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REVIEW ARTICLE

The Complex Landscape of Diabetic Neuropathy: A Review of Mechanisms and Management Approaches

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Abstract

Betanin, a natural pigment derived from beetroot, has demonstrated promising anticancer properties, particularly in colon cancer (CC). In this study, we employed a network pharmacology approach to elucidate the molecular mechanisms of betanin in CC treatment. Potential targets of betanin were identified through online databases and compared with CC-related genes to determine key overlapping targets. A protein-protein interaction (PPI) network was constructed, and core hub targets were analyzed. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses highlighted key biological processes and signaling pathways involved in CC treatment, such as apoptosis regulation, oxidative stress modulation, and inhibition of cell proliferation. Our findings suggest that betanin exerts anticancer effects by modulating critical molecular targets and signaling pathways, providing a basis for further experimental validation and therapeutic development.

1. Introduction

Diabetic neuropathy (DN) is a major microvascular complication of diabetes mellitus (DM) and a leading cause of morbidity, significantly impairing quality of life and increasing the risk of secondary complications such as foot ulcers and amputations (Ansari et al., 2021; Fan et al., 2025). The condition manifests in various forms, including sensory, motor, and autonomic neuropathies, with distal symmetric polyneuropathy (DSPN) accounting for nearly 75% of cases (Samakidou et al., 2021). The global prevalence of DN is rising in parallel with the increasing incidence of diabetes, underscoring the urgent need for improved diagnostic and therapeutic strategies.

The pathophysiology of DN is highly complex, involving a cascade of metabolic, vascular, and inflammatory processes that collectively contribute to nerve damage (Méndez-Morales et al., 2022). Persistent hyperglycemia initiates a series of detrimental pathways, including increased polyol flux, accumulation of advanced glycation end products (AGEs), activation of protein kinase C (PKC), and mitochondrial dysfunction, all of which exacerbate oxidative stress and impair neuronal function (Luo et al., 2016). Furthermore, microvascular insufficiency and neuroinflammation play critical roles in the progression of nerve fiber degeneration (Madeira et al., 2015). Despite extensive research, the translation of mechanistic insights into effective clinical therapies has been limited, leaving a significant unmet need for disease-modifying treatments.

This review aims to synthesize current knowledge on the pathogenesis, clinical manifestations, diagnostic approaches, and management of DN, with a particular focus on emerging therapeutic strategies. By integrating findings from preclinical and clinical studies, we provide a comprehensive overview of the challenges and opportunities in DN research and clinical care.

2. Classification and Clinical Presentation of Diabetic Neuropathy

Diabetic neuropathy is not a single entity but rather a spectrum of disorders classified based on the distribution of affected nerves and the type of fibers involved. The most widely recognized classification system divides DN into generalized symmetric polyneuropathies, autonomic neuropathies, and focal or multifocal neuropathies.

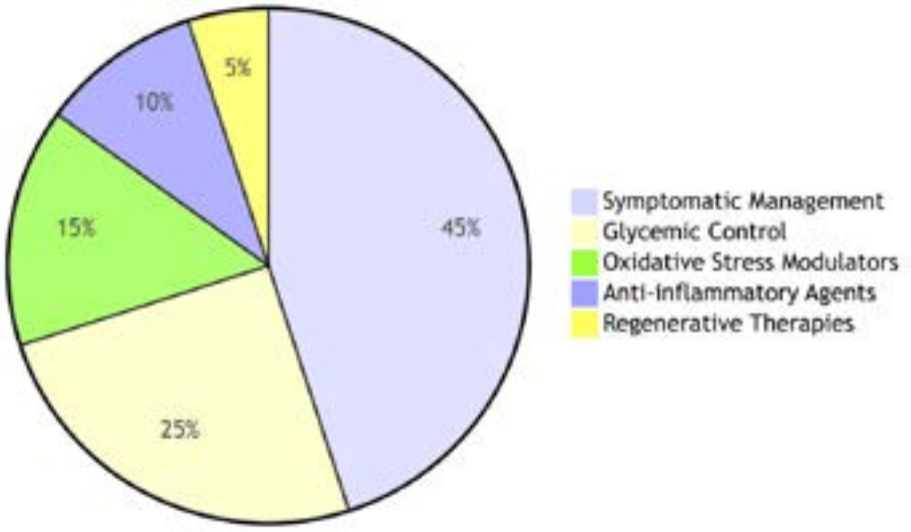

Figure 1: Current vs Emerging Treatment Approaches

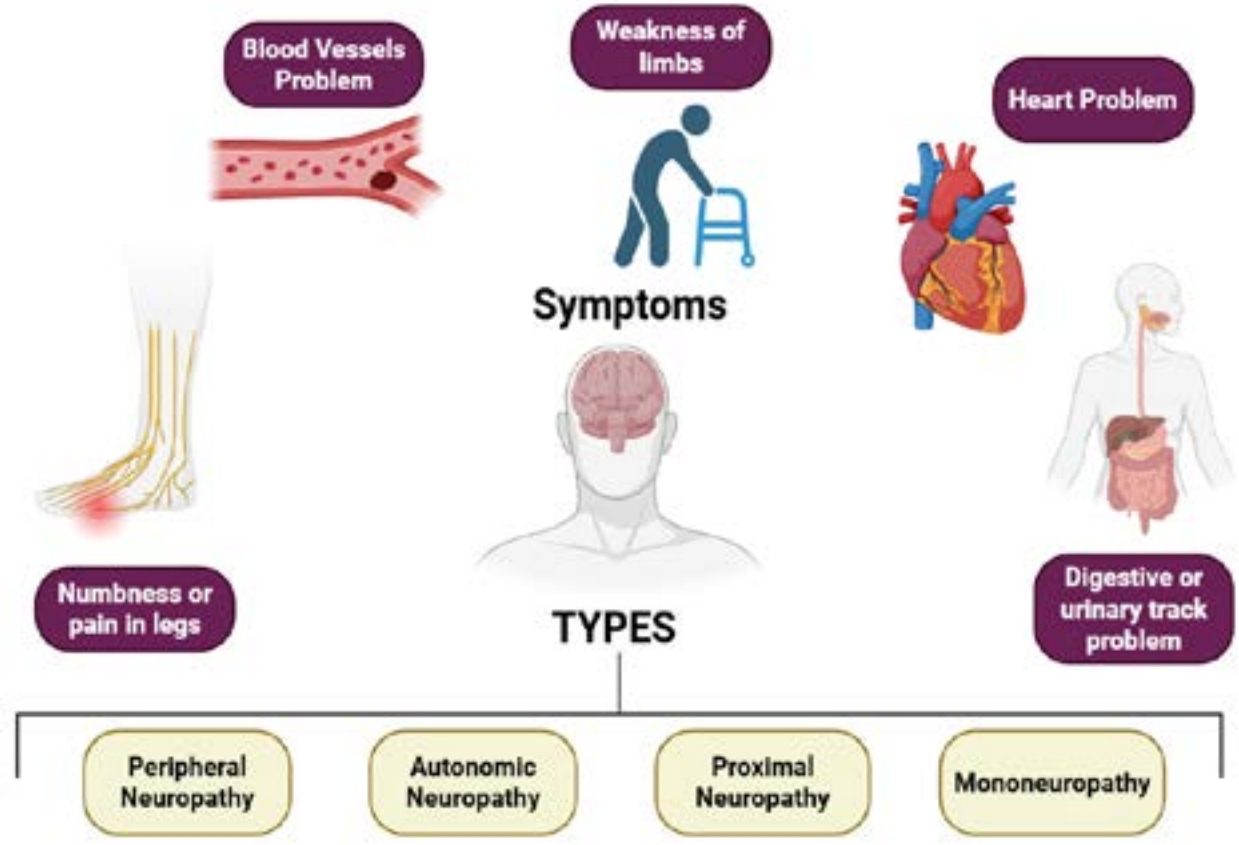

Figure 2: Overview of diabetic neuropathy symptoms and types. Common symptoms include numbness or pain in the legs, weakness of limbs, and complications related to blood vessels, heart, and digestive or urinary systems. The major types of diabetic neuropathy are peripheral neuropathy, autonomic neuropathy, proximal neuropathy, and mononeuropathy

2.1. Distal Symmetric Polyneuropathy (DSPN)

DSPN is the most prevalent form, accounting for approximately 75% of all diabetic neuropathies (Smith et al., 2022). It typically presents with a progressive, length-dependent pattern, initially affecting the distal extremities in a "stocking-glove" distribution. Early symptoms often include tingling, burning pain, and heightened sensitivity to touch (allodynia), which may progress to complete sensory loss in advanced stages. The loss of protective sensation significantly increases the risk of foot ulcers and subsequent amputations, making DSPN a major contributor to diabetes-related morbidity (Savelieff et al., 2025; Sloan et al., 2021).

2.2. Autonomic Neuropathy

Autonomic neuropathy affects nearly 20-40% of diabetic patients and can involve multiple organ systems, including the cardiovascular, gastrointestinal, and genitourinary systems (Balcıoğlu, 2015). Cardiovascular autonomic neuropathy (CAN) is particularly concerning, as it may lead to resting tachycardia, exercise intolerance, and an increased risk of silent myocardial ischemia. Gastrointestinal manifestations include gastroparesis, constipation, or diarrhea, while genitourinary involvement often results in bladder dysfunction and erectile dysfunction in men (Figure 1) (Bell, 2023).

2.3. Focal and Multifocal Neuropathies

Focal neuropathies, though less common (<10% of cases), present with sudden-onset deficits in specific nerves or nerve roots (Collins and Hadden, 2017). Cranial neuropathies (e.g., Bell's palsy), radiculopathies (e.g., diabetic lumbosacral radiculoplexus neuropathy), and compression mononeuropathies (e.g., carpal tunnel syndrome) are notable examples. These conditions often have a more acute presentation compared to the insidious progression of DSPN.

3. Pathophysiological Mechanisms of Diabetic Neuropathy

The development and progression of DN are driven by a complex interplay of metabolic, vascular, and inflammatory mechanisms. Chronic hyperglycemia serves as the primary instigator, activating multiple pathways that collectively contribute to nerve damage (Figure 2).

3.1. Hyperglycemia-Induced Metabolic Dysregulation

Sustained hyperglycemia triggers several metabolic disturbances that impair neuronal function. The polyol pathway is particularly significant, where excess glucose is converted to sorbitol by aldose reductase, consuming NADPH in the process (Yan, 2018). This depletion of NADPH reduces the availability of glutathione, a critical antioxidant, thereby exacerbating oxidative stress. Additionally, the accumulation of sorbitol within Schwann cells leads to osmotic stress and subsequent cellular damage (Gonçalves et al., 2017; Hao et al., 2015).

Another key mechanism involves the formation of advanced glycation end products (AGEs), which result from non-enzymatic glycation of proteins and lipids (Vekic et al., 2023). AGEs interact with their receptor (RAGE) to activate pro-inflammatory signaling pathways, including nuclear factor-kappa B (NF-κB), further promoting oxidative stress and neuronal injury. Protein kinase C (PKC) activation, particularly the β-isoform, contributes to microvascular dysfunction by impairing endothelial nitric oxide synthase (eNOS) activity, reducing blood flow to peripheral nerves (Fu et al., 2021; Pan et al., 2022).

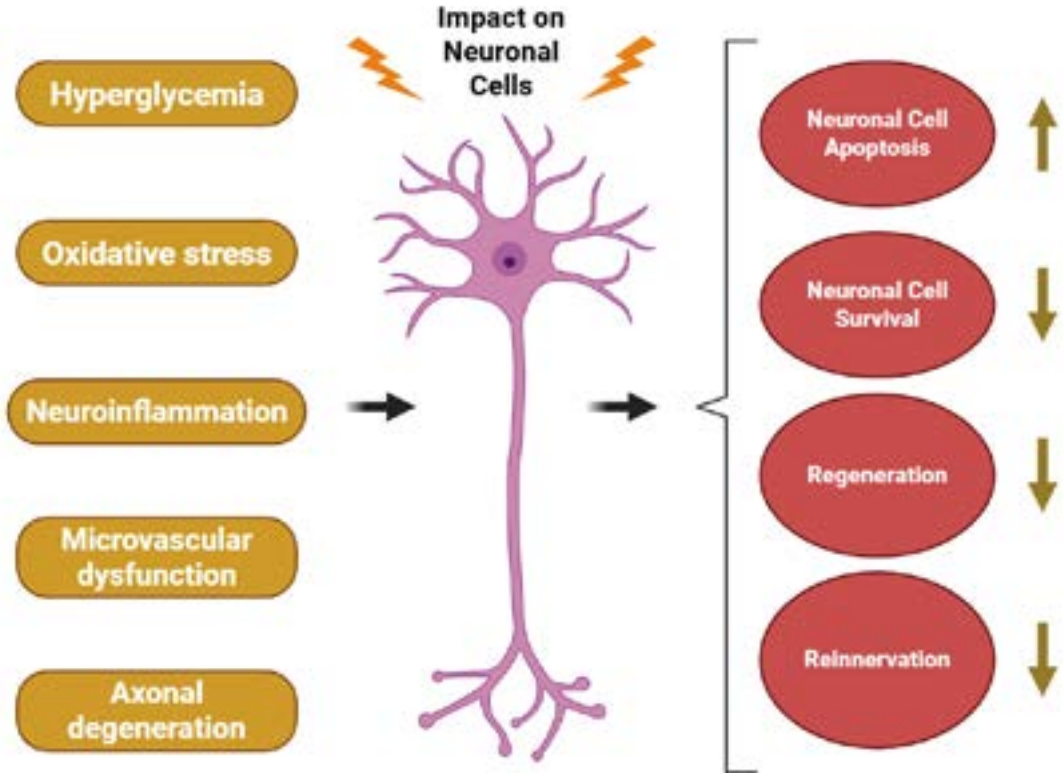

Figure 3: The key pathophysiological mechanisms underlying diabetic neuropathy. Hyperglycemia initiates oxidative stress, which contributes to neuroinflammation. Neuroinflammation further leads to microvascular dysfunction and axonal degeneration. The combined effects of these processes impact neuronal cells, resulting in neuronal cell apoptosis, impaired neuronal cell survival, and compromised regeneration and reinnervation

Table 1: Mechanistic Pathways and Therapeutic Targets in Diabetic Neuropathy

Pathogenic Mechanism	Key Molecular Players	Current Interventions	Emerging Approaches
Hyperglycemia-induced metabolic stress	Polyol pathway flux, AGEs, PKC activation	Aldose reductase inhibitors (epalrestat), Benfotiamine	PKC-β isoform-specific inhibitors
Oxidative stress	ROS, Nrf2 pathway, mitochondrial dysfunction	α-Lipoic acid (600mg IV/ oral)	Nrf2 activators (bardoxolone)
Microvascular dysfunction	Endothelin-1, VEGF deficit, NO deficiency	PDE-5 inhibitors (sildenafil)	Pro-angiogenic exosomes
Neuroinflammation	TNF-α, IL-6, NLRP3 inflammasome	Low-dose naltrexone	IL-17A monoclonal antibodies
Axonal degeneration	Neurotrophin deficiency, WNT signaling	Acetyl-L-carnitine	BDNF gene therapy

3.2. Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress is a central player in DN pathogenesis, driven by an imbalance between reactive oxygen species (ROS) production and antioxidant defenses (Afzal et al., 2023; Houldsworth, 2023). Hyperglycemia-induced mitochondrial dysfunction leads to excessive electron leakage from the electron transport chain, generating superoxide radicals that damage cellular lipids, proteins, and DNA. The resulting oxidative injury disrupts axonal transport, impairs nerve conduction, and promotes apoptotic signaling in neurons and Schwann cells (Frati et al., 2017; Lv et al., 2018).

3.3. Microvascular Insufficiency

Endothelial dysfunction and reduced perfusion of the vasa nervorum (small blood vessels supplying peripheral nerves) contribute significantly to DN progression (Maiuolo et al., 2019). Chronic hyperglycemia impairs vasodilation by diminishing nitric oxide (NO) bioavailability and promoting endothelin-1-mediated vasoconstriction (Gluvic et al., 2024). The resulting endoneurial hypoxia exacerbates oxidative stress and energy deficiency, further compromising nerve function.

3.4. Neuroinflammation

Emerging evidence highlights the role of low-grade chronic inflammation in DN. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) are elevated in diabetic nerves and contribute to neuropathic pain and axonal degeneration (Khan et al., 2017; Nashtahosseini et al., 2025). Immune cell infiltration, particularly macrophages, further amplifies inflammatory damage within the peripheral nervous system.

4. Diagnostic Approaches

Early and accurate diagnosis of DN is essential to prevent irreversible nerve damage and associated complications. A combination of clinical evaluation, electrophysiological testing, and specialized techniques is employed to assess neuropathy severity and subtype.

4.1. Clinical Assessment

A thorough clinical history and neurological examination remain the cornerstone of DN diagnosis. Symptoms such as burning pain, numbness, and tingling in the distal extremities are highly suggestive of DSPN (Chang and Yang, 2023; Kaku et al., 2015). Physical examination should include assessments of vibration perception (using a 128-Hz tuning fork), light touch (monofilament testing), and ankle reflexes, which are typically diminished or absent in advanced cases.

4.2. Electrophysiological Studies

Nerve conduction studies (NCS) are the gold standard for evaluating large fiber neuropathy, providing objective measures of sensory and motor nerve conduction velocities (NCV) and amplitudes (Ahn et al., 2018). Prolonged latencies and reduced amplitudes are indicative of axonal degeneration and demyelination (Simkins et al., 2021). However, NCS may be normal in early small fiber neuropathy, necessitating additional diagnostic modalities.

4.3. Quantitative Sensory Testing (QST)

QST assesses small fiber function by measuring thermal and vibration thresholds (Hansen et al., 2015). Although non-invasive, it is subjective and requires patient cooperation. Abnormalities in thermal perception are often early markers of small fiber involvement.

4.4. Skin Biopsy for Intraepidermal Nerve Fiber Density (IENFD)

Skin biopsy with quantification of IENFD is the most sensitive and specific method for diagnosing small fiber neuropathy (Kelley and Hackshaw, 2021). A reduction in epidermal nerve fibers is a hallmark of early DN and correlates with symptom severity. Declarations

5. Current and Emerging Management Strategies

The management of diabetic neuropathy (DN) requires a comprehensive, multimodal approach that addresses both the underlying metabolic dysfunction and the debilitating symptoms of nerve damage. Current strategies focus on glycemic control, pharmacological interventions for pain relief, and emerging therapies that target disease progression. Additionally, non-pharmacological interventions play a crucial role in improving patient outcomes.

5.1. Glycemic Control

Intensive glycemic control remains the cornerstone of DN prevention and management, particularly in type 1 diabetes. The landmark Diabetes Control and Complications Trial (DCCT) demonstrated that tight glucose control

Table 2: Clinical Management Algorithm by Neuropathy Stage

Disease Stage	Diagnostic Features	First-line Therapy	Adjunctive Options	Monitoring Parameters
Early (subclinical)	IENFD reduction, QST abnormalities	Intensive glycemic control + ALA	Lifestyle modification	Annual QST, skin biopsy
Moderate (painful)	NCS abnormalities, allodynia	Pregabalin + duloxetine	TENS, capsaicin patch	Pain diaries, NCS q2y
Advanced (insensate)	Foot deformities, ulcer history	Custom footwear + falls prevention	Regenerative therapies	Foot exams 3-6 monthly
Autonomic involvement	Orthostasis, gastroparesis	Fludrocortisone (CAN), prokinetics	Pyridostigmine	Tilt-table testing, GES

(HbA1c <7%) significantly reduces the incidence and progression of neuropathy in type 1 diabetic patients (Pinto et al., 2020). However, the benefits in type 2 diabetes are less clear, as evidenced by the UK Prospective Diabetes Study (UKPDS) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which showed only modest reductions in neuropathy risk despite aggressive glucose management. This discrepancy suggests that additional factors, such as insulin resistance, dyslipidemia, and hypertension, contribute to nerve damage in type 2 diabetes (Tangvarasittichai, 2015). Therefore, while optimizing blood glucose levels is essential, it must be combined with other therapeutic strategies to achieve meaningful neuroprotection. Emerging evidence also suggests that glucose variability, rather than sustained hyperglycemia alone, may exacerbate nerve injury, highlighting the need for continuous glucose monitoring (CGM) in high-risk patients.

5.2. Pharmacological Therapies

5.2.1. Gabapentin and Pregabalin:

These anticonvulsants modulate voltage-gated calcium channels (specifically the α2δ subunit) in the central nervous system, reducing neuronal hyperexcitability and pain transmission (Guo et al., 2025). Pregabalin, with its more predictable pharmacokinetics, is often preferred, though both drugs can cause dizziness, sedation, and peripheral edema. Clinical trials have demonstrated their efficacy in reducing pain scores by 30-50% in DN patients.

5.2.2. Duloxetine:

A serotonin-norepinephrine reuptake inhibitor (SNRI), duloxetine enhances descending inhibitory pain pathways in the spinal cord (de Liyis et al., 2024). It is particularly effective in diabetic neuropathy, with studies showing significant pain reduction compared to placebo. However, side effects such as nausea, dry mouth, and fatigue may limit its use in some patients.

5.2.3. Tricyclic Antidepressants (TCAs):

Amitriptyline, a non-selective TCA, has been used for decades due to its analgesic properties, which are independent of its antidepressant effects (Windsor et al., 2020). It inhibits norepinephrine and serotonin reuptake and blocks sodium channels, providing pain relief. However, anticholinergic side effects (e.g., dry mouth, constipation, urinary retention) and cardiac risks (prolonged QT interval) restrict its use, particularly in elderly patients. Second-line options include tramadol, a weak opioid with SNRI activity, and topical capsaicin, which depletes substance P in nociceptive fibers. Long-term opioid use is generally discouraged due to risks of dependence, tolerance, and opioid-induced hyperalgesia.

5.2.4. α-Lipoic Acid (ALA):

A potent antioxidant, ALA scavenges reactive oxygen species (ROS) and regenerates endogenous antioxidants like glutathione (Tripathi et al., 2023). Clinical trials, including the SYDNEY studies, have shown that intravenous ALA (600 mg/day) improves neuropathic symptoms and nerve conduction velocity. Oral ALA has more variable efficacy due to lower bioavailability.

5.2.5. Benfotiamine:

A lipid-soluble thiamine derivative, benfotiamine inhibits the formation of advanced glycation end products (AGEs) by activating transketolase, which redirects glycolytic intermediates toward the pentose phosphate pathway (Zaitseva et al., 2024). Small studies suggest it may improve nerve function and reduce pain, though larger confirmatory trials are needed.

5.3. Non-Pharmacological Approaches

5.3.1. Lifestyle Interventions:

Weight loss and regular exercise improve insulin sensitivity, glycemic control, and microvascular perfusion. The Look AHEAD trial demonstrated that intensive lifestyle intervention reduces neuropathy incidence in obese type 2 diabetic patients. Aerobic and resistance training also enhance nerve regeneration and reduce neuropathic pain (Chiaramonte et al., 2023).

5.3.2. Electrical Stimulation:

Transcutaneous electrical nerve stimulation (TENS) delivers low-voltage electrical currents to disrupt pain signals. While evidence is mixed, some patients report significant pain relief, particularly when combined with pharmacotherapy. High-frequency spinal cord stimulation (SCS) is an emerging invasive option for refractory pain (Bicket et al., 2016), showing promise in small trials.

5.4. Emerging Therapies

5.4.1. Stem Cell Therapy:

Mesenchymal stem cells (MSCs) promote nerve

regeneration through paracrine effects, secreting neurotrophic factors (e.g., NGF, BDNF) and anti-inflammatory cytokines (Sharifi et al., 2024). Preclinical studies show improved nerve conduction and vascularization, and early-phase human trials are underway.

5.4.2. Gene Therapy:

Viral vector-mediated delivery of neurotrophic genes (e.g., VEGF, NGF) enhances nerve repair in animal models (Kumari et al., 2025). Challenges include ensuring targeted delivery and avoiding off-target effects. CRISPR-based approaches to correct metabolic defects in Schwann cells are also being explored.

5.4.3. Immunomodulation:

Therapies targeting pro-inflammatory cytokines (e.g., TNF-α inhibitors) or the NLRP3 inflammasome may mitigate neuroinflammation (Thawkar and Kaur, 2019). SGLT2 inhibitors, beyond their glycemic effects, show potential in reducing oxidative stress and improving nerve function.

6. Future Perspectives

Despite advances, significant gaps remain in DN management. The identification of reliable biomarkers for early diagnosis, development of targeted therapies, and personalized treatment approaches based on genetic and metabolic profiling are critical areas for future research.

7. Conclusion

Diabetic neuropathy remains a major clinical challenge due to its complex pathophysiology and limited treatment options. While current strategies focus on symptom management, emerging research into oxidative stress, neuroinflammation, and regenerative therapies offers hope for disease modification. A multidisciplinary approach integrating early diagnosis, glycemic control, and novel interventions is essential to improve outcomes for patients with DN.

Declarations

Ethics approval statement

No ethical approval was required for the current study as it did not deal with any human or animal samples.

Consent to participate

Not applicable

Consent to publish

Not applicable

Data Availability Statement

The data are available from the corresponding author upon reasonable request

Competing Interests

The authors declare that they have no conflict of interest

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Author contribution

Conceptualization: M.D, Data curation, Investigation: S.P, A.J, G.S, Formal analysis: S.N.P.S.H. Writing—review and editing: T.V. All authors have read and agreed to the published version of the manuscript

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