

Review

A potential role of nanophytocompounds in diabetic foot ulcers

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Abstract: Diabetes mellitus (DM) is characterized by hyperglycemia, which is a common endocrine disease. DM and its complications may lead to diabetic foot ulcers (DFU). DFU is associated with reduced wound healing because of altered cellular and cytokine responses, inadequate vascularization, infection, and neuropathy. One novel and promising approach to treating diabetic wound healing is the administration of compounds based on nanotherapeutics, such as nanoparticles and nanoscaffolds. Plant extracts can be administered more successfully by using nanoscale delivery methods. Plant extracts and their related phytocompounds can be nanostructured to enhance their bioavailability, regulate their release via extended delivery techniques to the wound site, and increase their penetration to the deeper layers of the skin. All these benefits are critical for the healing process. This brief overview covers the most recent methods to develop phytomedicine nanotherapeutics for the treatment of diabetic wounds.

Keywords: diabetic mellitus; drug delivery system; foot ulcer; nanoformulation; phytocompounds; wound healing

1. Introduction

The worldwide prevalence of diabetes mellitus (DM), which has increased to 8.8% in adults (20–79 years old), is becoming one of the biggest threats to economies and global health. It is anticipated that there will be a 50% increase globally [1]. DM is ranked tenth among the leading causes of morbidity that have significant impacts on mortality. Three basic types of diabetes are widely recognized, even though the exact classification of the disease is still up for debate due to its complicated pathogenesis: type 1 diabetes (T1DM), type 2 diabetes (T2DM), and gestational diabetes (GDM). In addition to the growing effects of aging, chemical toxicity, sedentary lifestyles, and hereditary problems, the current T2DM epidemic has demonstrated a notable global rise, resulting in almost 90% of diabetes cases [2,3]. Furthermore, an abundance of complications related to both macrovascular and microvascular diseases add to the mortality of the disease and worldwide economic impact. Innate immunity has long been thought to be a key player in the pathophysiology of diabetes, even though the disease and its consequences are caused by a variety of functionally related factors. In T1DM, autoimmunity specifically plays a major role in triggering an inflammatory response in pancreatic islet cells, which leads to β -cell failure [4,5]. In the same way, systemic low-grade inflammation acts as a shared mediator between the onset of type 2 diabetes and the development of micro- and macrovascular problems. According to recent research, phytochemicals may be able to prevent or treat many forms of harmful cellular damage, such as chronic wounds [6]. Numerous phytochemicals show pleiotropic properties, including the stimulation of fibroblast proliferation, which is the primary stage in wound healing.

These phytochemicals include polyphenols, alkaloids, flavonoids, terpenoids, and glycosides. The process also includes the activation of migration, epithelialization, and collagen formation, as well as their antibacterial, antioxidant, anti-inflammatory, and immunomodulatory properties [7]. Likewise, the administration of phytochemicals either in isolation or in conjunction with conventional therapy has shown encouraging outcomes in the management of diabetic foot ulcer complications (DFU). As of right now, phytochemicals have demonstrated a wide range of possibilities in managing diseases, including reducing clinical symptoms, averting degenerative diseases, and curing disease. Growing research on the anti-inflammatory and anti-infective properties of phytochemicals points to their potential utility in the treatment of diabetic foot ulcers [8].

2. Materials and methods

The authors initially selected the keywords after that extensive literature review by employing these keywords on different search engines such as Google Scholar, PubMed, Springer Nature, Science Direct, and Google. After that title of the review was selected and relevant data was collected. Then framework of the review was developed and after that interpretation of data was carried out. After completion of the interpretation of data, the review was concluded.

3. Pathophysiology of DFU

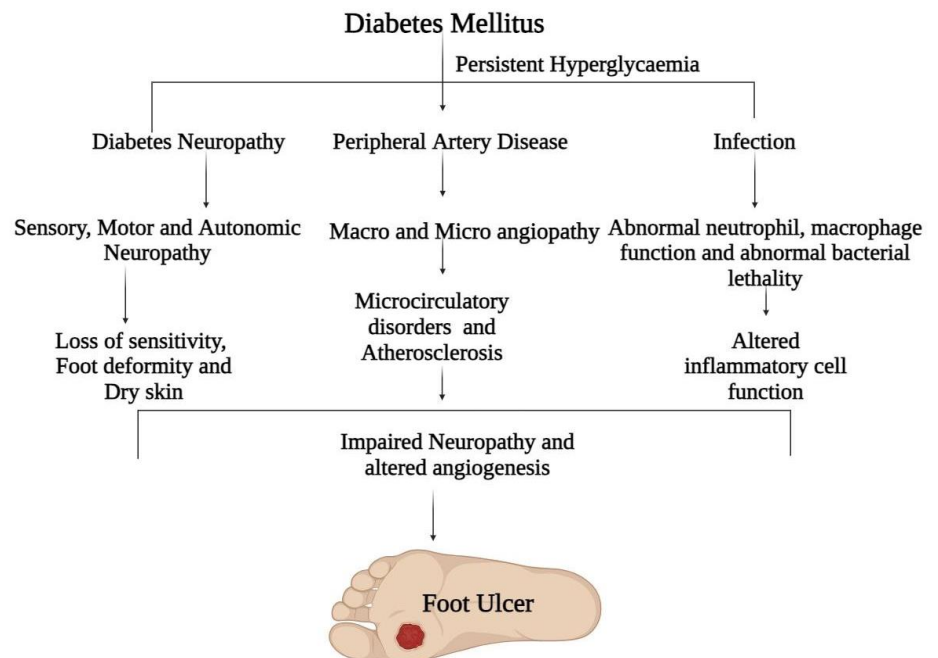


Figure 1. Basic pathophysiology of DFU.

There is an essential connection between the hyperglycemic condition of diabetes and the neuropathic, vascular, and immune system parts of DFU [9]. Neuropathy is the result of oxidative damage to brain cells caused by hyperglycemia. Moreover, nerve damage caused by glycosylation of nerve cell proteins causes ischemia [10]. The autonomic, motor, and sensory aspects of neuropathic DFU exhibit these cell

alterations. The inability of the sweat glands to generate sweat is a result of autonomic nerve breakdown, which can cause skin cell deterioration and epidemic fissures [11]. Additionally, the ability of the foot to moisturize skin cells may decline. To sum up, people who have impaired peripheral sensation might not be able to respond to DFU. The amount of blood required for managing a DFU is more than the amount needed to keep the skin healthy, which might result in a persistent ulcer [12,13]. The speed of treatment for diabetic foot wounds is impacted by immune changes. Healing is hindered in DFU patients by increased T lymphocyte cell death [14] (**Figure 1**).

3.1. Mechanism of wound healing

The process of wound healing is a complex and multi-step process that involves multiple cell types, growth hormones, cytokines, and the extracellular matrix (ECM). The main stages of wound healing include hemostasis, inflammation, cell migration, and proliferation. Wound compression and regeneration are also involved [15]. A wound is any bleeding caused by a trauma that causes the dermis of the skin to penetrate [16]. The clotting mechanism known as hemostasis, which is the first stage of wound healing, includes the coagulation cascade that stops the bleeding. The first type of cells to enter the wound site are platelets. Hemostasis develops in conjunction with the inflammatory stage, which is also demonstrated by vascular transit of inflammatory substances and cell movement to the wound site [17].

Mast cells release inflammatory mediators such as prostaglandins, histamine, and leukotrienes, which promote angiogenesis and increase permeability, allowing blood and other components to enter the wounded area [18,19]. Monocytes, neutrophils, and lymphocytes are examples of white blood cells (WBCs) that penetrate the wound site. Neutrophils and macrophages both fight bacterial infections by the secretion of Vascular endothelial growth factor (VEGF), Transforming growth factor (TGF) and Fibroblast growth factor (FGF) [20,21]. The wound begins to heal approximately two weeks after it develops on the skin. During the granulation phase of tissue regeneration, fibroblasts become myofibroblasts and strengthen their alpha-smooth muscle actin (α -SMA) cytoskeleton. When freshly grown tissue covers the wound bed, keratinocytes are stimulated to migrate, differentiate, and multiply, resulting in the formation of stratified epidermis throughout the injury site. This process is known as re-epithelialization [22,23]. Wound regeneration is the final stage of the healing process, which may require six to twenty-four months. At this stage, granular tissue starts to form, and with the help of TGF- and Platelet-derived growth factor (PDGF), type I collagen—rather than collagen III—replaces the lost collagen in the extracellular matrix.

3.2. Nanotechnology-based drug delivery system

Nanotechnology is one of the most prominent fields of study for the management of DM patients and its adverse effects. Two primary categories of nanomaterials for diabetic wound healing management comprise (1) nanomaterials with intrinsic properties that promote the healing of wounds, and (2) nanomaterials that act as drug delivery systems by encapsulating therapeutic agents [24,25]. Additionally, they encourage the local development of blood vessels by acting as chemical angiogenic

substrates. Nanomaterials promote the development of blood vessels in diabetic wounds by stimulating angiogenesis, encouraging endothelial cell migration, controlling cytoskeleton reorganization, initiating redox signaling, and producing focal adhesions [26]. It has been demonstrated that redox signaling pathways produce reactive oxygen species (ROS) when angiogenesis develops. It has been recorded that the treatment of DFU includes the use of a variety of nanomaterials, including nanoemulsions, nanoliposomes, nanoparticles, and nanofibers, that support, angiogenesis, vascularization, epithelialization, and tissue healing, in a variety of wound tissue repair conditions situations [27,28]. Polymeric nanoparticles like gold (AuNPs) and silver nanoparticles (AgNPs) are frequently employed as therapeutic agents due to their anti-inflammatory and anti-infective properties [29]. Effective antibacterial chemicals and a novel antibiofilm strategy are still lacking, and silver nanotechnology-based treatments have drawn the interest of healthcare professionals to improve patient care [30]. AgNPs have a broad range of applications in clinical practice, including the treatment of burns, persistent ulcers, diabetic wounds that have become resistant to antibiotics, and hospital-acquired bacterial infections. Wounds treated with AgNPs have demonstrated extensive collagen deposition in addition to anti-inflammatory properties, which could accelerate the healing process. Zinc oxide (ZnO) nanoparticles have demonstrated potential for wound healing applications and therapeutic activity against bacterial infection, diabetes, inflammation, and melanoma [31]. ZnO nanoparticles have demonstrated potential for wound healing applications and therapeutic activity against bacterial infection, diabetes, inflammation, and melanoma [32]. Inorganic-component ceramic nanoparticles exhibit basic therapeutic potential and can deliver medications to the areas of damage [33]. Lipid-based nanoparticles are widely employed to deliver hydrophilic and hydrophobic medicines because they are safe. By decreasing the toxicity caused by the massive release of medications through traditional administration, liposomes support the long-term release of pharmaceuticals [34]. Chitosan is a natural polymer that can be utilized in polymeric nanoparticles because of its biocompatibility and antibacterial activities. Many natural ingredients, like curcumin, vitamin E, and aloe vera, can be encapsulated and may be advantageous for the healing of skin wounds [35,36]. The Food and Drug Administration (FDA) has approved four synthetic polymers: poly (lactic acid) (PLA), poly (ϵ -caprolactone) (PCL), poly (ethylene glycol) (PEG), and poly (lactic-co-glycolic acid), or PLGA. Because it may produce lactate, a consequence of decomposition, PLGA has been the most biodegradable of these polymers. PLGA nanoparticles, despite their low drug loading, have been shown to promote cell proliferation and reduce the amount of time it takes for wounds to heal in diabetic rats [37,38]. This suggests that they could be a promising delivery vehicle for growth factors. Turmeric contains a natural polyphenol called curcumin. This organic bio-substance can help at different phases of the wound healing process and is frequently utilized as an antioxidant and anti-inflammatory agent [39]. Curcumin, however, exhibits poor stability in the treatment of wound healing, particularly when used topically, similar to other small hydrophobic compounds [40]. Liu et al. [41] incorporated thermosensitive hydrogel to accelerate and speed up the healing process with Cur nanoparticles (CNPs) contained in gelatin microspheres (GMs). These GMs can react to the upregulation of MMP-9 in the wound area. A hyaluronic acid (HA)

and chitosan-based hydrogel (OHA-CMC) for carrying and administering CNPs was recently reported by Hu et al. [42]. The encapsulated CNP formulation demonstrated exceptional antioxidant and anti-inflammatory properties, together with immediate drug release. Strong anti-inflammatory effects have been demonstrated for antidiabetic drugs, including glibenclamide (GB), pioglitazone (PHR), and metformin (MET). These effects can be used in studies to speed up the healing of diabetic wounds. Further to enhance diabetic wound healing type I, Cam et al. [43] loaded three different kinds of oral antidiabetic medications into nanofibrous scaffolds based on two distinct polymer composite combinations (CS/GEL/PCL and PVP/PVL). PHR-loaded fibrous mats have a strong therapeutic potential for addressing the proliferative and inflammatory stages of DFU, as proved by a previous study by Cam et al. [44]. In conclusion, it was reported that both PHR&MET and PHR&GB showed better wound healing than PHR alone.

3.3. Nanoformulations of phytochemicals for the management of DFU

The diabetic foot ulcer is a life-threatening condition among diabetic patients. Almost 15%–20% of DFU patients are affected by one or multiple foot ulcers annually. Diabetic patients' lower limb amputations, whether minor or major, are frequently associated with serious infections. Further, the colonization of bacteria like *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus* species, *Klebsiella pneumoniae*, and *Enterobacter* species in DFU occurs as a result of major tissue damage [45]. Nanotechnology is gaining more popularity in the research development for the enhanced therapeutic efficacy of drugs by reducing the dosage frequency, improving bioavailability, establishing sustained-release characteristics, assisting selectivity, and diminishing various other adverse biopharmaceutical properties. The advancement of nanophytochemical formulations such as liposomes, dendrimers, niosomes, polymeric nanoparticles, metallic nanoparticles, nano micelles, stimuli-responsive nanoparticles, nanostructured lipid carriers, and nanofabricated devices can be used for wound healing improvement due to the therapeutic properties of phytochemicals for wound healing management [46]. Preclinical evidence on utilizing nanoformulations of phytochemicals against DFU has already been reported. These research studies showed the enhanced therapeutic potential of nanophytochemicals in supporting the healing of wounds by various sustained release mechanisms and targeted delivery. Natural product-based nanoformulations utilizing *Dendrocalamus hamiltonii* Nees & Arn. ex-Munro and *Bambusa bambos* (L.) Voss, which has been shown to have antibacterial and wound-healing properties in the past, a nanobiocomposite hydrogel was produced as cellulose nanocrystals [47,48]. Many diabetic wound healing applications employ nanoemulsions because of their high patient tolerance and physicochemical properties. Recent reports on the use of nanoemulsions-based therapies in diabetic wound healing techniques have been published [49,50]. Chakraborty et al. [51] used polyethylene glycol 400, oleic acid, and Tween 80 to develop a homogenized aloe vera gel that was combined with insulin-loaded nanoemulsions to develop a topical gel formulation containing nanosized particles. The physical and chemical properties of the gel-based formulations demonstrated good stability, spreadability, and penetration. When insulin was

administered to diabetic rats, there was a significant ($p < 0.001$) reduction in glucose and insulin levels. The enhancement in wound contraction (75%) with gel-based formulations including both homogenized Aloe vera gel as well as insulin-loaded nanoemulsions was a significant indicator of the diabetic wound healing activity. A tocotrienol-rich naringenin (NAR)—based nanoemulgel was developed by Yeo et al. [52] for managing diabetic wound infections. The droplet size, surface charge, spreadability, viscosity, polydispersity index, in vitro release kinetics, and mucoadhesive characteristics of stable nanoemulgel were evaluated. Researchers observed that the mucoadhesive property of the nanoemulgel improved as the polymer content decreased, accompanied by a slower rate of drug release. In a 24-hour duration, the in vitro release kinetic behavior of naringenin demonstrated a consistent and regulated mode of release up to $74.62\% \pm 4.54\%$. As a result, using nanoemulgel to treat wounds associated with the consequences of diabetes is a potential strategy. In diabetic rats induced by streptozotocin. In another study [53], the antidiabetic effects of oil/water nanoemulsions using nettle extract and cumin essential oil were investigated. Several histological alterations were assessed, including oxidative stress, apoptosis, and inflammatory reactions. The blood levels of insulin and glucose were also assessed. The nettle and *Cuminum cyminum* L. essence nanoemulsions decreased serum levels of glucose and cytokines, raised insulin levels, decreased glutathione (GSH) levels, and increased oxidized levels of glutathione peroxidase (GPx) and superoxide dismutase (SOD) in the sciatic tissue of diabetic rats. Quercetin nanoemulsions (Que-NE) were assessed and investigated by Mahadev et al. [54] as a medication delivery method with enhanced therapeutic efficacy and bioavailability in diabetic-induced rats. Que-NE was determined to have a droplet size of 125.51 nm, a polydispersity index of 0.215, and an entrapment effectiveness of 87.04%. When compared to pure quercetin, que-NE showed a better mechanism of release and faster oral absorption. As per the research, Que-NE has good therapeutic efficacy as well as protective effects in regulating blood glucose levels, tissue injury biomarkers, body weight, and lipid profiles. Additionally, it protects the structural organization of hepatocytes and pancreatic β cells. As a result, Que-NE with ultrasonically helped delivery demonstrated enhanced oral bioavailability and protective as well as therapeutic anti-diabetic benefits as summarized in **Table 1**. *Turbinariaconoides* aqueous extract was used by ChitrikhaSuresh et al. [55] to synthesize AgNPs (TCAgNPs). Testing revealed that AgNPs were present, with an absorption at 452 nm confirming their presence. The resulting particles were round and polydisperse. Based on the lowest inhibitory concentration and disc diffusion method, the TCAgNPs shown outstanding antibacterial efficacy against multidrug-resistant pathogens in DFUs such as *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. They concluded that TCAgNPs are a useful healing tactic for diabetic wound infections. Turmeric contains a natural polyphenol called curcumin. This organic bio-substance can help at different phases of the wound healing process and is frequently utilized as an antioxidant and anti-inflammatory agent [56–59]. Curcumin, however, exhibits poor stability in the treatment of wound healing, particularly when used topically, similar to other small hydrophobic compounds [57]. Self-carried Cur nanoparticles (CNPs) were enclosed by Liu et al. [60] in gelatin microspheres (GMs) to help in the healing process. The GMs can

respond to the overexpression of MMP-9 in the wound environment. The CNPs@GMs have been put into a thermosensitive hydrogel. Curcumin and silk fibroin-based nanofibers coated with polyvinyl alcohol (PVA) and polycaprolactone (PCL) were developed by Agarwal et al. [61], which improved the ability of nanofibers to repair diabetic wounds. The microscopic results revealed a consistent distribution of nanofibers with tensile strengths ranging from 12.41 to 16.80 MP and diameters between 200 and 350 nm. In comparison to standard formulations, the animal studies employing nanofibers in diabetic models produced by streptozotocin demonstrated a higher wound healing efficacy. Therefore, curcumin and silk fibroin nanofibers emerged to be an excellent choice for nanomaterials, exhibiting antioxidant and anti-inflammatory effects for the treatment of diabetic wounds. In diabetic rat models, another study [62] developed nanofibrous mats encapsulated with bioactive anemoside B4 to improve wound healing of wounds. The multifunctional attributes of the nanofibrous wound dressing material included hemostatic qualities, excellent water absorption, mechanical stability, and a sustained mode of anemoside release behavior. According to the *in vitro* findings, nanofibrous mats encapsulated with anemoside could considerably lower the production of ROS and the release of cytokines that cause inflammation as summarized in **Table 1**. According to the *in vivo* conclusions, the anemoside-loaded nanofibers accelerated wound healing, improved angiogenesis, stimulated hair follicle regeneration, and improved re-epithelialization by depositing a collagen matrix. Using a thin-film hydration technique, Pandey et al. [63] developed a Resveratrol (RV)-loaded liposome-in-hydrogel system to successfully treat DFU. Skin penetration of the liposomal gel loaded with RV was enhanced. The animal model known as DFU was employed to evaluate the effectiveness of the formulation developed. On day nine, the developed formulation was applied topically to promote ulcer healing and wound closure. It achieved this by considerably lowering blood glucose and increasing glycosaminoglycans (GAGs). There were also observed faster re-epithelization, fibroblast proliferation, collagen synthesis, and decreased infiltration of inflammatory cells at the wound site. The results show that by correcting the impaired wound-healing process in diabetics, RV-loaded liposomes in hydrogel-based wound dressing dramatically accelerate wound healing in DFU as summarized in **Table 1**. Using an excision wound model, Ghaisas et al. [64] investigated the ability of Ferulic acid (FA) to promote wound healing in streptozotocin-induced diabetic rats. In comparison to the diabetic wound control group, wounds treated with FA were shown to epithelise more quickly. Comparing the hydroxyproline and hexosamine content to the diabetic wound control showed a significant rise. In addition to raising serum zinc and copper levels and efficiently inhibiting lipid peroxidation, FA also increased levels of catalase, superoxide dismutase, glutathione, and nitric oxide, which may have helped in the healing of wounds. Naringenin-Ferulic acid-loaded beeswax-based nanostructured lipid carriers (NAR-FA-NLCs) were developed and assessed by Emad et al. [65] for topical administration for DFU using a homogenization–sonication technique. The combination of FA and NAR (ratio 8:2) exhibited reduced IC₅₀ (13.49 µg) and synergistic antioxidant activity (CI < 1). The sustained release of NAR and FA from NLC was found to be 2.6 and 3.7 times, respectively, greater than that of drug solution, according to *in vitro* release tests. Significant penetration (3.5-fold) across the rat skin

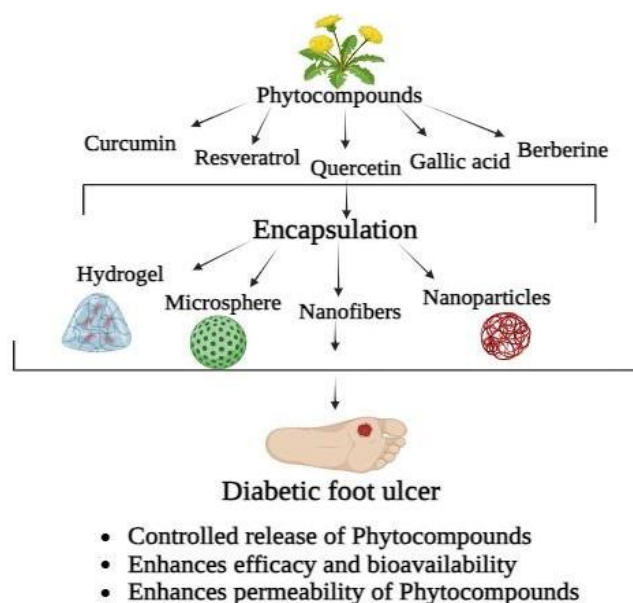
was found by confocal laser scanning microscopy (CLSM) investigation. An irritation score of 0.51 ± 0.01 was observed in HET-CAM tests, suggesting that the formulation is non-irritable and biocompatible, whereas NLC hemolysis (%) was $2\% \pm 0.365\%$. A recent study formulated clitoria ternate L. flower ethanolic extract encapsulated in the gel in a diabetic animal model. In conclusion, it is reported that clitoria ternate L. flower ethanolic extract gel exhibited 15% of the best wound healing activity in the diabetic animal model significantly with p -value < 0.05 and thus acting as a promising therapeutic strategy in the management of diabetic wound healing [66] (**Figure 2**).

Table 1. Summary of potential nanoformulations of phytochemicals in DFU.

Bioactive compounds or Medicinal Plants	Nanoformulations	Inference	Advantage	Reference
Aloe Vera gel	Nanoemulsions	The combination of homogenized Aloe vera gel and insulin-loaded nanoemulsions produced a synergistic effect that accelerated wound closure in diabetic rats, indicating that this technique holds promise for treating diabetic wounds.	High stability, spreadability, and permeation	[49]
Naringenin (NAR)	Nanoemulgel	The in vitro release kinetic behavior of NAR demonstrated a controlled and sustained release of up to $74.62\% \pm 4.54\%$ over the course of 24 h.	Enhanced mucoadhesive characteristics and prolonged absorption	[50]
Cumin essential oil	Nanoemulsions	The streptozotocin-induced diabetic rats treated with the essence of Cuminum cyminum L. and nettle nanoemulsions showed increased levels of insulin, decreased levels of glutathione (GSH), and increased oxidized levels of superoxide dismutase (SOD) and glutathione peroxidase (GPx). Additionally, the serum levels of cytokines and glucose were decreased.	Decreased inflammatory reactions and oxidative stress.	[51]
Quercetin	Nanoemulsions	In diabetic-induced rats, the quercetin nanoemulsions demonstrated enhanced therapeutic efficacy and bioavailability through the regulation of blood glucose levels, tissue injury markers, body weight, and lipid profiles, as well as the preservation of hepatocyte and pancreatic β cell structures.	Better oral bioavailability and prolonged release	[52]
<i>Turbinariaconoides</i>	Silver Nanoparticles (AgNPs)	The minimal inhibitory concentration of TCAgNPs showed remarkable antibacterial action against multidrug-resistant strains of DFUs, including <i>Pseudomonas aeruginosa</i> , <i>Enterococcus faecalis</i> , <i>Staphylococcus aureus</i> , and <i>Klebsiella pneumoniae</i> .	Increased antibacterial activity and prolonged release	[53]
Curcumin	Silk fibroin-based electrospun nanofibers	In comparison to traditional formulations, the in vivo studies employing nanofibers in streptozotocin-induced diabetes animals demonstrated a higher wound healing efficacy.	Increased antioxidant and anti-inflammatory properties, prolonged medication release, and tissue structure restoration.	[59]

Table 1. (Continued).

Bioactive compounds or Medicinal Plants	Nanoformulations	Inference	Advantage	Reference
Anemoside B4	Nanofibrous mats	The nanofiber mats improved wound closure rates, sped up excellent angiogenesis, and encouraged the deposition of collagen matrix and re-epithelization in diabetic rats during every stage of the healing process.	Exhibited multifunctional characteristics including prolonged release, biomimetic elastic mechanical characteristics, and notable absorption of water.	[60]
Resveratrol (RV)	liposome-in-hydrogel system	To enhance ulcer healing and wound closure on day nine, the RV-loaded liposomal gel dramatically lowered blood glucose and raised glycosaminoglycans (GAGs).	Increased collagen production, fibroblast growth, quicker re-epithelization, and decreased infiltration of inflammatory cells at the wound site.	[61]
Naringenin-Ferulic acid	Nanostructured lipid carriers	The combination of FA and NAR (ratio 8:2) exhibited reduced IC ₅₀ (13.49 µg) and synergistic antioxidant activity (CI < 1). Studies on the release of drugs in vitro revealed that NAR and FA from NLC were sustained at a rate 2.6 and 3.7 times, respectively, higher than that of pure drug suspension.	Enhanced swelling and penetration capabilities	[63]

**Figure 2.** Illustration of the therapeutic potential of nanoformulations of phytocompounds in diabetic foot ulcer.

3.4. Mechanistic of nanophytocompounds in wound healing in DFU

Nanophytocompounds have emerged as a potential treatment for chronic wound healing management. They are harmless, less toxic, and more cost-effective treatments in comparison to conventional therapies that may support wound healing by targeting various molecular signaling pathways such as extracellular signal-regulated kinase (ERK), nuclear factor erythroid 2–related factor 2 (Nrf2), nuclear factor kappa B (NF-κB), Smad, Jun N-terminal kinase (JNK), etc. [67,68]. In addition, they also maintain the expression of different growth factors such as insulin-like growth factor-1 (IGF-

1), vascular endothelial growth factor (VEGF), transforming growth factor- β (TGF- β) together with pro-inflammatory cytokines, and oxidative mediators like interleukin-1 (IL-1) IL-6, IL-8, tumor necrosis factor-alpha (TNF- α), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), etc. to advance wound healing [69,70]. Various studies suggest that phytochemicals like alkaloids, flavonoids, triterpenes, polyphenols, etc., showed numerous molecular processes such as antioxidant, reactive oxygen species (ROS), scavenging, anti-inflammatory and antibacterial responses that have an essential role to play in successful wound healing management [71]. The general practice for phytoconstituents towards wound healing is topical application, as they have low bioavailability at the wound site when given systemically or orally [72]. Therefore, significant attention has been given to the advancement of several phytocompounds-based topical nanoformulations as possible promising strategies for the chronic healing of wounds. They can enhance the pharmacokinetics, pharmacodynamics, and physicochemical properties of the phytochemicals, hence improving the therapeutic index of wound healing [73]. These topical nanoformulations thus give the advantage of administration of water-insoluble drugs, support them to pass the biological barriers, facilitate the administration of numerous drugs, support retention in the skin, help in the controlled release of drugs, and protection of the therapeutic drugs from degradation, hence enhancing the therapeutic efficacy of the phytochemicals [74,75]. According to previous studies, investigators have formulated numerous topical nanoformulations like foams, hydrogel, sponges, nanofibers, nanoparticles (NPs), liposomes, micelles, films, membranes, etc. for the sustained release of the various phytoconstituents at the wounded target area. For example, wound repair actions of curcumin are specifically related to its anti-inflammatory action that is triggered by the suppression of expressions of TNF- α , COX-2, IL-1b, IL-8, and IL-6. Curcumin suppresses signal transducer and activator of transcription (STAT), NF- κ B, and cyclin D1 signaling processes, together with inhibition of the MMP-8 and acute phase proteins expression. A previous study reported that transdermal patches of curcumin successfully enhance wound healing by exhibiting potential granulation tissue formation, re-epithelialization, and anti-inflammatory responses on full-thickness excisional wounds [76]. In a separate study, the biodegradable thermosensitive hydrogel encapsulated with curcumin exhibited enhanced wound healing through a similar mechanism [77].

3.5. Toxicological aspect of nanophytocompounds

The toxicological aspect of nanophytocompounds is an essential element to discuss while utilizing them in therapeutic applications to ensure safety and effectiveness. While nanotechnology increases the therapeutic effectiveness of phytocompounds, it also adds complications to their toxic effects. Understanding the relationship between nanophytocompounds and living systems is critical for reducing possible negative consequences such as immunogenicity, cytotoxicity, and organ toxicity [78]. A comprehensive understanding of physicochemical parameters, biodistribution, as well as long-term effects is needed to confirm the safety and biocompatibility of nanophytocompounds, therefore rationalizing their transformation into clinically effective treatments. In the context of acute toxicity, investigations

consistently show that nanophytocompounds provide a minimal risk [79]. For instance, *in vivo* models tested with curcumin nanoparticles at high concentrations showed no signs of acute toxicity. Similarly, studies regarding chronic exposure have yielded promising results, for example, such as resveratrol exhibiting no deleterious effects on hepatic and renal function over extended periods. Issues about genotoxicity have been highlighted, notably with specific nanophytochemicals such as nanoparticles encapsulated with quercetin. Despite this, advanced research is required to completely understand the underlying molecular mechanisms and establish any potential adverse effects [80,81]. In the same way, whereas limited research reveals that nanophytocompounds may modify immunological reactions, such as nanocurcumin has shown immunomodulatory effects with low toxic effects. Understanding the environmental impact of nanophytocompounds is similarly important. Research into their eco-toxicological effects on aquatic creatures indicates that reactions vary depending on the type of component and recommended dose [82]. Surface chemistry, particle size, and dosage all play an essential role in determining the toxic effects. Small-size nanoparticles may infiltrate cells more simply, posing a potential threat, while surface alterations can affect bioavailability as well as toxicity profiles [83]. Recent research shows that a very small number of investigations have focused on defining the hazardous threshold of various effective herbal wound healing formulations. Thus, evaluation of toxicity could be a primary factor for future advancement. Hence, in this context, extensive research will be required to emphasize the internalization of the nanoparticles, their specific location and immune response, and, most crucially, their release.

4. Discussion

Diabetes mellitus (DM) and its related issues are becoming increasingly common all over the world, so effective treatment strategies are critically needed. Diabetic foot ulcers can be effectively cured using both surgical as well as non-surgical procedures and conventional synthetic drugs. Although, there are significant disadvantages, including unfavorable adverse effects, high costs, and non-availability for most of the world's population. Consequently, the current research efforts are concentrated on investigating new sources of wound healing and antidiabetic therapies, particularly plant-based medicines. There is evidence that using nanophytocompounds to treat infections and DFU can have positive outcomes. Scientific research should be done to determine how plant extracts affect diabetic wounds to develop possible adjuvant drugs for wound care. Extensive clinical trial investigations involving both nondiabetic and diabetic patients are necessary to better understand the mechanism of action of nanophytocompounds or their components on related diseases. The depth and scope of employing nanophytocompounds to treat diabetic foot wounds are limited, but they still represent a promising possibility and might potentially promote the development of new wound-healing techniques. Furthermore, scientific research is imperative to elucidate and authenticate the exact molecular pathways of the investigated anti-diabetic phytochemicals pharmacological effects. Even though dietary plant compounds or extracts are usually reviewed as safe for consumption, potential antidiabetic phytochemicals should be evaluated for toxic effects to

formulate therapeutically efficacious and safe phytomedicines. A prospect in which furthermore diabetic patients depend on phytochemicals as an adjuvant therapy for treating diabetes-related complications is the one in which there is improvement of bioavailability and standardization of dose is attained, either for crude plant extracts or purified bioactive compounds. The goal is that, when used in conjunction with conventional therapy, phytochemicals will significantly reduce the difficulties associated with diabetes-related complications.

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