

Apocynin in Diabetes: Modulation of Oxidative Stress and Inflammatory Signaling

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Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia and progressive development of microvascular and macrovascular complications. Increasing evidence identifies oxidative stress and redox-sensitive inflammatory signaling as central mechanisms underlying diabetes-associated organ injury. Apocynin, a naturally occurring methoxy-substituted phenolic compound, has gained attention as a redox-modulating agent with potential therapeutic relevance in diabetes. The present review summarizes the chemical characteristics, mechanistic actions, and protective effects of apocynin in experimental models of diabetic complications. Apocynin primarily acts through inhibition of NADPH oxidase assembly, thereby limiting excessive reactive oxygen species generation and suppressing downstream activation of redox-sensitive pathways. Through modulation of oxidative and inflammatory cascades, apocynin demonstrates protective effects in diabetic nephropathy, neuropathy, cardiomyopathy, and retinopathy. In addition to reducing oxidative burden, apocynin supports endogenous antioxidant defenses and improves cellular and metabolic stability. However, despite these promising findings, no clinical studies have yet evaluated apocynin in patients with diabetes or its associated complications. Although preclinical findings are promising, translational challenges, including pharmacokinetic limitations and limited clinical evaluation, remain to be addressed. Collectively, apocynin emerges as a promising candidate targeting convergent redox-inflammatory pathways implicated in diabetic complications.

Keywords: Apocynin; Diabetes Mellitus; NADPH Oxidase; Oxidative Stress; Reactive Oxygen Species.

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin action, or both, and remains one of the most prevalent non-communicable diseases worldwide.¹ Recent estimates from the International Diabetes Federation indicate a rapidly increasing global burden, with approximately 536.6 million individuals affected in 2021 and projections suggesting an increase to 783.2 million

by 2045. Notably, nearly half of these cases remain undiagnosed, reflecting the insidious and progressive nature of the disease.^{2,3} This expanding prevalence is accompanied by a substantial increase in disease burden, driven largely by the development of chronic complications that significantly impair quality of life and increase the risk of premature mortality.⁴ Collectively, these epidemiological trends and clinical factors underscore the growing challenge posed by diabetes and highlight the need

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for improved management strategies as well as a deeper understanding of the molecular mechanisms underlying disease progression.

At the molecular level, chronic hyperglycemia triggers multiple pathogenic processes, with oxidative stress (OS) acting as a key mediator of cellular dysfunction and tissue injury.⁵ OS arises from an imbalance between the production of reactive oxygen species (ROS) and the capacity of endogenous antioxidant defense systems to neutralize them.⁶ In diabetes, persistent hyperglycemia enhances ROS generation through several mechanisms, including glucose autooxidation, protein glycation, mitochondrial dysfunction, and activation of enzymatic sources such as NADPH oxidase (NOX).^{5,7} Excess ROS disrupts cellular redox homeostasis and activates stress-responsive inflammatory signaling pathways.⁸ As a result, this redox imbalance contributes to metabolic dysregulation, progressive tissue injury, and the development of major diabetes-associated complications, including nephropathy, neuropathy, cardiomyopathy, and retinopathy, which collectively account for significant morbidity and mortality in individuals with diabetes.^{5,9}

Despite advances in understanding the role of OS in diabetes pathogenesis, current pharmacological strategies for DM management primarily focus on achieving glycemic control through insulin therapy and oral antidiabetic agents.¹⁰ While effective in lowering blood glucose levels, these interventions do not adequately address the underlying oxidative imbalance and chronic low-grade inflammation that drive disease progression.¹¹ Notably, OS and inflammatory signaling often persist even in patients with well-controlled glycaemia, partly due to metabolic memory, a phenomenon in which prior hyperglycemic exposure induces sustained cellular and molecular damage, and consequently patients remain vulnerable to progressive tissue injury and long-term complications.¹² In addition, conventional therapies are associated with limitations such as adverse effects, declining efficacy, and incomplete protection against diabetes-related organ dysfunction.¹³ These challenges highlight the need for complementary therapeutic approaches that target redox-dependent

and inflammatory pathways involved in diabetes pathogenesis.

In this context, increasing attention has been directed toward plant-derived bioactive compounds with antioxidant and anti-inflammatory properties as potential modulators of OS-driven pathology. These compounds often exhibit multi-targeted actions and favorable safety profiles, enabling simultaneous regulation of key pathogenic pathways.¹⁴ Among these, apocynin has emerged as a promising candidate due to its ability to inhibit NOX-mediated ROS generation and modulate redox-sensitive signaling cascades. Accumulating evidence suggests that apocynin confers protective effects across multiple diabetes-associated complications by attenuating OS, suppressing inflammatory responses, and preserving cellular and tissue integrity.^{15,16} This review therefore aims to critically evaluate the mechanistic role of apocynin in modulating OS-driven inflammatory pathways and to highlight its therapeutic potential in the prevention and management of diabetes-associated complications.

Apocynin: Chemical Properties, Botanical Sources, And Ethnomedicinal Relevance

Apocynin is a naturally occurring phenolic compound belonging to the class of methoxy-substituted catechols and is predominantly isolated from plant species traditionally used in diverse systems of medicine.¹⁷ *Picrorhiza kurroa* is widely acknowledged as the primary botanical source of apocynin.¹⁸ Additionally, there are reports of apocynin being present in other plants used in Ayurveda, traditional Chinese medicine, and various folk medicinal systems. The plants mentioned have a long history of use in managing inflammatory, hepatic, respiratory, and metabolic disorders. Their traditional applications have offered early insights into the therapeutic potential of apocynin, which in turn has led to systematic pharmacological investigations.¹⁸⁻²²

Structurally, apocynin possesses a well-defined phenolic framework characterized by a hydroxyl group, a methoxy substituent, and an acetyl side chain attached to an aromatic ring (figure 1).¹⁷ The phenolic hydroxyl group contributes to ROS scavenging activity, whereas the methoxy group enhances molecular stability and lipophilicity, thereby facilitating cellular uptake.²³

Together, these structural attributes underpin its redox-modulating capacity and contribute to its biological activity in OS-driven conditions. The defined chemical framework of apocynin has also enabled its synthesis and structural modification, facilitating further exploration of structure-activity relationships relevant to pharmacological applications.²⁴ On the basis of these chemical and ethnomedicinal characteristics, subsequent investigations have focused on elucidating the molecular mechanisms through which apocynin exerts its biological actions, particularly its capacity to modulate OS and inflammation-Fig. 1. Structure of apocynin related pathways central to DM and its complications.^{23,24}

Mechanism Of Action Of Apocynin In Diabetes

Apocynin is widely recognized as an inhibitor of NOX, a family of membrane-associated enzyme complexes that represent a major source of ROS under diabetic conditions.²⁵ NOX enzymes catalyze the transfer of electrons from NADPH to molecular oxygen, resulting in the formation of superoxide and related reactive intermediates. Structurally, these enzymes consist of membrane-bound catalytic subunits and cytosolic regulatory components, such as p47^{phox} and p67^{phox}, which translocate to the membrane upon activation to assemble the functional oxidase complex.²⁶ Sustained activation of NOX isoforms contributes to excessive ROS production and amplification of OS and inflammatory signaling pathways in diabetes.²⁷ Apocynin has been reported to inhibit NOX activity by interfering with the assembly of this active enzyme complex, particularly by preventing the translocation of cytosolic subunits such as p47^{phox}, thereby limiting superoxide generation. On this basis, apocynin has been regarded as a pharmacological inhibitor of NOX-derived ROS and a potential therapeutic agent for mitigating OS-mediated damage in diabetes.^{17,25}

However, subsequent experimental evidence has challenged the view of apocynin as a classical direct NOX inhibitor. The precise mechanism of apocynin remains a subject of active investigation and appears to be highly context-dependent.²⁸ Apocynin is proposed to function as a prodrug requiring peroxidase-mediated activation, particularly by myeloperoxidase, to generate reactive dimeric species such as diapocynin, which interfere with enzyme assembly.²⁹ This

mechanism is most prominent in peroxidase-rich phagocytic cells.³⁰ In contrast, in vascular endothelial and smooth muscle cells, which exhibit limited peroxidase activity, apocynin often fails to directly inhibit NOX and instead exerts its effects primarily through antioxidant mechanisms, including modulation of ROS-dependent signaling pathways.³¹ Consistent with this cell-type specificity, apocynin has been reported to exhibit relatively weak direct free radical scavenging activity while demonstrating greater efficacy in neutralizing non-radical oxidants such as hydrogen peroxide (H₂O₂) and hypochlorous acid.³⁰ Its effects also appear to vary across cellular systems, with studies reporting both increases and reductions in ROS levels in non-phagocytic cells, likely reflecting differences in cellular redox environments, enzyme expression, and experimental conditions.²⁸

In addition, apocynin has been associated with preservation of endogenous antioxidant defenses, including superoxide dismutase and catalase.³² It has also been reported to influence multiple signaling pathways associated with diabetic complications, including modulation of eNOS-dependent superoxide production and suppression of nuclear factor- κ B (NF- κ B) and nod-like receptor pyrin domain-containing 3 (NLRP3) inflammasome activation.^{28,33} By modulating these interconnected oxidative and inflammatory pathways, apocynin may enhance the efficiency of insulin signaling, regulate cellular stress responses, and support metabolic homeostasis.³⁴ Apocynin thus acts as a context-dependent modulator of OS, which may contribute to its protective effects in diabetes-associated complications.

Apocynin In Diabetic Complications

Apocynin in Diabetic Nephropathy

Diabetic nephropathy (DN) is a chronic microvascular complication of DM characterized by progressive damage to the glomeruli, mesangial expansion, injury to podocytes, thickening of the glomerular basement membrane, interstitial fibrosis, and a gradual decline in renal function. This decline ultimately leads to chronic kidney disease and, in some cases, end-stage renal failure. Clinically, patients with DN exhibit albuminuria, a declining glomerular filtration rate, hypertension, and progressive proteinuria as the disease progresses. This condition significantly

diminishes the quality of life and elevates mortality rates among individuals with diabetes.^{35,36} Globally, DN accounts for a significant proportion of chronic kidney disease cases. Nearly one-third of individuals with DM develop clinically significant nephropathy during their lifetime. This condition represents a major public health burden due to its associated risks of cardiovascular disease and the necessity for renal replacement therapy.³⁷ The pathogenesis of DN is multifactorial, involving metabolic, hemodynamic, oxidative, and inflammatory mechanisms. Chronic hyperglycemia leads to excessive generation of reactive oxygen species (ROS), formation of advanced glycation end-products, activation of protein kinase C, and deregulation of growth factor signaling. These processes contribute to endothelial dysfunction, proliferation of mesangial cells, accumulation of extracellular matrix, and tubulointerstitial fibrosis.^{38,39}

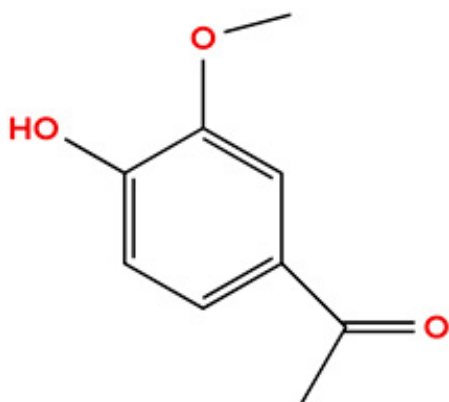


Fig. 1. Structure of apocynin

Preclinical studies indicate that apocynin mitigates structural and functional renal injury in DN through multiple mechanisms (figure 2). In streptozotocin-induced diabetic rats, OS is characterized by increased renal H₂O₂ levels, elevated lipid peroxidation products, and significant proteinuria, reflecting oxidative injury and renal dysfunction. This oxidative imbalance is partly driven by activation of the NOX system and the associated overproduction of ROS. These alterations are associated with mesangial expansion and increased expression of fibronectin and type I collagen, contributing to extracellular matrix accumulation and progressive glomerular injury.^{40,41} Apocynin attenuates these changes by reducing ROS generation, normalizing p47^{phox} translocation and gp91^{phox} expression, and limiting mesangial matrix expansion, thereby preserving renal architecture and function.⁴²

It has also been reported that innate immune and inflammatory mechanisms contribute significantly to the progression of DN, with pattern recognition receptors (PRRs) playing central roles. Among these, nucleotide-binding oligomerization domain-like receptors (NLRs), particularly NLRP3, are critically involved.⁴³ In the diabetic milieu, PRR activation together with excessive ROS generation sustains renal inflammatory signaling. NLRP3 forms the inflammasome complex, promoting activation of caspase-1 and release of pro-inflammatory cytokines such as interleukin-1 α and interleukin-18, thereby driving inflammation and fibrotic remodeling.⁴⁴ X-linked inhibitor of apoptosis protein (XIAP) is functionally linked to this pathway.⁴⁵ Apocynin has been shown to attenuate this process by reducing

Table 1. Natural sources of apocynin and their traditional medicinal uses

Plant source	Plant part used	Traditional medicinal uses
<i>Picrorhiza kurroa</i>	Roots and rhizomes	Used in Ayurveda for diabetes, liver disorders, fever, asthma, and inflammatory conditions. ¹⁸
<i>Apocynum cannabinum</i>	Roots	Traditionally used as a cardiotonic, diuretic, and anti-inflammatory agent. ¹⁹
<i>Apocynum venetum</i>	Leaves and stems	Used in traditional Chinese medicine for hypertension, anxiety and cardiovascular disorders. ²⁰
<i>Iris germanica</i>	Roots and rhizomes	Employed in folk medicine for antimicrobial and anti-inflammatory purposes. ²¹
<i>A. androsaemifolium</i>	Roots	Traditional remedies for circulatory disorders and in cold remedies. ²²

the diabetes-induced upregulation of NLRP3 and XIAP, thereby suppressing inflammasome activation and associated renal injury.⁴⁶

In addition, modulation of pro-inflammatory mediators and activation of HO-1/Nrf2 cytoprotective signaling contribute to its renoprotective effects.⁴⁷ In vitro studies using renal mesangial cells demonstrate that apocynin suppresses key inflammatory mediators, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and monocyte chemoattractant protein-1 (MCP-1). This effect is associated with activation of the HO-1/Nrf2 pathway, a major endogenous antioxidant defence system. Apocynin-induced activation of Nrf2 and subsequent induction of HO-1 enhance antioxidant

capacity and suppress MCP-1 expression, thereby attenuating inflammatory signaling and contributing to cytoprotection in diabetic renal injury.⁴⁸

Apocynin further exerts protective effects by preserving glomerular structure and preventing renal apoptosis.⁴⁹ In diabetic rats subjected to contrast-induced nephropathy, apocynin significantly reduced plasma urea and creatinine levels, indicating improved renal function. Histopathological findings demonstrated reduced tubular degeneration, diminished interstitial oedema, decreased vascular congestion, and preservation of glomerular architecture. In addition, apocynin markedly reduced renal apoptosis, highlighting its protective role against superimposed renal injury in diabetic conditions.⁵⁰

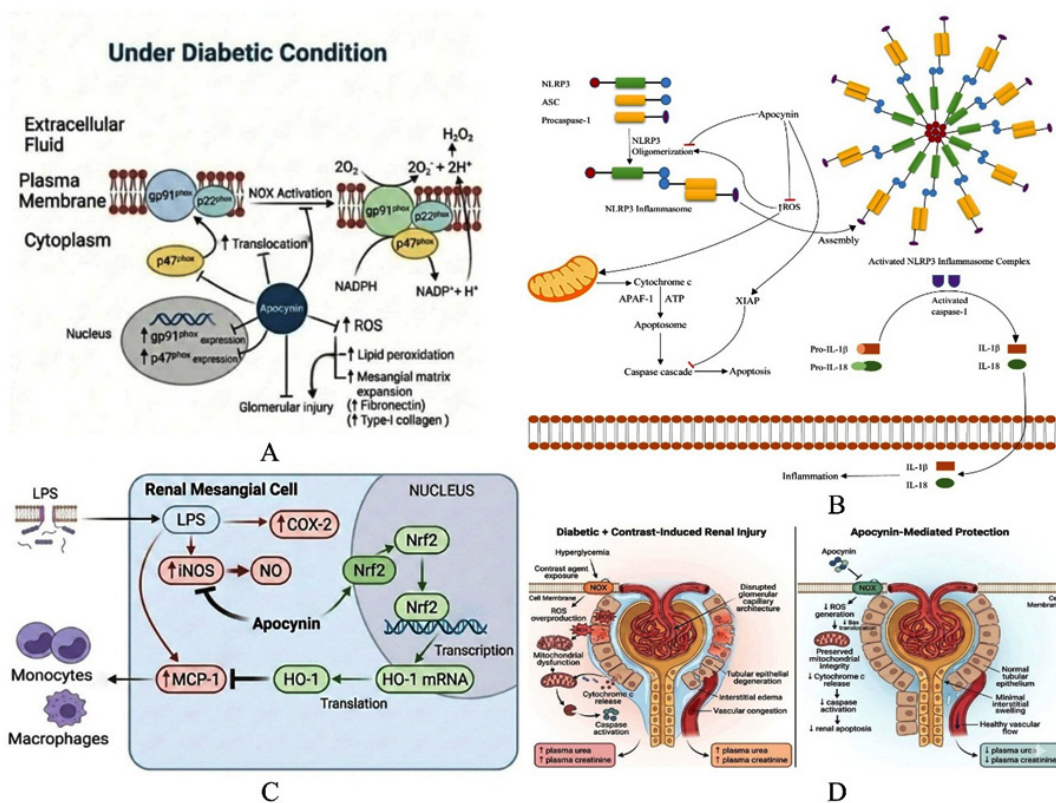


Fig. 2. Mechanistic pathways underlying the renoprotective effects of apocynin in diabetic nephropathy. (A) inhibition of NOX activation reduces ROS production and limits extracellular matrix accumulation; (B) suppression of NLRP3–XIAP inflammasome signaling decreases caspase-1 activation and pro-inflammatory cytokine release; (C) downregulation of pro-inflammatory mediators (iNOS, COX-2, MCP-1) and activation of the Nrf2/HO-1 pathway enhance antioxidant defenses; (D) preservation of glomerular structure and reduction of apoptosis support renal function

Collectively, these findings indicate that apocynin exerts multifaceted renoprotective effects by targeting OS, inflammatory signaling, and structural remodeling in DN.

Apocynin in Diabetic Neuropathy

Diabetic neuropathy (Dn) is a common microvascular complication of DM, affecting a substantial proportion of patients over the course of the disease. It is characterized by progressive damage to peripheral nerves and typically presents with sensory loss, neuropathic pain, tingling, and altered pain perception, often beginning in the distal extremities in a characteristic stocking–glove distribution.⁵¹ The development of Dn is closely associated with chronic hyperglycemia–induced OS, which disrupts neuronal and glial function, impairs nerve blood flow, and compromises nerve conduction. In addition, hyperglycemia-induced metabolic disturbances, including activation of the polyol pathway and accumulation of advanced glycation end products, further exacerbate neuronal injury. Excessive oxidative and nitrosative stress is recognized as a central driver of nerve damage, positioning redox-modulating pathways as important therapeutic targets.^{51–53}

Preclinical studies indicate that apocynin exerts neuroprotective effects in Dn primarily through attenuation of hyperglycaemia-induced oxidative and nitrosative stress, which underlies

both functional and structural nerve damage, as depicted in figure 3. In streptozotocin-induced diabetic models, apocynin exerts neuroprotective effects by modulating OS–related mechanisms. In addition to inhibiting NOX activity, it improves nociceptive pain thresholds, indicating attenuation of hyperalgesia. Catalase expression is reduced, suggesting diminished oxidative burden rather than impaired antioxidant defence. Histopathological analysis of sciatic nerve tissue shows reversal of extracellular matrix expansion, axonal and myelin degeneration, and Schwann cell loss, indicating preservation of peripheral nerve architecture.⁵⁴ In addition to its direct neuroprotective effects, apocynin has been shown to improve neurovascular function in Dn. A study by Cotter et. al⁵⁵ evaluated the effect of apocynin on peripheral nerve perfusion in diabetic animal models and demonstrated a significant improvement in endoneurial blood flow. This effect was attributed to alleviation of OS mediated microvascular dysfunction, resulting in enhanced nerve perfusion and oxygen delivery. Restoration of endoneurial blood flow by apocynin contributed to improved nerve conduction and functional recovery, underscoring the importance of microvascular protection as a complementary mechanism in its overall neuroprotective action. These findings suggest that apocynin attenuates neuropathic pain and structural nerve damage via OS modulation.

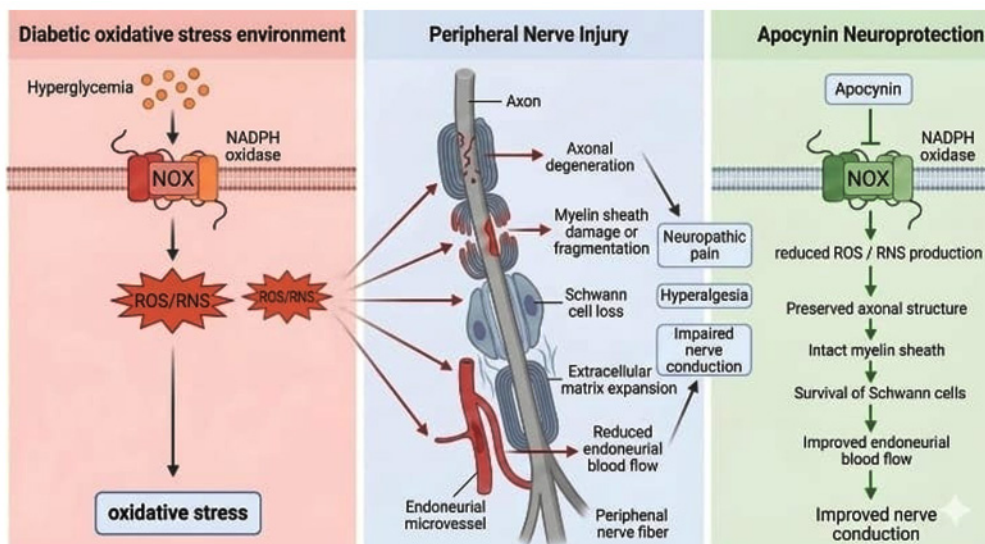


Fig. 3. Apocynin-mediated attenuation of oxidative stress and neurovascular dysfunction in diabetic neuropathy

Apocynin in Diabetic Cardiomyopathy

Diabetic cardiomyopathy (DCM) is a distinct cardiac complication of DM characterized by structural and functional abnormalities of the myocardium that occur independently of coronary artery disease, arterial hypertension, or valvular disorders. Clinically, DCM typically progresses from early diastolic dysfunction to overt systolic impairment and heart failure.⁵⁶ At the cellular and molecular levels, chronic hyperglycemia promotes OS, low-grade inflammation, cardiomyocyte apoptosis, and myocardial fibrosis, collectively driving adverse cardiac remodeling and contractile dysfunction. Among these processes, dysregulated redox signaling and excessive generation of ROS play a central role by activating stress-responsive pathways that impair cardiomyocyte survival and myocardial metabolism. This mechanistic framework provides a strong rationale for targeting redox-driven pathways in the prevention and management of DCM.^{57,58}

The co-existence of DM and arterial hypertension is a common clinical scenario that accelerates myocardial remodeling and functional decline. Evidence from hypertensive–diabetic animal models has provided insight into the cardioprotective potential of apocynin. Rosa et al.⁵⁹

demonstrated that apocynin significantly reduced OS and attenuated pathological cardiac remodeling in spontaneously hypertensive rats with DM. Treatment was associated with reduced myocardial hypertrophy, decreased interstitial fibrosis, and improved left ventricular function, indicating protection against diabetes-associated cardiac alterations. In experimental models of DCM, apocynin also limits myocardial injury by reducing ROS accumulation and suppressing redox-sensitive signaling pathways. In particular, inhibition of the apoptosis signal-regulating kinase-1 (ASK1)–p38/c-Jun N-terminal kinase (JNK) pathway contributes to reduced cardiomyocyte apoptosis, attenuation of inflammatory signaling, and limitation of pathological remodeling.⁶⁰ Apocynin further restores endogenous antioxidant defenses, including superoxide dismutase, catalase, and glutathione-dependent enzymes, thereby re-establishing redox balance within the diabetic heart. These effects are accompanied by reduced inflammatory cytokine expression, preservation of mitochondrial integrity, and decreased extracellular matrix deposition. In addition, apocynin improves myocardial insulin Fig. 4. Pathophysiological basis of myocardial injury and protective mechanisms of apocynin in diabetic cardiomyopathy sensitivity

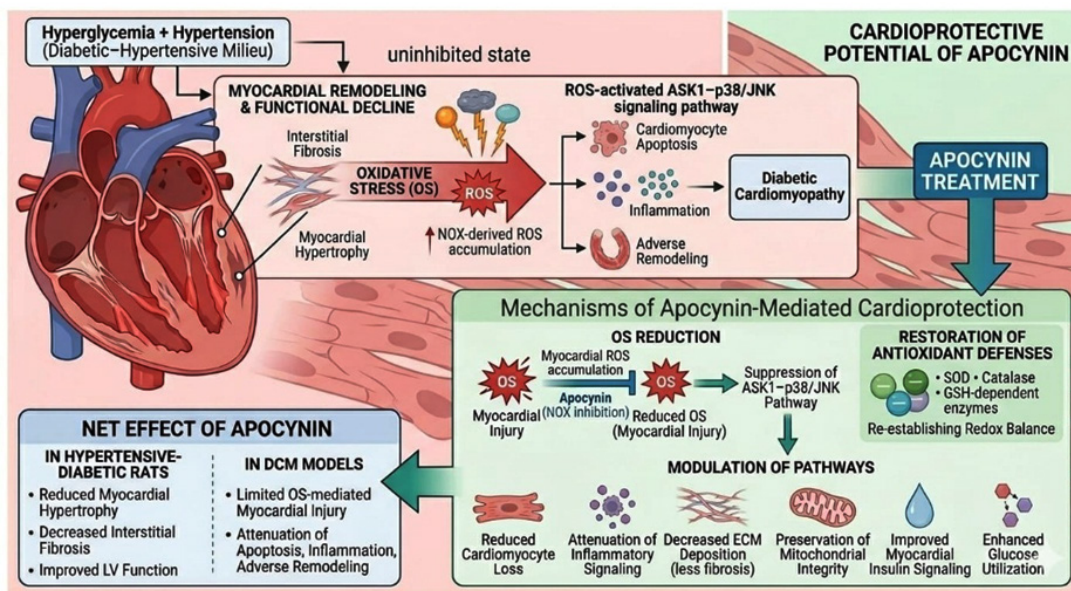


Fig. 4. Pathophysiological basis of myocardial injury and protective mechanisms of apocynin in diabetic cardiomyopathy

and glucose utilization, supporting enhanced cardiac metabolic efficiency.⁶⁰⁻⁶³ These findings suggest that apocynin protects against DCM by attenuating OS-mediated myocardial injury and modulating inflammatory, apoptotic, and metabolic pathways involved in disease progression (figure 4)

Apocynin in Diabetic Retinopathy

Diabetic retinopathy (DR) is a progressive microvascular complication of DM characterized by retinal vascular dysfunction, neuroglial injury, and chronic inflammation. Sustained hyperglycaemia promotes OS, inflammatory signaling, and breakdown of the blood-retinal barrier, ultimately leading to retinal ischemia, neuronal apoptosis, and visual impairment. In addition, hyperglycaemia-induced microvascular damage, increased vascular permeability, and

dysregulated angiogenic signaling, including vascular endothelial growth factor activation, contribute to capillary degeneration and pathological neovascularization. Among these pathogenic factors, OS mediated inflammatory pathways play a central role in the initiation and progression of DR, making them important therapeutic targets.^{64,65}

Experimental evidence suggests that apocynin has protective effects in DR, primarily by modulating the inflammatory and redox-sensitive signaling pathways that are influenced by OS, as illustrated in Figure 5. In streptozotocin-induced diabetic rats, apocynin improves retinal structural and vascular abnormalities by inhibiting the Toll-like receptor 4 (TLR4)/NF- κ B pathway. This inhibition leads to decreased nuclear translocation of NF- κ B and a downregulation of pro-

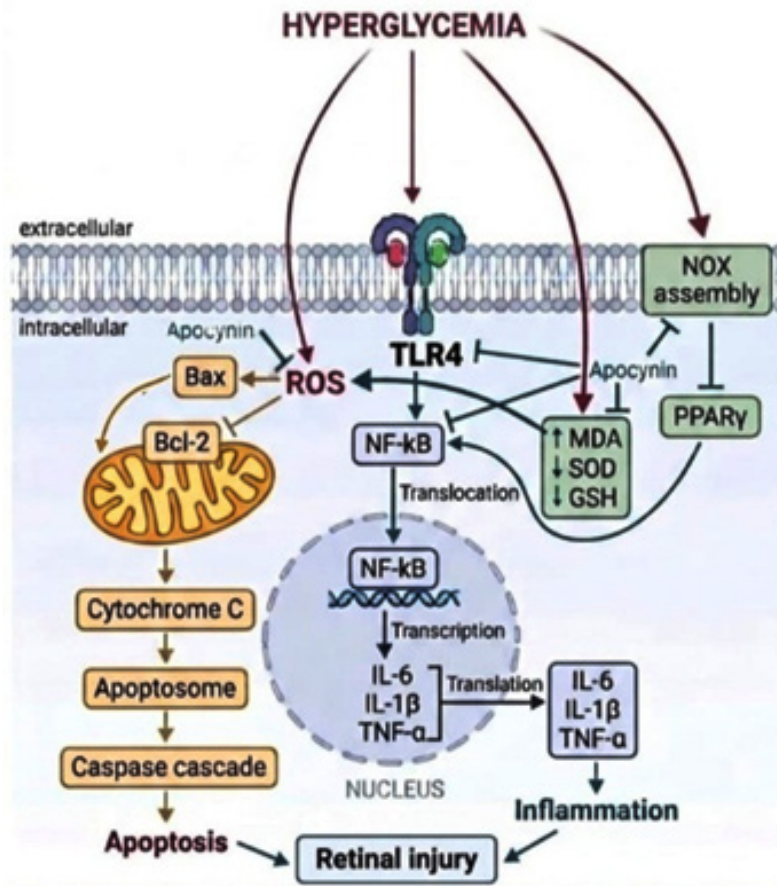


Fig. 5. Interplay of oxidative stress, inflammation, and apoptosis in diabetic retinopathy and the protective influence of apocynin.

Table 2. Molecular mechanisms and protective effects of apocynin in major diabetic complications

Diabetic complications	Major pathological changes	Key molecular targets of apocynin	Therapeutic outcomes
Diabetic nephropathy	Glomerular injury; mesangial expansion; podocyte damage; GBM thickening; ECM accumulation; proteinuria; ↓ GFR	↓ NOX-derived ROS; ↓ p47phox translocation and gp91phox expression; ↓ NLRP3/XIAP signaling; ↓ iNOS, COX-2, MCP-1; activates HO-1/Nrf2 pathway	↓ OS and inflammation; ↓ proteinuria and fibrosis; preserves glomerular structure; improves renal function; anti-apoptotic effects
Diabetic neuropathy	Peripheral nerve degeneration; Schwann cell loss; axonal/myelin damage; neuropathic pain; impaired nerve blood flow	↓ NOX activity and ROS accumulation; ↓ p47phox-associated signaling; ↓ nitrosative stress; improves microvascular function and endoneurial blood flow	↓ Hyperalgesia and neuropathic pain; preserves peripheral nerve structure; improves nerve conduction and functional recovery
Diabetic cardiomyopathy	Myocardial hypertrophy; interstitial fibrosis; cardiomyocyte apoptosis; mitochondrial dysfunction;	↓ Myocardial ROS; inhibits ASK1-p38/JNK signaling; restores antioxidant enzymes (SOD, catalase, GSH); improves mitochondrial integrity and metabolic signaling	↓ Hypertrophy, fibrosis, and apoptosis; improves myocardial contractility, ventricular function, and cardiac metabolic efficiency
Diabetic retinopathy	Retinal vascular dysfunction; neuroglial injury; inflammation; OS; retinal apoptosis	Suppresses TLR4/NF-κB signaling; ↓ TNF-α, IL-1β, IL-6, and MDA; ↑ SOD and GSH; modulates Bax/Bcl-2 balance; preserves PPARα signaling	↓ Retinal inflammation and oxidative damage; inhibits apoptosis; preserves retinal neurovascular integrity; delays DR progression/retinopathy

inflammatory mediators, such as tumour necrosis factor- α , interleukin-1 β , and interleukin-6.⁶⁶ Apocynin also modulates OS markers by reducing malondialdehyde levels and enhancing antioxidant defences, such as superoxide dismutase activity and glutathione levels. Additionally, apocynin regulates apoptotic pathways by decreasing the expression of the pro-apoptotic protein Bax while increasing the levels of the anti-apoptotic protein Bcl-2, which helps limit retinal cell apoptosis.⁶⁶ Further evidence suggests that the reduction of excessive ROS generation aids in preserving the activity of peroxisome proliferator-activated receptor- α (PPAR α), an important transcriptional regulator for maintaining retinal vascular stability and anti-inflammatory signaling.⁶⁷ This preservation is crucial for limiting retinal dysfunction associated with inflammation. The findings by Ahmad et al.⁶⁸ indicate that apocynin provides protection to glial cells, which play a vital role in neurovascular homeostasis. This protection arises from apocynin's capacity to diminish oxidative damage and promote cell survival in hypoxic retinal Müller cells and diabetic retinal tissue. The findings indicate that apocynin provides retinal protection by reducing inflammation driven by OS, preserving signaling pathways sensitive to redox changes, and maintaining the integrity of retinal cells. This ultimately helps to slow the progression of DR.

Limitations And Translational Challenges Of Apocynin

A key limitation in the current evidence base is the heavy reliance on animal models, particularly streptozotocin induced and high fat diet induced models.^{32,34,40,54,62,66} While these models provide important mechanistic insights, they do not fully reflect the complexity and progressive nature of human diabetes.⁶⁹ STZ models primarily mimic acute insulin deficiency rather than the gradual development of type 2 DM,⁷⁰ whereas HFD models show variable metabolic phenotypes across strains.^{71,72} In addition, interspecies differences in NOX expression, redox regulation, and inflammatory signaling limit direct extrapolation to human biology.⁷³ Moreover, doses used in preclinical studies often exceed levels that may be achievable in clinical settings, and study durations are typically short, limiting their ability to model chronic disease progression.^{40,54,62,66}

The absence of human clinical trial data represents the most critical evidentiary gap limiting the translation of apocynin to clinical practice. To date, no studies have evaluated apocynin in patients with DM or its associated complications. Evidence in humans is limited to small exploratory investigations in oxidative stress-related conditions such as chronic obstructive pulmonary disease and osteoarthritis, where modest reductions in oxidative biomarkers have been reported. However, these studies did not progress to advanced trial phases, and no definitive conclusions regarding clinical efficacy can be drawn.^{74,75} This limited translational progress likely reflects challenges related to pharmacokinetics, bioavailability, and sustained target engagement, which remain insufficiently characterized in humans.

Beyond the absence of clinical data, several pharmacokinetic and mechanistic barriers further complicate the translational development of apocynin. Following oral administration, it undergoes rapid first-pass metabolism, resulting in low bioavailability and uncertainty regarding whether effective concentrations can be maintained in target tissues.⁷⁶ Its context-dependent mechanism, consistent with the mechanistic considerations outlined above, further complicates its activity, as effective NOX inhibition requires myeloperoxidase-mediated activation, which is limited in many tissues relevant to diabetic complications. Consequently, its effects in these settings may rely predominantly on non-specific antioxidant activity, potentially limiting sustained efficacy.²⁸⁻³¹

These challenges are further reflected in the considerable variability of dosing protocols across preclinical studies, where inconsistent doses and routes hinder identification of a clear therapeutic window, compounded by the lack of systematic dose-response evaluation.^{40,54,62,66} Several emerging strategies have been proposed to improve bioavailability, including nanoparticle-based delivery systems and targeted formulations designed to exploit myeloperoxidase rich inflammatory environments for site-specific activation. However, these approaches remain in early stages of development.⁷⁷ Additional constraints, including formulation instability, limited tissue penetration, and the risk of disrupting

physiological redox signaling at higher doses, further complicate the design of safe and effective therapeutic regimens.⁷⁸

When considered alongside other antioxidant and NOX-targeting strategies investigated in diabetes, apocynin presents a distinct but incompletely validated therapeutic profile. Among NOX-targeting agents, compounds such as setanaxib (GKT137831) have progressed further in clinical evaluation; however, clinical studies have not consistently demonstrated clear therapeutic benefit, highlighting the challenges associated with translating NOX-targeted therapies into effective treatments.⁷⁹ In comparison, commonly studied antioxidants such as resveratrol and curcumin have shown variable clinical efficacy, largely due to limitations in bioavailability and target engagement.^{80,81} In this context, the therapeutic relevance of apocynin remains uncertain, and its clinical potential will depend on systematic bioavailability optimization, well-designed dose-finding studies, and ultimately randomized clinical trials in diabetic populations.

CONCLUSION

Diabetes mellitus is characterized not only by chronic hyperglycemia but also by sustained oxidative stress and redox-sensitive inflammatory signaling that collectively drive the development of multiorgan complications. The present review highlights apocynin as a mechanistically coherent redox-modulating agent with the capacity to target these convergent pathogenic pathways. By inhibiting NOX assembly and limiting excessive reactive oxygen species generation, apocynin attenuates downstream activation of NF- κ B and inflammasome signaling, thereby reducing oxidative injury, inflammation, fibrosis, and cellular dysfunction. Experimental evidence consistently demonstrates protective effects of apocynin in diabetic nephropathy, neuropathy, cardiomyopathy, and retinopathy, where modulation of oxidative and inflammatory cascades contributes to preservation of structural integrity and functional outcomes.

Importantly, apocynin acts not merely as a conventional antioxidant but as a regulator of redox-dependent signaling networks influencing metabolic stability, insulin responsiveness,

mitochondrial integrity, and cellular survival. Its ability to simultaneously modulate oxidative, inflammatory, and metabolic pathways positions apocynin as a promising adjunct therapeutic candidate in diabetes. However, despite encouraging preclinical findings, translation into clinical application remains limited, underscoring the need for further pharmacological and translational evaluation.

Future research should focus on addressing key translational challenges associated with apocynin, including optimization of formulation strategies to improve bioavailability, detailed pharmacokinetic and pharmacodynamic profiling, and clarification of tissue-specific mechanisms of action. Well-designed clinical studies are required to establish safety, efficacy, and long-term therapeutic benefit in diabetic patients. Additionally, exploration of combination strategies integrating apocynin with standard antidiabetic therapies may offer synergistic benefits by targeting both glycemic control and redox-inflammatory pathways. A deeper understanding of its interaction with emerging molecular targets, including inflammasome signaling and redox-sensitive transcription factors, will further define its therapeutic potential in mitigating diabetic complications.

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Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

Permission to Reproduce Material from other Sources

Not Applicable

Author Contributions

Ubaidur Rahman Khan: Conceptualization, Visualization, Methodology, Writing; Kishor Otari: Visualization, Supervision, Review; Ajay Kale: Visualization, Supervision, Review.

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