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REVIEW

Therapeutic Targets, Pharmacological Mechanisms, and Delivery Strategies for Diabetic Peripheral Neuropathy

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Abstract: With the global diabetes population projected to reach 783 million by 2045, diabetic peripheral neuropathy (DPN) remains a common and debilitating complication characterized by metabolic stress, inflammation, and microvascular dysfunction. This review summarizes current interventions for DPN from the perspective of therapeutic targets, pharmacological mechanisms, and emerging delivery strategies. Conventional pharmacotherapy mainly provides symptomatic relief; first-line analgesics such as duloxetine and pregabalin offer only moderate benefit, with a number needed to treat of approximately 4–5. Natural products, including resveratrol, ginkgo biloba, and tanshinone IIA, show antioxidant and anti-inflammatory potential, although supporting evidence remains largely preclinical. Emerging targeted therapies and nanocarrier-based delivery systems may improve disease modification and drug bioavailability. Overall, DPN treatment remains limited by the lack of disease-modifying therapies, insufficient high-quality clinical evidence, and major translational barriers. Future priorities include mechanism-based stratification, combination strategies, and rigorous trials incorporating objective and patient-reported outcomes.

Keywords: diabetic peripheral neuropathy, therapeutic targets, natural products, targeted therapy, drug delivery

Introduction

Diabetes is a leading cause of mortality and contributes substantially to global healthcare burdens. According to the latest statistics, approximately 537 million adults were living with diabetes in 2021, and this number is projected to rise to 783 million by 2045.[1] Diabetic peripheral neuropathy (DPN) is one of the most common and clinically burdensome complications of diabetes. Clinically, DPN presents as a symmetrical, length-dependent sensorimotor polyneuropathy. Although factors such as poor glycemic control, obesity, impaired renal function, and smoking are associated with increased risk,[2] the core pathology is primarily driven by chronic hyperglycemia-induced metabolic and microvascular injury. Typical symptoms include symmetric sensory loss, discomfort, numbness, and pain, usually affecting the lower limbs earlier and more severely than the upper limbs.

While canonical mechanisms such as polyol pathway activation, oxidative stress, and AGE–RAGE signaling are well established, the broader interplay among inflammatory, mitochondrial, endoplasmic reticulum stress, and microvascular pathways remains under active investigation. Multiple mechanisms contribute to peripheral nerve injury, including hyperglycemic stress, dyslipidemia, metabolic inflammation, insulin resistance, and microcirculatory dysfunction. As

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illustrated in Figure 1, these pathological processes are interconnected rather than isolated, with extracellular metabolic stress converging on oxidative injury, inflammatory signaling, mitochondrial dysfunction, endoplasmic reticulum stress, and microvascular impairment, which together drive neuronal and cell damage in DPN. Hyperactivity of the polyol pathway accelerates redox imbalance involving nicotinamide adenine dinucleotide phosphate (NADPH) and nicotinamide adenine dinucleotide (NAD+), while excess glucose flux through glycolysis promotes the generation of reactive oxygen species (ROS). Increased ROS production can induce endoplasmic reticulum (ER) stress and DNA damage. ROS and reactive nitrogen species are widely regarded as key pathogenic mediators in diabetic neuropathy.[3,4] In parallel, glucose binding to the receptor for advanced glycation end products (RAGE) activates PKC-dependent MAPK cascades, leading to AP-1 and NF-κB activation and accelerating inflammatory responses. Blocking RAGE can correct NF-κB activation and its downstream gene expression in peripheral nerves of diabetic mice.[5] Oxidized low-density lipoprotein (ox-LDL) binds to LOX-1, TLR4, and RAGE, thereby activating NADPH oxidase and exacerbating oxidative stress.[6,7] Elevated plasma free fatty acids also contribute to insulin resistance and β-cell dysfunction, both of which are important contributors to diabetic neuropathy.[8] Beyond these classical pathways, emerging evidence implicates mitochondrial dysfunction, ER stress, and impaired autophagic flux as key contributors to neuronal injury in DPN.[9–11]

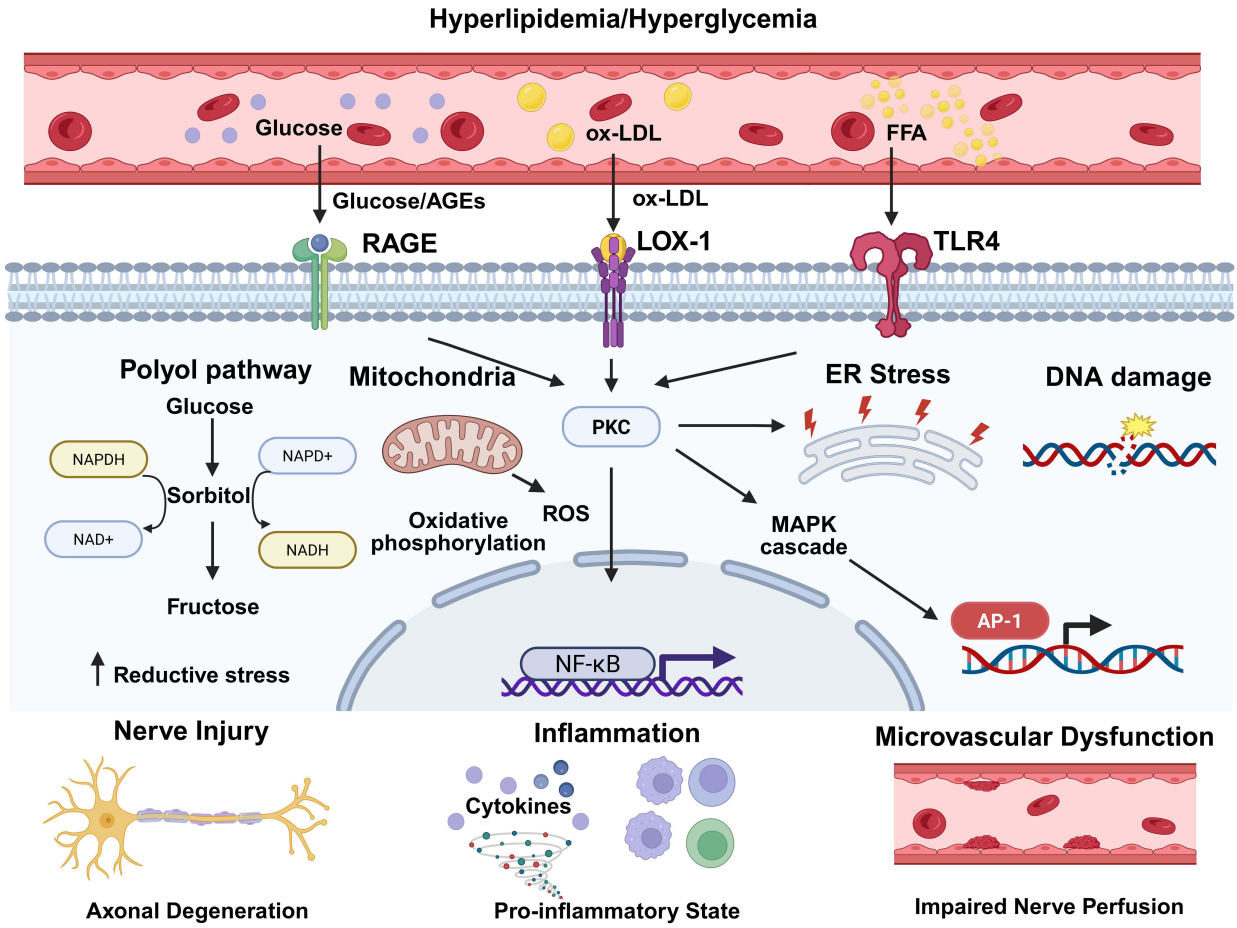

Figure 1 Major pathogenic mechanisms involved in diabetic peripheral neuropathy. Chronic hyperglycemia and related metabolic disturbances contribute to multiple interconnected processes, including polyol pathway activation, oxidative stress, AGE–RAGE signaling, inflammatory activation, mitochondrial dysfunction, endoplasmic reticulum stress, and microvascular impairment, which together promote peripheral nerve injury in DPN.

Abbreviations: AGE, advanced glycation end product; RAGE, receptor for advanced glycation end products; ox-LDL, oxidized low-density lipoprotein; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; TLR4, Toll-like receptor 4; PKC, protein kinase C; ROS, reactive oxygen species; ER, endoplasmic reticulum; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; NADPH, nicotinamide adenine dinucleotide phosphate.

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Despite decades of research, current treatment for DPN remains largely symptomatic. Pain management relies on a limited set of FDA-approved drugs (eg, duloxetine, pregabalin), which provide moderate relief but are often limited by side effects. Disease-modifying therapies—those that arrest or reverse nerve damage—are lacking. In recent years, several novel drug classes (eg, SGLT2 inhibitors, GLP-1 receptor agonists, NaV1.8 blockers) have entered clinical trials, offering hope for mechanism-based interventions. Parallel efforts have explored traditional Chinese medicine (TCM) as a source of multi-target compounds, though their clinical translation faces substantial hurdles. Rather than treating conventional pharmacotherapy and TCM-derived interventions as separate therapeutic silos, the following sections compare how these approaches act on overlapping pathogenic nodes and where they may complement one another in future DPN management.

Clinical Drug Treatment of DPN

Current pharmacological management of DPN focuses on symptomatic pain relief, while disease-modifying therapies remain investigational. In this review, conventional pharmacotherapy is discussed not only as the current clinical standard, but also as a reference framework for understanding why multi-target strategies may be needed in DPN. The following sections are organized by therapeutic target and mechanism, integrating conventional drugs, emerging candidates, and failed approaches within each thematic domain. Table 1 provides a critical evidence summary that distinguishes study type, key outcomes, efficacy signals, and major limitations for each pharmacological class.

Table 1 Mechanism-Based Classification and Critical Evidence Review of Pharmacotherapies for Diabetic Peripheral Neuropathy

Mechanism Class	Drug	Primary Target/ Mechanism	Key Outcome (s)	Efficacy Summary	Major Limitation (s)	Refs
I. Central Pain Modulation	Duloxetine	Blocks serotonin and norepinephrine reuptake; enhances descending inhibition	FDA-approved first-line; OPTION-DM 2022; number needed to treat ~5	Superior to pregabalin monotherapy	Nausea 25%, sleepiness 15%; discontinuation 15%	[12]
II. Ion Channel Modulation	Pregabalin	Binds α_2-δ calcium channels; reduces glutamate release	FDA-approved first-line; OPTION-DM 2022; number needed to treat ~4–5	Effective alone or combined	Dizziness 20–30%, edema 15%; abuse potential; respiratory depression risk	[13]
	Gabapentin	Same mechanism (lower affinity)	Off-label; number needed to treat ~6; requires titration	Lower cost alternative	Off-label; cognitive impairment; saturable absorption	[14]
	Mirogabalin	Preferential α_2 -δ-1 binding	Japan approved; 2025 network meta-analysis: superior to pregabalin (34 trials, 8630 patients)	Average daily pain score reduced by 0.29 points more than pregabalin 300 mg; odds ratio 2.87 for ≥50% pain relief vs gabapentin	Limited global approval	[15,16]
	Crisugabalin (HSK16149)	Selective α_2-δ binding	China approved 2024; JAMA Network Open Phase 3 trial (725 patients)	Average daily pain score significantly reduced; sustained effect at 52 weeks	China approval only	[17]
	Suzetrigine	Selective sodium channel 1.8 blocker	Phase 3 ongoing	Non-opioid mechanism	Cardiovascular safety monitoring; not approved	[18]
	Capsaicin 8% patch	Overstimulates and desensitizes pain-sensing nerves	FDA-approved; NICE guideline CG173; number needed to treat 7	≥30% responder; effect lasts 12 weeks	Application site pain 92%; high cost	[19]

(*Continued*)

Table 1 (Continued).

Mechanism Class	Drug	Primary Target/ Mechanism	Key Outcome (s)	Efficacy Summary	Major Limitation (s)	Refs
III. Metabolic/ Mitochondrial Modulation	Dapagliflozin	Sodium-glucose cotransporter-2 inhibition; antioxidant	DINE study 2025 (40 patients)	Intraepidermal nerve fiber density increased; corneal nerve fiber density increased; glutathione peroxidase increased	Small open-label study; confirmatory trials needed	[20]
	Empagliflozin	Sodium-glucose cotransporter-2 inhibition; AMPK activation	Phase 2 DPN trial ongoing	Trend toward fewer neuropathy events (exploratory)	Not FDA-approved; requires dedicated trial	[21,22]
	Canagliflozin	Sodium-glucose cotransporter-2 inhibition; anti-inflammatory	Post-hoc analysis of CREDENCE trial (Liao 2022)	Exploratory: possible impact on neuropathy events	Not approved for DPN; indirect evidence	[23]
	Semaglutide	Glucagon-like peptide-1 receptor activation; anti-inflammatory	Phase 4 DPN trial ongoing	Cardiovascular benefit; weight loss; preclinical nerve protection	No DPN endpoint published; gastrointestinal side effects 35%	[24,25]
	GLP-1 receptor agonists	Restores nerve sodium-potassium pump function	2025 Journal of Neurophysiology study (24 patients)	Total neuropathy score improved from 3.7 to 2.3; sural nerve amplitude increased from 11.9 to 14.2 microvolts	Small uncontrolled study	[26]
	Epalrestat	Reduces sorbitol accumulation in nerves	Japan/China approved; 2006 trial	Motor nerve conduction velocity +1.6 m/s vs −0.8 m/s	Not approved in US/EU; liver toxicity	[27]
	Alpha-lipoic acid	Activates Nrf2; scavenges reactive oxygen species	2024 Cochrane review: no consensus; removed from ADA 2023	No disease-modifying effect	Low oral bioavailability (<15%); not recommended	[28]
	Mecobalamin	Supports myelin maintenance	2020 meta-analysis (73% high risk of bias)	No effect on pain or quality of life; relative risk 1.17 for clinical efficacy	High bias; not recommended as monotherapy	[29]
	Acetyl-L-carnitine	Fatty acid transport into mitochondria	2019 Cochrane review: no conclusive evidence	No significant pain reduction	Not recommended by 2024 guidelines	[28,30]
IV. Anti-Inflammatory/ Epigenetic	LX9211	AAK1 inhibitor; high brain penetration	Phase 1 completed	Phase 1: significantly greater pain reduction vs placebo	Phase 1 results	[31]
	Ricolinostat	HDAC6 inhibitor	Phase 2 completed 2023 (n=282)	Pain reduction −1.21 vs placebo −1.03 (not significant)	No significant efficacy; no further development reported	[32]
	Roflumilast	PDE4 inhibitor; anti-inflammatory	Phase 3 trial completed Oct 2023 (n=60)	Results pending; primary endpoints: fasting blood glucose, insulin, HOMA-IR	No published efficacy data; not FDA-approved	[33]
V. Neurotrophic/ Regenerative	VM202 (Engensis)	Delivers hepatocyte growth factor gene to nerves	Phase 3 completed; 2023 interim analysis	Neuro-ischemic diabetic foot ulcer closure improved	Invasive injection; regulatory pending	[34]
	Autologous bone marrow stem cells	Anti-inflammatory, nerve growth support	Phase 3 ongoing	Early studies show nerve regeneration	High cost; standardization challenges	[35]
	Benfotiamine	Blocks advanced glycation end-product formation; antioxidant	Phase 2 BOND study completed (DRKS00014832)	12-month trial completed; results pending	No significant efficacy	[36]

(*Continued*)

Table 1 (Continued).

Mechanism Class	Drug	Primary Target/ Mechanism	Key Outcome (s)	Efficacy Summary	Major Limitation (s)	Refs
VI. Discontinued/ Failed	Tanezumab	Blocks nerve growth factor signaling	Phase II trial in DPN (Bramson 2015, n=73); program terminated 2021 due to OA safety signals	Significant pain relief vs placebo (mean improvement −2.7 vs −1.1; P=0.009); ≥50% pain response in 47% vs 20%	No Phase III trials in DPN; development terminated due to RPOA and joint safety concerns in OA/CLBP indications; long-term safety and efficacy in DPN unknown	[37,38]

Targeting Central and Peripheral Pain Signaling

Pain in DPN arises from central sensitization and aberrant peripheral afferent activity. First-line treatments target two distinct classes of pain-signaling molecules: serotonin and norepinephrine transporters in the central nervous system, and α_2-δ subunits of voltage-gated calcium channels in both central and peripheral neurons.

Duloxetine, the only SNRI approved for DPN, inhibits serotonin and norepinephrine reuptake. This enhances descending inhibitory pathways, providing pain relief with a number needed to treat (NNT) of approximately 5. However, nausea and somnolence lead to discontinuation in about 15% of patients.[12]

Pregabalin and gabapentin target the α_2-δ subunit of voltage-gated calcium channels, thereby reducing excitatory neurotransmitter release. Pregabalin (FDA-approved) has a number needed to treat (NNT) of 4–5, whereas gabapentin (used off-label) appears to be slightly less effective (NNT ~6). Both carry risks of dizziness, edema, and, particularly when combined with central nervous system depressants, respiratory depression.[13,14] Next-generation α_2-δ ligands with improved subunit selectivity, such as mirogabalin (approved in Japan) and crisugabalin (approved in China), aim to reduce off-target effects.[15,17] Recent network meta-analyses suggest mirogabalin may offer superior efficacy and tolerability compared with pregabalin.[16]

Voltage-gated sodium channel 1.8 (NaV1.8) is expressed selectively in peripheral pain-sensing neurons. Suzetrigine alleviates DPN by blocking the generation of action potential through Nav1.8.[18] The capsaicin 8% patch targets TRPV1 by activating and subsequently desensitizing TRPV1 receptors on nociceptive nerve endings, thereby depleting substance P and providing localized relief for up to 12 weeks. Application-site burning and high cost limit its use.[19] Nerve growth factor (NGF) was targeted by tanezumab; a Phase II trial in DPN showed significant pain relief, but subsequent development in osteoarthritis revealed a dose-dependent risk of rapidly progressive osteoarthritis requiring joint replacement, leading to program termination.[37,38]

While current analgesics provide moderate relief by targeting established pain pathways, their utility is constrained by side effects, abuse potential, and a ceiling effect. Newer approaches targeting NaV1.8 and refined α_2-δ ligands may improve tolerability, but their ultimate value depends on demonstrating superiority in head-to-head trials. However, because these agents primarily relieve pain rather than reverse nerve injury, attention has increasingly shifted toward metabolic and mitochondrial targets.

Targeting Metabolic and Mitochondrial Pathways

The recognition that DPN involves bioenergetic failure has shifted attention to targets upstream of neuronal damage: sodium-glucose cotransporter-2 (SGLT2), glucagon-like peptide-1 receptor (GLP-1R), and aldose reductase.

SGLT2 inhibitors attenuate oxidative stress, activate AMP-activated protein kinase (AMPK), and improve mitochondrial function. In the DINE study, dapagliflozin increased intraepidermal nerve fiber density, a structural marker of nerve regeneration, thereby suggesting disease-modifying potential.[20] Empagliflozin and canagliflozin have also shown signals of reduced neuropathy events in exploratory analyses, although dedicated trials in DPN remain ongoing.[21–23]

GLP-1R agonists improve axonal function by restoring sodium-potassium pump activity.[26] A 2025 mechanistic study showed improvements in nerve excitability and total neuropathy scores in patients treated with semaglutide or exenatide.[24,25] Direct DPN-specific evidence for semaglutide remains limited, and further dedicated trials are needed.

Aldose reductase is inhibited by epalrestat, which blocks the polyol pathway. Approved in Japan and China, it showed preserved nerve conduction velocity in a 2006 trial, but a 2007 Cochrane review found no consistent clinical benefit. It is not approved in the US or EU.[27]

By contrast, several widely used nutraceuticals, alpha-lipoic acid, acetyl-L-carnitine, and mecobalamin, have failed to demonstrate disease-modifying effects in high-quality studies.[28,29] Alpha-lipoic acid was removed from the American Diabetes Association (ADA) Standards of Care in 2023; the other two are not recommended by current guidelines.[30]

Thus, while SGLT2 inhibitors and GLP-1R agonists are promising targets for disease modification, direct DPN-specific clinical evidence remains limited and their efficacy must be confirmed in dedicated trials. The failure of aldose reductase inhibitors and nutraceuticals underscores the importance of robust clinical endpoints and the danger of relying solely on mechanistic plausibility. Against this background, interventions targeting neuroinflammation, epigenetic regulation, and regeneration have also attracted increasing interest.

Targeting Neuroinflammation, Epigenetic Regulation, and Regeneration

Beyond metabolic pathways, interventions targeting neuroinflammation, epigenetic modifiers, and nerve regeneration are under active investigation.

Adaptor-associated kinase 1 (AAK1) is targeted by LX9211, an inhibitor with high brain penetration. Phase 1 DPN trials showed significantly greater pain reduction versus placebo.[31] Histone deacetylase 6 (HDAC6) was targeted by ricolinostat. Phase 2 was completed in 2023 but did not demonstrate significant efficacy (pain reduction −1.21 vs −1.03 with placebo), and no further development has been reported.[32] The phase 3 clinical trial of roflumilast (phosphodiesterase-4 inhibitor) in the treatment of DPN has proved that it can improve the level of serum neurotensin, neuropathic symptoms and neuropathic pain.[33]

Hepatocyte growth factor (HGF) is delivered via gene therapy with VM202 (Engensis). A phase 3 interim analysis demonstrated improved closure of neuro-ischemic diabetic foot ulcers,[34] suggesting possible relevance to diabetic neurovascular complications, although direct DPN-specific evidence remains limited. Experimental evidence shows that bone marrow-derived mesenchymal stem cells can repair diabetic peripheral neuropathy.[35] The phase 2 study of advanced glycation end-products (AGEs) inhibitor benfotiamine showed that it had no significant effect on a variety of clinical indicators of neuropathy.[36]

These strategies represent a departure from symptom control toward disease modification, targeting fundamental processes such as neuroinflammation, epigenetic regulation, and tissue regeneration. However, with the exception of the discontinued tanezumab, none have yet achieved regulatory approval. This high failure rate reflects several translational challenges in DPN drug development. Many preclinical systems capture only selected pathogenic mechanisms and do not fully reproduce the chronic, heterogeneous, and multisystem nature of human DPN. In addition, clinical trials often enroll patients at stages when structural nerve damage is already established, thereby limiting the impact of mechanism-based interventions. Another persistent obstacle is the lack of sensitive biomarkers for early patient stratification and for monitoring treatment response beyond pain relief alone. Together, these limitations suggest that future progress will depend not only on novel targets, but also on better trial design, earlier intervention windows, and more informative efficacy endpoints. The limited progress of SARM1-directed and mitochondria-focused strategies further illustrates that targeting a single downstream degenerative node may be insufficient once DPN has become structurally established and biologically heterogeneous. In this context, combination strategies that pair symptom-controlling interventions with disease-modifying candidates may warrant priority over single-target approaches alone, because they are more likely to address both pain and the multifactorial pathogenic processes underlying DPN. This therapeutic rationale also helps explain the growing interest in multi-target natural products discussed in the following section.

Natural Products and Derived Compounds for DPN

Natural products have long served as sources of bioactive compounds for neurological disorders. In the context of DPN, they offer a theoretical advantage: multi-target modulation, which aligns with the multifactorial pathogenesis of the disease. Unlike single-target pharmacotherapy, TCM-based interventions are commonly used as multi-component therapies intended to address complex and overlapping pathological processes. In this review, isolated natural compounds

and TCM formulas are discussed at complementary levels: studies of single compounds help clarify molecular targets and mechanistic plausibility, whereas studies of whole formulas better reflect the multi-component and potentially synergistic nature of TCM practice. Nevertheless, the current evidence base remains predominantly preclinical, and high-quality clinical data are still limited.

This section therefore organizes the literature around three mechanistic themes—energy metabolism, inflammation and oxidative stress, and neuronal survival—while also considering how these themes relate to formula-based interventions used in TCM. Table 2 summarizes the representative natural products and compound combinations discussed here, together with their primary targets, evidence level or study model, key outcome measures, and major translational limitations.

AMPK Activation and Mitochondrial Enhancement

A recurring mechanism among natural compounds involves AMPK activation and improved mitochondrial function. This aligns with the growing interest in metabolic modulators such as SGLT2 inhibitors and GLP-1 agonists.

Resveratrol, a polyphenol found in grapes and Polygonum cuspidatum, has shown antioxidant and anti-inflammatory potential in preclinical studies relevant to diabetic complications. Animal studies demonstrate that it inhibits ROS production, suppresses NF-κB activation and TNF-α expression, and enhances antioxidant enzyme activity.[49,50] Indirect mechanistic evidence from non-DPN cell models also suggests that resveratrol may influence insulin sensitivity and glycolytic regulation through SIRT2-related pathways.[39] However, rapid metabolism and low systemic bioavailability after oral administration pose significant challenges for clinical translation. This limitation is common to many polyphenolic compounds.[51]

The TCM formula Jinmaitong contains several herbs, including *Cuscuta chinensis* and *Ligustrum lucidum*. A targeted metabolomics study showed that this formula activates the AMPK/PGC-1α pathway, inhibiting excessive glycolysis and

Table 2 Representative Natural Products and Compound Combinations for Diabetic Peripheral Neuropathy: Mechanisms, Evidence Level, and Translational Limitations

Category	Name	Source/Key Components	Primary Target/ Mechanism	Evidence Level/Study Model	Key Outcome (s)/ Findings	Major Limitation (s)	Refs
Single compound	Resveratrol	Grapes, Polygonum cuspidatum	Activates SIRT2; improves insulin sensitivity; inhibits NF-κB; reduces ROS	Preclinical (mainly diabetic rat models; indirect mechanistic evidence from non-DPN cell models)	Upregulates SIRT2; increases glucose consumption; inhibits ROS, NF-κB, TNF-α	Low oral bioavailability; rapid metabolism; no Phase 2/3 DPN trials	[39]
	Astragaloside IV	Astragalus membranaceus	Blocks TLR4/NF-κB pathway; reduces inflammation; improves insulin sensitivity	Preclinical (primarily STZ-induced diabetic rats; supportive mechanistic evidence from related inflammatory models)	Reduces inflammatory mediators; improves insulin sensitivity in adipocytes	No standardized formulation; human data sparse	[40,41]
	Ginkgo biloba extract (EGb761)	Ginkgo biloba leaves	Improves nerve conduction; antioxidant; anti-inflammatory	Clinical trial (156 DPN patients)	Significantly improved sensory and affective pain scores after 6 months; enhanced motor nerve conduction velocities	Mixed clinical results; not FDA-approved for DPN	[42]
	Tanshinone IIA	Salvia miltiorrhiza	Anti-inflammatory; inhibits proinflammatory cytokines; reduces glial activation	Preclinical (STZ-induced diabetic rats)	Inhibits IL-1β, IL-6, TNF-α; increases IL-10; attenuates mechanical allodynia and thermal hyperalgesia	Poor water solubility; low bioavailability; no clinical trials	[43]

(*Continued*)

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Table 2 (Continued).

Category	Name	Source/Key Components	Primary Target/ Mechanism	Evidence Level/Study Model	Key Outcome (s)/ Findings	Major Limitation (s)	Refs
Formula	Jinmaitong	Cuscuta chinensis, Ligustrum lucidum, Corydalis yanhusuo, leech, Cinnamomum cassia	Activates AMPK/ PGC-1α pathway; improves mitochondrial energy metabolism	Preclinical (DPN rat model, targeted metabolomics)	Inhibits excessive glycolysis; enhances TCA cycle function in sciatic nerve	Individual active constituents unidentified; no clinical trial data	[44]
	Huangqi Guizhi Wuwu Decoction	Astragalus membranaceus, Cinnamomum cassia, Angelica sinensis, Paeonia lactiflora	Activates AMPK/ TrkA/TRPM7 pathway; improves cardiac autonomic function	Clinical trial (202 patients with diabetic cardiovascular autonomic neuropathy); preclinical (STZ-induced diabetic rats); limited direct DPN evidence	Improves heart rate variability; reduces ventricular premature beats; corrects cardiac autonomic nerve imbalance	Evidence primarily for diabetic cardiovascular autonomic neuropathy; limited direct DPN data	[45]
	Buyang Huanwu Decoction	Astragalus membranaceus, Angelica sinensis, Paeonia rubra, Ligusticum chuanxiong, Carthamus tinctorius, peach kernel, Pheretima aspergillum	Increases SOD activity; decreases MDA; improves nerve conduction velocity	Meta-analysis (21 RCTs, 1945 DPN patients)	Significantly improves clinical efficacy and nerve conduction velocity in DPN; reduces plasma viscosity	Low methodological quality of included studies; limited high-quality RCTs	[46]
	Taohong Siwu Decoction	Angelica sinensis, Rehmannia glutinosa, Ligusticum chuanxiong, Paeonia lactiflora, peach kernel, safflower	Suppresses neuronal apoptosis via PI3K-Akt, MAPK, TNF, IL-17, NF-κB pathways	Network pharmacology (CIPN model)	Identifies multi-target anti-inflammatory and anti-apoptotic mechanisms	Evidence from chemotherapy-induced peripheral neuropathy model; direct DPN clinical data lacking	[47]
	Compound Danshen Dripping Pills	Salvia miltiorrhiza, Panax notoginseng, borneol	Improves microcirculation; reduces oxidative stress; anti-apoptotic	RCT (early diabetic retinopathy); systematic review	Improves retinal microcirculation and vision; may enhance nerve conduction velocities in DPN	Primary evidence from retinopathy; DPN-specific RCT data limited	[48]

enhancing tricarboxylic acid cycle function in the sciatic nerve of DPN rats.[44] These findings suggest that combinations of natural compounds may achieve synergistic effects on energy metabolism. However, the individual active constituents remain unidentified.

From a translational perspective, certain natural products share molecular targets with emerging disease-modifying drugs. Yet unlike SGLT2 inhibitors and GLP-1 receptor agonists, which have demonstrated cardiovascular benefits in large-scale trials, the evidence for AMPK-activating natural compounds remains confined to preclinical models. A deeper obstacle lies in bioavailability. Many active compounds, including resveratrol, have poor water solubility and undergo rapid metabolism, limiting systemic exposure after oral administration.[52] Without formulations that achieve meaningful tissue concentrations, even potent mechanism-based compounds cannot deliver clinical benefit. Beyond impaired energy metabolism, oxidative stress and inflammatory signaling constitute another major axis of DPN progression.

Suppressing Inflammation and Oxidative Stress Through NF-κB and Nrf2 Modulation

A second major theme centers on NF-κB and Nrf2 pathway modulation. These pathways are central to neuroinflammation and oxidative damage in DPN.[3,4]

Astragaloside IV, isolated from Astragalus membranaceus, has shown anti-inflammatory effects through inhibition of the NF-κB pathway in related experimental models.[40] Supportive evidence from metabolic models also suggests insulin-sensitizing effects.[41] Ginkgo biloba extract (EGb761) improves peripheral sensorimotor nerve function in patients.[42] Tanshinone IIA, a lipophilic compound from *Salvia miltiorrhiza*, exerts anti-inflammatory effects in diabetic peripheral

neuropathic pain. It inhibits proinflammatory cytokines (IL-1β, IL-6, TNF-α) and increases anti-inflammatory IL-10 in dorsal root ganglion, attenuating mechanical allodynia and thermal hyperalgesia in diabetic rats.[43]

Several multi-herb formulas, interpreted in TCM as formula-based rather than single-target interventions, may also act through these inflammatory and oxidative stress pathways. From a modern pharmacological perspective, such formulas appear to regulate overlapping processes including oxidative injury, inflammatory signaling, and microcirculatory dysfunction. This overlap also provides one point of contact between TCM and Western pathophysiology: in TCM, patterns such as Blood Stasis may partially correspond to impaired microcirculation and tissue perfusion, both of which are central to DPN progression. For example, Huangqi Guizhi Wuwu Decoction promotes neurological recovery in diabetic cardiovascular autonomic neuropathy by activating the AMPK/TrkA/TRPM7 pathway, improving heart rate variability and correcting cardiac autonomic nerve imbalance.[45] However, this evidence is indirect with respect to DPN, and its direct evidence base for DPN remains limited. Similarly, Buyang Huanwu Decoction increases superoxide dismutase activity and decreases malondialdehyde levels in diabetic patients. A 2023 meta-analysis of 21 randomized controlled trials (1945 patients) demonstrated that this formula improves nerve conduction velocity and clinical efficacy in DPN,[46] although the methodological quality of the included studies remains a limitation.

The mechanistic overlap with established drug targets is notable alpha-lipoic acid, a conventional antioxidant, was removed from ADA guidelines due to lack of disease-modifying effects.[28] This raises a critical question: do natural products that modulate NF-κB/Nrf2 offer any advantage over single-agent antioxidants? Currently, the answer is unclear. Comparative studies are absent, and the bioavailability of many compounds is limited.[53] Moreover, most studies rely on surrogate biochemical markers (eg, NF-κB, MDA, SOD) rather than patient-centered outcomes. As seen with alpha-lipoic acid, positive mechanistic effects do not guarantee clinical benefit.[28] Future studies must integrate objective biomarkers, such as intraepidermal nerve fiber density and corneal confocal microscopy, to bridge the gap between mechanism and clinical outcome. At the same time, because attenuation of inflammation alone may be insufficient once neuronal injury is established, increasing attention has also been directed toward apoptosis- and endoplasmic reticulum stress-related pathways.

Promoting Neuronal Survival by Targeting Apoptosis and ER Stress

A third theme involves the inhibition of neuronal apoptosis through modulation of ER stress and Bcl-2 family protein modulation. These mechanisms are also being explored in drug development, although successful clinical translation remains limited.

Taohong Siwu Decoction combines Angelica sinensis, Rehmannia glutinosa, peach kernel, and safflower. Current evidence for this formula is derived mainly from a chemotherapy-induced peripheral neuropathy model, in which network pharmacology analysis suggested multi-target anti-inflammatory and anti-apoptotic mechanisms involving PI3K-Akt, MAPK, TNF, IL-17, and NF-κB pathways.[47] Similarly, Compound Danshen Dripping Pills have shown benefits in early diabetic retinopathy and may have only indirect relevance to DPN through microcirculatory and oxidative stress-related mechanisms; direct DPN-specific clinical evidence remains limited.[48]

Although these pathways are discussed separately for clarity, they are highly interconnected rather than independent. Metabolic stress, oxidative injury, inflammatory activation, and apoptosis converge on a limited number of shared pathogenic nodes, particularly NF-κB/MAPK-related inflammatory signaling, mitochondrial dysfunction, endoplasmic reticulum stress, and impaired neuronal survival. From this perspective, interventions that improve energy homeostasis, attenuate inflammatory signaling, or suppress apoptosis may not act on isolated pathways, but instead modulate overlapping components of the same pathological network. This mechanistic convergence helps explain why conventional pharmacotherapies and multi-target natural products may produce partially overlapping neuroprotective effects and provides a rationale for combination strategies that simultaneously target multiple nodes within the DPN pathogenic web. At the same time, this overlap also underscores a shared set of translational challenges that extends across these approaches.

Common Challenges and Future Directions

Despite promising mechanistic findings, the translation of natural products for DPN remains limited by several shared challenges. First, the current evidence base is still dominated by preclinical studies, whereas DPN-specific randomized clinical trials of natural products remain scarce.[54] Second, many natural compounds suffer from poor water solubility, rapid metabolism, low systemic exposure, and insufficient formulation standardization, all of which hinder clinical translation and reproducibility.[55] Third, a substantial proportion of existing studies rely on surrogate biochemical markers rather than objective neuropathy-related endpoints, such as intraepidermal nerve fiber density, corneal confocal microscopy, nerve conduction studies, and validated patient-reported outcomes.[56] In addition, some compounds or formulas are supported mainly by indirect evidence from related disease models rather than direct DPN-specific studies, which further weakens their translational value.[57,58]

Future research should therefore move beyond mechanistic plausibility alone and prioritize standardized formulations, rigorous dose-finding studies, and well-designed randomized controlled trials incorporating DPN-relevant structural and functional endpoints together with patient-reported outcomes. Better alignment between mechanistic studies and clinically meaningful outcome measures will be essential for improving the translational value of natural product-based therapies for DPN.

Nanocarrier-Based Drug Delivery Systems for DPN

The preceding sections have highlighted a recurring obstacle in DPN treatment: many promising interventions, including FDA-approved analgesics, emerging metabolic modulators, and natural products, remain limited by suboptimal pharmacokinetics. In DPN, this problem is especially relevant because the disease requires long-term treatment and involves distal peripheral nerves exposed to chronic metabolic injury, neuroinflammation, and impaired microvascular perfusion. Low water solubility, rapid metabolism, and limited tissue exposure can therefore reduce drug availability at sites of nerve injury. Nanocarrier-based delivery systems offer a potential strategy to address these disease-relevant barriers by improving solubility, protecting drugs from premature degradation, enhancing tissue targeting, and enabling sustained or localized release.[59] Figure 2 summarizes the major nanocarrier platforms currently explored for DPN-related therapeutics and highlights their relevance in overcoming key delivery barriers, including poor water solubility, rapid degradation, limited oral bioavailability, insufficient tissue targeting, and the need for sustained or localized drug release. Recent advances focus on formulations that enhance pharmacokinetic properties while improving drug exposure within disease-relevant cellular and tissue microenvironments.

Targeted Nanocarrier Platforms for DPN Therapy

Neural stem cell-derived extracellular vesicles (NSC-EVs) have emerged as innovative targeted delivery vehicles. Chen et al developed ZH-1c-EVs@SIN, a system composed of NSC-EVs modified with the ZH-1c aptamer and loaded with sinomenine.[60] This formulation specifically targets microglia and inhibits the WNT5a/TRPV1 signaling pathway, a key driver of neuroinflammation in DPN. Functional assays demonstrated that ZH-1c-EVs@SIN shifts microglial polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, reduces inflammatory cytokine expression, and restores neuronal regulatory proteins. In murine DPN models, the formulation improved pain-related behavior and reversed histopathological signs of nerve damage.[60] While these findings are promising, the study remains preclinical, and manufacturing complexity, batch-to-batch variability, and the need for rigorous safety evaluation of exogenous extracellular vesicles continue to pose substantial hurdles to clinical application.

Exosomes from mesenchymal stromal cells (MSCs) represent another actively investigated platform. Engineered MSC-derived exosomes enriched with miR-146a (Exo-146a) have shown amplified therapeutic efficacy in DPN mice compared to native MSC exosomes.[61,62] This approach addresses the vulnerability of naked miRNAs to degradation and their low stability in serum. The engineered exosomes shortened treatment duration and achieved better recovery outcomes as measured by nerve conduction velocity and pain thresholds.[61] Despite this amplified efficacy, critical questions remain regarding the optimal cell source for exosome production, the standardization of isolation and loading protocols, and the long-term safety of repeated administration.

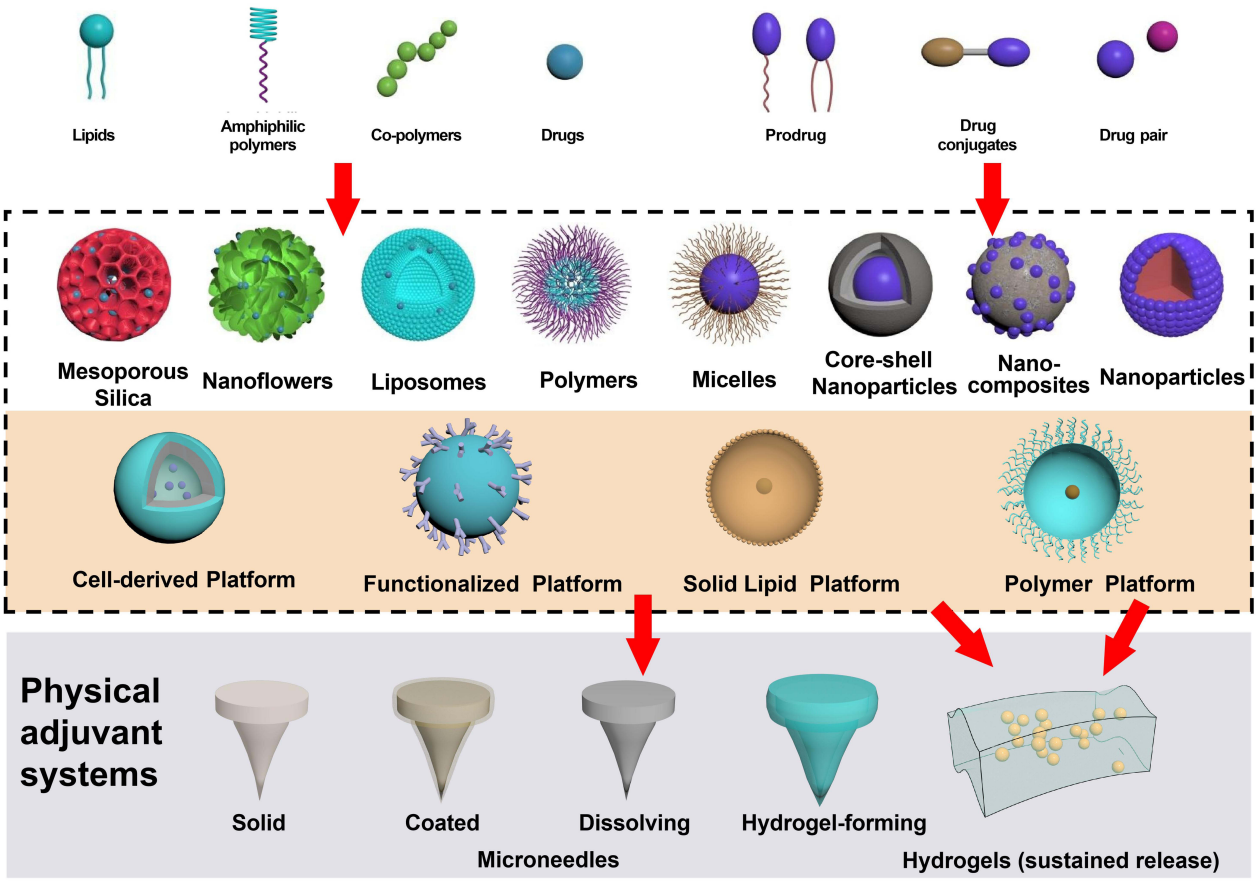

Figure 2 Representative nanocarrier platforms potentially applicable to diabetic peripheral neuropathy. The figure schematically summarizes major carrier types discussed in this review, including extracellular vesicle-based systems, lipid-based nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, lipid–polymer hybrid nanoparticles, hydrogels, and microneedle-based systems. These platforms may help improve solubility, stability, tissue exposure, and sustained or localized release of therapeutics relevant to DPN.

Lipid-based nanoparticles, including solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), have been extensively investigated as strategies to improv the oral bioavailability of poorly soluble drugs. Zaheer et al reported that naringenin-loaded SLNs significantly alleviated oxidative stress and enhance oral bioavailability in diabetic models.[63] Similarly, chitosan-coated SLN delivering berberine achieved a 2.8-fold increase in relative bioavailability and exhibited sustained release properties in diabetic models.[64] These systems can be also surface-modified to achieve sustained release or to target specific cells types, such as dorsal root ganglia neurons or Schwann cells. However, a persistent translational gap remains. Despite the wealth of preclinical data, only a handful of lipid-based formulations have progressed to clinical trials for DPN.

Lipid-polymer hybrid nanoparticles combine the advantages of both systems. Recent work using a Quality by Design (QbD) approach developed dual-drug nanocarriers co-encapsulating pregabalin and alpha-lipoic acid.[65] The optimized nanoparticles exhibited a mean size of 135 nm, high entrapment efficiency, and sustained release extending up to 72 hours. In vivo studies in streptozotocin-induced diabetic rats revealed significant improvements in nerve conduction, oxidative stress markers, and pain thresholds compared with free drugs.[66] While these results demonstrate synergistic neuroprotective efficacy, the study highlights a common limitation: most preclinical studies use small animal models with short treatment durations, making it difficult to predict long-term efficacy and safety in human DPN patients.

Biomaterial-Based Delivery Systems

Hydrogels and microneedles represent alternative strategies for local and sustained drug delivery. Thermosensitive hydrogels delivering basic fibroblast growth factor (bFGF), nerve growth factor (NGF), or angiotensin II have shown the potential to promoted nerve regeneration and pain relief in DPN models. Das et al developed an injectable, reversibly thermoresponsive,

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captopril-laden hydrogel for the local treatment of sensory loss in diabetic neuropathy.[67] The system enabled sustained drug release and improved nerve function in animal models. However, the invasive nature of intramuscular or intraneural administration may limits clinical acceptability.

Microneedle (MN) technology has attracted increasing attention as a minimally invasive transdermal delivery strategy. Recent studies have showed developments in MN platforms for diabetic neuropathy management, categorizing them into solid, coated, dissolving, and hydrogel-forming systems.[68] Dissolving and hydrogel-forming microneedles loaded with antioxidants, growth factors, and stem cell-derived exosomes have been shown to enhance nerve regeneration and reduce inflammation in animal studies. The technology offers several distinct advantages: it bypasses the stratum corneum, enables direct dermal delivery of therapeutics to affected peripheral nerves, improves patient compliance, and permits sustained release.[69–71] Nevertheless, significant barriers continue to impede clinical translation. Manufacturing scalability, batch-to-batch consistency in microneedle fabrication, biological stability of loaded therapeutics, and complex regulatory pathways remain unresolved. Furthermore, the available evidence remains predominantly preclinical, with few large-scale clinical trials validating efficacy in patients with DPN.

A novel electrospinning-hydrogel composite (Fiber-SIN/Gel-LidC) was developed for synergistic release of sinomenine and lidocaine.[72] This system enabled sustained drug release over 7 days and produced significant improvements in thermal and mechanical pain thresholds in diabetic rats. Mechanistic studies highlighted neuroprotective effects through MMP9 regulation and sodium channel inhibition. While innovative, the technology faces familiar challenges. The complexity of manufacturing electrospun-hydrogel composites, potential for batch variability, and unknown long-term biocompatibility require systematic evaluation before clinical consideration. These recurring concerns point directly to the broader barriers to clinical translation discussed below.

Critical Barriers to Clinical Translation

The clinical translation of nanocarrier-based therapies from laboratory to clinic faces formidable obstacles. Manufacturing scalability and batch-to-batch consistency represent major technical challenges. Small variations in particle size, surface properties, or drug loading can significantly impact therapeutic outcomes.[73,74] Microfluidics-based synthesis has emerged as a promising approach, offering precise control over particle characteristics and improved reproducibility.[75,76] However, transition from laboratory synthesis to commercial manufacturing requires stringent quality control measures and compliance with Good Manufacturing Practice (GMP), infrastructure that many academic research groups lack.[77]

Regulatory uncertainty compounds these challenges. Nanomedicines do not fit neatly within existing regulatory frameworks developed for conventional pharmaceuticals. Agencies such as the FDA and EMA therefore adopt case-by-case, risk-based approaches approaches because of the heterogeneity of nanomedicine platforms.[78] The absence of globally harmonized regulatory pathways forces developers to navigate complex, often contradictory requirements across different jurisdictions.[79] Standardized protocols for nanoparticle characterization, stability testing, and quality control insufficiently developed, thereby hampering regulatory approval.[80]

Safety concerns present another major hurdle. Nanoparticles exhibit complex interactions with biological systems that are difficult to predict on the basis of preclinical models. Intravenously administered nanoparticles are rapidly sequestered by Kupffer cells in the liver and spleen, leading to potential accumulation, oxidative stress, and pro-inflammatory responses.[81] Long-term toxicity, immunogenicity, and the fate of non-biodegradable nanomaterials in non-target organs require comprehensive evaluation.[82,83] The enhanced permeability and retention (EPR) effect, which is often robust in rodent models, is heterogeneous and limited in human tissues, thereby complicating targeting strategies.[84]

Finally, the clinical evidence base remains weak. Most nanocarrier studies for DPN are confined to proof-of-concept in small animal models, using single-dose or short-term endpoints.[85] Patient-centric outcomes such as sustained pain relief, quality of life improvement, and preservation of nerve function are rarely assessed. Without rigorous, well-controlled clinical trials measuring these endpoints, the true therapeutic value of nanocarrier-based DPN therapies remains uncertain.

In the context of DPN drug development, nanocarrier technology serves as a translational bridge. It offers a means of improving the translational potential of compounds that are mechanistically potent yet clinically impractical because of pharmacokinetic limitations—a category that includes many natural products (Natural Products and Derived Compounds for DPN) and even some conventional drugs (Clinical Drug Treatment of DPN). However, without concurrent advances in scalable manufacturing, safety evaluation, and regulatory harmonization, the field risks repeating the pattern of promising preclinical

results that fail to reach patients. Among the available preclinical directions, biomimetic extracellular vesicles and lipid-based nanocarriers loaded with multi-target natural compounds may deserve particular translational priority, because they directly address poor solubility, rapid metabolism, and limited tissue exposure while preserving the mechanistic breadth of natural products.[86] Addressing these interconnected challenges through collaborative efforts is essential to realize the potential of nanocarrier-based delivery systems to transform DPN pharmacotherapy. Against this translational backdrop, the broader therapeutic landscape of DPN remains defined by substantial unmet need.

Conclusion

Diabetic peripheral neuropathy remains a major clinical challenge because current therapies are still dominated by symptomatic pain control and do not effectively halt underlying nerve degeneration. Emerging targeted therapies show mechanistic promise, but convincing disease-modifying efficacy has not yet been established. Natural products, including TCM-derived compounds and formulas, may offer a multi-target approach to interconnected processes such as neuroinflammation, oxidative stress, and microcirculatory dysfunction, although their clinical translation remains limited. Nanocarrier-based delivery systems may help overcome pharmacokinetic barriers and improve tissue exposure of both conventional and natural therapeutics. Overall, the development of effective disease-modifying treatment for DPN remains a major unmet need.

Future Perspectives

Against this background, future progress in DPN treatment will depend on several priorities. First, rigorous randomized controlled trials are needed that incorporate objective structural biomarkers, such as intraepidermal nerve fiber density and corneal confocal microscopy, together with patient-reported outcomes. Second, improved patient stratification based on dominant pathogenic mechanisms may help identify those most likely to benefit from specific interventions. Third, combination strategies that pair symptom-controlling agents with disease-modifying candidates may represent a promising direction, particularly approaches combining analgesic therapies with metabolic modulators such as SGLT2 inhibitors or GLP-1 receptor agonists. Fourth, nanocarrier systems should be advanced toward scalable, GMP-compliant manufacturing and systematic safety evaluation. In particular, biomimetic extracellular vesicles and lipid-based nanocarriers loaded with multi-target natural compounds may provide an attractive translational direction for overcoming persistent pharmacokinetic limitations. Until these multidimensional approaches are rigorously validated, symptomatic management is likely to remain the clinical mainstay.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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