Readers Insight
Publisher of open access books and journals
PJMLS OPEN ACCESS
Print ISSN: 2707-4471. Online ISSN: 2707-448X

Review Article	Pak-Euro Journal of Medical and Life Sciences
DOI: 10.31580/pjmls.v8i4.3427	Copyright © All rights are reserved by Corresponding Author
Vol. 8 No. 4, 2025: pp. 807-820	
www.readersinsight.net/pjmls	**Revised:** December 01, 2025 **Accepted:** December 20, 2025
Submission: September 17, 2025	**Published Online:** December 31, 2025

INTEGRATED MOLECULAR, REGENERATIVE, AND TECHNOLOGICAL INNOVATIONS IN THE MODERN MANAGEMENT OF DIABETIC PERIPHERAL NEUROPATHY

Shaheen Perveen[1], Amber Nawab[2], Mehwish Nisar[3]*, Adam Ali[4], Seema Shahab[2], Mahnoor Jamil[2], Javeria Sheikh[3]

[1]**Department of Pharmaceutics,** Faculty of Pharmacy, Jinnah Sindh Medical University, Karachi, Pakistan
[2]**Department of Pharmaceutics,** Faculty of Pharmacy, Jinnah University for Women, Karachi, Pakistan
[3]**Department of Pharmaceutics,** Faculty of Pharmacy, Hamdard University, Karachi, Pakistan
[4]**General Manager of Swiss Pharma,** Karachi, Pakistan
***Corresponding Author:** Mehwish Nisar. E. mail: mehwish.nisar@hamdard.edu.pk

Abstract
By combining molecular, regenerative, and technological advancements, the treatment of diabetic peripheral neuropathy (DPN) is moving away from insufficient symptomatic pain relief and towards disease-modifying approaches. This all-encompassing method critically investigates pharmacological agents such as novel ion channel modulators for selective pain control and Mitochondria-Targeted Antioxidants (MTAs) to fight metabolic stress. Along with individualized lifestyle interventions like supervised exercise to increase IENF density and AI-driven precision nutrition, it also integrates state-of-the-art regenerative techniques, such as the paracrine effects of MSC-derived exosomes and the creation of smart biomaterial scaffolds for guided axonal repair. The review creates a vital framework for multi-modal, neuroprotective, and regenerative approaches that are critical for greatly enhancing functional outcomes and quality of life for DPN patients by bridging these disparate fields.
Keywords: *Biomaterial scaffolds, Diabetic peripheral neuropathy (DPN), Mitochondrial dysfunction, MSC exosomes, Neuro regeneration, Precision medicine*

INTRODUCTION

Thirty to fifty percent of people have DPN, a common consequence of diabetes; poor glycaemic control and longer illness duration are linked to increased frequency (1-3). Sensory loss, discomfort, and motor dysfunction characterize diabetic peripheral neuropathy (DPN), a leading cause of non-traumatic lower-limb amputations globally (4, 5). Chronic pain affects up to 50% of persons with DPN, negatively compromising quality of life and boosting the risk of depression and sleep disturbances (6, 7).

One major risk factor for diabetic foot ulcers is DPN, which puts 15–34% of diabetics at risk at some point in their lives (8-10). Previous foot ulcers are linked to up to 85% of diabetes-related amputations; the loss of protective sensibility can result in infections, invisible lesions, and even amputations (1). Peripheral artery disease, nephropathy, and retinopathy are examples of comorbidities that greatly increase the risk of amputation (11, 12).

Despite significant advancements in our understanding of DPN, the majority of current clinical treatment is symptomatic and does not alter the underlying disease process (13). Gabapentinoids, antidepressants, opioids, antioxidants, and vitamin supplements are examples of standard therapy that only temporarily and partially relieves pain, does not stop neurodegeneration, and is not very effective at repairing nerve structure or function. Additionally, integrated strategies that concurrently target the metabolic, mitochondrial, neuroimmune, vascular, and regenerative pathways now known to propel DPN progression are absent from current guidelines (14). While a number of reviews address specific mechanisms or therapeutic classes, none offer a cohesive, interdisciplinary synthesis that links molecular pathogenesis with new developments in pharmacology, regeneration, technology, and lifestyle (15).

Copyright © 2025 Authors. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

By providing a thorough, systems-level integration of cutting-edge mitochondrial therapies, neuroimmune modulators, advancements in growth factors and stem cells, sophisticated biomaterials, neuromodulation technologies, and customised metabolic interventions, this review closes that gap. This paper offers a fresh viewpoint that emphasises how multi-target, mechanism-informed strategies can move DPN management from symptomatic relief towards true disease modification by combining these quickly developing fields into a single translational framework—an angle not fully covered in the literature currently in publication (16).

METHODOLOGY

In order to integrate and critically assess therapeutic advancements in three different areas of DPN management molecular targets, regenerative therapies, and technological applications—this article is a thorough narrative review.

When conducting a literature search for diabetic neuropathy, the following keyword combinations were used: "Diabetic Neuropathy", "Mitochondria-Targeted Antioxidants", "Exosomes", "Nerve Guidance Conduits", "IENF Density" and "Artificial Intelligence in Neuropathy", to methodically search the electronic databases PubMed, Scopus, and Web of Science.

This search concentrated on original research, systematic reviews and meta-analyses, and publications from the past 5-7 years, when reviewing the treatment options for Diabetic Peripheral Neuropathy (DPN). Coming hotfooting into the picture, the studies we looked for were those that showed brand-new ideas, brand-new therapies for DPN, including preclinical work on drug targets, animal studies that mimic the disease and human trials of physical exercise and nutrition.

Synthesis and Integration: This approach didn't stick to the usual review style. Instead, it pulled together insights from different fields, looking for where therapies overlap or work together—like spotting how exercise, nutrition, and MTAs all target mitochondrial health in their own ways. The real value comes from weaving these separate threads into a single, clear strategy for the future.

MODERN UNDERSTANDING OF DPN PATHOGENESIS

MITOCHONDRIAL DYSFUNCTION & METABOLIC STRESS

Chronic hyperglycemia raises NADH/NAD^+ ratios and causes excessive ROS production due to mitochondrial electron transport chain overload (17, 18). It starts to leak protons, which disrupts the membrane potential cripples ATP production, when a mitochondrial is subjected to stress. Moreover, it triggers mtDNA mutations that feed back to cause more oxidative stress (19). This, as seen in Fig. 1, leads to abnormal mitochondrial dynamics. Mitochondrial fragmentation is caused by DRP1 and results in a reduction in MFN-2 dependent fusion, basically splitting the mitochondria into a network that is unable to pump out enough energy for the axon and ultimately contributes to neurodegeneration (19-21).

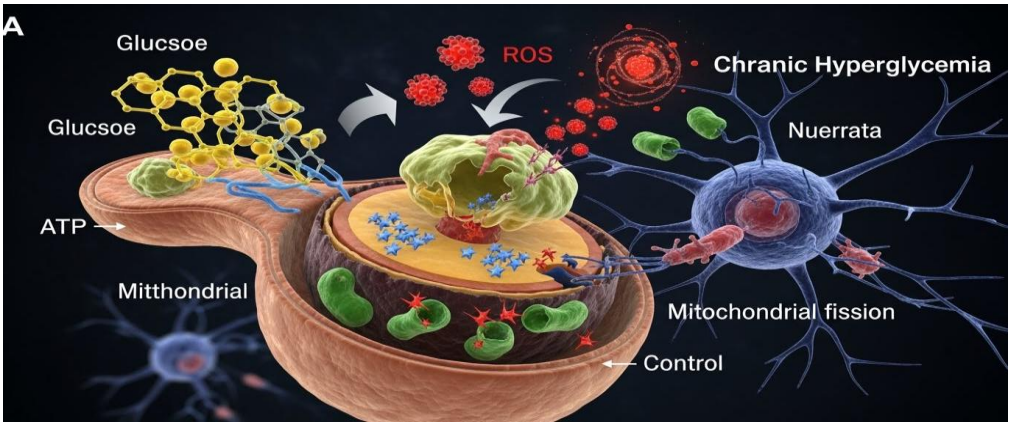

Fig. 1. Schematic representation of the effects of long-term hyperglycemia, showing mitochondrial dysfunction, increased reactive oxygen species (ROS) production, and the progression of neurodegeneration

Although MTAs like MitoQ, SkQ1, and Mito-TEMPO exhibit potent mechanistic activity improving ETC electron flux, lowering lipid peroxidation, and restoring—their transfer from animal models to clinical

Copyright © 2025 Authors. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

therapy is fraught with difficulties (22). Although their lipophilic triphenylphosphonium (TPP^+) moiety improves mitochondrial targeting, it may limit systemic distribution and result in inconsistent absorption (23). Ironically, excessive mitochondrial accumulation, especially at higher clinical doses, may cause oxidative stress or reduce ETC activity (24).

Concerns regarding off-target bioenergetic disruptions are raised by the possibility that long-term administration of TPP-conjugated antioxidants may impact cardiac and hepatic mitochondrial pools.(25) Most evidence remains preclinical; few controlled human trials exist for DPN, limiting regulatory progression.(26)

IMPORTANCE OF DRUG SELECTIVITY IN MODERN CHANNEL MODULATION

Older agents (e.g., carbamazepine, lamotrigine) lack specificity, interacting with multiple sodium channels and causing CNS adverse effects such as sedation or dizziness (27). New-generation modulators exhibit high isoform selectivity, improving safety and therapeutic precision: Targets Nav1.7 with far higher specificity than older sodium channel blockers. Spares Nav1.5 and Nav1.6 reduce cardiac and motor neuron adverse events.Its selectivity allows analgesia without global sensory suppression (28).

Next-generation Cav2.2 and Cav3.2 inhibitors designed to avoid widespread calcium channel inhibition seen in pregabalin. Lead to improved pain control with fewer CNS side effects (28). TRPA1/TRPV4 antagonists are highly targeted to peripheral sensory neurons, minimizing systemic exposure (29). Kv7 channel openers (e.g., SCR2682) compared to older K^+ modulators, restore inhibitory M-current with less interaction with cardiac Kv channels, increasing safety (30). Therefore, the primary distinction between contemporary and traditional ion-channel analgesics is enhanced selectivity, indicating a move towards precision neuropharmacology in DPN (31).

Neurovascular unit dysfunction damage to the endothelium lowers blood flow and causes nerve ischaemia. Agents that promote angiogenesis and nitric oxide signalling show promise (32, 33).

NEW PHARMACOLOGICAL TREATMENTS

Restoring membrane integrity, enhancing ATP synthesis, and reducing mitochondrial ROS production are the goals of mitochondrial-targeted therapies, such as MitoQ, SkQ1, CoQ10 nano formulations, and PQQ. In diabetic models, these substances improve mitochondrial respiration and restore axonal energy homeostasis (34-36).

Despite encouraging results in preclinical research, a number of significant obstacles prevent their clinical use in DPN. Due to variations in TPP accumulation kinetics, MitoQ and SkQ1 exhibit uneven plasma mitochondrial distribution among patients (37). Their antioxidant benefit may be undermined by high concentrations that disrupt electron flow or uncouple oxidative phosphorylation (38). Human data are restricted to safety or general antioxidant trials rather than DPN-specific RCTs; the majority of studies use animal neuropathy models (39). There is still not enough research on off-target accumulation in the mitochondria of the liver, kidney, and heart (40). Approval procedures are complicated by their designation as "mitochondria-active nutraceuticals". Therefore, careful optimisation and thorough clinical trials are required before incorporating MTAs into DPN management guidelines, even though they are still a high-potential therapeutic class (41). Table I depicted echanism-based pharmacological agents targeting mitochondrial dysfunction in DPN.

Table I. Summary of echanism-based pharmacological agents targeting mitochondrial dysfunction in DPN

Drug/Class	Mechanism of action	Key effects on Mmitochondria and cells	References
MitoQ (mitoquinone)	Mitochondria-targeted antioxidant; accumulates in mitochondria, scavenges ROS	Reduces oxidative biomarkers, protects ETC complexes, improves neuronal function, delays neurodegeneration	(42, 43)
SkQ1	TPP-conjugated plastoquinone; targets mitochondrial membranes, reduces ROS	Protects mitochondrial membranes, reduces oxidative injury, potential neuroprotection	(44)
CoQ10 nanoformulations	Enhanced delivery (nanoparticles, liposomes,	Improves mitochondrial respiration, ATP production, reduces oxidative damage, protects	(44-46)

Copyright © 2025 Authors. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

	phytosomes) for mitochondrial uptake	against I/R injury	
PQQ (pyrroloquinoline quinone)	Stimulates mitochondrial biogenesis via SIRT1/PGC 1α and AMPK pathways; antioxidant	Promotes mitochondrial synthesis, enhances ATP, reduces oxidative stress, supports neuronal survival	(47, 48)

Nav1.7 inhibitors (Vixotrigine and analogs) exhibit strong isoform selectivity for Nav1.7 vs. Nav1.5 (cardiac) or Nav1.6 (motor).Avoid the sedation and psychomotor impairment associated with older sodium channel blockers by providing analgesia through targeted suppression of nociceptor firing (27, 49). Cav2 and Cav3 modulators designed for subtype-selective inhibition, reducing the CNS adverse profile of pregabalin. Potential to modulate pain transmission with minimal cognitive effects (50). TRP channel antagonists (TRPA1, TRPV4) target mechano-cold transduction pathways implicated in allodynia. High peripheral specificity reduces systemic toxicity (51).

Kv7 channel openers restore the suppression of M-current brought on by inflammatory and diabetic signalling. Enhanced subtype selectivity avoids interference with the cardiac potassium channel. When taken as a whole, these advancements show a significant change from broad-spectrum ion-channel modulation to precisely targeted, subtype-specific analgesics that are consistent with contemporary neuropathic pain pharmacology (30). Anti-inflammatory neuroimmune modulators minocycline decreases microglial activation (52). TNF-α inhibitors are being tested for severe neuropathic pain (52). Natural NF-κB blockers – curcumin, baicalein, rosmarinic acid (53). Growth factor based therapeutics neurotrophic factors are crucial for nerve repair. Mimetics of BDNF IGF-1 therapy increases neurone sprouting (54). Thymosin β4 analogues encourage axonal regeneration (54). NGF-loaded nanoparticles (55).

Novel analgesics with dual mechanisms metformin activates AMPK and reduces neuropathic pain (56, 57). DHA and omega-3 derivatives: enhance opioid receptor sensitivity.(58, 59). Apigenin and quercetin: modulate microglial activation and synaptic morphology (60, 61).

ADVANCEMENTS IN NATURAL & NUTRACEUTICAL THERAPIES

Natural polyphenols and innovative delivery techniques are becoming effective treatments for diabetic peripheral neuropathy (DPN) by focussing on oxidative stress, inflammation, and neurodegeneration. Polyphenol Rich botanicals: Mechanisms and efficacy, Salvianolic acid A (SalA) by reducing reactive oxygen species (ROS), improving mitochondrial function, and triggering Nrf2 signaling which is essential for cellular defence against oxidative stress Salianolic Acid A (SalA) exhibits notable antioxidative and anti-inflammatory effects in diabetic peripheral neuropathy (DPN) models. In animal experiments, SalA also reduces neuroinflammation and enhances neuronal conduction (62).

Naringenin citrus flavonoid alleviates nitrosative and oxidative stress, lowers inflammatory cytokines, and inhibits MMP-9, increasing nerve function and lowering neuropathic pain in diabetic rats (63, 64). Deguelin, in diabetic neuropathy models, a natural rotenoid improves Nrf2 signalling, decreases oxidative stress, lowers plasma glucose levels, and reduces neuroinflammation, all of which improve nerve conduction and reduce pain (65). Black turmeric (Curcuma caesia) targets inflammation and neuronal damage (66). Herbal nanoformulations increase bioavailability of natural compounds. Nano-curcumin in diabetic peripheral neuropathy (DPN), curcumin's limited bioavailability is successfully addressed, allowing for tailored distribution and improved nerve tissue penetration, which significantly lowers oxidative and inflammatory indicators (66). The neuroprotective and metabolic functions of a number of functional nutrients are supported by current research, with differing degrees of evidence supporting each pathway. Functional nutrients: mechanisms and outcomes are depicted in Table II.

REGENERATIVE MEDICINE & TISSUE ENGINEERING

Mesenchymal stem cell (MSC)-derived exosomes have emerged as a core regenerative strategy in DPN because they deliver bioactive miRNAs, neurotrophic factors, and immunomodulatory molecules that directly restore nerve integrity can also see in Fig. 2 (75, 76).

Copyright © 2025 Authors. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Table II. Summary of mechanisms and neuro-protective effects of key functional nutrients

Nutrient	Mechanism/Effect	Key outcomes/benefits	References
Vitamin D	Modulates neuroimmune function, reduces inflammation	Neuroprotection, improved brain health	(67, 68)
Alpha-lipoic acid	Mitochondrial antioxidant, redox balance	Reduced oxidative stress, neuroprotection	(69, 70)
Acetyl-L-carnitine	Fatty acid metabolism, axonal repair	Enhanced energy, axonal/myelin repair	(71, 72)
Folic acid + B12	Regulate homocysteine, nerve conduction	Lower homocysteine, improved nerve function	(73, 74)

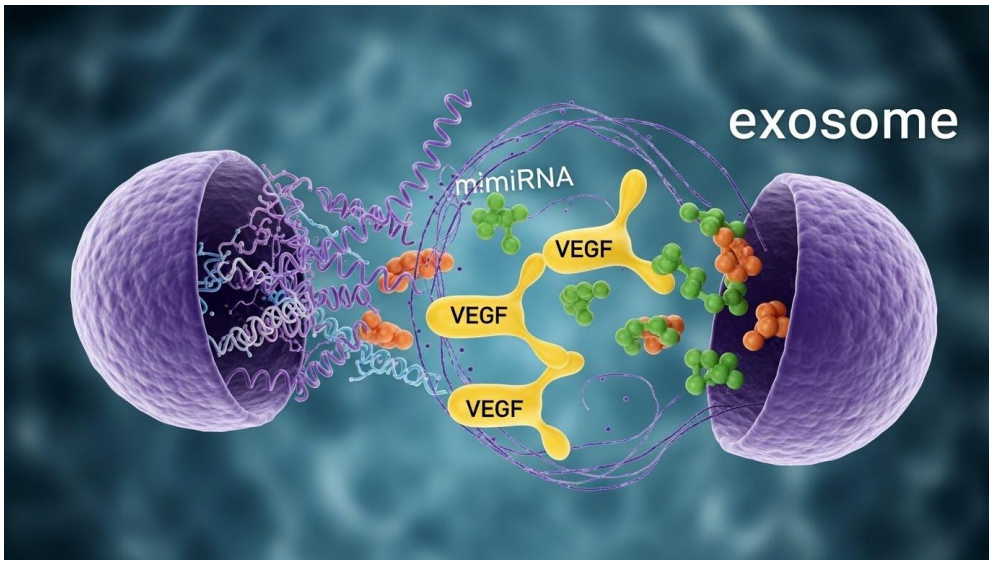

Fig. 2. Illustration of the regenerative mechanism of an MSC-derived exosome, showing the release of its cargo, including microRNAs (miRNAs) and growth factors such as VEGF, and their effects on recipient neurons and Schwann cells during nerve repair

GROWTH FACTORS DELIVERED BY MSC EXOSOMES

MSC exosomes carry a rich profile of regenerative growth factors, including; VEGF (Vascular Endothelial Growth Factor), a potent angiogenic mediator restoring endoneurial blood flow (77); PDGF-D (Platelet-Derived Growth Factor-D) enhances fibroblast activation, extracellular matrix repair, and Schwann cell survival (78); NGF (Nerve Growth Factor) stimulates sensory axon regeneration and neuronal survival; IGF-1 (Insulin-like Growth Factor-1) promotes myelin repair, axonal metabolism, and glucose utilization in neurons (79); GDNF (Glial Cell–Derived Neurotrophic Factor) supports dopaminergic and sensory neuron survival and function (80).

Exosomes derived from MSCs facilitate regeneration via these mechanisms PI3K/AKT and ERK signalling activation for neuronal survival.Suppression of inflammatory cascades (NF-κB, NLRP3 inflammasome) Enhancement of angiogenesis via VEGF and PDGF-D. Schwann cell myelination restoration and oxidative damage reversal via miRNA-mediated ROS regulation.Engineered exosomes integrated with hydrogels or nanoparticles further improve targeted delivery, retention at injury sites, and sustained release of functional cargo (81, 82).

MSC exosomes can promote nerve regeneration, repair bone and cartilage, and speed up wound healing. They can transport neurotrophins, lower inflammation in neural and retinal tissues, and pass-through biological barriers like the blood-brain barrierTargeted delivery and therapeutic efficacy are improved by the use of engineered exosomes and biomaterial combinations like hydrogels (83, 84).

Conventional nerve scaffolds served mainly as passive conduits that provided structural support and physical alignment to direct axonal growth. nerve guidance conduit/scaffold (e.g., electrospun nanofibers or a hydrogel) implanted into an injured peripheral nerve to guide axonal growth (Fig. 3). Modern scaffold engineering has shifted toward active, smart biomaterials that interact dynamically with the microenvironment and deliver regenerative cues (85).

Copyright © 2025 Authors. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

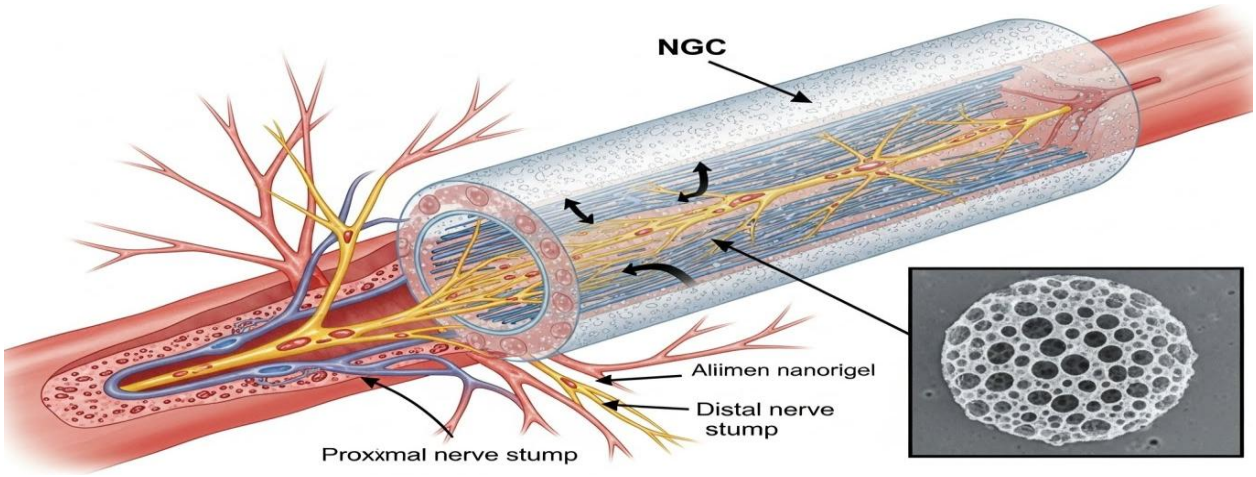

Fig. 3. Illustration of a nerve guidance conduit or scaffold, such as electrospun nanofibers or a hydrogel, implanted at the site of peripheral nerve injury to support and guide axonal regeneration

Smart, bioactive scaffolds provide biochemical + mechanical cues customized to DPN pathology. Support long-term presence of growth factors without rapid degradation. Improve axon alignment, remyelination, and vascularization better than passive conduits. Serve as platforms to integrate exosomes, nanoparticles, and gene therapies (86).

This paradigm shift significantly enhances the therapeutic potential of regenerative medicine in DPN by combining structural support with targeted molecular therapy (87).

Table III. Comparison of scaffold types, additives, and regenerative effects and Scaffold types and key Innovation

Scaffold type	Key features & additives	Effects on nerve regeneration	References
Electrospun nanofibers	Aligned fibers, conductive additives, plant extracts	Guide axonal growth, enhance myelination, improve function	(88-90)
Collagen/gelatin hybrids	Collagen, gelatin, chitosan, growth factors	Support cell adhesion, angiogenesis, axonal elongation	(91-93)
Hydrogels with growth factors	VEGF, NGF, GDNF, CNTF, IGF-1, bioactive peptides	Sustained release, promote neurite outgrowth, vascularization	(94-96)

GENE MODULATION THERAPY

Silencing miR-21 has shown promise in reducing fibrosis and inflammation in chronic Chagas disease, diabetic nephropathy, spinal cord injury, and myocardial infarction models, with inhibition achieved through antisense oligonucleotides or nanoparticle delivery. Meanwhile, miR-155 is overexpressed in autoimmune and inflammatory diseases, and its silencing can modulate immune cell activity, reducing inflammation. Preclinical studies indicate that inhibiting miR-155 may alleviate symptoms in multiple sclerosis and other autoimmune diseases (97-99), upregulation of miR-146a reduces neuropathic pain (100). CRISPR-based editing for correcting ion channel abnormalities (future approach). miRNA silencing (miR-21, miR-155), upregulation of miR-146a, and CRISPR-based modulation of voltage-gated ion channels remain future-focused strategies with potential synergy when combined with exosome or scaffold-based delivery systems (101).

INNOVATIVE NON-PHARMACOLOGICAL APPROACHES

Next-Generation acupuncture techniques such as Electro-acupuncture modulates: ER stress pathways, GRP78 signaling and caspase-12–mediated apoptosis. Leading to functional nerve recovery (102-104). Gua Sha, a traditional East Asian skin scraping therapy, is being examined for its physiological effects and potential benefits in conditions such as diabetic peripheral neuropathy (DPN). Recent studies focus on its influence on microcirculation, immune modulation, and inflammation, which offer a mechanistic understanding of its clinical effects (105-107).

Wearable neurostimulation technologies, including high-frequency TENS and transcutaneous magnetic nerve stimulation (TMNS), are increasingly crucial for home-based pain management (107). While closed-loop and AI-driven systems are promising but yet in development, high-frequency TENS has moderate data supporting its efficacy in relieving chronic pain (108, 109).

Copyright © 2025 Authors. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Mobile and internet-based CBT therapies substantially reduce pain perception and catastrophising in chronic pain populations, as indicated by randomised controlled trials that report significant improvements in pain acceptance and functioning, with persistent effects for several months (110). These treatments can be used for a number of illnesses, such as musculoskeletal ailments and fibromyalgia (111, 112).

LIFESTYLE AND METABOLIC INTERVENTIONS

Short-term (10 weeks) and long-term (up to one year) exercise enhances nerve plasticity and regeneration, which correlates with a reduction in neuropathic symptoms and pain(113) the difference in Intraepidermal Nerve Fiber (IENF) density between a healthy control and a DPN patient as shown in Fig. 4.

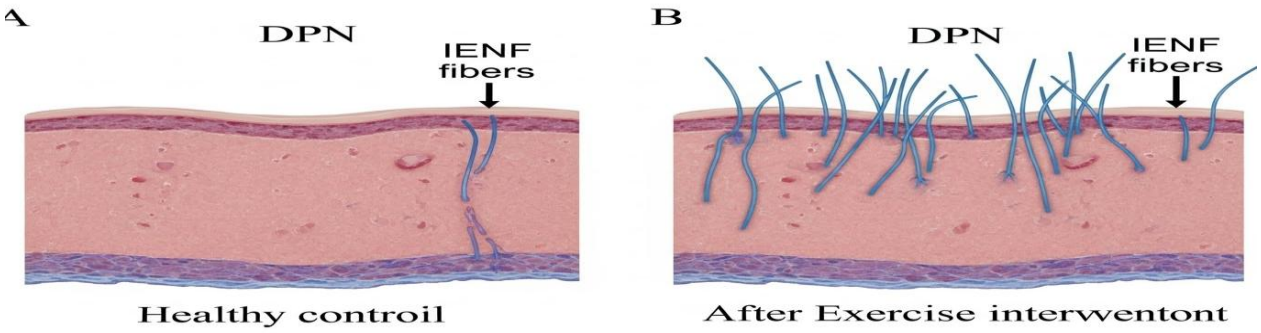

Fig. 4. Diagram illustrating differences in intraepidermal nerve fiber (IENF) density between a healthy control and a patient with diabetic peripheral neuropathy (DPN), and the subsequent increase in IENF density following exercise intervention (114)

Plant-based and Mediterranean diets, which are high in antioxidants and good fats, successfully reduce oxidative stress and systemic inflammation. They act by modifying inflammatory pathways, improving lipid profiles, and promoting insulin sensitivity, which helps to stabilise blood glucose and dramatically reduce metabolic load on nerves as shown in Fig. 5.

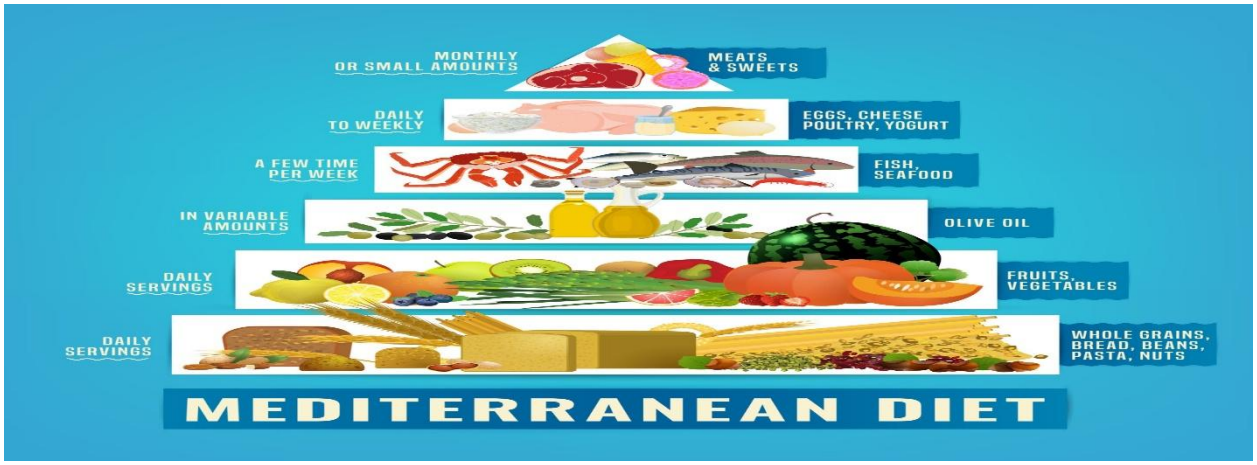

Fig. 5. The mediterranean diet pyramid/wheel: A personalized nutrition strategy

Up to 93% of patients recover completely after bariatric surgery, which dramatically lowers neuropathic pain.(115) However, a small percentage of patients may have chronic or recurrent pain, which may have an impact on long-term weight loss results (116). Small nerve fibre function is most consistently improved by bariatric surgery, with obvious regeneration (117); large fibre changes are negligible, with the exception of disorders like as carpal tunnel syndrome (118). Following surgery, there is also a noticeable improvement in autonomic nerve function, including sudomotor and cardiac C-fiber activity (119).

Bariatric surgery effectively decreases systemic inflammatory indicators such as CRP, IL-6, and TNF-α within months, with effects lasting up to four years, contributing to improved metabolic outcomes independent of the surgical approach used (120, 121).

Copyright © 2025 Authors. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

DISCUSSION

This review highlights the shift in the treatment of diabetic peripheral neuropathy (DPN) from symptom relief to disease-modifying strategies. The main causes of nerve damage are listed as oxidative stress, neuroimmune activation, ion channel dysregulation, and mitochondrial dysfunction. The review emphasises how challenging it is to translate new therapies, like antioxidants that target mitochondria and selective ion-channel modulators. Two examples of regenerative technologies that are being investigated as potential methods for nerve repair are exosomes made from MSCs and smart biomaterial scaffolds. Exercise and a tailored diet are examples of evidence-based non-pharmacological strategies that are highlighted. The review concludes that customised, multimodal therapies are necessary for both successful DPN management and enhanced patient quality of life.

CONCLUSION

Diabetic Peripheral Neuropathy (DPN) treatment is about to change in a big way. Instead of just easing symptoms, the focus is shifting to actually protecting nerves and helping them heal. A whole wave of new therapies is pushing this forward. We're talking about everything from targeting problems inside cells—like fixing mitochondrial issues or tweaking ion channels—to using the healing power of MSC-derived exosomes and advanced biomaterials. What really makes the difference, though, is when experts from different fields work together. Combine precise molecular science, regenerative engineering, and personalized tech, and you get treatments that help people actually recover function, not just manage pain. In the end, this approach offers real hope for a better future and a much higher quality of life for people living with DPN around the world.

Future directions:

If we want to bring these new ideas into real treatment for Diabetic Peripheral Neuropathy, we need to focus on four key areas. First up are clinical validation and delivery. That means creating delivery systems that actually get through the blood-nerve barrier, and running solid, multi-center randomized controlled trials for new treatments like MitoQ and MSC-derived exosomes.

Funding:

The conducted study is not funded from any platform or organization.

Acknowledgment:

Through this study we show our gratitude to our organization, Hamdard University, Karachi, which has always motivated and supported in the whole journey of this research.

Conflict of interest:

There is no conflict of interest among authors.

Authors' contribution:

MN Conceived the idea & designed the structure of the review; ANC Analyzed recent literature; JS, NF & SP Data compilation, referencing, and critical revision of the draft; ST Helped in literature review, language editing.

Declaration of generative AI and AI-assisted technologies in the writing process:

During the preparation of this manuscript the authors used Chat GPT to enhance the readability of the article. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

References:

Copyright © 2025 Authors. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

1. Hicks C, Selvin E. Epidemiology of Peripheral Neuropathy and Lower Extremity Disease in Diabetes. Current Diabetes Reports. 2019;19:86.
2. Zhu J, Hu Z, Luo Y, Liu Y, Luo W, Du X. Diabetic peripheral neuropathy: pathogenetic mechanisms and treatment. Frontiers in Endocrinology. 2024;14:1225684.
3. Savelieff M, Elafros M, Viswanathan V, Jensen T, Bennett D, Feldman E. The global and regional burden of diabetic peripheral neuropathy. Nature reviews Neurology. 2024; 20:77–92.
4. Sloan G, Selvarajah D, Tesfaye S. Pathogenesis, diagnosis and clinical management of diabetic sensorimotor peripheral neuropathy. Nature Reviews Endocrinology. 2021;17:400-20.
5. Yang Y, Zhao B, Wang Y, Lan H, Liu X, Hu Y. Diabetic neuropathy: cutting-edge research and future directions. Signal Transduction and Targeted Therapy. 2025;10:12.
6. Zhou P, Zhou JS, Li JJ, Qin L, Hu W, Zhang XY. Prevalence and risk factors for painful diabetic peripheral neuropathy: a systematic review and meta-analysis. Frontiers in Neurology. 2025;16:1342216.
7. Yang H, Sloan G, Ye Y, Wang S, Duan B, Tesfaye S. New Perspective in Diabetic Neuropathy: From the Periphery to the Brain, a Call for Early Detection, and Precision Medicine. Frontiers in Endocrinology. 2020;10:929.
8. Edmonds M, Manu C, Vas P. The current burden of diabetic foot disease. Journal of clinical orthopaedics and trauma. 2021;17:88-93.
9. Khan S, Ahmad S, Khan M, Lohani M, Khan MS, Haneef M. Diabetic Peripheral Neuropathy: Navigating Controversies and Pioneering Advances. Advancements in Life Sciences. 2025;12:240–252.
10. Nube V, McMorrow R, Manski-Nankervis J. Preventing diabetes-related foot ulcers through early detection of peripheral neuropathy. Australian journal of general practice. 2022;51 11:833-8.
11. Khawaja N, Abu-Shennar J, Saleh M, Dahbour S, Khader Y, Ajlouni K. The prevalence and risk factors of peripheral neuropathy among patients with type 2 diabetes mellitus; the case of Jordan. Diabetology & Metabolic Syndrome. 2018;10:67.
12. Lu Y, Xing P, Cai X, Luo D, Li R, Lloyd C. Prevalence and Risk Factors for Diabetic Peripheral Neuropathy in Type 2 Diabetic Patients From 14 Countries: Estimates of the INTERPRET-DD Study. Frontiers in Public Health. 2020;8;534372.
13. Preston FG, Riley DR, Azmi S, Alam U. Painful diabetic peripheral neuropathy: practical guidance and challenges for clinical management. Diabetes, Metabolic Syndrome and Obesity. 2023:1595-612.
14. Hieronymi A. Understanding systems science: A visual and integrative approach. Systems research and behavioral science. 2013;30(5):580-95.
15. Sorger PK, Allerheiligen SR, Abernethy DR, Altman RB, Brouwer KL, Califano A., editors. Quantitative and systems pharmacology in the post-genomic era: new approaches to discovering drugs and understanding therapeutic mechanisms. An NIH white paper by the QSP workshop group; 2011: NIH Bethesda Bethesda.
16. Othman ZK, Ahmed MM, Kasimieh O, Musa SS, Branda F, Cue EG. Artificial intelligence for natural product drug discovery and development: current landscape, applications, and future directions. Intelligence-Based Medicine. 2025:100316.
17. Otero M, Henao-Romero N, Krysak T, Vu-Lu M, Morales OM, Momeni Z. Hyperglycemia-induced mitochondrial abnormalities in autonomic neurons via the RAGE axis. Scientific Reports. 2025;15.
18. Zhang Z, Huang Q, Zhao D, Lian F, Li X, Qi W-W. The impact of oxidative stress-induced mitochondrial dysfunction on diabetic microvascular complications. Frontiers in Endocrinology. 2023;14.
19. González P, Lozano P, Ros G, Solano F. Hyperglycemia and Oxidative Stress: An Integral, Updated and Critical Overview of Their Metabolic Interconnections. International Journal of Molecular Sciences. 2023;24.
20. Tashkandi A, Gorman A, Mathers EM, Carney G, Yacoub A, Setyaningsih W. Metabolic and Mitochondrial Dysregulations in Diabetic Cardiac Complications. International Journal of Molecular Sciences. 2025;26.
21. Rudokas M, McKay M, Toksoy Z, Eisen J, Bögner M, Young L. Mitochondrial network remodeling of the diabetic heart: implications to ischemia related cardiac dysfunction. Cardiovascular Diabetology. 2024;23.
22. Fields M, Marcuzzi A, Gonelli A, Celeghini C, Maximova N, Rimondi E. Mitochondria-Targeted Antioxidants, an Innovative Class of Antioxidant Compounds for Neurodegenerative Diseases: Perspectives and Limitations. International Journal of Molecular Sciences. 2023;24.

Copyright © 2025 Authors. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

23. Jiang Q, Yin J, Chen J, Xiaokang, Wu M, Liu G. Mitochondria-Targeted Antioxidants: A Step towards Disease Treatment. Oxidative Medicine and Cellular Longevity. 2020;2020.
24. Fernandes C, Videira A, Veloso C, Benfeito S, Soares P, Martins. Cytotoxicity and Mitochondrial Effects of Phenolic and Quinone-Based Mitochondria-Targeted and Untargeted Antioxidants on Human Neuronal and Hepatic Cell Lines: A Comparative Analysis. Biomolecules. 2021;11.
25. Trnka J, Elkalaf M, Andel M. Lipophilic Triphenylphosphonium Cations Inhibit Mitochondrial Electron Transport Chain and Induce Mitochondrial Proton Leak. PLoS ONE. 2015;10.
26. Kalyanaraman B, Cheng G, Hardy M, You M. OXPHOS-targeting drugs in oncology: new perspectives. Expert Opinion on Therapeutic Targets. 2023;27:939-52.
27. Alles S, Smith P. Peripheral Voltage-Gated Cation Channels in Neuropathic Pain and Their Potential as Therapeutic Targets. Frontiers in Pain Research. 2021;2.
28. Flinspach M, Xu Q, Ad P, Fellows R, Hagan R, Gibbs A. Insensitivity to pain induced by a potent selective closed-state Nav1.7 inhibitor. Scientific Reports. 2017;7.
29. Wang J, Liu Y, Hu F, Ju C. A novel and potent neuronal Kv7 channel opener SCR2682 alleviates chronic pain in rats. The FASEB Journal. 2020;34.
30. Wang J, Liu Y, Hu F, Yang J, Guo X, Hou. Activation of Neuronal Voltage-Gated Potassium Kv7/KCNQ/M-Current by a Novel Channel Opener SCR2682 for Alleviation of Chronic Pain. The Journal of Pharmacology and Experimental Therapeutics. 2021;377:20-8.
31. Xie Y-F, Yang J, Ratté S, Prescott S. Similar excitability through different sodium channels and implications for the analgesic efficacy of selective drugs. eLife. 2024;12.
32. Kang S, Kim H-J, Sukhwal, Oh D-Y, Jang J, Seo C. Liquid plasma promotes angiogenesis through upregulation of endothelial nitric oxide synthase-induced extracellular matrix metabolism: potential applications of liquid plasma for vascular injuries. Cell Communication and Signaling : CCS. 2024;22.
33. Hayashida R, Kondo K, Morita S, Unno K, Shintani S, Shimizu. Diallyl Trisulfide Augments Ischemia-Induced Angiogenesis via an Endothelial Nitric Oxide Synthase-Dependent Mechanism. Circulation journal : official journal of the Japanese Circulation Society. 2017;81 6:870-8.
34. Șerban M, Toader C, Covache-Busuioc R-A. The Redox Revolution in Brain Medicine: Targeting Oxidative Stress with AI, Multi-Omics and Mitochondrial Therapies for the Precision Eradication of Neurodegeneration. International Journal of Molecular Sciences. 2025;26.
35. Hibino M, Filosi T, Carrion LL, Porcu E, Malhotra A, Lüdtke-Buzug K. An effective approach to modulate mitochondrial function in murine primary macrophages by a mitochondria-targeted nanocapsule, MITO-Porter. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2025;186:118019.
36. Cheng Q, Chen J, Guo H, Lu J, Zhou J, Guo X. Pyrroloquinoline quinone promotes mitochondrial biogenesis in rotenone-induced Parkinson's disease model via AMPK activation. Acta Pharmacologica Sinica. 2020;42:665-78.
37. Zinovkin RA, Zamyatnin AA. Mitochondria-targeted drugs. Current Molecular Pharmacology. 2019;12(3):202-14.
38. Del Campo A, Valenzuela R, Videla LA, Zuniga-Hernandez J. Cellular functional, protective or damaging responses associated with different redox imbalance intensities: a comprehensive review. Current Medicinal Chemistry. 2023;30(34):3927-39.
39. Sirbiladze G, Sikharulidze A. Insufficient Data and Fuzzy Averages. Journal of Applied Mathematics and Informatics. 2001;6(2):76-95.
40. McAleer CW, Long CJ, Elbrecht D, Sasserath T, Bridges LR, Rumsey JW. Multi-organ system for the evaluation of efficacy and off-target toxicity of anticancer therapeutics. Science translational medicine. 2019;11(497):eaav1386.
41. Donnelly J, Berry K, Ulmer JB. Technical and regulatory hurdles for DNA vaccines. International journal for parasitology. 2003;33(5-6):457-67.
42. Almikhlafi M, Karami M, Jana A, Alqurashi T, Majrashi M, Alghamdi B. Mitochondrial Medicine: A Promising Therapeutic Option Against Various Neurodegenerative Disorders. Current Neuropharmacology. 2022;21:1165-83.
43. Liang Z, Currais A, Soriano-Castell D, Schubert D, Maher P. Natural products targeting mitochondria: emerging therapeutics for age-associated neurological disorders. Pharmacology & therapeutics. 2020:107749.
44. Belenichev I, Popazova O, Bukhtiyarova N, Ryzhenko V, Pavlov S, Suprun E. Targeting Mitochondrial Dysfunction in Cerebral Ischemia: Advances in Pharmacological Interventions. Antioxidants. 2025;14.

Copyright © 2025 Authors. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

45. Li X, Zhao X, Wang J, Xu B, Feng J, Huang W. High-Pressure Microfluidic Homogenization Improves the Stability and Antioxidant Properties of Coenzyme Q10 Nanoliposomes. Biology. 2025;14.
46. Rizzardi N, Liparulo I, Antonelli G, Orsini F, Riva A, Bergamini C. Coenzyme Q10 Phytosome Formulation Improves CoQ10 Bioavailability and Mitochondrial Functionality in Cultured Cells. Antioxidants. 2021;10.
47. Xie T, Zhang Z, Feng M, Kong L. Current study on Pyrroloquinoline quinone (PQQ) therapeutic role in neurodegenerative diseases. Molecular biology reports. 2025;52 1:397.
48. Zhang Z, Gao Z, Jia Z. Pyrroloquinoline quinone promotes porcine oocyte in vitro maturation and subsequent embryo development by enhancing lipid metabolism and improving mitochondrial function. Animal Bioscience. 2025;38:1644-56.
49. Hinckley C, Kuryshev Y, Sers A, Barre A, Buisson B, Naik H. Characterization of Vixotrigine, a Broad-Spectrum Voltage-Gated Sodium Channel Blocker. Molecular pharmacology. 2021;99 1:49-59.
50. Ziegler D, Duan R, An G, Thomas J, Nothaft W. A randomized double-blind, placebo-, and active-controlled study of T-type calcium channel blocker ABT-639 in patients with diabetic peripheral neuropathic pain. Pain. 2015;156:2013-20.
51. Ito M, Ono K, Hitomi S, Nodai T, Sago T, Yamaguchi K. Prostanoid-dependent spontaneous pain and PAR2-dependent mechanical allodynia following oral mucosal trauma. Molecular Pain. 2017;13.
52. Zhou Y-T, Xu Y, Ren X, Zhang X-F. Inactivation of microglia dampens blood-brain barrier permeability and loss of dopaminergic neurons in paraquat-lesioned mice. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association. 2023:113692.
53. Khayatan D, Razavi SM, Arab Z, Niknejad A, Nouri K, Momtaz S. Protective effects of curcumin against traumatic brain injury. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2022;154:113621.
54. Numakawa T, Kajihara R. The Role of Brain-Derived Neurotrophic Factor as an Essential Mediator in Neuronal Functions and the Therapeutic Potential of Its Mimetics for Neuroprotection in Neurologic and Psychiatric Disorders. Molecules. 2025;30.
55. Giannaccini M, Calatayud M, Poggetti A, Corbianco S, Novelli M, Paoli M. Magnetic Nanoparticles for Efficient Delivery of Growth Factors: Stimulation of Peripheral Nerve Regeneration. Advanced Healthcare Materials. 2017;6.
56. Vazirizadeh-Mahabadi M, Azimi A, Yarahmadi M, Zarei H, Tahmasbi F, Zarrin A. Metformin's therapeutic potential in spinal cord injury: a systematic review and meta-analysis on locomotor recovery, neuropathic pain alleviation, and modulation of secondary injury mechanisms. Acta Neurochirurgica. 2025;167.
57. Inyang K, Szabo-Pardi T, Wentworth E, McDougal T, Dussor G, Burton M, . The antidiabetic drug metformin prevents and reverses neuropathic pain and spinal cord microglial activation in male but not female mice. Pharmacological Research. 2019;139:1.
58. Hakimian J, Minasyan A, Zhe-Ying L, Loureiro M, Beltrand A, Johnston C. Specific behavioral and cellular adaptations induced by chronic morphine are reduced by dietary omega-3 polyunsaturated fatty acids. PLoS ONE. 2017;12.
59. Watson J, Kim J, Das A. Emerging class of omega-3 fatty acid endocannabinoids & their derivatives. Prostaglandins & other lipid mediators. 2019;143:106337.
60. Carniglia L, Ramírez D, Durand D, Saba J, Turati J, Caruso C. Neuropeptides and Microglial Activation in Inflammation, Pain, and Neurodegenerative Diseases. Mediators of Inflammation. 2017;2017.
61. Zhang X, Cao Y, Li L, Liu Y, Zhou P, Lai Y, et al. Quercetin targets the Ccl4–Ccr5 axis to relieve neuropathic pain after spinal cord injury. APL Bioengineering. 2025;9.
62. Xu C-Y, Hou B-Y, He P, Peng, Yang X, Yang X-Y, et al. Neuroprotective Effect of Salvianolic Acid A against Diabetic Peripheral Neuropathy through Modulation of Nrf2. Oxidative Medicine and Cellular Longevity. 2020;2020.
63. Singh P, Bansal S, Kuhad A, Kumar A, Chopra K. Naringenin ameliorates diabetic neuropathic pain by modulation of oxidative-nitrosative stress, cytokines and MMP-9 levels. Food & function. 2020.
64. Kabir M, Tabassum N, Uddin ME, Aziz F, Behl T, Mathew B, . Therapeutic Potential of Polyphenols in the Management of Diabetic Neuropathy. Evidence-based Complementary and Alternative Medicine : eCAM. 2021;2021.

Copyright © 2025 Authors. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

65. Chen J, Liu W, Yi H, Hu X, Peng L-Y, Yang F. The Natural Rotenoid Deguelin Ameliorates Diabetic Neuropathy by Decreasing Oxidative Stress and Plasma Glucose Levels in Rats via the Nrf2 Signalling Pathway. Cellular Physiology and Biochemistry. 2018;48:1164-76.
66. Barati S, Yadegari A, Shahmohammadi M, Azami F, Tahmasebi F, Rouhani MR. Curcumin as a promising therapeutic agent for diabetic neuropathy: from molecular mechanisms to functional recovery. Diabetology & Metabolic Syndrome. 2025;17.
67. Menéndez SG, Manucha W. Vitamin D as a Modulator of Neuroinflammation: Implications for Brain Health. Current pharmaceutical design. 2024.
68. Calvello R, Cianciulli A, Nicolardi G, De Nuccio F, Giannotti L, Salvatore R. Vitamin D Treatment Attenuates Neuroinflammation and Dopaminergic Neurodegeneration in an Animal Model of Parkinson's Disease, Shifting M1 to M2 Microglia Responses. Journal of Neuroimmune Pharmacology. 2017;12:327-39.
69. D'Elia M, Marino C, Celano R, Napolitano E, Colarusso C, Sorrentino R, . Impact of a Formulation Containing Chaga Extract, Coenzyme Q10, and Alpha-Lipoic Acid on Mitochondrial Dysfunction and Oxidative Stress: NMR Metabolomic Insights into Cellular Energy. Antioxidants. 2025;14.
70. Shanaida M, Lysiuk R, Mykhailenko O, Hudz N, Abdulsalam A, Gontova T, . Alpha-lipoic Acid: An Antioxidant with Anti-Aging Properties for Disease Therapy. Current medicinal chemistry. 2024.
71. Ferreira G, McKenna M. l-Carnitine and Acetyl-l-carnitine Roles and Neuroprotection in Developing Brain. Neurochemical Research. 2017;42:1661-75.
72. Traina G. The neurobiology of acetyl-L-carnitine. Frontiers in bioscience. 2016;21:1314-29.
73. Ekundayo B, Adewale O, Obafemi T. Neuroprotective Effects of Folic Acid: A Review. Journal of Dietary Supplements. 2024;22:345-63.
74. Kucha W, Seifu D, Tirsit A, Yigeremu M, Abebe M, Hailu D, . Folate, Vitamin B12, and Homocysteine Levels in Women With Neural Tube Defect-Affected Pregnancy in Addis Ababa, Ethiopia. Frontiers in Nutrition. 2022;9.
75. Joo HS, Suh JH, Lee HJ, Bang ES, Lee JM. Current Knowledge and Future Perspectives on Mesenchymal Stem Cell-Derived Exosomes as a New Therapeutic Agent. International Journal of Molecular Sciences. 2020;21.
76. Liu B, Kong Y, Shi W, Kuss M, Liao K, Hu G, . Exosomes derived from differentiated human ADMSC with the Schwann cell phenotype modulate peripheral nerve-related cellular functions. Bioactive Materials. 2021;14:61-75.
77. Hassanzadeh A, Rahman HS, Markov A, Endjun JJ, Zekiy AO, Chartrand MS, . Mesenchymal stem/stromal cell-derived exosomes in regenerative medicine and cancer; overview of development, challenges, and opportunities. Stem cell research & therapy. 2021;12(1):297.
78. Goradel NH, Jahangiri S, Negahdari B. Effects of mesenchymal stem cell-derived exosomes on angiogenesis in regenerative medicine. Current Regenerative Medicine Formerly: Recent Patents on Regenerative Medicine. 2017;7(1):46-53.
79. Rabinovsky ED. The multifunctional role of IGF-1 in peripheral nerve regeneration. Neurological research. 2004;26(2):204-10.
80. Bianchi VE, Locatelli V, Rizzi L. Neurotrophic and neuroregenerative effects of GH/IGF1. International journal of molecular sciences. 2017;18(11):2441.
81. Salehpour A, Karimi Z, Zadeh MG, Afshar M, Kameli A, Mooseli F, . Therapeutic potential of mesenchymal stem cell-derived exosomes and miRNAs in neuronal regeneration and rejuvenation in neurological disorders: a mini review. Frontiers in Cellular Neuroscience. 2024;18.
82. Li Q, Zhang F, Fu X, Han N. Therapeutic Potential of Mesenchymal Stem Cell-Derived Exosomes as Nanomedicine for Peripheral Nerve Injury. International Journal of Molecular Sciences. 2024;25.
83. Zhang X, Zhang Y, Peng X, Yang L, Miao J, Yue Y, . Targeting Neuroinflammation in Preterm White Matter Injury: Therapeutic Potential of Mesenchymal Stem Cell-Derived Exosomes. Cellular and Molecular Neurobiology. 2025;45.
84. Zou J, Yang W, Cui W, Li C, Chiyuan, Ji X, . Therapeutic potential and mechanisms of mesenchymal stem cell-derived exosomes as bioactive materials in tendon–bone healing. Journal of Nanobiotechnology. 2023;21.
85. Amalakanti S, Mulpuri RP, Avula VCR. Recent advances in biomaterial design for nerve guidance conduits: a narrative review. Advanced Technology in Neuroscience. 2024;1(1):32-42.
86. Kong L, Gao X, Qian Y, Sun W, You Z, Fan C. Biomechanical microenvironment in peripheral nerve regeneration: from pathophysiological understanding to tissue engineering development. Theranostics. 2022;12(11):4993.

Copyright © 2025 Authors. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

87. Weiss A, Ding Y, Rodriguez M. A literature review on neuron scaffolding for repairing peripheral nerves: Advances, challenges, and future directions. Brain Circulation. 2025:10.4103.
88. Ghosh S, Dhiman M, Chauhan S, Roy P, Lahiri D. Dual Functional Electroconductive Biofortified Electrospun Scaffold Functionalized With MWCNTs and Bacopa Monnieri for Accelerated Peripheral Nerve Regeneration. Small. 2025.
89. Zheng C, Yang Z, Chen S, Zhang F, Rao Z, Zhao C, . Nanofibrous nerve guidance conduits decorated with decellularized matrix hydrogel facilitate peripheral nerve injury repair. Theranostics. 2021;11:2917-31.
90. Najafabadi SS, Karizmeh MS, Rafienia M, Kazemi M, Dastjerdi HA, Bahramian H,. Bioactive aligned PCL/CQD/Moringa nanofiber conduits accelerate peripheral nerve regeneration: in vitro and in vivo breakthroughs in sciatic nerve repair. Biomaterials science. 2025.
91. Milbreta U, Nguyen L, Diao H, Lin J, Wu W, Sun C, . Three-Dimensional Nanofiber Hybrid Scaffold Directs and Enhances Axonal Regeneration after Spinal Cord Injury. ACS biomaterials science & engineering. 2016;2 8:1319-29.
92. Entekhabi E, Nazarpak MH, Shafieian M, Mohammadi H, Firouzi M, Hassannejad Z. Fabrication and in vitro evaluation of 3D composite scaffold based on collagen/hyaluronic acid sponge and electrospun PCL nanofibers for peripheral nerve regeneration. Journal of biomedical materials research Part A. 2020.
93. Poongodi R, Chen Y-L, Yang T, Huang Y-H, Yang K, Lin H-C, . Bio-Scaffolds as Cell or Exosome Carriers for Nerve Injury Repair. International Journal of Molecular Sciences. 2021;22.
94. Taisescu O, Dinescu V, Rotaru-Zavaleanu A, Gresita A, Hadjiargyrou M. Hydrogels for Peripheral Nerve Repair: Emerging Materials and Therapeutic Applications. Gels. 2025;11.
95. Xia B, Lv Y. Dual-delivery of VEGF and NGF by emulsion electrospun nanofibrous scaffold for peripheral nerve regeneration. Materials science & engineering C, Materials for biological applications. 2018;82:253-64.
96. Viezuina D-M, Musa I, Aldea M, Matache I-M, Zavaleanu A-DR, Gresita A, . Gelatin-Based Hydrogels for Peripheral Nerve Regeneration: A Multifunctional Vehicle for Cellular, Molecular, and Pharmacological Therapy. Gels. 2025;11.
97. Nonaka C, Sampaio G, De Aragão França LS, Cavalcante B, Silva K, Khouri R, . Therapeutic miR-21 Silencing Reduces Cardiac Fibrosis and Modulates Inflammatory Response in Chronic Chagas Disease. International Journal of Molecular Sciences. 2021;22.
98. Hasan A, Ardizzone A, Giosa D, Scuderi S, Calcaterra E, Esposito E, . The Therapeutic Potential of MicroRNA-21 in the Treatment of Spinal Cord Injury. Current Issues in Molecular Biology. 2025;47.
99. Li Y, Chen X, Jin R, Chen L, Dang M, Cao H,. Injectable hydrogel with MSNs/microRNA-21-5p delivery enables both immunomodification and enhanced angiogenesis for myocardial infarction therapy in pigs. Science Advances. 2021;7.
100. Wang Z, Liu F, Wei M, Qiu Y, Chao, Shen L. Chronic constriction injury-induced microRNA-146a-5p alleviates neuropathic pain through suppression of IRAK1/TRAF6 signaling pathway. Journal of Neuroinflammation. 2018;15.
101. Yin X, Harmancey R, McPherson D, Kim H, Huang S. Liposome-Based Carriers for CRISPR Genome Editing. International Journal of Molecular Sciences. 2023;24.
102. Zhang Y, Xu H, Chen S, Sun H. Electroacupuncture Regulates Endoplasmic Reticulum Stress and Ameliorates Neuronal Injury in Rats with Acute Ischemic Stroke. Evidence-based Complementary and Alternative Medicine : eCAM. 2021;2021.
103. Sun X, Liu H, Sun Z, Zhang B, Wang X, Liu T. Acupuncture protects against cerebral ischemia–reperfusion injury via suppressing endoplasmic reticulum stress-mediated autophagy and apoptosis. Molecular Medicine. 2020;26.
104. Tian M-Y, Yang Y-D, Qin W-T, Liu B-N, Mou F-F, Zhu J. Electroacupuncture Promotes Nerve Regeneration and Functional Recovery Through Regulating lncRNA GAS5 Targeting miR-21 After Sciatic Nerve Injury. Molecular Neurobiology. 2023;61:935-49.
105. Chen T, Liu N, Liu J, Zhang X, Huang Z, Zang Y. Gua Sha, a press-stroke treatment of the skin, boosts the immune response to intradermal vaccination. PeerJ. 2016;4.
106. Ryter S. Heme Oxygenase-1: An Anti-Inflammatory Effector in Cardiovascular, Lung, and Related Metabolic Disorders. Antioxidants. 2022;11.
107. Funes S, Ríos M, Fernández-Fierro A, Covián C, Bueno S, Riedel C. Naturally Derived Heme-Oxygenase 1 Inducers and Their Therapeutic Application to Immune-Mediated Diseases. Frontiers in Immunology. 2020;11.

Copyright © 2025 Authors. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

108. Gozani S. Fixed-site high-frequency transcutaneous electrical nerve stimulation for treatment of chronic low back and lower extremity pain. Journal of Pain Research. 2016;9:469-79.
109. Johnson M. Resolving Long-Standing Uncertainty about the Clinical Efficacy of Transcutaneous Electrical Nerve Stimulation (TENS) to Relieve Pain: A Comprehensive Review of Factors Influencing Outcome. Medicina. 2021;57.
110. Morcillo-Muñoz Y, Sánchez-Guarnido A, Calzón-Fernández S, Baena-Parejo MI. Multimodal Chronic Pain Therapy for Adults via Smartphone: Randomized Controlled Clinical Trial. Journal of Medical Internet Research. 2022;24(5):e36114.
111. Kristjansdottir Ó, Fors E, Eide E, Finset A, Stensrud T, Van Dulmen S, . A Smartphone-Based Intervention With Diaries and Therapist-Feedback to Reduce Catastrophizing and Increase Functioning in Women With Chronic Widespread Pain: Randomized Controlled Trial. Journal of Medical Internet Research. 2013;15(1):e5.
112. Kristjansdottir Ó, Fors E, Eide E, Finset A, Stensrud T, Van Dulmen S. A Smartphone-Based Intervention With Diaries and Therapist Feedback to Reduce Catastrophizing and Increase Functioning in Women With Chronic Widespread Pain. Part 2: 11-month Follow-up Results of a Randomized Trial. Journal of Medical Internet Research. 2013;15(3).
113. De Ciuceis C, Rizzoni D, Palatini P. Microcirculation and Physical Exercise In Hypertension. Hypertension. 2023.
114. Grevendonk L, Connell N, McCrum C, Fealy C, Bilet L, Bruls Y. Impact of aging and exercise on skeletal muscle mitochondrial capacity, energy metabolism, and physical function. Nature Communications. 2021;12.
115. Ponirakis G, Azmi S, Ferdousi M, Petropoulos I, Marshall A, Ammori B. The Impact of Bariatric Surgery on Neuropathic Pain and on Objective Markers of Neuropathy. 2016;2016.
116. Kerver G, Bond D, Crosby R, Cao L, Engel S, Mitchell. Pain is adversely related to weight loss maintenance following bariatric surgery. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2021.
117. Azmi S, Ferdousi M, Liu Y, Adam S, Iqbal Z, Dhage S. Bariatric surgery leads to an improvement in small nerve fibre damage in subjects with obesity. International Journal of Obesity. 2021;45:631-8.
118. Alemrajabi M, Raissi G, Sajadi S, Ahadi T, Madani S, Mansouri K. Effects of weight loss after bariatric surgery on the median and ulnar nerves conduction studies. American journal of surgery. 2022.
119. Reynolds E, Watanabe M, Banerjee M, Chant E, Villegas-Umana E, Elafros. The effect of surgical weight loss on diabetes complications in individuals with class II/III obesity. Diabetologia. 2023;66:1192-207.
120. Askarpour M, Khani D, Sheikhi A, Ghaedi E, Alizadeh S. Effect of Bariatric Surgery on Serum Inflammatory Factors of Obese Patients: a Systematic Review and Meta-Analysis. Obesity Surgery. 2019:1-17.
121. Fachim H, Iqbal Z, Gibson J, Baricevic-Jones I, Campbell A, Geary. Relationship between the Plasma Proteome and Changes in Inflammatory Markers after Bariatric Surgery. Cells. 2021;10(10):2798.

Copyright © 2025 Authors. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.