Journal of Pharmacognosy and Phytochemistry
Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
Impact Factor (RJIF): 6.35
www.phytojournal.com
JPP 2025; 14(6): 211-226
Received: 23-09-2025
Accepted: 28-10-2025

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Phytochemical-based therapeutics for diabetic foot ulcer management: Mechanistic insights and advances in wound healing strategies

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DOI: https://www.doi.org/10.22271/phyto.2025.v14.i6c.15660

Abstract
DFUs represent a complex and severe manifestation of diabetes, arising from various interlinked pathological factors, often resulting in chronic infections, tissue necrosis, and lower-limb amputations. The complex pathophysiology of DFUs marked by impaired angiogenesis, excessive oxidative stress, persistent inflammation, and peripheral neuropathy renders conventional treatment modalities largely insufficient. In this context, phytochemicals, naturally occurring bioactive compounds derived from plants, have emerged as promising therapeutic agents in wound management due to their multifaceted biological activities. These include antioxidant, anti-inflammatory, antimicrobial, and pro-angiogenic properties, which collectively contribute to enhanced tissue regeneration. This review delineates the integral roles of phytochemicals in modulating key phases of wound healing, such as cellular proliferation, extracellular matrix remodelling, neovascularization, and immunological balance. It further classifies and explores major phytochemical groups flavonoids, alkaloids, terpenoids, polyphenols, and tannins highlighting their underlying molecular mechanisms and relevance in preclinical and clinical settings. The special attention is given to recent advances in phytochemical-loaded delivery systems, including hydrogels, electro-spun nanofibers, and biomimetic scaffolds, which offer controlled and sustained therapeutic release. This review concludes by addressing current limitations and proposing future research directions, emphasizing the translational potential of phytochemicals in the development of integrative and effective strategies for diabetic wound care.

Keywords: Phytochemicals, diabetic foot ulcer, wound healing, anti-inflammatory, antioxidant, angiogenesis, nanocarriers, tissue regeneration, diabetic wound management

1. Introduction
Diabetic foot ulcers (DFUs) are skin lesions caused by mechanical stress and diabetic peripheral neuropathy [1, 2]. Up to 30% of diabetic patients develop DFUs, and 85% of lower limb amputations are preceded by ulceration [3, 4]. Management includes debridement, offloading, and infection control, though impaired blood flow limits systemic antibiotic efficacy [1-5]. Nearly 53% of DFUs harbor multidrug-resistant, biofilm-forming pathogens [6]. Plant-derived bioactive compounds like essential oils and alkaloids offer therapeutic potential [7, 8]. Neuropathy, PAD, foot deformities, and poor glycemic control are key risk factors [9-12]. DFU prevalence is higher in Europe/USA than Asia, partly due to dietary patterns [13, 14]. Wagner and University of Texas systems classify DFUs based on depth, infection, and ischemia [17-19]. Advanced treatments like NPWT and hyperbaric oxygen are effective but costly [20, 21]. Regular monitoring, proper footwear, debridement, and regenerative approaches like stem cell therapy enhance healing [22-25].

2. Pathophysiology of Diabetic Foot Ulcers
The pathophysiology of Diabetic Foot Ulcers comprises of metabolic causes, angiopathy, neuropathy, and immune system changes. The diabetic foot infections promoted by the interaction between diabetic neuropathy, diabetic angiopathy, diabetic immunopathy and metabolic dysfunction and ultimately leads to diabetic neuroarthropathy.

2.1 Metabolic dysfunction
In diabetes, compromised epineural microvasculature and chronic hyperglycemia trigger polyol pathway activation, PKC overactivity, and oxidative stress, leading to axonal damage and Schwann cell dysfunction [26-30]. Excess sorbitol accumulation, NADPH depletion, and

ROS generation disrupt ionic balance and antioxidant defenses, accelerating neuropathic degeneration [29-31]. Additionally, PKC-mediated vascular dysfunction, basement membrane thickening, and low-grade intraneural inflammation contribute to progressive diabetic neuropathy [32-39].

2.2 Diabetic immunopathy

Hyperglycemia elevates ROS production by inhibiting endothelial NO synthase, leading to peroxynitrite formation, lipid peroxidation, and microvascular complications such as atherosclerosis and thrombosis [40]. Excess hydrogen peroxide and AGEs amplify oxidative stress, impairing tissue function and repair [41, 42]. NO synthase decoupling further reduces NO availability, delaying wound healing in diabetic ulcers [43].

2.3 Diabetic neuropathy

Peripheral neuropathy, the most common diabetic complication, accounts for over 60% of DFUs and is strongly associated with glycated hemoglobin levels and diabetes duration [44-49]. Hyperglycemia-induced alterations in sodium (Nav1.3, Nav1.7) and potassium channel activity increase neuronal excitability, leading to sensory, motor, and autonomic dysfunction [50-55]. These changes cause foot deformities, dry skin, callus formation, and unnoticed injuries, collectively predisposing patients to ulceration [56-61].

2.4 Diabetic angiopathy

Hyperglycemia-induced endothelial dysfunction, dyslipidemia, and hypercoagulation drive atherosclerosis and PAD, contributing to ischemia and delayed wound healing in DFU patients [62-64]. Excess mitochondrial ROS production activates PKC and hexosamine pathways, promoting endothelial injury, platelet aggregation, and inflammation [65, 66]. Gliclazide offers vascular protection by reducing oxidative stress, inhibiting platelet aggregation, and downregulating VEGF expression, thereby mitigating diabetic vascular complications [67].

2.5 Diabetic foot infections

In diabetes, neuropathy, immune dysfunction, and poor circulation collectively increase susceptibility to infections, ischemic ulcers, and gangrene, often leading to amputation if untreated [68, 69]. Staphylococcus aureus, particularly MRSA, is the predominant pathogen in DFIs and is associated with prolonged hospitalization and higher amputation rates [70, 71]. Despite interventions, five-year survival after ulcer onset remains only 56%, underscoring the need for early diagnosis and prevention strategies [72, 73].

2.6 Neuroarthropathy

Charcot neuroarthropathy is a progressive diabetic complication marked by joint subluxation, bone resorption, and skeletal deformities due to neuropathy-induced microtrauma and autonomic hyperemia [69]. Proinflammatory cytokines (TNF-α, IL-1β) activate RANKL-NF-κB signaling, driving osteoclastogenesis and bone destruction while anti-inflammatory cytokines are downregulated. The resulting "rocker-bottom" deformity alters foot biomechanics, heightening the risk of recurrent ulceration and infection [74].

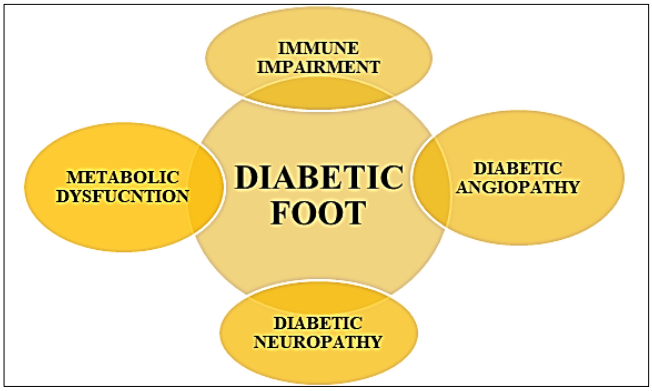

Fig 1: Diagram of pathophysiological factors in diabetic foot.

3. Phytochemicals - An overview

Natural products have been valued for centuries for their therapeutic efficacy, particularly in the treatment of infectious diseases. Sourced from plants, herbs, and other natural origins, these substances provide a rich array of bioactive compounds that can function as viable alternatives or adjuncts to conventional pharmaceuticals [75].

3.1 Eugenol

Eugenol, a phenolic compound from clove oil, exhibits potent antimicrobial, anti-inflammatory, antioxidant, and analgesic properties, making it valuable in managing MDR infections and chronic wounds [76, 82]. Its lipophilic nature disrupts microbial membranes, induces ROS generation, and inhibits key enzymes, leading to cell death, while synergizing with antibiotics [78, 82]. Eugenol-based formulations, including hydrogels and electrospun nanofibers, have shown significant antibiofilm, pro-angiogenic, and wound-healing effects in DFU models [83, 84]. Beyond infection control, eugenol improves insulin sensitivity, activates GLUT4-AMPK signaling, reduces hyperglycemia, and mitigates complications such as neuropathy, muscle dysfunction, and cardiomyopathy through antioxidant and anti-inflammatory mechanisms [90, 93]. Its dual COX-2/5-LOX inhibition and neuroprotective effects further underscore its potential as a natural therapeutic and adjunct in diabetes management [86-89].

3.2 Thymol

Thymol, a phenolic monoterpene from *Thymus vulgaris*, exhibits potent antimicrobial, anti-biofilm, antioxidant, and anti-inflammatory activities by disrupting microbial membranes, inhibiting NF-κB/MAPK signaling, and scavenging ROS [94-99, 105-107]. It synergizes with antibiotics, downregulates virulence and biofilm genes (e.g., PIA, eDNA), and enhances wound healing when formulated with nanocarriers like chitosan-ZnO [110, 111]. Preclinical and clinical studies show thymol improves glycemic control, reduces systemic inflammation, and protects organs in diabetes and

gastrointestinal disorders, underscoring its therapeutic potential [112-114].

3.3 Carvacrol
Carvacrol, a phenolic monoterpenoid from *Origanum vulgare* and *Thymus vulgaris*, exhibits potent antimicrobial, antioxidant, and anti-inflammatory effects by disrupting microbial membranes, downregulating COX-2/PGE2, modulating TRPM2 channels, and enhancing endogenous antioxidant defenses [115-122]. Nanoformulations like PCL nanoparticles and nanostructured lipid carriers (NLCs) improve its stability, dermal penetration, and sustained antimicrobial action, accelerating wound closure in diabetic models [123-127]. These findings position carvacrol as a promising candidate for advanced wound care and diabetes-related complication management.

3.4 Curcumin
Curcumin, the principal bioactive of *Curcuma longa*, exhibits potent antimicrobial, anti-inflammatory, and antioxidant activities by disrupting bacterial membranes, inhibiting NF-κB/COX-2/iNOS signaling, scavenging ROS, and promoting M2 macrophage polarization [128-136]. Advanced delivery systems including nanoparticles, nanofibrous scaffolds, phytosomes, and CNC films enhance its bioavailability, stability, and targeted release, accelerating wound closure and collagen deposition in diabetic foot ulcers [137-140]. Synergistic formulations combining curcumin with adjuvants or natural antimicrobials (e.g., oregano oil, chitosan) show superior infection control and re-epithelialization, positioning curcumin as a promising therapeutic for chronic wound care [141, 142].

3.5 Aloe Vera
Aloe vera, rich in polysaccharides (acemannan), anthraquinones (aloin, emodin), and glycoproteins, exhibits potent antimicrobial, anti-inflammatory, and wound-healing properties crucial for diabetic foot ulcer (DFU) management [143-146]. Its bioactives disrupt bacterial membranes, inhibit protein synthesis, suppress NF-κB and COX pathways, and promote fibroblast proliferation and collagen synthesis, thereby accelerating wound repair [147-150]. Advanced formulations, including methanolic extracts and nanoemulsion-based Aloe vera gels, have demonstrated strong antibacterial activity against MRSA, E. coli, and S. aureus, significantly enhancing wound closure in diabetic models [151-155].

3.6 Neem
Azadirachta indica (neem) contains bioactive compounds like nimbidin, nimbin, and azadirachtin that exhibit strong antimicrobial, anti-inflammatory, antioxidant, and wound-healing properties, making it effective in diabetic foot ulcer (DFU) management [156-158]. Neem disrupts bacterial membranes, inhibits biofilm formation, suppresses NF-κB activation, and reduces pro-inflammatory cytokines (TNF-α, IL-6), thereby controlling infection and enhancing tissue regeneration [159-161, 165]. Studies confirm neem extracts and oils show significant antibacterial activity against multidrug-resistant pathogens, including MRSA and Pseudomonas aeruginosa, while also improving glycemic control in diabetic models [162-166].

3.7 Resveratrol
Resveratrol, a polyphenolic stilbene found in grapes and berries, exhibits potent antioxidant, anti-inflammatory, and antimicrobial effects, making it valuable for managing diabetic foot ulcers (DFUs) [167-170]. It disrupts bacterial division (FtsZ inhibition), biofilm formation, and membrane integrity while modulating NF-κB, MAPK, and TLR-4 pathways to suppress cytokines (IL-6, TNF-α) and reduce oxidative stress [171-179]. Studies confirm resveratrol's ability to accelerate wound healing, inhibit bacterial and fungal growth, enhance insulin sensitivity, and mitigate diabetic complications, underscoring its therapeutic potential [180-183].

4. Mechanisms of Action of Phytochemicals in Wound Healing
4.1 Anti-inflammatory and immunomodulatory effects
Curcumin modulates NF-κB, PI3K/AKT, and MAPK pathways, suppressing TNF-α and IL-1β to resolve chronic inflammation and accelerate wound healing [184-186]. Curcumin-loaded chitosan nanoparticles and electrospun nanofibers enhance bioavailability, promote keratinocyte/fibroblast migration, upregulate VEGF, and restore redox balance by reducing ROS and boosting SOD/catalase activity [187, 188]. Meta-analyses confirm its role in angiogenesis, collagen synthesis, and accelerated closure in diabetic wounds [189]. Quercetin complements this effect by elevating IL-10, suppressing TNF-α/IL-1β, and promoting fibroblast proliferation, collagen deposition, and angiogenesis [190, 191]. Quercetin-4-formyl phenyl boronic acid further improves re-epithelialization and vascularization, showing enhanced efficacy in diabetic rat wound models [192].

Table 1: The synergistic benefits of nanotechnology and phytotherapy for diabetic wound healing

Feature	Chitosan-Curcumin Nanoparticles	Curcumin-PCL/PVA-Silk Nanofibers
Delivery System	Nanoparticles (injectable/topical)	Electrospun nanofiber scaffold
Mechanism	NF-κB inhibition, cytokine suppression	Anti-inflammatory & antioxidant
Key Advantages	Angiogenesis, cell migration	ECM mimicry, sustained release
Model	*In vitro* & diabetic rat	*In vitro* & diabetic rat
Outcome	Accelerated healing & inflammation resolution	Enhanced tissue regeneration & vascularization

4.2 Antioxidant mechanisms and ROS scavenging
Ferulic acid (FA) mitigates oxidative stress by scavenging ROS, inhibiting lipid peroxidation, and upregulating antioxidant enzymes (CAT, SOD, GSH), thereby preserving fibroblast viability and promoting collagen synthesis in diabetic wounds [193]. FA also enhances nitric oxide (NO) production, improving angiogenesis, fibroblast migration, and tissue perfusion for faster wound closure. Syringic acid complements this action by promoting keratinocyte/fibroblast migration, upregulating VEGF and TGF-β, and accelerating re-epithelialization and ECM deposition [194]. Fusion protein therapy synergistically downregulates IL-6, TNF-α, and COX-2 while upregulating VEGF, FGF-2, p-ERK, and p-Akt, driving angiogenesis and granulation tissue formation [195]. Chlorogenic acid (CGA) enhances collagen deposition (hydroxyproline content), reduces lipid peroxidation (MDA), and restores GSH levels, creating a pro-regenerative wound microenvironment [196].

Table 2: The therapeutic roles of ferulic acid (FA), syringic acid, and the fusion protein in diabetic wound healing

Therapeutic Agent	Mechanism of Action	Biological Effects	Reference
Ferulic Acid (FA)	Scavenges ROS; inhibits lipid peroxidation	Protects fibroblasts, preserves membrane integrity, and enhances tissue regeneration	[193]
	Prevents oxidative DNA and protein damage	Maintains cellular function and gene expression for wound repair	[193]
	Upregulates antioxidant enzymes (CAT, SOD, GSH)	Enhances intrinsic antioxidant defenses and cellular viability	[193]
	Increases nitric oxide (NO) production	Promotes vasodilation, angiogenesis, and collagen synthesis	[193]
	Enhances bioavailability of Zn and Cu	Supports keratinocyte/fibroblast activity and enzymatic antioxidant systems	[193]
Syringic Acid	Stimulates cell migration and proliferation	Facilitates re-epithelialization and granulation tissue formation	[194]
	Anti-inflammatory, upregulates VEGF and TGF-β	Promotes angiogenesis and tissue remodelling	[194]
Fusion Protein	Reduces IL-6, TNF-α, and COX-2 expression	Mitigates systemic and local inflammation	[195]
	Boosts SOD, GPx, and catalase activities	Decreases oxidative stress and preserves tissue	[195]
	Elevates VEGF, FGF-2, p-ERK, and p-Akt	Enhances neovascularization and ECM remodelling	[195]

4.3 Antimicrobial activity and biofilm inhibition

Phytochemicals, including phenolics, alkaloids, and terpenoids, exhibit potent antibiofilm activity by disrupting quorum sensing, inhibiting EPS production, and impairing efflux pumps, thereby enhancing antimicrobial efficacy [197, 198]. Their synergistic action with antibiotics improves drug bioavailability and penetration, offering a promising approach against antimicrobial resistance (AMR). Notably, rhein from rhubarb inhibits multidrug resistance transporters, boosting antibiotic activity up to 2000-fold [199].

Table 3: Phytochemicals with Antibiofilm and Antimicrobial Activities

Phytochemical	Classification	Plant Source	Mechanism of Action	Ref.
Gallic acid	Phenolic compound	Gallnuts, tea leaves	Disrupts membrane integrity, inhibits quorum sensing and EPS production	[197]
Carvacrol	Phenolic compound	Oregano, thyme	Inhibits efflux pumps, alters membrane permeability	[197]
Catechin	Flavonoid	Green tea	Reduces biofilm formation, scavenges ROS, inhibits quorum sensing	[197]
Coumarin	Phenolic compound	Tonka beans, cinnamon	Inhibits QS-regulated biofilm formation	[197]
Quercetin	Flavonoid	Onion, apples, berries	Interferes with biofilm EPS matrix, inhibits virulence gene expression	[197]
Eugenol	Phenolic compound	Clove oil	Disrupts cell membrane integrity, inhibits QS	[197]
Piperine	Alkaloid	Black pepper	Enhances antibiotic penetration, inhibits drug efflux pumps	[198]
Reserpine	Alkaloid	Rauwolfia serpentina	Inhibits multidrug resistance transporters	[198]
Sanguinarine	Alkaloid	Bloodroot	Binds to bacterial DNA, inhibits EPS and adhesion	[198]
Carnosic acid	Terpenoid	Rosemary	Antioxidant activity, membrane destabilization	[198]
Farnesol	Terpenoid	Essential oils (e.g., citronella)	Inhibits biofilm formation, targets membrane synthesis	[198]
Oleanolic acid	Terpenoid	Olive oil, medicinal herbs	Inhibits bacterial adhesion, enhances antibiotic activity	[198]
Rhein	Anthraquinone (phenolic-like)	Rhubarb	Inhibits multidrug resistance transporters, enhances antibiotic efficacy	[199]
Curcumin	Polyphenol	Turmeric	Inhibits biofilm formation, EPS matrix disruption, synergizes with antibiotics	[197]
Berberine	Isoquinoline alkaloid	Berberis spp.	Inhibits FtsZ protein in bacteria, blocks efflux pumps	[197]

4.3.1 Inhibition of extracellular polymeric substance synthesis

Extracellular polymeric substances (EPS) are vital for biofilm stability, and targeting their components polysaccharides, eDNA, and proteins can effectively disrupt biofilm architecture [200]. Phytochemicals such as luteolin inhibit EPS production in *E. coli* and *Enterobacter cloacae*, reducing biofilm mass. Similarly, quercetin downregulates rhl quorum-sensing genes in *Pseudomonas aeruginosa*, lowering extracellular polysaccharide synthesis and impairing biofilm maturation [201]. Elucidating these molecular mechanisms is crucial for developing EPS-targeted antibiofilm therapies.

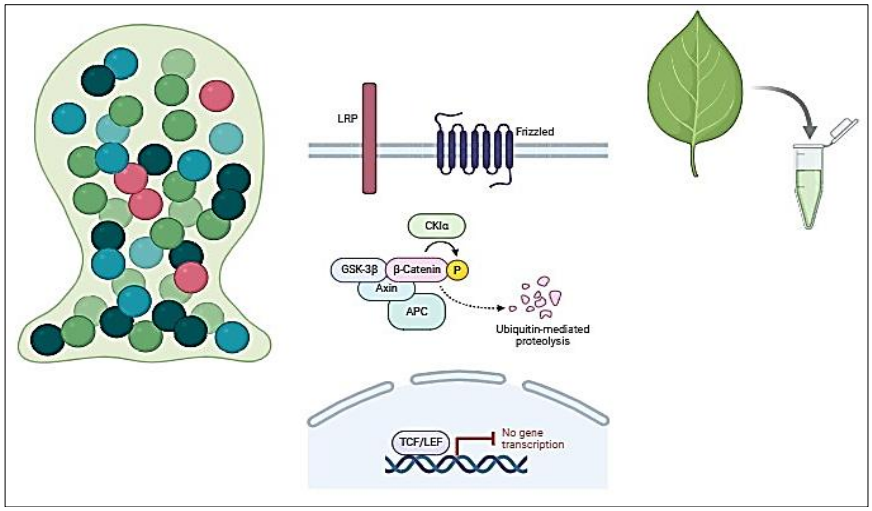

Fig 2: Phytochemical-Mediated Disruption in Bacterial Biofilms

4.3.2 Membrane disruption

Phytochemicals, including essential oils, phenolics, and terpenes, disrupt bacterial membranes by altering permeability, ion flux, and membrane potential, leading to ATP depletion, leakage of intracellular contents, and bacterial death [198, 203]. Their lipophilic nature enables penetration of biofilms, with terpenes causing depolarization and biofilm disintegration in *Shigella flexneri* and *Staphylococcus aureus* [204]. Phenolics like carvacrol further impair membrane integrity and energy metabolism, enhancing antimicrobial effects. Combined with antibiotics, these agents improve drug uptake and efficacy, offering a strategy to counter antimicrobial resistance [202].

4.3.3 Inhibition of quorum-sensing

Phytochemicals, including flavonoids (quercetin, naringenin), phenolics (cinnamaldehyde, eugenol), tannins (hamamelitannin), and terpenoids (thymol), inhibit quorum sensing (QS) by blocking AHL- and AIP-mediated signaling, thereby reducing virulence, adhesion, and biofilm formation [205-208]. Hamamelitannin enhanced vancomycin sensitivity in *Staphylococcus aureus* graft infection models, while thymol and ginseng saponins suppressed QS-regulated virulence factors in *Pseudomonas aeruginosa* and *Listeria monocytogenes* [206-208]. QS-targeting phytochemicals weaken biofilm integrity without promoting resistance. These compounds offer promising adjunct strategies for managing persistent and drug-resistant bacterial infections.

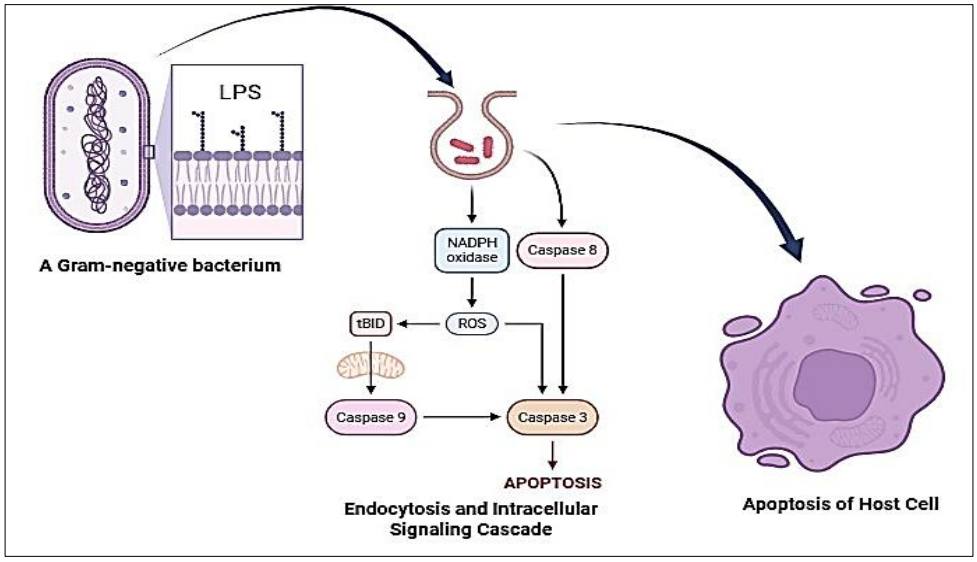

Fig 3: Quorum Sensing-Induced Endocytosis and Apoptotic Pathway in Host Cells

4.3.4 Efflux pump inhibition

Bacterial efflux pumps are key contributors to multidrug resistance (MDR) and biofilm-associated antimicrobial tolerance [202-208]. Phytochemicals, including geraniol, isoflavones, and coumarins, can inhibit efflux pump activity, downregulate associated genes (e.g., *acr*, *emr*, *mdt*), and disrupt biofilm formation, enhancing antibiotic efficacy [208, 209]. These compounds may interfere with ATPase activity and facilitate intracellular drug accumulation. By modulating efflux pumps and quorum sensing, phytochemicals restore antimicrobial susceptibility. This strategy highlights their potential as adjuncts in combating MDR bacterial infections.

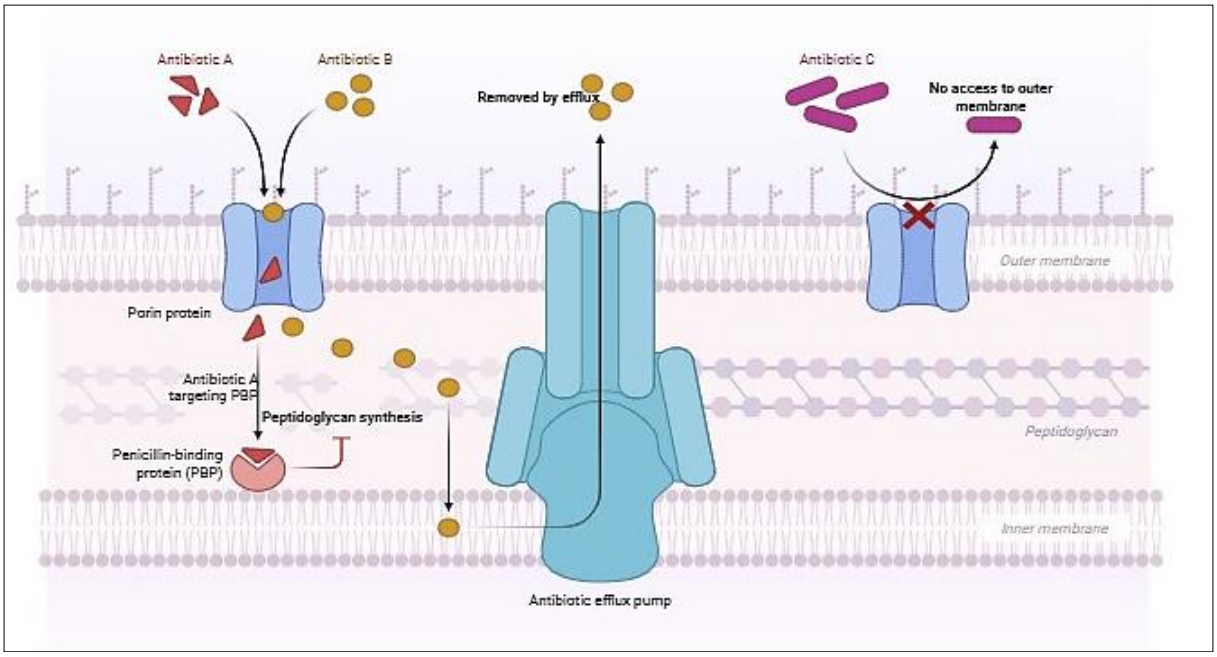

Fig 4: Intrinsic mechanism of antibiotic resistance in bacteria

4.3.5 Antibiotic potentiation

Phytochemicals can potentiate antibiotic efficacy against biofilm-associated and multidrug-resistant bacteria through mechanisms such as efflux pump inhibition, membrane disruption, and quorum-sensing interference [197-210]. Flavonoids (e.g., quercetin, daidzein) and phenolics (e.g., ellagic acid, thymol) enhance antibiotic penetration and disrupt biofilm integrity, improving therapeutic outcomes [197, 211]. Nanoparticle-based delivery systems further augment this synergism, offering a promising strategy for safe and effective biofilm-targeted treatments [211, 212].

5. Nanoscale drug delivery platform for wound repair

Nanoparticle-based drug delivery systems (NDDSs), defined by their nanoscale size, are specifically developed to improve drug stability, offer controlled and sustained drug release, and can be fabricated from a diverse range of biocompatible substances [213]. In recent years, a variety of NDDSs incorporating therapeutic compounds have demonstrated significant potential in managing diabetic wound healing. These systems are typically classified into several types, including liposomes, polymeric nanoparticles, inorganic nanoparticles, lipid-based carriers, nanofiber-based scaffolds, and nanohydrogel formulations.

5.1 Liposomes

Liposomes are biocompatible nanocarriers that encapsulate hydrophilic and lipophilic drugs, enabling targeted and sustained delivery with minimal systemic toxicity [214, 215]. Approved liposomal formulations, mainly in oncology, demonstrate enhanced efficacy and reduced adverse effects [216]. Next-generation liposomes with surface modifications, such as PEGylation or ligand conjugation, improve skin penetration and controlled release for chronic wound management [217]. Liposome-encapsulated bacteriophages have shown enhanced stability, reduced wound bioburden, and accelerated tissue regeneration in S. aureus-infected wounds [218]. Deformable liposomes, incorporating edge activators, overcome stratum corneum barriers, enabling deeper transdermal drug delivery [217, 220, 221].

Table 4: Liposome-based drug delivery systems

Aspect	Description	Advantages	Application Area	Ref. No.
Liposome Structure	Synthetic vesicles made of amphiphilic molecules forming bilayers	Mimics cell membrane, encapsulates hydrophilic/lipophilic drugs	General drug delivery	[214]
Biocompatibility	Liposomes are biodegradable and exhibit minimal toxicity	Safe for *in vivo* applications, site-specific delivery	Pharmaceutical nanocarriers	[215]
Approved Formulations	14 liposomal drugs approved for commercial use	Established clinical safety and efficacy	Mainly oncology	[216]
Surface Modifications	PEGylation, ligand conjugation, charge modulation to enhance functionality	Improved circulation time, targeting, penetration	Chronic wounds, cancer, infection	[217]
Phage-Loaded Liposomes	Liposomes used to encapsulate bacteriophages against infections	Improved phage stability, reduced wound bioburden, enhanced healing	Chronic wound infections (e.g., *S. aureus*)	[218]
Limitation of Conventional Form	Conventional liposomes limited by poor skin penetration	Drug delivery restricted to stratum corneum	Transdermal drug delivery	[219]
Deformable Liposomes	Liposomes with edge activators like surfactants or ethanol	Enhanced flexibility and skin penetration	Transdermal systems	[217]
Mechanism of Deformability	Edge activators destabilize lipid bilayers	Enables passage into deeper epidermal layers	Transdermal delivery of large molecules	[220]
Clinical Relevance	Liposomes enable targeted therapy with reduced systemic effects	Controlled release, reduced off-target effects	Clinical and commercial use	[215, 216]
Future Prospects	Advanced liposomal systems for antimicrobial therapy and chronic wound care	Overcoming resistance, improving drug efficacy	Wound healing, phage therapy, precision delivery	[217, 218]

5.2 Polymeric Nanoparticles

Polymeric nanoparticles offer biocompatible, controlled, and sustained drug delivery for wound healing, utilizing synthetic (PLGA) and natural polymers (alginate, chitosan, gelatin) [222-225]. Melatonin-loaded lecithin-chitosan NPs enhanced angiogenesis and re-epithelialization in diabetic wounds [226]. Ferulic acid-encapsulated PLGA NPs within hydrogels improved collagen synthesis and tissue regeneration, overcoming topical delivery limitations [227].

5.3 Inorganic Nanoparticles

Inorganic nanoparticles, including silver and zinc oxide, offer antimicrobial, angiogenic, and antioxidant benefits for diabetic wound healing [222]. Quercetin- and insulin-loaded AgNPs incorporated into hydrogels enhanced re-epithelialization, reduced inflammation, and promoted tissue regeneration [228, 229]. Multifunctional nanocomposite hydrogels co-encapsulating Ca-AlgNPs and AgNPs demonstrated superior wound closure and broad-spectrum antibacterial activity [229, 230].

5.4 Lipid Nanoparticles

Lipid nanoparticles (LNPs), including SLNs and NLCs, enhance the solubility, stability, and targeted delivery of therapeutic agents for diabetic wound healing [231, 232]. SLN-ATRA, pioglitazone-loaded COL-CS scaffolds, and protopanaxadiol-loaded NLCs have demonstrated improved wound contraction, collagen deposition, and angiogenesis in diabetic models [233-236]. Despite these benefits, LNPs face challenges such as limited drug loading and off-target accumulation in the liver and spleen [236].

Table 5: Lipid nanoparticles (LNPs) in wound healing applications

Formulation Type	Active Agent	Therapeutic Outcome	Reference
Lipid Nanoparticles (LNPs)	Various	Improve solubility and stability of therapeutic agents; enhance topical delivery efficiency	[231, 232]
Solid Lipid Nanoparticles (SLNs)	All-trans retinoic acid	Reduced leukocyte infiltration, enhanced wound contraction, improved collagen deposition, minimized scar formation	[233]
SLNs synthesized by hot melt homogenization	All-trans retinoic acid	High encapsulation efficiency, uniform particle size, solvent-free synthesis	[233]
Pioglitazone-loaded LNPs in COL-CS scaffold	Pioglitazone	Accelerated wound closure, reduced MMP-9 levels, prolonged drug release	[234]
Collagen/Chitosan (COL-CS) Scaffold	Pioglitazone	Optimal porosity and mechanical stability for diabetic wound healing	[234]
Nanostructured Lipid Carriers (NLCs)	20(S)-Protopanaxadiol	*In vitro* anti-inflammatory and proangiogenic properties	[235]
NLCs in silicone elastomer	20(S)-Protopanaxadiol	Suppressed inflammation, stimulated angiogenesis, promoted collagen deposition	[235]
SLNs and NLCs	Various	Enhance drug delivery and wound healing in diabetic wounds	[232-235]
LNP-integrated biocompatible scaffolds	Pioglitazone	Controlled degradation and sustained drug release suitable for chronic wounds	[234]
LNP-loaded silicone elastomer formulation	20(S)-Protopanaxadiol	Promoted tissue remodeling, enhanced perfusion, effective for chronic non-healing wounds	[235]
General LNP-based Systems	Various	Challenges: limited drug loading, off-target accumulation in liver and spleen	[231-235]

5.5 Nanofibers

Nanofibers fabricated via electrospinning offer high surface area, tunable porosity, and controlled drug release, making them ideal for diabetic wound healing applications [237-241]. Curcumin-, sesamol-, and insulin-loaded nanofibers have demonstrated accelerated wound closure, reduced inflammation, and enhanced angiogenesis in diabetic models [242-244]. Core-shell PLGA nanofibrous scaffolds delivering antibiotics and growth factors further improve vascularization and tissue regeneration, highlighting their therapeutic potential [245].

Table 6: Biomedical uses of Nanofiber Systems

Application Context	Material Used	Key Findings	Ref.
Advanced nanomaterial features	Nanofibers (<100 nm)	High surface area, tunable porosity, and ideal for biomedical adaptation	[237]
Versatile fabrication potential	Various nanofibers	Electrospinning enables diverse material selection and customizability	[238]
Multifunctional drug carriers	Electro-spun nanofibers	Enable loading of antibiotics, proteins, DNA, RNA, and growth factors	[239, 240]
Tunable release systems	Electrospun nanofibers	Exhibit high surface-to-volume ratio with various drug release profiles	[239, 241]
Diabetic wound healing via phytotherapeutics	Curcumin-loaded silk fibroin + PCL/PVA	Enhanced healing in diabetic mice, restored normal skin structure	[185, 242]
Antioxidant nanofiber platforms	Sesamol-loaded CA/Zein nanofibers	Activated TGF-β signaling, reduced pro-inflammatory cytokines, improved tissue repair	[243]
Regenerative combination therapy	CA/Zein + stem cells	Synergistic effect with stem cells for improved wound regeneration	[243]
Core-shell insulin delivery system	Insulin-loaded PLGA via coaxial electrospinning	Promoted diabetic wound healing through TGF-β modulation and superior scaffold hydration	[244]
Dual therapeutic nanoplatforms	PLGA nanofibers with dual-drug delivery	Versatility in delivering multiple agents for complex wound pathologies	[244]
Infection control and angiogenesis enhancement	PLGA nanofibers with vancomycin, gentamicin, PDGF	Sustained antibiotic and growth factor release; >3 weeks of therapeutic effect	[245]
Pro-angiogenic wound microenvironment	PLGA coaxial nanofibers	Induced angiogenesis via CD31 expression; reduced PTEN activity	[245]
Targeted diabetic wound therapies	Electro-spun nanofiber scaffolds	Customized for site-specific, sustained multi-drug delivery	[239-244]
NDDS integration in wound care	Nanofiber-based NDDS	Supports chronic wound healing via controlled and localized delivery	[240, 241]
ECM-mimetic scaffold systems	Electrospun nanofibers in wound healing	High biocompatibility and structural mimicry promote skin regeneration	[238, 242]
Multi-agent delivery for chronic wounds	Multifunctional nanofibers for diabetic wounds	Combines drug delivery, anti-inflammation, and pro-angiogenesis for robust healing	[243-245]

5.6 Nanohydrogels

Nanohydrogels composed of polymeric networks such as PVA, alginate, and hyaluronic acid provide a moist, mechanically stable environment that promotes tissue regeneration and angiogenesis in diabetic wounds [246-249]. Functionalized nanohydrogels incorporating exosomes, growth factors, or MnO_2 nanosheets enhance neovascularization, reduce oxidative stress, and support epithelial repair [250, 251]. Peptide-based self-assembling nanohydrogels enable sustained localized delivery, modulating TGF-β signaling and improving mitochondrial activity to accelerate wound healing [252].

6. Conclusion

Phytochemicals hold significant potential for treating diabetic foot ulcers (DFUs), addressing challenges such as impaired angiogenesis, extracellular matrix dysfunction, and infection. Despite advances in nanotechnology-enhanced wound healing, clinical application of phytochemicals is limited by insufficient mechanistic evidence and lack of standardized regulations. Comprehensive studies on bioactivity and herb-drug interactions are essential to ensure their safe and effective integration into DFU management.

Funding Declaration

This review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
The authors received no funding for this work.
The authors have no relevant financial disclosures.

Clinical trial number

not applicable.

Ethics, Consent to Participate, and Consent to Publish declarations

not applicable.

Author contribution declaration

Subhasini Kandasamy (S.K.): Conceptualization, literature review, manuscript drafting, and critical revisions.

Shanmugarathinam Alagarsamy (S.A.): Data curation, validation and final approval of the version to be published.

Competing Interests Declaration

The authors declare that they have no competing interests.

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