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Fucoidan-based nanoparticles for diabetic complications: mechanisms, therapeutic opportunities, and translational challenges

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ABSTRACT: Diabetes mellitus is a major chronic metabolic disorder that imposes a growing global health burden, largely because of its progressive microvascular and macrovascular complications. Persistent hyperglycemia promotes oxidative stress, chronic inflammation, endothelial dysfunction, fibrosis, and impaired tissue repair, while currently available therapies remain limited by incomplete target specificity and suboptimal tissue-level protection. Fucoidan, a sulfated polysaccharide derived from brown seaweed, has attracted increasing interest because of its antioxidant, anti-inflammatory, antifibrotic, and cytoprotective activities. However, the therapeutic performance of free fucoidan is often constrained by structural heterogeneity, variable bioavailability, and insufficient delivery to diseased tissues. This review examines the emerging role of fucoidan-based nanoparticles as a strategy to overcome these barriers and expand the translational relevance of fucoidan for diabetic complications. The discussion integrates current evidence on mechanistic pathways, complication-specific applications, formulation advantages, and translational bottlenecks. Overall, fucoidan-based nanoparticles appear capable of simultaneously modulating several core pathogenic drivers of diabetic complications, including oxidative stress, inflammatory signaling, vascular injury, extracellular matrix remodeling, apoptosis, and defective regeneration. Their strongest near-term potential appears to be in diabetic wound healing, although applications in diabetic nephropathy, retinopathy, neuropathy, and cardiovascular injury are also conceptually promising. Despite this promise, major challenges remain in source standardization, nanoformulation reproducibility, pharmacokinetic characterization, safety evaluation, and regulatory readiness. Fucoidan-based nanoparticles therefore represent a compelling but still preclinical therapeutic platform, and future progress will depend on more rigorous mechanistic studies, clinically relevant models, and translation-oriented formulation design.

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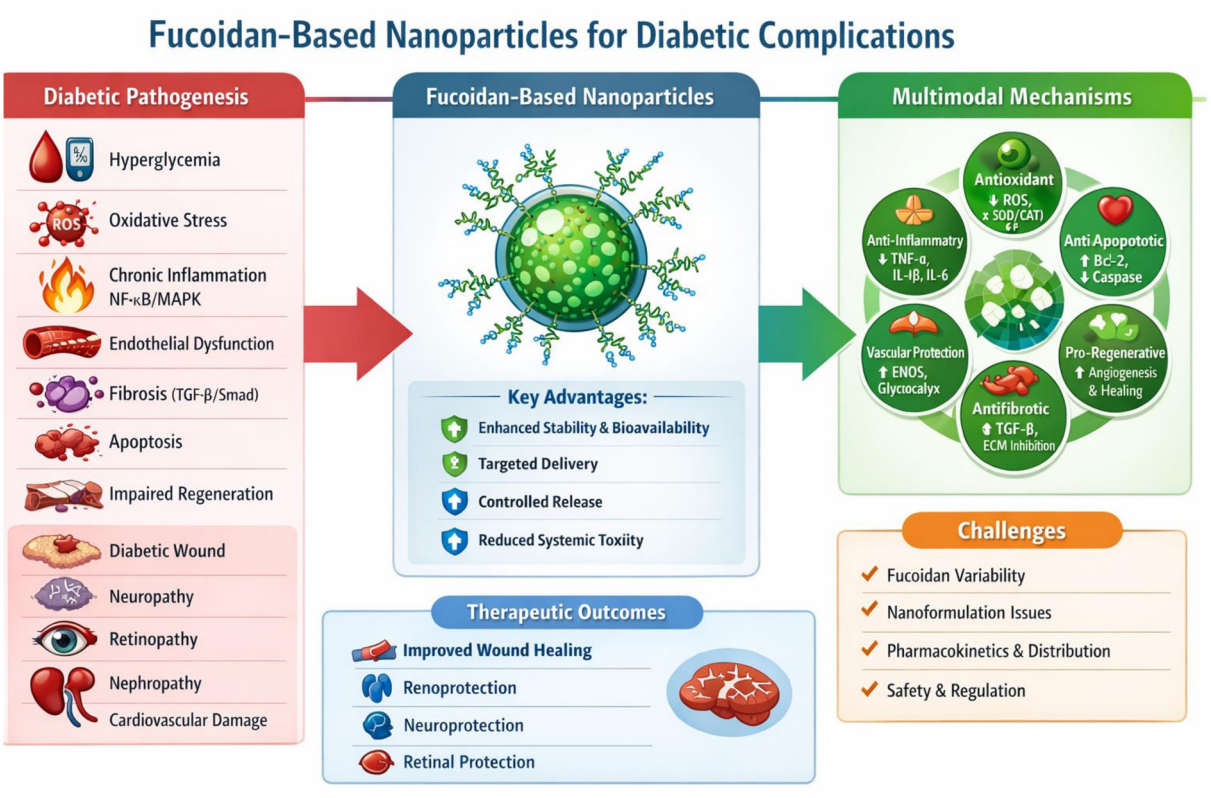
GRAPHICAL ABSTRACT



1. INTRODUCTION

Diabetes mellitus is among the most consequential chronic metabolic disorders in modern health systems because of its steadily rising prevalence and its profound impact on mortality, morbidity, disability, and healthcare expenditure. Beyond dysregulated glucose metabolism, diabetes is characterized by complex alterations in vascular homeostasis, immune responses, lipid metabolism, and tissue function, which together drive a broad spectrum of long-term complications. These complications, whether microvascular or macrovascular, are major determinants of reduced quality of life and premature death in patients with diabetes (Brownlee, 2001; Forbes and Cooper, 2013; International Diabetes Federation, 2025).

Microvascular complications such as diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy arise largely from persistent hyperglycemia, which promotes oxidative stress, advanced glycation end-product formation, protein kinase C activation, mitochondrial dysfunction, and chronic inflammatory signaling. In parallel, macrovascular complications including atherosclerosis, coronary artery disease, and peripheral vascular disease are aggravated by endothelial dysfunction, inflammatory activation, and pathological changes in the tissue microenvironment. Chronic diabetic wounds represent another highly complex manifestation in which impaired angiogenesis, microbial colonization, prolonged inflammation, neuropathy, and delayed tissue regeneration coexist (Brownlee, 2001; Forbes and Cooper, 2013).

Despite major advances in antidiabetic therapy, current treatment strategies still focus predominantly on glycemic control, reduction of cardiometabolic risk factors, and symptomatic management of established complications. Although these approaches can slow disease progression in some patients, they remain insufficient to prevent or reverse tissue damage once it has been established. Many currently used drugs are also limited by low tissue specificity, suboptimal bioavailability, repeated dosing requirements, systemic adverse effects, and a restricted capacity to target multiple pathogenic pathways simultaneously, particularly oxidative stress, inflammation, fibrosis, and apoptosis (Alicic et al., 2017; Feldman et al., 2019; Low Wang et al., 2016).

In recent years, marine-derived bioactive compounds have attracted increasing attention as sources of innovative therapeutics. One of the most promising candidates is fucoidan, a sulfated polysaccharide primarily isolated from brown seaweeds. Fucoidan possesses a complex structure composed mainly of L-fucose residues and sulfate groups, with marked compositional variation depending on the algal species, environmental conditions, and extraction method. Importantly, a growing body of evidence indicates that fucoidan exerts several biological activities relevant to the pathogenesis of diabetic complications, including antioxidant, anti-inflammatory, antidiabetic, antifibrotic, anticoagulant, angiogenic, and wound-healing effects. This multifunctional profile makes fucoidan an attractive candidate for development as a therapeutic agent in diabetic complications (Ale and Meyer, 2013; Fitton et al., 2019; Fitton, 2011).

Nevertheless, the therapeutic use of free fucoidan still faces several important obstacles. Variations in structure and molecular weight can lead to inconsistent biological effects, while limited stability, biological degradation, inefficient distribution, and poor tissue penetration reduce its translational potential. These limitations highlight the need for formulation strategies capable of improving fucoidan performance while preserving or enhancing its safety profile (Ale and Meyer, 2013; Fitton et al., 2019; Mabate et al., 2021).

Nanoparticle technology offers a promising solution to these challenges. Nanoparticle-based delivery systems can improve the stability of bioactive compounds, enhance bioavailability, enable controlled release, increase accumulation in target tissues, and reduce systemic toxicity. In the case of fucoidan, nanoparticle formulation may serve not only as a delivery system but also as a means to improve biological interactions, cellular internalization, and overall therapeutic efficacy. Fucoidan-based nanoparticles have therefore emerged as a compelling strategy for managing diabetic complications, which are mechanistically heterogeneous and clinically difficult to treat (Ezhilarasu et al., 2020; Shi et al., 2024).

To date, most published reviews on fucoidan have focused on its general biological activities or its broader relevance to metabolic disease, whereas discussion specifically linking fucoidan nanoformulations to diabetic complications remains relatively limited. Yet an integrated understanding of the relationship between fucoidan structure, nanoparticle design, molecular mechanisms, and therapeutic outcomes are essential to accelerate translation from basic research to clinical application.

Accordingly, this review examines the current progress of fucoidan-based nanoparticles as an emerging strategy for the management of diabetic complications. The discussion focuses on the pathophysiological basis of diabetic complications, the structural and biological characteristics of fucoidan, major nanoparticle platforms and formulation approaches, relevant mechanisms of action, available preclinical evidence, and key translational challenges and opportunities. By integrating these aspects, this review aims to provide a comprehensive conceptual framework for the future development of fucoidan-based nanoparticles as an innovative therapeutic platform in diabetic complication management.

2. METHODOLOGY OF THE REVIEW

This article was prepared as a narrative review with semi-systematic elements in order to achieve broad literature coverage while maintaining a focused synthesis. Literature retrieval was planned across major databases, including Scopus, PubMed, Web of Science, and ScienceDirect, using combinations of the following keywords: "fucoidan," "nanoparticle," "diabetes complications," "diabetic wound," "diabetic nephropathy," "diabetic retinopathy," "diabetic neuropathy," "oxidative stress," and "drug delivery." Priority was given to English-language publications, particularly those published within the last 10 years, that addressed fucoidan, nanoparticle-based delivery systems, and their relevance to the pathophysiology or treatment of diabetic complications (Page et al., 2021).

The inclusion criteria covered original research articles, reviews, and relevant preclinical studies aligned with the scope of this manuscript. Studies focusing on fucoidan without a meaningful connection to diabetic complications, nanoformulations without therapeutic relevance, or reports providing only very limited data were considered less suitable for inclusion in the main discussion. The selected literature was then synthesized thematically into several major domains: the pathogenesis of diabetic complications, fucoidan characteristics, nanoparticle development, mechanisms of action, applications in specific diabetic complications, and translational challenges. This approach enabled the identification of major trends, current knowledge gaps, and future research opportunities.

3. MECHANISTIC ROLES OF FUCOIDAN-BASED NANOPARTICLES IN DIABETIC COMPLICATIONS

The therapeutic potential of fucoidan-based nanoparticles in diabetic complications lies in their capacity to modulate several major pathogenic pathways simultaneously. Unlike

single-target agents, fucoidan nanoformulations offer a multimodal approach encompassing suppression of oxidative stress, regulation of inflammation, vascular protection, inhibition of fibrosis, attenuation of apoptosis, and stimulation of tissue regeneration. This profile is particularly relevant because diabetic complications develop through tightly interconnected molecular and cellular mechanisms.

3.1. Modulation of oxidative stress

Oxidative stress is a major driver of tissue injury in diabetic complications and represents one of the principal mechanisms linking chronic hyperglycemia to progressive cellular dysfunction (Figure 1). Under sustained hyperglycemic conditions, excessive mitochondrial electron transport, AGE formation, activation of the polyol pathway, protein kinase C signaling, and NADPH oxidase activity collectively increase the production of reactive oxygen species (ROS). When ROS generation exceeds endogenous antioxidant capacity, oxidative damage accumulates in the form of lipid peroxidation, protein oxidation, DNA injury, and mitochondrial dysfunction, thereby accelerating vascular, renal, neural, and wound-healing abnormalities associated with diabetes (Brownlee, 2001; Forbes and Cooper, 2013). This redox imbalance also amplifies inflammatory signaling, creating a self-reinforcing cycle between oxidative stress, inflammation, and tissue injury (Brownlee, 2001; Forbes and Cooper, 2013).

Fucoidan has attracted considerable interest as a marine sulfated polysaccharide with intrinsic antioxidant and cytoprotective properties. Available evidence suggests that fucoidan can reduce ROS accumulation, scavenge free radicals, and enhance endogenous antioxidant defence systems, partly through increasing the activity of key antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Wang et al., 2019, 2024). In diabetic settings, these effects may attenuate

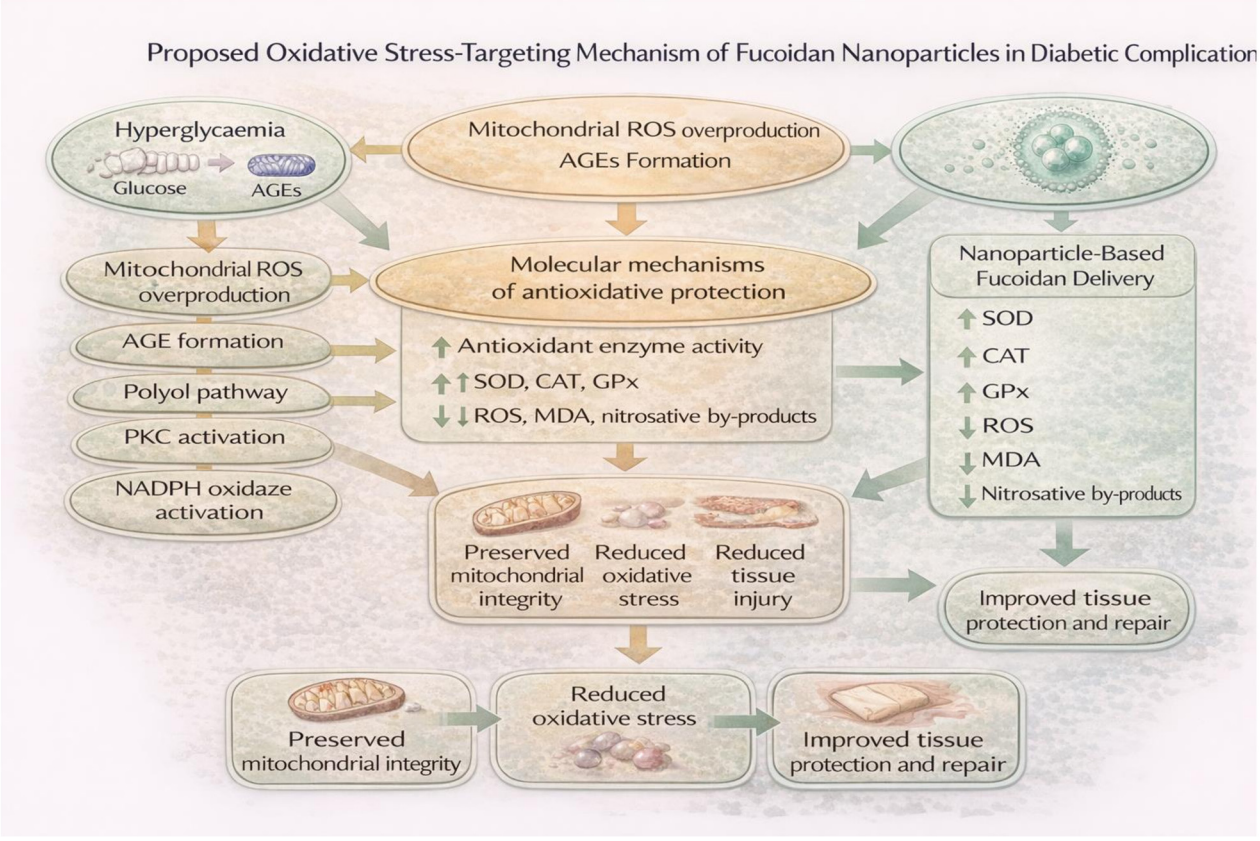


Figure 1. Proposed oxidative-stress-targeting mechanism of fucoidan nanoparticles in diabetic complications. Persistent hyperglycemia increases ROS generation through mitochondrial dysfunction, AGE formation, polyol-pathway activation, PKC signaling, and NADPH oxidase activity, leading to oxidative damage and tissue injury. Fucoidan nanoparticles may attenuate these effects by enhancing antioxidant defences (SOD, CAT, and GPx), reducing ROS and MDA levels, and preserving mitochondrial integrity, thereby supporting tissue protection and repair.

oxidative membrane damage and lower biochemical markers of oxidative injury, including malondialdehyde (MDA) and related reactive by-products. Fucoidan-based nanoformulations may further strengthen these benefits by improving physicochemical stability and supporting more sustained or localized delivery to injured tissues, thereby increasing therapeutic exposure at sites of oxidative damage (Augustine et al., 2020; Wang et al., 2024).

At the molecular level, fucoidan nanoparticles have been reported to increase antioxidant enzyme activity while reducing MDA in experimental diabetic complications, supporting the notion that they help rebalance redox homeostasis under chronic metabolic stress (Wardani et al., 2022). Additional experimental evidence also suggests that fucoidan nanoparticles may protect endothelial function in diabetic aortic tissue by modulating oxidative-stress-related injury pathways (Wardani et al., 2023). Although direct evidence on mitochondrial respiratory chain preservation in diabetic complications remains limited, the overall reduction in ROS burden may help preserve mitochondrial integrity and decrease secondary cellular damage. In this way, fucoidan nanoformulations may help interrupt the pathological cycle linking hyperglycemia, ROS overproduction, oxidative injury, and cellular dysfunction in diabetes (Brownlee, 2001; Forbes and Cooper, 2013; Wardani et al., 2022, 2023).

3.2. Regulation of inflammatory pathways

Low-grade chronic inflammation is now recognized as a unifying pathological feature of many diabetic complications, linking persistent metabolic disturbance to progressive structural and functional tissue injury. Under hyperglycemic conditions, excessive glucose flux promotes nonenzymatic glycation and the formation of advanced glycation end products (AGEs), while simultaneously increasing oxidative stress through ROS generation. These interrelated stimuli sustain inflammatory signaling by activating key transcriptional and kinase pathways, particularly nuclear factor-kappa B (NF-kappaB) and mitogen-activated protein kinase (MAPK) cascades, thereby amplifying the production of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta), and interleukin-6 (IL-6) (Brownlee, 2001; Forbes and Cooper, 2013). As illustrated in Figure 2, this chronic inflammatory state promotes immune-cell infiltration, tissue damage, vascular dysfunction, and defective repair processes, all of which contribute to the onset and progression of diabetic complications (Brownlee, 2001; Forbes and Cooper, 2013).

Fucoidan has emerged as a promising anti-inflammatory marine polysaccharide capable of interrupting several of these pathogenic events. Experimental and review evidence indicates that fucoidan can suppress the expression of major inflammatory mediators, including TNF-alpha, IL-1beta, IL-6, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS), while also attenuating upstream signaling through NF-kappaB-, MAPK-, ERK-, and related pathways (Apostolova et al., 2020; Fitton, 2011; Kim et al., 2010). In the context of diabetic complications, such effects may lessen inflammatory cell recruitment, limit secondary tissue injury, and improve the local milieu for repair (Apostolova et al., 2020; Wardani et al., 2022). Importantly, nanoparticle encapsulation may further enhance the therapeutic potential of fucoidan by improving formulation performance and supporting more sustained or targeted delivery at injured tissues, a principle that is widely exploited in nanotherapeutic approaches for chronic inflammatory wounds and other biomedical applications (Augustine et al., 2020). This delivery strategy may therefore strengthen the anti-inflammatory and tissue-protective actions of fucoidan, ultimately reducing chronic inflammation and creating a more favorable microenvironment for cellular recovery, vascular protection, and wound healing (Wardani et al., 2022; Wang et al., 2024).

3.3. Protection against endothelial dysfunction and vascular injury

Endothelial dysfunction is a defining pathological feature of both microvascular and macrovascular diabetic complications and serves as a key mechanistic link between chronic metabolic stress and progressive vascular injury (Brownlee, 2001; Low Wang et al., 2016; Zou et al., 2024). Under persistent hyperglycemic conditions, endothelial cells are exposed to excessive mitochondrial ROS, AGEs, protein kinase C (PKC activation, and low-grade inflammatory signaling, all of which disrupt vascular homeostasis and accelerate vascular damage (Brownlee, 2001; Zou et al., 2024). A central consequence of this disturbance is reduced nitric oxide (NO) bioavailability, caused by impaired endothelial nitric oxide synthase (eNOS) activity and increased oxidative inactivation of NO, which together compromise vasodilation and endothelial responsiveness (Du et al., 2001; Low Wang et al., 2016). In parallel, hyperglycemia promotes endothelial activation, enhances the expression of adhesion molecules, increases vascular permeability, and facilitates leukocyte recruitment, thereby intensifying vascular inflammation and microcirculatory dysfunction (Low Wang et al., 2016; Zou et al., 2024). These events collectively contribute to impaired tissue perfusion, capillary rarefaction, barrier disruption, and

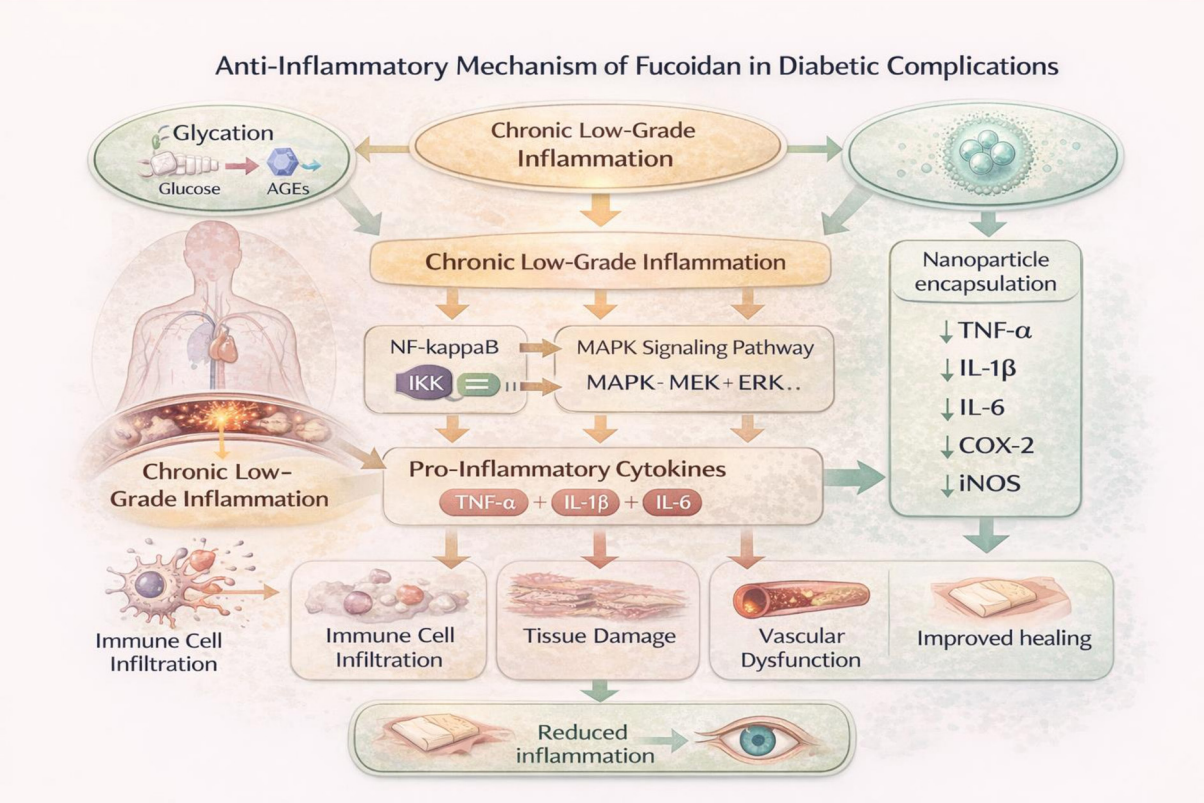


Figure 2. Proposed anti-inflammatory mechanism of fucoidan nanoparticles in diabetic complications. Persistent hyperglycemia promotes AGE formation and oxidative stress, which activate NF-kappaB and MAPK signaling and increase pro-inflammatory mediators such as TNF-alpha, IL-1beta, and IL-6. Fucoidan nanoparticles may suppress these inflammatory pathways and mediators, including COX-2 and iNOS, thereby reducing tissue injury and supporting tissue repair.

the progression of diabetic nephropathy, retinopathy, atherosclerosis, and chronic wound pathology (Brownlee, 2001; Low Wang et al., 2016).

As illustrated in Figure 3, fucoidan may protect the diabetic vasculature through several interconnected mechanisms. First, low-molecular-weight fucoidan has been reported to preserve the endothelial glycocalyx, a critical structure involved in barrier integrity, mechanotransduction, and leukocyte–endothelial interaction. In diabetic models, this effect has been linked to reduced glycocalyx shedding through targeting neuraminidase-2 (NEU2), thereby helping maintain endothelial barrier function (Li et al., 2024). Second, fucoidan exerts anti-inflammatory effects by suppressing NF-kappaB- and MAPK-associated signaling, which may reduce downstream mediators such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta), interleukin-6 (IL-6), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and endothelial adhesion molecules (Khadija et al., 2023; Li et al., 2024). Third, fucoidan may support restoration of eNOS/NO signaling and attenuate oxidative stress, thereby helping re-establish vasodilatory balance and limit endothelial injury (Li et al., 2024; Wardani et al., 2023). Together, these mechanisms are consistent with the scheme shown in the figure, in which fucoidan acts at the levels of glycocalyx preservation, inflammatory suppression, redox regulation, and NO signaling to improve endothelial function and reduce vascular inflammation.

Nanoparticle-based delivery may further enhance the vascular protective effects of fucoidan, particularly in tissues where perfusion is impaired and local drug exposure is difficult to sustain. In diabetic complications, such delivery systems may improve formulation stability and support more sustained local exposure at sites of endothelial injury, including the aorta and other vascular beds affected by diabetes. Experimental evidence from diabetic rat aortas indicates

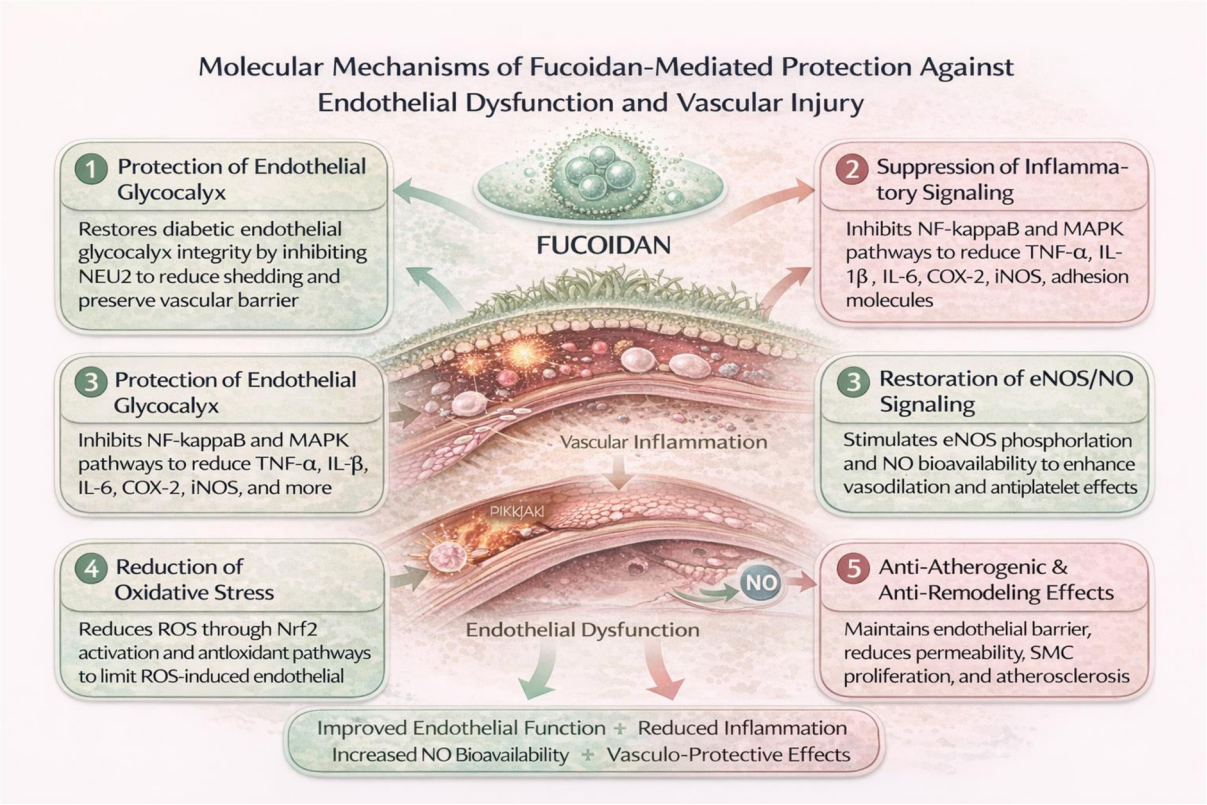


Figure 3. Proposed mechanisms of fucoidan-mediated protection against endothelial dysfunction and vascular injury in diabetic complications. Persistent hyperglyaemia disrupts endothelial homeostasis through oxidative stress, inflammation, glycocalyx injury, and reduced NO bioavailability, leading to vascular dysfunction and remodeling. Fucoidan nanoparticles may preserve the endothelial glycocalyx, suppress NF-kappaB- and MAPK-related inflammation, restore eNOS/NO signaling, and reduce oxidative stress, thereby improving endothelial function and providing vasculoprotective effects.

that fucoidan nanoparticles can reduce ROS and MDA while increasing SOD, GPx, nuclear factor erythroid 2-related factor 2 (Nrf2), eNOS, and NO, supporting a multi-target vasculoprotective mechanism (Wardani et al., 2023). At the tissue level, these effects may translate into reduced endothelial dysfunction, lower inflammatory burden, improved barrier function, and attenuation of vascular remodeling and atherogenic progression (Low Wang et al., 2016; Wardani et al., 2023; Zou et al., 2024).

3.4. Antifibrotic activity and extracellular matrix remodeling

Fibrosis represents a common end-stage pathway of chronic inflammation and tissue injury in diabetic complications, particularly in the kidney, heart, and vasculature. Under persistent hyperglycemic conditions, metabolic stress, oxidative stress, AGEs, and inflammatory signaling converge to activate profibrotic pathways that drive excessive extracellular matrix (ECM) deposition and progressive organ dysfunction. Among these pathways, transforming growth factor-beta (TGF-beta) is a central regulator of diabetic fibrogenesis, promoting Smad-dependent transcription of profibrotic genes, myofibroblast activation, and increased synthesis of collagen, fibronectin, and other ECM components. Connective tissue growth factor, inflammatory mediators, and redox imbalance further amplify this response, while disruption of matrix-degrading systems accelerates pathological ECM accumulation and tissue stiffening. As a result, diabetic tissues progressively undergo glomerulosclerosis, tubulointerstitial fibrosis, vascular remodeling, and structural loss of function (Alicic et al., 2017; Forbes and Cooper, 2013).

As illustrated in Figure 4, fucoidan may counter diabetic fibrogenesis through several complementary mechanisms.

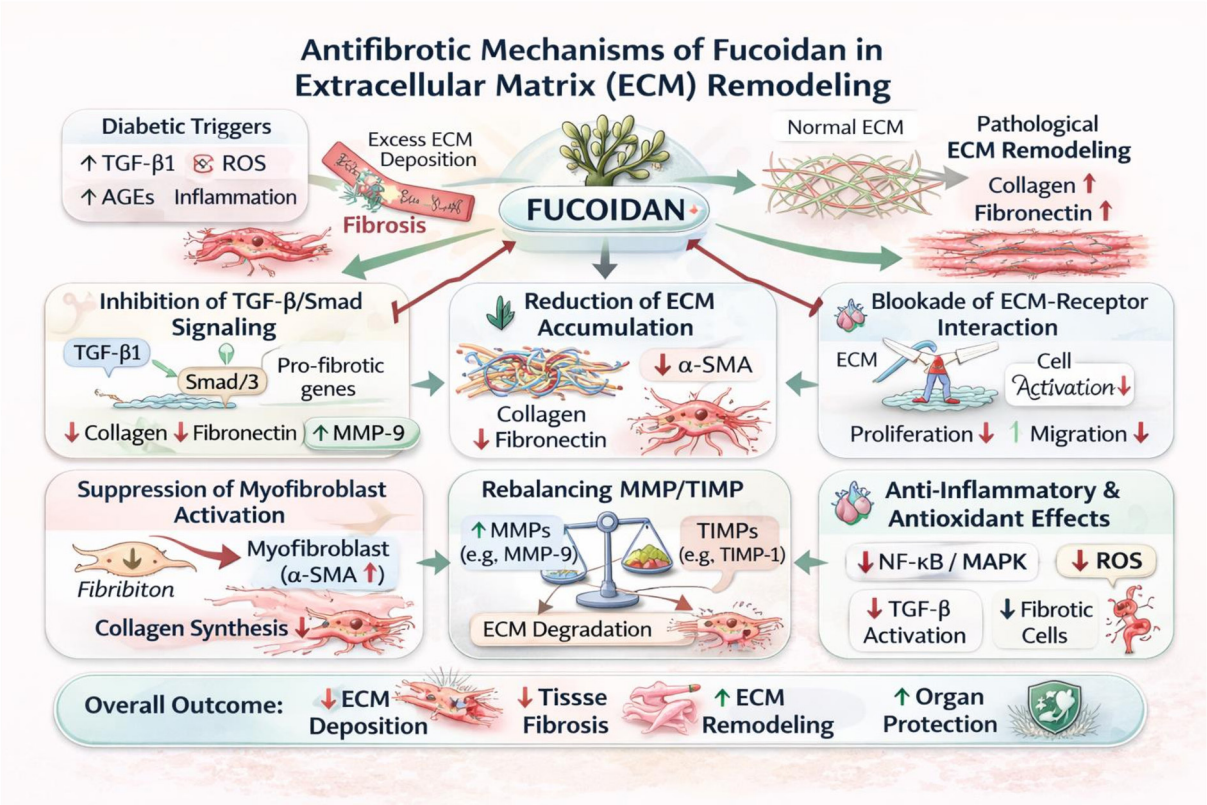


Figure 4. Proposed antifibrotic mechanisms of fucoidan in extracellular matrix remodeling during diabetic complications. Persistent diabetic stress promotes ECM accumulation and fibrosis through TGF-beta, ROS, AGEs, and chronic inflammation. Fucoidan may inhibit TGF-beta/Smad signaling, suppress myofibroblast activation, reduce collagen and fibronectin deposition, and rebalance MMP/TIMP-mediated matrix turnover, thereby limiting fibrosis and preserving organ function.

First, fucoidan has been reported to suppress the TGF-beta/Smad axis, thereby reducing the expression of profibrotic mediators and limiting the transcriptional program that drives collagen and fibronectin production. Second, fucoidan may attenuate myofibroblast activation, reflected by reduced alpha-smooth muscle actin (alpha-SMA), and decrease the accumulation of ECM proteins in injured tissues. Third, fucoidan may modulate ECM turnover by rebalancing matrix metalloproteinases and their tissue inhibitors, particularly by increasing MMP-9 activity and reducing TIMP-associated matrix retention, thus favoring ECM degradation over pathological deposition. These effects are consistent with the scheme shown in the figure, in which fucoidan inhibits TGF-beta/Smad signaling, suppresses myofibroblast activation, reduces ECM-receptor interaction, and promotes a more physiological ECM remodeling response (Wang et al., 2020; Xu et al., 2016; Yu et al., 2011).

Evidence from diabetic nephropathy models is particularly relevant because renal fibrosis is a major determinant of progressive loss of kidney function in diabetes. In streptozotocin-induced diabetic models, low-molecular-weight fucoidan has been shown to reduce TGF-beta-mediated renal fibrosis and improve inflammatory injury, while in human renal mesangial cells, fucoidan was reported to bind fibronectin and inhibit ECM–receptor interaction, thereby reducing pathological matrix signaling. These findings support the view that antifibrotic activity is one of the most promising therapeutic attributes of fucoidan in diabetic complications. Nanoparticle-based delivery may further strengthen these benefits by improving formulation stability and sustaining local tissue exposure, which may be especially valuable in organs highly susceptible to fibrosis, such as the kidney and vasculature. Accordingly, fucoidan nanoformulations may offer a broader therapeutic advantage than strategies focused solely on glycemic control, because they target downstream structural remodeling that directly contributes to irreversible organ damage (Wang et al., 2020; Xu et al., 2016).

3.5. Antiapoptotic and cytoprotective effects

Apoptosis contributes substantially to the progressive loss of functional cells across multiple diabetic complications, including podocytes in diabetic kidney disease, peripheral neurons in diabetic neuropathy, retinal ganglion and vascular cells in diabetic retinopathy, fibroblasts in chronic wounds, and endothelial cells in diabetes-associated vascular injury. Under persistent hyperglycemic conditions, apoptosis is driven by a combination of oxidative stress, mitochondrial dysfunction, intracellular calcium dysregulation, inflammatory signaling, and activation of the intrinsic caspase cascade. Excess ROS production disrupts mitochondrial membrane integrity, promotes cytochrome c release, and activates caspase-9 and caspase-3, thereby shifting the balance toward pro-apoptotic signaling and cellular loss. In parallel, chronic inflammation further amplifies apoptotic injury through mediators such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta), and stress-responsive kinase pathways, ultimately contributing to structural and functional deterioration of diabetic tissues (Brownlee, 2001; Feldman et al., 2019; Madsen-Bouterse and Kowluru, 2008; Zou et al., 2024).

As illustrated in Figure 5, fucoidan may counter diabetes-associated apoptosis through several complementary cytoprotective mechanisms. First, fucoidan may suppress the mitochondrial apoptotic pathway by increasing the Bcl-2/Bax ratio, reducing cytochrome c release, and limiting downstream caspase-9 and caspase-3 activation. Second, fucoidan may attenuate oxidative stress by reducing ROS accumulation and enhancing endogenous antioxidant defence, particularly through activation of the Nrf2/HO-1 axis and related redox-protective pathways. Third, fucoidan may stabilize cell survival signaling, including phosphoinositide 3-kinase/protein kinase B (PI3K/Akt)-associated pathways, thereby helping preserve mitochondrial function and improve resistance to metabolic injury. Fourth, fucoidan

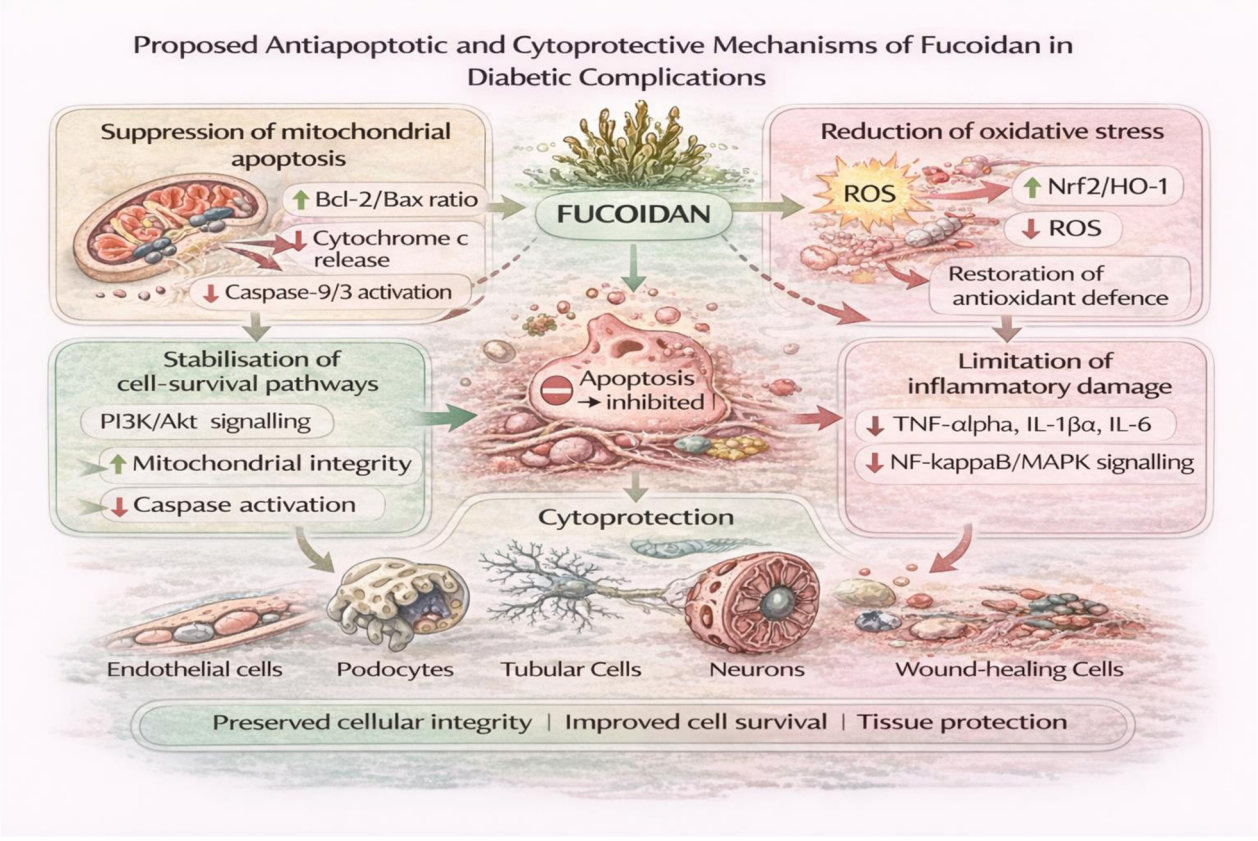


Figure 5. Proposed antiapoptotic and cytoprotective mechanisms of fucoidan in diabetic complications. Persistent hyperglyaemia induces oxidative stress, inflammation, mitochondrial dysfunction, and apoptotic signaling, leading to cellular injury. Fucoidan may suppress mitochondrial apoptosis, reduce ROS, enhance Nrf2/HO-1 antioxidant defence, stabilize PI3K/Akt survival signaling, and downregulate NF-kappaB, MAPK, and pro-inflammatory cytokines, thereby preserving cellular integrity and promoting tissue protection.

may limit apoptosis indirectly by suppressing NF-kappaB- and MAPK-related inflammatory signaling and reducing pro-inflammatory mediators such as TNF-alpha and IL-1beta. Collectively, these mechanisms are consistent with the figure, in which fucoidan acts by suppressing mitochondrial apoptosis, reducing oxidative stress, stabilizing survival pathways, and limiting inflammatory damage to promote overall cytoprotection (Wang et al., 2019; Wardani et al., 2023; Yu et al., 2020).

These cytoprotective effects are particularly relevant in tissues that are highly vulnerable to diabetes-induced cell loss. Preservation of podocytes may help slow glomerular barrier disruption and albuminuria, protection of endothelial cells may reduce vascular dysfunction, and survival of neurons and retinal cells may help delay neurovascular degeneration. In chronic wounds, suppression of apoptosis in fibroblasts and endothelial-associated repair cells may also improve the regenerative microenvironment and support more effective healing. Although the precise antiapoptotic contribution of fucoidan nanoparticles remains to be fully defined in every diabetic tissue, current evidence supports the concept that nanoformulation may strengthen fucoidan bioactivity by improving formulation stability and sustaining tissue exposure, thereby enhancing its antioxidant, anti-inflammatory, and cytoprotective effects in diabetes-associated injury (Feldman et al., 2019; Wardani et al., 2023; Yu et al., 2020).

3.6. Promotion of angiogenesis and tissue regeneration

Restoring impaired tissue regeneration is a major therapeutic objective in diabetic complications, particularly in chronic diabetic wounds. Diabetes disrupts the coordinated progression of healing by sustaining inflammation, impairing angiogenesis, reducing fibroblast proliferation, delaying keratinocyte migration, and promoting disorganized ECM deposition, which together compromise granulation tissue formation, re-epithelialization, and collagen remodeling. These abnormalities are further aggravated by oxidative stress, endothelial dysfunction, and defective cellular crosstalk within the wound microenvironment, thereby favoring chronic non-healing lesions rather than functional tissue restoration) (Figure 6).

Fucoidan has emerged as a promising regenerative marine polysaccharide because it can interact with heparin-binding growth factors, modulate inflammatory and redox pathways, and influence angiogenic and matrix-remodeling processes. Experimental studies indicate that fucoidan can promote wound closure, enhance granulation tissue formation, improve collagen deposition, and stimulate angiogenesis, partly through pro-survival and pro-angiogenic signaling pathways relevant to endothelial repair (Mafra et al., 2024; Wen et al., 2023). These properties are highly relevant in diabetic wound healing, where successful regeneration depends on restoring controlled vascularization and more physiological ECM organization.

Nanoparticle- and hydrogel-based delivery systems may further enhance these effects by improving fucoidan stability, prolonging local retention, and enabling sustained release within the wound bed. This is particularly important in diabetic tissues, where poor perfusion and chronic inflammation can reduce the effectiveness of freely delivered agents. Fucoidan-containing biomaterial platforms, including hydrogels and nanostructured dressings, have shown promise in supporting fibroblast activity, collagen organization, and tissue reconstruction, thereby facilitating the transition of chronic wounds from the inflammatory phase to the proliferative and remodeling phases (Augustine et al., 2020; Ezhilarasu et al., 2020).

Although wound healing is currently the best-supported regenerative application, the tissue-restorative properties of fucoidan may also be relevant to other diabetes-vulnerable tissues. Because fucoidan can influence angiogenesis, inflammation, oxidative injury, and cell survival, it may plausibly support repair in vascular tissues and, more cautiously, in retinal and peripheral neural compartments; however, the evidence remains strongest for wound-related and biomaterial-assisted healing applications.

3.7. Mechanistic integration in diabetic complications

Taken together, fucoidan-based nanoparticles can be viewed as a therapeutic platform operating at the intersection of several core mechanisms of diabetic complications. Suppression of oxidative stress limits early cellular and tissue injury. Inflammatory control helps arrest the progression of chronic damage. Endothelial protection and antifibrotic effects preserve organ structure, while antiapoptotic and pro-regenerative actions support functional recovery. This mechanistic breadth largely explains why fucoidan nanoformulations are increasingly considered promising candidates for translation in heterogeneous and progressive diabetic complications.

4. POTENTIAL APPLICATIONS IN SPECIFIC DIABETIC COMPLICATIONS

The clinical relevance of fucoidan-based nanoparticles should be considered in a complication-specific manner because each diabetic complication presents distinct

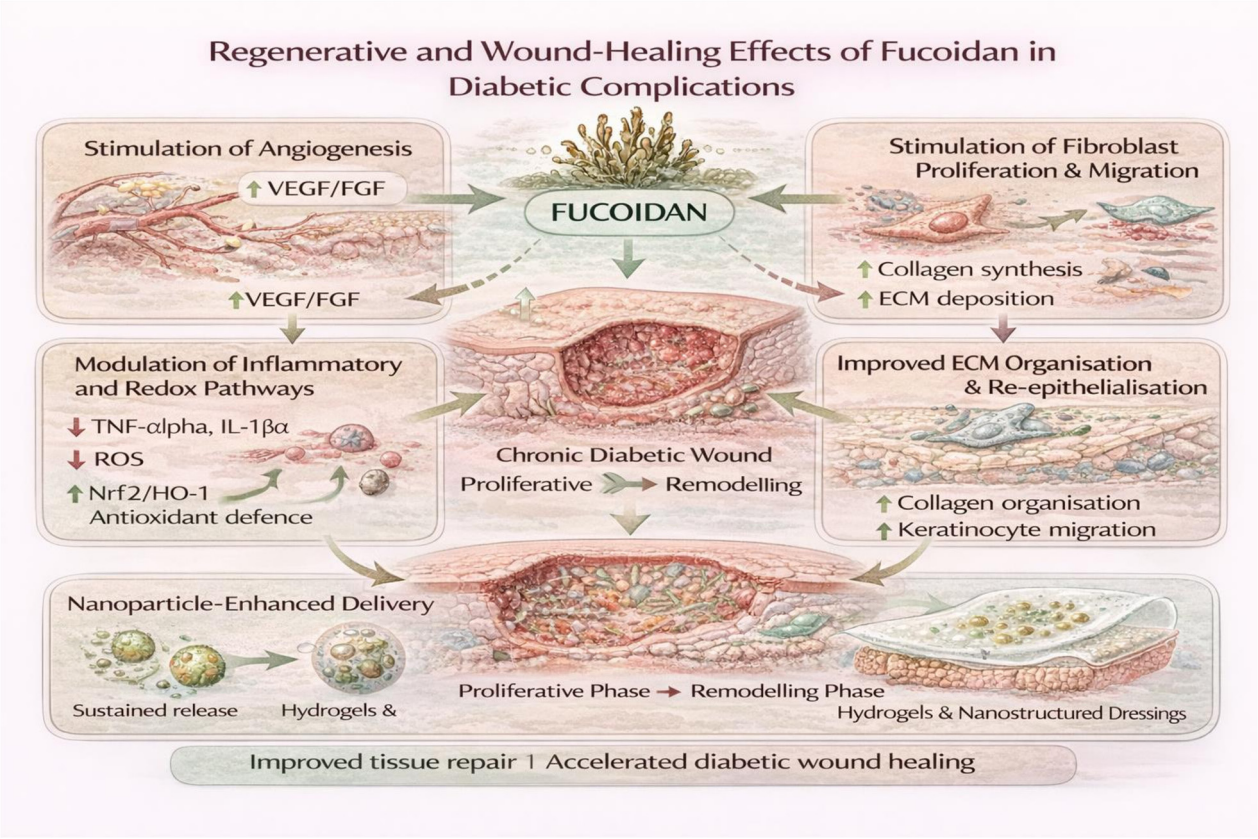


Figure 6. Proposed regenerative and wound-healing mechanisms of fucoidan in diabetic complications. Diabetic conditions impair tissue repair through inflammation, oxidative stress, defective angiogenesis, reduced fibroblast activity, impaired keratinocyte migration, and disordered ECM remodeling. Fucoidan may promote angiogenesis, enhance fibroblast proliferation and collagen synthesis, improve re-epithelialization, and reduce oxidative and inflammatory stress, thereby supporting tissue repair and wound healing.

pathological features, biological targets, and formulation requirements. Although several pathogenic pathways overlap, the tissue microenvironment of wounds, kidneys, retina, peripheral nerves, and the cardiovascular system requires tailored delivery strategies (Figure 7).

4.1. Diabetic wound healing

Diabetic wounds are among the most suitable indications for fucoidan-based nanoparticle therapy because impaired wound repair in diabetes involves nearly all of the pathways that fucoidan can modulate. Excessive oxidative stress, persistent inflammation, defective angiogenesis, secondary infection, fibroblast dysfunction, and peripheral neuropathy collectively prevent diabetic wounds from entering the proliferative phase in a timely and coordinated manner (Armstrong et al., 2017; Ezhilarasu et al., 2020; Shi et al., 2024).

In this setting, fucoidan-based nanoparticles may be applied topically as nanosuspensions, hydrogels, nanofibers, wound dressings, or scaffold-integrated systems. The main advantages of nanoformulation for diabetic wounds include improved local retention, protection of fucoidan from degradation, and sustained release at the wound site. Biologically, fucoidan nanoformulations may reduce inflammatory mediators, lower oxidative burden, support fibroblast and keratinocyte migration, enhance angiogenesis, and improve collagen deposition. Fucoidan may also be combined with antimicrobial agents, growth factors, or other bioactive polymers to create more effective multimodal wound therapies.

4.2. Diabetic nephropathy

Diabetic nephropathy develops through interactions among hyperglycemia, oxidative stress, inflammation,

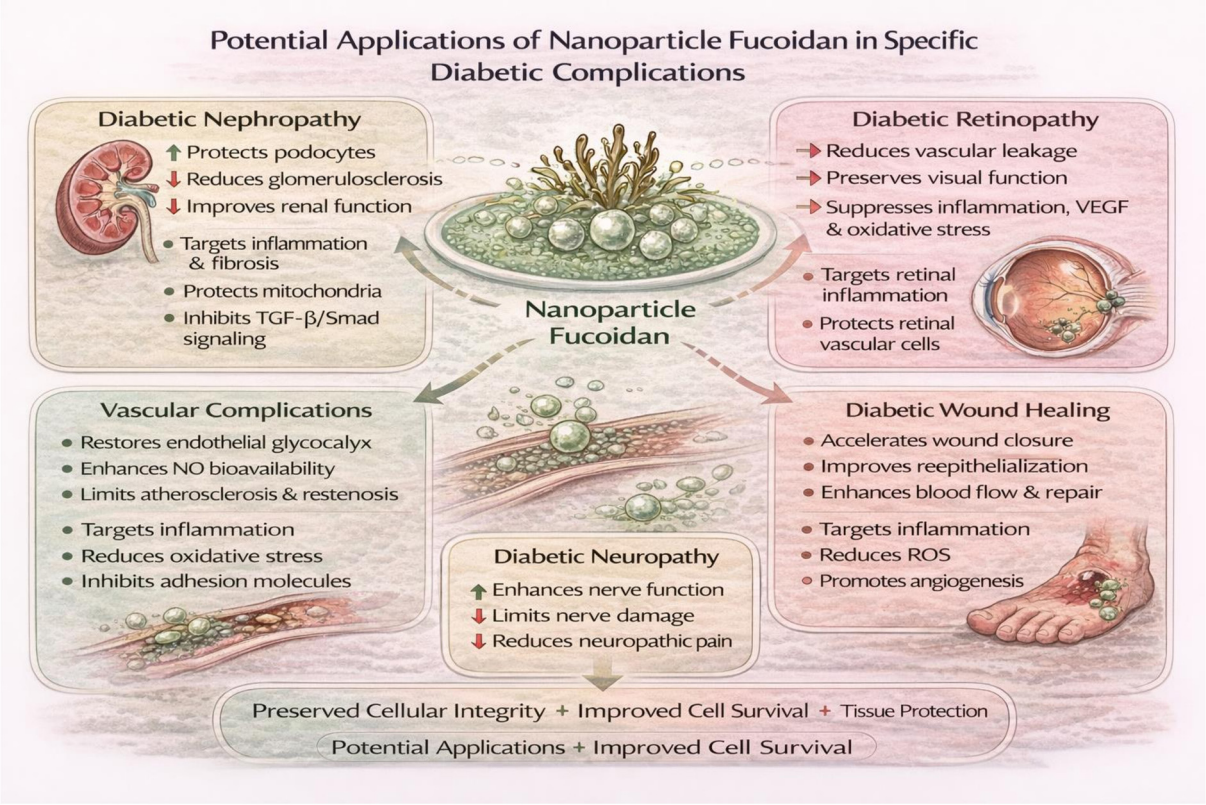


Figure 7. Potential applications of fucoidan-based nanoparticles in specific diabetic complications. Fucoidan-based nanoparticles may protect against diabetic nephropathy, retinopathy, neuropathy, vascular injury, and chronic wounds through antioxidant, anti-inflammatory, antifibrotic, vasculoprotective, and pro-regenerative effects. Overall, these nanoformulations support cellular integrity, improve cell survival, and promote tissue protection and repair.

glomerular hypertrophy, and progressive fibrosis. Podocyte injury, glomerular basement membrane thickening, and mesangial matrix expansion are key structural features that ultimately impair renal filtration. Conventional therapy can slow progression but does not fully block the structural damage pathways that drive long-term renal decline (Alicic et al., 2017; Wardani et al., 2022; Xu et al., 2016).

Fucoidan-based nanoparticles may offer renoprotective effects by suppressing ROSs, modulating pro-inflammatory cytokines, inhibiting profibrotic signaling, and protecting renal cells from apoptosis. From a delivery perspective, nanoparticle systems can potentially be designed to increase fucoidan accumulation in renal tissue or prolong systemic circulation, thereby improving the likelihood of therapeutic interaction within injured nephrons. Such properties make fucoidan nanoformulations attractive as adjunct strategies that target structural and molecular aspects of diabetic nephropathy beyond glycemic control alone.

4.3. Diabetic retinopathy

Diabetic retinopathy is a progressive microvascular complication characterized by retinal capillary injury, increased vascular permeability, inflammation, oxidative stress, and pathological neovascularization. Existing treatments, including intraocular injections and laser therapy, can be effective in selected settings but remain invasive and do not address all disease mechanisms comprehensively (Cheung et al., 2010; Yang et al., 2013).

Fucoidan-based nanoparticles may represent an alternative retinal therapeutic platform because of their antioxidant, anti-inflammatory, and vasculoprotective properties. The main challenge in this application is delivery to retinal tissue across multiple anatomical and biological barriers. Nevertheless, nanoparticle systems with optimized size, surface charge, and surface chemistry may improve tissue penetration and local retention, particularly in ophthalmic or intraocular formulations. In principle, nanoformulated fucoidan may help preserve retinal vascular integrity,

suppress local inflammation, and slow neurovascular injury progression.

4.4. Diabetic neuropathy

Diabetic neuropathy involves progressive peripheral nerve injury driven by oxidative stress, inflammation, microvascular ischemia, and chronic metabolic disturbance. Clinical manifestations include neuropathic pain, paresthesia, sensory loss, and, in advanced cases, motor dysfunction. Because of the multifactorial nature of its pathogenesis, current treatment is largely symptomatic rather than truly neuroprotective (Feldman et al., 2019).

The promise of fucoidan-based nanoparticles in diabetic neuropathy lies primarily in their ability to suppress ROSs, reduce inflammation, and protect neural cells from apoptosis. With further development, nanoparticle systems may be engineered to improve delivery to peripheral nerve tissue or to prolong systemic bioavailability. Such strategies may help preserve nerve function, slow degeneration, and possibly support a more favorable regenerative environment in chronically injured neural tissue.

4.5. Cardiovascular complications in diabetes

Cardiovascular complications are the leading cause of death in patients with diabetes and involve atherosclerosis, vascular inflammation, endothelial dysfunction, oxidative stress, and adverse cardiac remodeling. Although risk-factor management has improved outcomes, there is still a strong need for agents capable of directly protecting the vasculature and myocardium (Low Wang et al., 2016; Wardani et al., 2023; Yu et al., 2014).

Fucoidan-based nanoparticles may provide benefit through endothelial protection, attenuation of vascular inflammation, reduction of oxidative stress, and modulation of matrix remodeling. In addition, the capacity of fucoidan to interact with adhesion molecules and vascular components may create opportunities for more targeted delivery to injured vascular sites. When combined with suitable delivery strategies, fucoidan nanoformulations may become useful adjuncts for reducing the progression of diabetes-associated cardiovascular injury.

4.6. Comparative translational potential across complications

Among the various diabetic complications, diabetic wounds are likely to be the earliest realistic translational target for fucoidan-based nanoparticles because of easier local access, high unmet clinical need, and straightforward integration into biomaterials. Diabetic nephropathy and cardiovascular complications are also promising but will require tighter optimization of systemic biodistribution and more rigorous long-term safety evaluation. Diabetic retinopathy and neuropathy remain biologically compelling targets, although their delivery barriers are more complex. These differences indicate that fucoidan nanoparticle development should be tailored carefully to the intended clinical indication (Table 1).

5. CHALLENGES IN CLINICAL TRANSLATION

Despite their considerable therapeutic promise, fucoidan-based nanoparticles face multiple scientific, technological, and regulatory barriers on the path from laboratory research to clinical application. A critical discussion of these obstacles is essential if future work is to move beyond exploratory preclinical findings.

5.1. Structural heterogeneity and lack of fucoidan standardization

One of the most fundamental challenges lies in the heterogeneity of fucoidan itself. Its chemical composition, molecular weight, sulfation degree, and branching pattern vary substantially according to algal species, geographical origin, harvest season, and extraction method. Such variability can produce major differences in biological activity and compromise reproducibility across studies. For pharmaceutical development, this inconsistency is a serious limitation because reliable clinical translation requires a well-characterized and reproducible active material (Ale and Meyer, 2013; Fitton et al., 2019; Mabate et al., 2021).

Standardization of fucoidan should therefore include identification of the biological source, control of extraction and purification processes, and detailed characterization of chemical structure and critical quality attributes. Without such measures, it remains difficult to compare studies or establish a robust relationship among fucoidan structure, nanoparticle formulation, and therapeutic effect.

5.2. Formulation complexity and scalability

Nanoformulations that perform well at the laboratory scale are not necessarily easy to manufacture consistently at the industrial scale. Nanoparticle preparation methods are often sensitive to small variations in pH, ionic strength,

Table 1
Translational landscape of fucoidan-based nanoparticle applications across major diabetic complications.

Complication	Dominant pathogenic processes	Likely therapeutic roles of fucoidan nanoparticles	Most plausible delivery format	Relative translational readiness	Main barriers
Diabetic wounds	Oxidative stress, chronic inflammation, infection risk, poor angiogenesis, defective matrix remodeling	Local antioxidative and anti-inflammatory effects, improved angiogenesis, support for re-epithelialization and regenerative repair	Topical hydrogel, nanofiber dressing, scaffold-integrated system	High	Formulation stability, scale-up, wound-model standardization
Diabetic nephropathy	Inflammation, podocyte injury, fibrosis, glomerular and tubular oxidative damage	Renoprotection, antifibrotic activity, attenuation of inflammatory signaling	Systemic nanoparticles with renal targeting potential	Moderate	Biodistribution, renal targeting efficiency, long-term safety
Diabetic retinopathy	Microvascular leakage, inflammation, oxidative stress, pathological neovascularization	Retinal antioxidative and vasculoprotective effects, controlled delivery to ocular tissue	Intravitreal or ocular nano-delivery platform	Low to moderate	Ocular delivery barriers, sterility requirements, local tolerance
Diabetic neuropathy	Oxidative stress, neuroinflammation, microvascular ischemia, neuronal apoptosis	Neuroprotection, suppression of inflammatory injury, support for neural survival	Systemic or locally targeted neural delivery	Low	Blood-nerve targeting, limited efficacy models, chronic dosing concerns
Cardiovascular complications	Endothelial dysfunction, vascular inflammation, oxidative injury, adverse remodeling	Endothelial protection, anti-inflammatory vascular effects, possible antiremodeling activity	Systemic vascular-targeted nanoparticles	Low	Complex disease heterogeneity, systemic exposure, regulatory burden

polymer concentration, temperature, and mixing conditions, all of which can affect particle size, surface charge, loading efficiency, and release profile (Ezhilarasu et al., 2020; Shi et al., 2024).

Moreover, many nanoformulations require excipients or processing steps that may be difficult to validate for large-scale production. Formulation optimization must therefore consider not only biological effectiveness but also reproducibility, storage stability, production cost, and compatibility with good manufacturing practice. Overly complex systems may slow translation even when they appear scientifically attractive.

5.3. Pharmacokinetics, biodistribution, and targeting efficiency

The clinical performance of fucoidan-based nanoparticles depends strongly on their behavior in biological systems. After administration, nanoparticles may undergo opsonization, rapid clearance by the reticuloendothelial system, aggregation, or premature payload release. These challenges become even more important when the intended target is a specific organ such as the kidney, retina, or peripheral nervous system.

More systematic pharmacokinetic and biodistribution studies are needed to determine how particle size, zeta potential, material composition, and surface modification influence organ distribution, circulation time, tissue penetration, and target accumulation. Such information is crucial for designing nanoformulations that are not only biologically active but also delivery-efficient (Fitton et al., 2019; Mabate et al., 2021).

5.4. Safety, toxicity, and immunological concerns

Although fucoidan is generally regarded as biocompatible, nanoformulation may generate a safety profile that differs from that of the free compound. Nanoscale dimensions can alter interactions with cell membranes, plasma proteins, immune components, and excretory organs. Potential long-term toxicity, bioaccumulation, effects on hepatic and renal function, and unintended immune responses must therefore be assessed comprehensively (Fitton, 2011; Fitton et al., 2019).

Safety evaluation should include cytotoxicity, hemocompatibility, genotoxicity, immunotoxicity, and both short-term and long-term in vivo toxicity studies. These issues are especially important when fucoidan-based nanoparticles are intended for chronic or systemic administration, as would be the case for diabetic nephropathy or cardiovascular complications.

5.5. Limitations of the current evidence base

Most currently available evidence remains at an early in vitro or in vivo stage, and study designs are highly heterogeneous. Different animal models, fucoidan types, and formulation parameters are commonly used, which makes direct comparison difficult. In addition, only a limited number of studies clearly link nanoparticle physicochemical characteristics with biological outcomes in a quantitative manner (Shi et al., 2024; Wardani et al., 2022, 2023).

These limitations indicate that the field still requires more standardized mechanistic studies, comparative evaluation across nanoparticle platforms, and preclinical designs that better reflect clinical reality. Without a stronger and more coherent evidence base, claims regarding clinical translation will remain largely speculative.

5.6. Regulatory and translational barriers

Nanotechnology-based products are subject to more complex regulatory evaluation than conventional formulations. For fucoidan-based nanoparticles, key issues include validation of raw materials, quality specifications, stability, sterility where relevant, analytical methods, and demonstration of safety and efficacy. The combination of a heterogeneous natural product with a complex nanosystem may further prolong regulatory development (Ezhilarasu et al., 2020; Shi et al., 2024).

For this reason, translational strategy should be considered from the earliest stages of development, including realistic selection of the clinical indication, feasible administration routes, clinically relevant preclinical endpoints, and manufacturable formulation designs. Such planning will increase the likelihood that laboratory innovation can evolve into a usable therapeutic product.

6. FUTURE PERSPECTIVES

Despite these challenges, the future of fucoidan-based nanoparticles remains highly promising. This field creates a valuable intersection among natural products, nanotechnology, and precision-oriented therapy for complex chronic diseases such as diabetic complications.

6.1. Toward smart and targeted nanoparticle systems

Future development is likely to move toward smart nanoparticle systems that respond to pH, ROSs, enzymes, or other pathological microenvironmental cues. Such systems may enable more selective fucoidan release at sites of tissue injury. In addition, surface modification with suitable ligands may enhance targeting toward damaged endothelium, renal tissue, retinal tissue, or chronic wound beds (Ezhilarasu et al., 2020; Liu et al., 2022).

6.2. Combination therapy and multifunctional platforms

Fucoidan-based nanoparticles also have strong potential as combination platforms with conventional antidiabetic drugs, growth factors, additional antioxidants, antimicrobial agents, or anti-inflammatory compounds. Such combinations may generate synergistic effects and allow simultaneous intervention across several pathogenic pathways. In diabetic wound management, for instance, combination with active dressings or biofunctional biomaterials may be especially practical (Fitton et al., 2019; Shi et al., 2024).

6.3. Integration with biomaterials and regenerative medicine

For local indications such as diabetic wounds, integration of fucoidan nanoparticles into hydrogels, scaffolds, films, or nanofibers is particularly promising because it can improve local retention, moisture balance, and structural support for tissue regeneration. Within regenerative medicine more broadly, fucoidan may also serve as a bioactive component in systems designed to support cell migration, angiogenesis, and more physiological tissue remodeling (Ezhilarasu et al., 2020; Wen et al., 2023).

6.4. Need for robust preclinical models and translational study design

Progress in this field will depend heavily on stronger preclinical research design. Future studies should employ more representative models of diabetic complications, clinically relevant outcome measures, and analyses that directly connect formulation attributes with biological mechanisms. Direct comparison between free fucoidan and fucoidan-based nanoparticles is also essential to demonstrate the objective added value of nanoformulation.

6.5. Clinical translation roadmap

To accelerate translation, indications with lower delivery barriers and higher unmet clinical need should be prioritized first. On this basis, diabetic wounds appear to be the

most realistic starting point for early clinical development of fucoidan-based nanoparticles. Once initial safety and efficacy are established, expansion toward systemic complications such as diabetic nephropathy or diabetic vasculopathy may be considered. A staged translational roadmap of this kind may help bridge the gap between scientific innovation and actual clinical need (Armstrong et al., 2017; Shi et al., 2024).

7. CONCLUSION

Fucoidan-based nanoparticles have emerged as an innovative therapeutic strategy with substantial potential for the management of diabetic complications through a multimodal mechanism of action. Compared with free fucoidan, nanoparticle formulations offer important advantages in stability, bioavailability, controlled release, tissue penetration, and delivery efficiency to target sites. These advantages are especially relevant in diabetic complications, which are characterized by oxidative stress, chronic inflammation, endothelial dysfunction, fibrosis, apoptosis, and impaired tissue regeneration (Fitton et al., 2019; Wardani et al., 2022, 2023).

Biologically, fucoidan nanoformulations may suppress ROSs generation, inhibit inflammatory mediators, preserve vascular integrity, attenuate fibrotic remodeling, and support tissue healing. This mechanistic profile makes them relevant to a wide range of diabetic complications, including diabetic wounds, nephropathy, retinopathy, neuropathy, and cardiovascular injury. Among these indications, diabetic wounds appear to represent the most realistic near-term translational target because of easier local access and high unmet clinical demand (Brownlee, 2001; Forbes and Cooper, 2013; Wardani et al., 2023).

However, enthusiasm for this field must be balanced by critical recognition of the remaining challenges, particularly fucoidan heterogeneity, formulation complexity, limited pharmacokinetic and biodistribution data, safety concerns, and regulatory barriers. Future progress will therefore depend on raw material standardization, rational nanoparticle design, stronger preclinical evidence, and realistic translational roadmaps. With such an integrated approach, fucoidan-based nanoparticles may evolve from an experimental concept into a clinically meaningful therapeutic platform for diabetic complication management (Ale and Meyer, 2013; Fitton et al., 2019; Shi et al., 2024).

MANDATORY DISCLOSURE ON USE OF ARTIFICIAL INTELLIGENCE

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