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Ferulic Acid-Based Nanoengineered Systems for Diabetic Foot Ulcer Healing: Current Advances and Future Perspectives

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Abstract: Diabetic foot ulcer (DFU) represents one of the most challenging complications associated with diabetes mellitus and remains a major cause of chronic non-healing wounds, infection, and lower-extremity amputation. The impaired healing process observed in diabetic wounds is primarily linked to persistent hyperglycemia, excessive oxidative stress, peripheral neuropathy, vascular insufficiency, reduced angiogenesis, and prolonged inflammatory responses. These pathological abnormalities collectively disrupt normal tissue repair and delay wound closure. Although several conventional treatment approaches are currently available, their therapeutic effectiveness is often limited by poor drug penetration, insufficient retention at the wound site, and the growing problem of antimicrobial resistance. In recent years, ferulic acid, a plant-derived phenolic bioactive compound, has attracted increasing scientific interest because of its potent antioxidant, anti- inflammatory, antimicrobial, and regenerative activities. Despite its promising therapeutic potential, the clinical application of ferulic acid remains restricted due to low aqueous solubility, limited bioavailability, and rapid degradation under physiological conditions. To overcome these limitations, nanoengineered delivery systems such as polymeric nanoparticles, hydrogels, nanofibers, and lipid-based nanocarriers have been extensively investigated for improving drug stability, sustained release behavior, and targeted wound delivery. Moreover, recent advances in smart wound dressings, wearable sensing devices, artificial intelligence-assisted monitoring systems, and telemedicine have considerably transformed the management of diabetic wounds. This review summarizes the underlying pathophysiology of diabetic foot ulcers and discusses the therapeutic relevance of ferulic acid, current developments in nanoengineered delivery systems, and emerging technological approaches for advanced diabetic wound care.

INDEX TERMS: Diabetic foot ulcer, Ferulic acid, Nanotechnology, Wound healing, Nanoengineered systems

1. INTRODUCTION

Diabetes mellitus is a rapidly increasing metabolic disorder that has become a major global health concern because of its association with multiple chronic complications. Among these complications, diabetic foot ulcer (DFU) remains one of the most severe and difficult-to-manage conditions due to delayed healing, recurrent infection, and a high probability of lower-extremity amputation [1,2]. Chronic hyperglycemia adversely affects the physiological wound-healing cascade by inducing vascular impairment, peripheral neuropathy, oxidative stress, and prolonged inflammatory responses, which collectively contribute to impaired tissue repair and chronic wound formation [3,4]. Under normal physiological conditions, wound healing proceeds through highly regulated and overlapping phases involving hemostasis, inflammation, proliferation, and tissue remodeling [5]. However, in diabetic patients, these phases become dysregulated because of excessive production of reactive oxygen species (ROS), endothelial dysfunction, reduced angiogenesis, and impaired immune responses [6,7]. Elevated oxidative stress damages cellular proteins, lipids, and extracellular matrix components, while persistent inflammation suppresses fibroblast proliferation, collagen deposition, and re-epithelialization, ultimately delaying wound closure [8]. Furthermore, diabetic wounds are highly susceptible to microbial infection and biofilm formation, which further complicate the healing process and reduce therapeutic effectiveness [9]. Although conventional therapeutic approaches such as debridement, antimicrobial therapy, pressure off-loading, and traditional wound dressings are widely employed in DFU management, their clinical outcomes are often unsatisfactory [10]. Poor drug penetration, inadequate retention at the wound site, limited bioavailability, and increasing antimicrobial resistance remain major limitations associated with conventional wound care strategies [11]. Consequently, the development of advanced and multifunctional therapeutic systems has gained substantial research attention in recent years.

Naturally derived bioactive compounds have emerged as promising candidates for chronic wound management because of their diverse pharmacological activities and favorable safety profiles. Among these compounds, ferulic acid (FA), a phenolic phytochemical abundantly present in cereals, fruits, vegetables, and medicinal plants, has shown remarkable therapeutic potential in diabetic wound healing [12,13]. Ferulic acid possesses potent antioxidant activity and effectively scavenges free radicals responsible for oxidative tissue damage. In addition, it exhibits anti-inflammatory, antimicrobial, angiogenic, and collagen-promoting properties that are highly beneficial for tissue regeneration and wound repair [14,15]. Despite these therapeutic advantages, the clinical application of ferulic acid is significantly restricted by poor aqueous solubility, rapid degradation, and low bioavailability [16]. To overcome these challenges, nanotechnology-based delivery systems such as nanoparticles, nanofibers, hydrogels, and lipid-based nanocarriers have been extensively explored for enhancing the stability, controlled release, and wound-targeting efficiency of ferulic acid [17,18]. These nanoengineered systems not only improve drug delivery and retention at the wound site but also create a favorable microenvironment that supports accelerated tissue regeneration and wound healing. Therefore, ferulic acid- loaded Nano formulations represent a promising strategy for advanced diabetic wound

management.

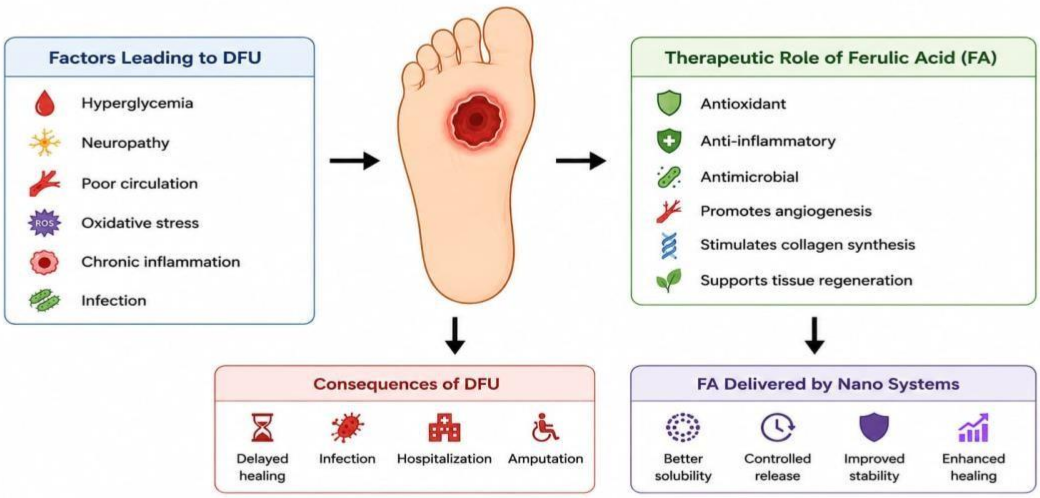

Figure 1. Overview of the major pathological factors involved in diabetic foot ulcer development and the

therapeutic role of ferulic acid-loaded nanoengineered systems in improving wound healing and tissue regeneration.

2. PATHOPHYSIOLOGY OF DIABETIC FOOT ULCER

Diabetic foot ulcer (DFU) is a complex and progressive complication of diabetes mellitus that develops due to the combined effects of metabolic imbalance, vascular impairment, neuropathy, and infection. Long-term hyperglycemia interferes with normal cellular activities involved in tissue repair and weakens the body's natural healing mechanisms, resulting in chronic non-healing wounds [19,20]. These alterations significantly increase the risk of tissue damage, infection, and lower-extremity complications in diabetic patients. Peripheral neuropathy is recognized as one of the major contributing factors in the initiation of diabetic foot ulcers [21,22]. Damage to sensory nerves reduces the patient's ability to detect pain, pressure, or thermal injury, allowing minor trauma to remain unnoticed for prolonged periods. Motor neuropathy can lead to structural deformities and abnormal pressure distribution in the foot, whereas autonomic neuropathy decreases sweat secretion, causing dry skin and fissure formation that facilitate microbial invasion [23]. Vascular dysfunction further worsens diabetic wound healing by reducing oxygen and nutrient supply to the affected tissues [24]. Impaired blood circulation limits angiogenesis and delays granulation tissue formation, thereby slowing the healing process. In addition, excessive generation of reactive oxygen species (ROS) creates oxidative stress, which damages fibroblasts, endothelial cells, and keratinocytes and interferes with collagen formation and extracellular matrix remodeling [25]. Chronic diabetic wounds also exhibit persistent inflammatory responses associated with increased levels of inflammatory cytokines, which prolong the inflammatory phase and prevent timely tissue repair [26].

Another important factor associated with DFU progression is microbial infection and biofilm formation. Because of compromised immune function and poor vascularization, diabetic wounds are highly susceptible to colonization by pathogenic microorganisms [27]. Biofilm-forming bacteria create a protective extracellular matrix that reduces antibiotic penetration and enhances bacterial survival, making infections more difficult to eradicate [28,29]. These interconnected pathological events collectively contribute to delayed wound healing and increase the likelihood of severe infection and amputation in diabetic patients.

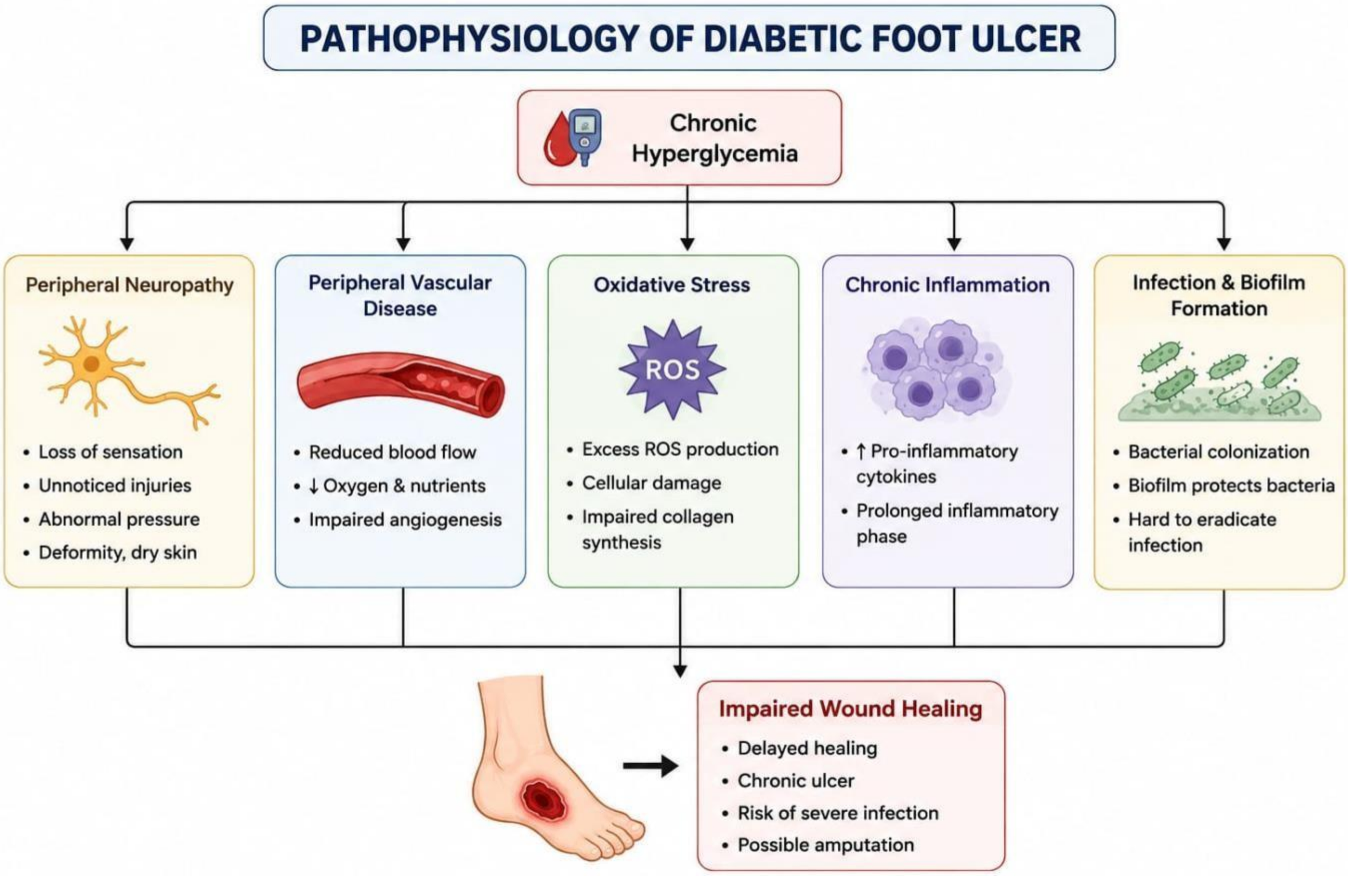

Figure 2. Pathophysiological factors involved in diabetic foot ulcer formation and impaired wound healing.

Table 1. Pathophysiological factors involved in Diabetic Foot Ulcer

Factor	**Effect on Wound Healing**
Hyperglycemia	Delays tissue repair
Neuropathy	Cause unnoticed injury
Vascular dysfunction	Reduces blood supply
Oxidative stress	Damages cell and collagen
Chronic inflammation	Prolongs healing phase
Infection	Increase tissue damage

3. Ferulic Acid in Diabetic Wound Healing

Ferulic acid is a naturally occurring phenolic compound belonging to the hydroxycinnamic acid family and is commonly found in cereals, fruits, vegetables, and various medicinal plants [30,31]. Owing to its diverse biological activities, ferulic acid has gained increasing attention as a promising therapeutic agent for chronic wound management, particularly in diabetic wound healing. One of the major therapeutic advantages of ferulic acid is its strong antioxidant potential. It effectively neutralizes reactive oxygen species (ROS) and minimizes oxidative damage at the wound site, thereby protecting cellular components and improving tissue repair processes [32,33]. By reducing oxidative stress, ferulic acid helps maintain cellular integrity and supports fibroblast proliferation and extracellular matrix formation. In addition, ferulic acid exhibits significant anti- inflammatory activity through the regulation of inflammatory mediators and inhibition of pathways associated with chronic inflammation, including NF-κB signaling [34,35]. Ferulic acid has also been reported to enhance angiogenesis and collagen deposition, both of which are essential for granulation tissue formation and wound closure [36]. Furthermore, its antimicrobial activity contributes to the reduction of microbial growth and biofilm formation in diabetic wounds, thereby improving the wound microenvironment and accelerating healing [37]. Despite its considerable therapeutic potential, the clinical application of ferulic acid remains limited because of its poor aqueous solubility, rapid degradation, and low bioavailability under physiological conditions [38]. Therefore, the development of advanced drug delivery systems has become essential for improving the stability, permeability, and sustained release behavior of ferulic acid in diabetic wound therapy.

4. Nanoengineered Systems for Ferulic Acid Delivery

The therapeutic application of ferulic acid in diabetic wound healing is often limited by poor aqueous solubility, instability, and rapid metabolism. To address these limitations, nanotechnology-based delivery systems have been extensively explored for improving drug stability, bioavailability, and localized therapeutic action at the wound site [39,40]. These advanced systems provide controlled drug release and enhance interaction between the therapeutic agent and damaged tissue, thereby supporting improved wound healing outcomes.

4.1 Polymeric Nanoparticles

Polymeric nanoparticles fabricated using biodegradable polymers such as chitosan and poly (lactic-co-glycolic acid) (PLGA) have shown promising potential in topical wound delivery. These nanosystems protect ferulic acid from degradation and maintain sustained drug release, which helps prolong therapeutic activity in diabetic wounds [41,42]. In addition, polymeric carriers improve tissue penetration and increase drug retention at the wound surface.

4.2 Hydrogel Systems

Hydrogels are hydrophilic polymeric networks capable of retaining a large amount of water and maintaining a moist wound environment favorable for tissue regeneration. Ferulic acid-loaded hydrogel systems have demonstrated improved wound hydration, enhanced cellular migration, and controlled release behavior, which collectively contribute to accelerated wound closure [43,44].

4.3 Electrospun Nanofibers

Electrospun nanofibers possess structural characteristics similar to the extracellular matrix and provide physical support for cell attachment and proliferation. Incorporation of ferulic acid into nanofibrous wound dressings has been associated with enhanced antimicrobial activity, collagen formation, and tissue regeneration in diabetic wound models [45,46].

4.4 Lipid-Based Nanocarriers

Lipid-based nanosystems including solid lipid nanoparticles and nanoemulsions have also been investigated for topical delivery of ferulic acid. These carriers improve drug solubility and permeability while facilitating sustained release and enhanced penetration into wound tissues [47,48]. Such systems may improve local therapeutic concentration and overall wound-healing efficiency. Overall, nanoengineered delivery platforms provide multiple advantages for diabetic wound therapy, including improved drug stability, prolonged release, enhanced wound retention, and better therapeutic effectiveness [49,50].

5. Smart and Advanced Approaches in DFU Management

Recent progress in biomedical engineering and digital healthcare has contributed significantly to the development of advanced strategies for diabetic foot ulcer management. Smart wound dressings capable of responding to changes in wound conditions such as pH, glucose level, temperature, and infection biomarkers have emerged as promising tools for chronic wound care [51,52]. Bioactive wound dressings containing antimicrobial agents, metallic nanoparticles, and naturally derived biomaterials help reduce microbial contamination and prevent biofilm formation within diabetic wounds [53,54]. Furthermore, regenerative approaches including stem cell therapy and growth factor-based systems have shown encouraging potential in promoting angiogenesis, collagen synthesis, and tissue remodeling [55,56]. Technological advancements such as wearable biosensors and artificial intelligence-assisted wound assessment systems have improved the monitoring of wound progression and infection status [57]. Telemedicine-based wound care has also gained attention because it enables remote monitoring and continuous clinical evaluation of diabetic patients, thereby improving healthcare accessibility and long-term wound management [58].

Table. 2 Nanoengineered systems for ferulic acid delivery in Diabetic Foot Ulcer

Delivery System	**Major Advantages**
Polymeric nanoparticles	Sustained drug release
Hydrogel	Maintain moist environment
Nanofibers	Mimics extracellular matrix
Lipid nanocarriers	Improved solubility
Smart dressings	Controlled therapeutic response

6. CONCLUSION

Diabetic foot ulcer is a serious complication of diabetes that continues to affect wound healing outcomes and patient quality of life. Multiple factors including oxidative stress, impaired blood circulation, neuropathy, persistent inflammation, and microbial infection contribute to delayed tissue repair in diabetic wounds. Although conventional therapies are commonly used in clinical practice, their effectiveness is often limited in chronic and non-healing ulcers.

Ferulic acid has gained increasing attention in recent years because of its ability to reduce oxidative damage, regulate inflammatory responses, and support tissue regeneration. These therapeutic properties make it a promising candidate for diabetic wound management. However, limitations such as poor solubility and low bioavailability restrict its direct clinical application.

The development of nanoengineered delivery systems has provided new possibilities for improving the therapeutic performance of ferulic acid. Nanoparticles, hydrogels, nanofibers, and lipid-based carriers can enhance drug stability, prolong release, and improve retention at the wound site, thereby supporting more effective healing. In addition, emerging technologies including smart wound dressings, biosensors, and digital monitoring systems are contributing to more advanced and personalized wound-care approaches.

Overall, ferulic acid-based nanoformulations represent a promising strategy for diabetic foot ulcer treatment. Further experimental and clinical studies may help translate these advanced systems into safer and more effective therapies for long-term diabetic wound management.

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