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REVIEW

Nanocarrier-Mediated Delivery Systems of Phytochemicals to Enhance and Accelerate Diabetic Wound Healing Processes

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Abstract: This review explores the mechanistic and translational potential of nanotechnology-based delivery systems for natural compounds in diabetic wound healing. Diabetic wounds present a persistent challenge due to impaired tissue regeneration and chronic inflammation. Phytochemicals such as flavonoids and polyphenols exhibit potent antioxidant, anti-inflammatory, and tissue-regenerative properties but are limited by low bioavailability and stability. Nanoparticle formulations—particularly silver nanoparticles (AgNPs) and chitosan-based nanoparticles (CNPs)—offer innovative solutions by enhancing stability, tissue penetration, and sustained release of these bioactives. Our analysis highlights how these nanocarriers facilitate targeted delivery, thereby amplifying antioxidant activity, antimicrobial effects, and tissue regeneration mechanisms critical for wound healing. The review underscores the mechanistic insights into how nanoparticle systems improve therapeutic efficacy and discusses their translational potential in clinical settings. Notably, AgNPs' antimicrobial properties and green synthesis, along with CNPs' biocompatibility and bioadhesive characteristics, position these nanomaterials as promising candidates for advancing diabetic wound care. This synthesis of current evidence emphasizes nanotechnology's role in overcoming the limitations of natural compounds and advancing sustainable, effective treatments for diabetic wounds.

Keywords: nanotechnology, diabetic wound healing, phytochemicals, nanoparticles, therapeutic efficacy

Introduction

Diabetes mellitus (DM) is a global health concern characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. According to the International Diabetes Federation, over 400 million people worldwide are affected by diabetes, and this number is expected to rise substantially in the coming decades. Among the myriad complications associated with diabetes, diabetic wounds—especially diabetic foot ulcers—pose significant clinical challenges. These wounds are often resistant to conventional therapies, leading to prolonged healing times, increased risk of infections, amputations, and substantial healthcare costs.[1] Despite advances in wound management, effective treatments that address the underlying pathophysiology of diabetic wounds remain limited, highlighting the urgent need for innovative therapeutic strategies.[2]

The impaired healing process in diabetic wounds stems from a complex interplay of factors such as persistent hyperglycemia, microvascular impairment, neuropathy, and immune dysfunction. Hyperglycemia induces oxidative stress by generating excessive reactive oxygen species (ROS), which damages cellular components and impairs cellular functions necessary for tissue repair. Furthermore, chronic inflammation persists due to an imbalance between pro-inflammatory and anti-inflammatory cytokines, which inhibits the progression of wound healing from the inflammatory to the proliferative phase. Angiogenesis,

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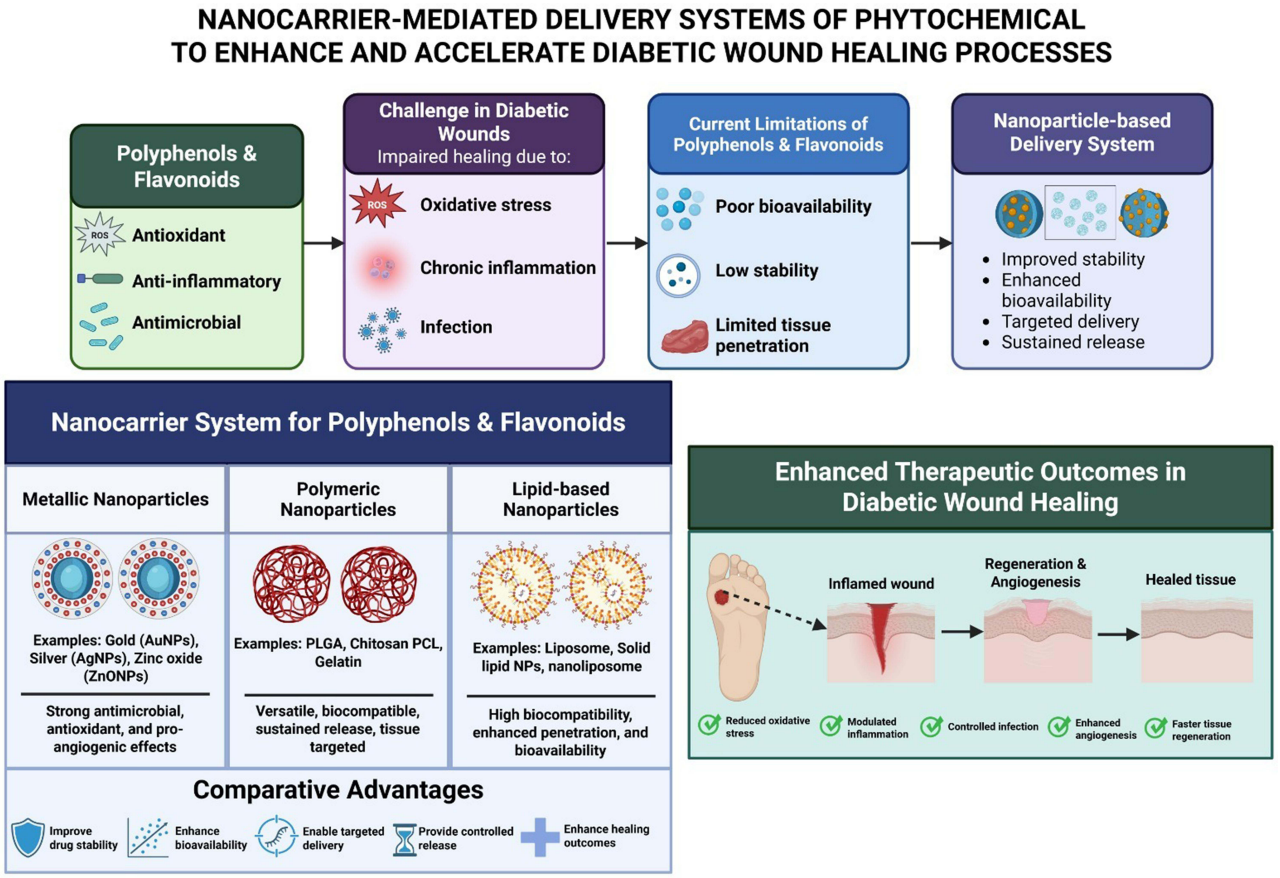
Graphical Abstract



essential for delivering nutrients and oxygen to regenerating tissue, is also compromised, resulting in ischemia and delayed tissue regeneration. These pathological features collectively contribute to the chronicity of diabetic wounds.[3]

Standard wound care strategies—including debridement, infection control, dressings, and offloading—are often insufficient for diabetic wounds. Advanced therapies such as growth factor applications, skin grafts, and hyperbaric oxygen therapy have shown some benefits but are limited by high costs, inconsistent efficacy, and potential side effects. Moreover, these approaches do not directly address the cellular and molecular alterations underpinning impaired healing in diabetes.[4–6]

Natural plant-derived compounds, or phytochemicals, have garnered increasing interest due to their multifaceted biological activities and relatively low toxicity. Among these, flavonoids and polyphenols are particularly notable for their potent antioxidant, anti-inflammatory, antimicrobial, and tissue-regenerative properties. Flavonoids—such as quercetin, kaempferol, and luteolin—have demonstrated abilities to scavenge ROS, modulate inflammatory responses, promote angiogenesis, and enhance collagen synthesis. Polyphenols such as resveratrol, curcumin, and epigallocatechin gallate (EGCG) also exhibit similar activities, contributing to improved wound healing outcomes.[7,8]

However, despite their therapeutic potential, the clinical application of phytochemicals is hampered by inherent limitations, including poor water solubility, low bioavailability, chemical instability, and limited tissue penetration. These pharmacokinetic challenges limit the concentration of active compounds at the wound site, diminishing their efficacy.[9–12]

Nanotechnology offers promising solutions to overcome these limitations through the development of nanocarrier-based delivery systems.[13] Nanocarriers—such as liposomes, solid lipid nanoparticles, polymeric nanoparticles, silver nanoparticles (AgNPs), and chitosan-based nanoparticles (CNPs)—can protect phytochemicals from degradation,

improve their solubility, facilitate targeted delivery, and enable sustained release at the wound site. By enhancing the bioavailability and tissue penetration of phytochemicals, nanocarriers can potentiate their biological activities and accelerate the wound healing process.[14]

The unique pathophysiological conditions of diabetic wounds require targeted and efficient delivery systems to maximize therapeutic benefits. Nanocarriers can be engineered to respond to the wound microenvironment—such as pH or ROS levels—allowing for controlled and site-specific release of encapsulated phytochemicals. Moreover, certain nanomaterials possess intrinsic antimicrobial properties (eg., AgNPs), which can further aid in infection control—a critical aspect of diabetic wound management.

Several types of nanocarriers have been explored for delivering flavonoids and polyphenols: Silver nanoparticles (AgNPs), known for their potent antimicrobial activity, AgNPs can also serve as carriers for phytochemicals, enhancing their stability and facilitating synergistic effects against wound pathogens; Chitosan-based nanoparticles (CNPs), chitosan is a biocompatible, biodegradable polymer with inherent antimicrobial and wound-healing properties. CNPs can encapsulate phytochemicals, prolong their release, and promote tissue regeneration; and Lipid-based and polymeric nanoparticles: These systems improve solubility and bioavailability, enabling higher concentrations of phytochemicals at the wound site.[12–14]

Nanocarrier-mediated delivery systems can amplify the therapeutic efficacy of phytochemicals through multiple mechanisms: Antioxidant activity, Enhanced ROS scavenging reduces oxidative stress, thereby protecting cellular components and promoting tissue repair; Anti-inflammatory effects: Modulation of cytokine profiles diminishes chronic inflammation, facilitating the transition to the proliferative phase; Angiogenesis promotion, Certain phytochemicals stimulate new blood vessel formation, improving oxygen and nutrient delivery. Antimicrobial action, Nanoparticles like AgNPs can directly kill pathogenic microbes, reducing infection risk; and Tissue regeneration, Enhanced collagen synthesis and cellular proliferation contribute to faster wound closure.

While preclinical studies demonstrate the promising potential of nanocarrier-encapsulated phytochemicals in diabetic wound healing, clinical translation remains in its early stages. Challenges such as large-scale manufacturing, biocompatibility, safety, and regulatory approval must be addressed. Nonetheless, integrating nanotechnology with phytochemical therapy offers a novel, multi-faceted approach that aligns with personalized and regenerative medicine principles.

The convergence of nanotechnology and phytochemistry presents an exciting frontier in diabetic wound management. By overcoming pharmacokinetic limitations and enabling targeted, sustained delivery of bioactive compounds, nanocarrier systems can significantly enhance and accelerate the healing process. Continued research into optimizing nanocarrier design, understanding mechanistic pathways, and conducting rigorous clinical evaluations will be essential to realizing the full therapeutic potential of this innovative approach.

Materials and Methods

This review was conducted regularly to gather, evaluate, and synthesize current research on nanocarrier-mediated delivery systems of phytochemicals—particularly flavonoids and polyphenols—for the purpose of enhancing and accelerating diabetic wound healing processes. The following methodology was employed:

Literature Search Strategy

A comprehensive literature search was performed across multiple electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search was conducted up to October 2023. The search terms included combinations of keywords and Medical Subject Headings (MeSH) such as:

- "nanocarrier," "nanoparticle," "liposome," "solid lipid nanoparticle," "polymeric nanoparticle," "silver nanoparticle," "chitosan nanoparticle"
- "phytochemicals," "flavonoids," "polyphenols," "natural compounds"
- "diabetic wounds," "diabetic foot ulcers," "wound healing"
- "drug delivery," "nanodelivery," "targeted delivery," "sustained release"
- "accelerated healing," "enhanced healing," "wound regeneration"
- Boolean operators (AND, OR) were used to optimize the search strategy.

Inclusion and Exclusion Criteria

Studies were selected based on the following criteria:

Inclusion Criteria

- Original research articles, reviews, or clinical studies published in peer-reviewed journals.
- Studies focusing on nanocarrier systems (eg., liposomes, nanoparticles, nanocomposites) designed for delivering flavonoids or polyphenols.
- Research investigating the application of such systems in diabetic wound models, whether in vitro, in vivo (animal models), or clinical settings.
- Articles published in English.

Exclusion Criteria

- Studies not involving phytochemicals or nanocarrier systems.
- Reports without specific focus on diabetic wound healing.
- Conference abstracts, editorials, commentaries, or non-peer-reviewed articles.
- Studies lacking sufficient experimental detail or outcomes relevant to wound healing.

Data Extraction and Analysis

Data from selected articles were extracted independently by two reviewers and included the following:

- Type of nanocarrier system used
- Phytochemicals delivered
- Wound model employed (eg., diabetic rat/mouse, cell culture)
- Key findings related to wound healing efficacy
- Mechanisms of action proposed
- Safety and biocompatibility data
- Any reported limitations or challenges

Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

Quality Assessment

The methodological quality of in vivo studies was assessed using adapted criteria from the ARRIVE guidelines, focusing on experimental design, sample size, controls, and outcome measures. In vitro studies were evaluated based on reproducibility, controls, and relevance to clinical scenarios.

Data Synthesis

A narrative synthesis approach was adopted to integrate findings across studies. The review emphasizes trends, common mechanisms, and the potential translational applications of nanocarrier systems for phytochemical delivery in diabetic wound healing. Particular attention was given to innovative nanocarrier formulations, phytochemical stability, targeting efficiency, and therapeutic outcomes.

Results and Discussion

Pathology of Diabetes Mellitus Wounds

Diabetic wounds, particularly diabetic foot ulcers, stem from a complex interplay of vascular, neuropathic, and immune dysfunctions associated with long-standing hyperglycemia. One of the primary pathological features is microvascular and macrovascular damage. Chronic high blood glucose levels lead to the formation of advanced glycation end products (AGEs), which cross-link with collagen and other extracellular matrix proteins, stiffening blood vessel walls and impairing their elasticity. These structural alterations result in reduced blood flow and oxygen delivery to tissues, creating a hypoxic environment critical

for wound healing. Additionally, atherosclerotic changes in larger arteries further diminish perfusion, especially in the lower extremities, aggravating ischemia. This compromised blood supply hampers the delivery of essential nutrients, oxygen, immune cells, and growth factors necessary for tissue regeneration, prolonging the inflammatory phase and delaying wound closure. As a result, the tissues become more vulnerable to necrosis and infection, setting the stage for chronic, non-healing wounds.[15]

Neuropathy is another hallmark of diabetic wound pathology, markedly contributing to the development and progression of ulcers. Elevated blood glucose damages peripheral nerves through metabolic and ischemic mechanisms, leading to sensory loss, particularly in the feet. Patients may not perceive minor trauma, repetitive pressure, or skin breakdown, allowing injuries to go unnoticed and untreated.[16] Motor neuropathy causes muscle weakness and deformities such as claw toes and Charcot foot, which alter biomechanics and increase pressure points on the skin, further predisposing to skin breakdown. Autonomic neuropathy impairs sweat and sebaceous gland function, resulting in dry, cracked, and fissured skin that is more susceptible to injury. The combined effects of sensory loss and abnormal foot mechanics create a perfect storm for ulcer formation. Moreover, the insensate skin fails to alert the patient to ongoing damage, leading to delayed presentation and increased risk of infection, which can rapidly advance to deep tissue involvement.

Once a wound forms, the immune response in diabetic patients is significantly impaired, further complicating healing. Hyperglycemia adversely affects the function of neutrophils and macrophages, key cells in the early inflammatory phase of wound healing. Neutrophils exhibit reduced chemotaxis, phagocytosis, and microbial killing, resulting in an increased risk of bacterial colonization and persistent infection. Macrophages, which are essential for clearing debris and orchestrating tissue repair, tend to shift towards a pro-inflammatory phenotype and fail to transition effectively into the reparative stage. This dysregulated immune response leads to a prolonged inflammatory phase characterized by elevated levels of cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins (IL-1, IL-6), which perpetuate tissue destruction and impede progression to proliferation. Additionally, oxidative stress induced by hyperglycemia exacerbates cellular damage, impairing keratinocyte migration and fibroblast function. This results in defective re-epithelialization and collagen deposition, essential steps for wound closure. The imbalance between ECM synthesis and degradation, driven by excessive matrix metalloproteinases (MMPs), causes fragile granulation tissue and prevents wound stabilization.[17]

Furthermore, the persistent inflammatory and ischemic environment fosters microbial colonization and biofilm formation within the wound bed. The compromised immune defenses, combined with tissue hypoxia and necrosis, create an ideal niche for bacteria to proliferate, often leading to chronic infections. These biofilms protect bacteria from antibiotics and immune clearance, making infections difficult to eradicate and further delaying healing. The ongoing cycle of infection, inflammation, and tissue destruction results in a chronic wound state, often culminating in tissue necrosis and, in severe cases, necessitating amputations. Collectively, the pathology of diabetic wounds is multifaceted, involving vascular insufficiency, neuropathy, immune dysregulation, oxidative stress, and infection, which together disrupt the normal wound healing process and establish a persistent, non-healing ulcer.[15–17]

The pathophysiology of diabetic wounds is complex, as these chronic wounds in diabetic patients result from a combination of metabolic and vascular dysfunctions. Central to this process is hyperglycemia, which causes nerve damage (neuropathy) and impairs blood flow (ischemia). These changes reduce the body's ability to heal wounds effectively. Diabetic wounds are most commonly found on the feet and often produce minimal exudate or wound fluid. One of the main challenges in healing these wounds is the prolonged or stalled healing process, which occurs due to decreased production of cytokines and growth factors, persistent inflammation, and infection. Consequently, these wounds are difficult to cure, increasing the risk of severe infections and sometimes leading to non-traumatic amputations in diabetic patients. In addition to wound healing issues, nerve complications caused by hyperglycemia, known as diabetic peripheral neuropathy (DPN), play a significant role in diabetic foot problems. DPN results in sensory deficits such as numbness and pain, along with motor dysfunction such as muscle weakness, especially in the lower limbs. These nerve impairments can lead to unnoticed injuries and contribute to the formation of foot ulcers, which, if left untreated, may progress to requiring amputation. Inflammation is another key factor impairing wound healing in diabetes. Chronic inflammation causes an increase in Matrix Metalloproteinases (MMPs), enzymes that break down tissue.[18] Elevated MMP levels inhibit collagen synthesis, which is essential for tissue repair and wound closure. If infections are not managed properly, they prolong the inflammatory response, further hindering healing. Overall, the interplay of vascular damage, neuropathy, and persistent inflammation creates a challenging environment that prevents normal wound resolution in diabetic patients. Figure 1 shows the pathogenesis of diabetes mellitus wounds.

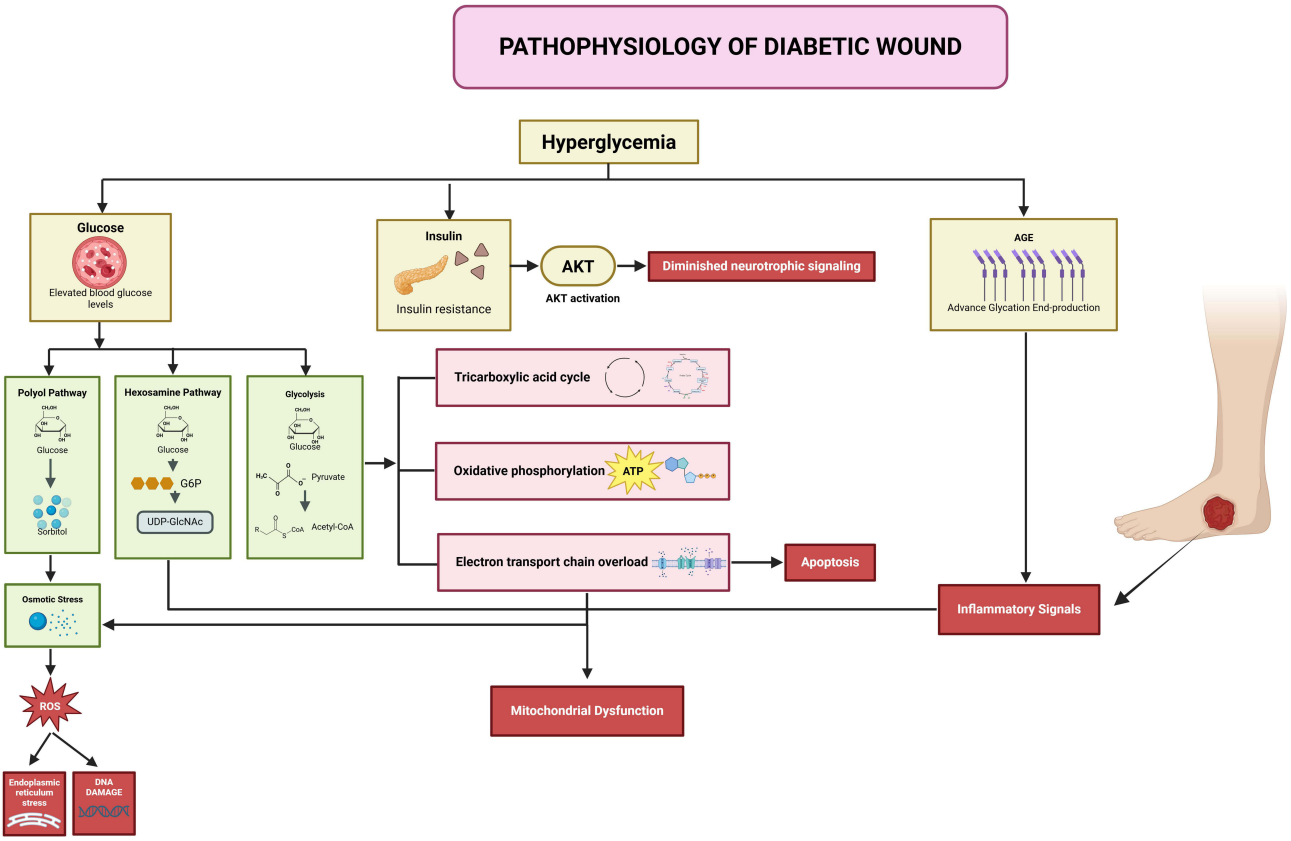


Figure 1 The pathogenesis of diabetic wounds (BioRender).

Conventional Products for Managing Diabetic Wounds

The management of diabetic wounds traditionally relies on a variety of conventional products aimed at promoting healing, preventing infection, and protecting the wound from further trauma. These products include basic dressings, which serve as the foundation of wound care. Simple dressings such as gauze, non-adherent pads, and cotton wool are commonly used to cover the wound surface, absorb exudate, and protect against external contaminants. These dressings are inexpensive and easy to apply but often require frequent changes due to limited moisture retention capabilities. To improve healing outcomes, healthcare providers often incorporate more advanced dressings that maintain a moist wound environment, which is crucial for cell migration and tissue regeneration. Examples include hydrocolloid dressings, foam dressings, and alginate-based products. Hydrocolloids create a protective, moist environment that promotes autolytic debridement, while foam dressings provide excellent absorption for wounds with higher exudate levels. Alginate dressings, derived from seaweed, are highly absorbent and form gels upon contact with wound exudate, helping to manage moisture and facilitate autolytic debridement.[19]

In addition to dressings, topical antimicrobial agents are widely used to prevent or treat infection in diabetic wounds. Silver-based products, such as silver sulfadiazine creams and silver-impregnated dressings, are among the most common due to their broad-spectrum antimicrobial properties. These agents help reduce bacterial colonization and biofilm formation, which are significant obstacles in wound healing.[20] Other topical antimicrobials include iodine-based preparations and honey-based products, which have natural antibacterial effects. However, careful consideration is necessary when using these agents, as excessive or prolonged application can impair tissue regeneration or cause local toxicity. Besides antimicrobial agents, debridement products such as enzymatic debriders or autolytic agents are employed to remove necrotic tissue, which can harbor bacteria and impede healing. Mechanical debridement, including sharp or wet-to-dry dressings, remains a standard approach but can be painful and less selective compared to enzymatic methods.[21]

Beyond dressings and antimicrobial agents, several adjunct therapies are used within conventional wound care to enhance healing. Moisture-retentive dressings combined with topical growth factors or skin substitutes have been implemented to stimulate tissue regeneration. For example, platelet-derived growth factor (PDGF) has been applied to stimulate cellular proliferation and angiogenesis.[19–21] Skin substitutes, such as collagen matrices or tissue-engineered skin equivalents, provide scaffolds for new tissue growth and are used in more complex or non-healing diabetic wounds. Moreover, offloading devices such as special footwear or braces are critical in reducing pressure on foot ulcers, preventing further tissue damage. Despite their widespread use, these conventional products often have limitations, such as frequent dressing changes, risk of infection, and the need for specialized application. Nonetheless, they remain the mainstay of initial and ongoing diabetic wound management, providing a foundation for wound healing and preventing complications.[21,22]

Treating diabetic wounds primarily relies on conventional management strategies due to the inherently slow healing process associated with diabetes mellitus and the increased risk of severe complications, including infections and limb amputation. The primary goal of conventional therapy is to prevent the progression of these complications and to facilitate wound closure. Typically, management involves a multidisciplinary approach that aims to control local infection, optimize the wound environment, and prevent further tissue damage. This approach is crucial because diabetic wounds are often complicated by impaired vascularization and neuropathy, which hinder natural healing mechanisms. Consequently, traditional methods focus on a combination of debridement, infection control, and wound protection to promote tissue regeneration and reduce the risk of amputation.[23]

Among the conventional treatments, advanced wound dressings such as hydrocolloids are frequently used. Hydrocolloid dressings provide a moist environment that supports autolytic debridement and facilitates cellular migration, thereby accelerating healing. In some cases, bioactive agents such as recombinant human platelet-derived growth factor (rhPDGF) are used to stimulate cellular proliferation, angiogenesis, and tissue regeneration. These growth factors have shown promising results in enhancing healing outcomes in chronic diabetic wounds.[22–24] Despite the emergence of newer therapies, these traditional treatments remain the cornerstone of diabetic wound management in many healthcare systems worldwide. They are widely accessible, cost-effective, and supported by extensive clinical experience. Table 1 provides an overview of the conventional products used for diabetic wound care, highlighting their roles and applications in clinical practice.

Table 1 Conventional Products for Diabetic Wound Care

Compounds		Intervention	Reference(s)
Topical and systemic antibiotics	Systemic antibiotics: Vancomycin, Ceftazidime, Cefazolin, Doxycycline, Sulfamethoxazole, and Cephalosporins Topical antibiotics: Mupirocin and Bacitracin.	Monitoring the level of Vancomycin in the bloodstream and ensuring effectiveness, preventing toxicity, and adjusting the necessary dosage. Selecting the appropriate type and dose, along with monitoring the clinical response and side effects, such as allergies or gastrointestinal issues. Used to control local infection and promote wound healing. Mupirocin is an antibiotic that is effective against *Staphylococcus* and *Streptococcus* bacteria, including resistant strains like MRSA so that it is often used to prevent and treat wound infections that are susceptible to antibiotic resistance.	[22–24]
Antiseptic and non-adhesive dressings	Antiseptic agents: Cadexomer Iodine (Iodosorb), Povidone-Iodine, Chlorhexidine, Aqueous Hydrogen, and Peroxide Hydrogel Non-adhesive dressing: Hydroclean	This dressing is used in wound management that requires treating biofilm and bacterial infection. Consequently, it is especially relevant for diabetic wounds. The use of an antiseptic solution involves direct application to the wound to either kill or inhibit the growth of pathogenic microorganisms on the wound's surface. Furthermore, certain treatments utilize a hydro-responsive wound dressing with active ingredients like PHMB (Polihexamethylene Biguanide) and surfactant components. This type of dressing is intended to create an optimal wound environment and assist in reducing biofilm and wound debris.	[22,24–26]

(*Continued*)

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Table 1 (Continued).

Compounds		Intervention	Reference(s)
Mechanical and enzymatic debridement	Mechanical debridement Enzymatic debridement	Surgical debridement involves the direct removal of necrotic (dead) and hyperinflamed tissue using surgical instruments, such as a scalpel, scissors, or curette. In contrast, mechanical debridement is performed using a wet-to-dry dressing and dry gauze applied to the wound, which is then removed after it dries. Alternatively, debridement can be accomplished by applying a cream or ointment that contains enzymes, such as papain, to slowly break down the necrotic tissue.	[22,25,27]
Ordinary bandages and gauze	Wet-to-dry dressing Hydrogel Hydrocolloid	Placing gauze acts as a bandage to cover the wound for routine care. Consequently, it functions as a secondary dressing that helps secure the primary dressing and shields the wound from outside contamination. Hydrogel dressing is a dressing that contains fluid or a gel-like substance capable of increasing the moisture level in the wound area. Furthermore, it is useful for certain types of wounds. A hydrocolloid is a polymer-based dressing that forms a layer to seal the wound and manage moisture.	[22,25]

Polyphenols and Flavonoids for Diabetes Mellitus Wounds

Polyphenols and flavonoids are a diverse group of naturally occurring phytochemicals found abundantly in fruits, vegetables, herbs, teas, and various plant-based foods. These bioactive compounds are renowned for their potent antioxidant, anti-inflammatory, and antimicrobial properties, which are highly relevant in the context of diabetic wound healing. Diabetes mellitus is characterized by chronic hyperglycemia, which leads to increased oxidative stress, inflammation, and impaired immune responses—factors that collectively hinder the natural wound healing process. The application or consumption of polyphenols and flavonoids offers a promising therapeutic avenue to mitigate these detrimental effects, ultimately promoting more efficient tissue repair in diabetic patients.[22–25]

Polyphenols and flavonoids exert their beneficial effects through multiple mechanisms. Their primary role involves neutralizing reactive oxygen species (ROS) and reducing oxidative stress, which is markedly elevated in diabetic wounds. Excessive ROS can damage cellular components, inhibit collagen synthesis, and impair angiogenesis—all critical processes in wound repair. By scavenging free radicals, these compounds protect tissues from oxidative damage, creating a more conducive environment for healing. Additionally, polyphenols and flavonoids possess significant anti-inflammatory properties; they modulate signaling pathways involved in inflammation, such as inhibiting pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β. This reduction in inflammation prevents chronic wound states and encourages progression to the proliferative phase of healing. Moreover, these phytochemicals promote angiogenesis —the formation of new blood vessels—by stimulating endothelial cell proliferation and increasing the expression of vascular endothelial growth factor (VEGF). Enhanced angiogenesis improves oxygen and nutrient delivery to the wound site, which is crucial in diabetic wounds characterized by poor vascularization.[23–25]

Beyond their antioxidant and anti-inflammatory roles, polyphenols and flavonoids exhibit significant antimicrobial activity. Diabetic wounds are highly susceptible to infections due to compromised immune defenses, and bacterial colonization can delay healing or lead to serious complications like gangrene. Several studies have demonstrated that these compounds can inhibit the growth of common wound-infecting bacteria, including *Staphylococcus aureus* and *Pseudomonas aeruginosa*. This antimicrobial property helps maintain a clean wound environment, reducing the risk of biofilm formation and persistent infections. Furthermore, polyphenols and flavonoids influence collagen metabolism, an essential aspect of wound closure. They can stimulate fibroblast proliferation and collagen synthesis, thereby accelerating tissue remodeling and strengthening the wound

bed. Some flavonoids, such as quercetin and kaempferol, have been shown to enhance the expression of genes involved in collagen production, facilitating wound contraction and scar formation.[25,26]

The therapeutic potential of polyphenols and flavonoids in diabetic wound management has been increasingly supported by preclinical and clinical studies. Topical formulations containing plant extracts rich in these compounds, such as green tea polyphenols, curcumin, and quercetin, have demonstrated improved wound closure rates, reduced inflammation, and decreased bacterial load in animal models.[26,27] Moreover, dietary intake of polyphenol-rich foods has been associated with improved glycemic control and reduced oxidative stress in diabetic patients, indirectly benefiting wound healing. The incorporation of these phytochemicals into wound dressings, gels, or ointments offers a promising adjunctive therapy, especially given their low toxicity and natural origin. However, challenges such as bioavailability, stability, and optimal dosing remain to be addressed through further research. Overall, polyphenols and flavonoids represent a promising, multifaceted approach to enhancing diabetic wound healing, leveraging their antioxidant, anti-inflammatory, antimicrobial, and tissue regenerative properties to overcome the complex hurdles posed by diabetes.[27]

The management of diabetic wounds using both synthetic and natural compounds has its respective unique advantages and drawbacks. Synthetic compounds include antibiotics (eg., vancomycin, ceftazidime, cefazolin, doxycycline, and sulfamethoxazole), topicals (eg., mupirocin, bacitracin, carbomer, pemulen TR1, and polyethylene glycol), antiseptics (eg., cadexomer iodine, povidone iodine, chlorhexidine, aqueous hydrogen, and polihexanide), anti-inflammatories (eg., diclofenac sodium and methyl salicylate), and antioxidants (eg., synthetic melanin particles and allantoin).[28–31] Treatment with conventional medicines is crucial and proven effective, provided that they match the characteristics of the wound and the infecting microorganisms.[32] Moreover, combining systemic and topical therapy with debridement may significantly increase the chance of healing and prevent complications.[33] Nevertheless, despite the efficacy of conventional drugs, there are risks for diabetic wounds, namely the possibility of microorganism resistance, which renders the drugs less effective, and occasionally the risk of allergies and their side effects.[34,35]

In contrast, natural compounds may offer potential as an alternative with fewer side effects and better bioavailability, especially for treating wounds that are difficult to heal or resistant to conventional treatment.[36] Natural compounds, such as polyphenols and flavonoids found in *Moringa oleifera, Glycyrrhiza glabra*, or turmeric (which contains curcumin), indicate anti-inflammatory, antioxidant, and antimicrobial properties that support holistic wound recovery.[37–39]

These compounds excel due to their low toxicity and diverse biological potential. However, their advantages are offset by a major drawback: low bioavailability when used topically, which results from inadequate solubility, rapid degradation, and limited skin penetration.[9] For this reason, modern methods, such as the development of nanoparticle formulations, are being widely researched to boost the performance and topical absorption of these natural compounds.[40]

Polyphenols and flavonoids are natural bioactive compounds with a primary role in healing diabetic wounds through various biological mechanisms. One key benefit is their antioxidant activity, which significantly reduces the excessive free radicals caused by chronic oxidative stress in diabetic wounds, an effect that normally inhibits cell regeneration and healing.[11] These compounds also have an equally important property, namely, anti-inflammation. Their function is to suppress the expression of pro-inflammatory cytokines, including TNF-α and IL-6, which helps create an environment conducive to the healing process.[9] Additionally, polyphenols and flavonoids can increase the proliferation of new blood vessels, which serve to supply oxygen and nutrients to the wound area. Consequently, this promotes collagen synthesis and accelerates tissue remodeling, leading to complete wound closure.[41] This makes the utilization of these compounds a growing subject of research as a major, safe, and potential natural therapy alternative for chronic wounds in diabetic patients. Figure 2 shows the method used by flavonoids to treat *diabetic mellitus* wounds.

Compounds like resveratrol and hydroxytyrosol possess potent antioxidant capabilities. Therefore, they can reduce the oxidative stress and chronic inflammation that slow tissue healing in diabetic wounds. In this context, responsive hydrogel-based delivery systems containing polyphenols are effective at releasing the compounds regularly. This can smooth the healing process by modulating the immune response. Furthermore, flavonoids such as rutin and quercetin show antibacterial and antibiofilm activity that can accelerate recovery, especially when used alongside antibiotics. Given these various mechanisms, polyphenols and flavonoids have significant potential as modern herbal therapeutic agents for managing chronic wounds caused by diabetes.[42]

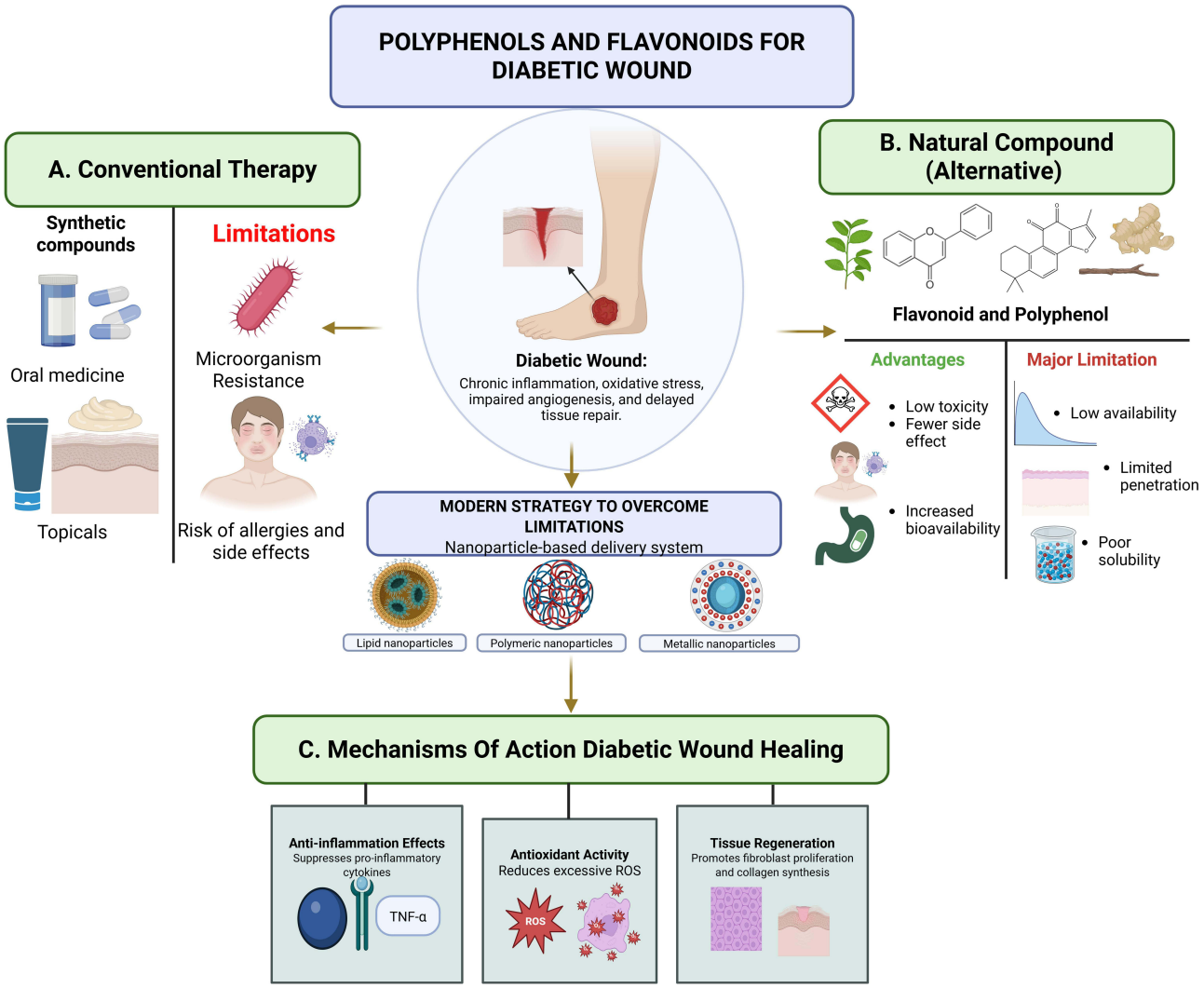


Figure 2 The mechanism by which flavonoids treat diabetic wounds. (**A**) Conventional therapy using synthetic compounds has its limitations, (**B**) Natural compounds such as flavonoids and polyphenols offer advantages, and (**C**) Mechanism of action of flavonoids and polyphenols in wound healing of diabetic ulcers.

Diabetic wounds, or diabetic foot ulcers (DFUs), are a chronic problem resulting from a combination of peripheral neuropathy, peripheral arterial disease, persistent hyperglycemia, foot deformities, and repetitive, unnoticed trauma.[43] Peripheral neuropathy causes a reduction or complete loss of sensation for pain and pressure, which frequently leaves patients unaware of small wounds that can develop into persistent ulcers. Peripheral arterial disease worsens the situation by reducing blood flow to the tissue, consequently inhibiting oxygen supply and the recovery process. Chronic hyperglycemia also lowers the body's defenses, increasing infection risk and subsequently hindering cell regeneration by boosting oxidative stress and inflammation.[44] In addition, foot deformities from musculoskeletal complications, such as Charcot foot, cause abnormal pressure distribution when the patient walks. This triggers the formation of calluses and ulceration. All these factors combine to create a chronic wound environment that is difficult to heal and highly susceptible to infection and amputation if not treated properly.[45]

During chronic hyperglycemia, cell damage, persistent inflammation, and impaired tissue regeneration are all caused by the increased production of free radicals.[46] Studies show that applying polyphenols, for instance, epigallocatechin gallate (EGCG) from green tea, can suppress ROS production and hasten the proliferation phase of wound healing.[47] As part of the polyphenol family, flavonoids also contain important pharmacological effects in the wound recovery mechanism. Flavonoids (eg., quercetin, kaempferol, and rutin) are capable of stimulating fibroblast activity, boosting collagen synthesis, and accelerating re-epithelialization.[47] Specifically, flavonoids can inhibit inflammatory pathways, such as NF-κB, which in

turn lowers the expression of pro-inflammatory cytokines like TNF-α and IL-6. This anti-inflammatory effect is crucially needed in diabetic wounds that suffer from chronic inflammation. Flavonoids can improve the quality of the extracellular matrix and prevent the formation of persistently chronic wounds.[48]

Polyphenols and flavonoids can be sourced from local plants, including those often found everywhere, or from agricultural waste, such as fruit peels, stems, and banana leaves. Therefore, they are an environmentally friendly and renewable raw material. The production process is also not harmful, unlike the manufacture of synthetic chemicals. Indirectly, this supports the concept of green pharmacy and the circular economy in the health sector.[49]

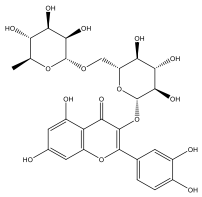
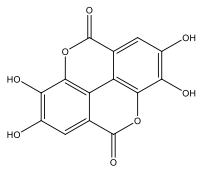
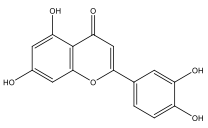
Current formulations frequently combine polyphenols and flavonoids into delivery systems, including nanohydrogels, nanoparticles, or polymeric scaffolds, which have been widely developed. This type of formulation can increase the stability of natural compounds while simultaneously allowing for controlled release and deeper penetration into the wound tissue. Studies indicate that carboxymethyl cellulose-based hydrogels embedded with polyphenol nanoparticles effectively accelerate diabetic wound healing in animals, yielding more satisfactory results than conventional hydrogels.[50,51]

Given their high effectiveness, good safety profile, resource sustainability, and potential synergistic effects between compounds, polyphenols and flavonoids have a significant chance of being integrated into future diabetic wound treatment strategies. Nevertheless, challenges such as standardizing dosage, ensuring bioavailability, and dealing with the variation in potency among different plant sources need to be addressed through further research and quality regulation. An interdisciplinary approach involving pharmacy, natural material technology, and biomedical engineering will accelerate the clinical adoption of this therapy.

Polyphenols and flavonoids provide novel and sustainable methods for treating *diabetes mellitus* wounds. Through continued research and the development of formulations, it is expected that these natural substances will become more widely recognized and used for diabetic wound treatment in the future. Table 2 below details the mechanisms of flavonoid and polyphenol compounds in treating *diabetes mellitus* wounds.

Polyphenols and flavonoids are beneficial in healing wounds caused by diabetes mellitus due to their anti-inflammatory, antioxidant, and antimicrobial effects, as well as their capacity to promote the wound healing process.[79]

Table 2 The Bioactive Roles of Polyphenols and Flavonoids in Promoting Diabetic Tissue Repair

Compound	Structure	Mechanism	Biological Pathway/ Target	Reference(s)
Rutin		Antioxidant, anti-inflammatory, anti-ulcer, antimicrobial (H. pylori)	ROS scavenging; NF-κB inhibition; COX-2 and iNOS suppression; Nrf2/HO-1 activation; H^+/K^+-ATPase inhibition; anti-H. pylori (urease inhibition, anti-biofilm)	[52]
Ellagic acid		Antioxidant, anti-inflammatory, antimicrobial; contributes to wound healing activity	ROS scavenging, inflammation modulation, antimicrobial defense, tannin-mediated tissue contraction	[53]
Luteolin		Antioxidant, anti-inflammatory, antimicrobial; enhances collagen synthesis and wound closure	ROS scavenging, inflammation inhibition, collagen deposition (↑ hydroxyproline), angiogenesis, re-epithelialization	[54]

(*Continued*)

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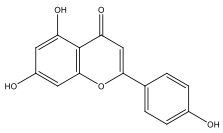
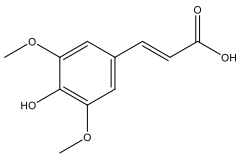
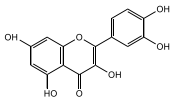
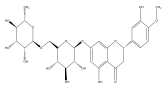
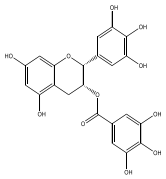
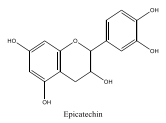
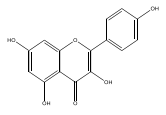
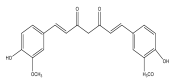
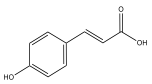
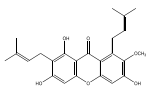
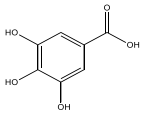
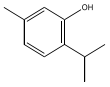
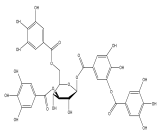
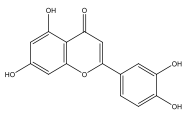
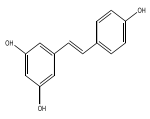
Table 2 (Continued).

Compound	Structure	Mechanism	Biological Pathway/ Target	Reference(s)
Apigenin		Antioxidant, anti-inflammatory, antibacterial; promotes cell proliferation and wound healing	ROS scavenging, NF-κB inhibition, angiogenesis-related signaling	[55]
Sinapic acid		Antioxidant, anti-inflammatory, promotes wound contraction and re-epithelialization	ROS inhibition, tissue regeneration pathways	[56]
Quercetin		Antioxidant, anti-inflammatory, antimicrobial, macrophage modulation	NF-κB inhibition, M1→M2 macrophage polarization	[51,57]
Hesperidin		Anti-inflammatory, antioxidant, promotes angiogenesis and collagen synthesis	TGF-β signaling, VEGF upregulation	[58–61]
Epigallocatechin gallate (EGCG)		Induces autophagy, anti-inflammatory, enhances keratinocyte activity	AMPK/ULK1 pathway activation	[62]
Epicatechin		Antioxidant, anti-inflammatory, promotes angiogenesis	ROS scavenging pathways	[63]
Kaempferol		Antibacterial, anti-inflammatory, promotes collagen formation	MMP-9 inhibition, macrophage modulation	[64,65]

(*Continued*)

Table 2 (Continued).

Compound	Structure	Mechanism	Biological Pathway/ Target	Reference(s)
Curcumin		Anti-inflammatory, antioxidant, enhances angiogenesis and tissue repair	NF-κB inhibition, cytokine modulation	[18–20]
Coumaric acid		Antioxidant, anti-inflammatory, enhances cell proliferation	ROS inhibition, collagen synthesis pathways	[66]
α-mangostin		Anti-inflammatory, promotes cell migration and proliferation	Growth factor modulation pathways	[67]
Gallic acid		Antioxidant, anti-inflammatory, promotes tissue regeneration	ROS inhibition, ECM remodeling	[68]
Thymol		Antioxidant, anti-inflammatory, promotes epithelialization	Redox regulation pathways	[68]
Tannic acid		Antioxidant, antibacterial, anti-inflammatory	ROS inhibition, antimicrobial pathways	[69]
Ferulic acid		Antioxidant, antimicrobial, enhances collagen production	ROS modulation, ECM synthesis	[70]
Resveratrol		Promotes angiogenesis, reduces apoptosis, enhances proliferation	SIRT1 activation, FOXO1 inhibition, c-Myc regulation	[71]

(*Continued*)

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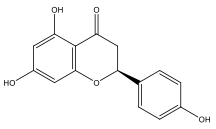
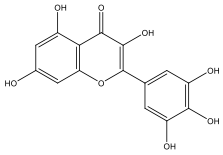
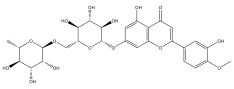
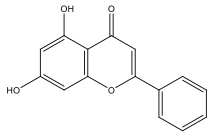
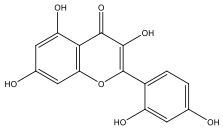
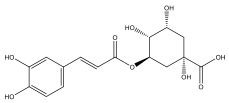
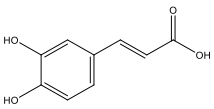
Table 2 (Continued).

Compound	Structure	Mechanism	Biological Pathway/ Target	Reference(s)
Naringenin		Anti-inflammatory, antioxidant, immunomodulatory, anti-infective	NF-κB inhibition; MAPK suppression; PI3K/Akt & AMPK modulation; Nrf2 activation; COX-2 and iNOS inhibition; Treg/Th17 regulation; antibacterial	[72]
Myricetin		Anti-inflammatory, antioxidant, antimicrobial, anticancer	ROS scavenging (ABTS, FRAP); oxidative stress reduction; anti-inflammatory activity	[73]
Diosmin		Anti-inflammatory, antioxidant, wound healing	Inhibition of prostaglandin and thromboxane synthesis	[74]
Chrysin		Anti-inflammatory, antioxidant	COX-2 inhibition	[75]
Morin		Anti-inflammatory, antioxidant	Inhibits pro-inflammatory cytokines (TNF-α, IL-1β, IL-12)	[76]
Chlorogenic acid		Anti-inflammatory, antioxidant, antiaging	Reduces ROS production	[77]
Caffeic acid		Anti-inflammatory, antioxidant	Inhibits NF-κB and IL-1β expression	[78]

These substances can reduce excessive inflammation, protect tissues from oxidative harm, and encourage cell growth necessary for new skin formation. Additionally, they help regulate inflammatory cytokines like TGF-β and TNF-α, which are frequently unregulated in diabetic wounds, thus accelerating healing and reducing the risk of infection and other complications (eg., catechin, epicatechin, garlic, and neem).[79,80]

Despite the promising nature of polyphenols and flavonoids for diabetic wound treatment, there are several limitations, as follows.

1. Low bioavailability: This is because many polyphenols have low water solubility, poor chemical stability, and are easily eliminated from the body, making it difficult to reach an effective therapeutic concentration at the wound site[39,79,80]
2. Poor chemical stability: Some flavonoids and polyphenols are susceptible to degradation due to light, temperature, and environmental pH, which can reduce their effectiveness when used topically and systemically.
3. Limited membrane penetration: The capacity of polyphenols to penetrate tissue or cell membranes is restricted, leading to less than optimal healing effects for deep or chronic wounds.[80]
4. Potential for allergy and immunological side effects: This occurs because some people may experience allergic reactions to flavonoid compounds, especially when used topically.[81]

Recent Studies on Plants Containing Polyphenols and Flavonoids Using the Nanoparticle Method for Treating Diabetic Wounds

Nanoparticles containing polyphenols and flavonoids can boost antioxidant activity and overall biological activity. The goal of formulating polyphenols and flavonoids into nanoparticles is to enhance their stability. This is because nanoparticles help protect these compounds from degradation caused by environmental factors, such as oxidation, light, and high temperatures. Consequently, this will extend the shelf life and preserve their activity. Flavonoids and polyphenols often have low solubility. However, nanotechnology allows for increased absorption through the use of nanoparticles, which facilitates membrane penetration and uptake.[82,83]

Bioactive compounds, like flavonoids and polyphenols, hold great potential for accelerating diabetic wound healing through various molecular mechanisms. Both groups of compounds are known to suppress oxidative stress, which is a leading cause of impaired tissue regeneration in diabetic wounds. This mechanism is achieved by increasing the activity of endogenous antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT), as well as reducing the production of reactive free radicals (ROS) in the wound area.[84,85]

In addition, flavonoids (eg., quercetin) and polyphenols (eg., gallic acid) also function as anti-inflammatory agents, lowering the expression of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. By reducing chronic inflammation, these formulations help accelerate the transition from the inflammatory phase to the proliferative phase of wound healing.[86] These compounds also boost fibroblast proliferation, collagen synthesis, and angiogenesis through the activation of the VEGF (vascular endothelial growth factor) pathway, all of which are crucial for new tissue formation.[87,88] However, a major challenge in the conventional use of flavonoid/polyphenol compounds is their low bioavailability, rapid degradation on the wound surface, and limited skin penetration.[89] Therefore, the nanohydrogel formulation approach is being used to overcome these obstacles. Nanohydrogels function as a delivery system that can enhance the stability, local absorption, and controlled release time of the active substance.[90]

The hydrophilic structure of the hydrogel helps maintain a moist environment in the wound area, which is known to be essential for optimal healing.[91] Furthermore, the small size of the nanoparticles (< 200 nm) facilitates the penetration of the active compounds into the deeper layers of the skin and maintains a therapeutic concentration for longer. Research also shows that this combination can increase the biological activity of the active substance by 3–5 times compared to ordinary topical preparations.[92] Thus, using nanohydrogel formulations from plant extracts rich in flavonoids and polyphenols can synergistically accelerate diabetic wound healing through antioxidant, anti-inflammatory effects, and tissue regeneration stimulation, all reinforced by the efficient nano-delivery system.

Advances in nanoparticle technology in pharmacy offer significant opportunities to enhance the effectiveness and safety of therapy. The application of nanoparticles heavily depends on selecting the appropriate formulation method, as well as controlling physical characteristics like particle size, charge, and surface area. Consequently, further research is required to optimize nanoparticle design for safe and effective use.[7,93] Table 3 shows plants containing polyphenols and flavonoids processed with the nanoparticle method for treating *diabetes mellitus* wounds.

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Table 3 Phytotherapeutic Potentials: Polyphenol- and Flavonoid-Rich Plants Utilizing Nanotechnology for Diabetic Wound Healing

Name of Plant	Compound	Intervention (Nanoparticle)	Type of Nanocarrier	Type of Nanoparticle	Functional Role of Nanocarrier	Conclusions	Reference(s)
Kigelia africana	Flavonoids, phenolics, tannins, saponins, terpenoids	Green synthesis of silver nanoparticles using ethanolic flower extract (Ka-AgNPs)	Phytochemical-based nanocarrier (self-capping system)	Silver nanoparticles (AgNPs; ~15–60 nm, avg. ~35–41 nm)	Phytochemicals act as reducing and stabilizing agents	Successfully synthesized stable AgNPs with strong antioxidant (DPPH IC50 ~27.88 µg/mL), antimicrobial activity (ZOI up to 20 mm), and enzyme inhibition activity; demonstrates multifunctional biomedical potential	[94]
Alchornea cordifolia	Phenols, flavonoids, terpenoids, alkaloids, saponins, steroids, anthraquinones	Green synthesis of silver nanoparticles using aqueous leaf extract (AC-AgNPs)	Phytochemical-based nanocarrier (self-reducing and capping system)	Silver nanoparticles (AgNPs; ~5–25 nm TEM, mean ~11.77 ± 5.57 nm)	Phytochemicals act as reducing and stabilizing agents	AC-AgNPs showed strong antiplasmodial activity (IC50 ~8.05–10.31 µg/mL), high larvicidal activity (LC50 ~5.85–18.41 µg/mL), and good hemocompatibility	[95]
Jatropha tanjorensis	Phenol, tannin, alkaloid, saponin, flavonoid	Green synthesis of silver nanoparticles using aqueous leaf and stem extract (JTL-AgNPs & JTS-AgNPs)	Phytochemical-based nanocarrier	Silver nanoparticles (AgNPs; ~42.66–48.33 nm; pseudo-spherical)	Phytochemicals act as reducing, stabilizing, and bioactive coating	JTL-AgNPs menunjukkan aktivitas terbaik untuk antidiabetic, antioksidan, dan antiinflamasi	[96]
Justicia secunda	Phenol, tannin, flavonoid, alkaloid, saponin, terpenoid, steroid, cardiac glycoside	Green synthesis of silver nanoparticles using aqueous extracts	Phytochemical-based nanocarrier	Silver nanoparticles (AgNPs; ~10–70 nm; pseudo-spherical; λmax 400–410 nm)	Phytochemicals act as reducing, stabilizing, and bioactive surface coating	AgNPs dari daun (AgNPs-JsL) menunjukkan aktivitas terbaik di semua uji biologis dibanding ekstrak biasa dan bagian tanaman lain	[97]
Lawsonia inermis	Flavonoid, alkaloid, terpenoid, phenolic compounds	Green synthesis ZnO nanoparticles + gel formulation	Phytochemical-based nanocarrier + hydrogel system	Zinc oxide nanoparticles (ZnO-NPs	Fitokimia sebagai reducing and stabilizing agent	Green ZnO-NP gel menunjukkan penyembuhan luka lebih cepat	[98]
Lithospermum officinale	Phenolic compounds, shikonin derivatives, flavonoids	Green synthesis silver nanoparticles	Phytochemical-based nanocarrier	Silver nanoparticles (AgNPs; spherical, ~7 nm)	Senyawa fenolik sebagai reducing, capping, dan stabilizing agent	AgNPs menunjukkan aktivitas antioksidan lebih tinggi dibanding ekstrak	[99]
Curcuma longa	Curcumin	Curcumin is dissolved in ethanol. A 0.5% chitosan solution with pH 5 is prepared, and PVP K30 (polyvinyl pyrrolidone) is added. Subsequently, the curcumin solution is dropped into the chitosan solution while stirring. A 0.125% TPP (sodium tripolyphosphate) solution is slowly added to form nanoparticles via crosslinking. The mixture is stirred for 45 minutes until nanoparticles are formed and ready for characterization.	Polymer-based nanocarrier; Chitosan nanoparticles (CUR-CSNPs)	Chitosan	Improves stability and controlled release	Chitosan nanoparticles (CUR-CSNPs) incorporated into a collagen-alginate scaffold demonstrate significant potential for accelerating diabetic wound healing by enhancing stability, enabling controlled release, and supporting tissue growth.	[19]

Gliricidia sepium (Jacq). Kunth. ex. Walp.	Kaempferol	The plant extract is utilized as a controlling and reducing agent during the preparation of zinc oxide nanoparticles. This process occurs by combining a zinc source solution (such as zinc sulfate or zinc acetate) with the plant extract, followed by incubation until the ZnO nanoparticles reach the desired size.	Natural material-based, green-synthesized metal oxide nanoparticle	Metal oxide nanoparticle - Zinc oxide nanoparticles (ZnONPs)	Antibacterial + ROS modulation	Assessment of GSL ZnONPs hydrogel has highlighted its capability to accelerate *diabetes mellitus* wound healing. Furthermore, HPLC analysis confirmed the presence of phenolic compounds like Apigenin-7-O-glucoside, kaempferol, and protocatechuic acid, all possessing anti-inflammatory and antimicrobial properties. The result indicates enhanced tissue regeneration and better inflammation modulation.	[21]
Teucrium polium	Apigenin, Kaempferol, and Gallic acid	Chitosan nanogel is created using the ionic gelation technique, involving mixing the extract with chitosan, followed by drying and washing the nanoparticles. The particles are then characterized for size, charge, pH, and active ingredient entrapment efficiency. In addition, active substance release testing is conducted gradually over 24 hours.	Polymer-based nanocarrier	Chitosan	Sustained release, enhanced bioavailability	The metabolic profile of *T. polium* using LCMS/MS indicates that the plant is a source of phenolic compounds, especially flavonoids. HPLC results confirm the presence of gallic acid, kaempferol, and apigenin. Consequently, the *T. polium* chitosan nanoparticles significantly accelerate wound healing in diabetic rats through their antioxidant, anti-inflammatory, and pro-angiogenic capabilities.	[100]
Chamaecostus cuspidatus	Flavonoid and phenolic	10 mL of leaf extract is mixed into a 1 mM chloroauric acid solution (chloroauric, HAuCl4) and stirred at room temperature. The formation of gold nanoparticles is signaled by a color change from light yellow to deep blue. The formed nanoparticles are separated by centrifugation, then dried.	Gold nanoparticle	Metal nanoparticle - AuNPs nanoparticle	Enhanced cellular interaction	Overall, the gold nanoparticles produced from the *C. cuspidatus* plant extract show higher potential at lower doses and more affordable costs, serving as an alternative treatment method for diabetes.	[101]

(*Continued*)

https://doi.org/10.2147/DDDT.S607020

Table 3 (Continued).

Name of Plant	Compound	Intervention (Nanoparticle)	Type of Nanocarrier	Type of Nanoparticle	Functional Role of Nanocarrier	Conclusions	Reference(s)
Citrus limon	Hesperidin	Lemon exosomes are extracted through an isolation process from lemon juice. **Subsequently**, they are loaded into a hydrogel made from gelatin methacryloyl (GelMA) and dialdehyde starch (DAS).	Polymer-based, hydrogel from gelatin methacryloyl (GelMA) and dialdehyde starch (DAS)	Exosome nanoparticle	Immune modulation and sustained delivery	The hydrogel made from GelMA and DAS, loaded with lemon exosomes, is a safe and flexible platform to accelerate diabetic wound healing. Specifically, the gel can regulate the immune environment, encourage blood vessel growth, and stimulate collagen formation, which, in turn, speeds up tissue regeneration. Utilizing exosomes from a natural source like lemon offers innovative and environmentally friendly therapeutic potential, capable of effectively improving chronic wound healing with constant delivery support, thereby optimizing an efficient and creative healing process.	[102]
Citrus aurantifolia	Quercetin	Nanotransfersomes are prepared by mixing lime peel extract into a CMC-Na solution as the gel base. Then, phospholipids and a surfactant (edge activator) are added to increase the deformability and stability of the transfersome vesicles.	Lipid-based nanotransfersome	Liposome	Enhanced skin penetration	The nanotransfersome gel made from lime peel extract has the ability to speed up wound healing by increasing the levels of FGF and VEGF in the labial mucosal wounds of Wistar rats. On the third day, the group treated with the lime peel extract nanotransfersome gel showed the highest average VEGF and FGF values. Research focused on lime peel extract nanotransfersome gel has the potential to be developed as an herbal medicine utilizing peel waste.	[103]

https://doi.org/10.2147/DDDT.S607020

Aloe barbadensis Miller	Aloin and Aloesin	Aloe vera gel is used to create a nanoemulsion. This nanoemulsion is prepared using components like oleic acid, Tween 80, and polyethylene glycol 400 to achieve nano-sized particles. Subsequently, this design enhances permeability and skin penetration, synergistically accelerating diabetic wound healing with the *Aloe vera*.	Lipid and surfactant-based nanoemulsion	Solid lipid nanoemulsion	Improves permeability and delivery	The insulin-loaded nanoemulsion formula combined with *Aloe vera* gel showed good stability, efficient skin penetration ability, and no skin irritation. Therefore, this method has the potential to improve the local release and absorption of insulin, possibly serving as a therapeutic option for diabetic wound management and increasing overall treatment effectiveness.	[104]
Azadirachta indica	Flavonoid, nimbin, and quercetin	Silver nanoparticles are synthesized from the leaf extract via green synthesis. Furthermore, these particles are applied to thermal wounds in diabetic model rats.	Plant-based silver nanoparticles (AgNPs)	Metal nanoparticle - AgNPs nanoparticle	Antibacterial delivery system	AgNPs derived from *Azadirachta indica* show significant wound healing effects, including increased angiogenesis and faster wound closure in diabetic rats.	[105]
Centella asiatica	Asiaticoside, flavonoid, and phenolic acid Asiaticoside (triterpenoid)	*Centella asiatica* extract is loaded into a poloxamer/zinc oxide (ZnO) nanocomposite to enhance wound regeneration. Alternatively, polymeric nanoparticles (AST PNP) are prepared in a gelatin hydrogel.	Poloxamer/ZnO Nanocomposite Polymeric nanoparticles (AST PNPs) in gelatin hydrogel	Metal oxide nanoparticles Polymeric nanoparticles (PNPs)	Promotes fibroblast migration	CAE@PLX/ZnO exhibits strong antibacterial effects, accelerating fibroblast cell migration and angiogenesis in diabetic wound models. The polymeric nanoparticles increase collagen biosynthesis, fibroblast migration, and the expression of COL-I and α-SMA, thereby accelerating diabetic wound healing.	[89,106]
Ocimum sanctum	Flavonoid, eugenol, and rosmarinic acid	Green synthesis of titanium dioxide (TiO_2) nanoparticles is carried out using *Ocimum sanctum* leaf extract. Subsequently, these are loaded into a 2% chitosan gel.	TiO_2 nanoparticles in chitosan gel	Metal oxide nanoparticles	Antioxidant & antimicrobial activity	The TiO_2 gel derived from *O. sanctum* leaves accelerates wound healing in diabetic models through its antioxidant and antibacterial activity.	[107]
Berberine	Berberine (alkaloid-phenolic) Berberine (alkaloid-polyphenol)	Berberine is encapsulated in lecithin-chitosan nanoparticles using the sonication method, then loaded into a topical gel. Alternatively, berberine is loaded into a lipid carrier to boost topical effectiveness.	Lecithin-chitosan nanoparticles (LC-CTS-NPs) Nanostructured lipid carriers (NLCs)	Chitosan Nanoscale metal-organic framework (NMOF)	Improves delivery and targeting	Berberine nanoparticles accelerate diabetic wound healing by promoting blood vessel, fibroblast, and collagen formation. NLCs enhance the effectiveness of diabetic wound healing with minimal systemic effects.	[84,90]

(*Continued*)

Table 3 (Continued).

Name of Plant	Compound	Intervention (Nanoparticle)	Type of Nanocarrier	Type of Nanoparticle	Functional Role of Nanocarrier	Conclusions	Reference(s)
Kunzea ericoides	Chlorogenic acid, gallic acid, quercetin, and (*E*)-ferulic acid	Leaf extract is loaded into a gelatin methacryloyl (GelMA)-based hydrogel for diabetic wound application.	GelMA-based hybrid hydrogel	Organic polymeric nanoparticles or nanogel	Sustained release and ECM support	KELE@Gel accelerates re-epithelialization, angiogenesis, and collagen deposition through its antioxidant, anti-inflammatory, and immunoregulatory activities.	[108]
Anredera cordifolia (*Binahong*)	Flavonoid, alkaloid, saponin, and tannin Polysaccharides and ginsenoside Rg_5	Ethanol leaf extract is loaded into chitosan nanoparticles and formulated as a topical ointment for hyperglycemic rats. A combination of *binahong* extract and ginsenoside is loaded into a composite nanohydrogel.	Chitosan nanoparticles Hydrogel nanocomposite (OACS + CF-ADH + F127-PEI@Rg_5 NPs)	Chitosan Organic polymeric nanogel	Enhances macrophage modulation	The nanochitosan ointment enhances angiogenesis, collagen density, and epithelial thickness, accelerating wound healing in diabetic rats. The nanohydrogel accelerates diabetic wound healing by up to 34% faster, increasing the number and polarization of macrophages.	[86,92]
Acalypha indica	Phenolic compounds in extract + AuNPs	Sunlight-based synthesis of gold nanoparticles from the plant extract is performed.	Gold nanoparticles (AuNPs) in hydrogel	Metal nanoparticle - AuNPs nanoparticle	Stimulates stem-cell-related pathways	Diabetic wound healing reaches 99% closure within 5 days. Crucially, it increases the expression of NANOG and CD-34 proteins.	[91]
Pterocarpus marsupium	Flavonoid and pterostilbene	Pterostilbene is formulated into solid lipid nanoparticles (SLNs) using the hot emulsification method followed by sonication.	Solid lipid nanoparticles (SLNs)	Solid lipid	Improves solubility and stability	SLNs successfully increase the solubility and bioavailability of pterostilbene, showing controlled drug release and good physical stability. Consequently, there is potential for application in wound healing and managing diabetic complications.	[109]
Syzygium cumini	Flavonoid and tannin	Silver nanoparticle (AgNP) synthesis is carried out using the leaf extract.	Silver nanoparticles (AgNPs)	Metal nanoparticles - AgNPs nanoparticles	Antibacterial + fibroblast stimulation	AgNPs from *S. cumini* demonstrate antibacterial, anti-inflammatory activity, and enhance fibroblast proliferation in diabetic wound healing.	[110]
Fumaria officinalis	Alkaloid and flavonoid	Metal nanoparticles (AgNP) are synthesized from the ethanolic leaf extract.	Silver nanoparticles (AgNPs)	Metal nanoparticles - AgNP nanoparticles	Antibacterial delivery system	The extract yields AgNP nanoparticles that are effective as antibacterial and anti-inflammatory agents, accelerating the diabetic wound healing process.	[110]

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Plantago major	Flavonoid, iridoid, and tannin	*P. major* leaf extract is used as a reducing agent for the green synthesis of silver nanoparticles (AgNPs).	Silver nanoparticles (AgNPs) (gelatin + PCL)	Green synthesis metal nanoparticle - AgNP nanoparticles	Antioxidant & antimicrobial	AgNPs derived from *P. major* show good antibacterial and antioxidant activity and accelerate diabetic wound healing in animal models.	[111]
Salvia hispanica (Chia) + *Bergenia ciliata*	Flavonoid, phenolics, and antioxidants	*B. ciliata* extract is loaded into a Chia hydrogel (CH) with AgNPs.	Silver nanoparticles (AgNPs) in chia hydrogel	Metal nanoparticles - AgNPs nanoparticles	Enhances bioavailability and sustained delivery	CH-BC AgNPs accelerate re-epithelialization and angiogenesis in diabetic wounds. Specifically, significant results were observed in the restoration of MMP2, GPx, and IL-6.	[112]
Sargassum sp. (Brown seaweed)	Fucoidan, phenols, and flavonoids	The extract is combined in a film composite based on chitosan nanoparticles.	Chitosan-based nanoparticle film	Chitosan	Supports epithelialization	The seaweed-based nanocomposite film accelerates wound closure, increases epithelial thickness, and promotes granulation.	[113]
Cinnamomum spp.	Cinnamaldehyde and polyphenols	The formulation involves creating nanofibers using the electrospinning method.	Electrospun nanofiber	Organic polymeric nanomaterial	ECM-mimicking scaffold	The nanofibers show high porosity, control over drug release, and a structure resembling the extracellular matrix. Consequently, this accelerates diabetic wound healing.	[98]
Gymnema sylvestre	Gymnemic acid and flavonoid	The ethanolic extract is used in the synthesis of chitosan nanoparticles.	Chitosan nanoparticles	Chitosan	Reduces inflammation	The nanoparticles show significant wound healing activity, reducing inflammatory infiltration and boosting the formation of new tissue.	[114]
Malva sylvestris	Flavonoid, mucilage, and phenolics	The extract is used in the green synthesis of silver nanoparticles (AgNPs).	Silver nanoparticles (AgNPs)	Metal nanoparticles - AgNP nanoparticles	Antioxidant & antibacterial	AgNPs based on *M. sylvestris* exhibit high antibacterial and antioxidant activity. Furthermore, they accelerate diabetic wound healing by reducing inflammation and stimulating tissue regeneration.	[115]
Mentha piperita	Flavonoid and menthol	Green synthesis of silver nanoparticles is carried out using the leaf extract.	Silver nanoparticles (AgNPs)	Green synthesis metal nanoparticles - AgNPs nanoparticles	Enhances wound contraction	AgNPs from *M. piperita* show high antibacterial and antioxidant activity, accelerating wound contraction and re-epithelialization in diabetic rat models.	[116]

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Table 3 (Continued).

Name of Plant	Compound	Intervention (Nanoparticle)	Type of Nanocarrier	Type of Nanoparticle	Functional Role of Nanocarrier	Conclusions	Reference(s)
Curcuma longa (Turmeric)	Curcumin	The ethanolic turmeric extract is formulated with oregano and chitosan nanoparticles into an ointment, hydrogel, and nanofiber.	Petrolatum, PVA hydrogel, and nanofiber matrix	Chitosan	Multi-modal delivery platform	The combination of 5% turmeric, 1% oregano, and 1% chitosan nanoparticles is effective in accelerating diabetic wound healing, demonstrating high antibacterial, anti-inflammatory, and antioxidant activity. Specifically, complete healing occurred on the 15th day in the rat model.	[117]
Origanum vulgare (Oregano)	Carvacrol and thymol (phenolic compounds)	1% oregano essential oil is combined with turmeric extract and chitosan nanoparticles in topical dosage forms (ointment, gel, and nanofiber).	Petrolatum, PVA hydrogel, and nanofiber matrix	Chitosan	Multi-modal delivery platform	Oregano contributes strong antibacterial effects (100% against *S. aureus* and *E. coli*), enhancing granulation. However, while 1% concentration is effective in vivo, it is not effective at lower concentrations.	[117]
Bambusa sp. (Bamboo)	Cellulose nanocrystals (CNCs) from bamboo leaves	In situ impregnation of silver nanoparticles (AgNPs) is performed on the CNC matrix, using *Syzygium cumini* leaf extract as a biological reducing agent.	CNC-based nanobiocomposite hydrogel	Metal nanoparticles - AgNPs	Growth factor stimulation	The CNC bamboo nanobiocomposite hydrogel + AgNPs accelerates diabetic wound healing to 98–100% closure within 18 days. Crucially, it increases re-epithelialization, collagen deposition, and growth factor expression (FGF, PDGF, and VEGF), while decreasing pro-inflammatory cytokines (TNF-α and IL-6).	[118]
Vitis vinifera (Grape)	Resveratrol (polyphenol)	Resveratrol is encapsulated into mesoporous silica nanoparticles (MSN-RES), combined with platelet-derived extracellular vesicles (PDEVs), and loaded into a GelMA/SFMA hydrogel.	Composite hydrogel based on gelatin methacrylate and silk fibroin glycidyl methacrylate (GelMA/SFMA)	Mesoporous silica nanoparticles (MSNs)	Controlled release and targeting	The MSN-RES/PDEV hydrogel shows sustained drug release, decreases the expression of pro-inflammatory cytokines (TNF-α, iNOS), increases the expression of healing factors (TGF-β1, Arg-1), promotes angiogenesis, and accelerates diabetic wound healing in the rat model.	[119]

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Camellia sinensis (Green tea)	Epigallocatechin gallate (EGCG)	EGCG is combined with silver nanoparticles (AgNPs) in a guar gum-based hydrogel (HG-Ag-EGCG hydrogel).	Biopolymeric hydrogel based on guar gum	Silver nanoparticles (AgNPs)	ROS regulation and antibacterial	The HG-Ag-EGCG hydrogel demonstrates effective ROS management, accelerates cell migration and proliferation, and increases collagen synthesis and re-epithelialization. Consequently, it is superior to the commercial product (Luofucon®) for Type II diabetic wound healing.	[120]
	Epigallocatechin gallate (EGCG)	EGCG is modified with calcium ions and melanin-like nanoparticles (CEMNPs), then loaded into a hydrogel based on dextran, carboxymethyl chitosan (CMCS), and chitosan oligosaccharide (COS). Tea extract is used as a reducing agent in the green synthesis of silver nanoparticles (AgNPs). Tea polyphenols (TP)	Polysaccharide-based nanobiocomposite hydrogel (Dex-CMCS-COS) with CP and CEMNPs Not specified (direct AgNPs use) Tea polyphenols (TP) are complexed with magnesium to form TP-Mg nanoparticles, which are then loaded into a double-network hydrogel made of PVA, sodium alginate, and gelatin.	Calcium-EGCG-melanin-like nanoparticles (CEMNPs) Silver nanoparticles (AgNPs) Polymer-based hydrogel (PVA-alginate-gelatin)		The DCPM hydrogel is photothermal antibacterial and conductive, allowing it to rapidly heal diabetic wounds. Furthermore, it is capable of recording physiological data (respiration and heart rate) in real time. Therefore, it is suitable for simultaneous wound care and health monitoring. AgNPs resulting from the green synthesis using green tea show strong antibacterial activity against *S. aureus* and *E. coli*. Consequently, they accelerate wound closure in diabetic wound models. The TP-Mg@PSG hydrogel possesses anti-MRSA and angiogenic properties. In addition, it improves mechanical strength and releases nanoparticles in a controlled manner within the acidic wound environment. Ultimately, this significantly accelerates the healing of MRSA-infected diabetic wounds.	[121–123]
Gelsemium elegans	Gelsevirine (GSV)	Gelsevirine is loaded along with MnO_2 nanoparticles into a selenium-responsive polyurethane nanofiber (PUF-PCLUSe polymer).	Elastic selenium-based polyurethane nanofiber	Manganese dioxide nanoparticles (MnO_2 NPs)	ROS scavenging and signaling control	The MnO_2/GSV/PUF dressing accelerates diabetic wound healing up to 92% in 14 days through two mechanisms: ROS scavenging and STING inflammatory signal inhibition. Moreover, it shows low cytotoxicity and enhanced collagen deposition and epithelialization.	[124]

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Table 3 (Continued).

Name of Plant	Compound	Intervention (Nanoparticle)	Type of Nanocarrier	Type of Nanoparticle	Functional Role of Nanocarrier	Conclusions	Reference(s)
Camellia sinensis (Green tea)	Polyphenols (including EGCG) and catechins	Tea extract is used as a reducing agent in the green synthesis of silver nanoparticles (AgNPs).	Not specified (direct AgNPs use)	Silver nanoparticles (AgNPs)	Antibacterial & ROS regulation	AgNPs resulting from the green synthesis using green tea show strong antibacterial activity against *S. aureus* and *E. coli*, and they accelerate wound closure in diabetic wound models.	[122]
Olea europaea (Olive leaf)	Oleuropein and flavonoid	Olive leaf extract is also used as a reducing agent in the formation of AgNPs.	Not specified (direct AgNPs use)	Silver nanoparticles (AgNPs)	Synergistic antimicrobial delivery	AgNPs from olive leaf also exhibit significant antibacterial activity and high effectiveness in accelerating wound healing, especially when combined with green tea (synergistic effect).	[122]
Nigella sativa (Black cumin)	Polyphenols (not specifically mentioned)	Green synthesis of ZnO NPs is performed using *N. sativa* leaf extract, then its activity is tested in vivo in diabetic rats.	No additional carrier mentioned	Zinc oxide nanoparticles (ZnO NPs)	Antibacterial & metabolic regulation	The green-synthesized ZnO NPs show strong antibacterial effects against *S. aureus, E. coli, P. aeruginosa*, and *B. cereus*. Additionally, they increase glycogen and insulin levels while decreasing blood glucose. Therefore, they are effective in accelerating diabetic wound healing at a low cost.	[125]
Raphanus sativus (Radish)	Polyphenols, flavonoids, and glucosinolates	Green synthesis of silver nanoparticles (AgNPs) is performed using radish leaf extract as a reducing and stabilizing agent.	No additional carrier mentioned	Silver nanoparticles (AgNPs)	Antioxidant & enzyme modulation	AgNPs synthesized from radish leaf extract show high antioxidant activity (DPPH & H_2O_2) and antibacterial activity against *E. coli, S. aureus*, and *B. subtilis*. Moreover, they decrease the activity of α-amylase and α-glucosidase enzymes (in vitro antidiabetic effect).	[126]
Punica granatum (Pomegranate peel)	Flavonoid, tannin, and polyphenols	Green synthesis of silver nanoparticles (AgNPs) is performed using a combination of pomegranate peel and guava leaf extracts.	No additional carrier mentioned	Silver nanoparticles (AgNPs)	Antibacterial & epithelialization	AgNPs resulting from the combined extracts of pomegranate and guava show antibacterial activity against *S. aureus* and *E. coli*. Furthermore, they accelerate epithelialization, promote good granulation, and are non-toxic to fibroblast cells. Ultimately, they are highly effective for diabetic wound healing.	[127]

Psidium guajava (Guava leaf)	Quercetin, tannin, and flavonoid	The preparation is the same as previously mentioned (used along with pomegranate peel extract as a reducing and stabilizing agent for AgNPs).	Not specified (direct AgNPs use)	Silver nanoparticles (AgNPs)	Synergistic antimicrobial effect	The combination of the two plants demonstrates a synergistic effect in antimicrobial activity and acceleration of wound healing compared to using either plant alone.	[127]
Clerodendrum glandulosum	Flavonoid and phenolic compounds	In situ biosynthesis of silver nanoparticles (AgNPs) is performed using the leaf extract, which is then loaded into a chitosan-PEG hydrogel.	Polymeric hydrogel (chitosan-PEG)	Silver nanoparticles (AgNPs)	Controlled release and ECM support	The CG-AgNP-chitosan-PEG hydrogel shows controlled drug release over 7 days. Furthermore, it is antioxidant, antimicrobial, anti-inflammatory, hemocompatible, and non-toxic. Ultimately, it accelerates diabetic wound healing by enhancing the extracellular matrix.	[128]
Gliricidia sepium	Apigenin-7-O-glucoside, kaempferol, and protocatechuic acid	Green synthesis of ZnO nanoparticles is performed from the ethanolic leaf extract of *G. sepium*, which is then loaded into a PVA hydrogel.	PVA-based hydrogel	Zinc oxide nanoparticles (ZnONPs)	ROS modulation and cytokine regulation	ZnONPs from *G. sepium* exhibit anti-inflammatory and antioxidant effects. Moreover, the GSL ZnONPs hydrogel enhances tissue regeneration, reduces apoptosis, stimulates the expression of IL-10 and PDGF, and decreases VCAM-1 and AGEs. Consequently, it is highly effective in significantly accelerating diabetic wound healing.	[21]
Althaea officinalis	Flavonoid, phenolics, and mucilage	Green synthesis of silver nanoparticles (AgNPs) is performed using *A. officinalis* leaf extract as a reducing and stabilizing agent.	Not specified (direct AgNPs use)	Silver nanoparticles (AgNPs)	Promotes collagen formation	AgNPs from *A. officinalis* leaves accelerate diabetic wound closure in rats, increasing tissue regeneration and collagen formation. In addition, they show significant antioxidant and antimicrobial activity, with no systemic toxicity observed in the test animals.	[129]
Punica granatum (Pomegranate)	Tannin, flavonoid, and polyphenols	Green synthesis of silver nanoparticles (AgNPs) is performed using pomegranate peel extract as a reducing and stabilizing agent.	Not specified (direct AgNPs use)	Silver nanoparticles (AgNPs)	Enhances epithelialization	AgNPs from pomegranate peel show an effect of accelerating diabetic wound healing by increasing wound contraction, rapid epithelial closure, and good tissue regeneration. Furthermore, they possess antibacterial activity and demonstrate no toxic effects in rats.	[130]

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Table 3 (Continued).

Name of Plant	Compound	Intervention (Nanoparticle)	Type of Nanocarrier	Type of Nanoparticle	Functional Role of Nanocarrier	Conclusions	Reference(s)
Archidendron pauciflorum (*Jengkol*)	Flavonoid, tannin, saponin, polyphenols, steroids, quinones, and glycosides	A topical ointment containing PLGA nanoparticles loaded with *jengkol* fruit peel ethanolic extract (EEJFP) is applied.	PLGA (polylactic-co-glycolic acid)	PLGA nanoparticles	Enhances angiogenesis	The 5% PLGA nanoparticle ointment from EEJFP accelerates diabetic wound healing in rats by increasing blood capillary formation, re-epithelialization, and collagen density, with higher effectiveness than a standard ointment.	[131]
Cinnamomum sp. (Cinnamon)	Flavonoid and polyphenols (not specified)	Cinnamon nanoparticles (CNPs) are loaded into a chitosan-gelatin-based nanoparticle system (CGNPs).	Polymeric nanoparticles (chitosan-gelatin)	Cinnamon nanoparticles (CNP-CGNPs)	Modulates apoptosis pathways	CNP-CGNPs significantly accelerate the healing of diabetic foot burn wounds in rats compared to the control and silver sulfadiazine groups. This is evident from the increased Bcl-2 expression, decreased Caspase 3, and accelerated wound closure.	[132]
Aloe vera and *Curcuma longa*	Aloin, aloesin, and curcumin	Extracts are combined with other compounds and formulated into a combination topical preparation.	Vaseline and lanolin-based ointment	Not specifically mentioned	Multi-compound synergy	The combination formula of all four extracts (*aloe vera*, curcumin, plantain peel, and rosella flower) shows the best improvement in diabetic wound healing compared to positive and negative controls. It enhances tissue regeneration and accelerates wound closure, acting as an anti-inflammatory and antioxidant.	[133]
Musa paradisiaca (Plantain peel)	Flavonoid and tannin	Plantain peel extract is included in a combination topical formulation.	Vaseline and lanolin-based ointment	Not specifically mentioned	Antibacterial support	It supports wound healing through its antibacterial and anti-inflammatory activity, thereby accelerating epithelialization.	[133]
Hibiscus sabdariffa (Rosella flower)	Anthocyanins, flavonoid, and vitamin C	Rosella extract is added as an antioxidant and anti-inflammatory component in the preparation.	Vaseline and lanolin-based ointment	Not specifically mentioned	Antioxidant enhancement	The rosella flower combination contributes significantly to the antioxidant activity, which is crucial for diabetic wound healing.	[133]
Curcuma longa (Turmeric)	Polyphenols (caffeic acid, rutin, and quercetin)	Ethanolic leaf extract	PLGA chitosan nanoparticles	Polymeric nanoparticles (PLGA, chitosan)	Improves stability and targeting	It increases stability, reduces ROS, accelerates epithelialization, and enhances angiogenesis.	[134]

Ipomoea quamoclit	Phenolic/flavonoid bioactives in leaf extract	Green synthesis of CuO nanoparticles is performed using a PDMS microfluidic lab-on-a-chip micromixer. Characterization includes UV-Vis, FTIR, SEM, and DLS. Assays cover antibacterial, antifungal, and antioxidant (DPPH; H_2O_2 scavenging) activities.	-	CuO nanoparticles	Antioxidant & antimicrobial	The nanoparticles are spherical, sized 65–94.5 nm, and possess N-H, C-H, C=O bioactive groups. Furthermore, they show significant antibacterial activity (zone of inhibition 10.45 ± 0.25 mm vs *A. niger*) and high antioxidant activity (IC_{50} = 33.94 µg/mL for DPPH and 42.54 µg/mL for H_2O_2). Therefore, they are potential candidates for biomedical and herbal-based medicinal applications.	[135]
Flueggea leucopyrus Willd	Leaf extract (containing phenolic/ flavonoid compounds)	Synthesis of copper nanoparticles (CuNPs) is performed using the leaf extract. Characterization includes UV-Vis, FTIR, FESEM, TEM, EDX, and zeta potential.	No additional carrier used (direct green synthesis from plant extract)	CuNPs (spherical; crystalline; ~20 nm)	Antibacterial & antidiabetic activity	CuNPs show antibacterial activity (zone of inhibition 13 mm against *S. aureus* and *P. aeruginosa*; strong against *E. faecalis*; inactive on *E. coli*), antioxidant activity (an IC_{50} value of 100.06 ppm), and antidiabetic activity (α-amylase inhibition; an IC_{50} value of 435.68 ppm). Hence, they hold potential as antimicrobial, antioxidant, and antidiabetic agents derived from this medicinal leaf extract.	[136]
Mangifera indica (Mango)	Flavonoid, phenol, terpenoid, tannin, and active biomolecules like magniferin and benzoquinone derivatives	AgNPs are synthesized using aqueous and ethanolic mango leaf extracts. These are tested for antibacterial activity against resistant strains (*E. coli, Klebsiella spp., P. aeruginosa*, and MRSA).	No additional carrier used (direct green synthesis from plant extract)	AgNPs (Silver nanoparticles)	Strong antibacterial activity	AgNPs based on the ethanolic extract show stronger antibacterial activity than the aqueous extract, with zones of inhibition of 19.7 mm (*E. coli*), 26.8 mm (*Klebsiella spp*)., 22.9 mm (*P. aeruginosa*), and 24.1 mm (*S. aureus*) at 100 mg/mL. Moreover, the MIC and MBC values are lower, indicating greater potential. These results confirm that the ethanolic AgNPs based on *M. indica* have potential as environmentally friendly antibacterial agents for tackling multidrug-resistant bacteria.	[137]

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Table 3 (Continued).

Name of Plant	Compound	Intervention (Nanoparticle)	Type of Nanocarrier	Type of Nanoparticle	Functional Role of Nanocarrier	Conclusions	Reference(s)
Clausena anisata		Polyphenols, flavonoids, alkaloids, terpenoids, tannins, saponins	Green synthesis of CuO nanoparticles using plant extracts as reducing and stabilizing agents; tested against *S. aureus, E. coli, E. cloacae*	Metal oxide-based nanocarrier	Plant-derived phytochemicals act as reducing, capping, and stabilizing agents; enhance nanoparticle stability and antibacterial activity via ROS generation and surface interaction	Successfully synthesized CuO NPs (19–47 nm); showed significant antibacterial activity	[138]
Euphorbia abyssinica		Polyphenols, flavonoids, alkaloids, terpenoids, tannins, saponins	Green synthesis of CuO nanoparticles using plant extracts as reducing and stabilizing agents; tested against *S. aureus, E. coli, E. cloacae*	Metal oxide-based nanocarrier	Plant-derived phytochemicals act as reducing, capping, and stabilizing agents; enhance nanoparticle stability and antibacterial activity via ROS generation and surface interaction	Successfully synthesized CuO NPs (19–47 nm); showed significant antibacterial activity,	[138]
Perovskia abrotanoides	Essential oil compounds (camphor, eucalyptol, terpenoids)	Essential oil nanoemulsion incorporated into chitosan hydrogel (P.a-NE-loaded gel)	Polymer-based nanocarrier (chitosan hydrogel)	Nanoemulsion (oil-in-water)	Nanoemulsion enhances solubility, skin penetration, and stability; chitosan provides sustained release, antimicrobial activity, and promotes tissue regeneration	Nanoemulsion (~13 nm) showed enhanced antimicrobial activity and significantly accelerated wound healing in vivo (95% closure at day 21)	[138]
Hypericum perforatum	Flavonoids, phenolics, hypericin, hyperforin	Hp-loaded chitosan nanoparticles incorporated into agarose film (CS-Hp/Agarose)	Polymer-based nanocarrier (chitosan + agarose film)	Chitosan nanoparticles (~156 nm)	Chitosan enhances antimicrobial activity and acts as delivery system; agarose improves film strength, moisture retention, and biocompatibility; enables controlled release of bioactive compounds	Film showed strong antimicrobial activity, sustained release (~84% in 48 h), high cell viability, and enhanced fibroblast proliferation → promising wound dressing	[139]
Calendula officinalis L.	Flavonoids, triterpenoids, lipids (dalam extracellular vesicles)	Hydrogel-loaded plant extracellular vesicles (PS-COEVs)	Hydrogel-based delivery system (Gel-BA/KGM)	Extracellular vesicles (~90–140 nm, modified with phosphatidylserine)	Hydrogel provides ROS-responsive release, improves stability and retention; PS modification enhances macrophage targeting; enables controlled delivery and immune modulation	Promotes macrophage polarization (M1→M2), enhances osteogenesis	[140]
Balanites aegyptiaca	Flavonoids, saponins (balanitin), phenolics, alkaloids, phytosterols	Chitosan nanoparticles loaded extract; green-synthesized AgNPs & CuO NPs	Chitosan-based carrier	Polymeric NP & metallic NP	Enhances bioavailability, stability, antimicrobial and antidiabetic activity; enables controlled delivery	Shows broad pharmacological effects (antibacterial, wound healing, antioxidant, antidiabetic); potential for nano-based formulations but still limited mechanistic validation	[141]

Flavonoids

Flavonoids are a major group of bioactive polyphenolic compounds widely distributed in medicinal plants and known to possess antioxidant, anti-inflammatory, antimicrobial, and wound-healing activities.[39] In diabetic wounds, flavonoids play an important role by modulating oxidative stress, suppressing chronic inflammation, and enhancing tissue regeneration. Their clinical application is often limited due to poor solubility, instability, and low bioavailability. To overcome these limitations, various studies have developed nanoparticle-based delivery systems from plant extracts rich in flavonoids to improve their therapeutic efficacy.

Quercetin, a representative flavonol found in plants such as *Azadirachta indica, Mangifera indica*, and *Ocimum sanctum*, has been extensively formulated into nanoparticles. Silver nanoparticles (AgNPs) synthesized using *Azadirachta indica* exhibit synergistic antimicrobial activity while also increasing quercetin stability and penetration into wound matrices. Meanwhile, chitosan-based nanoparticles from *Ocimum sanctum* provide controlled release and enhance bioadhesion, thereby prolonging local therapeutic effects.[105,107,137]

Curcumin, a polyphenolic compound with flavonoid-like characteristics derived from *Curcuma longa*, has been widely formulated into lipid-based systems such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), as well as polymeric nanoparticles (eg., PLGA and chitosan). These systems significantly improve curcumin solubility, protect it from oxidative degradation, and enable controlled drug release. Mechanistically, curcumin nanoparticles can reduce reactive oxygen species (ROS), promote angiogenesis, and accelerate re-epithelialization and collagen deposition in diabetic wounds.[19,21]

Other plants rich in flavonoids, such as *Centella asiatica* and *Acalypha indica*, contain compounds like kaempferol and isorhamnetin that stimulate fibroblast migration and keratinocyte proliferation. Formulations into gold nanoparticles (AuNPs), chitosan nanoparticles, and AgNPs have been shown to increase compound stability and enhance anti-inflammatory and antibacterial effects.[90,91,106] Similarly, *Teucrium polium*, rich in apigenin, luteolin, and rutin, has been formulated into AgNPs that not only improve delivery efficiency but also provide intrinsic antimicrobial activity, thus accelerating wound contraction and tissue regeneration.[100]

Recent studies indicate that flavonoid-based nanoparticle systems can target various pathological pathways simultaneously. *Gliricidia sepium* formulated into ZnO nanoparticle hydrogels has been shown to enhance wound healing by modulating cytokines, increasing collagen deposition, and promoting angiogenesis.[21] Flavonoid-rich citrus plants such as *Citrus limon* and *Citrus aurantifolia* have been formulated into AgNPs and ZnONPs, demonstrating increased antibacterial activity, fibroblast proliferation, and reduced inflammatory cell infiltration.[102,103]

Additionally, *Syzygium cumini* and *Fumaria officinalis* have been developed into AgNP systems, showing enhanced antioxidant, anti-inflammatory, and hypoglycemic effects, which are highly relevant for diabetic wound healing where oxidative stress due to hyperglycemia plays a major role.[110,142] Lipid-based delivery systems such as SLNs are also used for flavonoids from plants like *Pterocarpus marsupium*, improving solubility, providing sustained release, and protecting active compounds from degradation.[109]

Various plants such as *Punica granatum, Mentha piperita, Anredera cordifolia*, Cinnamomum spp., and *Fumaria officinalis* are sources of flavonoids that have been incorporated into nanoparticle systems for diabetic wound healing. *Punica granatum*, containing pelargonidin, formulated into chitosan nanoparticles, has been shown to increase epithelial thickness and promote angiogenesis.[84] *Mentha piperita*, containing luteolin and apigenin in the form of AgNPs, provides synergistic antibacterial and antioxidant effects.[116]

Some studies also utilize silver nanoparticles (AgNPs) as nanocarrier systems through green synthesis methods based on plant extracts such as *Psidium guajava, Punica granatum, Althaea officinalis*, and *Clerodendrum glandulosum*. AgNPs exhibit excellent antibacterial activity against wound pathogens like *Staphylococcus aureus* and *Escherichia coli*. The combination of flavonoids and AgNPs can accelerate epithelialization and extracellular matrix formation while reducing pro-inflammatory cytokine levels.[127–129] Meanwhile, *Gliricidia sepium* has been developed into ZnO nanoparticle hydrogels capable of modulating cytokine expression (IL-10, PDGF), reducing VCAM-1, and increasing collagen density and angiogenesis.21 Additionally, *Archidendron pauciflorum* formulated into biodegradable PLGA nanoparticles can provide controlled release, significantly enhancing tissue regeneration.[131]

Ipomoea quamoclit has been used to synthesize copper oxide (CuO) nanoparticles via microfluidic lab-on-a-chip technology, producing spherical nanoparticles sized 65–94.5 nm. These exhibit notable antibacterial and antifungal activities against various microorganisms, along with strong antioxidant activity with IC50 values of 33.94 μg/mL (DPPH) and 42.54 μg/mL (H_2O_2).[135] Meanwhile, leaf extract of *Flueggea leucopyrus* has been employed to synthesize approximately 20 nm copper nanoparticles (CuNPs), showing antibacterial, antioxidant, and antidiabetic effects through α-amylase inhibition.[143]

Beyond established systems, additional plants such as *Kigelia africana, Alchornea cordifolia, Jatropha tanjorensis, Justicia secunda, Lawsonia inermis*, and *Lithospermum officinale* are expanding the potential of flavonoid-based nanomedicine. AgNPs synthesized via green methods from *Kigelia africana* and *Alchornea cordifolia* demonstrate strong antioxidant and antimicrobial activities, linked to flavonoids and phenolic compounds acting as reducing and stabilizing agents.

Nanoparticles from *Jatropha tanjorensis* and *Justicia secunda* show multi-target activities, including antidiabetic, anti-inflammatory, antioxidant, and antiglycation effects. These mechanisms are important for inhibiting the formation of advanced glycation end-products (AGEs), reducing oxidative stress, and addressing chronic inflammation. *Lawsonia inermis* formulated into ZnO nanoparticle gel provides compelling in vivo evidence of accelerating wound healing, marked by increased epithelialization, collagen deposition, and decreased inflammatory infiltration.[98] AgNPs from *Lithospermum officinale* exhibit high antioxidant activity due to phenolic compounds like shikonin derivatives, which act as reducing and stabilizing agents.[99]

Polyphenols

Polyphenols are a group of secondary metabolites derived from plants with a wide range of structures and proven activities, including antioxidant, anti-inflammatory, antimicrobial, and wound-healing properties. These compounds play a crucial role in managing diabetic wounds by reducing oxidative stress and chronic inflammation, two main barriers to tissue repair in diabetes mellitus.[134] Their clinical application is often hampered by low stability, susceptibility to environmental degradation (light and oxygen), and poor bioavailability. To address these limitations, nanoparticle-based delivery systems have been extensively developed to improve the stability, bioavailability, and therapeutic efficacy of polyphenols.

Curcumin, one of the most studied polyphenols from *Curcuma longa*, exemplifies the need for nanocarrier-based delivery systems. Due to its hydrophobic nature and ease of degradation, curcumin has been formulated into lipid-based systems such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), as well as polymeric nanoparticles. These systems significantly enhance solubility, protect curcumin from oxidative degradation, and enable sustained release. Curcumin nanoparticles can reduce reactive oxygen species (ROS), suppress inflammatory mediators, promote angiogenesis, and accelerate re-epithelialization and collagen deposition in diabetic wounds.[19]

Other polyphenol-rich plants also show increased therapeutic effectiveness when formulated into nanocarrier systems. Extracts of *Kunzea ericoides* incorporated into chitosan nanoparticles exhibit enhanced antimicrobial activity and stimulate fibroblast proliferation, thereby accelerating wound contraction and epithelial regeneration.[85] *Aloe barbadensis* Miller (*Aloe vera*), formulated into chitosan nanoparticles, enhances antimicrobial effectiveness and speeds wound closure due to polyphenols like aloesin and aloin.[104]

More advanced polymeric systems have also been developed for targeted and controlled delivery of polyphenols. Rosmarinic acid from *Salvia miltiorrhiza* has been successfully encapsulated in PEG-PLGA nanoparticles, allowing for controlled release and efficient delivery to the wound site, while also reducing pro-inflammatory cytokine expression.[135] Caffeic acid and chlorogenic acid from *Gymnema sylvestre* have been formulated into polymeric nanoparticles to improve stability, reduce oxidative stress, and stimulate collagen synthesis.[114]

Beyond polymer-based systems, metal nanoparticles and hybrid structures also show synergistic therapeutic effects. Extracts of *Plantago major* (ferulic acid) and *Camellia sinensis* (EGCG) used in green synthesis of silver nanoparticles (AgNPs), where polyphenols act as reducing and stabilizing agents. These AgNP systems provide dual functions: enhancing antioxidant activity and delivering potent antimicrobial effects against wound pathogens.[111,122] Extracts of Punica granatum and Olea europaea formulated into AgNPs can accelerate wound closure, increase fibroblast proliferation, and decrease infection risk.[127]

Another innovative system includes hydrogels based on extracellular vesicles (EVs) derived from Sargassum sp., which facilitate efficient delivery of polyphenols and contribute to tissue regeneration and inflammation control.[85] Mesoporous silica

nanoparticles (MSNs) combined with bioactive compounds from *Vitis vinifera* (resveratrol) demonstrate targeted delivery, sustained release, and increased expression of healing-related genes such as TGF-β1 and Arg-1.[119]

Sargassum sp. (brown algae), known to be rich in gallic acid, has been developed into EV-based hydrogels. Although not traditional nanoparticles, these systems utilize nanoscale extracellular vesicles capable of optimal polyphenol delivery and have shown positive results in new tissue formation and inflammation regulation.[113]

Pterocarpus marsupium contains ellagic acid, which has anti-inflammatory and regenerative activities. Its formulation into PCL-PEG nanoparticles supports slow release and enhances stability of the compound in the dynamic environment of wounds.[109]

In other studies, Vitis vinifera (resveratrol) has been combined with mesoporous silica nanoparticles (MSNs) and platelet-derived extracellular vesicles (PDEVs) within a hydrogel system, creating a more targeted and gradual delivery system. MSNs allow for sustained release of active compounds, increase the expression of healing genes (TGF-β1, Arg-1), and promote angiogenesis. *Camellia sinensis* (EGCG) has also been developed into biopolymer hydrogel systems based on guar gum and melanin-like nanoparticles (CEMNPs).127,129 Both systems show abilities to control ROS, exhibit antibacterial activity, and enable real-time health condition monitoring.

Overall, nanocarrier systems offer several key advantages: preventing compound degradation caused by environmental factors, enhancing local/topical absorption, improving stable antioxidant activity, and prolonging pharmacological action duration.

Based on the review and compiled tables, it is clear that silver nanoparticles (AgNPs) and chitosan-based nanoparticles are the two most frequently used nanocarriers in formulating plant-based preparations for *diabetes mellitus* wound therapy. Systems based on solid lipid nanoparticles (SLNs) and nanofiber membranes are also used, but less often.

AgNPs are the most common nanocarrier in the reviewed studies, appearing with plants including *Teucrium polium, Kunzea ericoides, Fumaria officinalis, Mentha piperita*, and *Syzygium cumini*. This is primarily because of the following reasons.

a. Strong antibacterial properties from silver ions, which are vital for diabetic wounds prone to infection;
b. Easy green synthesis, often using plant extracts as the reducing and stabilizing agents;
c. Synergistic effects between the silver ions and bioactive compounds like flavonoids, polyphenols, or alkaloids; and
d. Good biocompatibility, especially when stabilized by the plant's respective compounds.

Although AgNPs are highly effective, careful use is still required due to potential toxicity at high doses and tissue accumulation.[58,85,100,116] AgNPs are known for their powerful antibacterial activity, which is essential in managing infection-prone diabetic wounds. A meta-analysis by Yi et al (2024) demonstrated that using silver-based dressings significantly improves the healing rate of diabetic foot ulcers (OR = 2.14; 95% CI = 1.52–3.00; p = 0.00) and reduces ulcer area and recurrence rates.[136] Additionally, AgNPs can be synthesized using the environmentally friendly and economical green synthesis method with plant extracts. A study by Hussein et al (2023) showed that cotton fabric loaded with AgNPs enhanced wound contraction and lowered inflammatory biomarkers in a diabetes model.[137]

Chitosan is the most frequently used natural polymer as a nanocarrier for plant bioactive compounds, appearing with plants such as *Anredera cordifolia, Ocimum sanctum, Centella asiatica*, and *Aloe barbadensis*. The main reasons for its widespread use are as follows.

a. Biocompatibility and biodegradability;
b. Ability to enhance transdermal penetration;
c. Inherent antibacterial and anti-inflammatory effects;
d. Ability to form a bioadhesive gel that keeps the preparation on the wound; and
e. Controlled release effect, where the active compound is released slowly and continuously.

Chitosan is also compatible for combining with unstable or easily degraded compounds, including flavonoids, terpenoids, and alkaloids.[86,92,107,111] Chitosan is a biocompatible and biodegradable natural polymer with the ability to form a bioadhesive gel that maintains wound moisture and supports tissue regeneration. A study by Jansirani et al (2025)

showed that chitosan nanoparticles encapsulating natural photosensitizers, like curcumin and C-phycocyanin, accelerated diabetic wound healing through photodynamic therapy.[144] Furthermore, chitosan has inherent antibacterial and anti-inflammatory activity, as well as the ability to increase the transdermal penetration of active compounds. This makes it an ideal nanocarrier for a wide range of plant bioactive compounds.

Generally speaking, AgNPs and chitosan nanoparticles are the dominant nanocarriers due to their combination of biological effectiveness, ease of production, and high compatibility with plant compounds. Moreover, both allow for a green synthesis approach, which is more environmentally friendly and economical. Therefore, they are the top choices in developing plant-based topical nanoparticle preparations for diabetic wound healing.

Nanoparticles as a Delivery System for Polyphenols and Flavonoids

Polyphenols and flavonoids are groups of bioactive compounds frequently found in plants and are well-known for their various pharmacological benefits, including antioxidant, anti-inflammatory, anticancer, and antidiabetic activities.[18] These compounds work by neutralizing free radicals and inhibiting cell-damaging oxidative processes, therefore showing great potential for use in treating various degenerative diseases.[19,145] However, despite their widespread benefits, the clinical application of polyphenols and flavonoids still faces major obstacles, primarily related to low bioavailability, instability against the pH and enzymes of the digestive tract, and rapid liver metabolism.[21] This results in only a small fraction of the compounds being absorbed when consumed orally, which consequently limits their therapeutic effectiveness.

While polyphenols and flavonoids are promising as natural therapeutic agents, the main challenge in their clinical utilization lies in their low oral bioavailability, caused by the chemical and biological nature of these compounds. Many polyphenols are only slightly water-soluble and are sensitive to environmental conditions, such as extreme pH, high temperatures, and exposure to oxygen and light, which can cause them to degrade before they reach the therapeutic target.[100,146] Furthermore, after consumption, these compounds undergo extensive metabolism in the gastrointestinal tract and liver. Digestive enzymes and conjugation processes in the liver (like glucuronidation and sulfation) cause significant chemical transformation. As a result, only a small amount of the active form is absorbed and becomes systemically available.[101] This process intensifies the challenge of distributing the compounds to target tissues, especially for applications targeting specific organs like the brain or skin. The large and polar molecular structure of flavonoids also makes it difficult for them to penetrate cell membranes, thus reducing their effectiveness within the body's system. Poor stability in the stomach or intestinal environment, in addition to the inability to remain in the bloodstream in their active form, makes the oral delivery of these natural compounds a significant challenge in therapy.[102]

Nanoparticles represent a modern drug delivery system designed to boost the effectiveness and stability of bioactive compounds, including polyphenols and flavonoids.[103] In essence, a nanoparticle is a particle measuring 1–100 nanometers that has a high surface-area-to-volume ratio. This allows for more efficient interaction with biological membranes and improves the solubility of poorly water-soluble compounds.[104] One of the main roles of nanoparticles is to protect the active compounds from premature degradation, whether caused by stomach pH, digestive enzymes, or environmental oxidation.[105,147] Moreover, this system allows for the slow and controlled release of the compounds, thereby increasing the therapeutic concentration at the target organ and extending the active substance's working time in the body.[106]

In the context of polyphenols and flavonoids, nanoparticles act not only as a protector but also as a transport system across cell membranes, accelerating the compounds' penetration into tissues and increasing their bioavailability.[107] Additionally, nanoparticles can be functionally modified to target specific tissues, such as inflamed or chronic wounds, which are often found in *diabetes mellitus* patients.[84] Given these characteristics, nanoparticles provide a strategic solution for the various limitations of natural compounds in medical treatment. The development of different types of nanoparticles, whether lipid, polymer, or metal-based, becomes a key to formulating preparations that are effective, safe, and geared towards long-term therapy. Figure 3 shows the formulation process of flavonoid nanoparticles to increase absorption and efficacy in *diabetes mellitus* wound care.

Metal-Based Inorganic Nanoparticles

Metal-based inorganic nanoparticles are one of the most widely used types of nanoparticles in wound therapy, including diabetic wounds. This is because of their ability to provide antimicrobial, anti-inflammatory, and antioxidant effects.[148]

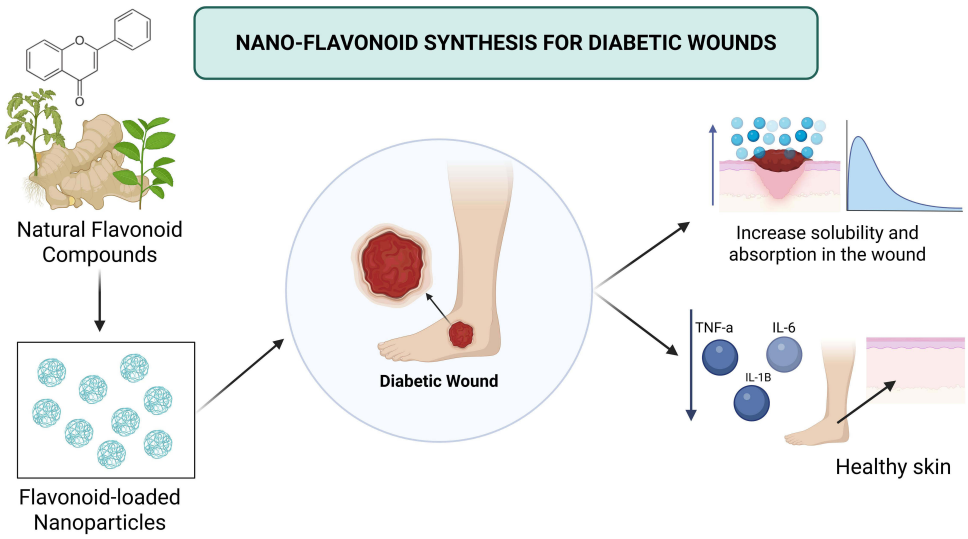

Figure 3 The formulation process of flavonoid nanoparticles to enhance absorption and efficacy in diabetic wound care.
Note: (↑) indicates increased solubility and absorption of nano-flavonoid at the wound area, and (↓) indicates a decrease in inflammatory mediators.

Metal nanoparticles typically consist of pure metal elements (eg., gold and silver) or metal oxide compounds (eg., zinc oxide and manganese dioxide). The unique physicochemical properties of metals, including high surface area, conductivity, and the ability to generate reactive oxygen species (ROS), make this group attractive for biomedical applications.[149] Below is an in-depth discussion of each type of metal-based nanoparticle used in these studies.

Silver Nanoparticles (AgNPs)

Silver nanoparticles (AgNPs) are nanoscale silver metal particles that show broad-spectrum antimicrobial activity. They have been proven to accelerate diabetic wound healing by inhibiting infection, stimulating angiogenesis, and reducing inflammation. AgNPs work by damaging microbial cell membranes, generating ROS, as well as modulating the expression of pro-inflammatory cytokines, such as TNF-α and IL-6.[150,151] In the reviewed articles, AgNPs were synthesized using various plants, including *Azadirachta indica, Syzygium cumini, Fumaria officinalis, Plantago major, Salvia hispanica, Malva sylvestris, Mentha piperita, Camellia sinensis, Olea europaea, Punica granatum, Psidium guajava, Raphanus sativus, Althaea officinalis, Cinnamomum sp*., and *Clerodendrum glandulosum*. Some studies combined AgNPs with carriers, such as chitosan (gelatin and chitosan) PEG hydrogels, to enhance their stability and effectiveness.[152]

Silver nanoparticles (AgNPs) possess unique physicochemical properties, including high surface area and enhanced reactivity, enabling their interaction with biological systems. In the context of diabetes, AgNPs exhibit antioxidant activity by scavenging reactive oxygen species (ROS), thereby reducing oxidative stress—a major factor in pancreatic β-cell dysfunction and insulin resistance. Additionally, AgNPs can modulate inflammatory pathways by inhibiting pro-inflammatory cytokines, which contribute to insulin resistance. Their ability to increase cellular glucose uptake and influence insulin signaling pathways further supports their potential as antidiabetic agents. Overall, AgNPs' multifunctional role in reducing oxidative damage and inflammation positions them as promising nanotherapeutics for diabetes management.[151,152]

Silver nanoparticles (AgNPs) exhibit broad-spectrum antimicrobial activity through multiple mechanisms, including disruption of bacterial cell membranes, generation of reactive oxygen species (ROS), and interference with microbial DNA and enzyme function. In diabetic wound healing, AgNPs help mitigate infection, which is a primary barrier to tissue regeneration, especially given the impaired immune response associated with diabetes. Their nanoscale size enhances bioavailability and facilitates interaction with microbial biofilms, reducing bacterial burden and preventing chronic inflammation.[152] Additionally, AgNPs modulate inflammatory cytokines and promote fibroblast proliferation and collagen synthesis, accelerating tissue repair. The controlled release of AgNPs within wound dressings optimizes antimicrobial efficacy while minimizing cytotoxicity, thereby supporting effective healing in diabetic ulcers.

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Gold Nanoparticles (AuNPs)

Gold nanoparticles (AuNPs) are noble metal nanoparticles that possess high chemical stability, good conductivity, and the ability to be surface-modified to carry bioactive compounds. AuNPs are known for their excellent biocompatibility and are inert towards biological systems, thereby making them a potential candidate in therapeutic applications, including diabetic wound healing.[153,154] In one reviewed study, gold nanoparticles were synthesized using the leaf extract of *Chamaecostus cuspidatus*, a plant widely known as the "insulin plant" because of its content of flavonoids and other phytochemicals that have antidiabetic effects.[155] The resulting AuNPs had an average size of 50 nm with a spherical shape and high stability. In vivo tests on animals showed that this formulation was able to lower blood glucose levels, increase insulin levels, and accelerate the wound healing process without causing toxicity to vital organs like the liver and kidneys. Additionally, gold nanoparticles were also synthesized from *Acalypha indica* extract through a green synthesis method without the use of additional nanocarriers.[153] The produced AuNPs had a size between 10 and 30 nm and were used directly as a topical agent in an open wound model in mice.

Gold nanoparticles (AuNPs) exhibit remarkable biocompatibility, stability, and surface functionalization capabilities, making them promising candidates for antidiabetic applications. AuNPs can enhance insulin sensitivity by modulating key signaling pathways involved in glucose homeostasis. They also possess antioxidant properties, scavenging reactive oxygen species (ROS) and mitigating oxidative stress, which is crucial in preserving pancreatic β-cell function. Moreover, AuNPs can serve as delivery vehicles for antidiabetic drugs or bioactive molecules, improving targeted delivery and bioavailability.[155] Their ability to influence inflammatory responses and improve cellular glucose uptake underscores their potential as nanotherapeutics in diabetes management, offering a multifaceted approach to controlling hyperglycemia and associated complications.

Gold nanoparticles (AuNPs) possess unique anti-inflammatory, antioxidant, and regenerative properties that are beneficial for diabetic wound healing. Their ability to modulate cytokine production reduces chronic inflammation, a key obstacle in diabetic wound repair. AuNPs also promote angiogenesis by stimulating endothelial cell proliferation and migration, enhancing neovascularization necessary for tissue regeneration.[153,154] Furthermore, their antioxidant activity neutralizes excess reactive oxygen species (ROS), which are elevated in diabetic wounds and impair healing. AuNPs can facilitate fibroblast proliferation and collagen deposition, accelerating tissue remodeling. Their biocompatibility and ease of functionalization allow for targeted delivery of therapeutic agents, making AuNPs a promising nanomaterial to improve healing outcomes in diabetic ulcers.

Zinc Oxide Nanoparticles (ZnONPs)

ZnONPs belong to the transition metal oxides that possess antioxidant and pro-angiogenesis capabilities. Zn^{2+} is an essential element in the wound healing process because it plays a role in collagen synthesis and reparative enzymes. ZnONPs are also antimicrobial and can stimulate fibroblast proliferation.[156] In the reviewed research, ZnONPs were used in formulations with plant extracts, such as *Gliricidia sepium, Nigella sativa*, and *Centella asiatica*. ZnONPs are usually loaded into a hydrogel matrix (like PVA) for gradual release and more effective topical application.

Zinc oxide nanoparticles (ZnONPs) possess unique physicochemical properties, including high surface area and bioavailability, which confer significant biological activity relevant to diabetes management. ZnONPs enhance insulin secretion by stimulating pancreatic β-cells and promote glucose uptake in peripheral tissues through modulation of insulin signaling pathways.[156] Additionally, they exhibit antioxidant properties, neutralizing reactive oxygen species (ROS) and reducing oxidative stress—a key contributor to β-cell dysfunction and insulin resistance. Zinc ions released from ZnONPs also play a crucial role in enzymatic processes involved in carbohydrate metabolism.[156] Their anti-inflammatory effects further mitigate chronic inflammation associated with diabetes, making ZnONPs promising nanomaterials for improving glycemic control and protecting against diabetic complications.

Zinc oxide nanoparticles (ZnONPs) exhibit potent antimicrobial, anti-inflammatory, and regenerative properties that are advantageous for diabetic wound healing. Their broad-spectrum antimicrobial activity helps reduce bacterial colonization and biofilm formation, which are common in chronic diabetic wounds.[156] ZnONPs also enhance cellular proliferation, migration, and collagen synthesis by stimulating fibroblasts and keratinocytes, facilitating tissue regeneration. Additionally, they modulate inflammatory responses by regulating cytokine production, thus reducing excessive

inflammation. ZnONPs' antioxidant capacity neutralizes reactive oxygen species (ROS), which are elevated in diabetic wounds and impair healing processes.[155,156] Their biocompatibility and ability to release zinc ions support enzymatic functions critical for tissue repair, making ZnONPs promising for improving diabetic wound healing outcomes.

Manganese Dioxide Nanoparticles (MnO_2NPs)

MnO_2NPs are metal oxides with high redox activity. In the ROS-rich environment of a diabetic wound, MnO_2 can act as an ROS scavenger, stabilizing the wound environment, as well as aiding in angiogenesis and cell proliferation.[157] In a study on *Gelsemium elegans*, MnO_2NPs were used to deliver the active compound (gelsevirine) to the wound via polyurethane-based nanofibers. This formulation showed increased epithelization speed, reduced inflammation, and improved histological structure of the wound. The effectiveness of MnO_2NPs in regulating oxidative stress makes them a promising candidate in chronic wound therapy.

Manganese dioxide nanoparticles (MnO_2NPs) exhibit notable catalytic and redox properties that are beneficial in antidiabetic applications. MnO_2NPs can modulate oxidative stress by scavenging reactive oxygen species (ROS), thereby protecting pancreatic β-cells from oxidative damage and preserving insulin secretion. They also influence glucose metabolism by enhancing the activity of enzymes involved in carbohydrate oxidation and insulin signaling pathways.[157] Furthermore, MnO_2NPs exhibit anti-inflammatory effects, reducing cytokine-mediated β-cell impairment. Their ability to facilitate electron transfer reactions and regulate oxidative homeostasis underscores their potential to improve glycemic control and mitigate diabetic complications, making MnO_2NPs promising nanotherapeutic agents in diabetes management.[157]

Manganese dioxide nanoparticles (MnO_2NPs) exhibit catalytic, antioxidant, and pro-angiogenic properties that enhance diabetic wound healing. Their catalytic activity facilitates the decomposition of reactive oxygen species (ROS), reducing oxidative stress prevalent in diabetic wounds, thereby protecting tissues from further damage. MnO_2NPs also promote angiogenesis by stimulating endothelial cell proliferation and migration, essential for restoring blood flow and nutrient delivery to the wound site.[157] Additionally, they modulate inflammatory responses by regulating cytokine expression, minimizing chronic inflammation. The release of manganese ions supports enzymatic activities involved in tissue regeneration and collagen synthesis. Due to their biocompatibility and multifunctionality, MnO_2NPs serve as promising nanomaterials to accelerate healing in diabetic ulcers.

Titanium Dioxide Nanoparticles (TiO_2NPs)

Titanium dioxide nanoparticles (TiO_2NPs) are a type of metal oxide-based inorganic nanoparticle widely used in biomedical applications, including as a wound healing agent.[158] In the reviewed study, TiO_2 nanoparticles were synthesized using the leaf extract of *Ocimum sanctum* (basil), which is known to be rich in flavonoids, eugenol, and rosmarinic acid. These nanoparticles were then incorporated into a chitosan-based gel, which served as a nanocarrier to enhance the bioavailability and stability of the nanoparticles for topical application. This combination demonstrated the ability to accelerate the diabetic wound healing process through reduced inflammation, stimulation of collagen synthesis, and improved tissue structure.[107]

Titanium dioxide nanoparticles (TiO_2NPs) possess unique physicochemical properties, including high surface area and photocatalytic activity, which underpin their potential in antidiabetic applications. TiO_2NPs can enhance insulin sensitivity and glucose uptake by activating key signaling pathways such as AMPK and PI3K/Akt, thereby improving glycemic control.[107] Their antioxidant properties enable the scavenging of reactive oxygen species (ROS), reducing oxidative stress-induced β-cell dysfunction and insulin resistance. Additionally, TiO_2NPs may modulate inflammatory responses associated with diabetes by decreasing cytokine levels. The biocompatibility and ability of TiO_2NPs to facilitate cellular interactions suggest their promising role in nanomedicine approaches aimed at preventing or managing diabetic complications.[107]

Titanium dioxide nanoparticles (TiO_2NPs) possess unique photocatalytic, antimicrobial, and regenerative properties that are beneficial for diabetic wound healing. Their antimicrobial activity reduces pathogenic microbial colonization and biofilm formation, common challenges in chronic diabetic wounds. TiO_2NPs also generate reactive oxygen species (ROS) under light exposure, which can be harnessed to eliminate bacteria and promote cellular signaling pathways

involved in tissue repair.[106,107] Additionally, TiO_2NPs enhance fibroblast proliferation, collagen synthesis, and angiogenesis, facilitating tissue regeneration. Their biocompatibility and ability to modulate inflammatory responses help mitigate chronic inflammation associated with diabetic wounds. Overall, TiO_2NPs support a conducive environment for accelerated wound closure and tissue regeneration in diabetic patients.

Polymeric Nanoparticles (Polymeric NPs)

Chitosan Nanoparticles

Chitosan, a natural polymer derived from the deacetylation of chitin, is widely applied as a nanoparticle-based drug delivery system. Chitosan's bioactive properties, including biocompatibility, biodegradability, and antimicrobial and hemostatic activity, make it an ideal candidate for wound therapy, particularly for chronic wounds like diabetic ulcers.[159] In nanoparticle form, chitosan is capable of boosting skin permeability, prolonging the release time of bioactive compounds, and protecting the compounds from enzymatic or oxidative degradation. Moreover, chitosan has a cationic charge, which enables it to interact with negatively charged cell membranes, facilitating the binding and penetration of active compounds into the wound tissue.[160]

In this review's findings, chitosan nanoparticles are used as a carrier for various plants containing bioactive flavonoids or polyphenols, such as *Teucrium polium, Anredera cordifolia* (*binahong), Gymnema sylvestre, Berberis vulgaris* (berberine), turmeric (*Curcuma longa*), brown seaweed, and combination plants like oregano and turmeric. The use of chitosan with these plants shows an increased effectiveness of the compound's bioactivity, ranging from anti-inflammatory and antioxidant effects to stimulating wound tissue regeneration. Consequently, this indicates that the chitosan nanoparticle system not only acts as a transport vehicle but also actively contributes to accelerating wound healing through various synergistic mechanisms.[113,161]

Chitosan nanoparticles (CNPs) are biocompatible, biodegradable polysaccharides with mucoadhesive and immunomodulatory properties, making them promising in antidiabetic therapy. CNPs enhance glucose metabolism by stimulating pancreatic β-cell proliferation and insulin secretion, partly due to their ability to improve cellular permeability and facilitate drug or gene delivery. Their antioxidant activity helps mitigate oxidative stress, a key factor in β-cell apoptosis and insulin resistance. Additionally, CNPs exhibit anti-inflammatory effects by downregulating cytokines involved in diabetic complications. The natural origin, low toxicity, and capacity to modulate key metabolic and immune pathways underpin the potential of chitosan nanoparticles as effective nanocarriers and therapeutic agents in diabetes management.[159–161]

Chitosan nanoparticles (CNPs) exhibit intrinsic antimicrobial, hemostatic, and immunomodulatory properties that facilitate diabetic wound healing. Their biocompatibility and biodegradability promote cellular adhesion, proliferation, and collagen synthesis at the wound site. CNPs enhance angiogenesis by stimulating endothelial cell migration and growth factor expression, accelerating tissue regeneration. Additionally, their antimicrobial activity helps prevent wound infections, a major complication in diabetic ulcers. CNPs also modulate inflammatory responses by reducing pro-inflammatory cytokines and promoting a favorable healing environment. These combined effects improve wound closure, re-epithelialization, and tissue remodeling, making chitosan nanoparticles a promising biomaterial for enhancing diabetic wound healing processes.[159–161]

Gelatin Methacryloyl (GelMA)

Gelatin methacryloyl (GelMA) is a semi-synthetic polymer frequently used in developing hydrogel-based drug delivery systems because of its biocompatibility, biodegradability, and ability to be gelled in situ.[162] In some of the reviewed studies, GelMA was used as a delivery medium for plant exosomes, such as exosomes from *Citrus limon* (lemon), for diabetic wound therapy. Combining GelMA with dialdehyde starch (DAS) produced a hydrogel that is not only flexible and adheres well to tissue but also capable of providing sustained drug release and creating a moist, protected wound environment. The addition of lemon exosomes to the GelMA/DAS system showed significant effects in regulating macrophage polarization, stimulating the proliferation of fibroblasts and vascular endothelial cells, and accelerating wound tissue regeneration in diabetic models. Thus, GelMA holds great potential as a platform carrier for plant exosomes in nanomedicine-based chronic wound healing applications.[102]

Gelatin methacryloyl (GelMA) is a photo-crosslinkable biomaterial derived from gelatin, incorporating methacryloyl groups to enable tunable hydrogel formation. Its biocompatibility, biodegradability, and cell-adhesive properties make it

an ideal scaffold for diabetic wound healing. GelMA promotes cellular infiltration, proliferation, and differentiation, supporting tissue regeneration.[102] Its adjustable mechanical strength and porosity facilitate nutrient diffusion and vascularization within the wound bed. Moreover, GelMA can be loaded with growth factors and therapeutic agents to enhance angiogenesis and modulate inflammation. The material's capacity to mimic native extracellular matrix promotes re-epithelialization and extracellular matrix deposition, thereby accelerating wound closure and tissue remodeling in diabetic ulcers.[162]

AST Polymeric Nanoparticles (AST PNPs) in Gelatin

Asiaticoside (AST) is the main active compound found in the *Centella asiatica* plant and is widely known for its ability to support wound healing through stimulation of collagen biosynthesis, anti-inflammatory activity, and increased angiogenesis. However, the physicochemical characteristics of AST (ie., its high molecular weight, low water solubility, and poor permeability) limit its pharmacological effectiveness. Therefore, to overcome these limitations, AST polymeric nanoparticles (AST PNPs) were developed and incorporated into a biodegradable gelatin hydrogel delivery system.[89]

AST polymeric nanoparticles (AST PNPs) encapsulated within gelatin matrices provide a targeted and sustained delivery system for therapeutic agents in diabetic wound healing. These nanoparticles enhance drug stability, bioavailability, and localized release, promoting angiogenesis, anti-inflammatory effects, and antimicrobial activity at the wound site. Incorporation into gelatin hydrogel scaffolds offers biocompatibility, biodegradability, and a conducive environment for cellular infiltration and tissue regeneration. The controlled release of AST PNPs modulates cytokine expression, reduces oxidative stress, and promotes collagen synthesis, thereby accelerating wound closure. This synergistic system improves wound healing outcomes in diabetic ulcers by addressing impaired angiogenesis, chronic inflammation, and infection.[87–89]

Polymeric Hydrogel (PVA-Alginate-Gelatin)

A polymeric hydrogel consisting of a mixture of polyvinyl alcohol (PVA), sodium alginate, and gelatin has been developed as a multifunctional drug delivery system for healing chronic infected wounds, including those caused by diabetes. The combination of these three polymers allows for the formation of a double-network structure that resembles the natural extracellular matrix, providing high mechanical strength, good adhesion to the wound, and controlled degradation capability that adjusts to the wound's micro-environmental conditions.[123] In the reviewed study, PVA-alginate-gelatin was used as a hydrogel matrix to carry self-assembled magnesium nanoparticles with tea polyphenols (TP-Mg NPs). This system demonstrated high antimicrobial activity against *Methicillin-Resistant Staphylococcus aureus* (MRSA) biofilms, as well as an angiogenic effect that accelerated the tissue regeneration process. The main advantage of this system is its ability to respond to the acidic conditions of the MRSA-infected wound micro-environment by releasing the active compound locally and continuously. Consequently, this reduces inflammation, increases cell proliferation, and speeds up wound closure.[123]

Several techniques exist for preparing microparticles and nanoparticles, with sonication-assisted emulsification being a versatile approach that involves adjusting polymer properties to control emulsion stability and particle features. Understanding how various polymers, such as ethyl cellulose, Eudragit, PLGA, and polycaprolactone, influence the transition from emulsion droplets to solid particles is essential for optimizing formulations. In the context of diabetic wound healing, these microparticles and nanoparticles can function as carriers for drugs or growth factors, enabling targeted and sustained delivery to support tissue regeneration and accelerate healing.[77] The selection of polymer type affects particle size, transformation duration, and stability, all of which are critical for ensuring effective treatment while reducing potential side effects. By optimizing sonication settings and choosing suitable polymers, researchers can create tailored microparticle and nanoparticles systems that improve healing outcomes, lower infection risks, and promote wound closure in diabetic patients. This strategy holds a significant promise for advancing wound care through precise and efficient delivery methods. Polymeric hydrogels composed of polyvinyl alcohol (PVA), alginate, and gelatin offer a multifunctional scaffold for diabetic wound healing by providing a moist, biocompatible, and biodegradable environment. PVA imparts mechanical stability and thermoresponsive properties, while alginate facilitates ion-mediated gelation and supports angiogenesis through calcium crosslinking.[122] Gelatin enhances cell adhesion, proliferation, and

extracellular matrix deposition due to its bioactive motifs. The synergistic network promotes sustained nutrient and oxygen diffusion, reduces infection risk, and modulates inflammation. This composite hydrogel can be loaded with growth factors or therapeutic agents, further stimulating neovascularization and tissue regeneration.[123] Overall, PVA-alginate-gelatin hydrogels effectively address impaired healing processes characteristic of diabetic wounds by supporting cellular functions and tissue remodeling.

Lipid-Based Nanocarriers

Lipid-based nanocarriers are advanced drug delivery systems composed of lipid molecules such as phospholipids, fatty acids, and surfactants. These nanocarriers are highly regarded for their biocompatibility and their ability to encapsulate both lipophilic (fat-soluble) and hydrophilic (water-soluble) compounds. Their unique structure allows them to penetrate biological barriers such as the skin's stratum corneum and mucosal membranes effectively. Common types of lipid-based nanocarriers include nanoemulsions, nanostructured lipid carriers (NLCs), and transfersomes.[162] These systems are particularly valuable for delivering therapeutic agents that require targeted delivery and controlled release, which are essential factors in managing chronic conditions like diabetes and its related complications.

In the reviewed studies, lipid-based nanocarriers have been employed to enhance the delivery of bioactive compounds from various medicinal plants. For example, extracts from Pterocarpus marsupium were formulated into solid lipid nanoparticles (SLNs) to carry active flavonoids such as pterostilbene. This formulation demonstrated improved wound tissue regeneration by enabling controlled release and better penetration into tissues, which is critical for diabetic wound healing.[109] Similarly, *Aloe vera* extracts were incorporated into solid lipid nanoemulsions, which increased the stability and absorption of key compounds such as aloin and flavonoids. These formulations showed enhanced anti-inflammatory and healing effects, which are advantageous for managing diabetic ulcers and promoting tissue repair.

Moreover, the fruit peel of Citrus aurantifolia (lime) was formulated into nanotransfersomes—elastic lipid vesicles known for their ability to penetrate deeper skin layers. This formulation was shown to increase the expression of growth factors such as VEGF and FGF by macrophages, which play vital roles in angiogenesis and tissue remodeling. These processes are crucial in diabetic wound healing, where impaired blood vessel formation and tissue regeneration are common challenges.[104] From an antidiabetic perspective, lipid-based nanocarriers can improve the bioavailability and targeted delivery of plant-derived compounds with antioxidant, anti-inflammatory, and insulin-sensitizing properties. By facilitating better absorption and sustained release, these nanocarriers can enhance the effectiveness of natural therapeutics, helping to regulate blood glucose levels, reduce systemic inflammation, and promote tissue repair in diabetic patients.[103]

Poly(Lactic-Co-Glycolic Acid) Nanoparticles (PLGA NPs)

Poly(lactic-co-glycolic acid) (PLGA) is a synthetic biodegradable and biocompatible polymer that has gained widespread approval from regulatory agencies such as the FDA and EMA for various medical and pharmaceutical applications. Its unique properties include controlled degradation rates and the ability to encapsulate a wide range of bioactive compounds, making it an ideal carrier for drug delivery systems.[130] In recent studies, PLGA nanoparticles have been utilized to deliver plant extracts efficiently, providing targeted and sustained release at the application site. For example, in a topical ointment formulation, PLGA nanoparticles were employed to deliver extracts from *Archidendron pauciflorum*, commonly known as jengkol fruit peel.[131] This approach aims to enhance wound healing, especially relevant for diabetic patients who often experience delayed tissue repair due to impaired angiogenesis, inflammation, and collagen synthesis.

Research conducted by Madihah et al (2020) demonstrated the promising potential of this delivery system in a diabetic mouse model induced by streptozotocin. The study found that topical application of the PLGA nanoparticle-based ointment containing jengkol extract significantly accelerated wound healing compared to control groups.[131] Key parameters assessed included wound contraction (reduction in wound length), the formation of new blood vessels (capillary density), and collagen fiber density—all crucial indicators of effective tissue regeneration. The results indicated that the nanoparticle formulation not only improved healing outcomes but also surpassed the efficacy of conventional

treatments like Betadine. This suggests that PLGA-based delivery systems can enhance the bioavailability and stability of plant-derived compounds, thereby promoting faster and more efficient wound repair.

From an antidiabetic perspective, the use of PLGA nanoparticles holds considerable promise due to their ability to improve the delivery of bioactive substances that modulate key metabolic pathways. Plant extracts like jengkol contain compounds with antioxidant, anti-inflammatory, and possibly insulin-sensitizing properties, which are vital for managing diabetic complications such as delayed wound healing. The encapsulation within PLGA nanoparticles prolongs the release of these compounds, increasing their stability and effectiveness in the body.[131] Moreover, enhanced delivery can help mitigate systemic inflammation and oxidative stress—both of which are underlying factors in insulin resistance and hyperglycemia. Overall, PLGA nanocarriers offer a versatile platform not only for accelerating wound healing in diabetes but also for delivering therapeutic agents aimed at improving glycemic control and metabolic health.

Mesoporous Silica Nanoparticles (MSNs)

Mesoporous silica nanoparticles (MSNs) are inorganic nanomaterials composed of silica (SiO_2) that feature a highly porous structure at the nanoscale, with pore sizes typically ranging from 2 to 50 nanometers. These nanoparticles are distinguished by their high specific surface area and large pore volume, which enable them to efficiently load and deliver a variety of therapeutic agents.[119] Additionally, MSNs are easily modifiable on their surface, allowing for targeted delivery, controlled release, and improved biocompatibility. Due to these properties, MSNs are increasingly being explored as carriers for bioactive compounds in biomedical applications, including wound healing and metabolic disorders such as diabetes.

In recent research, Zhu et al (2022) used MSNs to contain grape seed extract, rich in antioxidants like resveratrol. Their study demonstrated that a combination of MSN-loaded resveratrol (MSN-RES) and platelet-derived extracellular vesicles (PDEVs), embedded within a hydrogel matrix, significantly enhanced diabetic wound healing in a mouse model.[119] The MSN-RES system not only facilitated the sustained release of resveratrol, a compound known for its anti-inflammatory and antioxidant properties, but also protected PDEVs from degradation within the body. The hydrogel matrix, with its three-dimensional structure and biodegradability, provided a supportive environment that prolonged the activity of these bioactive agents, leading to reduced inflammation, promoted new blood vessel formation (angiogenesis), and accelerated tissue repair.[119]

From an antidiabetic perspective, MSNs could offer additional therapeutic benefits by addressing underlying metabolic disturbances. Resveratrol, for instance, has been extensively studied for its ability to improve insulin sensitivity, modulate glucose metabolism, and activate pathways such as SIRT1 and AMPK, which are crucial in regulating energy balance and reducing oxidative stress—a key factor in diabetes-related complications. The capability of MSNs to enhance the delivery and stability of resveratrol means higher bioavailability and targeted action, potentially contributing to better glycemic control.[119,120] Furthermore, the protective effect on PDEVs can facilitate the delivery of regenerative signals and anti-inflammatory factors, which are vital for managing diabetic wounds and systemic inflammation. Overall, MSNs represent a promising nanocarrier platform for improving both local wound healing and systemic metabolic regulation in diabetes management.

Composite Extract-Mediated Nanoparticles (CEMNPs)

Composite extract-mediated nanoparticles (CEMNPs) are innovative nanomaterials created through an eco-friendly synthesis process that combines plant extracts with metal or metal oxide cores. This green synthesis approach leverages natural reducing and stabilizing agents present in plant extracts to facilitate the formation of nanoparticles, reducing the need for toxic chemicals and making the process environmentally sustainable. In the context of diabetes management, particularly for wound healing, CEMNPs hold promising potential due to their ability to deliver bioactive compounds directly to the target site. In the reviewed study, researchers developed CEMNPs using a combination of green tea (Camellia sinensis) and olive oil (Olea europaea) extracts. These plant sources are rich in biologically active substances such as epigallocatechin gallate (EGCG), flavonoids, and natural phenols, which are well-documented for their potent anti-inflammatory, antioxidant, and antimicrobial properties.[122] These properties are especially relevant in diabetic wound healing, where persistent inflammation, oxidative stress, and infection are major barriers to tissue regeneration.

The synthesis process resulted in nanoparticles with highly desirable characteristics: a stable size distribution, narrow polydispersity, and enhanced biological activity. The stability of these nanoparticles is crucial for therapeutic efficacy, as it ensures consistent delivery of active compounds without premature degradation. The high bioactivity observed in these CEMNPs is attributable to the synergistic effects of the plant-derived phytochemicals. For example, EGCG and flavonoids are known to modulate inflammatory pathways, scavenge reactive oxygen species (ROS), and promote cellular proliferation—all critical processes in wound repair.[122] Since diabetic wounds are characterized by prolonged inflammation and oxidative damage, these nanoparticles could help mitigate these detrimental conditions, accelerating wound closure and tissue regeneration. Additionally, the natural phenols in the formulation further contribute to antimicrobial activity, helping prevent infection—a common complication in diabetic ulcers.

Relating to their antidiabetic relevance, these plant-based nanostructures could also influence glucose metabolism and insulin sensitivity, although this aspect requires further investigation. The antioxidant properties of the phytochemicals can reduce systemic oxidative stress, which is often elevated in diabetes and contributes to insulin resistance. Moreover, certain flavonoids have been shown to modulate key signaling pathways involved in glucose uptake and metabolism, such as the AMP-activated protein kinase (AMPK) pathway. By integrating these compounds into stable nanoparticle carriers, it becomes possible to enhance their bioavailability and targeted delivery, potentially exerting systemic antidiabetic effects alongside their localized wound healing benefits. Overall, CEMNPs derived from plant extracts represent a promising multifunctional platform for addressing both diabetic complications—such as chronic wounds—and underlying metabolic disturbances, paving the way for more effective, sustainable, and biocompatible therapeutic options.[121,122]

Enhanced Efficacy in Diabetic Wound Healing Through Nanoparticles

Chronic wounds in patients with diabetes mellitus (DM) present a significant clinical challenge due to impaired healing processes. These include prolonged inflammation, high levels of oxidative stress, reduced formation of new blood vessels (angiogenesis), and slow tissue regeneration. Traditional treatments often struggle to effectively address these issues. Recently, the use of nanoparticles as drug delivery systems has emerged as an innovative approach to enhance diabetic wound healing by targeting various molecular and cellular mechanisms.[113]

Nanoparticles can protect bioactive compounds such as flavonoids, polyphenols, and growth factors from enzymatic degradation and oxidative damage in the harsh wound environment. For example, nanoparticles made from chitosan and polyethylene glycol (PEG) containing silver can provide a slow, sustained release of active substances, extending their therapeutic effects and improving healing in diabetic animal models.[111] Additionally, nanoparticles can help reduce chronic inflammation and oxidative stress that hinder wound healing.[110]

Nanoparticles loaded with growth factors such as vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) can promote the formation of new blood vessels and tissue regeneration.[135] Encapsulating these growth factors within nanoparticles protects them from degradation and allows for controlled release, which has been shown to speed up wound closure and support tissue formation in diabetic animals. Furthermore, metal nanoparticles such as silver and zinc oxide possess strong antibacterial properties, which are crucial for preventing infections in diabetic wounds. Hydrogels infused with silver nanoparticles exhibit significant antibacterial activity against multidrug-resistant bacteria and aid healing by reducing bacterial load and stimulating the immune response.[112]

Moreover, nanoparticles can modulate the immune response by shifting macrophages from a pro-inflammatory (M1) state to an anti-inflammatory (M2) state, which is vital for wound repair. Hydrogels functionalized with lemon-derived nanoparticles have demonstrated the ability to reprogram macrophages, increase the proliferation of endothelial cells and fibroblasts, and ultimately accelerate wound healing in diabetic animal models.[163]

Challenges and Prospects

Developing nanoparticle-hydrogel formulations that incorporate plant extracts rich in flavonoids and polyphenols for diabetic wound therapy presents several significant scientific and technical challenges. One of the foremost obstacles is ensuring the stability of these bioactive compounds, which are inherently sensitive to environmental factors such as pH fluctuations, elevated temperatures, and exposure to oxygen and light.[109] These conditions can lead to rapid degradation

of flavonoids and polyphenols, thereby diminishing their therapeutic efficacy before they even reach the targeted wound tissue.[164] This instability is particularly problematic because the wound environment itself, especially in diabetic patients, is often characterized by oxidative stress and inflammation, which can further accelerate the breakdown of these compounds. To overcome this, advanced stabilization techniques—such as encapsulation within protective nanocarriers—are being explored to shield these molecules from environmental degradation, thus maintaining their biological activity during delivery.[109] However, optimizing these strategies requires a deep understanding of the physicochemical interactions between plant-derived compounds and nanoparticle materials, ensuring that the bioactivity is preserved without compromising biocompatibility and safety.[164,165]

Another critical challenge lies in the efficient delivery and penetration of these bioactive agents into the complex tissue architecture of chronic diabetic wounds. The effectiveness of nanoparticle-hydrogel systems depends heavily on the uniformity of nanoparticle size, surface charge, and hydrophobicity, all of which influence their ability to navigate the dense extracellular matrix and reach target cells within the wound bed.[110] Achieving consistent nanoparticle characteristics on a large scale remains difficult, as minor variations in synthesis parameters can lead to batch-to-batch inconsistencies, affecting reproducibility and therapeutic outcomes. Additionally, the design of these systems must consider the wound microenvironment, which often exhibits elevated levels of enzymes, inflammatory mediators, and reactive oxygen species that can alter nanoparticle stability and release profiles. Addressing these issues requires precise engineering of the nanoparticle surface properties and the development of stimuli-responsive systems—such as those sensitive to pH or temperature—that can adaptively modulate drug release based on the wound's changing conditions.[109] Nonetheless, scaling up production while maintaining quality and stability remains an ongoing challenge, requiring the establishment of standardized manufacturing protocols and quality control measures.

Despite these hurdles, the potential of plant-based nanoparticle-hydrogel systems for diabetic wound healing remains highly promising. Advances in nanotechnology and drug delivery research are paving the way for more sophisticated systems capable of providing controlled, targeted, and sustained release of therapeutic agents. Incorporating smart features into these formulations—such as responsiveness to wound-specific stimuli such as pH shifts, temperature variations, or inflammatory mediators—could lead to the development of "smart" dressings that automatically regulate the release of bioactive compounds.[163] This targeted approach would maximize therapeutic concentrations at the wound site, enhance healing efficiency, and reduce systemic side effects. Furthermore, leveraging natural active ingredients sourced from local biodiversity offers a sustainable and eco-friendly avenue for developing high-value phytogenic pharmaceuticals, which can be tailored to specific regional flora. Such strategies align with the global push toward sustainable medicine and could foster the development of cost-effective, environmentally friendly wound care solutions. Addressing the current scientific, manufacturing, and regulatory challenges will be crucial to translating these promising innovations into clinical practice, ultimately providing more effective and personalized treatments for chronic wounds in diabetic patients.[142]

The challenges of diabetic wound healing and the promising potential of regenerative medicine, particularly exosomes, as a cell-free therapy. Exosomes, which carry bioactive molecules like mRNA, miRNA, lipids, and proteins, can promote wound repair by regulating intercellular communication. They offer advantages such as biocompatibility and low immunogenicity but face challenges in maintaining therapeutic levels due to rapid clearance when injected. To address this, the development of biocompatible scaffolds and engineered exosomes—modified to enhance healing—are explored. The review emphasizes molecular mechanisms, benefits, limitations, and future directions for applying engineered exosomes in chronic wound treatment.[166]

The promising role of exosomes as biocompatible, low-toxicity delivery platforms for diabetic wound healing, owing to their ability to penetrate tissues and carry therapeutic agents. Engineered exosomes, enhanced through nanoengineering techniques, address challenges like heterogeneity and clearance, improving stability and targeting. Developing multifunctional wound dressings with properties such as biodegradability, antimicrobial action, and tissue adhesion is vital for optimal healing. Interdisciplinary research and coordinated efforts are essential to advance exosome-based therapies from conceptual studies to clinical applications, ultimately enhancing regenerative outcomes and minimizing side effects in diabetic wound treatment.[166]

The complex process of wound healing and the challenges of chronic wounds, which cause significant patient suffering and societal burden. It emphasizes the potential of nanotechnology in advancing wound treatment by enhancing healing efficacy. The article discusses the physiological stages of wound repair, the mechanisms by which nanomaterials

aid at various healing phases, and addresses current limitations in their application. It also offers new perspectives and innovative ideas to guide future research, aiming to improve wound healing outcomes and develop more effective nanomaterial-based therapies for diabetic wounds and other chronic wounds.[167]

The importance of nanoscale design in developing nanomaterials for wound healing, emphasizes control over their structure to enhance properties such as surface functionality, mechanical strength, and drug release. Understanding how nanomaterials interact with the wound environment, immune response, and repair processes is crucial for optimizing their effectiveness. Despite progress, further research is needed to fully grasp their molecular and cellular mechanisms, as well as their safety, cytotoxicity, and long-term effects. Future studies and clinical trials are essential to harness nanomaterials' full potential in advancing wound therapies, including diabetic wound healing.[167]

Tetrahedral framework nucleic acids (tFNAs) are an innovative DNA-based nanotechnology with promising applications in clinical wound healing, particularly for diabetic wounds. Due to their inherent stability, biocompatibility, and ability to be structurally programmed, tFNAs can withstand immune responses and degrade resistant nuclease activity, making them safe and effective for therapeutic use.[168] Their unique design allows for precise engineering to perform specific functions, such as delivering drugs or growth factors directly to the wound site, promoting tissue regeneration, and accelerating healing processes. This targeted delivery capability is especially beneficial for diabetic wounds, which often face delayed healing due to impaired blood flow, infection risks, and chronic inflammation. The versatility of tFNAs enables the development of multifunctional therapeutic platforms that can address various challenges associated with diabetic wound management, including infection control and tissue repair.[168]

Despite encouraging progress, challenges remain in translating tFNA technology from preclinical studies to practical clinical applications. Issues such as large-scale manufacturing, stability under physiological conditions, and ensuring targeted delivery need further investigation. Nonetheless, the potential of tFNAs to facilitate efficient, targeted, and biocompatible therapies makes them a promising tool for advancing diabetic wound treatment.[168] Continued research focusing on overcoming current limitations could lead to innovative therapies that significantly improve healing outcomes, reduce complications, and enhance the quality of life for diabetic patients. As such, tFNAs represent a cutting-edge approach with the capacity to revolutionize wound care in the context of diabetes.

Limitations

As a narrative review, this study does not include a meta-analysis. The heterogeneity of experimental models, nanocarrier types, and phytochemicals precluded quantitative synthesis. Future systematic reviews with meta-analytic techniques are encouraged as more data become available.

Conclusions

In conclusion, the integration of nanocarrier systems, particularly silver nanoparticles (AgNPs) and chitosan-based nanoparticles (CNPs), with phytochemicals such as flavonoids and polyphenols, presents a promising strategy to address the challenges associated with diabetic wound healing. These nanocarriers enhance the bioavailability, stability, and targeted delivery of phytochemicals, which are known for their potent antioxidant, anti-inflammatory, and antimicrobial properties. By improving the therapeutic efficacy of these natural compounds, nanocarrier-mediated delivery systems can significantly accelerate the healing process, reduce infection risks, and mitigate chronic inflammation commonly observed in diabetic wounds.

Furthermore, the unique physicochemical properties of AgNPs and CNPs facilitate their multifunctional roles in wound management. Silver nanoparticles are renowned for their broad-spectrum antimicrobial activity, which is crucial in preventing wound infections that hinder healing. Chitosan-based nanoparticles, on the other hand, possess biocompatibility, biodegradability, and inherent wound healing properties, making them ideal carriers for phytochemicals. The combination of these nanomaterials with plant-derived bioactives not only enhances their therapeutic potential but also offers a synergistic approach to modulate various stages of wound repair, including inflammation, tissue regeneration, and remodeling.

Looking forward, the application of nanocarrier systems in diabetic wound healing holds considerable potential for clinical translation. Future research should focus on optimizing nanoparticle formulations, understanding their

interactions within the biological environment, and evaluating their long-term safety and efficacy through in vivo studies. Overall, nanocarrier-mediated delivery of phytochemicals represents a frontier in wound care, promising to improve healing outcomes for diabetic patients and reduce healthcare burdens associated with chronic wounds.

Data Sharing Statement

No datasets were generated or analysed during the current study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no competing interests.

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