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Phytochemicals in Diabetic Neuropathy: From Traditional Remedies to Modern Science

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ABSTRACT

Diabetic neuropathy is one of the most prevalent and serious consequences of diabetes, characterized by chronic discomfort, sensory loss, and gradual nerve damage. Current pharmacological treatments give symptomatic relief but do not address underlying causes such as oxidative stress, inflammation, mitochondrial dysfunction, and advanced glycation end-product build-up. Phytochemicals are gaining popularity as viable therapeutic agents due to their varied bioactivities, which include antioxidant, anti-inflammatory, and glucose-modulating properties. Traditional systems such as Ayurveda, Traditional Chinese Medicine, and Unani have long used herbal formulations including turmeric, ginseng, fenugreek, and ashwagandha for nerve-related illnesses, and modern research has begun verifying these therapies through preclinical and clinical trials. Curcumin, resveratrol, ginsenosides, and alkaloids are examples of phytochemicals with neuroprotective properties. They improve nerve conduction, modulate oxidative stress, and promote neuronal regeneration. Experiments show that they can minimize oxidative and inflammatory damage, improve mitochondrial function, and control neurotrophic factors. However, clinical applicability is still limited due to difficulties such as low bioavailability, a lack of uniformity, and insufficient large-scale investigations. To address these limitations, researchers are investigating advances in nanotechnology-based delivery methods, herbal-drug combination tactics, and customized treatment approaches. Overall, phytochemicals serve as a bridge between traditional treatments and current science, providing multi-targeted techniques that may supplement or enhance existing therapies. These plant-derived chemicals have tremendous potential for safer, more effective, and long-term diabetic neuropathy care since they address both symptomatic alleviation and disease change.

Keywords: Diabetic neuropathy, phytochemicals, oxidative stress, neuroprotection, traditional medicine, nanotechnology

INTRODUCTION

Diabetic neuropathy (DN) is a microvascular and metabolic consequence of diabetes mellitus that causes gradual damage to peripheral, autonomic, and cranial nerves as a result of chronic hyperglycaemia and related metabolic changes. It is considered one of the most widespread and devastating consequences of diabetes, affecting an estimated 30–50% of diabetic individuals globally. (Pop-Busui et al., n.d.) (Tesfaye et al., 2012). Clinically, the illness appears as neuropathic pain, tingling, sensory loss, and motor dysfunction, all of which reduce quality of life and predispose patients to serious complications such as foot ulcers, recurring infections, and amputations. Diabetic neuropathy accounts for almost 75% of non-traumatic

lower limb amputations worldwide, posing a tremendous burden on both healthcare systems and patients. (Callaghan et al). The pathogenesis of diabetic neuropathy is multifactorial, involving oxidative stress, inflammation, mitochondrial dysfunction, impaired nerve blood flow, and accumulation of advanced glycation end products (AGEs). These processes culminate in axonal degeneration, demyelination, and loss of nerve conduction (Feldman et al., n.d.). Current treatment strategies, however, are primarily symptomatic rather than curative. Clinically prescribed medications such as anticonvulsants (gabapentin, pregabalin), antidepressants (duloxetine, amitriptyline), and opioid analgesics provide partial relief but fail to halt disease progression. Furthermore, these drugs are often limited by adverse effects such as sedation, dizziness, gastrointestinal disturbances, and cognitive dysfunction, which can reduce patient adherence (Brown et al., 1984). Importantly, no FDA-approved therapy currently exists that can prevent or reverse the underlying nerve injury in diabetic neuropathy, emphasizing the urgent need for safer, multi-targeted therapeutic approaches (Alberti et al., 2006). In recent years, phytochemicals bioactive secondary metabolites derived from plants have gained attention as potential neuroprotective agents**.** Historically, medicinal plants have been used in Ayurvedic, Chinese, and other traditional medicine systems to manage nerve-related disorders. Modern pharmacological evidence supports these practices, showing that phytochemicals such as flavonoids, terpenoids, alkaloids, polyphenols, and saponins possess antioxidant, anti-inflammatory, anti-apoptotic, and neurodegenerative propertie**s** (Kumar et al., n.d.) (Piccialli et al., 2022). These compounds act on multiple pathogenic pathways simultaneously, making them especially valuable in a disease as complex as diabetic neuropathy. Several phytochemicals have shown promise in experimental studies. For instance, curcumin, a polyphenol from turmeric (*Curcuma longa*), has been shown to reduce oxidative stress, suppress pro-inflammatory cytokines, and improve nerve conduction in diabetic models (Wang et al). Resveratrol, a stilbene found in grapes and berries, improves mitochondrial function and modulates inflammatory signalling, resulting in neuroprotection (Hu et al., 2022). Similarly, quercetin (a flavonoid), ginsenosides (triterpenoid saponins), and berberine (an alkaloid) have demonstrated strong neuroprotective effects in preclinical studies (Moradi et al., 2022).Despite promising laboratory findings, the clinical application of phytochemicals faces challenges, including poor solubility, low bioavailability, lack of standardization, and insufficient large-scale human trials (Rahman et al., 2022). Addressing these limitations through novel delivery systems (e.g., nanoparticles, hydrogels) and combination therapies may enhance their therapeutic potential.

Thus, phytochemicals represent a bridge between traditional remedies and modern science, offering a promising and multi-mechanistic approach to diabetic neuropathy management (Moradi et al., 2022). Understanding their roles and mechanisms provides a pathway toward developing effective, safe, and sustainable interventions for this chronic complication (Rahman et al., 2022).

PATHOPHYSIOLOGY OF DIABETIC NEUROPATHY

Diabetic neuropathy is a common and debilitating consequence of both type 1 and type 2 diabetes mellitus that causes progressive damage to the peripheral nerve system. The underlying etiology is complex, consisting of metabolic abnormalities, vascular dysfunction, and chronic inflammation caused by prolonged hyperglycaemia. These disruptions trigger a series of molecular and physiological processes, including oxidative stress, mitochondrial dysfunction, the build-up of advanced glycation end products (AGEs), polyol pathway

activation, and decreased neurovascular function. Understanding these pathways is crucial for developing therapeutic methods that address both symptom control and disease progression.

- **OXIDATIVE STRESS:** Oxidative stress is a key mechanism in diabetic neuropathy, serving as both a trigger and an amplifier of neuronal destruction. Chronic hyperglycaemia causes excessive glucose metabolism in mitochondria, resulting in high levels of reactive oxygen species (ROS), mainly superoxide anions. This overwhelms endogenous antioxidant defences such superoxide dismutase, catalase, and glutathione peroxidase, resulting in oxidative damage to neuronal DNA, proteins, and lipids (Vincent et al., n.d.). ROS disturb mitochondrial membrane potential, reducing ATP generation and axonal transport, both of which are required for neuronal survival. Oxidative stress also activates poly (ADP-ribose) polymerase (PARP), which consumes NAD+ and exacerbates energy failure (Gonçalves et al., n.d.-a). Furthermore, ROS increase other harmful pathways, including as the polyol pathway and AGE production, resulting in a self-sustaining cycle of injury. Clinical investigations show that patients with diabetic neuropathy have more lipid peroxidation products, such as malondialdehyde (MDA), which correlates with disease severity. Research indicates that antioxidants such as α-lipoic acid and resveratrol can reduce oxidative stress, increase nerve conduction velocity, and prevent neuronal death (Mallet et al., 2020). Thus, oxidative stress is still one of the most relevant treatment targets in diabetic neuropathy.
- **INFLAMMATION:** Inflammation plays an important role in the pathogenesis of diabetic neuropathy, linking metabolic failure to neuronal damage. Chronic hyperglycaemia stimulates the transcription factor NF-κB, upregulating pro-inflammatory cytokines such TNF-α, IL-1β, and IL-6 (Mallet et al., 2020). These cytokines cause demyelination, Schwann cell death, and increased neural excitability, which results in neuropathic pain. Furthermore, macrophage migration into peripheral nerves and activation of microglia in the dorsal root ganglia exacerbate neuroinflammation by releasing more inflammatory mediators (Singh Jaggi et al., 2014) . Chronic inflammation also compromises vascular endothelial function, lowering nitric oxide levels and causing microvascular ischemia. Clinical investigations show that diabetic patients with neuropathy have greater serum levels of pro-inflammatory cytokines than those without neuropathy, underscoring the clinical significance of this route (Vinik et al.)Preclinical studies show that anti-inflammatory phytochemicals such curcumin, quercetin, and resveratrol inhibit NF-κB activity and cytokine production, protecting neurons against inflammation-induced death. As a result, inflammation not only leads to neuronal deterioration but also promotes the long-term evolution of diabetic neuropathy.
- **ADVANCED GLYCATION END PRODUCTS (AGES):** Another major cause of diabetic neuropathy is AGEs, which are generated by non-enzymatic glycation of proteins, lipids, and nucleic acids during persistent hyperglycaemia. Their build-up changes protein structure, decreases enzyme activity, and disturbs cytoskeletal stability .Binding AGEs to their receptor (RAGE) stimulates oxidative stress and inflammatory signalling via NF-κB and MAPK pathways, exacerbating neuronal dysfunction (Singh Jaggi et al., 2014). AGE cross-linking stiffens extracellular matrix proteins and thickens vascular basement membranes, limiting nerve blood flow and causing ischemia. Furthermore, AGEs alter calcium homeostasis in neurons, inhibit axonal transport, and cause myelin destruction. Clinical investigations show that higher circulating AGEs in diabetic individuals with neuropathy are closely associated with nerve conduction impairments and pain severity(Forbes & Cooper, 2013). Importantly, drugs that block AGE production, such as aminoguanidine and naturally occurring flavonoids, have shown protective effects in preclinical studies. AGEs are regarded an important therapeutic target since they operate as metabolic poisons as well as amplifiers of oxidative and inflammatory pathways (Srinivasan et al.).

- **MITOCHONDRIAL DYSFUNCTION:** Mitochondria are extremely vulnerable to hyperglycaemia-induced damage and play a critical role in diabetic neuropathy development. Excess glucose metabolism in mitochondria produces ROS, which destabilizes the mitochondrial membrane and causes permeability transition holes to open (Srinivasan et al.). This alters membrane potential, lowers ATP generation, and impairs axonal transport. Damaged mitochondria also emit cytochrome C, which causes caspase-mediated apoptosis in sensory neurons and Schwann cells (Gonçalves et al.). Furthermore, mitochondrial dynamics including fusion, fission, and biogenesis are disrupted, restricting organelle repair and regeneration. Oxidative stress also damages mitochondrial DNA (mtDNA), which impairs energy production. Histopathological investigations show enlarged, structurally aberrant mitochondria in the peripheral nerves of diabetic individuals and animal models (Vinik et al., n.d.).Experimental therapy for mitochondrial dysfunction, such as coenzyme Q10, resveratrol, and exercise, have shown better bioenergetics and reduced neuropathic symptoms. Thus, mitochondrial dysfunction is both a cause and a consequence of neuronal damage in diabetic neuropathy.
- **POLYOL PATHWAY ACTIVATION:** Hyperglycaemia over activates the polyol pathway, which contributes to a variety of nerve injury. Normally, only a little amount of glucose is processed via this mechanism. In diabetes, however, excess glucose is turned into sorbitol by aldose reductase before being transformed into fructose by sorbitol dehydrogenase. Sorbitol build-up produces osmotic stress in neurons, resulting in axonal swelling and dysfunction. This mechanism depletes NADPH, which is necessary for glutathione regeneration, weakening antioxidant defences and aggravating oxidative stress. Furthermore, fructose metabolism generates reactive intermediates, which increase AGE production. Overactivation of the polyol pathway decreases Na^+/K^+-ATPase function, leading to impaired ion gradients for nerve transmission. Animal studies using aldose reductase inhibitors show enhanced nerve conduction and lower oxidative stress, but human clinical results have been variable. Interestingly, natural substances like quercetin and green tea catechins inhibit aldose reductase, providing safer options. Thus, the polyol route connects metabolic excess to oxidative and structural nerve damage (Yunus et al., 2011).
- **NEUROVASCULAR DYSFUNCTION:** Vascular anomalies are an important but often overlooked mechanism of diabetic neuropathy. Chronic hyperglycaemia affects vascular endothelial cells, resulting in decreased nitric oxide bioavailability and vasodilation. This causes microangiopathy of the vasa nervorum, or small blood arteries that supply peripheral nerves. Thickening of the capillary basement membrane and pericyte loss impair oxygen and nutrient delivery, resulting in ischemia and hypoxia. These alterations are linked to axonal degradation, Schwann cell death, and poor nerve regeneration. Furthermore, AGEs and oxidative stress increase vascular stiffness and inflammation, increasing microcirculatory dysfunction. Imaging investigations on diabetes patients reveal lower blood flow in peripheral nerves, which correlates with disease severity. Experimental research indicates that vascular endothelial growth factor (VEGF) injection enhances neuronal blood flow and function, but phytochemicals such as resveratrol and ginsenosides increase endothelial function by increasing nitric oxide generation. Thus, neurovascular dysfunction interacts with metabolic abnormalities, contributing to the onset and progression of diabetic neuropathy (Faheem et al., 2022) shown in **Fig.1**

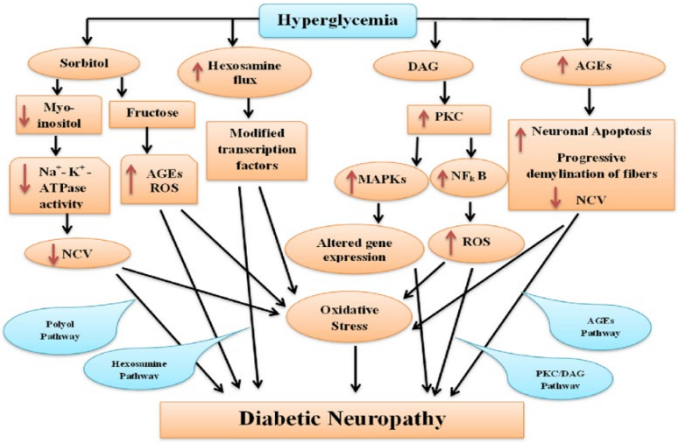

Figure 1. Major pathophysiological mechanisms of diabetic neuropathy, including oxidative stress, inflammation, AGEs accumulation, mitochondrial dysfunction, polyol pathway activation, and neurovascular damage.

TRADITIONAL REMEDIES FOR DIABETIC NEUROPATHY

Traditional medicine systems such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani have been used for centuries to treat chronic ailments, including diabetes and its consequences. While contemporary medicine provides pharmaceutical therapies, traditional systems stress comprehensive healing by restoring bodily equilibrium. As scientific validation grows, several of these medicines are being studied for their phytochemical contents and modes of action.

- **AYURVEDIC APPROACHES:** Ayurveda, the ancient Indian medical system, focuses on balancing body energy (doshas) and the use of herbs with neuroprotective and antioxidant qualities. Turmeric (Curcuma longa), ashwagandha (Withania somnifera), and triphala are used to treat nerve diseases. Turmeric's curcumin concentration decreases oxidative stress and inflammation by regulating NF-κB signalling, a key factor in diabetic neuropathy development. Ashwagandha possesses adapt genic and neuroprotective properties, which promote nerve regeneration and reduce pain. Ayurvedic formulations frequently contain numerous herbs, which may have synergistic effects in improving circulation, lowering glycation end products, and protecting neurons from hyperglycaemia-induced damage. Recent studies highlight Ayurveda's involvement in moderating mitochondrial dysfunction and enhancing microvascular health, both of which are fundamental to diabetic neuropathy pathogenesis.(Faheem et al., 2022)
- **TRADITIONAL CHINESE MEDICINE (TCM):** Diabetic neuropathy is commonly regarded in Chinese medicine as a disease of "Qi deficiency" and "blood stasis." The treatments include herbal remedies and acupuncture to restore energy flow and circulation. Panax ginseng, a traditional Chinese medicine herb, contains ginsenosides that increase glucose metabolism and neurotrophic factors. Another popular herb is Astragalus membranaceus, which improves peripheral nerve function by lowering oxidative stress and increasing endothelial nitric oxide generation. Herbal combinations, such as "Tang Luo Ning," have demonstrated encouraging benefits in clinical investigations, reducing neuropathic pain while improving nerve conduction. TCM combines herbs and acupuncture to accelerate nerve regeneration and enhance circulation, making it a more complete therapy than single-drug therapies.(Hao et al., 2012)
- **UNANI MEDICINE:** Unani medicine, based on Greco-Arabic tradition, treats diabetes problems by balancing humours and employing herbs to restore overall health. Fenugreek (Trigonella frenum-graecum) is a widely used plant with hypoglycaemic and neuroprotective

properties. Its bioactive component, 4-hydroxyisoleucine, boosts insulin secretion and lowers oxidative stress, hence reducing nerve damage. Cinnamon (Cinnamomum verum) is another important Unani treatment that boosts insulin sensitivity and circulation while also promoting nerve function. Unani physicians frequently prescribe polyherbal decoctions and oils for topical use to alleviate nerve pain and burning sensations in the limbs. Recent pharmacological investigations verify several of these therapies by revealing their efficacy in lowering advanced glycation end products and enhancing mitochondrial activity, both of which are significant players in diabetic neuropathy approaches.(A. Ali et al., 2022)

COMMON HERBAL REMEDIES ACROSS SYSTEMS

Herbal medications have long been utilized in traditional medical techniques such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani to treat diabetes problems including neuropathy. These herbs provide neuroprotective benefits largely through antioxidant, anti-inflammatory, anti-glycation, and circulation-enhancing mechanisms. Modern pharmacology has increasingly verified these plants' bioactive components, tying them to specific molecular pathways involved in diabetic neuropathy.

- **TURMERIC (CURCUMA LONGA):** Turmeric's therapeutic value is well understood in Ayurveda, Unani, and modern medicine. Curcumin, its main bioactive ingredient, functions as a powerful antioxidant by boosting enzymatic defences such superoxide dismutase and catalase (Hussain et al., n.d.). It decreases inflammatory cytokines (TNF-α, IL-6, IL-1β) and suppresses NF-κB activation, which is a fundamental mediator of diabetic neuropathy (Yadav et al., 2020). Curcumin also inhibits the production of advanced glycation end products (AGEs), which prevents axonal degeneration (Zamanian et al., 2024). Curcumin treatment of diabetic rats enhanced nerve conduction velocity and alleviated hyperalgesia, according to preclinical investigations. Pilot clinical trials have confirmed its efficacy in lowering neuropathic pain scores (Kumar Pasupulati et al., 2016a).
- **GINSENG (PANAX GINSENG, PANAX QUINQUEFOLIUS):** Ginseng is a key herb in Traditional Chinese Medicine, and it is rapidly being explored around the world. Its active components, ginsenosides, increase glucose absorption, improve insulin sensitivity, and stimulate neurotrophic factors like NGF (Zhao et al., 2022). Ginsenosides also protect neurons by regulating calcium signalling and reducing mitochondrial dysfunction (Norouzkhani et al., 2021). Furthermore, they boost nitric oxide-mediated vasodilation, which increases peripheral nerve blood flow. Clinical evidence suggests that ginseng supplementation improves nerve conduction and lowers burning pain in neuropathy patients (Park et al., 2020).
- **FENUGREEK (TRIGONELLA FOENUM-GRAECUM):** Fenugreek, a popular ingredient in Unani medicine, has powerful hypoglycaemic and neuroprotective effects. Its component 4-hydroxyisoleucine enhances insulin secretion and glucose tolerance (Haxhiraj et al., 2024).Fenugreek flavonoids and saponins function as antioxidants, lowering lipid peroxidation and protecting neurons from oxidative stress (Kim et al). Studies in diabetic animals demonstrate that supplementation improves nerve conduction and pain sensitivity. Its soluble fibre also regulates blood glucose, slowing the course of neuropathic problems (Norouzkhani et al., 2021).
- **ASHWAGANDHA (WITHANIA SOMNIFERA):** Ashwagandha, an Ayurvedic adaptogen, has antioxidant, anti-inflammatory, and neurodegenerative properties due to withanolides (Durg et al., 2020). It improves axonal healing and promotes remyelination, restoring nerve conduction (Konar et al., 2011). Ashwagandha lowers cortisol levels, which lessens systemic inflammation and worsens neuropathy. In animal models, studies have shown enhanced nerve conduction velocity, reduced hyperalgesia, and neuronal apoptosis prevention (Lim et al., 2018). It also increases NGF and BDNF expression, which promotes long-term nerve regeneration (Kuboyama et al., 2005).

- **CINNAMON (CINNAMOMUM VERUM / C. CASSIA):** Cinnamon is utilized in both Unani and modern herbal techniques to manage blood sugar and promote nerve function. Its bioactive cinnamaldehyde increases insulin receptor sensitivity, which boosts glucose absorption (Pasupuleti & Anderson, 2009). Cinnamon procyanidins are powerful antioxidants that lower nerve oxidative stress (Kirkham et al., 2009). Furthermore, it increases peripheral circulation and endothelial function, allowing nutrients and oxygen to reach nerves (Rafehi et al., 2012). Cinnamon supplementation in neuropathy models lowers hyperalgesia and allodynia by altering ion channel activity (Qin et al., 2010).
- **GREEN TEA (CAMELLIA SINENSIS):** Green tea, which has long been used in traditional Chinese medicine, contains epigallocatechin-3-gallate (EGCG), a potent antioxidant and anti-glycation agent(Tiwari et al., 2025). EGCG lowers AGEs, limiting structural damage to neuronal proteins, while also stabilizing mitochondria and inhibiting apoptosis (Nguyen et al.).Animal investigations have confirmed its capacity to alleviate allodynia and improve nerve conduction (Shah et al.). Furthermore, green tea improves endothelial function, which restores microvascular blood flow to peripheral neurons. Its global availability and safety make it a viable alternative for long-term neuropathy treatment (Li et al., 2024)
- **RESVERATROL (FROM GRAPES AND BERRIES):** Resveratrol, a stilbene polyphenol, has been extensively researched in modern medicine for neuroprotection. It stimulates SIRT1, promotes mitochondrial activity, and lowers oxidative stress (Wan et al., 2016).Resveratrol also reduces inflammatory cytokines and increases endothelial nitric oxide production, which improves nerve blood flow (Wan et al., 2016). Preclinical investigations have shown considerable improvements in nerve conduction velocity and neuropathic pain reduction (L. Zhu et al., 2025). Early clinical evidence suggests that resveratrol may supplement current therapy in pain relief and glycaemic management (Cao et al., 2018) shown in **Fig 2.**

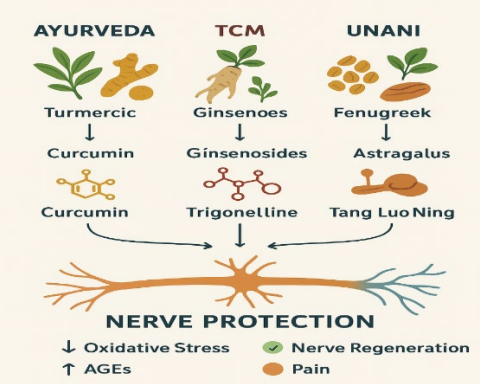

Figure 2. Traditional herbal systems and their bioactive compounds converging to protect nerves in diabetic neuropathy.

PHYTOCHEMICALS WITH NEUROPROTECTIVE POTENTIAL IN DIABETIC NEUROPATHY

- **POLYPHENOLS (FLAVONOIDS AND TANNINS):** Polyphenols are among the most intensively researched phytochemicals due to their antioxidant, anti-inflammatory, and neuroprotective properties. Flavonoids including quercetin, catechins, and rutin can pass the blood-brain barrier and directly affect neuronal survival pathways. They alleviate oxidative stress by scavenging reactive oxygen species (ROS) and activating endogenous antioxidant enzymes such as superoxide dismutase and catalase. Flavonoids can prevent neuronal death in diabetic neuropathy by inhibiting NF-κB signalling and reducing pro-inflammatory cytokines

like TNF-α and IL-6. Tannins, particularly ellagitannins, have been demonstrated to prevent advanced glycation end products (AGEs), which are associated with diabetic problems. Their Vaso protective function also enhances microcirculation, resulting in greater nutrition supply to peripheral neurons. Recent research reveals that polyphenols improve mitochondrial activity and increase nerve conduction velocity in diabetic animals, making them interesting options for treating neuropathy (Saikia et al., 2024) (Pandey et al., 2009a).

- **ALKALOIDS:** Alkaloids, a broad class of nitrogen-containing chemicals, have considerable neuroprotective capabilities in diabetes-induced nerve injury. Berberine, derived from Berberis vulgaris, is known to improve glucose metabolism and reduce oxidative stress in peripheral neurons. It promotes the AMPK signalling pathway, hence improving mitochondrial biogenesis and energy balance. Morphinan-type alkaloids have been found to suppress pro-inflammatory mediators and prevent neuronal death. Furthermore, alkaloids from Catharanthus roseus and Rauwolfia serpentina have antioxidant and vasodilatory properties, which improve peripheral blood flow. They also control calcium and sodium channels, which reduces neuropathic pain and neuron hyperexcitability. In experimental diabetic neuropathy models, alkaloid therapy reduced hyperalgesia and increased temperature sensitivity. Overall, alkaloids have both symptomatic (pain-relieving) and disease-modifying properties, making them dual-action possibilities (C. Zhu et al., 2020a) (Spandana et al.).
- **TERPENOIDS:** Terpenoids are plant-derived secondary metabolites that have potent antioxidant and anti-inflammatory activities. Monoterpenes such as limonene and linalool, as well as diterpenes like carnosic acid (derived from Rosmarinus officinalis), have been related to neuroprotection. Terpenoids work by altering Nrf2/HO-1 signalling, which boosts endogenous antioxidant defence and reduces oxidative stress in neurons. Terpenoids help in nerve regeneration in diabetic neuropathy by stimulating axonal development and Schwann cell activity. Ursolic acid, for example, is a triterpene that reduces AGE build-up while also protecting against mitochondrial dysfunction. Some terpenoids also block the overexpression of inducible nitric oxide synthase (iNOS), which prevents nitrosative stress. Clinical trials on essential-oil-derived terpenoids indicate enhanced nerve conduction and decreased neuropathic pain. Furthermore, their lipophilic structure allows passing through the blood-brain barrier, ensuring direct neuroprotective activity (Alam et al.) (Lima et al.-a).
- **SAPONINS:** Saponins are amphipathic glycosides found in many plants and well-known for their role in nerve protection. Ginsenosides, saponins produced from Panax ginseng, have been found to alter neurotrophic factors such as NGF (nerve growth factor) and BDNF (brain-derived neurotrophic factor), which are essential for nerve survival and regeneration. In diabetic neuropathy, saponins minimize oxidative damage and improve mitochondrial energy metabolism. They also reduce inflammatory cytokines and increase anti-apoptotic proteins like Bcl-2. Dioscin, a steroidal saponin, has been shown to protect neurons from AGE-induced damage. Saponins also increase vascular endothelial function, which ensures proper blood supply to peripheral neurons. Experimental investigations show that saponin therapy improves tactile sensibility, reduces hyperalgesia, and restores myelination. Their multi-targeted method shows their therapeutic usefulness in both the prevention and treatment of diabetes neuropathy (Yong et al., 2005) (Sun et al., 2015).
- **ESSENTIAL OILS:** Essential oils high in terpenes and phenolic compounds are gaining popularity as supplementary treatments for diabetic neuropathy. Lavender oil, which contains linalool and linalyl acetate, has analgesic and anxiolytic properties, lowering neuropathic pain and stress. Rosemary oil, which contains carnosic and rosmarinic acids, protects neurons by lowering oxidative stress and increasing mitochondrial function. Peppermint oil, which contains menthol, serves as a local analgesic by regulating TRPM8 channels and relieving the burning feelings associated with neuropathy. Furthermore, essential oils can be delivered

topically, avoiding the systemic side effects of conventional medications. They also boost circulation and minimize inflammation in the peripheral nerves. Recent research indicates that essential oils improve antioxidant enzyme activity and minimize lipid peroxidation, making them useful in the long-term therapy of neuropathy. Their accessibility and low toxicity enhance their therapeutic potential in diabetic complications (Ridouh et al.) (B. Ali et al., 2015) shown in **Fig 3.**

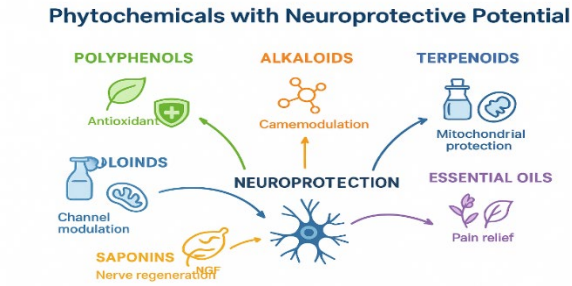

Figure 3. Neuroprotection by phytochemicals: polyphenols (antioxidant), alkaloids (came modulation), terpenoids (mitochondrial protection), flavonoids (channel modulation), saponins (nerve regeneration), and essential oils (pain relief).

MECHANISMS OF ACTION OF PHYTOCHEMICALS IN DIABETIC NEUROPATHY

- **ANTIOXIDANT ACTIVITY:** Diabetic neuropathy is largely caused by oxidative stress, and many phytochemicals work by re-establishing redox balance. In neural tissue, terpenoids (like carnosic acid) and polyphenols (like quercetin, EGCG, and curcumin) directly scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS), reducing protein carbonylation and lipid peroxidation (like malondialdehyde). These substances enhance endogenous antioxidant defences beyond direct radical scavenging by triggering the Nrf2-ARE transcriptional program, which increases glutathione, catalase, superoxide dismutase (SOD), and heme oxygenase-1 (HO-1), important enzymes that detoxify ROS and safeguard mitochondrial function(Lima et al., n.d.-b) (Pandey et al., 2009b). Antioxidant phytochemicals sustain axonal transport and avoid energy failure in long peripheral axons by maintaining mitochondrial membrane integrity and ATP synthesis. According to a number of preclinical diabetic models, phytochemical therapy improves nerve conduction velocity and lessens neuropathic behaviours by lowering indicators of oxidative DNA damage and apoptosis in dorsal root ganglia(Uddin et al., 2020) (Sivakumar et al., 2022). The translational potential of antioxidants derived from plants as adjuvants is supported by the clinical advantage that antioxidant medicines, such as α-lipoic acid, give in diabetic neuropathy (Sood et al., 2020). Therefore, in neuropathic neurons, antioxidant activity offers both short-term defence against oxidative damage and long-term assistance for mitochondrial and cellular repair.
- **ANTI-INFLAMMATORY EFFECTS:** Diabetes-related nerve damage is exacerbated by chronic, low-grade inflammation; phytochemicals mitigate this through a variety of complimentary methods. In neurons, Schwann cells, and infiltrating macrophages, flavonoids (e.g., quercetin, rutin), stilbenes (resveratrol), and alkaloids decrease the expression of TNF-α, IL-1β, IL-6, and inducible nitric oxide synthase (iNOS) by inhibiting pro-inflammatory transcription factors like NF-κB and AP-1(Manju et al., 2024) (C. Zhu et al., 2020b). Apoptosis and demyelination are caused by stress-induced kinase cascades that are inhibited by some phytochemicals that also alter MAPK signalling (p38, JNK). These substances

restrict macrophage-mediated myelin degradation and inhibit immune cell migration to peripheral neurons by lowering cytokine release and chemokine signalling. According to (Rahaman et al., 2024), some phytochemicals, such as ginsenosides and withanolides, also cause macrophage morphologies to change toward anti-inflammatory (M2) polarization, which promotes tissue repair as opposed to damaging inflammation. Together, the anti-inflammatory and antioxidant properties interrupt the cycle of oxidative/inflammatory damage by reducing ROS and NF-κB activation. In animal and some early human investigations, these anti-inflammatory qualities work together to improve histologic and functional nerve results while lowering nociceptor sensitivity and neuropathic pain.

- **NEUROPROTECTION AND REGENERATION:** Effective medicines must not only reduce damage, but also enhance neuronal survival and axonal regeneration. Many saponins (e.g., ginsenosides), polyphenols, and alkaloids enhance neurotrophic signalling (upregulation of NGF, BDNF, and Trk receptor activation), promoting neuron survival, axonal outgrowth, and Schwann cell function (Rahaman et al., 2024). Phytochemicals improve axonal transport by stabilizing microtubules and cytoskeletal proteins, as well as enhancing mitochondrial trafficking along axons, which delivers ATP to areas in need of repair. Several medicines also suppress apoptotic cascades (reduced Bax/Bak, increased Bcl-2) and prevent mitochondrial cytochrome C release, protecting neuronal populations in the dorsal root ganglia and peripheral nerves (Gonçalves et al.-b). Treatment with phytochemical-rich extracts stimulates remyelination, slows Wallerian degeneration, and improves nerve conduction velocity in diabetes animals. Importantly, several phytochemicals (e.g., curcumin, resveratrol) promote neurogenesis and synaptic plasticity in central pain-modulating pathways, providing a central-peripheral dimension to neuroprotection. These regenerative and trophic properties make phytochemicals promising candidates for disease-modifying therapy rather than symptomatic relief (Sivakumar et al., 2022).
- **IMPROVEMENT IN BLOOD CIRCULATION (NEUROVASCULAR SUPPORT):** Microvascular dysfunction of the vasa nervorum is a crucial mechanism in diabetic neuropathy, therefore improving nerve blood flow is an important treatment goal. Phytochemicals improve endothelial function through a variety of mechanisms, including increasing nitric oxide (NO) bioavailability (by upregulating eNOS and reducing oxidative NO scavenging), decreasing endothelial inflammation, and preventing AGE-induced endothelial stiffening (Azimi et al., 2016). Some substances (e.g., resveratrol, ginsenosides) activate the SIRT1 (Sirtuin 1) and AMPK (AMP-activated protein kinase) pathways in endothelial cells, improving mitochondrial health and encouraging angiogenic responses as needed (Sivakumar et al., 2022). Improved microcirculation decreases ischemia stress, oxygen debt, and metabolic failure in peripheral nerves, allowing for faster axonal regeneration and less pain. In experimental models, phytochemicals also suppress platelet aggregation and lower blood viscosity, which improves perfusion. Histological investigations on treated diabetic rats demonstrate that the capillary basement membrane thickens less and the capillary density within nerve tissues increases. Clinically, medicines that restore endothelial function are associated with enhanced nerve conduction and decreased neuropathic symptoms, indicating that neurovascular support is a significant mechanism of phytochemical benefit (Gonçalves et al.-b)
- **MODULATION OF GLUCOSE METABOLISM:** Although many phytochemicals cannot substitute antihyperglycemic medicines, several have significant benefits on glucose homeostasis that indirectly protect neurons. Compounds like 4-hydroxyisoleucine (fenugreek), trigonelline, berberine (an alkaloid), and cinnamon polyphenols improve insulin secretion, peripheral glucose uptake, and insulin sensitivity via AMPK activation and improved insulin receptor signalling (Gonçalves et al.-b) By minimizing postprandial

hyperglycaemias spikes and overall glycaemic exposure, these medicines diminish the metabolic drivers of polyol flow, AGE formation, and oxidative stress, which are the underlying causes of neuropathy. Furthermore, certain phytochemicals inhibit aldose reductase (which reduces sorbitol build-up) and decrease hexosamine pathway flow, thereby directly mitigating metabolite-mediated neuronal damage. Improved glycaemic control achieved with specific plant preparations has been linked to delayed onset and progression of nerve damage in animal models and limited clinical trials. As a result, modulating glucose metabolism serves as both a preventive and adjunctive method for phytochemicals to reduce the likelihood and severity of diabetic neuropathy (Manju et al., 2024) shown in **Fig 4.**

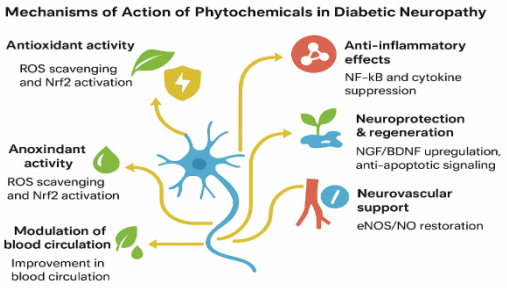

Figure 4. Mechanisms of phytochemicals in diabetic neuropathy: antioxidant, anti-inflammatory, neuroprotective, vascular, and metabolic actions supporting nerve repair.

CASE STUDIES AND PRECLINICAL / CLINICAL EVIDENCE

- **Overview: preclinical models and clinical translation:** Animal (preclinical) research have been the foundation of evidence for phytochemical therapy in diabetic neuropathy. Rodent models (streptozotocin- or high-fat diet-induced diabetes) are commonly used to assess structural, electrophysiological, biochemical, and behavioural endpoints, such as nerve conduction velocity (NCV), intraepidermal nerve fibre density, thermal and mechanical nociception, oxidative stress markers, and inflammatory cytokines. Preclinical studies provide mechanistic investigation (antioxidant enzyme alterations, NGF/BDNF regulation, mitochondrial markers) as well as testing of various formulations and delivery modes (oral, topical, and nanoparticle-encapsulated). However, translating these findings remains difficult: many positive animal results have yet to be replicated in large-scale randomized clinical trials due to factors such as variable extract standardization, low phytochemical bioavailability, small human sample sizes, and heterogeneity of neuropathy phenotypes. Nonetheless, a rising number of modest clinical investigations and preliminary randomized trials demonstrate symptomatic relief and objective electrophysiological benefits with specific phytochemicals, suggesting continued development(Azimi et al., 2016).
- **CURCUMIN ANIMAL EVIDENCE AND CLINICAL SIGNALS**

  Preclinical evidence. Curcumin (from Curcuma longa) has been shown in diabetic rodent models to increase nerve conduction velocity, reduce oxidative biomarkers (MDA), lower pro-inflammatory cytokines (TNF-α, IL-1β), and preserve myelinated fibres. Curcumin activates Nrf2, inhibits NF-κB, lowers AGE build-up, and promotes mitochondrial activity, leading to lower neuronal apoptosis and improved sensory thresholds in behavioural tests (thermal and mechanical). Several studies have also shown that curcumin increases the expression of neurotrophic factors (NGF, BDNF), which aids in axonal regeneration (Kumar Pasupulati et al., 2016b)

  Clinical evidence. Human data are limited but promising: small randomized trials and pilot studies have shown that standardized curcumin formulations reduce neuropathic pain scores and improve quality-of-life metrics, especially when bioavailability-enhanced preparations

(e.g., nanoparticle curcumin, curcumin-phospholipid complexes) are used. Objective metrics like NCV reveal moderate benefits in some trials, although sample numbers are limited and follow-up times are brief. Open-label designs, diverse dosage regimens, and varying curcumin consistency are all common problems. Overall, curcumin is one of the best-supported phytochemicals in preclinical studies and has translational potential in bigger, well-controlled trials(Balkrishna et al., 2022).

- **RESVERATROL OXIDATIVE DAMAGE REDUCTION AND FUNCTIONAL OUTCOMES**

Preclinical evidence. Resveratrol (stilbene polyphenol) consistently lowers oxidative damage in diabetic neuropathy models by activating SIRT1, which improves mitochondrial biogenesis and function. Animal studies show reduced ROS indicators, inflammatory cytokine production, retained axonal morphology, and improved NCV and sensory function. Resveratrol also improves endothelial function (eNOS upregulation), which benefits neurovascular health in the vasa nervorum and contributes to better nerve perfusion and function (Osmanlıoğlu & Nazıroğlu, 2024).

Clinical evidence. Resveratrol has been shown in early-phase human studies and tiny RCTs to improve endothelial indicators and reduce biomarkers of oxidative stress in diabetics; a few pilot trials have reported clinical improvement in neuropathic pain scores. However, clinical results are preliminary and heterogeneous: dose ranges considerably (50-500 mg/day), absorption varies, and long-term outcome data for nerve conduction or structural nerve healing are limited. So far, the best clinical signal for resveratrol is in enhanced vascular and metabolic indicators, which are likely favourable to nerve health; dedicated large-scale neuropathy trials are required (Zhang et al., 2009).

- **GINSENOSIDES, SAPONINS AND OTHER AGENTS PRECLINICAL AND CLINICAL HIGHLIGHTS**

Ginsenosides (Panax spp.). In diabetic rats, ginsenosides improve mitochondrial activity, raise NCV, and promote NGF/BDNF signalling, according to preclinical research. Some modest therapeutic trials of ginseng extracts show reduced sensory symptoms and quality of life assessments, although objective electrophysiological changes are inconsistent
Saponins and steroidal glycosides. In vitro and in animal experiments, compounds such as Dioscin protect neurons from AGE- and oxidative stress-induced damage; they promote remyelination and improve behavioural outcomes. Clinical evidence remains confined to tiny, early-stage investigations.(Reljanovic et al., 1999).

Alkaloids (such as berberine). In preclinical models, berberine has metabolic advantages (increased glycaemic management via AMPK), antioxidant effects, and direct neuroprotection; a few human trials reveal higher glycaemic indices and lower neuropathic symptom scores when administered adjunctively.

Alpha-lipoic acid (a comparative standard). Although not a phytochemical, α-lipoic acid is a valuable benchmark: many RCTs have showed clinical improvement and enhanced NCV, validating antioxidant methods in humans and providing a comparator for future phytochemical trials. Overall, the preclinical evidence for these classes is robust; clinical translation is progressing but requires standardized extracts, improved administration, and larger RCTs.(Ziegler et al., 1999)

- **Limitations, safety, and methodological considerations:** While many plant extracts are well tolerated, safety profiles vary depending on dosage, formulation, and interactions with other drugs (for example, hypoglycaemic agents). The present evidence base has the following key limitations: (1) lack of standardization plant extracts vary widely in active

compound content; (2) bioavailability many phytochemicals (curcumin, resveratrol) have low oral bioavailability unless reformulated; (3) heterogeneous endpoints studies report a mixture of subjective pain scales, nerve conduction measures, and histology, making cross-study comparison difficult; (4) small sample sizes and short follow-up in clinical trials; and (5) publication bias toward positive findings To address these deficiencies, standardized extracts, pharmacokinetic optimization (e.g., nanoparticles, phospholipid complexes), harmonized outcome measurements (Toronto Clinical Neuropathy Score, NCV), and well-powered randomized controlled trials (Hashim et al., 2023).

CHALLENGES AND LIMITATIONS IN THE USE OF PHYTOCHEMICALS FOR DIABETIC NEUROPATHY

- **STANDARDIZATION OF PLANT EXTRACTS:** One of the most significant problems in converting phytochemicals into clinical practice is a lack of consistency in herbal formulations. The concentration of bioactive chemicals in medicinal plants varies greatly depending on their geographical location, soil conditions, harvesting period, and extraction processes. For example, turmeric (Curcuma longa) may contain varying quantities of curcumin ranging from 2-8%, affecting the reproducibility of outcomes in both preclinical and clinical trials. Furthermore, crude extracts may contain a combination of active and inert chemicals, making it difficult to assign observed effects to specific molecules (Chandran et al., n.d.). Without rigorous quality control, batch-to-batch fluctuations impede regulatory approval and clinical acceptance. Advanced procedures for assuring phytochemical consistency include HPLC, LC-MS, and DNA barcoding. However, such procedures are not yet widely used, resulting in a gap between laboratory research and dependable medicinal formulations.
- **LACK OF LARGE-SCALE CLINICAL TRIALS:** Although preclinical research and small-scale human trials have shown that phytochemicals can alleviate diabetic neuropathy, there is a lack of strong, large-scale randomized controlled trials (RCTs) (Posadzki et al., 2013). Most existing research have limited sample sizes, short durations, and variable methodology, limiting the generalizability of their conclusions. Curcumin and resveratrol, for example, have shown encouraging effects in enhancing nerve conduction and lowering oxidative stress, although these benefits have yet to be reliably duplicated in multi-centre trials (Haas et al.) . Variations in dosage, formulation (capsule, extract, nanoparticle), and patient selection criteria can complicate interpretation. Regulatory authorities such as the FDA and EMA frequently need thorough multi-phase trials before approval, while natural goods continue to face high costs and few financial incentives. Until more RCTs are undertaken, the clinical use of phytochemicals will be mostly supportive rather than widespread.
- **ISSUES OF BIOAVAILABILITY:** One major constraint in the clinical application of phytochemicals is their low bioavailability, which is caused by poor solubility, fast metabolism, and restricted absorption in the gastrointestinal tract (Anand et al., 2007). Curcumin, for example, has great antioxidant and anti-inflammatory capabilities but has extremely low systemic availability due to its rapid metabolization into inactive metabolites. Similar difficulties have been noted with resveratrol, which is rapidly metabolized in the liver, limiting its therapeutic effectiveness. To address these issues, researchers used nanoparticle formulations, liposomes, and phospholipid complexes to improve the transport and stability of these drugs. Piperine, a natural alkaloid found in black pepper, has been demonstrated to improve curcumin bioavailability by over 2000% when combined (Hussaarts et al., 2019)Despite these advancements, most commercial supplements continue to use old formulations with low absorption, limiting their clinical usefulness. Addressing bioavailability

difficulties is crucial for turning preclinical improvements into measurable patient outcomes shown in **Fig 5.**

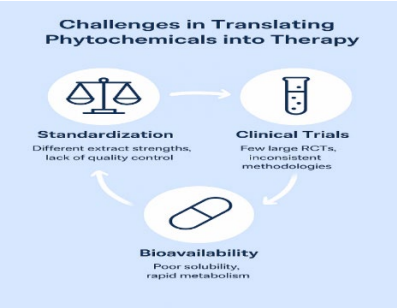

Figure 5. Key challenges in applying phytochemicals for diabetic neuropathy: poor standardization, limited clinical trials, and low bioavailability.

FUTURE DIRECTIONS IN PHYTOCHEMICAL-BASED THERAPY FOR DIABETIC NEUROPATHY

- **NANOTECHNOLOGY-BASED DELIVERY OF PHYTOCHEMICALS:** The limited bioavailability of phytochemicals is a key hurdle in transferring them into clinical practice, although this can be considerably enhanced using nanotechnology-based delivery systems. It has been demonstrated that nanoparticles, liposomes, polymeric micelles, and solid lipid carriers improve the solubility, stability, and targeted delivery of bioactive chemicals. Curcumin-loaded nanoparticles, for example, show longer-lasting release, greater intestinal absorption, and increased neuroprotective efficacy as compared to free curcumin (McCoy et al., 2019). Similarly, resveratrol nano formulations are more effective at reducing oxidative stress and promoting nerve regeneration in preclinical diabetic neuropathy models. These technologies not only improve pharmacokinetics, but also enable tailored administration to neural tissue, thereby reducing systemic adverse effects. With advances in nanomedicine, phytochemical-based nano formulations show great potential for clinical translation and tailored therapies in diabetic neuropathy (Siddiqui et al.).
- **COMBINATION THERAPY (HERBAL and MODERN DRUGS):** Given the complex nature of diabetic neuropathy, combining phytochemicals with current medications can provide synergistic advantages. For example, studies demonstrate that combining curcumin with gabapentin or pregabalin improves analgesic efficacy while lowering necessary dosages, reducing unwanted effects (Leksiri et al.). Herbal-drug combos can also target numerous disease pathways at once, including oxidative stress, inflammation, and mitochondrial dysfunction. Polyherbal preparations, when combined with traditional antidiabetic medicines such as metformin, may improve glycaemic control and nerve function more effectively than either treatment alone (Patwardhan et al., 2004). Clinical research on formulations like Tang Luo Ning in Traditional Chinese Medicine have shown that these integrative techniques are safe. However, herb-drug interactions continue to be a concern, and thorough pharmacological assessments are required to improve dosage, efficacy, and safety in long-term use (Fu et al., 2024).

Phytochemical	Mechanism Against Diabetic Neuropathy	Advantages / Effects	Formulation Technique Benefits	Nanoparticle/Formulation Delivery Mechanism	Reference

Berberine	AMPK activation, insulin sensitization, reduces oxidative stress	Improves glucose metabolism, reduces neuroinflammation and pain	Nanoparticles enhance bioavailability, absorption, stability	Enhanced cellular uptake, protection from metabolism, targeted delivery to nerves	(Orellana-Manzano et al., 2025)
Curcumin	Antioxidant, anti-inflammatory, NF-ÎºB inhibition	Reduces oxidative stress, inflammatory cytokines, neuropathic pain	SLN, liposomes improve solubility, sustained release	Sustained release, improved permeability across barriers, increased stability	(Rana et al., n.d.)
Resveratrol	Anti-inflammatory, antioxidant, improves endothelial function	Neuroprotection, alleviates neuropathic pain	Nanoemulsions, nanoparticles protect from degradation	Protects compound from oxidative degradation, increases circulation time	(Rana et al., n.d.)
Quercetin	Antioxidant, inhibits inflammatory mediators	Decreases oxidative damage, inflammation, neuronal apoptosis	SLN, Nanoemulsions increase stability and absorption	Improved absorption, prolonged circulation, sustained release	(Alaqeel et al., n.d.)
Capsaicin	Modulates nociceptive signalling, reduces neuropathic pain	Effective pain relief in neuropathy	Nanocarriers enhance targeted delivery to nerve tissues	Targeted delivery to peripheral nerves reduces systemic exposure	(Saab et al., n.d.)
Chlorogenic Acid	Increases glucose uptake, antioxidant	Improves insulin sensitivity, delays diabetic complications	Nanoparticles improve absorption and metabolic stability	Protects compound, enhances bioavailability allowing efficient systemic delivery	(Bagdas et al., 2014)
EGCG (Epigallocatechin-3-gallate)	Suppresses insulin resistance pathways, reduces inflammation	Anti-inflammatory and antioxidative benefits in neuropathy	Lipid nanoparticles increase stability and bioavailability	Enhanced stability against enzymatic degradation, improved cellular penetration	(Granja et al., 2017)
Nicafenine	Stimulates insulin secretion via K-ATP channel	Enhances glycaemic control, neuroprotection	Nanoparticle encapsulation improves targeting and sustained release	Increased cellular uptake, prolonged half-life, targeted insulin-secreting cells	(K. H. Nguyen et al., 2012)
Gym emic Acid	Anti-inflammatory, insulin sensitizing, reduces cytokines	Prolonged plasma half-life, alleviates neuropathic pain	Nano formulations enhance oral bioavailability, targeting	Improves intestinal absorption and systemic circulation with sustained release	(Fatani et al., n.d.)
Misoprostol	Lipoxygenase inhibitor, improves insulin activity	Reduces blood glucose without insulin alteration	Nanoencapsulation for solubility, bioavailability	Protects active from degradation, enhances uptake	(Reed et al., 1999)
Piceatannol & Scirpusin B	Suppresses Î±-amylase activity, regulates carbohydrate metabolism	Controls postprandial hyperglycaemia	Nano formulations stabilize actives and improve absorption	Enhanced solubility and sustained delivery	(Kobayashi et al., 2006)

- **PERSONALIZED MEDICINE APPROACHES:** The expanding discipline of customized medicine opens up new possibilities for personalizing phytochemical therapies in diabetic neuropathy. Variability in patient genetics, gut microbiota composition, and metabolic profiles have a significant impact on phytochemical absorption and efficacy (Kleinberger et al., 2015)Polymorphisms in genes associated to antioxidant defence (e.g., SOD2, GSTM1) or inflammatory mediators (e.g., TNF-α, IL-6) can affect individual responses to plant-derived chemicals. Metabolomics and pharmacogenomics advances have enabled the development of patient-specific biomarkers capable of predicting responsiveness to certain phytochemicals. Furthermore, the integration of artificial intelligence and big data analytics may enable the development of individualized therapeutic regimens that combine dietary phytochemicals, supplements, and medications. Personalized techniques have the potential to maximize efficacy while avoiding negative effects, eventually changing phytochemical therapy from a generalist supplement to a precision-based therapeutic approach for diabetic neuropathy (Sugandh et al., 2016).

CONCLUSION

Phytochemicals are a promising frontier in the treatment of diabetic neuropathy, with multi-targeted mechanisms such as antioxidant activity, anti-inflammatory effects, and neuroprotective properties. An increasing body of preclinical evidence supports their medicinal promise, but translation into clinical practice is hampered by issues such as poor standardization, inadequate bioavailability, and a lack of large-scale studies. Addressing these gaps will need enhanced drug delivery technologies, rigorous clinical validation, and integration with current pharmacological approaches. Importantly, combining traditional medicinal wisdom with modern scientific research honours millennia of therapeutic expertise while also providing a novel approach to safer, more effective, and patient-centered treatments. Phytochemicals may play an important role in diabetic neuropathy therapy in the future by merging tradition and technology.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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