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# A Comprehensive Review of the Application of Nanoparticles and Medicinal Plants in Diabetic Wound Healing

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**ABSTRACT**

Wound management in diabetic patient is of an extreme clinical and social concern. The delayed and impaired healing makes it more critical for research focus. The research on impaired healing process is proceeding hastily evident by new therapeutic approaches other than conventional such as single growth factor. The application of nanoparticles has been widely used in the treatment of diabetic wound healing due to their superior anti-inflammatory, antibacterial, and antioxidant activities. These nanoparticles can also be loaded with various agents, such as organic molecules (eg, exosomes, small molecule compounds, etc.), inorganic molecules (metals, nonmetals, etc.). This paper reviews the therapeutic potential and future perspective of nanoparticles in the treatment of diabetic wounds. Together, nanoparticles represent a promising strategy in the treatment of diabetic wound healing. The future direction may be to develop novel nanoparticles with multiple effects that not only act in wound healing at all stages of diabetes but also provide a stable physiological environment throughout the wound-healing process.

**Keywords**: Diabetes, Diabetic wounds, Wound healing, nanoparticles, growth factors

## I. INTRODUCTION

There are two types of diabetes mellitus: type I, which is caused by the autoimmune system destroying the pancreatic beta cells, and type II, which is associated with insulin resistance and consequent failure of the pancreatic beta cells. Diabetes mellitus is a metabolic disorder characterised by abnormal glucose metabolism[1]. Skin ulcers, diabetic nephropathy, neuropathy, cardiomyopathy, hearing loss, and insulin resistance are just a few of the consequences that result from high blood glucose levels Nowadays, hundreds of millions of people worldwide suffer from diabetes as a result of changes in living brought about by societal growth and changes in lifestyle [2, 3]. Diabetic wounds are among the most problematic consequences for persons with diabetes, and they are now one of the biggest global health risks. The main causes of amputation and disability, cellular dysfunction, microcirculatory abnormalities, high levels of oxidative stress, and hypoxia, can lead diabetic wounds to become chronic, intractable ulcers [4]. Blood glucose management, surgical debridement, skin transplantation, wound dressing, and hyperbaric oxygen therapy are among the conventional clinical treatments.[5-7]. These clinical interventions have a limited therapeutic impact on diabetic wound healing, despite being able to better control symptoms. Furthermore, because diabetic therapies are lengthy and prone to secondary harm, the patients suffer greatly on a psychological and physical level. Therefore, there is a pressing need for cutting-edge therapies for diabetic wounds that may be painless, successful, and leave no scars. According to published research, nanoparticles have long been employed as superior physiologically active wound-healing delivery systems[8].

Nanoparticles (NPs) derived from nanotechnology have drawn interest due to their revolutionary potential in understanding the biological milieu and offering customised therapeutic strategies for wound healing [9]. In addition to being tiny, stable, and readily absorbed by cells, they also effectively regulate drug delivery and release and have strong biocompatibility or targeting qualities [10].These characteristics of NPs serve as the primary impetus for the creation of innovative platforms based on nanotechnology, which have a significant influence on the production of extracellular matrix (ECM), collagen, and angiogenesis—all of which are critical elements to support wound healing. Because of

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their inherent nanoscale properties, NPs and various NPs-based platforms can interact with the wound healing process, impacting several cellular and molecular processes and promoting the repair of diabetic wounds. Because they have the ability to increase the stability and bioavailability of several bioactive compounds, they therefore constitute a viable technique in the treatment of diabetic wound healing [11]

Because of their distinct benefits, nanoparticles have garnered a lot of attention in the last ten years for the treatment of diabetic wounds. Several research teams have also published encouraging preclinical results. The potential and significance of one or more types of nanoparticles (such as polymeric or silver nanoparticles) have been covered in a number of reviews12–16. Additionally, potential uses of gene therapy and nanotechnology to increase the bioavailability of medications for diabetic wound healing have been investigated. To the best of our knowledge, none of them have, however, provided us with a thorough overview of nanoparticles. We outlined the most current developments in the field of nanoparticle treatment for diabetic wounds based on the literature. Active delivery methods for healing wounds. Nanoparticles (NPs) derived from nanotechnology have drawn interest due to their revolutionary potential in understanding the biological milieu and offering customised therapeutic strategies for wound healing.9. In addition to being tiny, stable, and readily absorbed by cells, they also offer high targeting or biocompatibility qualities and efficiently regulate the release and distribution of drugs. These characteristics of NPs serve as the primary impetus for the creation of innovative platforms based on nanotechnology, which have a significant influence on the production of extracellular matrix (ECM), collagen, and angiogenesis—all of which are critical elements to support wound healing. Because of their inherent nanoscale properties, NPs and various NPs-based platforms can interact with the wound healing process, impacting several cellular and molecular processes and promoting the repair of diabetic wounds.

Because they have the ability to increase the stability and bioavailability of several bioactive compounds, they therefore constitute a viable technique in the treatment of diabetic wound healing. Because of their distinct benefits, nanoparticles have garnered a lot of attention in the last ten years for the treatment of diabetic wounds. Several research teams have also published encouraging preclinical results. Numerous reviews have examined the potential and importance of one or more types of nanoparticles (such as polymeric or silver nanoparticles) [12–16]. Additionally, potential applications of gene therapy and nanotechnology to increase the bioavailability of medications for the treatment of diabetic wounds have been examined. To the best of our knowledge, none of them have, however, provided us with a thorough overview of nanoparticles. We outlined the most current developments in the field of nanoparticle treatment for diabetic wounds based on the literature.

## Wound Healing Process

### The Normal Wound-Healing Process

There are four phases in the physiological process recovering during wound healing: hemostasis, inflammation, proliferative, and remodelling. These phases are extremely complex and dynamic. Vascular constriction and thrombin activation to promote platelet aggregation result in the hemostasis phase (0 hours after injury), which is followed by the production of thrombi and the release of certain proinflammatory mediators, such as cytokines, to go on to the next phase.

Mast cells emit 5-hydroxytryptamine and histamine, which increases vascular permeability at the wound site. This encourages the recruitment of neutrophils, monocytes, and chemokines to the injury area and results in an inflammatory response, which lasts for one to three days during the inflammatory phase [17]. During the proliferative phase, which lasts between 4 and 21 days, lymphocytes and macrophages migrate to the wound to aid in the control of infection. Additionally, as cellular fragments break down, certain cytokines and growth factors are released, which encourage the multiplication of cells[18]. At the site of the injury, new epithelial tissue emerges during the remodelling phase, which lasts for at least 21 days. Additionally, fibroblasts proliferate into muscle fibroblasts in large quantities, new blood vessels are created, and the wound constricts. A scar is created as a result of this remodelling [19,20].

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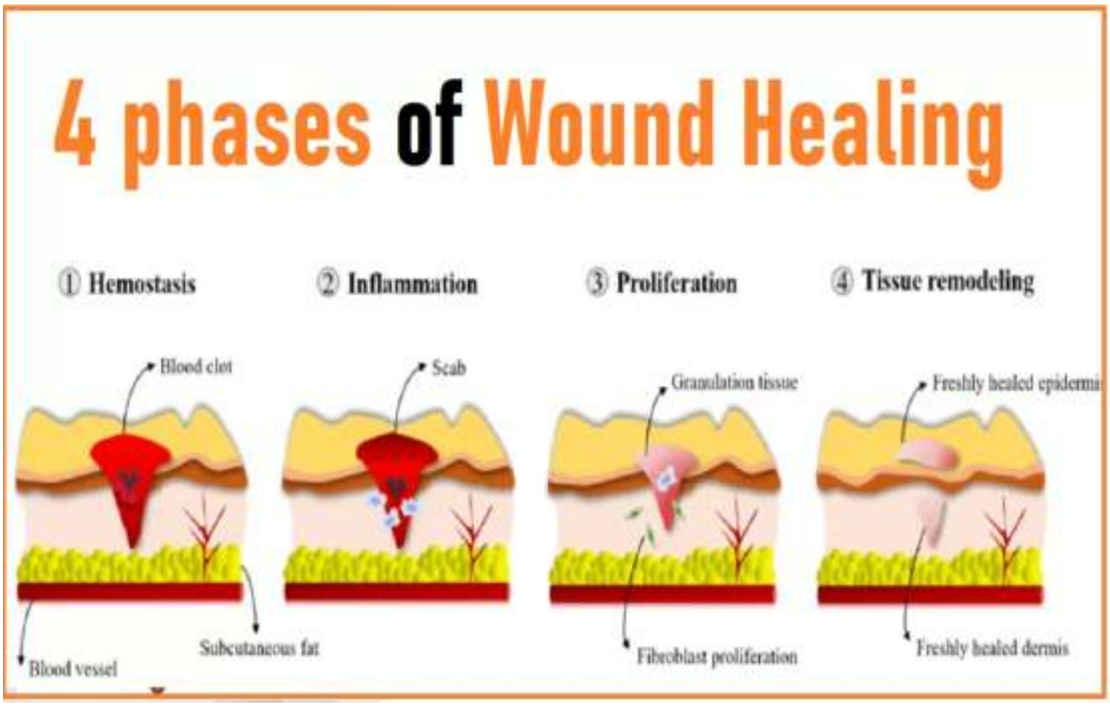


**Figure 1: Pictorial representation of normal wound-healing process**

**The Diabetic Wound-Healing Process**

The wounded organism should adhere to the standard wound processing under normal physiological conditions. Nevertheless, a chronic wound (such as a diabetic wound) develops when recovery is continuously aided or impeded by aberrant circumstances. Diabetic wounds can become chronic wounds that are difficult to cure for a number of reasons.First, diabetic wound damage is mostly caused by hypoxia. The importance of oxygen for wound healing is becoming increasingly evident since it boosts immunological response, encourages angiogenesis, and encourages fibroblast growth.16 Nevertheless, diabetes people need more oxygen in the places where they have wounds in addition to having an inadequate oxygen supply [21]. By elevating oxygen-free radical levels, hypoxia prolongs the efficient healing of wounds by enhancing the inflammatory response..Second, imbalanced angiogenic factors (e.g., transforming growth factor-α (TGF-α), TGF-β, fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), hypoxia-inducible factor (HIF-1α), and vascular inhibitory factors (e.g., platelet-activating protein, endothelial inhibitor, vasopressor) resulting in decreased local angiogenesis and a diminished blood supply in diabetic wounds.

Consequently, a connection between extended wound inflammation and postponed wound healing might exist. Patients with diabetes also experience macroangiopathy, which lowers blood flow. Microvascular failure arises from lower levels of nitric oxide synthase (NOS) and aberrant capillary control, which contribute to a drop in NO production and altered diastolic function of the vasculature. Third, diabetes wounds progress straight to a chronic inflammatory phase, unlike normal wound healing. Chronic inflammation, which is characterised by an excessive accumulation of M1 macrophages, significantly reduced fibroblast differentiation into myofibroblasts, inhibition of TGF-β type II receptor expression, and decreased collagen synthesis, can result from uncontrolled inflammation and persistent inflammatory cells in the wound site. This can impede the skin's reshaping process.. Fourth, keratinocyte migration and collagen degradation are controlled by matrix metalloproteinases (MMPs). But high blood sugar causes an overexpression of MMPs, which in turn causes an overabundance of extracellular matrix, growth factors, growth factor receptors, integrins, and their receptors to be broken down, slowing down the healing of diabetic wounds and escalating the local inflammatory response [22]. In conclusion, healing diabetes wounds is more difficult than healing regular wounds. Diabetes-related wounds heal more slowly than normal wounds because of hypoxia, poor angiogenesis, persistent inflammation, and high matrix metalloproteinase (MMP) expression. In clinical practise, we typically employ symptomatic interventions, such as GF usage, anti-inflammation, surgical debridement, and infection control, but their efficacy is restricted. It is crucial to use nanoparticles to tackle this challenging health issue.

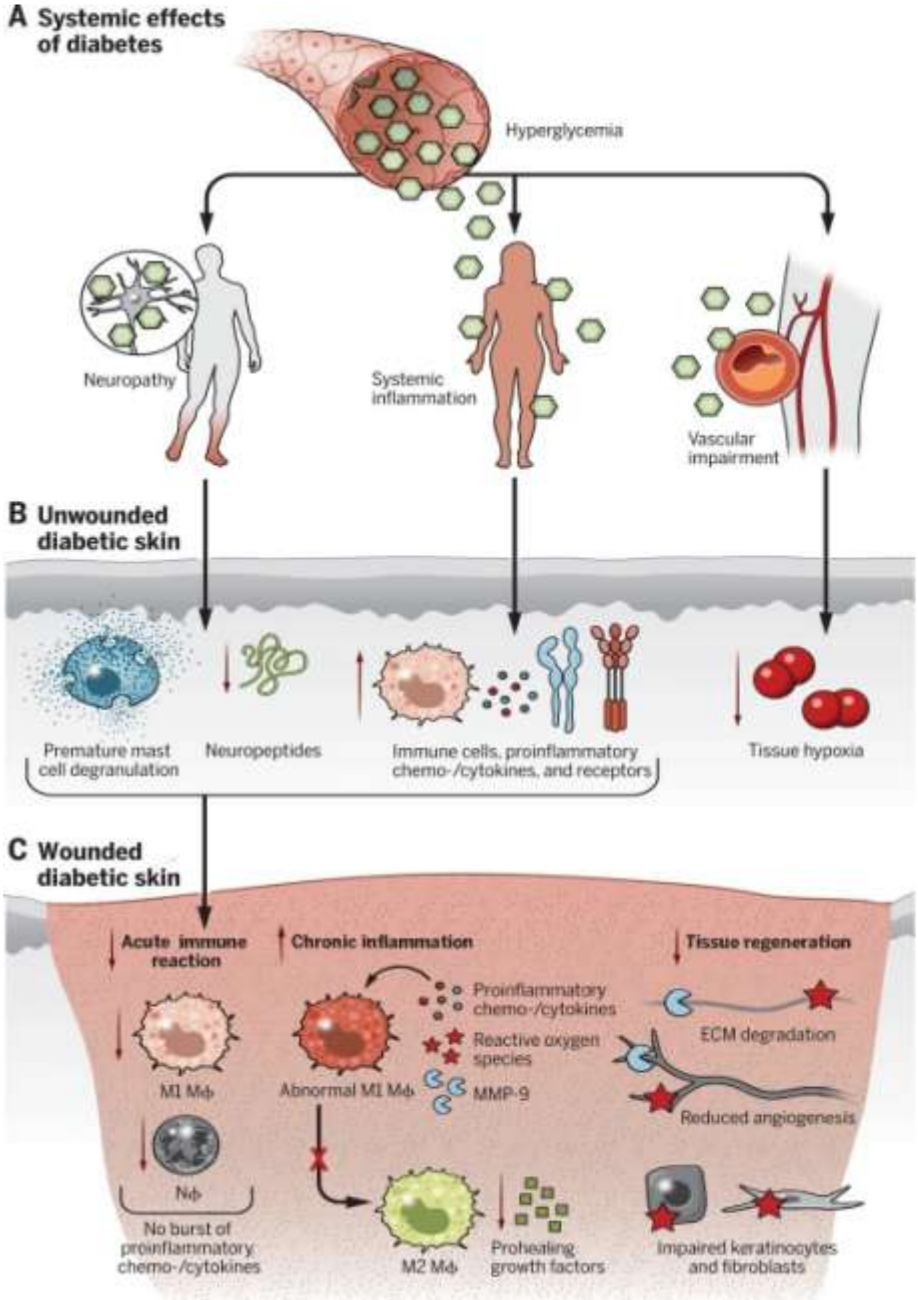


**Figure 2: Pictorial representation of diabetic wound-healing process**

**Application of Nanoparticles to Treat Diabetic Wounds**

Considering that organic nanoparticles have abundant functional group structures that can better bind to drugs and GFs and the ions brought

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by metal nanoparticles have good antibacterial properties, they show great potential in the treatment of diabetic wounds [23]. With the advancement of society and technology, researchers have discovered nanoparticles with numerous biological properties that can be applied to diabetic wound therapy to remedy some of the drawbacks of clinical treatment. This review summarizes the recent applications of organic nanoparticles (eg, polymeric nanoparticles exosomes, etc.) and inorganic nanoparticles (metal, non metal nanoparticles, etc.) in the treatment of diabetic wound healing.

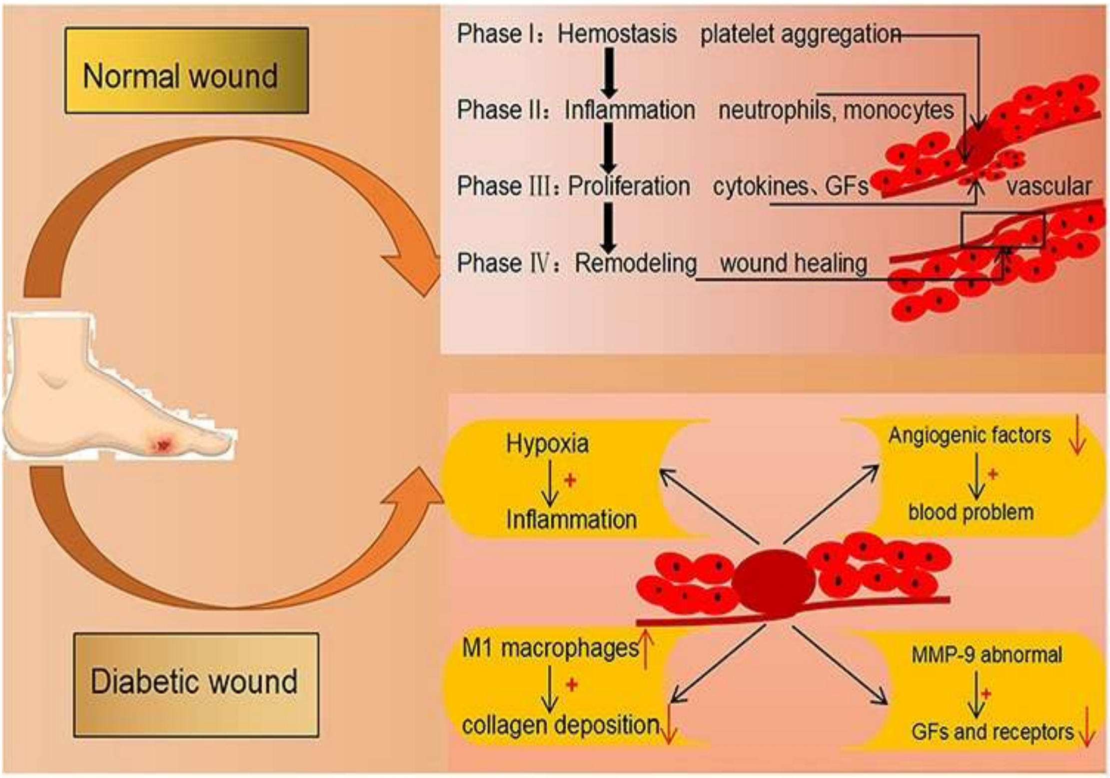


**Figure 3:** Mechanism of nanoparticles in normal and diabetic wound healing

### A) Role of photomodulation in Diabetic wound healing

**Nicolette Houreldet al., 2019** has studied on Photobiomodulation, a non-invasive light application, has been shown to accelerate wound healing, including diabetic foot ulcers, by promoting tissue regeneration, reducing inflammation, accelerating cell migration, and releasing growth factors.[1]. **Sandra Matabi Ayuk et al., 2016** has review on Wound healing involves cellular responses, with Matrix Metalloproteinases (MMPs) playing a crucial role in degradation, removing damaged ECM, breaking capillary membranes for angiogenesis, and remodeling tissue. The imbalance in matrix proteins (MMPs) in wounds can lead to impaired wound healing, a common issue in diabetic patients. This can result in chronic foot ulcers and amputation. The role of laser irradiation or photobiomodulation in diabetic wound healing is not fully understood [2].

### B) Role of Nano formulations in wound healing

**Lakshimipriya Sethuram et al., 2023** has analyzing. New advancements in wound care involve electrospun nanofibers impregnated with biological macromolecules, paving the way for the development of anti-scarring, high-effective wound scaffolds for drug delivery.[3]. **Yunwu Zhang et al., 2019** has evaluating One of the most obvious signs of diabetes mellitus is poor wound healing. Wounds heal more slowly in these patients due to reduced blood flow, chronic inflammatory reactions, infection, endothelial dysfunction, elevated reactive oxygen species, and metabolic disorders. Growth factors have been shown to have beneficial effects in the treatment of these wounds in earlier research. Nonetheless, a good delivery

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platform with a sustained release profile may increase their healing potential because of their short half-life and low stability. Previous studies have investigated the controlled and localized delivery of growth factors using electrospun fibers in great detail. The electrospinning technique, while not novel, has proven to be remarkably efficient in preparing growth factor delivery carriers.[4].

**Kang K et al., 2021** has studied on diabetes mellitus, a metabolic disorder, impairs barrier function and healing responses, particularly in the oral cavity, leading to exacerbated periodontal disease and delayed wound healing. It inhibits mitogenic growth factors and prevents mesengenic cell expansion [5]. **Wenqian Zhang et al.,2021** has explore Hyperglycemia leads to increased ROS and advanced glycation end products, activating metabolic pathways like the polyol pathway and PKC signaling, thereby suppressing antioxidant enzymes and compounds The study explores various factors that contribute to diabetic wound healing, including antioxidant therapy, vitamins, enzymes, hormones, medicinal plants, and biological materials.[6]. **Biruk Fentahun Adamuet al.,2021** has worked on Electrospun nanofibrous wound dressings are promising due to their unique properties, including morphological similarity to the natural extracellular matrix, high surface area to volume ratio, greater porosity, and continuous, flexible fibers. These dressings can promote tissue regeneration and wound fluid transportation.[7]. **Hira Choudhury et al., 2020** has studied about most severe co-morbidities are wounds related to diabetes mellitus, which may worsen and eventually result in cell necrosis and amputation. According to statistics on the current state of diabetic wounds, 15% of patients with the disease have amputations of limbs; 20% of these patients do not survive. Due to alterations in the damaged area's molecular architecture, conventional therapies are found to be ineffective, necessitating the use of novel deliveries. Current studies focus on creating novel, efficient materials for wound care. Under the general heading of nanotechnology, there is literature that offers potential instruments for topical medication delivery for wound healing; nano-scaffolds and nanofibers have demonstrated encouraging outcomes in this regard. The nano-sized particles are also known to promote healing of wounds by facilitating proper movement through the healing phases.[8].[46]. **Sandeep Shukla et al., 2019** has worked on Wound inflammation has a major influence on the cascade of wound healing; it is a swift and well-coordinated process. Following an injury, a sequence of processes begin, including phases of inflammation, proliferation, and maturation, which ultimately result in the closure of the wound and the restoration of normal skin integrity. Tissue damage and pathogenic microbial infection are examples of stimuli that can activate an inflammatory response or put the host immune system under stress. Numerous pieces of evidence demonstrate the beneficial effects of inflammation, including its crucial role in eliminating dead tissues from the site of injury and thwarting the attack of invasive pathogens. In addition to its beneficial effects, chronic inflammation can be harmful and cause the wound healing process to become deregulated, potentially resulting in excessive scarring.[9].[44]. **Denizhan Ozdemir et al., 2019** has outlined MicroRNAs regulate physiological processes in health and disease, including diabetic wound healing. They control gene expression and signaling pathways, potentially providing therapeutic opportunities through their versatile roles in inflammation, angiogenesis, and remodeling.[10]. **Naresh Kumar Rajendran et al.,2018** has developed The development of materials for wound dressings has reached a new level of research and understanding regarding the pathophysiology of chronic wounds. By promoting appropriate progression through the various stages of healing, nanotechnology provides an exceptional method for accelerating the healing of both acute and chronic wounds. Small-sized nanomaterials, nanoscaffolds, nanofibers, and biomaterials are employed in nanotechnology to deliver topical medications for wound healing. The use of nanomaterials in pharmaceutical and biomedical applications has grown significantly in popularity in recent years. As a result, a sizable portion of nanomaterials are employed in a variety of biomedical applications, such as medication delivery and wound dressings.[11].

**C) Role of medicinal plants and natural products in wound healing**

**Anuar Salazar-Gómez et al., 2022** has examined Scientific books and articles were consulted in order to perform an electronic database search. Based on traditional medicine, 305 plant species were found to have the ability to heal wounds. In Latin America, the majority of medicinal plants are applied topically to heal wounds; their preparation primarily involves infusing water into aerial parts. Five medicinal

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plants have had their wound-healing efficacy examined in clinical trials, but only 35 percent of the plants used in traditional medicine have had their pharmacological effects experimentally validated. All told, 25 compounds with the potential to heal wounds have been isolated from medicinal plants; therefore, a multidisciplinary approach evaluating the effects of medicinal plants on wound healing will require a great deal of work. These compounds are primarily terpenes and flavonoids.[12]. **Parmita Chanda et al.,2022** has studied on chemical investigation on Argemone mexicana reveals active compounds like Sanguinarine, Tetrahydrocoptisine, Chelerythrine, Dihydropalmatine Hydroxide, Protopine, and Berberine, with potential therapeutic properties for wound healing and anti-diabetic properties.[13]. **Elena Arribas-López et al.,2022** has review on a systematic review of the effect of Centella asiatica on wound healing. C. asiatica is a traditional medicinal plant used due to its antimicrobial, antioxidant, anti-inflammatory, neuroprotective, and wound healing properties.: Four clinical trials met the inclusion criteria. The following distinct areas were identified under C. asiatica: wound contraction and granulation; healing/bleeding time and re-epithelialization; VAS (visual analogue scale) scores; skin erythema and wound appearance. .c asiatica might enhance wound healing resulting from improved angiogenesis. This might occur due to its stimulating effect on collagen I, Fibroblast Growth Factor (FGF) and Vascular Endothelial Growth Factor (VEGF) production. Besides, C. asiatica has shown an anti-inflammatory effect observed by the reduction in Interleukin-1β (IL-1β), Interleukin-6 (IL-6) and Tumour Necrosis Factor α (TNFα), prostaglandin E2 (PGE2), cyclooxygenase-2.[14]. **Parmita Chanda et al., 2022** has extracted the Extracts of Argemone mexicana's leaves, stem, seeds, flowers, fruits, and roots have been shown to have anti-inflammatory, wound-healing, antidiabetic, anti-HIV, antimalarial, antifungal, and cytotoxic properties, among other properties. Native American tribes in Western parts of the United States and Mexico have long utilized Argemone mexicana, a stress-resistant member of the Papaveraceae family, as a traditional medicine. A. mexicana demonstrates sedative, antispasmodic, narcotic, and analgesic properties. A. Mexicana is used in Ayurveda, Unani, and Siddha traditional medicine in India to treat jaundice, ophthalmia, scabies, cutaneous affections, dropsy, and to maintain normal cholesterol and blood circulation in humans. These plant parts also have anti-venomous properties.[15]. **Jiaheng Liang et al., 2021** has evaluated Skin injury threatens health, and wound healing is crucial. Aloe vera, a medicinal plant, plays a significant role in wound healing, making its inclusion in wound dressings an ideal strategy.[16].[25].**Murugan Prasathkumar et al.,2021**Bioactive compounds from honey, plants, and marine resources are widely used in biomedical and tissue engineering applications. These biomaterials, including hydrogel, film, nanofiber, and sponge dressings, aid wound healing, cartilage repair, and antimicrobial effects.[17].[23].**Murugan Prasathkumar et al.,2021** has summarized that traditional herbal medicines are used to treat a variety of acute and chronic conditions with little to no harmful side effects. They have played a significant role in health systems throughout the world. Many health issues, such as TB, cancer, diabetes mellitus, heart disease, wound healing, asthma, pharyngitis, hypertension, and others, can be naturally treated with herbal plants. Because of their diverse pharmacological characteristics, plants rich in bioactive phytomedicine compounds, such as alkaloids, flavonoids, tannins, and polyphenols, have been used to treat illnesses. India has long been recognized as a rich source of medicinal plants, and many herbal medicine techniques are regarded.[18]..**Saeed Ebrahimi Fana et al.,2021** has studied on Wounds are physical and anatomical disruption in healthy skin and represent an important healthcare concern around the world. Wound healing is a complex and dynamic cascade of cellular and molecular interactions which include four main phases: hemostasis, inflammatory, proliferative, and remodeling. Therefore, some pharmacological activities such as anti-inflammatory, antioxidant, and antimicrobial activities can play a key role in the process of al to heal wound [19]. **Akshay Sharma et al.,2021** has review on the goal of the current review article is to include medicinal plants that have been shown to be useful in the management of wounds. Plant-based wound dressings, including patented formulations reported by various inventors, have also been systematically discussed. In conclusion, the collected data is intended to provide scientists and researchers with an updated perspective on the significance and function of plant-based components in the management and treatment of wounds.[20].[17]. **Era Refianiet al.,2021** has examined One of the conditions brought on by diabetes mellitus is diabetic foot pain and ulcers

(DM). According to Ministry of Health data from 2014, 54% of Indonesians had diabetic foot ulcers. Infection and tissue death are possible side effects of diabetic foot ulcers. Antimicrobials, biomaterials, and active compounds found in ointments or gels have been used to treat diabetic foot ulcers, hastening the healing process. It has been extensively documented that medicinal plants contain active compounds that can be used to treat diabetic foot ulcers. Examining the therapeutic effects of active substances involved in wound healing is the goal of this article.[21]. [18].

**Mikaella TB. Carvalho et al., 2021** has analyzed The inflammatory process, angiogenesis, re-epithelialization, and oxidative stress were all affected by flavonoids. It has been demonstrated that they have the ability to influence macrophages, fibroblasts, and endothelial cells through the facilitation of TGF-β1, VEGF, Ang, Tie, Smad 2 and 3, and IL-10 release and expression. In addition, they managed to lower the M1 phenotype, NFκB, ROS, and inflammatory cytokine release. The way that flavonoids acted was by positively regulating MMPs 2, 8, 9, and 13, as well as the NO, PI3K/Akt, and Ras/Raf/MEK/ERK pathways. The development of therapies for skin lesions can benefit from the use of flavonoids, and our review offers a solid scientific foundation for upcoming basic and translational studies.[22].[31]. **Omid Yazarlu et al.,2021**has expressed Certain herbal remedies elevate the expression of transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF), both of which are crucial in promoting angiogenesis, granulation tissue development, collagen fiber deposition, and re-epithelialization. A few other herbal medications that are used as wound dressings block the expression of TNF-α, IL-1β, and iNOS proteins, which results in the induction of antioxidant and anti-inflammatory characteristics during different stages of the wound healing process **[23]. Caroline Tyavambizaet al., 2021** has identified For centuries, Africans have utilized medicinal plants as a source of medicine. African medicinal plants are still used extensively in the treatment of wounds today. Even with the use of conventional therapies, chronic wounds are linked to significant healthcare and socioeconomic costs. The potential to develop effective wound healing therapeutics with improved wound repair mechanisms lies in the emergence of novel wound healing strategies utilizing medicinal plants in conjunction with nanotechnology. This review identified biogenic nanoparticles and African medicinal plants that have antibacterial, antioxidant, and anti-inflammatory properties in addition to improved wound contraction and epithelialization, all of which are used to promote wound healing.[24].[13].**Rajeshwari Prabha Lahareet al.,2020**has studied on Mostly used to treat diabetes and cancer, Catharanthus roseus is a significant evergreen medicinal herb belonging to the Apocynaceae family. With a height of one meter, the plant was widely grown for commercial purposes in Southern Europe, India, Australia, and Africa. The primary constituents of plants are flavonoids, phenolic, and alkaloids like vinblastine and vincristine. The plant has a number of biological characteristics, including wound healing, antimicrobial, anticancer, antioxidant, anti-hyperglycemic, and antihypertensive effects. We have attempted to gather information about the plant's pharmacological qualities, phytochemical components, and traditional uses in this study [25]. **Rachel Samuelson et al.,2020** has scientifically worked on the purpose of this review is to provide the scientific literature on therapeutic lavender essential oil in an effort to increase the number of affordable wound healing options currently offered to patients and doctors. This study makes use of in vitro research (n = 2), animal trials (n = 5), human clinical trials (n = 7), and earlier reviews (n = 6). Overall, these studies demonstrated that wounds treated with essential oil of lavender exhibited faster healing times, higher levels of collagen expression, and higher activity levels of proteins involved in tissue remodeling.[26].[30]. Mohammad Fazil et al.,2020 Wound healing is a significant research area in contemporary medicine, with Unani, a traditional medicine system, describing wounds under qarha and jarāhat headings. Several herbal, mineral, and animal drugs have been tested, but their potential remains unexplored.[27].[16].**Nusaibah Sallehuddin et al.,2020** has studied on Nigella sativa (NS) has been found to have therapeutic effects on skin wound healing due to its anti-inflammatory, tissue growth stimulation, and antioxidative properties. Thymoquinone, with its anti-inflammatory, antioxidant, and antibacterial properties, significantly aids in the healing process of wounds [28]. **Susmita Poddar et al.,2020**has examined that plant secondary metabolites serve as defense mechanisms against diseases, boosting human immunity. This review examines traditional medicinal plants in India, known for their pharmacological properties, and compiles ethnomedicinal plants that provide protection

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against various ailments [29]. **Constance Chingwaru et al.,2019** has studied on Many plants have long been used in remedies to treat various illnesses and encourage the healing of wounds. Nevertheless, it is still unknown what mechanisms and efficacies underlie their ability to heal wounds. Twenty Southern African medicinal plant species from 14 families were found in this review, and they have been used historically as wound-healing medicines. Overall, there is a high concentration of alkaloids, cannabinoids, phenolic acids, flavonoids, saponins, steroids, and/or tannins in the chosen medicinal plants listed here. According to reports, these substances accelerate wound healing by mopping up reactive oxygen species from injured tissues, inhibiting or eliminating infections that impede wound healing, reducing inflammation, and altering endocannabinoid system pathways.[30].[21]. **Oluwafemi et al., 2019** has studied the internal and external biological organs heal wounds through a number of intricate, overlapping processes that require efficient cell-to-cell communication. The process is characterized by hemostasis, inflammation, proliferation, and remodeling. It is highly controlled and organized. By 2040, it is expected that the number of people with diabetes worldwide would exceed 642 million. Vascular problems and the inability of the diabetic body's wound-healing mechanisms to function properly are the driving forces behind the rise in diabetes-related morbidity and death.[31]. **Amin Derakhshanfaret al.,2019** Physical injuries that alter the typical structure and function of the skin are called wounds. It also has a significant effect on health care costs. Similar in both human and mammalian species, wound healing is a multifaceted, dynamic process that involves four stages to restore skin cellular structures and tissue layers. Electronic databases, including.Many Iranian medicinal plants have the potentiounds on the skin; however, the volume of research on these plants is much less than that of their clinical applications and manufacturing.[32]. **Soliman Amro M.et al., 2019** has studied Many medications were tried to treat DM, but they had side effects. Patients frequently did not follow through on this kind of care. Alternative and complementary medicine now have easier access as a result. We examined the molecular theory of wound healing in its various stages in the current review, with a focus on diabetes mellitus. Additionally, we highlighted the potential herbal products, including NF3 (Chinese 2-Herb Formula), Zicao, Jing Wan Hong ointment, Aleovera, a combination of Commiphoramolmol, Adiantum capillus-veneris, Aloe vera, and henna, as well as Jinchuang ointment, San-huang-sheng-fu (S) oil, Yi Bu A Jie extract, and several others.[33]. [5]. **Aleksandra Shedoeva et al., 2019** has studied on dysregulation in any phase of the wound healing cascade delays healing and may result in various skin pathologies, including nonhealing, or chronic ulceration. Indigenous and traditional medicines make extensive use of natural products and derivatives of natural products and provide more than half of all medicines consumed today throughout the world. This study explores the use of 36 medical plant species, including Centellaasiatica, Curcuma longa, and Paeonia suffruticosa, for wound healing, highlighting their clinical uses, preparation methods, and clinical value **[34]. Rafia Rahman et al.,2019** has investigated Kalanchoe pinnata leaves contain "bufadienolides" with insecticidal, chemo-preventive, anti-tumor, and anti-bacterial potentials, including bryotoxin-A, bryotoxin-B, bryotoxin-C, cardiac glycoside, digitoxin, and digoxin. Kalanchoe pinnata leaves contain numerous anti-ulcer compounds, including triacontane, taraxerol, and other flavonoids. They also exhibit wound healing, insecticidal, anti-inflammatory, anti-allergic, anti-microbial, anti-tumor, and CNS depressant activities, as well as anti-oxidant and anti-diabetic potentials.[35]. **Soliman, Amro M et al.,2019** has looked at the molecular theory of various stages of wound healing, with DM receiving particular attention. Additionally, we highlighted some potential herbal remedies that could be used to treat diabetic wounds: NF3 (Chinese 2-Herb Formula), Zicao, Jing Wan Hong ointment, Aleovera, mixture of Adiantum capillus-veneris, Commiphoramolmol, Aloe vera, and henna; Phenol-rich compound sweet gel; Jinchuang ointment; San-huang-sheng-fu (S) oil; Yi Bu A Jie extract; Astragali Radix (AR) and Rehmanniae Radix (RR); YiqiHuayu, Tangzuyuyang ointment, ShengjiHuayu recipe; Angelica sinensis, Lithospermunerythrorhison, Hippophaerhamnoides L., Curcuma longa, and Momordica charantia.[36].[50].**Tarcisio Lordani et al.,2018** Out of the ten selected studies, eight were published between 2007 and 2016, with 503 patients in total. Twelve plant species from eleven families were included in the analysis of the species used to cure human skin problems. For the treatment of cutaneous lesions, every plant species under investigation showed great therapeutic

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promise. Rafael Vitor Augusto Lordani, Celia Eliane de Lara, Fabian Borges Padilha Ferreira, Mariana de Souza Terron Monich, Claudinei Mesquita da Silva, Claudia Regina FelicettiL ordani, Fernanda Giacomini Bueno, Jorge Juarez Vieira Teixeira, and Maria Valdrinez Campana Lonardoni are the names of the individuals who were involved.[37].[3].**Ashang et al., 2017** Growth factors (GFs) are considered a potential treatment for diabetic wounds, but their efficacy and environment make it challenging to find an ideal route. Using therapeutic genes and implantable biomaterial dressings could offer potential solutions to this overgrowing issue [38].**George Han et al., 2017** The intricate, tightly controlled process of wound healing is essential to preserving the skin's barrier function. The chain of events that leads to wound healing can be impacted by a variety of disease processes. This can lead to chronic, non-healing wounds that cause the patient great discomfort and an immense amount of resource depletion for the medical system. Many factors must cooperate for a superficial wound to heal, and wound dressings and treatments have advanced significantly to address potential obstacles to wound healing, such as infection and hypoxia. Chronic non-healing wounds can arise from multiple aberrant healing states, and even in the best of circumstances, wound tissue never recovers to its pre-injury strength.[39]. **Robert J. Snyder S et al**.,**2016** Macrophage therapy advances due to early recruitment crucial for wound healing, but higher quality evidence and understanding of macrophage polarization, activation, and repair mechanisms are needed.[40]. **Christian Agya et al.,2016** has studied Numerous wounds, such as burns, cuts, pressure ulcers, diabetes, gastric ulcers, and duodenal ulcers, continue to have a significant socioeconomic impact on the expense of medical care for patients, their families, and healthcare facilities in both developed and developing nations. But the majority of people in developing nations, particularly in Africa, rely on herbal remedies to effectively treat wounds. The functional activity of medicinal plants is assessed using a range of in vitro and in vivo parameters utilizing extracts, fractions, and isolated compounds. Finding African medicinal plants that have demonstrated the ability to heal wounds during the past 20 years is the review's main goal.[41].[7].**Kiran et al.,2016** has investigated the PLGA which is a biodegradable polymer approved by food and drug administration and European medicines agency for parenteral administrations, encapsulating drugs targeting wound healing phases.[42]. **Roodabeh et al., 2014** has reported the complex process of healing burn wounds involves granulation, neovascularization, contraction of the wound, inflammation, and re-epithelialization. The process of burn healing involves multiple biochemicals, such as cytokines, antioxidants, and biomarkers for liver and kidney damage. Even though there are a number of burn wound preparations available, research into effective medications is still necessary. The current study set out to assess the phytochemical components of herbal preparations and their potential for managing burn wounds. In order to achieve this, electronic databases from 1966 to July 2013 were searched, including Pubmed, Scirus, Scopus, and the Cochrane Library, for in vitro, in vivo, or clinical studies that looked at the impact of any herbal preparation on various burn wound types. This review only found three human studies to include. [43]. **Merish et al., 2014 has reported** the one of the oldest traditional medical specialties in the world, the specialty's significance is currently being felt and discussed extensively. In addition to its amazing healing abilities, it is also said to lack remedies for medical emergencies like heart problems, severe respiratory illnesses, bleeding disorders, etc. Nonetheless, our ancestors dealt with similar circumstances for centuries prior. The Siddhars, who founded Siddha Medicine, used a variety of herbs in the past to treat heart and respiratory ailments, wounds, snake and scorpion bites, and dreaded diseases like cancer and STDs/VDs. They also documented their treatments with palm leaf manuscripts, stone and copper scriptures, and other materials. The parameters and treatment options have evolved with the advancement of medicine.[44]. **Liane Moura et al., 2013** has investigated the diabetes-related diabetic foot ulcers (DFUs) are a chronic, non-healing complication that can result in expensive hospital stays and, in severe situations, amputation. Peripheral vascular disease, diabetic neuropathy, and aberrant cellular and cytokine/chemokine activity are some of the primary obstacles to diabetic wound healing. DFUs pose a significant and ongoing challenge to the creation of innovative and effective wound dressings. Generally speaking, the best wound dressing should remove exudate from the wound, offer protection against secondary infections, keep the wound moist, and encourage tissue regeneration. The choice of the appropriate dressing is contingent upon the type and stage of the wound, the extent of the injury, the patient's condition, and the tissues involved, as no dressing currently in use satisfies all the requirements associated with DFU treatment. There are various kinds of commercially available at the moment.[45]. **Kumarasamyraja et al., 2012** has reported that Ayurveda, the traditional Indian medical system, attributes anti-aging and wound-healing qualities to a variety of herbs, fats, oils, and minerals. Injuries to the skin that cause disruptions to the soft tissue result in wounds. One definition of wound healing is a complex, dynamic process that restores anatomic continuity and function. Over the years, many plant products have been used to treat wounds. Herbal extracts for wound healing help clot blood, prevent infection, and hasten the healing process [46]. **Gulzar Alam et al., 2011** has studied about the process by which tissue regenerates is called wound healing. The management and treatment of wounds can greatly benefit from the use of plants and their extracts. In addition to being inexpensive and accessible, phyto-medicines for wound healing are also said to be safe because overly sensitive reactions are not common when using these treatments. Through a variety of mechanisms, these natural agents promote the regeneration and healing of the lost tissue. [47]. **Nathan B. Menke et al.,2007** has reported that Monotherapies fail due to under appreciation of wound healing complexity, leading to no significant reduction in healing times. Inflammation profile shifts balance between synthesis and degradation [48].

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