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Review Article

Recent advancement and future strategies for the care and management of diabetic foot ulcer complications: A systemic approach to Pharmacotherapy for successful wound repair and healing

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Abstract

Diabetic foot ulcer is a pathological condition of multifactorial etiologies. The condition occurs in diabetic patients where the proper management and care is not adopted. Some important factors responsible for diabetic foot ulcer include peripheral neuropathy, peripheral arterial disease, foot deformities, and trauma. Diabetic foot ulcers affect approximately 15% of all individuals with diabetes at some point in their lives. India is often referred to as the "diabetes capital of the world" due to its large population and the increasing prevalence of diabetes. The International Diabetes Federation (IDF) estimated that in 2019, there were over 77 million adults aged 20-79 years living with diabetes in India. The prevalence of diabetic foot ulcers varies across different regions of the world, with higher rates typically observed in areas with poorer access to healthcare, lower socioeconomic status, and higher rates of diabetes. Complications of diabetic foot ulcers can be severe, leading to infections, gangrene, and ultimately, amputations if not properly managed. Hence, prevention, early detection, and effective management are crucial in reducing the burden of this condition. Herbal therapies for diabetic foot ulcers (DFUs) focus on targeting key pathological mechanisms such as inflammation, oxidative stress, infection, angiogenesis, and tissue regeneration. Bioactive such as Curcumin Inhibits NF-κB pathway, reduces pro-inflammatory cytokines (TNF-α, IL-6), and enhances collagen synthesis there by shown to accelerate wound healing by modulating inflammation and promoting fibroblast migration, Alovera, increase collagen deposition, and improve angiogenesis, Epigallocatechin gallate (EGCG) scavenges reactive oxygen species (ROS), reduces lipid peroxidation, Neem inhibit bacterial growth (*Staphylococcus aureus*, *Pseudomonas aeruginosa*) etc. This review highlights the systemic approach for management, care and pharmacotherapy for diabetic wound repair and healing

Keywords: Diabetic foot ulcer, NF-κB pathway, inflammatory cytokines, foot deformities, trauma, advanced therapies

Introduction:

A diabetic wound refers to an open sore or ulcer that develops in individuals with diabetes. These wounds typically occur on the feet or lower extremities and are caused by a combination of factors such as poor circulation, neuropathy (nerve damage), and impaired immune function.[1]The prevalence of diabetes in India has been steadily increasing over the past few decades due to various factors such as changing lifestyles, urbanization, and an aging population.According to the International Diabetes Federation (IDF), in 2019, India had an estimated 77 million adults aged 20-79 years living with diabetes. This number is projected to rise to over 100 million by 2030.[2] The etiology of diabetic foot ulcers is multifactorial, involving a combination of neuropathy, peripheral vascular disease, and other factors. Considering diabetic neuropathy is a common complication of diabetes. It affects the sensory nerves, leading to reduced sensation in the feet .[3] Patients may not feel pain or trauma, allowing injuries to go unnoticed and untreated; eventually leading to ulcers. Similarly, diabetes can also lead to damage to the blood vessels, reducing blood flow to the feet. This impairs the body's ability to heal wounds, making ulcers more likely to develop and harder to heal.[4] Other complications include Charcot foot (a condition where the bones weaken and fracture due to neuropathy) or hammertoes can increase pressure on certain areas of the foot, leading to the formation of ulcers.[5] Several other factors also contribute to the formation and aggravation of diabetes i.e. uncontrolled blood sugar levels can impair the body's ability to fight infection and heal wounds, making diabetic foot ulcers more likely. Once an ulcer forms, it can easily become infected due to the compromised immune response associated with diabetes. Even minor trauma, such as a small cut or blister, can lead to ulcer formation and if unnoticed and untreated due to reduced sensation.[6]

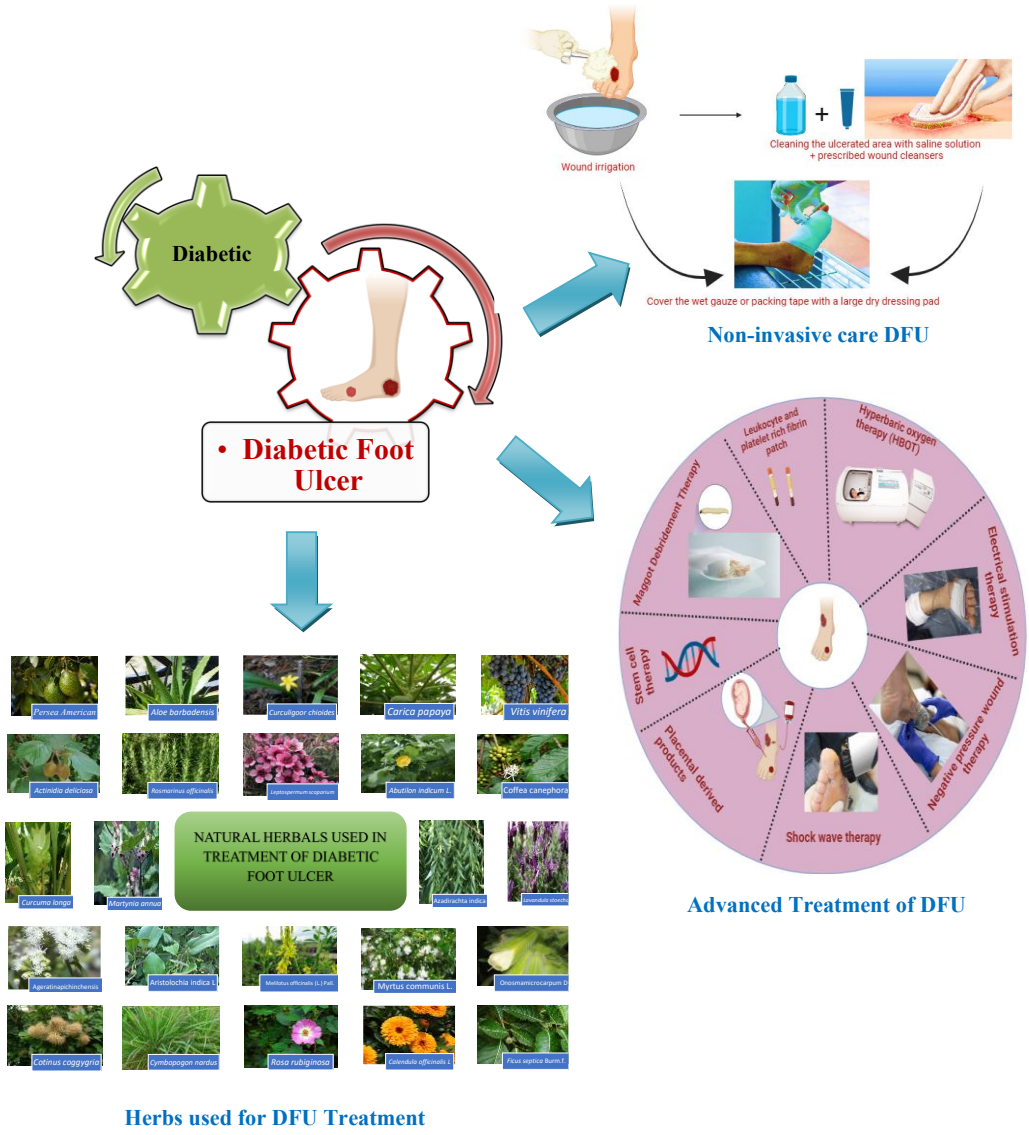


Figure 1: Graphical abstract of Diabetic Foot Ulcer

Etiology of DFU:

Peripheral vascular lesions:

Peripheral vascular lesions in diabetic foot ulcers (DFUs) are a significant complication often seen in patients with diabetes mellitus. These lesions result from a combination of peripheral artery disease (PAD) and the chronic hyperglycemic state characteristic of diabetes. Peripheral Artery Disease (PAD) includes atherosclerosis which is accelerated by diabetes and can leading to the narrowing and hardening of peripheral arteries.[7] Diabetes also leads to changes in the microcirculation, such as thickening of the capillary basement membranes, which further impairs nutrient and oxygen delivery to tissues.[8] Endothelial cells initiates to lose their ability to regulate vascular tone and maintain a barrier. These results decreased blood flow to the lower extremities impairs wound healing and increases the risk of infections.[9]

Peripheral Neuropathy:

Neuropathy is considered to be the most important determinant for occurrence of infection in diabetic foot wound. Among newly diagnosed patients of diabetes with DFU, almost half of the ulcers were neuropathic, 19.7% ischemic, 34.2% neuroischemic, and nearly 3% of subjects had history of minor or major amputation of extremities.[10]In individuals with diabetes, DFU does not develop spontaneously; factors such as loss of sensation due to neuropathy, structural deformities, and trauma contribute to DFU and studies from India showed that two-thirds of the DFUs are neuropathic in nature.Peripheral neuropathy reduces pain sensation, allowing minor injuries to go unnoticed and progress to ulcers.Impaired regulation of blood flow and sweating leads to dry cracked skin, increasing the risk of infection.[11]

Bacterial infection:

Patients suffered from Diabetic foot ulcer may infect with single bacteria or multiple bacteria. In case of single bacteria involved that mostly *S. aureus* and associated with mild infections where multiple bacteria includes Gram +ve*Cocci* such as *Enterococci, S. epidermidis as well as Staphylococcus Aureus.*[12] In severe infections of DFU, gram-ve microorganisms like *Pseudomonas spp, Escherichia coli* and *Enterobacter spp.*

were found associated.In case of polymicrobial infection, the combined effect of several multiple microorganisms and their resistance (antimicrobial) profile has been demonstrated to be associated with failure in the treatment leading to foot amputation .[13] Some scientific data revealed that, *Methicillin-resistant S. aureus* has been found in 16.8% of diabetic foot infections. Bacteria also possess natural intrinsic resistance mechanism and also demonstrated capability to acquire and develop resistance once exposed to antibiotics .[14] As there are much discrimination related to the use of antibiotics the bacterial resistance is accelerated that in turn precipitate many challenges for the effective treatments of DFU by using antibiotic therapy.

Epidemiology of Diabetic Foot Ulcer:

The probable risk of DFU in people living with diabetes is ranging between 15% and 25%.[15]According to the data available elsewhere, the annual incidence is approximately 3%. The prevalence of diabetes is expected due to the geographical variation as well as the socio-cultural factors that responsible for enhance the occurrence. The socioeconomic standard and education rate also affect the occurrence.[16] DFU has been considered as the major cause for hospitalization among patients with diabetes. As per the research data revealed, about 25% of admitted in patients are with diabetes. As the global prevalence of DFU is concern, some researchers keep their views to understand the intensity of DFU at different continents.[17] Zhang et. al. (2017) reported that, Belgium had the highest prevalence of Diabetic foot ulcer globally (16.6%). Global prevalence of foot complications includes 131.0 million people (1.77% of the global population) with diabetes-related lower-extremity problems.[18] It is higher in case of type 2 diabetes (approximately 6.4%) than compared to type 1 diabetes (approximately 5.5%). The prevalence of DFU in Canada was 14.8% and in the United States it was 13.0%. North America had the maximum prevalence of 13%. Similarly, Africa was prevalence of 7.2%, Asia was 5.5% and Europe was 5.1%. In India, out of 62 million diabetics, 25% develop DFUs, of which 50% become infected, requiring hospitalization while 20% need amputation.[18]

Preventive care:

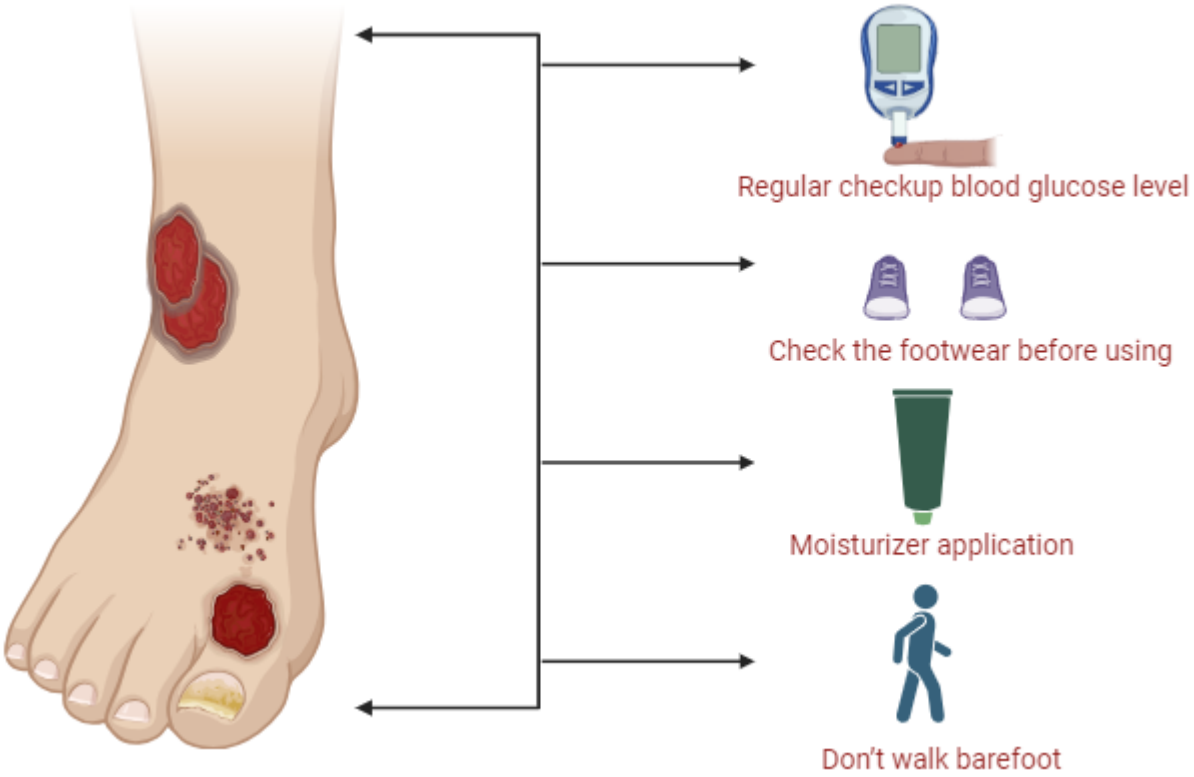


Figure 2: Diagrammatic representation of preventive care of diabetic foot ulcer

The goals of diabetic foot ulcer (DFU) preventive care are to reduce multiple risk factors, identify possible issues early, and preserve ideal foot health. Maintain blood glucose levels within the desired range and obtain regular checkups. In order to assist control blood sugar levels, patients should take their prescription diabetic medications or insulin as instructed by medical professionals. They should also lead healthy lifestyles, which include eating a meal balanced in calories and exercising frequently [19]

Non-invasive care:

Figure 3: Diagrammatic representation of non-invasive care during treatment of DFU

Non-invasive care refers to non-surgical treatments, including advanced wound dressings, offloading techniques, and local care. These are considered as critical elements in the comprehensive management of diabetic foot complications adopted for preventing infection, promoting healing, and reducing the risk of other complications. Cleaning of the wound and its surface is the foremost necessity to promote healing and to control bacterial infections. Regular cleaning the ulcerated area with saline solution or prescribed wound cleansers are required.[20] Debridement is a procedure for treating a wound in the skin. It involves thoroughly cleaning the infected wound and removal of hyperkeratotic (thickened skin or callus), infected, and nonviable (necrotic or dead) tissue, foreign debris, and residual material from dressings which improves the healing of the remaining healthy tissues. Depending on the wound tissue type, different debridement techniques are recommended. Surgical debridement is recommended for necrotic and infected wounds are the most effective and fastest method of debridement. Autolytic debridement is a second category of debridement in which the necrotic tissue is liquefied.[21-22] A wound associated with an occlusive dressing permits accumulation of tissue fluids containing macrophages, neutrophils, and enzymes, which remove bacteria and digest necrotic tissues. This can be achieved by a moist wound healing environment. Using a dressing that is changed often by wound irrigation (pressure: 4–15 psi), mechanical debridement removes diseased tissue without harming healthy or newly formed tissue.[23] The process of devitalized tissue being regenerated using topical enzymes like collagenase, fibrinolysin, or papain is known as enzymatic debridement. Sloughy, infected, necrotic wounds for which surgical debridement is not advised. Relieving pressure from the foot's weight-bearing area, either fully or partially, with the goal of resting the injured area with mechanical support promotes recovery. Once ulcers have formed, they tend to persist for two main reasons: high plantar pressure on the ulcer bed and repetitive trauma. Offloading plays a critical role in the healing of diabetic wounds. There are numerous unloading methods, such as wheelchair mobilization, wedge footwear, half shoes, removable cast footwear, and entire contact casts. The gold standard for treating and unloading diabetic patients with neuropathic ulcers is total contact castings.[24]For the treatment of diabetic foot wounds, a wide range of topical regimens and equipment are available, such as hydrogels, hydrocolloids, foam, alginates, growth factors, silicon impregnated atraumatic dressings, vacuum-aided devices, hyperbaric oxygen therapy, etc. But before deciding on a regimen, one should take into account things like the patient's overall health, the tissue repair process, the evaluation of the wound using grading, description, and classification, the wound's local environment, knowledge of the specific characteristics of the dressing materials and devices as well as their availability, and affordability.[25] One of the important dressings is Tulle dressings.These dressings are made of gauze that has been impregnated with paraffin to reduce dressing adherence; however, once the dressing dries out, this property is gone. Tulle dressings are mostly recommended for skin grafts and superficial, clean wounds. They can be applied to wounds to help granulate and epithelize them. Tulle dressings offer an excellent moist environment, which is ideal for the proliferation and migration of epithelial cells, as well as shield the delicate and young epithelium from damage during dressing removal. Polyurethane sheets are pleasant films have an adhesive (water-proof dressing) coating on them. The vapor-permeable coatings facilitate the flow of water vapor and gases, assisting in the preservation of a moist environment conducive to wound healing. Because of their transparency, wounds can be monitored without removing dressings, although there is a risk that the surrounding skin may get macerated. They can be used to wounds that don't leak much.[26-27]

Advanced Treatment of DFU:

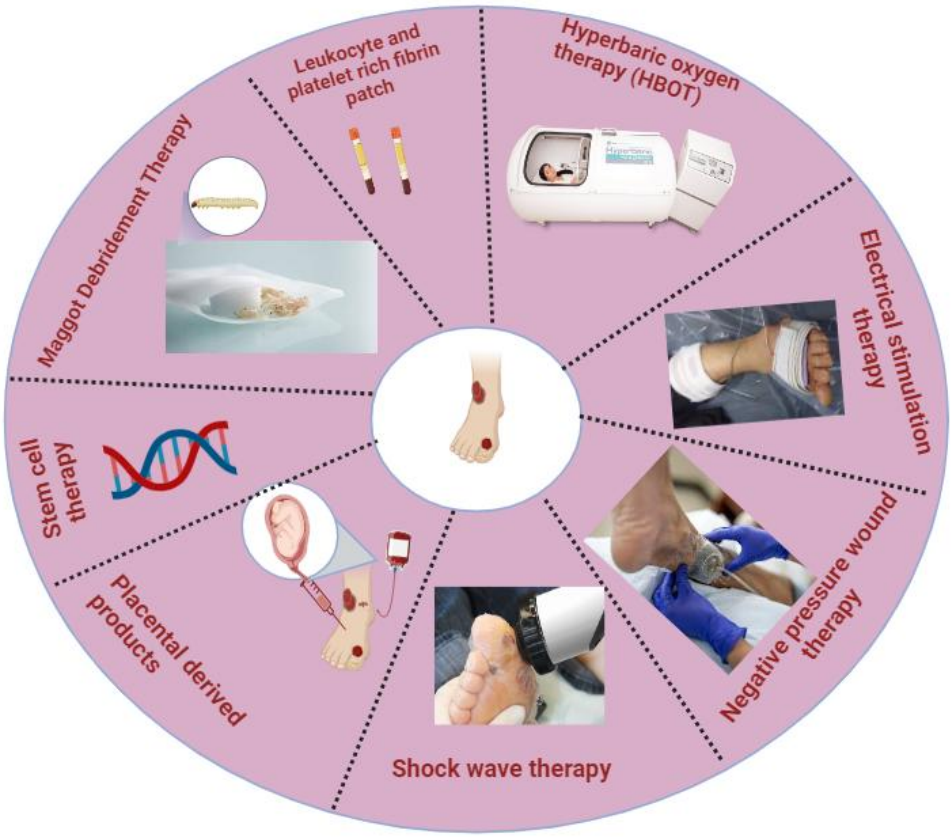


Figure 4: **Diagrammatic representation of types of advanced treatment of DFU**

Maggot Debridement Therapy (MDT):

Maggots are said to have been used therapeutically for the first time during the American Civil War. During the war, John Forney Zacharias served as a medical officer for the Confederacy and is thought to be the first doctor to purposefully leave his patient's open wounds to attract maggots. For diabetic foot ulcers (DFUs), maggot therapy, commonly referred to as maggot debridement therapy (MDT) is a successful non-conventional treatment.[28] In order to treat non-healing wounds, live, disinfected fly larvae of a certain fly species most often, *Lucilia sericata*are used to consume germs and necrotic tissue. Digestive enzymes secreted by maggots dissolve necrotic tissue, which they then consume and clean the wound. They generate antibacterial substances that aid in lowering the amount of bacteria present in the wound, so averting or curing infections. Through promoting microcirculation, their mobility within the wound can improve tissue granulation and epithelialization. Compared to surgical debridement, maggot therapy has the advantage of allowing for more exact wound cleansing because the larvae only eat dead tissue, sparing healthy tissue.[29] Furthermore, because bacterial biofilms are frequently resistant to drugs, maggots can disturb them. The clinical data from earlier research demonstrated the effectiveness of maggot treatment in treating DFUs. It has been demonstrated to improve the formation of granulation tissue, decrease the size of the wound, the bacterial burden, and in certain situations, lessen the necessity for amputation.[30]

Leukocyte and platelet rich fibrin patch:

Biomaterials such as Leukocyte and platelet-rich fibrin (L-PRF) patches, which are derived from the patient's own blood, have gained significant popularity in the fields of regenerative medicine and tissue engineering. The L-PRF patch was initially developed by Dr. Joseph Choukroun, a distinguished French dentist and implantologist, in collaboration with his colleagues in 2001.[31] These patches are composed of a fibrin matrix, enriched with leukocytes (white blood cells) and platelets. The presence of these components is pivotal in the healing process. Platelets, for instance, contain growth factors including Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor Beta (TGF-β), and Vascular Endothelial Growth Factor (VEGF), which are instrumental in promoting tissue repair and angiogenesis, the formation of new blood vessels. Leukocytes, on the other hand, play a crucial role in immune response and the regulation of inflammation, both of which are essential for wound healing and tissue regeneration.[32]The process of preparing a platelet-rich fibrin patch involves centrifuging a sample of the patient's own blood to separate and concentrate the platelets and leukocytes into a fibrin clot. This clot can then be processed into various forms, including membranes or patches, for application. The applications of L-PRF patches extend beyond diabetic foot ulcers (DFU), encompassing oral surgery (such as periodontal surgery and dental implants) and other dermatological conditions, including chronic wound management and

skin regeneration.One of the primary advantages of L-PRF is its biocompatibility. Since L-PRF is derived from the patient's own blood, it significantly reduces the risk of rejection or adverse reactions. Furthermore, the growth factors and cytokines present in L-PRF contribute to accelerated wound healing and tissue regeneration. The preparation process is relatively straightforward and can be performed in a clinical setting without the need for complex equipment. Previous research has demonstrated promising outcomes in terms of improved wound healing rates, reduced infection risk, and enhanced tissue regeneration compared to conventional methods.[33-34]

Hyperbaric oxygen therapy (HBOT):

Hyperbaric oxygen therapy (HBOT) is a medical treatment that involves breathing pure oxygen in a pressurized room or chamber. Hyperbaric Therapy was utilized in 1662 for the first time by a British physician named Henshaw.After several years of new founding, the Hyperbaric oxygen therapy was finally established by Paul Bert, in 1878, who is also known as "father of the hyperbaric physiology".[35] During this therapy, 100% oxygen under increased atmospheric pressure allows the lungs to gather more oxygen than normal. This oxygen is then dissolved into the bloodstream at higher concentrations. In the later stage, the increased oxygen levels in the blood promote greater delivery of oxygen to tissues and organs throughout the body. This can support healing and recovery processes. HBOT is often used to treat non-healing wounds, especially in diabetic patients or those with compromised circulation. In case of radiation Injury, this therapy helps in healing tissues damaged by radiation during cancer treatment. In Carbon Monoxide Poisoning this therapy speeds up the removal of carbon monoxide from the bloodstream.[36] During this therapy, patients are placed in a specially designed chamber where the atmospheric pressure is increased to two to three times higher than normal.They are asked to breathe pure oxygen either through a mask or a hood inside the chamber for a specified period, typically ranging from 30 minutes to 2 hours per session.Multiple sessions over a period of weeks may be required depending on the condition being treated. The main advantages of this therapy is enhanced healing, promotes tissue repair and wound closure by increasing oxygen delivery to damaged tissues. It also helps to reduce swelling and inflammation, which can aid in recovery .[37] Pure oxygen at higher concentrations can have direct antimicrobial effects, assisting in fighting infections.In some situations, Hyperbaric oxygen therapy (HBOT) is considered as risky because of its potential for ear or sinus discomfort due to changes in pressure during chamber compression and decompression. It also causes oxygen toxicity if prolonged exposure to high levels of oxygen can damage lung tissues. This therapy is contraindicated in certain conditions, such as untreated pneumothorax (collapsed lung), can make HBOT unsafe .[38]

Placental derived products

The placental-derived-product was first used asclinical application in wound healing in 1910 by Davis,who used Amniotic Membrane (AM) as a substrate for transplantation of skin.[39] Placental-derived products have received significant interest within the medical community, especially for their potential in the treatment of diabetic foot ulcers (DFUs). Placental tissue, which is derived from human placentas, is typically sourced from healthy donors who have undergone scheduled cesarean sections. These products are characterized by a diverse array of bioactive molecules, including growth factors, cytokines, extracellular matrix proteins, and others, which are known to facilitate tissue repair and regeneration.[40] Placental-derived products are particularly abundant in growth factors (such as Platelet-Derived Growth Factor (PDGF), Epidermal Growth Factor (EGF), and Fibroblast Growth Factor (FGF)), cytokines, and proteins that stimulate angiogenesis (the formation of new blood vessels), cell proliferation, and tissue regeneration. Therapies based on Vascular Endothelial Growth Factor (VEGF) aim to enhance tissue perfusion within DFUs, thereby supporting the healing process by augmenting the delivery of oxygen and nutrients to the wound bed.[41] Transforming Growth Factor-Beta (TGF-β) plays a pivotal role in regulating inflammation, stimulating collagen synthesis, and promoting tissue remodeling. It is involved in various stages of wound healing, including the inflammatory phase and scar formation. The application of TGF-β in DFUs is focused on modulating the wound environment to foster healing. Furthermore, it aids in reducing inflammation, which is essential in the context of chronic wound healing, such as DFUs, where impaired circulation and neuropathy are common challenges .[42] Placental-derived products offer a rich source of bioactive compounds that can surmount these obstacles and promote healing. Additionally, some products possess antimicrobial properties, which can diminish the risk of infection in DFUs, a prevalent complication. These products can be directly applied to the wound bed in the form of a gel, cream, or membrane. In certain instances, they may be administered around or directly into the wound to enhance healing. Clinical trials and case studies have demonstrated promising outcomes in terms of accelerated healing rates, reduced healing times, and overall wound closure in patients with DFUs treated with placental-derived products. These products are generally well-tolerated, as they are derived from donor tissues that undergo rigorous screening and are processed under stringent regulatory standards (Huerta et al., 2023; Protzman et al., 2023).[43-44]

Stem cell therapy:

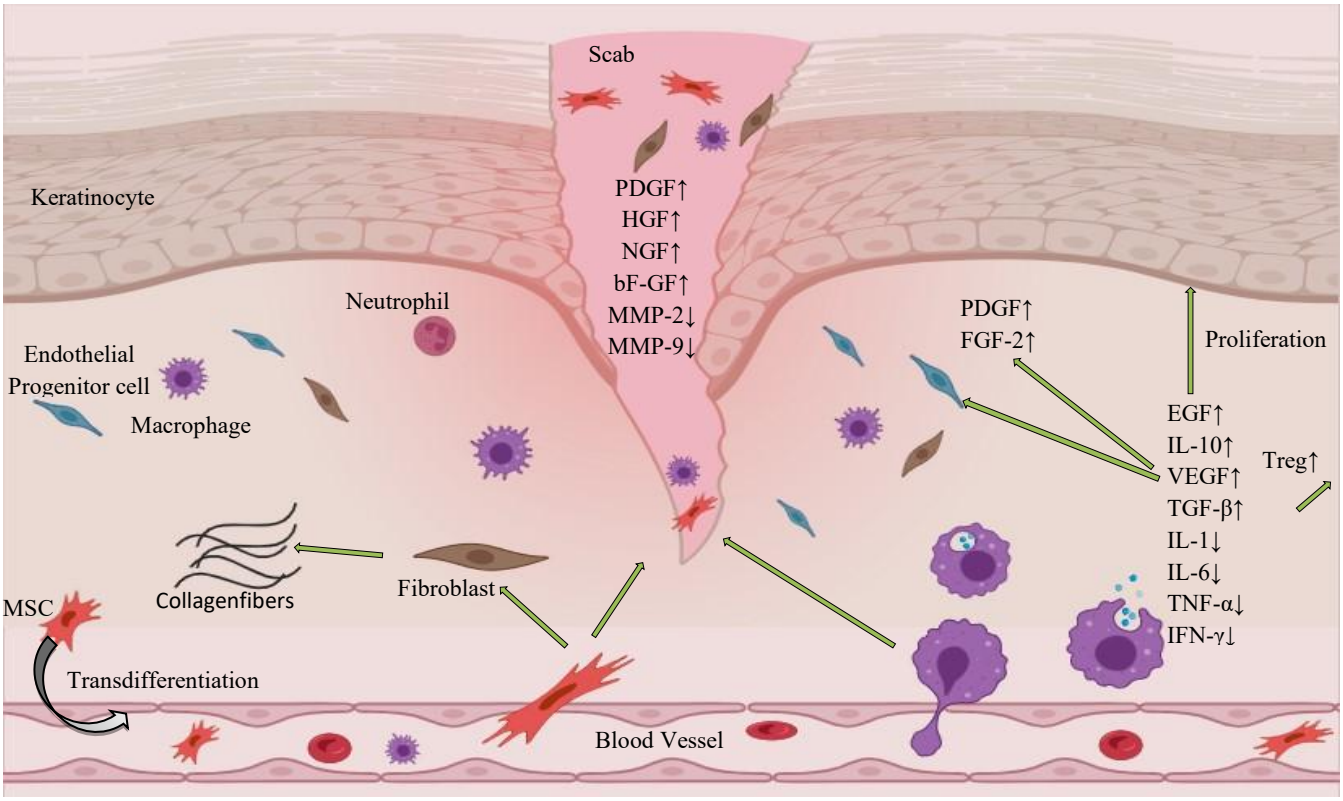


Figure 5: Diagrammatic representation of mechanism of stem cell therapy in DFU

Stem cell therapy as a concept began to be explored in the mid-20th century, but the actual discovery of stem cells and their potential for therapy can be traced back to the work of Canadian scientists Ernest McCulloch and James Till in 1961.[45] Stem cell therapy has emerged as a promising therapeutic approach in the treatment of diabetic foot ulcers (DFUs), harnessing the regenerative capabilities of stem cells to facilitate wound healing. Mesenchymal Stem Cells (MSCs) are derived from various sources, including bone marrow, adipose tissue, and umbilical cord tissue. These cells possess therapeutic potential due to their capacity to differentiate into various cell types and their paracrine effects, which involve the release of growth factors and cytokines.[46] Hematopoietic Stem Cells (HSCs) located in the bone marrow are capable of differentiating into various blood cell types, including those involved in the immune response and angiogenesis.[47] Induced Pluripotent Stem Cells (iPSCs) are adult cells reprogrammed to have the potential to differentiate into any cell type in the body, offering the possibility of personalized therapies. Stem cells secrete growth factors (such as VEGF, PDGF, and TGF-β) and cytokines that stimulate angiogenesis, reduce inflammation, and promote tissue repair. Their ability to differentiate into various cell types directly contributes to tissue regeneration and wound healing.[48] Stem cells enhance the vascularization of the wound bed, thereby improving blood flow and oxygenation, which are essential for the healing process. By secreting anti-inflammatory factors, stem cells help to modulate the inflammatory response in DFUs, thereby reducing chronic inflammation and fostering a conducive environment for healing. Stem cells play a crucial role in the formation of new tissue and the extracellular matrix, which aids in the closure of chronic wounds like DFUs. They can be directly injected into the wound bed or the surrounding tissue to target the site of injury. Alternatively, they can be applied as part of a dressing or scaffold that supports their retention and interaction with the wound environment.[49] Numerous clinical studies have demonstrated the efficacy of stem cell therapy in enhancing healing outcomes in DFUs, including reductions in wound size, accelerated healing rates, and improved rates of limb salvage. Research is ongoing to identify the optimal sources of stem cells, the most effective delivery methods, and the criteria for patient selection to maximize therapeutic benefits. However, the major challenges and considerations associated with stem cell therapies include regulatory scrutiny and approval processes across different countries, which can affect their availability and clinical application. Safety concerns, such as immune rejection, tumor formation (particularly with iPSCs), and potential complications, require careful consideration and monitoring.[50]

Energy based therapy:

Physical modalities or biophysical agents, which are also known as energy-based therapies, utilize different types of energy to aid in the healing and symptom management of diabetic foot ulcers (DFUs). These treatments use various energy sources to promote tissue healing, decrease inflammation, and enhance blood flow. Electrical Stimulation (ES) is the process of administering electrical currents to the area of the

wound. It can be administered in different ways, such as direct current (DC) which is utilized for promoting wound healing and managing infection. Secondly, alternating current (AC) assists in relieving pain and stimulating muscles.[51] Another technique commonly utilized for wound healing is the use of pulsed current (PC) to stimulate cell migration and promote angiogenesis. ES has been proven to speed up the healing of wounds, decrease healing time, and enhance wound closure rates in DFUs. It also assists in pain management and infection control. Ultrasound waves go through tissues, producing warmth and enhancing cellular function. It improves tissue healing by boosting collagen production, enhancing blood circulation, and decreasing inflammation. Ultrasound therapy helps with wound cleaning, increases the growth of granulation tissue, and boosts the effectiveness of topical treatments for DFUs.[52]

Shock wave therapy:

Shockwave therapy, also known as Extracorporeal Shockwave Therapy (ESWT), was initially introduced for treating urologic conditions in clinical settings in 1982. Shock wave therapy (SWT) is a medical treatment that does not require surgery and utilizes sound waves to promote healing and repair of tissues.[53] Although SWT is often connected with musculoskeletal issues such as tendinopathies, researchers are investigating its use in treating diabetic foot ulcers (DFUs) because of its capability to improve the healing of wounds. Radial Shock Waves are produced by a portable device and radiate outward from the tip of the applicator. Concentrated Shock Waves created by a machine that directs the waves to a precise location within the body. Shock waves cause physical strain and small injuries in tissues, triggering cellular reactions and encouraging tissue healing.[54] Neo-vascularization assists in promoting angiogenesis in the treated region, enhancing blood flow and oxygen levels to the wound site. It aids in decreasing chronic inflammation linked to non-healing wounds such as DFUs. It also boosts the generation of growth factors and cytokines which aid in the healing of wounds, such as VEGF and TGF-β. SWT has been proven to speed up the healing process of DFUs by boosting tissue regrowth, encouraging the formation of granulation tissue, and aiding in the closure of wounds. It encourages the production and restructuring of collagen, which is crucial for healing wounds.[55] SWT can assist in reducing the pain linked to DFUs and enhancing patient comfort as they heal. SWT can decrease infection risk and create a better healing environment by enhancing blood flow and oxygen levels in the wound area. Clinical trials have shown encouraging outcomes of SWT in enhancing healing rates and decreasing wound size in individuals with DFUs. SWT is typically seen as safe when carried out by skilled professionals, with little chance of negative impacts. The best treatment plans for Shockwave Therapy in Diabetic Foot Ulcers involve establishing the right energy levels, session frequency, and treatment duration according to each patient's needs and wound characteristics.[56] The efficacy of SWT can be influenced by different factors, including the duration of the ulcer, vascular condition, and general health of the patient. SWT is frequently utilized in conjunction with regular wound care methods like debridement, offloading, and infection control in order to enhance therapeutic results. Shock wave therapy is demonstrating potential as a non-invasive method for treating diabetic foot ulcers by stimulating tissue regeneration, improving blood flow, and decreasing inflammation. Ongoing research and trials are crucial to continue confirming its effectiveness, improve treatment procedures, and broaden its use in managing DFUs.[57]

Phototherapy:

Phototherapy, which involves the use of light to treat various medical conditions, was first introduced in 1903 by Danish physician Niels Finsen.[58] The utilization of light energy in medical treatments, known as phototherapy, has been studied for its ability to improve the healing of diabetic foot ulcers (DFUs). Low-Level Laser Therapy (LLLT) utilizes low-energy lasers or LED lights to activate cellular functions. It improves mitochondrial function, boosts ATP formation, enhances collagen creation, and decreases inflammation. LLLT has displayed potential in enhancing wound healing, alleviating pain, and enhancing circulation in DFUs.[59] Photodynamic Therapy (PDT) involves the use of light energy and a photosensitizing agent (such as a photosensitizer drug) to create reactive oxygen species that specifically attack and eliminate unusual cells or bacteria. PDT possesses antimicrobial characteristics and can promote tissue healing mechanisms. PDT can assist in managing infection and enhancing wound healing in patients with DFUs, especially when bacterial colonization is a worry.[60] Phototherapy, especially LLLT, boosts cell metabolism and enhances tissue healing, speeding up the healing process in DFUs. Enhancing collagen production and structure is vital for repairing the skin's structural integrity. LLLT possesses anti-inflammatory properties that aid in decreasing chronic inflammation in DFUs, which may impede the healing process. It can help reduce pain from DFUs, enhancing patient comfort and adherence to treatment.[61] Clinical research has shown that phototherapy has positive effects on healing rates, wound size reduction, and tissue repair in patients with DFUs. Phototherapy is typically safe with minimal side effects when given by trained professionals following proper protocols. The best parameters for phototherapy in DFUs involve wavelength, energy density, treatment session duration, and session frequency, customized based on patients' needs and wound characteristics. The success of phototherapy can be influenced by variables like the seriousness of the wound, the condition of the blood vessels, and the general well-being of the individual. Phototherapy is commonly combined with traditional wound care methods like debridement, offloading, and infection control to enhance treatment results.[62]

Electrical stimulation therapy:

Electrical stimulation therapy (EST) is a method of treatment that is non-invasive and uses electrical currents to help heal diabetic foot ulcers (DFUs). Johann Gottlob Kruger provided the initial documented therapy

of a patient using electricity in 1743.[63] In 1747, John Wesley advocated for electricity as a cure-all, but it was not accepted by traditional medicine.[64] It operates by administering regulated electric impulses to the injury area or nearby tissues, with the goal of boosting cell function, enhancing blood flow, and speeding up the recovery procedure. An outline of electrical stimulation therapy and its clinical uses in DFUs includes Direct Current (DC) which aids in wound healing by stimulating tissue repair processes. AC is a type of oscillating current utilized for managing pain and stimulating muscles. Pulsed Current (PC) is a series of interrupted bursts of current commonly employed in wound care to reduce tissue resistance and avoid muscle contractions. Electricity stimulation boosts cell metabolism and protein creation, encouraging tissue regrowth and collagen manufacturing. It enhances the growth of new blood vessels (angiogenesis) in the wound area, enhancing blood circulation and oxygen levels. It aids in decreasing swelling and inflammation, which are frequent issues in DFUs. It additionally encourages the contraction of muscle and connective tissue, which helps in closing wounds.[65] Electric stimulation therapy has been proven to speed up the healing of DFUs by boosting the growth of granulation tissue, improving epithelialization, and shortening healing duration. It aids in transforming persistent wounds into a better healing setting. Electrical stimulation therapy can lower infection risk and enhance antibacterial activity by increasing blood flow and oxygen supply to the wound area. Electric stimulation therapy (EST) may assist in reducing pain related to diabetic foot ulcers (DFUs), enhancing patient comfort throughout the healing journey. Clinical trials have shown that electrical stimulation treatment notably increases healing speeds, decreases wound size, and improves overall wound closure in DFUs when compared to traditional wound care alone. Electrical stimulation therapy is typically safe with minimal risks or side effects when given by trained healthcare professionals. The best settings for electrical stimulation therapy in DFUs involve adjusting frequency, treatment duration, current intensity, and electrode placement to match each patient's requirements and wound features. The efficacy of EST can differ depending on variables like wound size, duration, location, vascular status, and patient adherence. Electric stimulation therapy is commonly used alongside traditional wound care methods like debridement, offloading, and infection control to enhance treatment results.[66]

Electromagnetic therapy:

The use of electromagnetic fields (EMFs) on biological tissues for therapeutic reasons is known as electromagnetic therapy (EMT). One of the earliest documented uses of electromagnetic therapy was in the 1891 by Nikola Tesla, who experimented with electromagnetic fields for potential therapeutic effects (Sethi et al., 2016). This treatment has attracted attention for its ability to improve the healing of diabetic foot ulcers (DFUs). Pulsed Electromagnetic Field (PEMF): Creates sporadic pulses of electromagnetic energy. Constant Electromagnetic Field (CEF) offers a continuous flow of electromagnetic energy. EMFs pass through tissues and cause alterations at the cellular level, affecting cellular metabolism, ion movement, and protein production.[67] EMT induces angiogenesis by increasing endothelial cell growth and improving new blood vessel formation in the wound area. It decreases inflammation by regulating cytokine levels and immune response, establishing a better environment for healing wounds. It also enhances fibroblast function and collagen production, crucial for healing tissues and closing wounds. EMT speeds up the process of skin regrowth and the development of new tissue, leading to quicker healing of diabetic foot ulcers. Electromagnetic therapy has been proven to greatly enhance healing rates and decrease the size of DFUs by stimulating tissue regeneration and improving wound closure.[68] It assists in transforming long-lasting wounds into a state of healing that responds better. Electromagnetic therapy could decrease infection risk and enhance antibacterial activity by enhancing blood flow and oxygen levels in the wound bed. EMT can assist in reducing pain linked to DFUs, enhancing patient comfort while they heal.[69] Clinical research and organized evaluations have shown that electromagnetic therapy has positive effects on healing rates, wound size reduction, and overall wound closure in DFUs when compared to only using standard wound care. Electromagnetic therapy is usually safe with few risks or side effects when given by trained healthcare providers. The best parameters for electromagnetic therapy in DFUs involve the frequency of treatment sessions, the length of exposure to electromagnetic fields, the strength of the energy, and the location of electrodes or applicators, customized to suit each patient's needs and wound attributes. The efficacy of electromagnetic therapy can be influenced by factors like wound size, duration, location, vascular condition, and patient adherence. Electromagnetic therapy is frequently combined with other traditional wound care methods, like debridement, offloading, and infection control, to enhance therapeutic results.[70]

Negative pressure wound therapy:

Negative pressure wound therapy (NPWT), also called vacuum-assisted closure (VAC) therapy, is a commonly utilized method for treating diabetic foot ulcers (DFUs). NPWT was first introduced in the late 1980s. It was developed by Dr. George D. Winter and Dr. Robert G. Mathes at the University of Texas Medical Branch, utilizing controlled negative pressure (vacuum) on a wound aids in healing and controlling wound fluids.[71]This technique involves placing a specific dressing containing an adhesive layer and a layer of foam or gauze onto the wound. A dressing connected to a vacuum pump applies negative pressure ranging from -50 mmHg to -200 mmHg continuously or intermittently. NPWTenhances the healing process of wounds by various means, such as enhancing blood flow. This involves a negative pressure that boosts local perfusion and oxygen levels, both essential for cell metabolism and tissue restoration. It additionally aids in eliminating surplus wound liquid, decreasing swelling, and encouraging wound shrinkage. Encouraging the

growth of granulation tissue can also be achieved by maintaining a damp environment, which aids in the development of crucial healthy tissue needed for healing wounds. It helps in wound healing by encouraging the movement of epithelial cells and shrinking wound size.[72] NPWT is particularly beneficial for managing large, deep, or complex DFUs that are difficult to heal with traditional wound care methods alone. The controlled environment created by NPWT helps in reducing the risk of infection by removing exudates and infectious materials from the wound. NPWT supports tissue regeneration by maintaining a moist wound environment and enhancing cellular proliferation. Numerous clinical studies have demonstrated that NPWT accelerates wound healing, reduces healing time, and improves outcomes in DFUs by promoting granulation tissue formation and facilitating wound closure.[73] NPWT is generally safe when used appropriately by trained healthcare professionals. However, careful monitoring is required to prevent complications such as bleeding, pain, and tissue damage. NPWT is suitable for a wide range of DFU types and sizes, but its effectiveness may vary based on the wound characteristics, patient's vascular status, and overall health. NPWT is typically applied for several days to weeks, depending on the wound's response and healing progress. NPWT is often used in combination with other wound care modalities, such as debridement, offloading, and infection control, to optimize therapeutic outcomes.[74]

Cultured keratinocytes or fibroblasts:

In 1975, Dr. Howard Green and his team successfully cultivated human epidermal keratinocytes in culture for the first time, which laid the foundation for the use of cultured keratinocytes in skin grafts and wound healing .[75] Cultured keratinocytes and fibroblasts are innovative treatments for diabetic foot ulcers (DFUs), utilizing the regenerative abilities of these cells to boost wound healing.[76] Keratinocytes are taken from a small skin biopsy of the patient and grown in a lab setting in vitro. Keratinocytes sourced from donors are cultured and prepared for therapeutic use in an allogeneic manner. Cultured keratinocytes support re-epithelialization by moving over the wound surface and creating a fresh epidermal layer. They promote the generation of collagen and other necessary extracellular matrix elements for healing wounds. Keratinocytes release growth factors like EGF and TGF-β that aid in the healing of wounds. Cultured keratinocytes are utilized for severe or chronic DFUs when traditional wound care approaches have not worked. They are especially helpful for big wounds that need extensive epidermis coverage to support healing. The delivery and effectiveness of keratinocytes can be improved by combining them with dermal substitutes or scaffol.[77-78] Fibroblasts are collected from the patient's skin tissue, grown in a lab, and multiplied in a controlled environment. Cultured fibroblasts produce and store proteins in the extracellular matrix - including collagen and elastin - that are essential for the structure and function of tissues. They assist in wound healing by encouraging tissue tightening and minimizing scar development. Fibroblasts secrete cytokines and growth factors that regulate the inflammatory response and enhance the healing process. Cultured fibroblasts are employed in the treatment of stubborn chronic wounds that do not respond to traditional treatments. They speed up the healing of wounds by improving tissue growth and facilitating a more structured healing process. Frequently utilized along with other advanced wound care methods, like skin replacements or growth factors, to enhance treatment results. These treatments are commonly incorporated into a holistic wound care strategy which also involves debridement, offloading, infection management, and additional supportive actions (Basso et al., 2012; Spiekstra et al., 2007).[78-80]

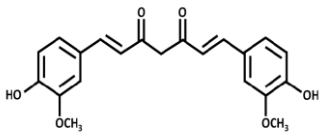
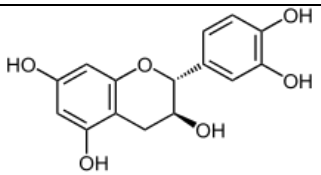
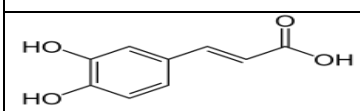
Herbal Therapy:

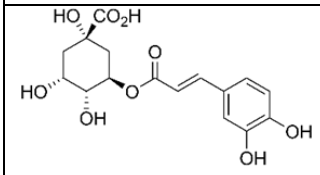
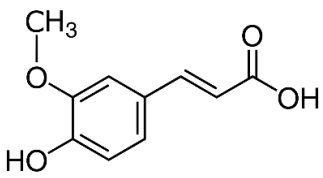
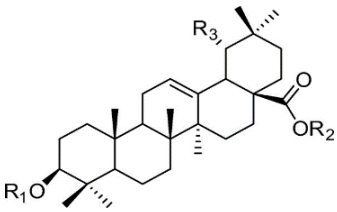
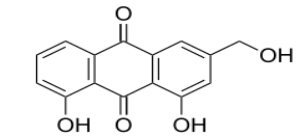
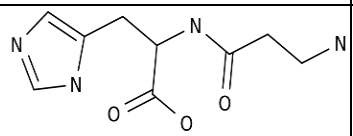
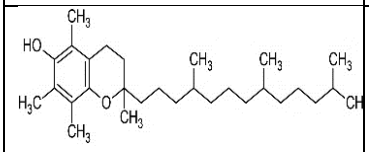
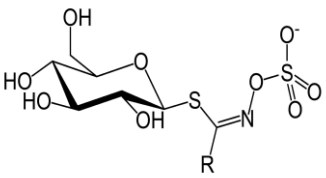
Herbal therapies have been explored for their potential benefits in the treatment of diabetic foot ulcers (DFUs), offering natural alternatives to conventional treatments. While scientific evidence supporting their efficacy is often limited and varies, some herbal therapies have shown promising effects in promoting wound healing and managing symptoms associated with DFUs. In this review, we have tried to explore many herbal based compounds with their chemical structures and possible mechanism for their therapeutic and pharmacological effects for the effective treatment in diabetic foot ulcers.

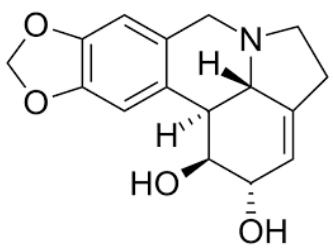
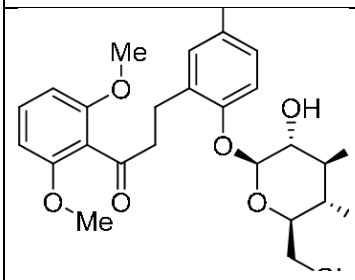
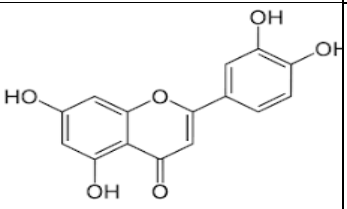
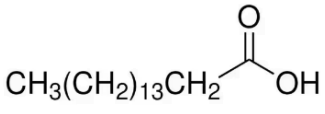
Fig 6- Various traditional herbs used in treatment of Diabetic foot ulcer (wound)

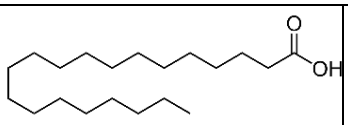
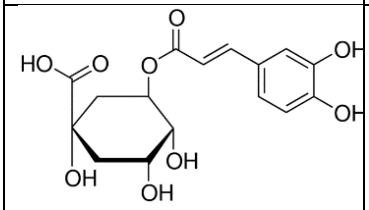
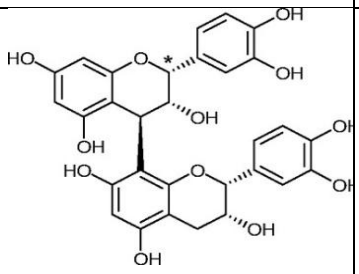
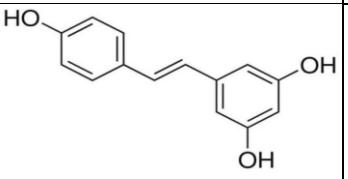
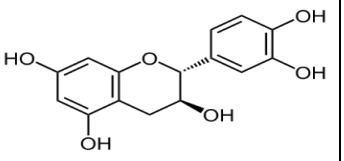
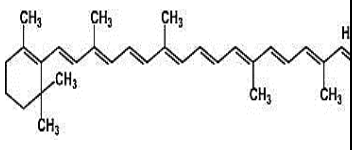
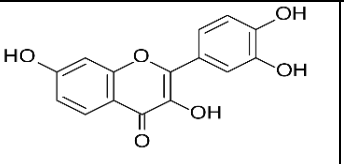
TRADITIONAL MEDICINES FOR THE TREATMENT OF DFUs

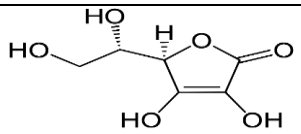
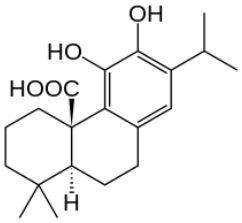
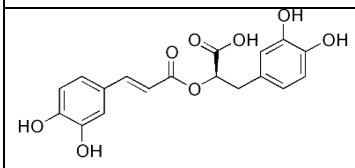
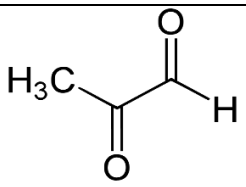
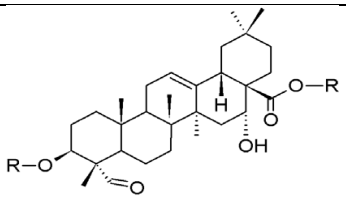
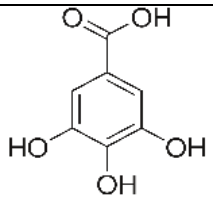
Table 1) Herbals drugs used for the DFU Treatment

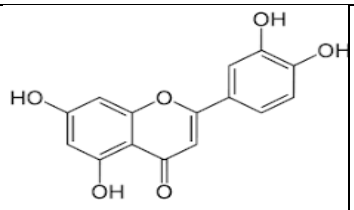
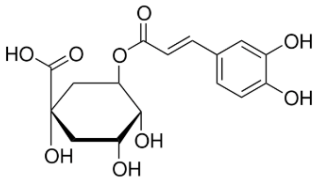
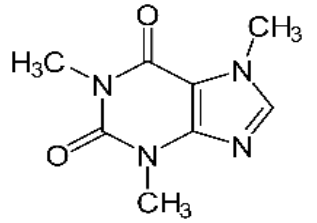
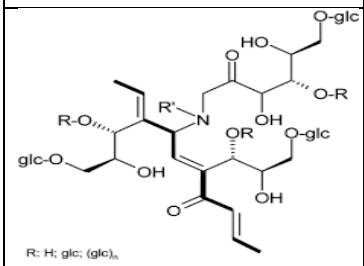
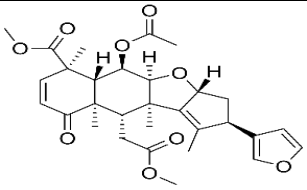
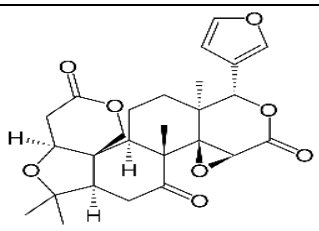
S.N.	Herbal	Chemical constituents and Chemical structure	Mechanism	Observation
1	Turmeric (*Curcuma longa*)	 Curcumin	Curcumin exerts its therapeutic effectiveness for the treatment of DFUs by inhibiting miR-152-3p and activating the FBN1/TGF-β Pathway.	The result of Karri VV et. al. revealed that, Curcumin possesses multiple biological activities that are useful in treating various DFU-related complications.[81]
2	Avocado (*Persea American*)	 Catechin	Catechin manages diabetes by boosting mitochondrial function, mainly by supporting oxidative phosphorylation and ATP production, promoting mitochondrial growth, and providing protection to mitochondria.	Ekom SE and colleagues found that the gel containing *P. americana* extract significantly enhanced wound healing and decreased the number of *S. aureus* bacteria at the infection site.[82]
		 Coffeic acid	Coffeic acid triggers the inflammatory process, which hinders the formation of AGEs and increases the levels of vascular endothelial growth factor and insulin-like growth factors. This leads to blood vessel formation and regrowth of the outer layer of tissue at	

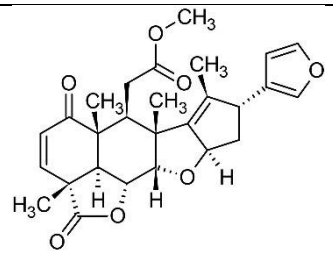
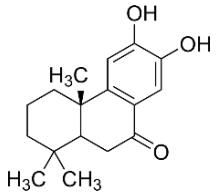
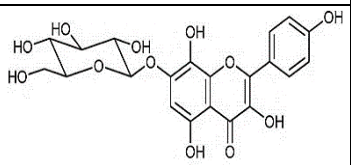
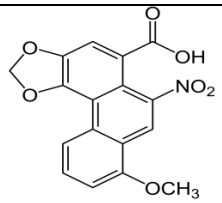
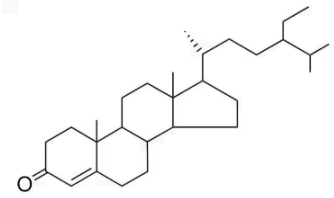
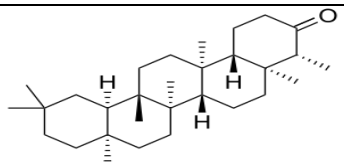
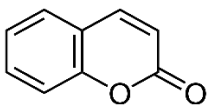
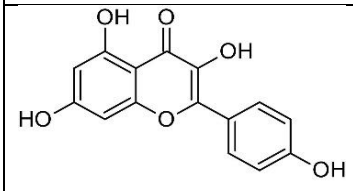
			the injury site.	
		 Chlorogenic acid (CGA)	Chlorogenic acid has the capability to replenish Na+ K+ ATPase levels, demonstrating neuroprotective effects.	
		 Ferulic acid	Ferulic acid lowers blood sugar and increases insulin levels by increasing glucokinase activity and glycogen production in the liver, while also reducing inflammatory responses by decreasing PGE2, TNF-α, and iNOS expression.	
3	Aloe vera (*Aloe barbadensis*)	 Saponins	Saponin functions as a diabetes treatment by enhancing glycogen production, blocking disaccharide functions, and regulating insulin secretion in pancreatic beta cells.	According to Daburkar M et al., the study found that Aloe parenchyma extract displayed impressive ulcer healing effects on test animals. Additionally, Aloe vera dressing led to a significant decrease in ulcer area.[83]
		 Anthroquinones (Aloe Emodin)	Anthroquinone prevents hemoglobin (Hb) from aggregating and control cell migration and proliferation of dermal fibroblast cells.	
4	Papaya (*Carica papaya*)	 Papain	Papain speeds up healing time, enhances slough removal, and encourages granulation, all without any complications.	The findings from Hakim RF's study showed that Carica papaya extract can enhance both epithelial thickness and fibrillation which is effective in wound healing.[84]
		 Tocopherol	Tocopherol, an antioxidant, controls the production of reactive oxygen species (ROS) as alpha-tocopherol (Vitamin E; AT).	
		 Glucosinolates	Glucosinolates could potentially be beneficial for treating biofilms created by problematic pathogenic bacteria like Pseudomonas aeruginosa and Staphylococcus aureus on medical implants and catheters. It functions as a debridement agent, converting proline to hydroxyproline, while also	

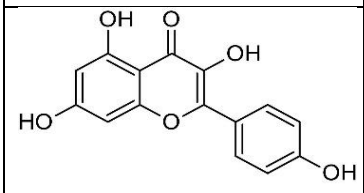
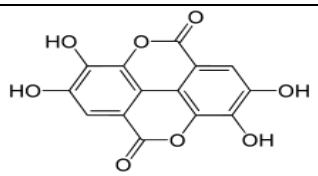
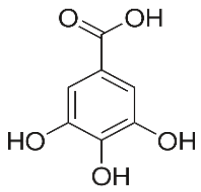
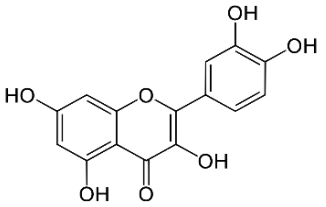
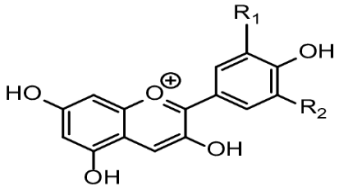
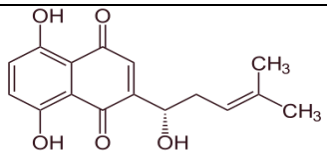
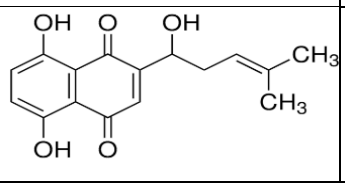
			serving as an antioxidant, and anti-inflammatory.	
5	Curculin (*Curculigoorchioides*)	 Lycorine	Lycorine enhances peripheral nerve function in diabetic peripheral neuropathy by stimulating Schwann cell autophagy through activating the AMPK pathway and reducing MMP9, and it also possesses anti-inflammatory, antiviral, antibacterial characteristics.	The extract of root tubers of C. orchioides increases the rate of angiogenesis and improves antioxidant enzymes status that eventually leads to faster wound healing in diabetic condition. However, further studies are needed to explore the molecules present in C. orchioides that lead to faster wound healing. The extract of root tubers of C. orchioides increases the rate of angiogenesis and improves antioxidant enzymes status that eventually leads to faster wound healing in diabetic condition. However, further studies are needed to explore the molecules present in C. orchioides that lead to faster wound healing. Singh A et al. reported that the root tuber extract of C. orchioides enhances angiogenesis and boosts antioxidant enzymes, resulting in quicker diabetic wound healin.[85]
		 Curculigoside	Curculigoside exhibits both phagocytic and immunoadjuvant activities, promoting higher levels of superoxide dismutase and nitric oxide while reducing lipid peroxidation in granuloma tissue.	
6	*Martynia annua*	 Luteolin	Luteolin exerts its pharmacological effects by altering signaling pathways such as AKT/GSK 3β, AKT/PKB, and NFκB-AF1. Also, Luteolin exhibits its ability to treat diabetes by controlling blood sugar levels and enhancing insulin sensitivity in body cells through its effects on the Akt2 kinase.	Santram L et al found a notable rise in tensile strength and hydroxyproline content when compared to the control group, which was similar to the reference group ($P<0.01$) in diabetic animals.[86]
		 Palmitic acid	Palmitic acid triggers inflammation in macrophages by activating Toll-like receptors (TLRs) like TLR4, which are crucial in the innate immune response.	

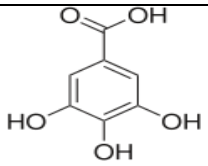
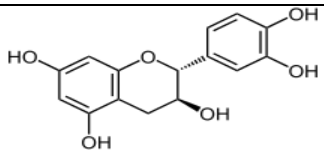
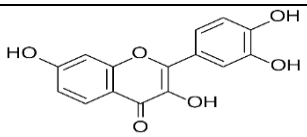
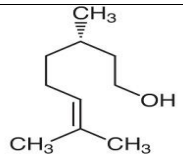
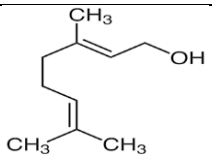
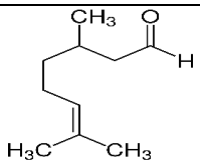
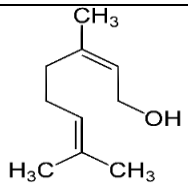
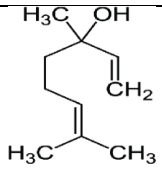
		 Arachidic Acid (ARA)	Metabolites derived from ARA lead to the production of resolvins, which aid in the resolution of inflammation as well as healing wounds and lesions.ARA metabolites, such as PGE2, PGI2, leukotriene B4, and leukotriene D4, effectively enhance wound healing by controlling the production of angiogenic factors and the functions of endothelial cells.	
		 Chlorogenic Acid	Chlorogenic acid reduces levels of malondialdehyde and nitric oxide, while also increasing reduced glutathione and hydroxyproline content in wounds.	
7	Grape seed (*Vitis vinifera*)	 Oligomeric procyanidins	Oligomeric procyanidins stimulated the growth factor for vascular endothelial cells and sped up the healing of damaged skin.	Al-Warhi T et al. found that the *Vitis vinifera* seed extract showed impressive healing abilities by speeding up wound closure, boosting TGF-β1, VEGF, and Type I collagen levels, and reducing inflammation markers (TNF-α and IL-1β).[87]
		 Resveratrol	Resveratrol (RV) possesses the ability to enhance endothelial function and displays potent pro-angiogenic properties in the management of diabetic foot wounds.	
		 Catechins	Catechinsdemonstrates great promise in wound healing by stimulating the growth and movement of human fibroblast cells. Its antioxidant properties are primarily responsible for this effect.	
8	Kiwi fruit (*Actinidia deliciosa*)	 Beta-carotene	β-carotene helps in wound healing by triggering the immune response by increasing the amount of monocytes and macrophages during inflammation.	Mohajeri G et al. found that the extract of *Actinidia deliciosa* significantly reduced the surface area of the foot ulcer as compared to the control group. It increases the amount of collagen and granulation tissue in kiwifruit-treated individuals.[88]
		 Fisetin	Fisetin possessed the immunomodulatory function of promoting macrophage M2 polarization and the release of anti-inflammatory cytokines.	

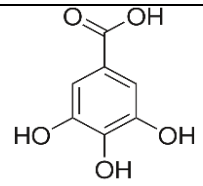
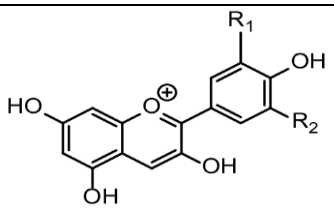
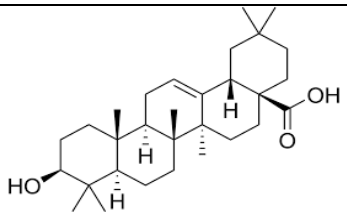
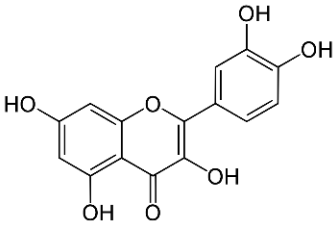
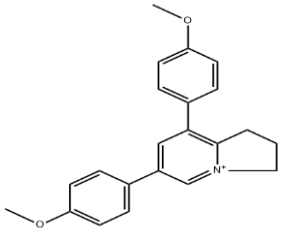
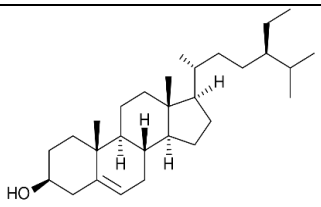
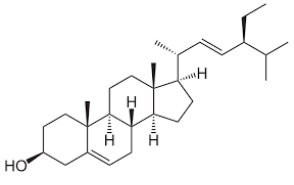
		 Vitamin C	Vitamin C has important functions in the nervous, cardiovascular, and immune systems that are implicated in DFU development.	
9	Rosemary (*Rosmarinus officinalis*)	 Carnosic acid	Carnosic acid is a compound that works against diabetes and oxidative stress by blocking NLRP3 activation in human and mouse macrophages through reducing the generation of mitochondrial ROS.	Abu-Al-Basal MA's research revealed that the Essential oil derived from the above-ground parts of *Rosmarinus officinalis* demonstrated a more effective healing impact compared to the aqueous extract when applied topically on the wounds of diabetic mice, influencing different phases of the healing procedure.[89]
		 Rosmarinic Acid	Rosmarinic acid decreases inflammation and helps with wound healing by promoting tissue regeneration, blood vessel formation, and collagen production.	
10	Manuka honey (*Leptospermum scoparium*)	 Methylglyoxal	Methylglyoxal is a potent antimicrobial that works effectively against various strains of MRSA.	Kapoor N and colleagues discovered that using Manuka honey as a wound dressing helps to keep the wound moist and also helps with debriding wounds by acting as an autolytic agent.The quick healing seen with topical honey may be attributed to its dual impact on the inflammatory reaction.[90]
11	Indian mallow (*Abutilon indicum L.*)	 Saponin	Saponin can reduce the increment of blood glucose by inhibiting the enzymes that break down disaccharides into monosaccharides	Rajesh J et al. discovered that solid lipid nanoparticle loaded extract shows notable antimicrobial effects against different gram positive and gram negative bacteria derived from DFU.[91]
		 Gallic Acid(GA)	GA accelerates wound healing by protecting skin cells from oxidative stress and by activating FAK, JNK, and Erk in human keratinocytes. More importantly, GA also significantly improved wound healing under a hyperglucidic condition by promoting cell migration	

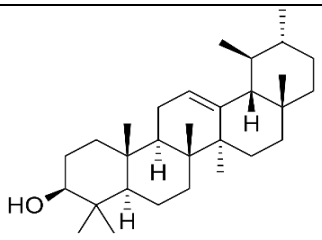
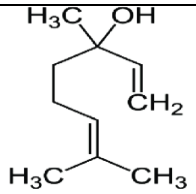
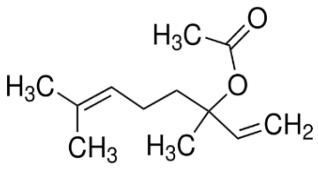
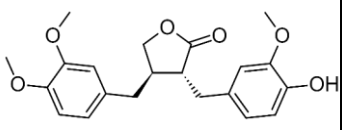
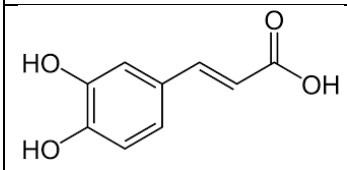
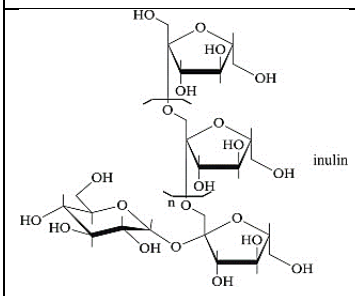
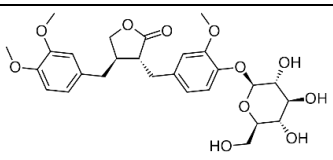
		 Luteolin	luteolin decreased the expression of vascular endothelial growth factor (VEGF) and increased the expression of ubiquitin carboxy-terminal hydrolase (UCH)-L1, as evidenced by angiogenesis and neuronal regeneration in completely healed wound and it is promotes wound restoration by ameliorating inflammation and oxidative stress through the inactivation of NF-κB and upregulation of Nrf2.	
12	Coffee (Coffea canephora)	 Chlorogenic Acid	chlorogenic acid supports wound healing with antibacterial, antioxidant, and proliferative effects of pro-healing cytokines genes	Yuwono HS found that utilizing coffee powder extract led to a notable acceleration in the formation of granulation tissue and enhanced the wound's infection-fighting capabilities within 3-4 days of consistent treatment.[92]
		 Caffeine	It is antioxidant and anti-inflammatory agent in wound healing mechanisms. It acts as adenosine-receptor antagonist. Although it has been shown that adenosine and antioxidants promote wound healing	
		 Melanoidins	Melanoidins has antioxidant, antimicrobial, anticariogenic, anti-inflammatory, antihypertensive, and antiglycative activities, have been attributed to coffee melanoidins.	
13	Neem (*Azadirachta indica*)	 Nimbin	Nimbinimprove wound healing by cell proliferation and to reduce the reactive oxygen species.	Srinivasan JM demonstrated that the plant extract of *Azadirachta indica* enhances the healing of diabetic ulcers when applied topically.[93]
		 Limonoids	Limonoids shows antidiabetic activity due to pancreatic α-amylase inhibition.	

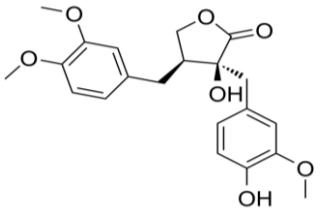
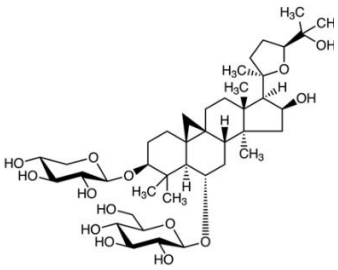
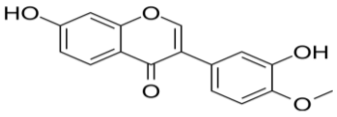
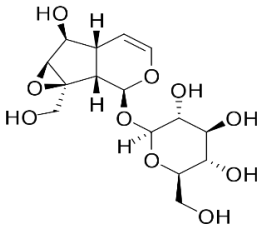
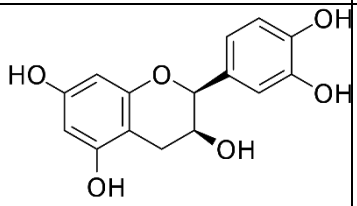
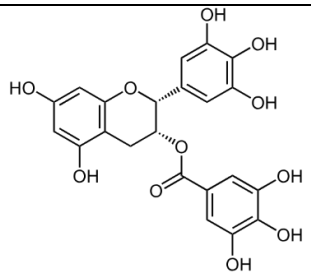
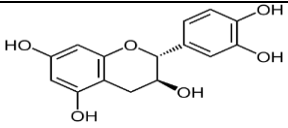
		 Nimbolide	Nimbolide inhibits specifically both TNF-α and NF-κB, and activates the anti-inflammatory mechanism.	
		 Nimbidiol	Nimbidiol is reversibly inhibits the activities of sucrase-isomaltase, maltase-glucoamylase, lactase, trehalase and microbial α-glucosidases that helps treatment of diabetic.	
14	*Ageratinapichinchensis* (Kunth)	 Flavonoid 7-O-(β-D-glucopyranosyl)-galactin	It shows antibacterial, antiulcer, antifungal, and anti-inflammatory activities.	Romero-Cerecero O et al. reported that after 24 weeks of treatment, the plant extract of *Ageratinapichinchensis* effectively cured diabetic foot ulcers.[94-95]
15	*Aristolochia indicaL.* (Snake root)	 Aristolochic Acids	It has anti-inflammatory activity.	Steffy K et al. discovered that the aqueous extract of the *Aristolochia indica* plant containing ZnO nanoparticles has potent antimicrobial properties that contribute to the death of bacterial cells.[96]
		 Stigmast-4-en-3-one	It has antimicrobial activity against some bacteria including Streptococcus gordonii and Streptococcus sanguinis.	
		 Friedelin	It is antioxidant, antidiabetic agent that enhanced the translocation as well as activation of GLUT2 and GLUT4 through PI3K/p-Akt signaling.	
16	*Melilotus officinalis* (L.) Pall. (Yellow Sweet Clover)	 Coumarin	Coumarin treats diabetic complication such as nephropathy.	Chorepsima S et al. reported that the *Melilotus Officinalis* herbal extract aids in healing experimental autoimmune encephalomyelitis (EAE) by utilizing its immunomodulatory and antioxidant characteristics.[97]
			Quercetin has antioxidant and anti-inflammatory effects. kaempferol inhibit the expression of the transcription factor PPARγand decrease the pro-	

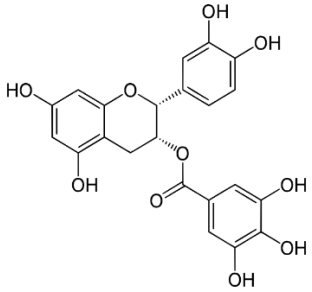
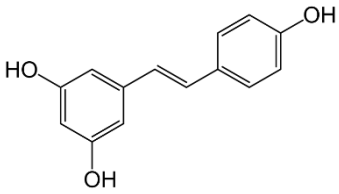
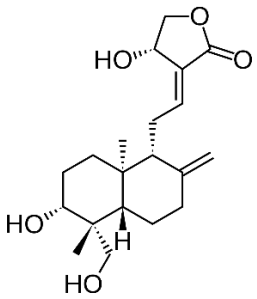
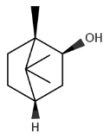
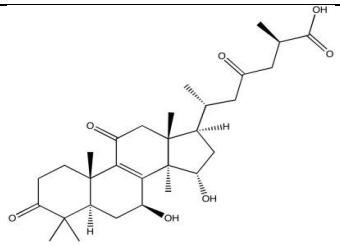
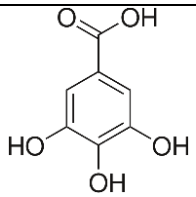
		Quercetin	inflammatory signals TNF-α, IL-6, IL-1β, and NF-κB	
		 Kaempferol flavonoids	Kaempferol influencing collagen breakdown and MMP-2 activity which regulating angiogenesis during wound healing through the activation of proangiogenic cytokines, including TNF-α and VEGF, and by generating antiangiogenic peptides.	
17	*Myrtus communis L.*	 Polyphenols	Polyphenols use reduces ROS quantity. This results in a decrease in the infiltration of pro-inflammatory cells (neutrophils and monocytes/macrophages) and inhibition of keratinocyte and fibroblast apoptosis.	Khodaie SA and colleagues found that the fruit portion of this plant has the potential to treat diabetic foot ulcers by preventing inflammatory response and oxidative stress.[98]
		 Gallic acid	It has antioxidant activity, anti-inflammatory activity, promoting the cell proliferation and cell migration of human fibroblasts.	
		 Quercetin	Quercetin inhibits inflammatory reactions via modulating macrophage polarization switching from M1 to M2 phenotype, thereby accelerating the diabetic wound repair. It activates multiple factors to promote the cell proliferation, collagen deposition and angiogenesis.	
		 Anthocyanins	It has anti-inflammatory effects by inhibit the elevation of IL-17, IL-1β, TNF-α, and IL-6	
18	*Onosmamicrocarpum* DC.	 Alkannin	Alkannin leads to activation of TGF-β/Smad3 signaling and reduces wound pain or scar formation.	According to Mohammadi N et al., the root section of the plant resulted in total healing of the diabetic foot ulcer in 20 days of consistent treatment.[99]
			Shikonin stimulate fibroblast and endothelial cell proliferation and angiogenesis.	

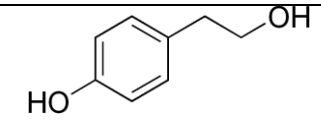
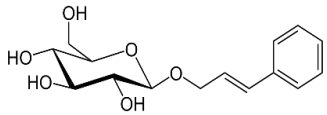
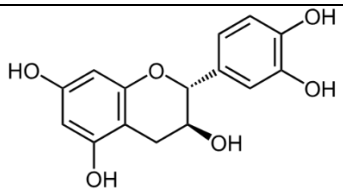
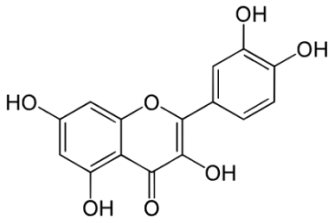
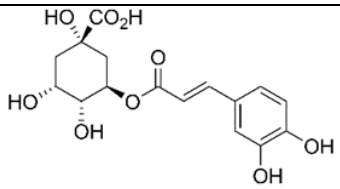
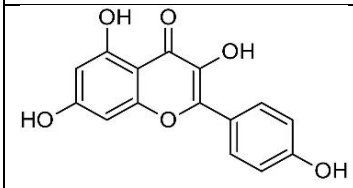
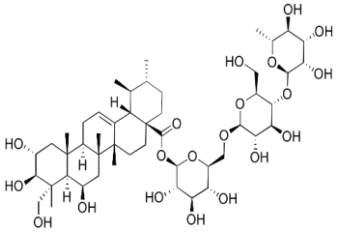
		Shikonin		
17	*Cotinus coggygria* (Eurasian smoke tree)	 Gallic acid	It has antioxidant activity, anti-inflammatory activity, promoting the cell proliferation and cell migration of human fibroblasts.	According to Aksoy H et al., the treated group showed a notable rise in hydroxyproline content and GSH levels, as well as a statistically significant reduction in MDA level compared to the control group.[100]
		 Catechin	Catechin promotes the cell proliferation and cell migration of human fibroblasts. This effect may be attributed mainly to its antioxidant properties.	
		 Fisetin	Fisetin possessed the immunomodulatory function of promoting macrophage M2 polarization and the release of anti-inflammatory cytokines.	
18	*Cymbopogon nardus*, (citronella grass)	 Citronellol	It helps in reducing the ulcer area and regeneration of tissues.	Kandimalla R et al. found that it reduced the growth of the fungus on diabetic wounds and also decreased inflammation, resulting in faster healing of the wounds.[101]
		 Geraniol	It is used in prevention and treatment of diabetic neuropathy.	
		 Citronellal	It has antiseptic, antifungal, antibacterial and insecticidal properties.	
19	*Rosa rubiginosa* (rose)	 Geraniol	It is used in prevention and treatment of diabetic neuropathy	Nascimento IAM et al. found that applying *Rosa rubiginosa* oil topically improved the healing of skin wounds in diabetic rats.[102]
		 Linalool	It is antidiabetic by enhanced the peripheral utilization of glucose.	

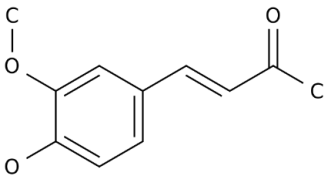
		 Gallic Acid	Antioxidant activity, anti-inflammatory activity, promoting the cell proliferation and cell migration of human fibroblasts.	
		 Anthocyanins	Anti-inflammatory effects by inhibit the elevation of IL-17, IL-1β, TNF-α, and IL-6.	
20	*Calendula officinalis L*	 Oleanolic Acid Glycosides	Anti-inflammatory, antioxidant, antibacterial, antiviral, antifungal and migration responses, with platelet-derived growth factor (PDGF).	Saravanan VS et al. demonstrated that Low-level laser therapy, either on its own or combined with *Calendula officinalis* oil, was successful in reducing pain and speeding up the healing of diabetic foot tissue.[103]
		 Quercetin	Quercetin has antioxidant and anti-inflammatory effects. Kaempferol inhibit the expression of the transcription factor PPARγand decrease the pro-inflammatory signals TNF-α, IL-6, IL-1β, and NF-κB.	
21	*Ficus septica* Burm.f.	 Alkaloid Ficuseptine	Antibacterial and anti-inflammatory effects in vitro. A significant dose-dependent decrease in the expression of IL-6 and TNF-α, from neutrophils and M1 macrophages,	Deli J et al. discovered that the exudate of *F. septica* does not cause mutations and possesses bactericidal and anti-inflammatory qualities. When used on small skin ulcers, the exudate heals just as effectively as Savlon antiseptic cream and standard soap and water treatment by day 14.[104]
		 β-sitosterol	β-sitosterol can promote angiogenesis, alternatively activated macrophages (M2 macrophage) proliferation, and collagen synthesis in diabetic wounds.	
			Stigmasterol induces the release of insulin from pancreatic α-cells, resulting in an anti-hyperglycemic effect.	

		Stigmasterol		
		 β-amyrin	β-amyrin has anti-diabetic property.	
22	*Lavandula stoechas*(wild lavender)	 Linalool	It shows anti-diabetic property by enhancing the peripheral utilization of glucose.	Boukhatem MN et al. demonstrated that applying *Lavandula stoechas* essential oil cream led to reduced inflammation and enhanced tissue perfusion, proliferation, remodeling, and re-epithelization.[105]
		 Linalyl acetate	Linalyl acetate restores endothelial dysfunction and hemodynamic alterations.	
23	*arctiumlappa*(Niu Bang Zi / burdock)	 Arctigenin	Arctigenin could improve inflammation via accumulating granulocytic MDSCs and strengthen the immunosuppressive effects of MDSCs.	Amish Burn Study Group found that using B&W/burdock leaf dressing resulted in minimal to no pain, without any infections, and healing in less than two weeks on average.[106]
		 Caffeic acid (CA)	CA responsible for their antidiabetic, antioxidant, and anti-inflammatory properties which aids in managing foot ulcers.	
		 Inulin	Inulin control levels of glycemic status and improve lipid profile in type 2 diabetic patients.	
		 Arctiin	Arctiinis anti-infective agent and anti-inflammatory agents. It inhibits cell death and cytotoxicity and enhances DNA repair and wound healing in UVB-exposed keratinocytes.	

		 Trachelogenin	Trachelogenin exhibits effective antiviral, anti-inflammatory and analgesic effects.	
24	*Astragalus propinquusRehmaniaglutinosa* (Huang Qi Di Huang)	 AstragalosideIV(AS-IV)	AS-IV improves vascular endothelial dysfunction.	According to Tam JC et al., the healing properties of NF3 (RA and RR in a ratio of 2:1) could be attributed to its ability to regulate and coordinate inflammation, angiogenesis, and tissue regeneration. The effects of wound healing, however, appear to not be affected by blood glucose control.[107]
		 Calycosin	Calycosin has anti-inflammatory effects.	
		 Catalpol	Catalpol has anti-diabetic activity.	
25	*Camellia sinensis* (green tea)	 Epicatechin	Epicatechin reduces scar formation and anti-inflammatory activities for both TGF-β and TNF-α.	Al-Rawaf HA stated that the presence of green tea polyphenols in green tea extract greatly enhanced the healing of diabetic wounds.[108]
		 Epigallocatechin-3- gallate	Epigallocatechin-3- gallate activates keratinocytes and promoting re-epithelialization.	
26	*Ampelopsis japonica* (Bai Lian)	 Catechins	It promoting the cell proliferation and cell migration of human fibroblasts.	Lee K et al. found that *Ampelopsis japonica* extractexhibited quicker and more efficient wound healing properties compared to SSD (1 %

		 Epicatechin gallate	Epicatechin gallate acts as anti-inflammatory, antibacterial, anti-oxidant, and may improve wound healing and scarring, though its precise effect on TGF-β1 remains unclear.	Silver sulfadiazine) and Vaseline on the skin of experimentally scalded rats. The *Ampelopsis japonica* extracttreated groups displayed superior re-epithelialization, vascularization, granulation tissue formation, and collagen deposition compared to the other groups based on histopathological evaluation results.[109]
		 Resveratrol	Resveratrol accelerates wound healing by attenuating oxidative stress-induced impairment of cell proliferation and migration. It protect against hyperglycemia, inflammation, oxidative stress, vascular pathology, infection, and peripheral neuropathy.	
27	*Andrographis paniculata* (Kalmegh)	 Andrographolide	Andrographolide is an antidiabetic agent that increases the hepatic apelin gene expression as a result the levels of blood glucose significantly decrease in blood plasma. It enhances epithelisation rate, Upregulation of human collagen I expression, Stimulation of formation of collagen fiber, Proliferation, and angiogenesis of tissue.	Al-Bayaty FH and colleagues reported that extracts from *A. paniculata* notably increased the rate of wound healing in rats.[110]
28	*Blumea balsamifera* (Ngai camphor and sambong)	 L-Borneol	L-Borneol increases fibroblast cell growth and angiogenesis, and IL-2 levels.	Masyudi M et al. found that the wound healing process was accelerated by the effective reduction of wound length with 10% *B. balsamifera* leaf gel.[111]
29	*Ganoderma lucidum* (Reishi mushroom)	 *Ganoderma lucidum* polysaccharide	*Ganoderma lucidum* polysaccharide helps in suppression of cutaneous MnSODnitration, p66Shc and mitochondrial oxidative stress	According to L et al., *Ganoderma lucidum*polysaccharide treatment notably raised the average perfusion rate surrounding the wound in diabetic mice.[112]
30	*Rhodiola imbricata* (Rose root/Arctic root)	 Gallic acid	Gallic acid exhibits antioxidant activity, anti-inflammatory activity, promoting the cell proliferation and cell migration of human fibroblasts.	Gupta A et al. discovered that wounds treated with *Rhodiola imbricata* healed faster than those in the control group, with the plant extract enhancing cell growth and collagen production at the site of

		 p-Tyrosol	Tyrosol is an antioxidant, anti-inflammatory, neuroprotective and protective action on circulating low-density lipoproteins.	injury in Sprague–Dawley rats.[113]
		 Rosin	Rosin is antimicrobial against a wide range of bacteria, fungi, and yeasts.	
31	*Dioscorea bulbifera L.*	 (+)-Catechin	(+)-Catechin is a major active compound responsible for the wound healing effect of *D. bulbifera* and shows high potential for wound healing by promoting the cell proliferation and cell migration of human fibroblasts. This effect may be attributed mainly to its antioxidant properties.	Chaniad P et al. discovered that the crude extracts, solvent fractions, and flavonoid compounds demonstrated significant antioxidant activity in both DPPH and •OH radical scavenging tests.[114]
		 Quercetin	Quercetin inhibits inflammatory reactions via modulating macrophage polarization switching from M1 to M2 phenotype, thereby accelerating the diabetic wound repair. It activates multiple factors to promote the cell proliferation, collagen deposition and angiogenesis.	
32	*Moringa oleifera*	 Chlorogenic acid	Chlorogenic acid acts as antidiabetic agents by inhibiting glucose absorption in intestine and improve insulin sensitivity	Muhammad *et al.* found that the *Moringa oleifera* enhanced wound healing by reducing the levels of inflammatory mediators like TNF-α, IL-1β, IL-6, iNOSsynthase, and COX-2 while increasing VEGF expressio.[115]
		 Quercetin	Quercetin has antioxidant and anti-inflammatory effects. Kaempferol inhibit the expression of the transcription factor PPARγ and decrease the pro-inflammatory signals TNF-α, IL-6, IL-1β, and NF-κB.	
33	*Centella asiatica* (gotu kola)	 Madecassoside	Madecassoside inhibit protease-activated receptor-2 expression and its signalling pathway, cyclooxygenase-2, prostaglandin E2 and prostaglandin F2 alpha in keratinocytes.	Wang L and colleagues found that the *Centella asiatica* extract capsule is a Thai herbal preparation capsule that is effective in promoting wound healing and reducing scarring in diabetic wound patients.[116]

34	*Zingiber officinale*	 Dehydrozingerone	Dehydrozingerone has antioxidant, anti-inflammatory, and anti-microbial activity. It stimulates collagen synthesis, improving wound strength and promoting closure of wound.	Begum, F. et al. discovered that Dehydrozingerone accelerates the healing of diabetic foot ulcers in Wistar rats with type-II diabetes induced by a high fat diet and low dose of streptozotocin.[117]

Conclusion and future Prospect:

Diabetic foot ulcers (DFUs) are still a major consequence of diabetes, causing severe morbidity and, in some cases, amputations. Over time, DFU management has progressed from traditional wound care to more sophisticated and creative approaches. Current treatment strategies include conventional therapies, which continue to rely on standard wound dressings, debridement, offloading, and infection control, as well as advanced wound care, which has shown improved healing outcomes with bioengineered skin substitutes, negative pressure wound therapy (NPWT), and hyperbaric oxygen therapy. Stem cell therapy, platelet-rich plasma (PRP), and gene therapy show significant potential for improving tissue repair and angiogenesis. Pharmacological interventions such as growth factors and antibacterial drugs are still being studied for their efficacy in wound healing and infection prevention. Other emerging technologies, such as smart dressings, nanotechnology, and artificial intelligence-based monitoring systems, open up new opportunities for DFU control. The future of DFU therapy looks bright, with research concentrating on personalized and precision medicine, stem cell and gene therapy, artificial intelligence (AI) and digital health, 3D bio-printing and tissue engineering, and nano-based drug delivery methods for targeted therapy and improved efficacy. With continued study and technical advancements, the outlook for DFU treatment is growing more positive. A multidisciplinary strategy that incorporates established approaches and innovative medicines will be critical to improving patient outcomes and lowering the worldwide burden of diabetic foot problems.

List of abbreviations

+ve- Positive
AC-Alternating Current
AGEs-Advanced glycation end products
AKT2 -AKT serine/threonine kinase 2
AKT-Ak strain transforming
AM-Amniotic Membrane
AMPK-Adenosine Monophosphate-Activated Protein Kinase
ARA-Arachidic Acid
ATP- Adenosine Triphosphate
CEF-Constant Electromagnetic Field
CGA -Chlorogenic acid
DC-Direct current
DC-Direct Current
DFU- Diabetic foot ulcer
EAE-Experimental autoimmune encephalomyelitis
EGF-Epidermal Growth Factor
EMFs -The use of electromagnetic fields
EMT-Electromagnetic therapy
EOLS-*Lavandula stoechas* essential oil
ES-Electrical Stimulation
EST-Electrical stimulation therapy
ESWT -Extracorporeal Shockwave Therapy
FBN1-fibrillin-1 gene
FGF -Fibroblast Growth Factor
GA-Gallic Acid
Gl-PS -*Ganoderma lucidum* polysaccharide
GSK 3β -Glycogen synthase kinase-3β
GTE- Green tea extract
GTPs-Green tea polyphenols
Hb -Hemoglobin
Hb -Hemoglobin
HBOT-Hyperbaric oxygen therapy
HSCs-Hematopoietic Stem Cells
IDF-International Diabetes Federation
iNOS -Inducible nitric oxide synthase
iPSCs -Induced Pluripotent Stem Cells
LLLT-Low-Level Laser Therapy
L-PRF-Leukocyte and platelet-rich fibrin
MDT- Maggot Debridement Therapy
miR-MicroRNA
MMP9-Matrix Metallopeptidase 9
MRSA-Methicillin-resistant Staphylococcus aureus
MSCs - Mesenchymal Stem Cells
NF-κB-Nuclear factor kappa B
NLRP3 -Nucleotide-binding domain, Leucine-Rich–containing family, Pyrin domain–containing-3
NPWT- Negative pressure wound therapy
NPWT-Negative pressure wound therapy
PAD-Peripheral Artery Disease
PC-Pulsed Current
PDGF -Platelet-Derived Growth Factor
PDGF -Platelet-derived growth factor
PDT -Photodynamic Therapy
PEMF- Pulsed Electromagnetic Field
PGE2-Prostaglandin E2
PGI2-Prostaglandin I2
PKB-Protein kinase B
ROS -Reactive oxygen species
ROS-Reactive Oxygen Species
RV-Resveratrol

SSD -Silver sulfadiazine
SWT -Shock wave therapy
TGF-β - Transforming Growth Factor Beta
TGFβ -Transforming growth factor-beta
TLRs -Toll-like receptors
TLRs -Toll-like receptors
TNF-α-Tumour Necrosis Factor alpha
UCH -Ubiquitin carboxy-terminal hydrolase
VAC-Vacuum-assisted closure
-Ve- Negative
VEGF - Vascular Endothelial Growth Factor

Ethics approval and consent to participate: This manuscript is a review. Hence, no experiments in animals or humans are included in this study, so ethical approval and consent are not required.

Clinical Trial No: The manuscript is a review article (not a part of Clinical trial), hence no Clinical trial no is applicable.

Consent for publication: This manuscript does not contain any personal data. Hence, no consent is required/Not applicable

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