamins A and E.
8	Asteraceae	*snakeroot*	*Ageratina pichinchensis*	benzochromenes, benzofurans, glycosylated flavonoids, and terpenes	Effects on cell proliferation and anti-inflammatory properties, which also protect skin damage from fungus infections, help wound healing.
9	Lamiaceae	Rosemary	*Rosmarinus officinalis*	Terpenoids and polyphenols like carnosol, carnosic acid, and rosmarinic acid	Carnosic acid and rosmarinic acid reduce the inflammation of wound and facilitate wound contraction and re-epithelialization, regeneration of granulation tissue.

VI. CONCLUSION

DFU management and treatment continue to be difficult for medical professionals. The majority of ulcers are resistant to normal wound care, and treatment is quite expensive. Herbal remedies are preferable alternatives to pharmaceuticals for treating DFUs because to their safer profiles, lower costs, extensive availability, lower chance of adverse effects, and effectiveness with long-term illnesses. Herbal medicines work in a variety of ways that allopathic ones do not, which enhances the overall effects of wound healing. The ideal way to deal with the difficulties involved in the treatment of DFUs will be an alternative therapy using herbal remedy**.**

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