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EXPLORING THE TOPICAL FORMULATION FOR MANAGEMENT OF DIABETES WOUND HEALING - A REVIEW

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ABSTRACT: Diabetes is a multifaceted metabolic disorder that impacts individuals worldwide, and delayed wound recovery is a prevalent symptom of diabetes. There is a plethora of methods available now to heal these wounds. Since, chronic inflammation and untreated stages may lead to amputation and death. So, their consequences may cause a patient's financial strain. However, this review focuses on the most recent formulation, such as miRNA, biomarkers, exosomes, leucine-rich glycoprotein, neutrophils, pro-inflammatory (M1) macrophages, pro-remodeling (M2) macrophages, sustained activation of neutrophils, endothelial progenitor cells, Scaffold, biofilms, carriers, fibers, mats, and antibiotic management for diabetic wound treatment. We discussed their roles as well as therapy plans for managing diabetic wounds with the latest technologies.

INTRODUCTION: Diabetes Mellitus, is a serious metabolic disorder, is recognized as a global epidemic by WHO [1, 5, 7]. In Diabetes, body cannot produce enough and sufficient hormone insulin which occurs hyperglycemia. is chronic metabolic disorder with severe complications i.e. cardiopathy, nephropathy, retinopathy and macro vascular disease, kidney impairment and diabetic wounds. Diabetes is a chronic metabolic disorder which is accomplished with the disturbance of metabolism of carbohydrates, fats and protein. The risk of foot ulcers, amputation, peripheral neuropathy, and autonomic dysfunction may be associated with the dysfunction of pancreatic hormones, such as insulin secretion, action, or both, in diabetes [7]. Diabetes elevates the risk of micro and macro vascular impairment, which is complicated and devastating.

This kind of impairment any lead to chronic lesions and amputations [8]. Worldwide, 25% of patients of Diabetes Mellitus have a chances to develop diabetic wounds. Diabetic wound may associate with poor healing with gangrene and amputation [9]. These wounds could elevate the risk of mortality, reduce patients' quality of life, and place a financial burden on them [10].

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Wound healing may altered or delayed in each phase i.e. the homeostasis, inflammation, proliferation and remolding phase due to the decreased production of college content and oxidative stress [9]. Though wound healing required proper and complete management of improving quality of life [9]. Diabetic wounds may develop as open and non-healing ulceration on toes, foot or legion the study basis, approximately 15% of all people with diabetes concurrently have non-healing type diabetes wounds [7].

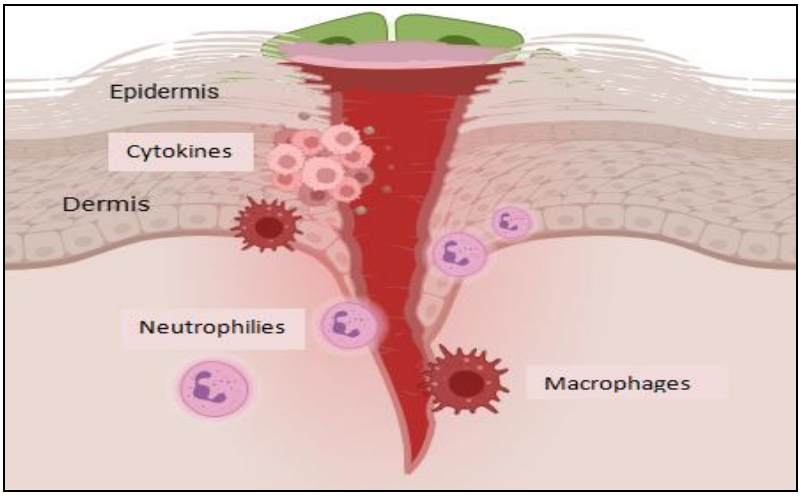

FIG. 1: MECHANISM OF DIABETIC WOUNDS

Pathogenesis of Wound (Mechanism): Diabetes-related wounds with poor healing are among the most prevalent significant complications, resulting in severe infections, probable amputation, and a low quality of life.

Wounds related of hyperglycemic conditions associated with the destruction of multiple layers of dermal tissues likewise it covers the epidermis and dermis part of the skin. In cases, it is related to the subcutaneous tissues as well. According to the studies, 15% of diabetic patients experience skin ulcerations on the lower extremities i.e. thigh portion, lower leg and the foot (it is mostly occurring on the feet). Due to the high risk and life-altering procedure, it may lead to non-healing wounds. The exceptionally complex path physiology occurred due to persistent hyperglycemia which results in complications associated to the diabetic wounds [10, 11]. Diabetes foot ulcers, on the other hand, can cause foot deformities and increased skin pressure when walking [3]. However, it may increase the risk of limb invasive infection, potentially leading to lower limb amputation [4]. As a result, when diabetes patients have DFU, it is critical to improve wound healing [12].

Wound healing in diabetics might be impaired because the chronic nature of the disease and its effects on several physiological processes. Diabetes may disrupt wound healing through a variety of pathways, and each stage of wound etiology in diabetes presents unique obstacles.

Here are the Key Stages:

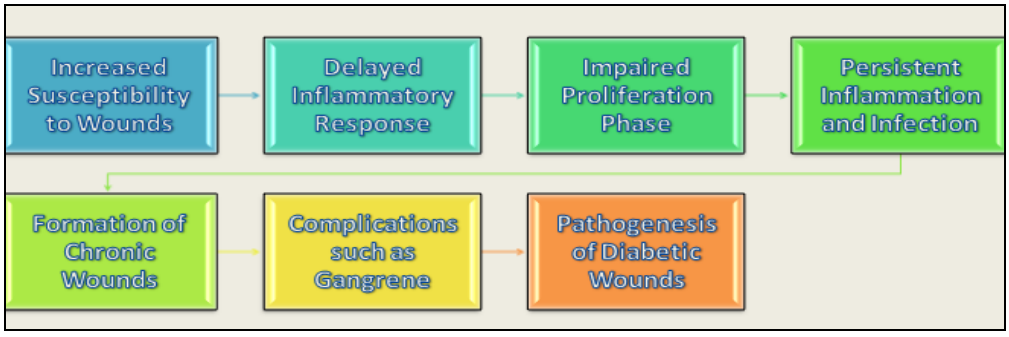

FIG. 2: PATHOGENESIS OF DIABETIC WOUNDS

Increased Susceptibility to Wounds:

- Diabetes can lead to peripheral neuropathy (nerve damage), reducing sensation in the extremities.
- Neuropathy can lead to unrecognized injuries or wounds which lead to pain or discomfort.

Delayed Inflammatory Response:

- ❖ Diabetes patients may have impaired inflammatory phase.
- ❖ Reduced recruitment and function of immune cells (such as neutrophils and macrophages) can hinder the clearance of debris and pathogens from the wound site.

Impaired Proliferation Phase:

- Diabetes can affect the function of fibroblasts and endothelial cells, leading to delayed collagen production and blood vessel formation.
- Reduced growth factor activity may further slow down tissue repair and regeneration.

Persistent Inflammation and Infection:

- ❖ Uncontrolled diabetes can cause persistent inflammation and delay wound healing.
- ❖ Elevated blood glucose levels raise the risk of infection by encouraging the growth of germs.

Formation of Chronic Wounds:

- Patients with diabetes are at an increased risk of developing chronic ulcers from wounds.
- Chronic wounds often have a prolonged inflammatory phase and impaired tissue repair, contributing to persistent open sores.

Complications such as Gangrene:

In severe cases, impaired blood flow (due to diabetes-related vascular complications) can lead to tissue death, a condition known as gangrene.

Additionally, these issues are linked to–

a) Barrier disruption and infection

b) High oxidative stress

c) Neuropathy

d) Micro vascular complications

e) Suboptimal chronic inflammatory response.

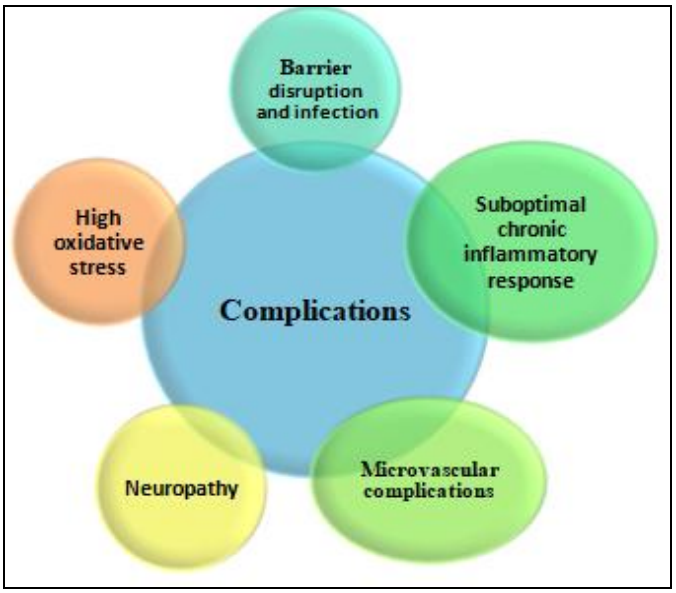

FIG. 3: COMPLICATIONS ASSOCIATED WITH DIABETIC WOUND HEALING

Angiogenesis: Angiogenesis is the formation of additional blood vessels from existing ones. In addition to providing nutrition and oxygen to the injured area, it aids in wound healing and is crucial for human growth and development. The process by which endothelial cells stimulated by extracellular matrix proliferate quickly, migrate to the stimulation site, and finally accumulate cells to support the development of new blood arteries and networks is known as angiogenesis. The restoration of angiogenesis facilitates diabetes-associated foot ulcer wound healing, as high glucose may directly block normal angiogenesis through endothelial dysfunction and an imbalance among components related to angiogenesis [12].

Topical Formulations and Management for Diabetic Wounds:

Role of Neutrophil Extra Trap for Foot Ulcers [13]: Study the role of neutrophil in diabetic foot ulcers. In hyperglycemia, inflammation and tissue damage may occurs frequently. Formulation of neutrophil extracellular traps can promote the release pattern of neutrophil that worked against the infection. Protein arginine deiminase 4 (PAD4)

deletion inhibits NETosis, and deoxyribonucleic I (DNase I) disrupts NETs, which speeds up wound healing in diabetic foot ulcer cases, according to studies. ETs-specific indicators were highly correlated with delayed wound healing and limb amputation in DFU patients treated in a multidisciplinary environment. The microenvironment around the foot ulcer stimulates neutrophils to release NETs, which contribute to poor wound healing.

Ulandari R., (2023) [17] and coworkers explore the involvement of neutrophils in ulcers caused by diabetes. In their investigation, the neutrophil lymphocyte ratio was utilized as an indicator for the evaluation of a retrospective analysis of 120 patients. Among 120 patients, two groups were formed: 60 with diabetic foot ulcers patients and 60 without ulcers. Flow Cytometry method is used for routine test of Leukocytes, neutrophils, lymphocytes and Neutrophil Lymphocyte Ratio (NLR). Mann-Whitney test, Krushal –Wallis test were performed to observe the relationship between NLR and Wager's. With significant statistical test results ($p<0.037$), the correlation between the NLR and Wagner's classification was lowest at Wagner grade 2 (6.18±7.83) and highest at Wagner grade 5 (12.87±5.0). Systemic inflammation caused an increase in NLR in T2DM patients. The NLR incorporates multiple immunological pathways, including lymphocytes that regulate inflammation and neutrophils that initiate an inflammatory response. T2DM patients with diabetic foot ulcers had greater lymphocyte counts and NLR levels than those without.

Ibrahim I *et al.*, (2024) [2] the prospective study included three cohorts: 200 persons with type 2 diabetes mellitus (T2DM) with DFU, 42 newly diagnosed T2DM patients, and 38 healthy donors. Serum levels of NETs were measured in all groups, and the predictive value for DFU-related disability was investigated. The findings revealed that serum NET levels in the DFU group were considerably greater than in the T2DM group. Multivariate Cox regression revealed that blood NET levels, diabetic foot surgery historical events, and Wagner grade were all risk factors for amputation. Elevated serum NET levels are a simple serological prognostic diagnostic for determining the likelihood of DFU-related amputation.

Bernhardt, G.V. (2021) [19] the study comprised 43 persons with non insulin type diabetes and their coworkers, with 18 having foot ulcers and 25 not. During the study, neutrophil phagocytic activity was measured, and the proportion of neutrophil phagocytic impairments was calculated after two weeks of usual treatment for foot ulcers. Oxidative imbalances and disruptions in glucose metabolism served as the foundation for phagocytic activity. Because the immune system in diabetes is weakened, phagocytic deficiencies are uncontrollable. NADPH was used by sorbitol-aldose reeducates in the metabolism of carbohydrates, which reduced its availability to phagocytes and oxidation. Consequently, it undermines the body's defense system. Patients with diabetes would have higher respiratory brute forces, which generate free radicals, if they had unstipulated neutrophils. In diabetic individuals, the amount of oxidative stress is increased by free radicals. As a result, it lowered bactericidal activity. As a result, it may reduce the ulcer effect in diabetes patients.

Sathvik, M., *et al.*, (2023) [20] studied the link between neutrophil-lymphocyte ratio (NLR) and diabetic foot ulcers was examined since the NLR is a specialist instrument used to measure the body's prognosis for inflammation. The link between NLR and diabetic foot ulcer healing lends validity to the notion. The study comprised 100 diabetic foot ulcer patients who had surgery. The demographics of ulcer patients were documented on a daily basis. The ulcer status was improved after six weeks, and the outcomes were compared to the NLR value. The neutrophil-lymphocyte ratio averaged 6.65%, whereas neutrophils averaged 94.73%, lymphocytes averaged 14.97%. 58% of ulcers healed, whereas 42% did not. About 44% of research participants have an NLR <6, while 56% have an NLR >6. In 58 participants with healing ulcers, 75.9% had NLR < 6, whereas in 42 subjects with non-healing ulcers, 100% had NLR >6, suggesting statistical significance. As a result, NLR is used as a biomarker to track the healing of wounds of foots.

Kaur, T., *et al.*, (2020) [21] research on the diabetic milieu for the creation of neutrophil extracellular traps (NETs), which destroy neutrophils. As a result, the decreased availability of neutrophils

inhibits the growth of inflammation in the initial stages of ulcers. They developed the alginate-GelMa based hydrogel scaffold. These scaffolds contained tripeptide that antagonized the PADA4 enzyme. One of the objectives of the study was to inhibit the PADA4 enzyme since it improves wound healing in diabetes. The scaffolds' physicochemical and biological properties were thoroughly investigated. Neutrophil-scaffold interactions are also examined in terms of NETosis capacity and the release of other important biomarkers. A cell migration experiment is performed to assess wound healing capacity. The in vivo wound healing effectiveness of the newly developed scaffolds was determined using a diabetic rat model. The findings suggest that NETosis is reduced in the existence of a PAD4 inhibitor. Thus, the study introduces a new scaffold technique for delivering the PAD4 inhibitor, which can potentially be employed to treat NETosis and enhance wound healing.

Huang, W., and coworkers (2020) [22] Investigate the involvement of neutrophil extracellular traps (NETs) in diabetic wound healing. In diabetic foot ulcers, neutrophils produce more neutrophil extracellular traps (NETs), which significantly increase growth factor VIII (MFG-E8) levels. In the Diabetic mice model, MFG-E8 exaggerated inflammatory response that further enhanced the leukocyte infiltration, excessive activation of IL-1β, IL-18, and TNF-α. Largely lodged NETs, resulting in poor angiogenesis and wound closure. MFG-E8-deficient neutrophils create more NETs than wild-type neutrophils whenever stimulated with high doses of glucose or IL-18. When stimulated with high dosages of glucose or IL-18, MFG-E8-deficient neutrophils produce more NETs than wild-type neutrophils do. Recombinant MFG-E8 injection effectively reduced IL-18-induced NETosis in WT or Mfge8−/− neutrophils. MFGE8−/− macrophages had much more NLRP3 inflammation activation and IL-1β/IL-18 production than WT macrophages. Administration of rmMFG-E8 greatly reduced these effects. NET and mCRAMP (component of NETs, the murine equivalent of cathelicidin LL-37 in human). As a result, study found that exogenous rMFG-E8 enhances angiogenesis and accelerates wound healing by inhibiting the "NLRP3 inflammation-NETs" inflammatory loop, implying that DFUs may have therapeutic potential.

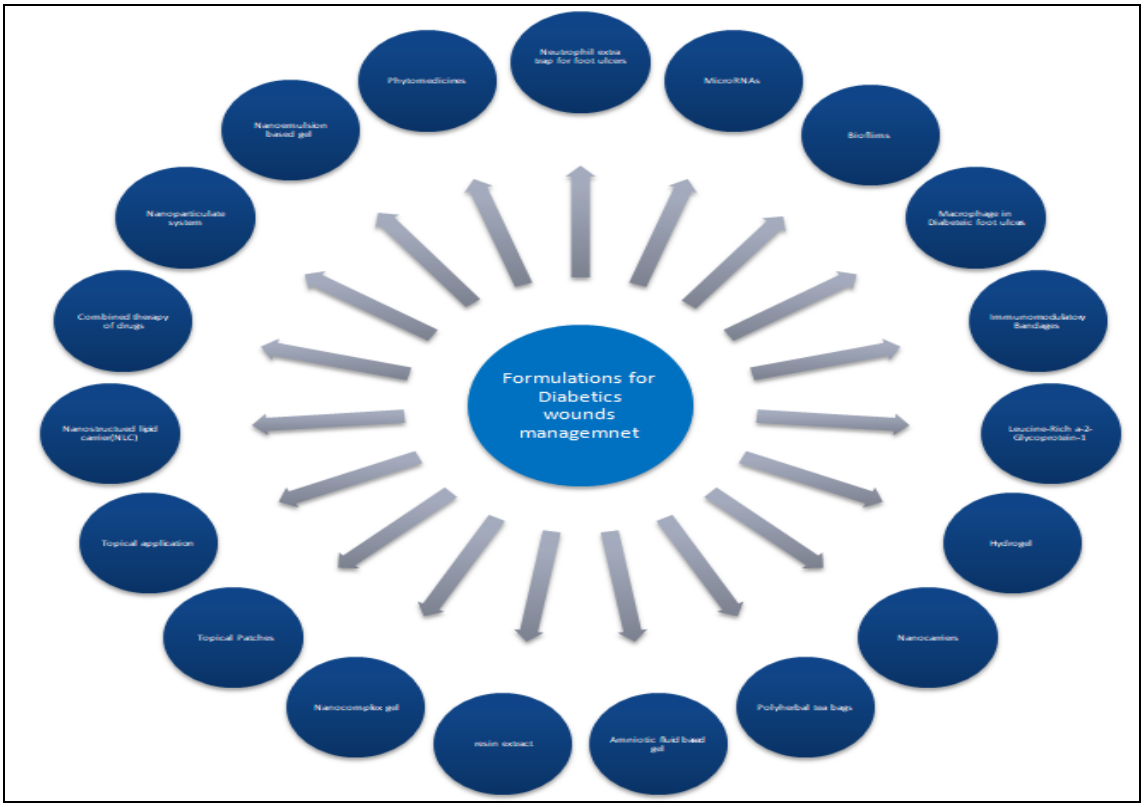

FIG. 4: TOPICAL DRUG MANAGEMENT FOR DIABETIC WOUND HEALING

Role of MicroRNAs: Zhao., *et al.,* (2022) [14] MicroRNA was analyzed for its significance in diabetic wound healing. MicroRNA is a type of endogenous non-coding RNA that contributes in wound healing. The experiment determines the expression of the wound gene using miRNA-103 and investigates the association between miRNA-103 and diabetic wound healing. The healing of wounds is a complex process that consists of four distinct stages: homeostasis, inflammation, proliferation, and remodeling. These mechanisms are pathologically increased in diabetic wounds, which may contribute to DFU healing delay. Diabetics are more vulnerable to bacterial infections and have poor wound healing abilities. This susceptibility is thought to be due to abnormalities in glucose metabolism and related changes in metabolic pathways. In addition, diabetes had significant impacts on macrophages and the wound healing process, which is most likely caused by alterations in many components of the diabetic environment. The PCR approach is used to study the procedure of wound regeneration in diabetics after miRNA-103 administration. It was utilized to measure the gene expression levels in volunteer wound border tissues. In vitro investigations were also carried out to determine how miR-103 affects the damage caused by high glucose levels on normal human dermis fibroblasts (NHDFs).

Xu, J., *et al.,* (2020) [23] prepared miRNA derived exosomes for the healing of diabetic wound. These exosomes were developed from endothelial progenitor cells which accelerated skin wounds effectively in control and diabetic mice in experiment. Endothelial progenitor cells (EPCs) are precursor cells for the inflammatory reaction and high-sugar milieu of a diabetic wound, however, can impede the proliferation, adhesion, and migration in blood vessel synthesis and reduce their quantity, ultimately impairing blood vessel function. EPC inhibit function, preventing wound angiogenesis and slowing wound healing. Exosomes serve an important function in transporting autocrine and paracrine information throughout cells. Cells targeted may coordinate the exchange of data between cells and regulate physiological and pathologic functioning by fusing with exosomes, which subsequently transmit encapsulated substances such as proteins, lipids, or RNA to such cells. EPC-derived exosomes include numerous types of regulatory chemicals, particularly miRNAs, which have been demonstrated to play an important role in angiogenesis. We used high-throughput sequencing to determine if miRNAs found in EPC-produced exosomes are important for wound healing. The skin healing gene sequence MiRNA-221-3p was employed to manufacture Exosomes. The skin wound improved significantly with the treatment of MIRNA-221-3p. Immunohistochemical analysis demonstratred that when EPC-derived exosomes and miRNA-221-3p were introduced, the level of expression of the angiogenesis-related proteins VEGF, CD31, and the cell proliferation marker Ki67 increased. Through bioinformatics assessment, miRNA-221-3p has been connected to the AGE-RAGE signaling pathway *via* cell cycle control and pathway involves p53 that may contribute to diabetic complications. Researchers determined that miRNA-221-3p is one of the foremost prevalent miRNAs in EPC-derived exosomes and enhances cutaneous wound healing in diabetic mice. The study presents a potentially groundbreaking strategy for medical management of diabetic skin lesions and elucidates the molecular process underlying exosomes formed from extracellular matrix (ECM).

Li, B., [24] and their coworkers (2020) studied role of MSC-derived exosomes which containing long non-coding RNA. It was projected that lncRNA H19 would bind to microRNA-152-3p (miR-152-3p), which was intended to target the chromosometen deletion of phosphatase and tensin homolog (PTEN). In DFU samples, fibroblasts expressed low levels of lncRNA H19 and PTEN but high levels of miR-152-3p, indicating an active PI3K/Akt1 signaling pathway. These fibroblasts were co-cultured with MSCs expressed with lncRNA H19 and MSC-derived exosomes to investigate the effect of the lncRNA H19/miR-152-3p/PTEN axis on fibroblast biological activity and inflammation.

Streptozotocin was used to create mouse models of DFU by injecting MSC-derived exosomes that over expressed lncRNA H19. The mechanism of increased wound healing in DFU related to promoted fibroblast proliferation and migration, as well as decreased apoptosis and inflammation.

lncRNA H19 in MSCs was transmitted through exosomes to fibroblasts. Mice with DFU showed improved wound healing after injecting MSC-derived exosomes that over expressed lncRNA H19.When combined; MSC-derived exosomal lncRNA H19 inhibited miR-152-3p-mediated PTEN suppression, which in turn promoted the wound-healing process in DFU by preventing fibroblast death and inflammation.

Ban, E., [25] and coworkers (2020) focused on the role that miRNA plays in controlling diabetic wound healing. Intradermal miRNA injection demonstrated a possible response for diabetic wound healing. The effects of miRNA-4997 on inflammatory cytokines were examined in human dermal fibroblast cells underwent treatment with lipopolysaccharide and high glucose, as well as diabetic mouse ulcer infections. In diabetic mice, intradermal administration of miRNA-497 around full-thickness lesions on the skin significantly accelerated wound closure compared to control miRNA. In vivo and in vitro, miRNA-497 lowered pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. The anti-inflammatory effects of miRNA-497 give information about how rapidly diabetic wounds heal. Finally, miRNA-497's capacity to decrease the level of pro-inflammatory cytokines makes it an intriguing potential replacement therapy for wound healing in diabetic patients.

Liechty, C., [26] and coworkers (2020) investigated and discovered that the lasting chronic inflammation is the major reaction contributing to the creation of diabetic wounds. The pro-inflammatory (M1) macrophages' prolonged discharge is what causes wounds to regularly grow. miRNAs have been employed to regulate gene modeling in wound healing by improving the macrophage remodeling mechanism. MicroRNA-21 (miR-21) plays a critical role in the inflammatory immune response. MiR-21 regulates inflammation by stimulating the polarization of M1 macrophages as well as the development of reactive oxygen species (ROS). miR-21 regulates inflammation by boosting M1 macrophage polarization and ROS generation. To assess miR-21 transcription and macrophage polarization, both an *in-vitro* and *in-vivo* mouse wound healing model were used. First, we discovered that miR-21 expression patterns differ at each stage of the healing process in diabetic wounds. During wounds caused by diabetes, the prevalence of miR-21 was greater in the initial and final phases of wound healing, but it dropped dramatically in the middle of the period of wounding (days 3 and 7 following wounding). In addition to the M1 marker, M1-polarized macrophages expressed higher levels of pro-inflammatory markers such as IL-1b, TNFa, iNos, IL-6, and IL-8. Over expression of miR-21 in macrophage cells increased miR-21 expression as well as the production of M1 markers such as TNFa, iNos, IL-6, and IL-1b. Furthermore, hyperglycemia elevated NOX2 expression and ROS production through the HG/miR-21/PI3K/NOX2/ROS regulatory pathway. These findings show that miR-21 has an essential role in inflammation management.

Role of Bioflims: Xie, X., (2020) [27] and coworkers studied Biofilms of *S. aureus* is formulated for the treatment of diabetes foot ulcers. Biofilm is prepared from the advance form of *S. aureus* strains; *in-vitro* methicillin-resistant strain is used. The biofilms were generated primarily by increasing the release of extracellular DNA (eDNA), as revealed by component analysis; interestingly, the S. Following AGE treatments, the aureus global regulator sigB was elevated and its downstream component lrgA was down regulated. According to the study, AGEs may encourage S. via controlling sigB, aureus biofilm development occurs through an eDNA-dependent mechanism.

Role of Macrophage in Diabetic Foot Ulcers: Zhu, L., (2022) [28] and coworkers studied at four stages of diabetic wound healing-: homeostasis, inflammation, proliferation, and remodeling. After an injury, the homeostasis phase begins, which includes vasoconstriction, platelet aggregation, and clotting. After that, neutrophils are recruited to start the inflammatory response, which attracts macrophases. The inflammatory phase is dominated by macrophages. Two days later, the recruited neutrophils attract macrophages by releasing chemokines. The macrophages secreted TNFα, IL-1β, IL-6, and IL-12 cytokines. As wound healing proceeds, anti-inflammatory or M2-like macrophages begin to proliferate and become more numerous. On the seventh day after wound healing, macrophages (M2) generate and secrete substances

that cause fibroblasts and keratinocytes to proliferate, differentiate, and move to the wound, depositing collagen and other ECM proteins.

Role of Immunomodulatory Bandages: Raghavan, J.V., [18] and coworker (2022) designed an immunomodulatory bandage to speed up the immune system's healing of diabetic wounds. The myeloid cell mouse model a knockout mouse model lacking the leptin receptor was used to characterize it. In this model, the blood of KO mice had greater monocyte and neutrophil numbers than the blood of the untreated control mice. For immunological responses, they created a chitosan scaffold filled with rapamycin. Compared to healing with blank scaffolds, the application of these immunomodulatory scaffolds at a wound site produced faster healing. Rapamycin has also been observed the impact monocyte and macrophage polarization while decreasing the production of chemokines that that engage innate and adaptive immune cells. Rapamycin scaffolds may accelerate healing by altering the patterns of migration and functioning of intrinsic immune cells which have become unusually plentiful in long-term diabetes wounds.

Role of Leucine-Rich a-2-Glycoprotein-1: Liu, C., *et al.,* (2020) [22] recommended Lucien-rich a-2-glycoprotein 1 (LRG1) be studied for its role in normal and diabetic wound healing. LRG1 levels were elevated throughout the inflammation phase of marine wound recovery, and bone marrow-derived cells were the major source of LRG1. LRG1 deletion affects enhanced re-epithelialization, angiogenesis, and immune cell infiltration, but it also delays wound healing. LRG1 was significantly elevated in people and animals with diabetic wounds. Mice deformed LRG1 showed resilience to the diabetes-induced latency in healing of wounds. It also revealed that the lowering of increased neutrophil extracellular traps (NETs) in wounds caused by diabetes could explain this. LRG1 promotes NETosis *via* the TGFb type I receptor kinase ALK5, which is Akt-dependent. LRG1 regulates NETosis in an Akt-dependent manner via the TGFb type I receptor kinase ALK5. All of these studies suggest to a metabolic role for the glycoprotein LRG1 that is produced by bone marrow cells and demonstrate that excessive amounts of LRG1 expression in diabetes are detrimental and may result in the formation of chronic wounds.

Role of Hydrogel: Dmitriyeva *et al.* (2022) [28] examined, in an animal diabetic wound model, the effects of polydeoxyribonucleotide loaded in hydrogel on wound healing, both individually and in combination. Diabetes mellitus patients experience a largest pattern of healing time for wounds due to excessive glucose levels, which may additionally cause poor circulation, decreased cell proliferative activity, and impairment in the generation and preservation of new blood vessels. With a molecular weight ranging from 50 to 1500 kDa, polydeoxyribonucleotide (PDRN) is a DNA isolated from the sperm cells of Oncorhynchus mykiss (Salmon trout) or Oncorhynchus keta (Chum Salmon). It is known to degrade by unspecific DNA nuclease and subsequently be expelled as urine or feces. Enhancing angiogenesis is one of the many beneficial therapeutic benefits of PDRN that are well-established. Polydeoxy-ribonucleotide (PDRN) is a material that promotes tissue repair and is utilized in wound healing.

A hydrogel is a reticular material that is typically applied as a scaffold or carrier that can be bioapplied, as well as a dressing formulation to speed up wound healing. The implications of PDRN on a diabetes-related recovery deficiency in male diabetic rats were analysed by using an incisional skin lesion model on their backs. The wounds were segregated into three groups: an untreated group, a hydrogel-only group, and a PDRN-loaded hydrogel combined therapy group. An insulin-dependent rat wounds model skin specimen sample was examined histological for fibroblast proliferation and collagen synthesis at 3, 7, 14, and 21 days following skin damage to measure tissue remodeling. Furthermore, the assortment of blood vessels was assessed in all specimens. If PDRN maintained in CMC hydrogel was applied topically to full-thickness skin wounds in mice with generated type 2 diabetes, the regeneration process was accelerated. In contrast to the control group, the group that received only PDRN saw a significant acceleration in wound healing; however, the distinction between the groups who received only hydrogel was not as significant. In addition, while evaluating the group receiving both treatments to the control population

and populations that only received hydrogel on day 7, there were significant differences were reported and changes in the number of blood vessels per unit area. On day 7, contrasted to the control group, and on day 14, contrasted to the group that was receiving only the hydrogel, the amount of fibroblasts in the PDRN group fluctuated substantially. On day 21, the total amount of collagen fibers differed significantly between the groups that got only PDRN and those that received only the hydrogel and the control. Thus, it is feasible to conclude that the use of PDRN accelerates the process of angiogenesis and promotes the formation of collagen fibers and fibroblasts. Furthermore, the group that received hydrogel-only treatment saw an increase in the overall number of blood vessels.

Thus, it is assumed that the hydrogel's wet environment promotes angiogenesis through cell migration. The combined therapy group's favorable outcomes are assumed to be due to the hydrogel's action as a scaffold for angiogenesis, improving maintenance and expression, and hastening wound healing. Because it acts as a scaffold for PRP, the hydrogel increases the proliferation of developmental factors and aids in both the maintenance and acceleration of wound healing. This study explained that using hydrogel and PDRN together enhanced wound healing in diabetics more effectively. According to the research that the hydrogel acts as a scaffold for PDRN, angiogenesis is expedited, while collagen production and fibroblast expression are increased.

In comparison to the control and hydrogel single-treatment groups, the PDRN loaded in hydrogel group showed higher differences in wound size decrease and change. Histological investigation of fibroblast proliferation, collagen production, and blood vessel count demonstrated a progressive increase in the PDRN load in the hydrogel combined-treatment group. The study's findings revealed that, as contrasted with each of the two groups, the combination therapy of PDRN loaded in hydrogel increased the healing of wounds, resulting in a reduction in diabetic wound size and healing time [34].

Investigated the topical effect of hydrogel for wound healing and wound angiogenesis. Nitric oxide based liquid hydrogel release phosphor-diesterase 5 inhibitors which impaired wound angiogenesis. The drug-loaded hydrogel stimulated re-epithelialization and angiogenesis in diabetes wounds from healthy and healing-impaired animals. Using a non-intrusive label-free Photo acoustic microscopes approach in conjunction with automated vessel analysis, we demonstrate that topical administration of TOP-N53 formulation increases micro vascular network density and encourage the functionality of newly formed blood vessels, which leads to improved wound blood perfusion. These findings show that the TOP-N53 formulation, when applied topically, has extraordinary healing-stimulating effect, which supports its further development as a wound treatment.

Role of Nanocarriers: Quitério, M. *et al* (2021) [29] examined the function of insulin as a nanocarrier. Insulin is a peptide hormone that is used to heal diabetic and diabetes wounds; however it is extremely sensitive to sunlight. Therefore, we must use a polymeric-based nanoacrier to retain and protect it. The primary goals of this work were to create the nanocarriers or nanoparticles to help with the healing of diabetic wounds and to investigate the topical delivery efficacy of insulin-based nanoparticles. Insulin-loaded poly-DL-lactide/glycolide (PLGA) nanoparticles were made and studied, and they were discovered to have a neutral surface charge and a mean size of approximately 500 nm.

Phenolic-shaped nanoparticles are verified by means of scanning electron microscopy and atomic force microscopy. Insulin's encapsulation method preserved both its secondary structure and integrity, as demonstrated by SDS-PAGE and circular dichroism studies. In vitro experiments indicated a regulated release profile. Cell lines were employed to confirm the formulation's safety and demonstrate that cell viability varied with concentration and duration. Furthermore, positive findings from initial safety *in-vivo* investigations were found.

El-Salamouni NS, *et al.*, (2021) [4] reported an experimental investigation on the potential repurposing of valsartan (Val) in the local management of untreated diabetic foot ulcers. *In-vitro* and *in-vivo* descriptions were conducted. The

produced nanoparticles have a tiny particle size, high encapsulation efficiency, and prolonged drug release. The produced nanoparticles demonstrated tiny particle size, great entrapment efficiency, and long-term drug release. Microbiologically, Val-SLN significantly reduced biofilm mass production for gram-positive as well as gram-negative bacteria, with a comparable minimal inhibitory value to levofloxacin alone. Therapy with Valsartan SLN for twelve days improved healing through COX-2, NF-κB, NO, TGF-β, MMPs, and VEGF pathways.

Role of Nanocomplex Gel: Md, S., Abdullah. *et al.*, (2022) [30] investigated that Ginkgo biloba nanocomplex gel (GKNG) was developed and tested as a persistent formulation for wound treatment potential. According to pharmaceutical analysis, the average particle size for GKNG was 450.14±36.06 nm, the encapsulation efficiency was 91±1.8%, and the zeta potential was +0.012 ± 0.003 mV. The rheological experiment also indicated the appropriate speed of diffusion and viscosity for topical drug delivery. GKNG's success was further substantiated by evaluation with Fourier transform infrared spectroscopy (FTIR), powder X-ray diffractometry (PXRD), scanning electron microscopy (SEM), and transmission electron microscopy, among others. Following GKNG administration, *in-vivo* studies demonstrated an associated reduction in lipid per oxidation (MDA) and an increase in antioxidant enzymes such as glutathione peroxides (GPx), and superoxide dismutase (SOD). The antioxidant enzymes glutathione peroxides (GPx) and superoxide dismutase (SOD) increased, and the in vivo study revealed that GKNG therapy reduced lipid per oxidation (MDA). Collagen type I (COL1A1) & collagen type IV (COL4A1) were also increased in the GKNG group. The GKNG led to increased levels of hydroxyproline, VEGF, EGF, and TGF-β1 in vivo. Furthermore, when compared to the sodium alginate (SA) gel and GK gel, GKNG significantly accelerated wound contraction. GKNG enhanced wound healing by regulating antioxidant enzymes, collagens, angiogenic factors, and TGF-β1, as evaluated *in-vitro* and *in-vivo*.

Role of Polyhebral Tea Bags: Quazi, A., *et al.*, (2022) [31] polyhebral tea bags were found to be effective in both the management and therapy of wounds. Ichnocarpus frutescens, *Ficus dalhousiae*, *Crateva magna*, *Alpinia galanga*, and *Swertia chirata* are well-known plants found throughout India that are frequently used to treat diabetes. A polyherbal tea bag including *Ichnocarpus frutescens*, *Ficus dalhousiae*, C*rateva magna*, *Alpinia galanga*, and *Swertia chirata* plants was chosen for the creation of 5% and 10% ointments to promote wound healing. The eradication wound model was utilized to examine wound healing activities in both diabetic and non-diabetic rats.

The average percentage closure of the wound area has been determined on the 3rd, 6th, 9th, 12th, 15th, 18th, and 21st days. The formulation have significantly higher wound healing activity when compared to the standard of reference and untreated groups. On the 21st day, animals with diabetes treated with ointment preparations (F1 and F2) had closure rates of 93.91±1.65% and 99.12±5.21%, respectively, whereas chloram-phenicol sodium medication solution had closure rates of 99.81±3.16%. At the 21st day, nondiabetic animals administered the ointment formulations (F1 and F2) had 96.81± 2.04% and 98.13±1.14% wound closure, respectively, whereas chloram-phenicol sodium medication solution had 99.15 ± 1.41%. As per the studies, it was concluded that this polyherbal medicament can be used clinically to treat diabetic and nondiabetic wounds.

Role of Resin Extract: Carvalho, G., *et al.*, (2022) the effects of Virola oleifera resin extract on skin and mucosal healing were investigated. *Virola olerifera* is an antioxidant rich resin which is used for wound healing caused by hypertension and diabetes. The *Virola oleifera* resin based cream was formulated and studied its effect on Wistar rats. Then, four 15 mm excisions were performed on the shaved skin. All treatments were given to the wound area on a daily basis. Macroscopic measurements of the tissue from the wound expansion and histological examination of the features of inflammatory cells were performed at the conclusion of the tests (0, 3, and 10 days). VO cream administration enhanced wound contraction (15%, $p < 0.05$) and lowered lipid and protein oxidation rates (118% and 110%, $p < 0.05$, respectively) compared to the control group. Our findings indicated the healing potential of a new formulation containing VO, which might be

attributed in part to antioxidant mechanisms that promote re-epithelialization, making it a promising dermo-cosmetic for wound healing treatment.

Role of Amniotic Fluid Based Gel: Niami, F., *et al.,* (2022) [33] studied the effect of the amniotic fluid based gel on diabetic foot ulcers. This studied performed clinical trials on 92 diabetic (type-2) patients at the Diabetes Clinic of Golestan Hospital of Ahvaz, southwest of Iran in 2019-2020. Amniotic fluid based gel is commonly used in the chronic wound management by replacing or regenerating human cells. For analyzing the, Chi-square tests and other generalized estimation equations (GEE) with the significance level of 0.05 were used. Amniotic fluid is considered as regenerative medicine which contains prostaglandins, carbohydrates, peptides, lipids, lactate, amino acids, proteins, enzymes, minerals, growth hormone and prolactin. Growth factor (Fibroblast growth factor) transformed the cutaneous fibroblast proliferation process. Based on these several properties, amniotic fluid gel is regarded as a new formulation for the treatment of diabetic foot ulcers. At the end of the eighth week of assistance, there was additionally a statistically significant variation among the four groups in terms of wounds grade, color, tissue surrounding the wound, overall wound state, and wound healing length ($P < 0.05$). Based on our observations of the patients in the current trial, we feel that amniotic fluid gel is a beneficial and safe formulation for the treatment of persistent diabetic foot ulcers.

Role of Topical Application: Tombulturk *et al.,* (2023) [35] and collaborators considered metformin's role in topical applications. Metformin's influence on the apoptotic index was evaluated utilizing the terminal deoxynucleotidyl transferase model and the reverse transcription polymerase chain reaction methodology in wound samples. Metformin increases cellular proliferation and anti apoptotic effect by increasing collagen-I and II expression. The topical effect of metformin on diabetic wounds reversed the adverse effects caused by diabetes, increasing the wound healing rate and improving the wound repair process [39].

Investigated the cerium-containing N-acethyl-6-aminohexanoate acid molecule and identified major molecular targets of the chemical's mode of action in diabetic animals for the healing of wounds. Cerium N-acetyl-6-aminohexanoate (LHT-8-17), a 10 mg/mL aquatic spray, was utilized as wound investigational topical therapy. A linear wound was replicated in 18 out bred white rats with streptozotocin-induced diabetes (60 mg/kg i.p.); a planar cutaneous defect was mimicked in 60 C57Bl6 mice with streptozotocin-induced diabetes (200 mg/kg i.p.) and 90 diabetic db/db mice. On days 5, 10, 15, and 20, histological examination of the skin defect filling was performed. Tissue TNF-α, IL-1β, and IL-10 levels were measured by quantitative ELISA. Oxidative stress production was detected using Fe-induced chemiluminescence. Immunohistochemistry was used to determine Ki-67 expression and CD34 cell positivity.

FGFR3 gene expression was measured using real-time PCR. The antimicrobial potency of LHT-8-17 was evaluated in MRSA-contaminated wound tissues. LHT-8-17 4 mg twice daily hastens linear and planar wound healing in mice with type 1 and type 2 diabetes. The topical treatment reduced tissue TNF-α, IL-1β, and oxidative reaction activity while maintaining IL-10 levels and antioxidant capacity. LHT-8-17 raised Ki-67 positivity in fibroblasts and pro-keratinocytes, boosted FGFR3 gene expression, and improved tissue vascularization. The formulation possessed antimicrobial characteristics. The results concluded that the formulation is a potential therapeutic agent for insulin-dependent wound topical therapy.

Kulkarni, S., *et al.,* (2022) [42] examined that healing of skin lesion is delayed in diabetics due to reduced nitric oxide synthesis, advanced glycation end products (AGE), and inadequate epithelial cell motility. An innovative topical formulation was designed of esmolol hydrochloride, named Galnobax, and evaluated its wound healing capabilities in diabetic hairless rats induced by streptozocin. The research was conducted in an animal laboratory setting within a tertiary-care research institution.

The results of these experiments demonstrated that esmolol exhibited significant aldose reductase inhibition and reduced AGE formation in a dose-dependent manner. Furthermore, the scratch assay revealed improved wound healing rates in the presence of esmolol under high-glucose conditions.

The *in-vivo* investigation found that topical treatment of Galnobax promoted wound healing in diabetic rats, with higher concentrations of endogenous nitrite and hydroxyproline in the treatment tissue. These data imply that Galnobax could have therapeutic effects in wound healing, particularly in diabetic patients. Increased nitric oxide levels and hydroxyproline content in the wound region suggest enhanced tissue regeneration and collagen formation. Further research is needed to understand the underlying processes of Galnobax's actions and to assess its long-term safety and efficacy in clinical settings.

Role of Topical Patches: Afzal, S., *et al.,* (2023) [36] developed topical patches filled with bacitracin zinc as a novel wound-healing treatment. Free radical polymerization technology was used for topical patch formulation, with polyethylene glycol-8000, carbopol 934, tween 80, ammonium per sulfate, and N, N'-Methylenebisacrylamide used for synthesis. Patches were tested using DSC, TGA, SEM, sol gel analysis, and *in-vitro* release of drugs in various media. For the permeation research, the Franz diffusion cell test was used.

The formulations with the highest Polyethylene glycol-8000 concentrations and the lowest N, N'-Methylenebisacrylamide concentrations showed the greatest swelling and release of medication. Patches' pH-sensitive behavior was also validated, with increased swelling, drug release, and drug penetration across skin at pH 7.4. The Draize scale found no evidence of inflammation or erythematic in the fabricated patches. Fabricated patches also demonstrated faster wound healing than marketed versions. As a result, such a polymeric structure could be a viable solution for accelerating wound healing and small skin damage by improving drug deposition. It was decided that patches have more promise than creams, ointments, and solutions for wound healing De Francesco F, Riccio M, 2022 [37].

Role of Combined Therapy of Drugs [37]: It was investigated that wound healing is related with bacterial infection, which causes extended inflammation and delayed re-epithelialization. Silver sulfadiazine combined with hyaluronic acid is used to inhibit wounds deformation and tissue regeneration. This retrospective study was conducted to evaluate the efficacy of cream and gauze pads containing low molecular weight hyaluronic acid (200 kDa) and 1% silver sulfadiazine in wound healing. In addition, we investigated silver sulfadiazine's action on biofilms *in-vitro* and on animal wounds, and found positive results. 80 patients with complex chronic wounds of various etiologies, such as diabetes mellitus (10), burns (15), post-traumatic ulcers (45), and superficial abrasions (10), were chosen for this investigation. After 8 weeks, 95 ± 2% of treated patients had smaller ulcers.

There was also a substantial reduction in inflammation from day 14 onwards ($p < 0.01$ vs. baseline), indicating improved skin and reduced bacterial load. Silver sulfadiazine therapy reduced bacterial colony proliferation in plankton and biofilm states on the wound in a dosage-dependent manner. However, at the maximum dose (800 µg/wound), it impeded tissue granulation. Silver sulfadiazine coupled with hyaluronic acid has been shown in clinical trials to improve wound healing Loera-Valencia R, 2022 [3].

Role of Nanoparticulate System [3]: A calcium alginate dressing containing ZnO nanoparticles (CAZnODs) has been created for the management of ulcers of diabetic feet in people. To determine the efficacy of CAZnODs, we conducted a randomized controlled study on 26 T2D patients who had foot ulcers. The patients were divided into two groups: G1 received calcium alginate with Nanoparticles (n = 16), and G2 received no NPs (n = 10). The dressing change was conducted every 48 hours. The protocol's duration was set at ten weeks. We report the healing process had been observed in patients, with 75% closure of the wound in G1 treated with calcium alginate NPs versus 71% in G2 (calcium alginate without Nanoparticles) ($p = 0.0111$). In G1, the average recovery time was 48 days, while in G2, it was 72. Our findings suggest that CAZnODs were tolerated well and were not disruptive with wound healing. The final wound area and healing time support the concept that using calcium alginate dressing with nanoparticles can promote improved tissue regeneration while minimizing T2D consequences such secondary infections. Panda, D. S., *et al.,* (2021) [38] developed a lecithin chitosan-based nanoparticulate system. Berberine can be applied topically.

Soybean lecithin, isopropyl myristate, and berberine were dispersed in ethanol before being introduced gradually to an aqueous solution of chitosan. The Box-Behnken method is used to formulate the optimum amount of soybean lecithin, isopropyl myristate, and berberine dispersed in an ethanolic solution. The influence of lecithin quantity, chitosan quantity, and isopropyl myristate amount on particle size, zeta potential, and entrapment was investigated using a Box-Behnken statistical design. The optimized BER-LC-CTS-NPs had an average size of 168.4 nm, an external charge of 33.1 mV, and an entrapment rate of 82.3%.The improved BER-LC-CTS-NPs demonstrated a consistent in vitro release pattern. The effectiveness of optimized BER-LC-CTS-NPs in a topically applied gel preparation for wound healing in streptozocin-induced rats with diabetes was investigated. The results integrating that chitosan and berberine in nanoparticles have synergistic impact for wound healing.

Role of Nanoemulsion Based Gel: Algahtani, M. S., *et al.,* (2021) [40] was discovered that a thymoquinone nano-emulsion-based hydrogel system might improve wound healing efficacy. A nano-based hydrogel system was created with black seed oil using an ultrasonication high-energy emulsification approach. The average globule size and polydispersity index of the produced nanoemulsion were examined as a function of formulation composition and ultrasonication process parameters. The ultrasonication period significantly ($p < 0.05$) influenced the mean droplet size and the polydispersity index of the produced nanoemulsion, regardless of surfactant/co-surfactant ratio or surfactant/co-surfactant mixture percentage concentration.

The created thymoquinone nanoemulgel system exhibited pseudoplastic actions with thixotropic features, making it suitable for topical administration. The nanoemulgel system of thymoquinone showed considerable improvement ($p < 0.05$) in skin penetration and deposition following application to the skin compared to the standard hydrogel method. The created nanoemulgel system containing thymoquinone displayed faster and earlier therapeutic in wounded Wistar rats contrasted to the standard hydrogel of thymoquinone, while displaying equivalent healing efficacy with the commercial silver sulfadiazine (1%) cream. Additionally, the development of the thick epidermal layer and papillary dermis, as well as the existence of well-organized collagen fibers in freshly healed tissues, were shown by histopathological evaluation in animals treated with a created formulation system. The findings of this study suggest that topical distribution of thymoquinone *via* nanoemulgel technology is an intriguing possibility for accelerating healing of wounds in preclinical studies.

Role of Nanostructued Lipid Carrier (NLC): Hsueh, Y. S., *et al.,* (2021) [43] investigated that the angiogenesis factor recombinant human thrombomodulin (rhTM) stimulates keratinocyte migration, cell proliferation, and wound healing. Creating nanostructured lipid carrier (NLC) formulations that encapsulate rhTM in order to facilitate chronic wound healing was the aim of this work. NLCs loaded with RhTM were made and described.

The efficiency of encapsulation exceeded 92%. The rate profile of rhTM production was influenced by the formation of lipids of the different NLC formulations, and it was sustained for over 72 hours. Research on a diabetic mouse wound model revealed that rhTM-NLC 1.2 µg sped up wound healing and was comparable to rhEGF-NLC (20 µg), a recombinant human epidermal growth factor. When 0.085% carbopol, a freshly cross linked polyacrylic acid polymer, was added to rhTM NLC, the NLC-gel showed comparable particle properties and showed stability over a 12-week period as well as continuous release. Both rhTM NLC and rhTM NLC-gel significantly improved human epidermal keratinocyte cell migration (HaCaT) and diabetic mouse wound healing. After NLC and NLC-gel composition treatments, the plasma levels of rhTM were lower and remained stable over a 24-hour period than those of rhTM solution. The convenience of the manufacturing process, stability, and convenience of applying to the wound with minimum systemic exposure may justify the development of intriguing methods of delivery for the treatment of population with prolonged wounds.

Role of Phytomedicines: Sitohang, N. A., *et al.,* (2022) [44] noted the growing popularity of

phytomedicines in the realm of wound care and the demonstrated potential of *Barringtonia racemosa* to heal wounds. This study attempted to establish whether B. racemes kernel extract may speed up wound healing in animal models. The seed kernel of *B. racemosa* was extracted with an ethanol: water (7:3) solvent in four different concentrations (1, 3, 5, and 7 ppm) and then used as a bioactive component in a gel composition based on Carbopol 940. A 3 cm diameter wound was made in the back part of a *Rattus norvegicus* rat, and the DESIGN (Depth, Exudate, Amount of Inflammation/ Infection, Granulating tissue, and Necrotic tissue) scoring system was used to assess the wound healing process during a 12-day period. Based on our findings, it indicates that *B. racemosa* extract accelerated wound healing because the DESIGN scores differed significantly across concentration groups after the third day. Compared to rats treated with topical Metcovazin, rats treated with a gel formulation containing 7 ppm of *B. racemosa* kernel extract showed quicker wound healing. On day 6, a macroscopic evaluation of the 7 ppm group revealed that the site of injury had 80% healthy granulation, which a lesion size of less than 3 cm2, and sustained redness, but no apparent effusion or redness. *B. racemosa* kernel extract was reported to speed up wound healing in rats.

TABLE 1: FORMULATIONS FOR DIABETIC WOUND MANAGEMENT

S. no.	Drug	Formulation development	Reference
1.	Neutrophil extra trap	Elevated serum NET levels for diagnosis of DFU-related amputation.	Ibrahim I *et.al*.,2024
2.	Insulin	nanoemulsion with Aloe vera gel. insulin-loaded nanoemulsion with Aloe vera gel	T. Chakraborty *et al.*,2021
3.	Helichrysum italicum	Essential Oil Formulations for Wound Healing	Andji´s *et.al.*,2021
4.	Calcium alginate dressing containing ZnO nanoparticles	Management of ulcers of diabetic feet	Loera-Valencia R., *et. al*., 2022
5.	Pioglitazone	pioglitazone-loaded fibrous mats on diabetic wound healing and its sustained release effect.	Cam ME et al. 2020
6.	Valsartan Solid lipid nanoparticle	Valsartan was repurposed and successfully treated an untreated diabetic foot ulcer.Diabetic foot ulcers heal through COX-2, the NF-κB, NO, TGF-β, MMPs, and VEGF pathways.	El-Salamouni NS, *et.al.*, 2021
7.	Micro RNA-103	miroRNA-103 expression in wound Healing, miroRNA-103 expression in wound Healing of diabetec foot ulcers	Zhao, X., *et. al*., 2023.
8.	Biofilms	Extraction and Quantification of eDNA and RNA Extraction From *S. aureus*, AGEs Enhanced Biofilm Formation of *S. aureus* Strains.	Xie, X., *et. al*., 2020.
9.	rapamycin-loaded bandges	Immunomodulatory Bandage for Accelerated Healing of Diabetic wounds, rapamycin-loaded chitosan scaffold	Raghavan, J.V., *et.al.*, 2022.
10.	Alginate-GelMa based hydrogel scaffold	Used to promote healing of wounds.	Kaur, T., *et.al*.,2020.
11.	Growth factor VIII MFG-E8	In diabetics, MFG-E8 facilitates wound healing by controlling the "NLRP3 inflammasome-NETs" axis.	Huang, W.,*et. al*., 2020.
12.	Leucine-Rich a-2-Glycoprotein-1	Leucine-Rich a-2-Glycoprotein -1 in Cutaneous Wound Healing	Liu, C., Teo, *et.al*., 2020.
13.	Endothelial progenitor cell (EPC)-derived exosomes	Skin wound healing in diabetic and control mice was greatly improved by EPC-derived exosomes and miRNA-221-3p treatment.	Xu, J., Bai, S., *et., al*.,2020.
14.	MSC-Derived Exosomal	Mesenchymal stem cells (MSC) - derived exosomes containing long noncoding RNA (lncRNA) H19.	Li, B., *et.al*.,2020
15.	miRNA-497	Accelerated wound healing in diabetic mice by miRNA-497 and its anti-inflammatory activity	Ban, E., *et.al*.,2020.
16.	microRNA-21	miR-21 has an unique y role in controlling inflammation.	Liechty, C., *et. al.*, 2022
17.	Exosomes Mesenchymal stem cells (MSCs)-derived exosomes	The effect of exosomes produced from MSCs pretreatment with pioglitazone (PGZ-Exos) on diabetes-related wound healing.	Hu, Y., *et. al*.,2021
18.	Topical Polydeoxyribonucleotide	Hydrogel	Dmitriyeva, M., *et. al*.,2022

	Loaded in Hydrogel		
19.	Insulin is a peptide hormone	A neutral surface charge and a mean size of around 500 nm were observed in the synthesized and studied insulin-loaded poly-DL-lactide/glycolide (PLGA) nanoparticles. In vitro experiments indicated a regulated release profile. Cell lines were employed to confirm the formulation's safety and demonstrate that cell viability varied with concentration and duration.	Quitério, M. *et.al*.,2021
20.	*Ginkgo biloba*/Sodium Alginate Nanocomplex Gel	This combination enhanced ginseng's capacity to heal wounds. facilitating simple dermal application. The diffusion study's findings showed that ginseng diffused from NHG for over 20 hours.	Md, S., Abdullah, *et.al*.,2022.
21.	Ointment Prepared from Infusion Extract of Polyherbal Tea Bag	Evaluation of Polyherbal Tea Bag Infusion Extract's Wound Healing Activity in Diabetes-Induced Rats (Excision Wound Model).	Quazi, A., *et.al*.,2022
22.	*Virola oleifera* Formulation f	Cream Composition	Carvalho, G. R.,*et.al*.,2022.
23.	Gel made with amniotic fluid formulation	Evaluation of the efficacy of an amniotic fluid-based gel on diabetic foot ulcers.	Niami, F.,et., al.,2022
24.	Nitric oxide-releasing phosphodiesterase 5 inhibitor (TOP-N53)-containing liquid hydrogel.	Applying TOP-N53 formulation topically improves the density of the microvascular network and encourages the new blood vessels to operate, which increases the blood flow to the wounds.	Ben-Yehuda Greenwald, *et.al*.,2022
25.	Metformin topically	Metformin improved the wound healing rate and the wound repair process in diabetic wounds, reversing the negative effects of diabetes. Metformin improved the wound healing rate and the wound repair process in diabetic wounds, reversing the negative effects of diabetes.	Tombulturk, F. K.,et., al.,2024
26.	Bacitracin zinc-loaded topical patches	The fabricated patch performed better than the marketed product in terms of healing time.	Afzal, S.,*et.,al*.,2023.
27.	Topical Agents such as Hyaluronic Acid and Silver Sulfadiazine to Wound Healing	Topical Agents such as Hyaluronic Acid and Silver Sulfadiazine to Wound Healing and Management of Bacterial Biofilm	De Francesco F,*.et.al*., 2022
28.	Berberine Encapsulated Lecithin–Chitosan Nanoparticles	The combination of chitosan and berberine in nanoparticles has a synergistic effect on wound healing. The optimized nanoparticulate technology reduces inflammation, stimulates blood vessel and fibroblast proliferation, and promotes mature collagen fiber deposition.	Panda, D. S.,*et. al*.,2021
29.	Cerium-Containing N-Acetyl-6-Aminohexanoic Acid Formulation	Accelerates Wound Reparation in Diabetic Animals	Blinova, E.,*et.al*., 2021
30.	Thymoquinone Loaded Topical Nanoemulgel	Topical Nanoemulgel for Wound Healing	Algahtani, M. S., *et.al*.,2021
31.	Topical Application of Chinese Formula Yeliangen	Chinese Formula Yeliangen Promotes Wound Healing	Al-Romaima, A.,*et.al*., 2022
32.	Novel topical esmolol hydrochloride	wound healing in diabetes	Kulkarni, S. A.,*et. al*., 2022
33.	Nanostructured Lipid Carrier Gel	Topical use of an application of recombinant human thrombomodulin improves diabetic wound healing.	Hsueh, Y. S.,*et, al.*, 2021
34.	Gel formulation of *Barringtonia racemosa* (L.) Spreng kernel extract	B. racemosa extract in the form of gel is used to treat wounds that are open in rat models. Barringtonia acutangula fruit given topically at a dosage of 20% w/w resulted in an 86.3% recovery after 14 days of treatment.	Sitohang, N. A., *et.al*.,2022
35.	Exosome	Exosome and antibacterial cryogel wound dressing.	Shiekh, P. A.,*et. al*.,2020

36.	Exosomal miR-20b-5p Inhibition	Exosome-mediated miR-20b-5p suppression restores Wnt9b activation and reverses diabetic wound healing.	Xiong, Y., *et.al*.,2020

CONCLUSION: Currently, there is an enhanced comprehension of the processes involved in and management of wound healing through the use of innovative wound dressings, which include miRNA, biomarkers, exosomes, leucine-rich glycoprotein, neutrophils, pro-inflammatory (M1) macrophages, pro-remodeling (M2) macrophages, sustained induction of neutrophils, endothelial progenitor cells, scaffolds, biofilms, carriers, fibers, mats, and antibiotic strategies for diabetic wounds. With a rising number of diabetic patients, there will be a larger demand for effective chronic wound management. More study is needed to determine how to accelerate diabetic wound healing and improve patients' quality of life. In this review, we will aim to present recent findings on healing wounds in diabetes.

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