

Smart Nanoplatforms for Plant derived Bioactive-Based Diabetic Wound Healing: Trends, Challenges, and Breakthroughs

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Abstract

Diabetic wounds pose a major global health burden, it is characterized by impaired healing, chronic inflammation and high fatality rate for infections. Novel therapeutic opportunities are arising by the combination of nanotechnology and bioactive compounds from plants. This review discusses the latest developments of smart nanoplatforms for delivering plant-derived bioactives, their potential mechanisms in the treatment of diabetic wounds, and the current and prospects of their clinical and translation practice. A literature search was performed focusing on preclinical and clinical studies about polymeric, lipid based and metal nanoparticle systems loaded with phytoconstituents. Action mechanisms, delivery efficiencies, and therapeutic results were thoroughly reviewed. Stimuli-responsive systems, bioactive scaffolds, and integrated biosensors received particularly attention. Nanoplatforml-based phytosomes, nanofibers, and lipid-based carriers have greatly improved the stability, solubility, and targeted delivery of plant bioactives such as curcumin, quercetin, and asiaticoside. These systems modified the oxidative stress, suppressed pro-inflammatory cytokines and promoted angiogenesis and re-epithelialization. The introduction of biosensors and gene-loaded nanoparticles increased the efficacy of therapy. In animal models, faster wounds closure, increased collagen deposit, and reduced microbial load have been shown. The smart nano-delivery systems based on plant bioactives exhibit a promising impact in diabetic wound management providing a platform to overcome the various pathological barriers associated with this disease. Further refinements in the design of nanocarrier,

incorporation of bio-sensing technologies and rigorous clinical validation are required to translate these promising platforms into routine wound therapy.

Keywords: Diabetic wound, phytosomes, bioactives, drug delivery, nanotechnology, clinical therapy

Introduction

Diabetes mellitus is among the most prevalent on a global scale among metabolic disorders. Low insulin action or insulin secretion is the main cause of persistently elevated blood sugar. [1] Although there are many factors that contribute to the difficulty of diabetic wound healing, issues such as peripheral neuropathy, vascular insufficiency, and the patient's compromised immune system become more significant as the patient's chronically high blood sugar levels continue to rise.

One study found that 9.1–26.1 million people with diabetes had foot or ankle sores on a global scale. Chronic inflammation is a feature of diabetic lesions, such as foot ulcers. When the balance of matrix metalloproteinases, which degrade the extracellular matrix, which is necessary for new tissue growth, is in diabetic patients, it impacts skin repair. This is because in these conditions, a range of pro-inflammatory cytokines, including IL-6 and TNF- α 1, are overproduced and function over time. [2] The positive aspect is that innovative solutions to these problems are emerging quickly in the field of diabetic wound treatment. Hyperbaric oxygen therapy and bioengineered skin replacements are all part of the arsenal for quickening the healing process. Cellular therapies that enhance angiogenesis through the utilization of stem cells are similarly in the works.

A novel approach to medication delivery known as nano-delivery systems of bioactive substances has recently evolved. Liposomes, polymer nanoparticles, and dendrimers are examples of carriers that encase bioactive substances like peptides, small-molecule medications, or phytochemicals.[3] This is the way forward, which increases solubility, stability and bioavailability of these drugs. Even though bioactive substances are usually very potent medicine, their potential for use is often hindered by characteristics such as low aqueous solubility and easy loss due to decomposition or poor systemic absorption rate.

Protection from degradation and regulated delivery upon receipt at the target location of action are thus provided by nano-delivery systems. In addition, nano-carrier systems

improve pharmacokinetic profiles by extending half-lives and lowering renal clearance. Such systems are particularly well matched for chronic diseases like cancer, diabetes and neurodegenerative disorders. Furthermore, the nanoscale size facilitates cellular uptake and the penetration of in vivo barriers, such as difficulties in getting past the blood-brain barrier. This allows medicinal agents which previously could not reach their target (because they were too large for passive diffusion); or that otherwise were metabolized before ever reaching it to get there and do so in a high level. These two effects greatly improve the efficacy of a medicine's action.

Most importantly, bioactive-based nano-delivery systems can be organized for directed targeting through specific receptor ligands.[4] Therefore, to accomplish the greatest possible results for each patient, without causing any harm through side effects or overtreatment, the ideal combination of several therapeutic methods is applied. [5] As bioactive-based nano-delivery systems are advancing, their promise for reshaping the treatment of many diseases has been increasing.

Pathophysiology of diabetic wounds

By inducing vascular abnormalities, diabetic nerve damage, and immunologic disturbance, hyperglycemia—the hallmark of diabetes and its complications—plays an almost pivotal role in the formation of diabetic wounds. [6] Finally, blood cannot circulate as well in the periphery. In addition to other explanatory components, this chronic ischemia plus capillary basement membrane thickening may hamper wound oxygen transport and nutrition and thus implicate tissue healing. In the wound microenvironment of diabetic patients, oxidative stress is common. Predominately proteases over their inhibitors means that there is excessive degradation in extracellular matrix and less re-epithelization. Systemic metabolic dysfunctions such as insulin resistance and disturbed lipid metabolism in diabetes can further impede the normal vital cell-level operations involved in processes such as wound healing. [7] Diabetic wounds seem to develop a greater tendency for the establishment and persistence of microbial films, which themselves provide both a barrier to invasion by immune cells and potentially mutual detriment. Those influences work together to form a vicious circle that perpetuates wounds' failure to heal, makes it more likely they will lead to amputation and increase the mortality rate of people with diabetes.

Figure 1 shows the almost opposing biological processes that are at work in normal and diabetic wound healing. On the left, the normal cascade of wound healing clearly occurs in a structured and properly timed manner – the neutrophils and macrophages respond to the

tissue injury in the dermis clearing the debris and orchestrating repair. Fibroblasts are functionally active in Etrich IV and depositing extracellular matrix for tissue regeneration. A functional microcirculation in the hypodermis is maintained to supply sufficient oxygen and nutrition. In the right side, however, healing of wound in diabetes is depicted as disorganized and delayed. The epidermis itself is structurally broken open, and local yet bacterial perfusion further enhances inflammation. There are an excess of neutrophils and macrophages, indicating a prolonged inflammatory phase, and fibroblasts seem to be less active in remodelling the tissue. Compromised perfusion and continued infection also serve to derange the constructive process. This comparative perspective highlights the role of chronic inflammation, microbial load and cellular pathology in retarded healing of diabetic wounds.

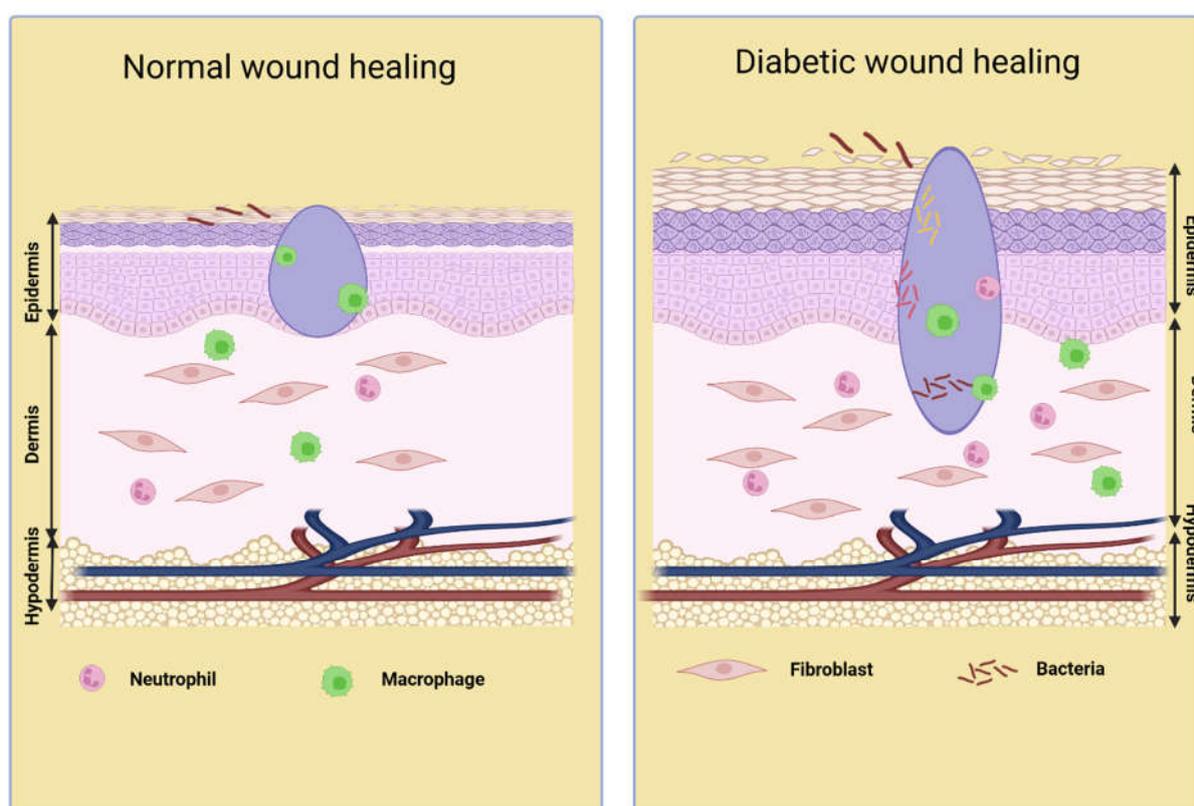


Figure 1 Pathophysiology of wound healing process in normal wound and diabetic wound

Bioactive compounds in wound healing

Bioactive compounds are these natural substances in the body, which helps in healing wounds and converting in potential therapeutic uses. The bioactive chemicals with antioxidant, anti-inflammatory, and antibacterial activities that have been extensively researched include

polyphenols, flavonoids, alkaloids, and terpenoids. The turmeric polyphenol curcumin is currently attracting attention for its potential antioxidant properties, namely its ability to bind to reactive oxygen species (ROS). [8] Because of this, keratinocyte movement and fibroblast growth are both enhanced, while cell damage caused by free radicals is prevented. Similarly, quercetin, a flavonoid, increases collagen synthesis and helps construct proliferation phase results at the cellular level; this property is used, for instance, in artificial silica gel pens. The production of pro-inflammatory cytokines TNF- α and IL-6 were suppressed by one serving of substances like resveratrol and epigallocatechin gallate (EGCG). There are antimicrobial functions of bioactive compounds. Allicin from garlic and berberine from *Berberis* species are both useful aids to the treatment of chronic wounds infection prevention. Bioactive derived from the sea, chitosan, are potent in their wound-healing properties: albeit no longer composed of protein, they congeal and promote cellular migration but keep out foreign body material for some time.

During the remodeling phase, bioactive compounds influence matrix metalloproteinase (MMP) activity and thus the turnover equilibrium of extracellular matrix proteins to improve tissue tensile strength. [9] Asiaticoside in *Centella asiatica* stimulates collagen production and angiogenesis. This contributes not only to improved tissue structure within healed wounds but also helps new blood vessels form. In addition, advances with bioactive compounds of interest include nanotechnology that has led to their incorporation into nano-carriers. These carriers increase the rate of release for bioactive compounds so as to improve drug solubility, cast stability, and afford targeted delivery when treating wound sites. These systems not only increase the bioavailability of bioactive compounds but also ensure their sustained effect through controlled release. Bioactive compounds have multifaceted actions, and they work together to address oxidative stress, inflammation, infection, and tissue excavation. [10]

Plant-derived bioactives

Natural chemicals derived from therapeutic plants and herbs are known as plant-derived bioactives, and they can heal injured tissue [11] The antioxidative capabilities of polyphenolic compounds, such as curcumin found in the rhizome of *Curcuma longa* and resveratrol in grapes, are well-known. These chemicals aid in neutralizing oxidative damage caused by free radicals. Cells and tissues are shielded from oxidative stress by this. Green tea's flavonoids, like quercetin and catechins, promote revascularization and re-

epithelialization of damaged tissues by scavenging ROS and increasing the formation of new blood vessels through the upregulation of vascular endothelial growth factor (VEGF). [12]

Plant-derived bioactives not only have antioxidant activities, but their anti-inflammatory effects are also powerful too and severity becomes necessary for resolving that chronic inflammation often seen in non-healing wounds. [13] Tannins from such plants as *Camellia sinensis* (tea) and *Punica granatum* (pomegranate) have been shown to speed up blood coagulation, prevent colonization by microorganisms all natural astringent to improve the course of wounds. [14] Terpenoids, such as Artesunate from *Artemisia annua* and Menthol derived from *Mentha* help also to promote wound healing since they can control oxidation and inflammatory phenomena whilst at the same time possess some antimicrobial activity.

By using nanotechnology, plant-derived bioactives' efficacy has thus been further increased: their bioavailability may be improved, and they are now stable for longer periods as well. It is also possible to deliver these compounds directly to the site of injury repair. Wound healing results have been improved in preclinical animal models using hydrogels containing quercetin and nanoparticles loaded with curcumin. With their broad spectrum of biological effects, plant-derived bioactives which have little or no side effects and are biocompatible have positioned themselves as promising agents in contemporary wound management: especially important for chronic or non-healing wounds. [15]

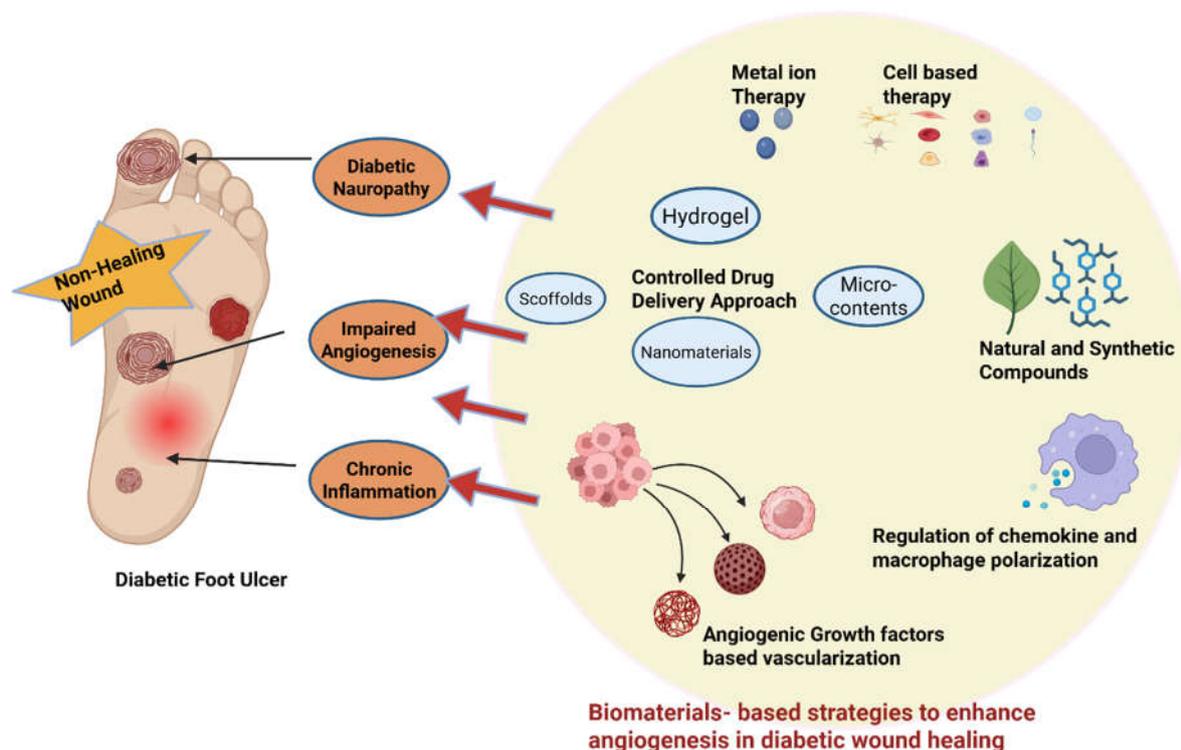


Figure 2 Plant derived nano delivery systems in the treatment of diabetic wound

Table 1 Drug delivery of bioactive compounds for improved diabetic wound healing

Bioactives	Methods	Mechanism	Inference	References
Curcumin	Electrospun nanofibrous mat based on polycaprolactone/polyvinyl alcohol/silk fibroin; curcumin-micelles; gelatin microspheres (GMs)	Reduce inflammation and oxidative stress while increasing angiogenesis and collagen deposition.	Solid swelling characteristics; a regulated release frequency	[16]
Insulin	PLGA nanofibrous scaffolds; injectable hydrogels that respond to both glucose and pH	Enhance the healing process by promoting neovascularization and collagen deposition.	Sensitive to both pH and glucose; core-shell structure	[17]
Quercetin	Topical hydrogel system	Improved scratch-	Highly skin-	[18]

		wound recovery of keratinocytes and fibroblasts.	permeable; topical delivery of QCN and oxygen	
Phallo dendron liquid	Nanofibers made of silk fibroin (SF) and poly-(L-lactide-co caprolactone) (PLCL) cell membrane	As wounds heal, the TGF- β signaling pathway and collagen are upregulated, while pro-inflammatory factors are downregulated.	Enhanced medication concentration; antimicrobial activity against <i>Staphylococcus aureus</i> and <i>Escherichia coli</i> .	[19]
Dimethyl oxalylglycine	Electrically spun fibrous membrane with holes	Facilitate the development of new blood vessels, epithelialization, and collagen.	Release of DMOG medications from aligned porous membranes	[20]
Hyaluronan	Calcium alginate hydrogel that responds to changes in pH	Increase the production of vascular endothelial growth factor and encourage angiogenesis.	Multifunctional	[21-23]
Gallic acid	Patch with microneedles	Assists neutralize free radicals and promotes antioxidant defenses.	Topical application and therapeutic combinations	[24-25]
Gentiopicroside and	m-PEG/PVP nanofibers	Antibacterial effect, achieve better skin architecture.	Could be fabricated via electrospinning	[26-27]

Thymoquinone			method	
Berberine	Hydrogel composed of nano-colloids derived from polyvinyl alcohol (PVA) and sodium alginate (Alg).	Inhibit NF- κ B and TNF- α , and promote wound healing	Evidence of an intracellular mechanism has been found: opening the Sirt 1/NF- κ B pathway the way	[28]
Resveratrol	Nanoparticles containing resveratrol	Advantages antioxidants and lower levels of iNOS in macrophages	The synergistic effects of two medicines and the sustained release of one substance	[29]
Asiaticoside	Polymeric nanoparticles	Boost the production of collagen and the amount of the protein COL-1.	Achieve optimal medication release kinetics and enhance intracellular absorption	[30]

Smart nanoplatforms: Types and functionalities

Advanced nanoplatforms are intelligent nanoscale systems designed for biomedicine, particularly in targeted drugs dispensation, diagnostics and regenerative medicine. [31] As such when biological stimuli such as changes in pH, enzymes that break down proteins, temperature fluctuations are induced or light from the outside world triggers them to start moving about and magnetic fields cause a response in their materials: the platform reacts accordingly This allows controlled release of medication at specific sites with minimal systemic side effects. The smart nanoplatforms take many forms, including polymeric nanoparticles, liposomes, dendrimers, inorganic nanoparticles and hybrid nanostructures,

each tailored to different needs in biomedicine. [32] Polymeric nanoparticles, are made of biodegradable materials such as PLGA and chitosan. Under the effect of stimuli-responsive drug delivery systems, these nanospheres carry out microencapsulation reactions to yield more effective treatment while liposomes which consist entirely of phospholipid bilayers can make themselves into encapsulating capsules. Dendrimers, highly branched polymers, enable precise drug conjugation. Inorganic nanoparticles, such as gold, silica and magnetic iron oxide gets outstanding optical and magnetic properties for imaging systems and medicine [33] Inorganic as well as organic components are combined to form multifunctional "hybrid" nanostructures. Such platforms support targeted drug delivery, prolonged release, enhanced tissue penetration and real-time diagnostics, all of which markedly improve wound healing and disease treatments. Despite the hurdles of scalability, long-term safety and getting regulatory approval, on-going research endeavors continue to improve and develop these technologies.

Polymeric nanoparticles

Owing to their malleable physicochemical properties, biodegradation that works like a slow-release system, and potential for controlled drug delivery therefore providing a handy carrier for therapeutic agents meant to heal wounds or beat back cancer cells polymeric nanoparticles (PNPs) have become today's focus of interest in the art of nanomedicine. The various components of these microscopic particles, which range in size from 10 to 1000 nanometers, include synthetic resins such as polycaprolactone (PCL) and gelatin, as well as natural or regenerated polymers such as poly(lactic acid) (PLA), polylactic co glycolic acid (PLGA), chitosan, and others. Each component is selected for its specific combination of biocompatibility, decomposition profile deductibility, and other desirable properties. [34] Precise control over drug loading efficiencies, release kinetics, and targeting capabilities is achieved by moulding the polymer composition, deriving variable molecular weights, and executing prespecified surface treatments. In the case of wound healing, polymeric nanoparticles are also used extensively for administering antigrowth factor, anti-inflammatory drugs and nucleic acids to long-term inflamed or infected wounds that conventional treatments often cannot effectively cure. [35] For instance, chitosan nanoparticles' positive charge stimulates hemostasis and fibroblast development in addition to their inherent antibacterial and wound healing characteristics; this charge combines with the negatively charged bacterial cell membrane.

Managed drug release can be facilitated mechanically by polymeric nanoparticles. This is accomplished by means of polymer breakdown, diffusion, or stimuli-responsive mechanisms that adapt to changes in wound microenvironmental pH, temperature, or enzyme activity. [36] Biodegradable polymeric nanoparticles can be incorporated into hydrogels, films, and scaffolds, further extending its versatility as multifunctional wound dressings that provide moisture retention, mechanical protection and sustained therapy release. [37] In the realm of personalized medicine and wound healing, polymeric nanoparticles have emerged as a game-changing tool. [38]

Inorganic Nanoparticles

Due to their unique antibacterial activity, biological effects, and physiochemical features, inorganic or metal nanoparticles (M-NPs) can promote diabetic wound healing. They can be chemically changed for wound targeting, and their vast surface area makes medicine loading and release efficient. Covalent interaction [39] and encapsulation are two of the several pathways that M-NPs exploit for efficient drug delivery. Metallic nanoparticles (MNPs) made of metals like gold, silver, and zinc have antibacterial properties that vary depending on whether they disrupt bacterial membranes or produce reactive oxygen species (ROS). It also has antioxidant and anti-inflammatory properties that can boost the production of angiogenic proteins, which aids in wound healing [40]. Additionally, zeta potential, surface functionalization, porosity, and hydrolytic stability are crucial for their effectiveness in biological applications [41]. It is possible that this targeted approach can accelerate recovery by delivering medicinal substances precisely when they are required.

Silver Nanoparticles

Antibacterial and anti-inflammatory silver nanoparticles (Ag-NPs) have been widely investigated and employed as M-NPs. Therefore, it has been used to treat burns, open wounds, and infected chronic wounds [42]. The antibiotic method of action involves protein binding, deactivation, DNA replication decrease, and ROS production. At low concentrations, Ag-NPs can permeate *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus subtilis* membranes [43]. This is because Ag⁺ interacts with proteins that contain sulfur and phosphorus, disrupting ATP synthesis and leading to unstable membranes and cell death caused by oxidative stress. People with diabetes often deal with inflammation and chronic wound infections. Scientists have so far developed Ag-NPs that are protein-based. The short peptide ϵ -polylysine, for example, is highly biocompatible and insoluble in water. Bypassing

the bacterial membrane, it renders the protein inactive [44]. Additionally, AgNPs stimulate the growth and migration of keratinocytes and release chemokines and cytokines that promote inflammation. This leads to the formation of macrophages and neutrophils, which enhance wound healing. In both laboratory and animal studies, the combination of AgNPs with insulin therapy increased insulin activity by modulating inflammation-related factors. [45]

Copper Nanoparticles

Copper nanoparticles, or Cu-NPs, are crucial to metabolic disorders and many biological functions. Skin regeneration, angiogenesis, and the maintenance of normal skin-essential proteins are all processes in which it is involved in the human body [46]. Copper unexpectedly has a significant antibacterial action against specific types of bacteria, which can cause serious infections in burn wounds and deep flesh ulcers (DFUs). Researchers found that Cu-NPs derived from chitosan were more efficient than Cu ions alone. Cells, cytokines, and growth factors are essential to wound healing, and CCuNPs have the potential to change all three, according to one research. The overexpression of TGF- β 1 and VEGF promotes the accumulation of collagen, the development of blood vessels, and the expansion of fibroblasts. Additionally, inflammation is reduced because it decreases TNF- α and increases IL-10 [47].

Zinc Oxide Nanoparticles

Zinc oxide nanoparticles (ZnO-NPs) are a stable antibacterial agent that can cross bacterial cell membranes. To facilitate epithelial regeneration, ZnO-NPs prolong the amount of time that keratinocytes spend in contact with the lesion, which in turn aids in their migration [48]. Microporous chitosan and ZnO-NPs have demonstrated impressive wound exudation ability, hemostatic clot production capabilities, and potent antibacterial effects with minimal cytotoxicity [49]. Combining essential oils with collagen gel to functionalize ZnO-NPs sped up wound closure and inhibited bacterial growth in animal studies. In addition to, they have the greatest regenerative capacity while also exhibiting non-acidic properties, biodegradability, and exceptional biocompatibility [50, 51]. Khan et al. [52] investigated the production of Au/ZnO core-shell nanocomposites. This nanocomposite has demonstrated antibacterial activity against *S. aureus* because of reactive oxygen species (ROS) release and the creation of an antibiotic film. By successfully closing the wound and repairing it from an aesthetic perspective in a model animal with skin wounds, ZnO-NP demonstrated its ability to follow approved antibacterial tissues. [53]

Gold Nanoparticles

Due to their biological, electrical, magnetic, and optoelectronic capabilities, gold nanoparticles (Au-NPs) may heal wounds. After damage, Au-NPs promote epithelialisation, collagen deposition, fast angiogenesis, and reduced collagen tissue regeneration, improving wound healing. Using Au-NPs with antioxidants such α -lipoic acid and epigallocatechin gallate in mice wound healing models resulted in faster healing. The variables that improve diabetic wound healing—including increased cell proliferation and angiopoietin-1 expression—caused this [54]. Using Au-NPs in cutting-edge low-level laser therapy for wound healing (e.g., photobiomodulation) is gaining a lot of consideration. In the first stage of wound healing, it reduces inflammation, pain, speeds healing, and promotes angiogenesis [55]. The modified Au-NPs were coupled with VEGF-A165 and (11-mercaptoundecyl)-N,N,N-trimethylammonium cation in another investigation. This combination demonstrated potent antibacterial and proangiogenic effects against methicillin-resistant *S. aureus* in a mouse model. The antibacterial peptide (LL37) showed improved antibacterial activity when coupled with Au-NPs, likely due to its improved nuclear and cell entrance mechanisms. It has demonstrated that gene transfection using nanoconjugates (Au-NPs/LL37/p DNAs) promotes angiogenesis in keratinocyte cells. It may speed wound healing by reducing infection, speeding up re-epithelialization, increasing granulation development, and decreasing healing time.

Table 2 Nanoparticle-based strategies for wound healing therapy

NPs	Properties	Mechanism	Applications	Reference
Ag-NPs	Antibacterial activity	Block the replication of DNA, render proteins inactive, and enhance signaling molecules	Burn wound; chronic infection	[42,43,]
Cu-NPs	Antimicrobial activity	Promote angiogenesis, cell regeneration, and increased cell proliferation while decreasing	Treat DFU, burn wound infections	[46,47]

		inflammation.		
ZnO-NPs	Antibacterial activity	Epithelial regeneration, keratinocyte migration, increase biocompatibility	Accelerates wound closure	[48-50]
Au-NPs	Antioxidant activity	Regeneration of damaged tissues, epithelialization of new blood vessels, alleviation of pain and inflammation	Wound healing	[54-56]
NA-NPs	Antibacterial activity	Increase cell division, cell specialization, and wound healing	Treat DFU, chronic wound infection	[57-59]
P-NPs	Antibacterial activity	Boost the production of fibroblasts, reepithelialization, growth factors, and new cartilage.	Diabetic wound healing	[60-62]
HGs	Antibacterial activity	Increase Repair of damaged cartilage, production of new collagen, and expansion of blood vessels	Treat polymicrobial disease, wound healing, drug delivery system, medicine	[63–66]
EVs	Antioxidative agents	Boost macrophages, angiogenesis, and tissue regeneration	Diabetic wound healing, drug delivery	[67-70]
LS	High therapeutic effect	Accelerate the healing process while decreasing inflammatory and painful responses	Drug delivery system, wound infection, gene therapy	[71-74]

Lipid-based nanocarriers (liposomes, solid lipid nanoparticles, niosomes)

Among the various lipid-based nanocarriers, liposomes, solid lipid nanoparticles (SLNs), and niosomes are the most widely researched and applied in biomedical fields, especially in targeted drug delivery, gene therapy, and wound healing. [75] Liposomes have the potential to encapsulate specific antibiotic sizes for the treatment of infected wounds or cancer, among other tissue engineering and drug delivery applications. [76] Solid lipid nanoparticles (SLNs) are a novel type of lipid-based nanocarrier that utilizes surfactants to stabilize the lipids. Protecting labile pharmaceuticals from breakdown and improving stability during dilution are two advantages of this design, in addition to enhanced control over controlled drug release. [77] By improving medication penetration through the skin barrier and maintaining therapeutic concentrations at the wound site, SLNs have shown encouraging outcomes in topical and transdermal drug delivery systems for chronic wounds. [78]

A desirable alternative to liposomes for drug administration, niosomes are physically similar but composed of non-ionic surfactants instead of phospholipids; they additionally provide better chemical stability, less production costs, and easier storage. [79] In comparison to liposomes, these vesicular carriers exhibit greater membrane stiffness and resilience to oxidative degradation; their bilayered form makes it possible to encapsulate substances with different hydrophilic and lipophilic properties. Research on the use of niosomes to transfer growth factors, antioxidants, and antibiotics to the wound healing process demonstrates promise due to the niosomes' enhanced cellular absorption, sustained release, and drug bioavailability. Their surfactant composition also helps niosomes to be functionalized with target moieties and stimuli-responsive components, which allows for the release of drugs on demand. [80]

With lipid-based carriers, new ideas have emerged on ways to evade the immune system, extend half-life in the circulation, and deliver actively drugs to the specific disease tissues using a receptor-mediated process. [81] Formulation methods that are applicable to the needs of any drug; stimuli-responsive designs; and hybrids based on liposomes combined with polymers or inorganic materials which eliminate toxicity problems while opening up entirely new applications in precision medicine and recent wound care developments. [82]

Phytosomes

Many diseases have been cured with great use of phytoconstituents. Complexing with phospholipids may help them to improve their bioavailability and targeted distribution.

Phytosomes are the complexes forming between phytoconstituents and phospholipids. Our cell membrane consists of phospholipids, which are safe for use and biocompatible. High entrapment efficiency and successful usage of phytosomes for topical, distribution of phytoconstituents for wound healing. [83,84] Few of the phyto-extracts pass over biomembrane and are not very soluble in aqueous solutions. Phytosomes can be created from these extracts. Demir et al. [85] created phytosomes from an extract of *Calendula officinalis*.

The phytosomal formulations made use of the wound-healing and antioxidant properties of gold nanoparticles by loading them with these particles. It was demonstrated that the Au-loaded phytosomes had a particle size of around 100 nm and had excellent entrapment efficacy. The availability of polyphenols was enhanced when phospholipids were mixed with a water-soluble extract of *Moringa oleifera* to create phytosomes. [87] The phytosomes were tested for cell cytotoxicity and cell migration using normal human dermal fibroblast cells cultured in a controlled environment.

Nanofibers

Drug-loaded nanofibers used topically in wound healing can prevent bacteria from penetrating due to their high specific surface area and 60–90% permeability. Nanofibers' nanoporosity network limits bacterial growth. Electrospinning facilitates continuous medication release. Thus, nanofibers create an optimal barrier and regulated wound healing. [88] Yao et al. [89] created a bilayer nanofiber scaffold with *Lithospermi radix* (LR) extract to promote rat wound healing. Traditional herbal medicine LR speeds injury recuperation. Almasian et al. created *Malva sylvestris*-derived polyurethane nanofibers. [90] These nanofibers were tested on diabetic wounds. Researchers tested different amounts of carboxymethyl cellulose to improve wound exudate absorption. *Staphylococcus aureus* and *E. coli* were strongly inhibited by this extract-loaded PU-based nanofiber dressing. By day 14, the wound dressing with 15% herbal extract showed a healing rate of 95.05%±0.24%. Histological analysis showed that neovascularization activity, fibroblastic proliferation, and macrophage penetration all improved by the seventh day. Collagenization and the degree to which the epithelium regenerated both increased on day 14.

Metallic and hybrid nanostructures

Nanomedicine and targeted therapeutic drug delivery have been greatly enhanced by metallic and hybrid nanostructures, which possess unique physicochemical features, magnetic characteristics, adjustable size and surface plasmon resonance (SPR), and several

functionalities. Magnetic, electrical, and optical characteristics are all uniquely MNPs. The main components of MNPs are magnetic metal elements like iron oxide (Fe_3O_4) and precious metals including gold (Au), silver (Ag), and platinum (Pt). [91] As a medication delivery method, they work effectively, and they can also be used as devices for diagnostic imaging, photothermal treatments, or antimicrobials. One example is the biocompatibility of gold nanoparticles (AuNPs). They can be easily functionalized with thiol chemistry and can convert near-infrared (NIR) light into locally focused heat. This allows for the precise photothermal removal of cancer cells without harming nearby healthy tissue. Wound dressings and coatings often contain silver nanoparticles (AgNPs), which are well-known for their broad-spectrum antibacterial action and can prevent the colonization of wounds by bacteria and the formation of biofilms. This eliminates an important problem that patients with chronic wounds face: infection.

One of the many medical uses for magnetic nanoparticles (MNPs) is as a contrast agent in MRI. Another is as a carrier for magnetically guided drug administration and hyperthermia therapy. One type of MNP is superparamagnetic iron oxide nanoparticles (SPIONs). [92] Because of their magnetic properties, they can be manipulated externally to target specific locations in the body, which increases the accumulation of drugs and thus their therapeutic index while reducing systemic toxicity. Silver and gold nanoparticles, their potent antibacterial effect is due to reactive oxygen species (ROS) generation--a process that disrupts microbe membranes and interferes with DNA copying, two things which are essential to the prevention of infection in a chronic wound. [93]

Stimuli-responsive and targeted systems

The development of targeted and drug-laden systems represents an advanced approach to drug administration. Increase drug efficacy and reduce side effects to promote the therapeutic effect: It is possible to exercise considerable control over when and where a given drug comes off a carrier by exploiting settings and phases in the body most of us know nothing about something only those with considerable expertise can handle. [94] This term "stimuli-responsiveness" is used to refer to the property of a drug release process which follows some form or another stimulation. Passive-active mechanism for promoting drug delivery on target is frequently employed: passive targeting utilize the "enhanced permeability and retention" (EPR) effect of pathological tissues such as tumors, inflamed wounds to encourage preferential localisation of nanoparticles. [95]

The various stimuli, pH-sensitive nanocarriers have drawn particular attention due to the distinctly acidic microenvironments which occur in tumors, inflamed tissues, and chronic wounds. Many of these systems include acid-labile linkages and/or pH-responsive polymers that are broken down or swollen by acidity, in the precise area where treatment is required, to release encapsulated therapeutics. When disease-specific enzymes such as matrix metalloproteinases (MMPs), hyaluronidases or phospholipases are present enzyme-responsive carriers [96] are engineered to either undergo structural changes or be destructed, which are often up-regulated in cancerous tissues and chronic wounds as well as provide a biologically precise trigger for the drug to be released. Carrier systems responsive to external stimuli afford the clinician unprecedented control over when drug release begins. Nanocarriers based on light-responsive materials, for instance, incorporate photosensitive groups that undergo structural transitions or generate reactive oxygen species (ROS) as soon as light strikes them. This permits the spatially-restricted photodynamic therapy and photothermal ablation of tumors in a way one could ordinarily not achieve using drugs alone. [97]

In wound healing, using responsive and directed nano-carriers together has created new opportunities for treating chronic wounds. These conditions are characterized not only by persistent inflammation, infection and bad angiogenesis, they also exhibit all sorts of difficulties that have hitherto made drug delivery to the local tissue cells difficult in practice. Ligand-modified nanoparticles can deliver antibiotics or growth factors to keratinocytes and fibroblasts more effectively and at sites of the wound pH- or enzyme-responsive release mechanisms ensure drugs are released only once they reach their destination, which significantly improves therapeutic efficacy. [98] Such systems have become necessary for clinical translation and mature use on patients suffering such chronic maladies. However, the rapidly developing field of responsive, addressable nano-carrier vaccines holds unimaginable promise for precision medicine. [99]

Bioactive Molecules

Stem Cells/Exosomes

The ability to self-renew and differentiate into various cell types are two of the primary features of stem cells (SCs), along with pluripotency and the ability to divide indefinitely. SCs can also promote the production of cytokines. [100, 101] It is important to think about the way their immune system normally responds; studies have shown that controlling the immune system speeds up the healing process of wounds. [102] While most mesenchymal stem cells (MSCs) originate in bone marrow, ADSCs are formed from fat, which is less

invasive and has no ethical limitations. By transforming into endothelial cells and secreting VEGF, ADSCs can promote wound healing. [103] Despite multiple studies showing that stem cell therapy improves skin regeneration, stem cells have a low survival rate and limited ability to multiply, which limits their usefulness in clinical settings. Therefore, a tailor-made strategy may involve combining SCs-exosomes with meticulously crafted NDDSs. An injectable hydrogel containing hyperbranched PEG macromer was created by Xu et al. [104] to facilitate the continuous delivery of ADSCs, which promote tissue regeneration. [105] However, there are a few limitations to stem cells, such as the potential for tumor formation and issues with transportation and storage. [106] Extracellular vesicles of 40–100 nm in size, exosomes are produced by the paracrine secretion of most cell types. Because of their longevity and ease of preservation, they can circumvent the limitations of stem cell treatment. [107-108] hUCMSC-exos are hydrogels filled with Pluronic F127 that contain human umbilical cord-derived mesenchymal stem cells. [109–111] This method of administration was successful in administering hUCMSC-exos and facilitated wound healing in diabetics. It can also express signals connected to proliferating cells, enhance granulation tissue development, and increase growth factor expression. [112–114] Therefore, exosome therapy based on biomaterials shows great promise in regenerative medicine and cutaneous wound care. [115-117]

Table 3 Stem Cell/Exosomes Loading Nanomaterial for Diabetic Wounds

Stem Cells/ Exosomes	Delivery Systems	Functions	Models	References
ADSCs	Injectable hydrogels	Promote regenerative capabilities.	STZ-induced mice	[101,102]
BMSCs	Hydrogels composed of N-chitosan and HA-ALD	Encourage the development of new connective tissues, new blood vessels, and collagen by shifting the immune system's focus to regenerative processes.	Wounds on the skin of diabetic mice produced by streptozotocin	[106,107]

Gingival mesenchymal stem cells (GMSCs)	Aquagel sponge made of chitosan and silk	Enhance angiogenesis and neural ingrowth to promote re-epithelialization, collagen deposition, and remodeling.	STZ-damaged rats	[108]
hFDSPC	HA	Enhance maturation, re-epithelialization, anti-inflammatory, angiogenesis, and collagen regeneration.	Mice infected with STZ	[110]
MSCs	PLGA NPs	Start the process of building capillaries and depositing collagen.	STZ-induced mice	[113]
hUCMSC-exos	Hydrogel created from Pluronic F-127 (PF-127)	Improved transport of hUCMSC-exos; increase the process of wound healing.	STZ-induced rats	[111]
Platelet-rich plasma exos	Aquagel sponge made of chitosan and silk	Quicken the process of blood vessel formation and collagen formation.	STZ-induced rats	[112]
Mesenchymal stem cells (MSCs)	Composite scaffolds made of ADM-RGO	Diabetic wounds heal quickly by promoting strong blood vessel formation.	STZ-induced rats	[109]

Growth Factors

Growth factors and other multifunctional polypeptides mediate, regulate, and coordinate cellular interactions by attaching to specific, high-affinity membrane receptors. [118] By inducing cell proliferation and differentiation, growth hormones can expedite the overlapping phases of wound healing. [119] To promote collagen production and skin regeneration, PDGF targets a wide variety of cells, one of which being dermal fibroblasts. [120] Cell migration

and proliferation are induced by the epidermal growth factor (EGF), which activates downstream signaling systems. [121] Keratinocyte migration is promoted by EGF interactions, which are essential for re-epithelialization. [122] This suggests that wound injury treatment with local application of exogenous growth factors can be effective.[123] Heberprot-P®,60 Regen-DTM 150, and Easyef® are rhEGF medications that are available for purchase and have been utilized in clinical trials. Traditional systems are unable to control the spatial and temporal release of GFs, despite multiple studies showing a spatial relationship between GF function and release. Recent publications have detailed various intricate methods for administering growth elements to diabetic wounds. Between the cellular membranes of epithelial, fibroblastoid, and endothelial types.[124-131] Additional EGF treatment is now plagued by problems such as a short half-life and the need for repetitive administration. A hybrid biomaterial patch is an intriguing option for GF loading.[132]

Genes/Proteins/Peptides

Transfection of genes is the basis of a gene treatment to fix genetic problems. Diabetic wound settings have a complex genetic condition; so, for the non-healing wound, changing gene levels indicates to be interesting. [133] The use of viruses for transfection carries the risk of cancer, and there are several challenges associated with gene therapy. [134] The use of electroporation improved cell absorption, and Yan et al. found that exosomes generated from milk contain miRNA that is resistant to destruction. The results of this novel approach showed enhanced angiogenesis and faster wound healing in diabetics when tested in vivo. [135] Gene silencing occurs post-transcriptionally because of small interfering RNA (siRNA), which is mostly caused by RNA interference (RNAi). [136] In order to improve angiogenesis factors in the diabetic wound area, Shaabani et al. integrated siRNA into a multi-layer platform with a customizable outside surface. The primary focus was on ensuring the stability of HIF-1 α , a factor crucial for activating angiogenesis elements. Nanocarriers that self-assemble layer-by-layer and contain siRNA can reduce PHD-2, stabilize HIF-1 α , and increase the level of pro-angiogenic factors. [137-155]

Table 4 Nanocarrier-delivered genes, proteins, and peptides for the healing of diabetic wounds

Cargos	Carriers	Functions	References
Keap1 siRNA	Nanoparticle containing lipopolyplex (LPP)	Accelerate diabetes tissue regeneration, improve reduction-oxidation equilibrium in wound environments, and restore Nrf2 antioxidant function.	[138]
siRNA-29a gene	nanoparticles with HF-PEI	The production of angiogenesis factors (α -SMA and CD31) and diabetic wound healing can be accelerated, while pro-inflammatory factors (IL-6 and TNF- α) may remain.	[141]
MMP-9 siRNA (siMMP-9)	Hydrogel composed of Pluronic F-127 (PF) and methylcellulose (MC); chitosan nanoparticles; or hyperbranched cationic polysaccharide derivatives (HCP).	Improving diabetic wound healing by decreasing MMP-9 expression.	[139,140,]
Small interfering RNA (DsiRNA) on the Dicer substrate	Gold nanoparticles (AuNPs)	Improve vascularization by blocking the expression of the PGT gene; increase vascularization and PGE2 synthesis.	[142,143]
siRNA (downregulation of PHD-2)	Gold nanoparticles (AuNPs)	Facilitate the activation of pro-angiogenic pathways; enhance the endosomal escape of siRNA; and induce fibroblast PHD-2 silencing.	[137]

Bioactive peptides	Nuclear particles of chitosan	Accelerate neovascularization and decrease the inflammatory phase.	[146]
MicroRNA (miRNA) miR-31-5p	Milk-derived exosomes	Promote the proliferation, migration, and angiogenesis of endothelial cell.	[135]
LncRNA-H19	High-yield extracellular vesicle-mimetic nanovesicles (EMNVs)	Neutralize the regeneration-inhibiting effect of hyperglycemia.	[144]
miR146a	Cerium oxide nanoparticles (CNP)	Scavenge free radical, inhibit NFκB pathway, anti- inflammation performance.	[152]
Neurotensin (NT)	PLGA/CNC nanofiber membranes are a combination of polylactide and polyglycolide.	The levels of the inflammatory cytokines IL-1β and IL-6 were reduced, leading to quicker recovery.	[149]
Antimicrobial peptide (LL37)	nanoparticles of ultra-small gold	Maximize the efficiency of gene delivery by improving cellular and nucleus entrance.	[145]
PDGF-BB proteins	Hydrogel derived from fibrin	Spark the formation of new blood vessels and arteries.	[147]
P311 peptides	Micelles	Ros-triggered release of P311 to decrease inflammation and oxidative damage.	[153]
CCN1	Nanoformulation	Decrease inflammation by increasing CCN1 intracellular expression.	[154]
Recombinant human collagen type III (rhCol III)	PDA@Ag NPs	Encourage fibroblast and endothelial cell migration and proliferation in mice; raise VEGF and basic fibroblast growth factor expression levels.	[150]

L-Glutamic acid	Chitosan (CS) hydrogels	Accelerate the process of vascularization and the attraction of macrophages.	[148]
VEGF-A mRNA	Lipidomic nanoparticles loaded with ionizing agents (LNP)	Accelerate the healing process by upregulating VEGF-A expression.	[155]
Recombinant human thrombomodulin (rhTM)	Lipidomic acid nanostructured carrier	Promote the process of cell migration and wound healing.	[151]

Biomaterial-driven interventions for angiogenesis in diabetic wound

A novel approach to enhancing angiogenesis within the context of diabetic wound has emerged with the introduction of biomaterial-based treatments, which have renewed the field of regenerative medicine [156-159]. In addition to their inherent static characteristics, these biomaterials can be used as dynamic scaffolds to target the adherence and proliferation of cells. Their utility, however, extends much beyond that of basic architectural supports. Biomaterials transport therapeutic chemicals, such as cytokines and growth factors, to specific wound sites, where they can exert their transformative effects [160]. Demonstrating the vital role of biomaterials in regulating the healing processes within the intricate environment of diabetic wound, the interplay between structural elements and therapeutic agents encapsulates the emerging synergy.

Bioactive coatings and surface functionalization

Several novel strategies for diabetic wound healing using bioactive coatings and surface functionalization techniques have recently been studied [161]. Aligned porous electrospun fibrous membranes embedded with dimethyloxallylglycine-containing mesoporous silica nanoparticles (DS) [162] constitute one approach. These membranes promote angiogenesis through regulating the release of DMOG and Si ions; they are identified by their compatible fibers and surface nano-pores. Important for wound healing, in vitro studies show how much they stimulate HUVECs (human umbilical vein endothelial cells) to proliferate, migrate, and express genes relevant to angiogenesis. Gallic acid (GA) and konjac glucomannan (KGM) [163] can be combined to form a composite hydrogel (GAK), which is an additional intriguing technique. The surface adhesion, stability, swelling, and antibacterial action of this

composite hydrogel are superior to those of GA alone. In diabetic rats, it accelerates up wound healing, collagen deposition, and angiogenesis.

Biomedical scaffolds for angiogenesis

In the complex environment of DWs, scaffolds have gained popularity as a dynamic and promising approach to enhance angiogenesis [164,165]. Synthetic scaffolds are an essential part of this field. Intentional change can be made to these scaffolds since they are flexible substrates [166]. 3D-PT-P/GM, a novel nanofiber/hydrogel core-shell scaffold [167] features a 3D multilayer patterned structure. To improve diabetic wound healing, this scaffold is engineered to stimulate angiogenesis. Using scaffolds that are already present in nature is another scaffold-based therapy technique [168,169]. By providing an environment like the initial ECM, these natural scaffolds—hyaluronic acid, fibrin, and collagen—encourage cellular adhesion and growth. They stimulate angiogenesis because of their ability to encapsulate growth factors and other medicinal substances. In addition, these scaffolds can be designed with certain physical properties that can regulate cellular activity and facilitate angiogenesis, including porosity or stiffness. An additional layer of complexity is introduced to this approach by decellularized scaffolds in particular [170,171]. After treatment to remove biological components while maintaining the ECM, these naturally occurring scaffolds offer an environment comparable to the natural ECM for cell adhesion and proliferation. The inclusion of growth factors or medical medications in them can enhance angiogenesis.

Application of hydrogels for pro-angiogenesis

Hydrogels are incredibly good at absorbing a lot of water and other biological fluids because they are complex 3D networks made of hydrophilic polymers. Their well-planned structure facilitates the controlled release of medicinal chemicals, such as cytokines and growth factors, providing a versatile platform for the targeted administration of pharmacological payloads while also encouraging myogenesis [172]. Peptide hydrogels are an intriguing new treatment possibility [173]. The hydrogels' bioactive motifs improve their functional design, which mimics that of the natural extracellular matrix (ECM). The addition of Arg-Gly-Asp (RGD) peptides in particular shows the potential, these peptide hydrogels transport angiogenesis-promoting medications to the site of the wound, and there they will serve as a scaffold to facilitate the proliferation of new blood vessels. Peptide hydrogel CBPGCTS-SF@PRP, which was synthesized by Qian et al. [174]. The ability of growth factors and angiogenic moieties to undergo transformation is enhanced through the functional

modification of these substances, which aids in the controlled release of therapeutic entities [175-176]

Natural hydrogels, such as alginate and collagen hydrogels, have also contributed to the scene's creation [177]. These hydrogels encase cultivated cells and offer a nurturing environment, functioning as natural scaffolds. They play a significant role in setting the stage for DW regeneration after receiving angiogenic inducers. A prior study demonstrated that 45S5 Bioglass® (BG) ion products can inhibit MMP-9 production in cells that are involved in tissue formation when combined with MMP9-siRNA, a short interfering RNA targeting MMP9. Even ECMs can synthesize themselves with the help of this synergy [178]. BG ionic products cause macrophages to adopt the M2 phenotype, leading to an inflammatory environment that promotes tissue regeneration. The result is a decrease in MMP-9 expression in the cells responsible for the indirect formation of tissues.

Clinical trials of angiogenesis-promoting biomaterials

The development of improved biomaterials that stimulate angiogenesis is crucial to the ongoing attempt at better diabetic wound repair. Hydrogels, which are biocompatible three-dimensional matrices of hydrophilic polymers, stand out among the many biomaterials now undergoing clinical evaluation. These hydrogels provide a possible solution for diabetic wound treatment by facilitating cell migration and delivering growth factors, which create an environment suitable for angiogenesis. A biodegradable and bioactive scaffold that mimics the natural extracellular matrix (ECM), fibrin-based scaffolds are derived from fibrinogen and can aid in the process of angiogenesis. [179]. Clinical trials are investigating into nanofiber scaffolds, which are constructed to mimic the natural ECM and have a high surface area, to enhance angiogenesis and tissue repair in diabetic wound [180]. Collagen, chitosan, or alginate are components of bioactive dressings that are designed to promote an environment that is favorable for wound healing. Because they secrete growth factors or medications to stimulate angiogenesis in clinical studies, these dressings provide a novel approach to diabetic wound treatment. Jointly, these biomaterials provide a range of options for dealing with the issues brought on by decreased angiogenesis in diabetic wound.

In vitro and in vivo models for diabetic wound healing activity

Reliable outcomes can only be achieved with products that are based on first-hand scientific findings, which in turn require both preclinical research and clinical trials. [181] Therapeutic response and nanocarrier distribution in clinical trials can be real-time monitored using

advanced imaging and biomarker tracking for personalized therapy.[182] With the spread and effectiveness of Dianoyal, the conversation on adaptive wound-specific patient care is gathering momentum. This is a trend concurrent with the manipulation of these bio-cages to aid wound healing functions: now that surgery and hospitals are widely using them as tools, some are even allowed for routine treatment of the newly amputated diabetic foot ulcer.

Skin cultures from humans or other animals serve as the basis for these in vitro models. [183] Among these cells, the most common kinds are keratinocytes, which represent the outer layer, fibroblasts, which form scar collagen, endothelial cells, and immune system lineage cells. Some Co-Culture systems and three-dimensional skin equivalents have been developed to mimic better the complex cellular interactions and structural organization of natural skin. [184] This allows for more relevant testing of the efficacy of drugs, as well as the performance of nanocarriers, than thinner models could match. Advanced in vitro platforms like the microfluidic "Wound-on-a-Chip" devices model actual wounds and the dynamic environment around them, including things such as nutrient gradients and shear flow. Diabetic mice or rats Heida for example, a rat model with streptozotocin is administered after which its wounds become very much like those seen in human diabetes.[185] However, on the positive side, price and ob / ob mice can provide important information in this respect. An IR model with diabetes, developed on the research animal, includes at least one type of wound. So far they have developed diabetic wounds and IR mouse models on the abdominal muscles of rats. [186]

Challenges and Limitations

The development and clinical application of advanced wound healing therapies, particularly those involving bioactive compounds and nanotechnology-based delivery systems, bring various problems. [187] The intricate and unique pathophysiological mechanisms for chronic wounds, especially diabetic wounds, might have to do with impaired angiogenesis, persisting inflammation, a persistent high level of infection risk, oxidation state, and neuropathy, rendering any single cure ineffective. Patient compliance, problems in monitoring the wound and the need for personalized or combinatorial therapeutic strategies further restrict the therapeutic efficacy of treatments. Smart nano-carriers must strike a balance between stability and drug release, needing a close collaboration between several different branches of study in order to further refine original designs, improve preclinical models and introduce cost-beneficial, safe and clinically viable solutions. [188]

Emerging Trends and Future Perspectives

Innovative trends in bioactive-based nanoplatforms for treating diabetic ulcers are taking off as fast as a baby's first steps with rapid development in nanotechnology, materials science and molecular biology. Using wound microenvironment signals such as pH, temperature, enzymes, and redox, smart nanoplatforms are beginning to respond dynamically, allowing for targeted drug release with minimal side effects. [189] Inclusion of biosensors in nanocarriers enables real-time monitoring for healing conditions such as infection and inflammation, which will in turn be beneficial to the tailored treatment strategies used. Biomimetic materials like ECM-mimicking scaffolds and cell membrane-coated nanoparticles improve biocompatibility and targeting efficiency.

A bacterial inoculum above 10^4 colony-forming units (CFU) can potentially cause abscess development, bacteremia, cellulitis, osteomyelitis, or sepsis, most of which might ultimately be fatal. [190-191] In order to combat wound infections, phage therapy has advanced greatly in recent years. [192]

In acidic wound situations, liposome-sheltered phage (LSP) systems may be more effective than normal phage therapy due to their improved phage stability, retention, and efficiency. Liposomes improve phage retention at wound infection sites by coating lesion surfaces, retaining moisture, and speeding healing [193]. Alternatively, phages that include bacterial byproducts such as cytosolic and cell membrane proteins linked to them can enhance the immune response [194]. Phages can regulate the immune response in addition to targeting bacteria..

CRISPR, AI, and biosensor-integrated nanocarriers

By incorporating CRISPR technology, artificial intelligence (AI), and nanocarrier-based biosensors, precision medicine and personalized treatment have all but transformed diabetic wound healing. [195] The same technique is linked to analyzing patient data, predicting therapeutic outcomes, and developing nanoparticle formulations faster. Despite these advances, major challenges remain to be addressed, such as long-term safety, regulatory approval, data privacy and scalability. Interdisciplinary collaborations among various fields may be necessary for full realization of the potential of new technologies and highly adaptable personalized wound care systems are on the drawing board. [196]

Personalized nanomedicine in wound care

In wound care, personalized nanomedicine specializes in treatments that seeks to treat each patient according to the specific biological and pathological specificities. [197] Traditional approaches often fail a wound nothing interests because of the variability in its etiology, microbial colonization and patient-specific factors; nanomedicine is thus full of promise. Multifunctional nanocarriers make it possible to transport selectively the release with controlled-growing factors and antibacterials, and other bioactive compounds. Personalized diagnostics including genomic, proteomic and metabolomic profiling identify particular wound obstacles such as tumor cells. 3D bioprinting paves the way for patient-specific wound dressings that incorporate nanomaterials to promote regeneration. [198] Although there are challenges in terms of price, regulation, interdisciplinary cooperation and other factors, ongoing research is pushing ahead with the clinical application of personalized nanotherapeutics.

Translational potential and commercialization prospects

The commercial prospects of bioactive nano-platforms in healing diabetics' chronic wounds based upon biologic drugs are promising. The development of nanotechnology, biomaterials and precision medicine further drives up license income. Compared with traditional therapies, these nano systems can make sure that the medicine is released where and when it should be precisely. [199] Given the global increase in diabetes-related wounds, recurrence of wound infections, and the difficulties in caring for so many old people with so few children to look after them, theologically-inspired conscious applications of nanotechnology make an excellent opportunity for wound management. [200]

Conclusion

In conclusion, the combination of nanoplatforms with plant-based bioactives offers a new paradigm for diabetic wound treatment. These systems not only combat some of the multifactorial etiologies of chronic wounds like oxidative stress, persistent infection, and deficient angiogenesis, but also provide a controllable, sustained, and localized drug release. Including polymeric and inorganic nanoparticles, lipid-based carriers and phytosomes, these nanostructures improve bioavailability, extend the therapeutic duration, and reduce systemic side effects. In addition, the advent of gene and peptide filled carriers, biosensor embedded systems and CRISPR-augmented therapeutics is propelling personalized wound care into a new age. While scalability, regulatory paths and long-term safety remain current challenges

for these platforms, interdisciplinary collaboration is narrowing the gap between the lab and clinic in the development of these innovative technologies. With continued experimental investigation and technological advancement, nano-bioactive platforms can be projected to suffice the need of future diabetic wound treatments that promote rapid healing, reduced complications, and improve quality of life for millions around the world.

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