Review

Exercise, an Important Step for Peripheral Nerve Injury Recovery

Ziwei Zhang[1,†] , Jielun Huang[2,†] , Hu Zhang[2,*] , Jiawen Shen[1,*]

[1]Taizhou Key Laboratory of Bone and Joint Degeneration Research, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, 317000 Taizhou, Zhejiang, China
[2]College of Sports Medicine, Wuhan Sports University, 430079 Wuhan, Hubei, China
*Correspondence: huzhang0703@163.com (Hu Zhang); shenjw10032@enzemed.com (Jiawen Shen)
[†]These authors contributed equally.

Abstract

Peripheral nerve injury is a relatively common clinical condition that predominantly results from sensory, motor, and nutritional disorders. These can be due to aging, external forces, diseases, or changes in physical and chemical environments. Although interventions, including relevant drugs and surgeries, have led to advancements in peripheral nerve repair, achieving complete recovery remains a challenge. Untimely treatment and rehabilitation can lead to lifelong disabilities and neurological pain. Exercise is a low-cost intervention that plays an active role in the rehabilitation of patients with many diseases, including peripheral nerve injuries. This narrative review, conducted in accordance with the Scale for the Assessment of Narrative Review Articles guidelines, synthesized evidence from searches of PubMed, Scopus, Web of Science, and Google Scholar databases to summarize the molecular mechanisms of exercise and adjuvant therapies in peripheral nerve injury rehabilitation and the synergistic benefits of combined exercise and adjuvant therapy for peripheral nerve repair. This study revealed that the combination of exercise with either physical therapy or traditional Chinese medicine yielded superior therapeutic outcomes for peripheral nerve injuries attributable to aging, pathological conditions, and environmental factors. These benefits appear to be mediated by the suppression of oxidative stress and inflammatory responses, upregulation of neurotrophic factor expression, activation of autophagic pathways, modulation of endocrine homeostasis, and promotion of vascular network reconstruction. Furthermore, this study provides a theoretical foundation and a potential research direction for elucidating the targeted molecular mechanisms through which exercise ameliorates peripheral nerve injury.

Keywords: combined modality therapy; exercise therapy; peripheral nerve injuries; physical therapy modalities; rehabilitation; sports medicine

1. Introduction

Peripheral nerve injury (PNI) is often accompanied by a long recovery period and possible sequelae, including pain, sensory abnormalities, and motor dysfunction. Accidental injury, body strain, aging, and disease are the primary causes of PNI. In the United States, the number of reported cases of PNI caused solely by sports injuries between 2008 and 2019 was 36.9 cases per million people [1]. Owing to the aging population, increased participation in sports and exercise activities, and war-related injuries, the number of PNI cases has increased annually. Surgical intervention and pharmacotherapy remain the primary treatment modalities for neural injury, although emerging therapeutic avenues—including fasting regimens and gut microbiome modulation, continue to be identified [2–4]. However, enhancing the recovery process of PNI and minimizing its associated sequelae have emerged as critical areas of global research. The regeneration and repair of PNI are intricately linked to multiple factors, including remyelination [5], axon regeneration [6], vascular reconstruction [7], suppression of inflammatory responses [8], regulation of reactive oxygen species (ROS) [9], supplementation of neurotrophic factors [10], and modulation of associated molecular signaling pathways. Currently, several pharmacological agents, such as methylcobalamin, B vitamins, aminopyridines, and exogenous neurotrophic factors, are used for neurological rehabilitation. However, their efficacy is frequently constrained by prolonged treatment durations and inconsistent therapeutic outcomes. Compared to the central nervous system, peripheral nerves have a relatively low degree of differentiation and a high possibility of returning to normal. When effectively amplified, the body's recovery mechanisms, when effectively amplified, can enhance disease recovery and reduce the occurrence of sequelae. Exercise, the focus of our study, plays a well-documented and positive role in PNI repair [11]. However, the mechanism of PNI rehabilitation during exercise is complex. This review was based on the Scale for the Assessment of Narrative Review Articles (SANRA) criteria, which is used to evaluate exercise-based rehabilitation for PNI. The analysis encompasses its standalone therapeutic efficacy, synergistic effects when combined with other treatments, and the underlying molecular mechanisms. The primary objectives were to establish a theoretical foundation for research on exercise-accelerated neural recovery and to promote exercise engagement among individuals with neuro-

Table 1. Peripheral nerve injury classification.

Seddon classification	Sunderland classification
I. Neurapraxia: The mildest form of nerve injury is where the nerve's function is temporarily impaired, but the structure remains intact. There is no Wallerian degeneration, and recovery is usually spontaneous and complete.	I: There is a temporary conduction block with no axonal damage.
II. Axonotmesis: The axon is severed, but the endoneurial tube (the structure surrounding the axon) remains intact. Wallerian degeneration occurs in the distal segment of the nerve, and some degree of recovery can occur spontaneously, but functional recovery may be incomplete.	II: Axons are severed, but the endoneurial tubes remain intact, allowing for some potential for spontaneous regeneration. III: The nerve fibers are completely transected, but the epineurium (the outermost connective tissue layer) remains intact, providing a pathway for regeneration.
III. Neurotmesis: The most severe type of nerve injury is where the entire nerve trunk is severed, including the axons, myelin sheaths, and the surrounding connective tissues. There is no spontaneous recovery, and surgical intervention is usually required for any chance of recovery.	IV: The nerve is severely damaged with some fascicles (bundles of nerve fibers) being completely severed, while others may be intact. V: Complete transection of the nerve with no continuity between the proximal and distal stumps, requiring surgical repair for any chance of functional recovery.

logical impairments. The potential implications of this approach extend to enhancing recovery trajectories while simultaneously alleviating the socioeconomic burden on affected families, healthcare systems, and society.

2. PNI and Repair

In 1943, Seddon classified nerve injuries into three categories: neuropraxia, axonotmesis, and neurotmesis. Currently, the five-degree classification system proposed by Sunderland remains the most widely adopted approach in clinical practice (Table 1) [12,13]. In human, when the nerve length defect is <5 mm, peripheral nerve damage can be repaired using a tension-free nerve end-to-end anastomosis. Autologous and artificial nerve transplantation are primary treatments for nerve defects when the nerve defect is more than 3 cm. Nerve damage quickly induces the secretion of pro-inflammatory cytokines at the site of injury, which triggers a local inflammatory response. Schwann cells further enhance the inflammatory response and facilitate the accumulation of a significant number of neutrophils at the site of nerve injury. Neutrophils are responsible for clearing damaged debris and assisting in the recruitment and activation of other cells that participate in the immune responses [14]. Wallerian degeneration, occurring 24–48 hours after nerve damage, includes collapse, self-sealing, enlargement of the proximal and distal segments of the damaged neuronal axon, and reverse disintegration and deformation of the myelin sheath to the surrounding nodes of Ranvier. Wallerian degeneration causes myelin shedding, proliferation, phagocytosis of debris, apoptosis, and cytokine release in injured neurons, as well as the recruitment of monocytes and macrophages from the blood to clear damaged myelin and contribute to the regeneration of damaged nerves. At 5–7 days post-injury, Schwann cells secrete monocyte sequestrant-1 (MCP-1), interleukin 1α and β (IL-$1\alpha/\beta$), and tumor necrosis factor-α (TNF-α). These signals recruit and activate monocytes and macrophages to clear axonal disintegration debris, forming empty endoneurial tubes that guide the growth of regenerated nerves during Wallerian degeneration [15]. Subsequently, Schwann cells gradually align to form Büngner bands, secreting a variety of neurotrophic factors and improving cellular matrix components to induce axonal sprouting at the nodes of Ranvier, thereby supporting neural connections. After axonal regeneration, Schwann cells form a myelin sheath around the axons, which, as the electrophysiological properties mature, leads to the gradual restoration of functional connections and signal transmission, promoting the recovery of overall neurological function. Due to the slow growth rate of nerves (1 mm/day in humans), full recovery can take months or even years [16]. However, neural connections can substantially regain motor control functions within 12–18 months after nerve injury; beyond this timeframe, the degeneration of motor end plates may become irreversible [17]. Notably, a variety of signaling pathways are involved in the nerve repair process, including those mediated by neurotrophic factors [18], phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) [19,20], mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (Erk) [2], cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) [21], wingless (Wnt) [22], Notch [23], janus kinase (JAK)/signal transducer and activator of transcription (STAT) [24], ras homolog family member (Rho)/Rho-associated coiled-coil containing protein kinase (ROCK) [25], and transforming growth factor-beta (TGF-β) [26]. Overall, the repair process after nerve injury involves a coordinated interplay of various cellular and molecular mech-

anisms, including inflammation, axonal regeneration, remyelination, synaptogenesis, neurotrophic factor signaling, extracellular matrix remodeling, and electrophysiological maturation.

3. Exercise and PNI

The beneficial effects of exercise in repairing PNI caused by external forces, such as traction, laceration, and compression are well-documented. Exercise has been shown to positively influence neurological recovery by promoting angiogenesis, facilitating axonal sprouting and elongation, enhancing neuromuscular junction reinnervation, and alleviating neuropathic pain [27,28].

3.1 Exercise Intervention Window and PNI

The degree of natural recovery post-PNI varies among mice of different ages, with newborn mice showing significantly better recovery than young mice. Aerobic running exercise intervention five times a week for 5 weeks can significantly accelerate the recovery of impaired neurological function, electrophysiology, and morphology in young rats, whereas such effects are markedly reduced in adult rats [29,30]. Therefore, younger age demonstrated superior PNI recovery potential, and exercise interventions may further accelerate this regenerative process. This differential response could be attributed to factors such as the plasticity of peripheral nerves, metabolic activity of nerve cells, and rate of axonal regeneration.

Exercise intervention immediately after injury can effectively increase the regeneration of damaged axons [31], as confirmed in rat models of nerve injury [32]. A two-week running exercise intervention, initiated on day 3 post-PNI and conducted five times per week (1 h/session), significantly enhanced axonal regeneration [33]. However, when considering the induction of M2-type macrophages during Wallerian degeneration, it seems that exercise initiated on the 3rd day has a less pronounced effect on nerve regeneration compared to that begun on the 14th day [34]. Another study demonstrated that a 30-day swimming exercise intervention (1 h/day), initiated immediately, 14 days, or 30 days post-injury accelerated nerve regeneration and reversed synaptic loss induced by crush injury [35]. Assessments conducted using horseradish peroxidase neurohistochemistry and the modified Pal-Weigert method revealed that the positive effects of exercise on nerve regeneration may not be significantly discernible until the fourth week [36]. Current animal studies suggest that exercise interventions initiated immediately after PNI or at 3, 14, or 30 days post-injury, can promote nerve regeneration and repair [33–35]. Notably, multiple studies have reported positive effects of immediate exercise initiation [31]. However, clinical research on exercise timing in humans with PNI remains limited, making it difficult to establish specific optimal timeframes. This is an important area for future clinical investigation.

3.2 Exercise Methods and PNI

Short-term exercise can positively affect PNI, regardless of passive, active, or vibration stimulation [37,38]. Although 5 weeks of whole-body vibration (WBV) intervention (5 sessions/week, 15 min/session, 15 or 30 Hz cycle) in sciatic nerve crush injury rats failed to demonstrate statistically significant improvements in nerve regeneration histomorphometrics [39], another study employing an eight-week WBV protocol (5 sessions/week, 20 min/session, 50 Hz) reported significant functional recovery following compressive nerve injury [37]. This discrepancy may be attributed to differences in the vibration parameters and intervention duration. Similarly, local vibration can achieve comparable effects, possibly due to the proliferation of Schwann cells and activation of Erk1/2 and Akt signaling pathways [40]. However, a previous study demonstrated that short-term exposure to vibrations following sciatic nerve transection and suturing did not promote nerve regeneration after repair [41]. The divergent outcomes observed with similar vibration interventions may stem from differences in vibration modalities and dosage parameters, as current evidence confirms that prolonged high-intensity mechanical vibration can induce neural damage.

Mice that performed voluntary movements regenerated sensory neuron axons, with the growth length of their nerve axons showing a positive correlation with the distance traveled during voluntary movement [42]. The improvement in nerve regeneration and remodeling of central neurons during active and passive exercises is likely due to the release of neurotrophic factors [43]. Low-intensity exercises can also effectively promote peripheral nerve axon elongation [44]. In addition, slow exercise before and after injury can increase the axonal growth of injured nerves [44,45]; even in cases of repeated nerve compression, functional recovery may improve as a result of such physical activity [46]. These findings demonstrate that both active and passive exercises enhance PNI recovery, even at lower exercise intensities.

Studies have reported mixed results regarding the effects of exercise on nerve damage repair. Excessive swimming exercise has been demonstrated to positively impact nerve repair in some cases [47], while other study has indicated that it might not only fail to improve nerve damage repair but could also potentially worsen the extent of nerve injury [48]. This discrepancy may be attributed to variations in nerve types, PNI modeling methods, and differential effects of exercise on distinct body regions. For example, uphill treadmill exercise may foster the regeneration of exercise axons but appears to be less effective in achieving functional recovery [49]. In contrast, moderate-intensity running exercises have been found to enhance nerve crush injuries [50], suggesting that exercise efficacy depends on both modality and injury type. A study examining the effects of aerobic and resistance exercises on nerve regeneration suggested that aerobic endurance exercise can boost

nerve damage repair, whereas resistance exercise, either alone or in combination with aerobic exercise, may delay functional recovery or have no effect on nerve regeneration [51]. This was further complicated by findings that showed no significant difference between weight-bearing and non-weight-bearing swimming exercises in their ability to improve nerve damage [52]. Another study reported that both aerobic and anaerobic exercises could promote recovery from sciatic nerve injury, with no significant differences observed between the various exercises performed [53]. Debate exists regarding the recovery of nerve damage through overload exercise, as research has indicated that an overload of physical activity at any stage of nerve regeneration can be detrimental [34].

In a comparative study on the efficacy of different exercises for PNI rehabilitation, short-term running exercises were found to have a better effect on nerve regeneration than long-term running, although this finding warrants further investigation [54]. Additionally, balance and coordination training has been investigated in nerve regeneration and shown to exert positive effects [55], although its impact on improving the neural ultrastructure appears less pronounced than that of aerobic endurance exercise [56].

Therefore, a conclusive comparison of the efficacy of various exercise methods in PNI repair may require more extensive research with larger sample sizes. The overall positive effect of exercise on nerve regeneration has already been confirmed. The specific type and intensity of exercise play pivotal roles in the observed outcomes of nerve regeneration. According to the current research findings, non-weight-bearing aerobic exercises appear to be particularly effective in repairing nerve damage.

3.3 Exercise Mechanism in PNI Repair

Systematic reviews and analyses of relevant studies demonstrate that consistent moderate exercise can enhance the clearance of myelin debris, foster myelin formation and regeneration, and the promote expression of associated proteins [36,57]. Repetitive hindlimb standing training in rats can reverse the reduction in nerve conduction velocity induced by crush injury [58]. Even in models of axotomy and repeated sciatic nerve crush injury, running exercise ($\leq$2 weeks, 5 days/week, 1 h/session) similarly enhanced muscle reinnervation and motoneuron synaptic input, leading to improved limb motor function and attenuation of aberrant innervation patterns [46,59]. Moreover, the immediate initiation of a 2-week swimming exercise regimen (30 min/session) following PNI accelerated axotomy-induced nerve regeneration and synaptic pruning [35], which enhanced sciatic nerve injury regeneration and repair and significantly improving electrophysiological measures [60,61]. Among the observed effects, the mechanism through which exercise improves PNI nerve regeneration and function may involve promoting the nuclear translocation of neuronal hypoxia-inducible factor 1-alpha

(HIF-1α) and activating phosphorylated Erk1/2 in Schwann cells [62,63]. The current findings indicate that exercise facilitates PNI repair mainly by enhancing axonal regrowth and myelin formation by modulating key molecular pathways.

3.4 Exercise Environment and PNI

The mechanisms by which exercise affects peripheral nerve axon regeneration appear to differ according to sex. This effect was more pronounced in male mice during treadmill training. These differences may be related to testicular androgens [64]. The exercise environment can also affect neurological injury recovery; for example, swimming exercises in cold water have produced significant improvements [65,66]. Therefore, environmental temperature modulation during exercise-mediated PNI recovery may accelerate rehabilitation by potentiating axonal regeneration and remyelination.

4. Exercise and Disease- and Aging-Induced PNI

Disease-related PNI related to disease mainly results from hyperglycemia, hypoxia, radiation, and autoimmunity. The role of exercise in PNI repair in patients with chronic autoimmune diseases has been extensively investigated. The main mechanisms involved include improving the disease environment, increasing blood circulation, and improving immune function.

4.1 Exercise and Diabetes Mellitus-Induced PNI

Diabetes mellitus, a disease caused by impaired blood sugar regulation leading to elevated systemic blood sugar levels, can induce various injuries, including PNI. In a diabetes model, a 16-week exercise intervention (30 min/session, 8 m/s speed, 0% incline) potentiated the beneficial effects of insulin therapy on the PNI [67]. Skin biopsy analyses in early stage diabetic patients revealed significantly increased nerve fiber density following exercise intervention compared to non-exercise controls [68]. Long-term exercise regimens have also been shown to prevent the development of diabetic peripheral neuropathy (DPN) [69]. For durations ranging from 8 to 12 weeks, moderate physical exercise in various forms, including aerobic, resistance, sensory, and gait training, has been shown to significantly increase the conduction velocities in the tibial, peroneal, and sural nerves of patients [70]. Notably, even in the well-established streptozotocin-induced diabetic rat model, aerobic running training not only significantly promotes axonal regeneration of the sciatic nerve but also increases myelin formation, inhibits myelin degradation, and prevents ultrastructural changes in axonal morphology [71–73]. However, other studies have shown that a 12-week program of aerobic exercise, isokinetic strength training, or a combination of both aerobic and isokinetic strength training does not alter the electrodiagnostic outcomes of sen-
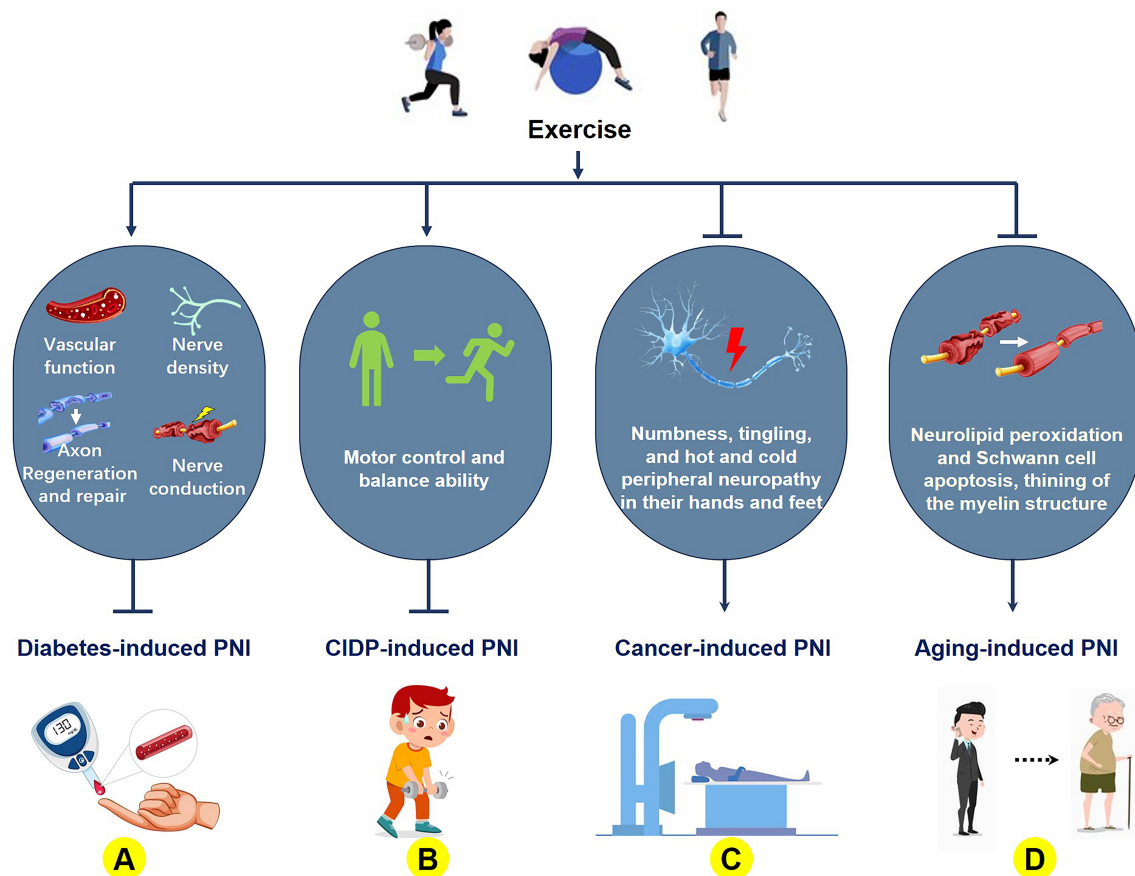
Fig. 1. The molecular mechanism of exercise improvements of aging- and disease-related peripheral nerve damage. (A) Exercise ameliorates diabetes-induced peripheral nerve injury (PNI) by enhancing vascular function, promoting axonal regeneration and repair, increasing synaptic density, and improving nerve conduction velocity; (B) Exercise improves PNI caused by chronic inflammatory demyelinating polyneuropathy (CIDP) through enhancing motor postural control and balance capacity; (C) Exercise mitigates PNI secondary to cancer and its treatments by suppressing distal limb numbness, tingling, and hot and cold peripheral neuropathy in their hands and feet; (D) Exercise attenuates aging-associated PNI via inhibiting lipid peroxidation in nerves, Schwann cell apoptosis, and myelin sheath thinning. The figure was created using Microsoft Office PowerPoint (Microsoft 365, Microsoft Corporation, Redmond, WA, USA).

sory or motor nerves in patients with diabetes [74], but also suggest that larger sample sizes may be needed to support the current conclusions. Nevertheless, exercise may also suppress the progression of nerve damage [75], possibly due to increased levels of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) [76]. For individuals with type 2 diabetes, aerobic exercise positively affects nerve function and symptoms related to neuropathy, such as an increase in the branching of skin nerve fibers, and is associated with a lower rate of adverse events [77,78]. In summary, exercise exerts beneficial effects on diabetes-associated PNI, primarily through the neuroprotective preservation of neural architecture, enhanced nerve conduction velocity, and elevated NGF levels. Additional mechanisms require further investigation (Fig. 1A).

4.2 Exercise and Chronic Inflammatory Demyelinating Polyradiculoneuropathy-Induced PNI

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune peripheral motor and sensory neuropathy characterized by chronic demyelination of the proximal peripheral nerves. CIDP primarily manifests as muscle weakness, respiratory involvement, and reflex loss. Although the mechanisms by which exercise improves peripheral nerve function in CIDP remain unclear, exercise has demonstrated significant efficacy in ameliorating clinical manifestations in patients with CIDP. Resistance and aerobic exercise interventions have been shown to improve muscle strength and aerobic capacity in patients with CIDP [79]. When combined with Russian current stimulation, exercise significantly increased the quadriceps strength and clinical performance [80] (Fig. 1B). After a 6-week clinical intervention, significant improvements in motor control and balance were reported

[81]. Therefore, exercise can significantly enhance motor control abilities in patients with CIDP by improving peripheral nerve function. However, the mechanisms underlying nerve repair require further investigation to develop new therapeutic strategies for patients with CIDP.

4.3 Exercise and Chemotherapy-Induced PNI

Certain cancers can gradually erode the peripheral nervous system, and chemotherapy can exacerbate this damage. Exercise interventions are effective in mitigating such damage. An 8-week multimodal exercise intervention improved chemotherapy-induced peripheral neuropathy [82]. This finding was further validated in a cohort of 178 patients with chemotherapy-induced peripheral neuropathy secondary to cancer treatment [83]. Patients undergoing chemotherapy who received only 6 weeks of walking and resistance training experienced significantly reduced symptoms of numbness, tingling, and hot and cold peripheral neuropathy in their hands and feet [84]. In addition, endurance and balance training can improve chemotherapy-induced neuropathy [85], while regular swimming can alleviate neuroma-related pain, which may be related to increased adiponectin [86]. Overall, exercise ameliorated the symptoms of chemotherapy-induced PNI in patients with cancer (Fig. 1C). However, owing to the large differences in type, dose, and patient status, further research is required to determine the most beneficial exercise prescription [87,88].

4.4 Exercise and Aging-Induced PNI

As age increases, peripheral nerve function undergoes degenerative changes. Exercise not only slows age-related cognitive decline [89] but also plays a crucial role in the repair of PNIs. After 10 months of swimming exercise in rats aged 17–27 months, a 10-month swimming exercise intervention prevented the degeneration of peripheral nerves associated with aging [90], reduced neurolipid peroxidation and Schwann cell apoptosis, and demonstrated thickening of the myelin structure, thereby achieving nerve protection [91]. Simultaneously, low-intensity aerobic exercise in aged rats can enhance peripheral nerve health by increasing the tibial nerve blood vessels, which diminish with age to protect these blood vessels [92] (Fig. 1D). Therefore, the ameliorative effects of exercise on age-related PNI primarily involve the modulation of peripheral nerve biological mechanisms through enhanced myelination and vascular protection. However, implementation of specific exercise regimens may require individualized clinical information and monitoring to ensure effectiveness.

5. Molecular Mechanisms of Exercise in PNI Rehabilitation

Exercise has become an important intervention in the clinical rehabilitation of patients with PNI. Its effectiveness is not only reflected in improving physical function and nerve regeneration but also involves complex molecular mechanisms. These mechanisms include the regulation of neurotrophic factors, oxidative stress, sex hormones, inflammation, vascular regeneration, autophagy, and neural Erk1/2 and Akt/mechanistic target of rapamycin (mTOR) pathways.

5.1 Neurotrophic Factor (NTF)

Neurotrophic factors (NTFs), which comprise a series of proteins that support nerve survival, growth, development, and repair, play indispensable roles in PNI repair. The observed improvement in PNI with running exercises may be closely related to increased concentrations of glial cell line-derived neurotrophic factor (GDNF), BDNF, and insulin-like growth factor 1 (IGF-1) [93]. Voluntary exercise also increases brain-derived BDNF levels and improves neuroplasticity, thereby aiding recovery after PNI [94]. However, BDNF secretion typically decreases following exercise cessation, as evidenced by a significant decrease in its levels [95]. The role of exercise in reducing PNI-related pain may be related to reduced glial cell responses to sciatic nerve pain, increased BDNF expression in nonglial cells, and suppression of the BDNF/Akt/mTOR signaling pathway, which inhibits autophagy and regulates microglial polarization (Fig. 2A) [96,97]. Exercise ameliorates neural damage by preserving or restoring synaptic inputs to the axonal motor neurons. Conditional knockout of BDNF results in a significant reduction in synaptic contact, and transplantation of BDNF-knockout neurons greatly reduces the effect of exercise on axonal regeneration [98]. The Val66Met *BDNF* polymorphism is linked to activity-dependent impairments in BDNF secretion, and exercise does not enhance the axonal regeneration capacity of heterozygous and homozygous Val66Met *BDNF* polymorphic mice after nerve injury through the promotion of BDNF secretion [99]. Similarly, Schwann cells lacking BDNF expression fail to recapitulate the regenerative potential observed in their wild-type counterparts, as demonstrated in transplantation experiments [100]. Study has shown that exercise may increase the number of tropomyosin receptor kinase B (TrkB) receptors in the growth cones of regenerating axons [59]. TrkB inhibition partially offsets the positive effects of exercise; however, pharmacological activation of TrkB does not completely mimic the effects of exercise [101]. While the importance of BDNF in PNI repair has been confirmed, one study indicated that *BDNF* mRNA levels significantly increased after sciatic nerve injury, and exercise reduced the increase in mRNA levels to promote nerve regeneration and recovery [102]. Additionally, exogenous nerve NGF inhibits p38 mitogen-activated protein kinase (p38 MAPK) activation, protects hypoglossal neurons, and promotes nerve regeneration [103]. Variations in neurotrophic factors may help distinguish between types of nerve injuries [104]. Therefore, exercise-induced upregulation of NTFs in the neural and somatic tissues may represent a critical therapeutic strategy for PNI recovery.
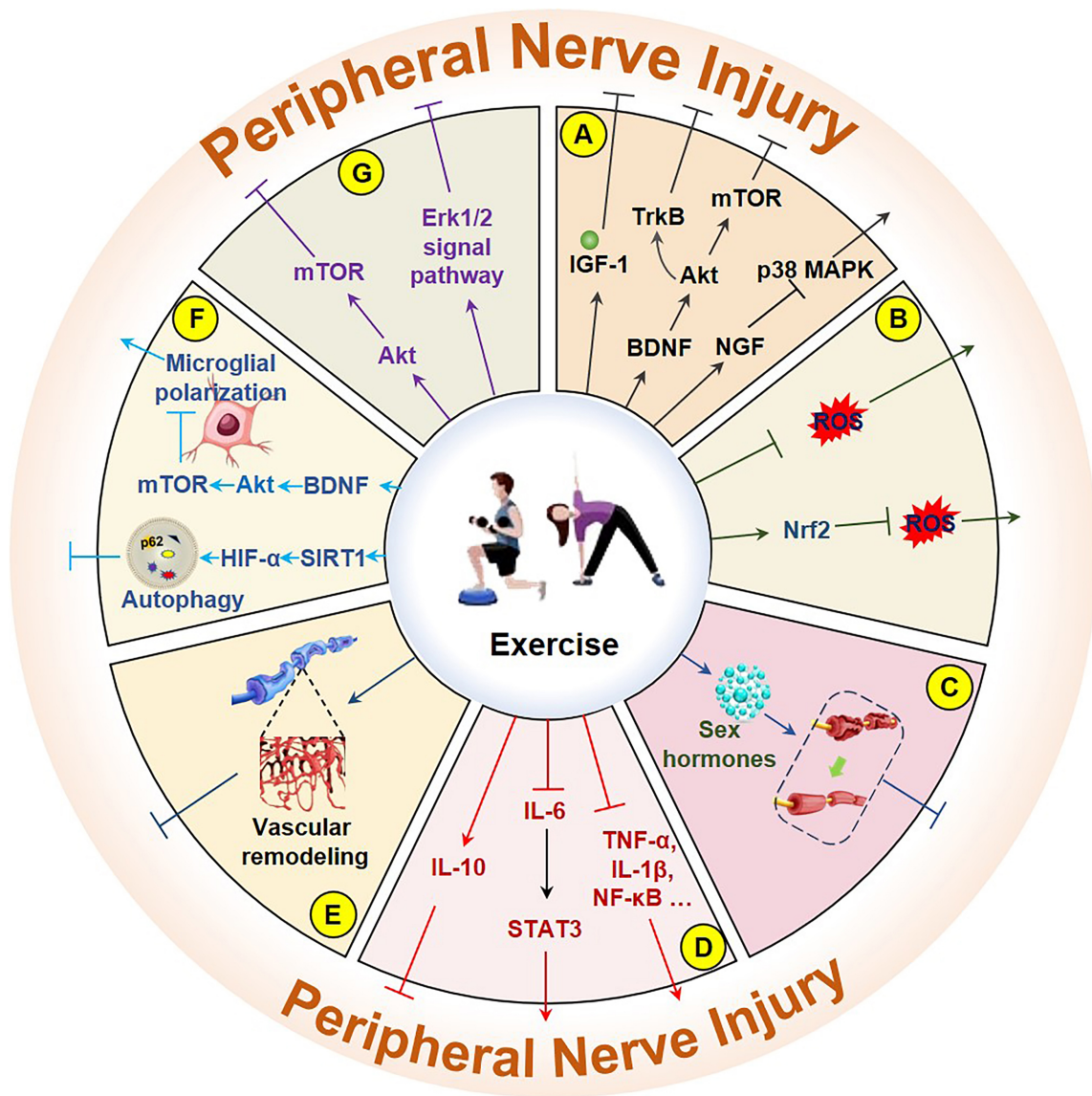
Fig. 2. Molecular mechanisms of exercise improving PNI. (A) Exercise mitigates neuronal damage by increasing IGF-1, BDNF/Akt/mTOR, BDNF/TrkB, and NGF/p38 MAPK. (B) Exercise mitigates neuronal damage by directly reducing ROS and by activating the Nrf2/ROS pathway. (C) Exercise improves neuronal damage by increasing sex hormones. (D) Exercise improves neuronal damage by promoting IL-10, inhibiting the IL-6/STAT3 signaling pathway and inflammatory factors (NF-κB, IL-1β, TNF-α). (E) Exercise accelerates the repair of nerve damage by promoting angiogenesis. (F) Exercise activates microglia through BDNF/Akt/mTOR and improves neuronal damage through SIRT1/HIF-1α. (G) Exercise improves neuronal damage by activating the neuronal Akt/mTOR and Erk1/2 signaling pathways. The figure was created using Microsoft Office PowerPoint. IGF-1, insulin-like growth factor 1; BDNF, brain derived neurotrophic factor; Akt, protein kinase B; mTOR, mechanistic target of rapamycin; TrkB, tropomyosin receptor kinase B; NGF, nerve growth factor; p38 MAPK, p38 mitogen-activated protein kinase; ROS, reactive oxygen species; Nrf2, nuclear factor erythroid 2–related factor 2; IL, interleukin; STAT, signal transducer and activator of transcription; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; TNF-α, tumor necrosis factor-α; SIRT1, Sirtuin 1; HIF-1α, hypoxia-inducible factor 1-alpha; Erk, extracellular signal-regulated kinase.

5.2 ROS

ROS can damage cell function and survival as byproducts of mitochondrial energy production. PNI is often accompanied by an increase in ROS levels, and the antioxidant effect of exercise plays a positive role in the repair and improvement of both the peripheral and central nervous systems [105,106]. Aging-induced PNI is more common in older adults, and aerobic exercise can protect peripheral nerves by attenuating oxidative reactions and pathological changes [91]. The inhibition of ROS generation plays a

protective role [107]. In addition, preconditioning exercise activates nuclear factor erythroid 2-related factor 2 (Nrf2), which in turn reduces ROS levels and relieves neural pain (Fig. 2B) [108]. Forced exercise can also increase total antioxidant capacity and reduce TNF-α levels to reduce pain [109]. Although resistance exercise significantly reduces body ROS levels in PNI models [110], study has reported that aerobic exercise can increase ROS levels in the sciatic nerve in a diabetic neuropathy model, further exacerbating damage [111]. Therefore, reducing ROS levels may be an important target for accelerating PNI recovery; however, its effects may vary depending on the underlying disease.

5.3 Sex Hormones

Sex differences appear to influence the effect of exercise on peripheral nerve axon regeneration, with a greater effect previously reported in males during treadmill training. However, this difference was not observed in castrated male mice, suggesting a potential role for testicular androgens [64]. When testosterone is administered within the normal physiological range, it reduces dendritic atrophy and increases excitability [112], an effect that appears to be comparable to the effects of exercise [113]. The regenerative effects of exercise or electrical stimulation on nerves are weakened after blocking androgens [114]. Additionally, the anti-androgen flutamide has been shown to significantly attenuate exercise-induced preservation of synaptic connectivity following sciatic nerve transection [115]. Importantly, flutamide-mediated androgen receptor blockade similarly diminishes the regenerative effects of exercise and electrical stimulation on axonal growth, with comparable outcomes observed in orchiectomized animal models [116]. In addition, increased testosterone levels can accelerate peripheral nerve regeneration [117], a mechanism that may be related to intraneuronal BDNF levels and TrkB receptor regulation [118]. However, systemic androgen receptor blockade significantly decreased exercise-induced axonal regeneration in both sexes. Although the effect of exercise on PNI repair is more pronounced in male mice, it also plays an important role in neural repair in female mice [119]. However, to achieve the same effect, females may need a higher training intensity. Notably, the advantage of this intervention was lost in castrated male mice during treadmill training [64]. Administering estradiol increases the number of axonal regenerations in peripheral neurons and shows effects similar to those of exercise [120]. Thus, sex hormones may play a positive role in PNI repair, with androgens particularly important for nerve repair (Fig. 2C).

5.4 Inflammation

PNI is accompanied by inflammation, which is an important link between PNI and repair. Proinflammatory factors play a role in nerve damage repair by recruiting macrophages, which aid in the repair and reduction of inflammation through the action of anti-inflammatory fac-

tors. Exercise accelerates the regeneration of damaged nerves by activating macrophages [121]. Exercise before and after nerve injury significantly reduces nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and TNF-α levels [45]. Prolonged swimming exercises reverse astrocyte and microglial overactivity, and this promotional effect persists even after exercise cessation [95], indicating that exercise has a prolonged benefit. In addition, progressive exercise training reduces neuropathic pain and lowers TNF-α and interleukin-1 beta (IL-1β) levels [122]. Exercise training on an inclined treadmill increases interleukin-10 (IL-10) and reduces TNF-α and interleukin 6 (IL-6) levels, thereby inhibiting inflammation and improving pain hypersensitivity resulting from PNI (Fig. 2D) [123]. In addition, in a sciatic nerve injury model, running alleviates nerve pain by increasing M2 macrophage activity [124], and forced exercise exerts an inhibitory effect on autoimmune neuritis [125]. Exercise can promote sciatic nerve regeneration via the IL-6/STAT3 signaling pathway [126]. In a diabetic PNI model, aerobic endurance exercise significantly reduced inflammation levels [127]. Therefore, controlling inflammation plays an important role in recovery after PNI. However, whether the premature elimination of inflammation is beneficial for nerve damage repair requires further investigation.

5.5 Vascular Reconstruction

Nervous tissue damage is often accompanied by vascular tissue damage, posing a significant obstacle to nerve tissue repair. Because peripheral nerves have a poor vascular supply, vascular remodeling is crucial for accelerating the healing process and quality by providing nutrients and bioactive substances. Furthermore, exercise can promote vascular regeneration of damaged nerves, thereby accelerating the regeneration and repair of nerve axons [27]. Regular moderate aerobic exercise improves neurological degeneration in aged rats by increasing the thickness of myelin around myelinated fibers and by dilating capillaries [128]. In terminal diabetes mellitus-related microcirculatory disorders, exercise significantly improved blood circulation and oxygen concentration in the feet by increasing microvessel density (Fig. 2E). Exercise positively affects nerve terminal diseases [129–131] and significantly improves nerve conduction velocity [132]. Therefore, improving circulation by enhancing neurovascular remodeling through exercise positively affects PNI repair.

5.6 Autophagy

Autophagy, as a scavenging process in the body, removes aging damaged organelles and misfolded proteins in cells and plays an active role in nerve injury recovery. In models of nerve injury, sirtuin 1 (SIRT1)/HIF-1α-mediated activation of autophagy has been shown to accelerate synaptic growth and length extension of injured neurons [133]. Autophagy activation also promotes nerve

regeneration in nerve injury models resulting from nerve compression [134]. In injured neurons, swimming can promote axonal regeneration and accelerate functional recovery by activating the energy sensor AP2-associated kinase 2 (AAK-2)/adenosine monophosphate-activated protein kinase in injured neurons [135]. Exercise regulates microglial autophagy through the BDNF/Akt/mTOR signaling pathway, participates in the regulation of microglial polarization state, and plays a role in neurological rehabilitation (Fig. 2F) [96]. This was confirmed in a sciatic nerve crush injury model in which moderate-intensity exercise increased the levels of the autophagy marker microtubule-associated protein 1 light chain 3 (LC3) [50]. Therefore, regulation of autophagy may play a positive role in PNI, and activating autophagy through exercise is a recognized intervention.

5.7 Erk1/2 and Akt/mTOR Pathways

Exercise also involves the regulation of related classical molecular signaling pathways in the PNI repair process. In animal models of sciatic nerve injury and diabetes-related PNI, treadmill exercise activated p-Erk1/2 levels in Schwann cell and improved nerve damage [131]. Conversely, the Erk1/2 inhibitor PD98059 significantly inhibited axonal regeneration [136]. In a postoperative sciatic nerve model, running training promoted sciatic nerve regeneration by activating the Erk1/2 signaling pathway [137]. This activation may also activate the Akt/mTOR signaling pathway [138]. Therefore, the molecular mechanism by which exercise regulates the Erk1/2 and Akt/mTOR signaling pathways to enhance recovery from PNI injury deserves further investigation (Fig. 2G).

6. Exercise Combined With Other Interventions and PNI Rehabilitation

Exercise plays an active role in the repair and regeneration of PNI. Furthermore, a combination of various therapies may enhance the benefits of exercise for PNI treatment. In physical therapy, the integration of therapeutic ultrasonography (TU), light, electricity, and heat, along with traditional Chinese medicine practices such as acupuncture, and modern interventions, such as stem cell transplantation, may be beneficial (Table 2, Ref. [110,139–155]).

6.1 Exercise Combined With Physical Therapy
6.1.1 Electrical Stimulation

In conventional physical therapy, neuromuscular electrical stimulation promotes nerve regeneration [156]. In a rat sciatic nerve injury suture model, a combination of exercise and electrical nerve stimulation significantly improved synapse regeneration and neuromuscular innervation in the initial stage and reduced the occurrence of hyperreflexia [139]. This combination therapy also alleviated pain resulting from nerve damage by regulating BDNF, IL-1β, and IL-4 concentrations (Fig. 3A) [140]. Compared with exercise or electrical stimulation alone, a combination of both better regulates the expression of BDNF and GDNF during recovery from sciatic nerve injury [141]. Similarly, in patients with brachial plexus injuries, a combination of exercise and low-frequency pulse electrical stimulation effectively improved nerve conduction, promoted nerve injury recovery, and improved quality of life [142]. Furthermore, a combination of water-based exercise and low-frequency electrical stimulation resulted in a significant recovery of neurological function and pain reduction [143]. In addition, running interventions following nerve injury and repair may accelerate the recovery of afferent nerves and help suppress the sequelae of nerve injury, including spasms and mechanical and metabolic sensitivity [157]. However, brief periods of repeated electrical stimulation do not achieve better efficacy and may lead to the preservation of excessive reflexes [144]. In conclusion, the current evidence demonstrates that a combination of exercise therapy and electrical stimulation can significantly enhance rehabilitation outcomes in patients with PNI. However, there is a lack of well-established quantitative criteria regarding the optimal parameters for exercise modality, intervention duration, and treatment protocols in human applications [158].

6.1.2 TU

TU can improve microcirculation by penetrating the surface tissues and heating deeper tissues. In a rat model of chronic constriction injury of the sciatic nerve, the combined intervention of TU and exercise alleviated pain resulting from nerve injury by suppressing IL-6 and Iba1 and upregulating IL-10 [145]. Similarly, running exercise combined with TU showed an improved reduction in IL-6 and TNF-α levels (Fig. 3B) [146]. The combined effect of exercise and TU was mainly related to the inhibition of inflammation; however, further research is required.

6.1.3 Laser Therapy

As a highly penetrating and noninvasive physical therapy method, high-energy lasers are commonly used for skeletal muscle and nervous system rehabilitation, and laser therapy is widely recognized. In a sciatic nerve crush injury model, a 14-day regimen of low-level laser therapy significantly promoted recovery from nerve injury [159]. In the same rat model of sciatic nerve injury, low-intensity laser therapy alone augmented the morphometric area of nerve myelin, without exerting a positive impact on the functional recovery of the nerve [160]. This suggests that both the laser treatment parameters and PNI models can significantly influence the extent of recovery. However, low-power laser irradiation combined with exercise significantly reduces inflammation, increases nerve regeneration, and improves nerve function [147], indicating that the integration of exercise with laser therapy may have synergistic effects on both nerve injury and functional recovery. This was further confirmed in a rat sciatic nerve crush injury

Table 2. Molecular mechanisms of exercise combined with other treatments in PNI.

PNI model	Exercise and dosage	Combination treatment and dosage	Microstructure or molecular mechanism changes	Ref
Rat (sciatic nerve transection and suture repair)	TR: 2 h/time/every day, for 4 weeks	ES: 20 Hz (3 V, 0.1 ms); 1 h/day, for 4 weeks	Myelinated fibers, muscle reinnervation, and function↑	[139]
Rat (neuropathic pain of sciatic nerve constriction injury)	TR: 20 min/time/day for 8 days	tDCS: 20 min/time/day for 8 days	BDNF, IL-1β, IL-4↓; pain↓	[140]
Rat (sciatic nerve section and suture repair)	TR: 1 h/time, 1 time/day for 4 days	ES: 20 Hz (3 V, 0.1 ms), 4 h, 1 time	GDNF, BDNF, and function↑	[141]
Human (brachial plexus injury and transplantation)	Shrugging, abduction, and other movements (200 repetitions/time, 6 times/day, for 1 month); lift the forearm of affected limb (25–30 min/time, 2 times/day; for 1 month)	LFES: 25–30 min/time, 2 times/day, for 1 month	Nerve conduction velocity and amplitude↑; brachial plexus function scores↑	[142]
Rat (surgery for sciatic nerve injury)	Swimming: 10 min/time, 5 times/week, for 4 weeks	LFES: 20 min/time, 5 times/week, for 4 weeks	Function↑; neuropathic pain↓	[143]
Mouse (sciatic nerve section and suture repair)	TR: 1 h/time/every 3 days, for 2 weeks	ES: 20 Hz, 1 h/time/every 3 days, for 2 weeks	Regeneration of axons↑	[144]
Rat (sciatic nerve chronic constriction injury)	TR: 14–16 m/min, 0.5 h, 5 times/week, for 4 weeks	TU: 1 MHz, 1-W/cm^2 intensity, and 100 Hz frequency, 5 min/day, for 4 weeks	IL-10↑; IL-6, Iba1, and neuropathic pain↓	[145]
Rat (sciatic nerve chronic constriction injury)	TR	TU	IL-10↑; IL-6, and neuropathic pain↓	[146]
Rat (surgery for sciatic nerve injury)	Aerobic exercise: 10 min/time/day, for 2 weeks	Laser: 5 min/time/day, for 2 weeks	Neuroregeneration and neurological function↑; Inflammation↓	[147]
Rat (surgery for sciatic nerve injury)	Swimming: 10 min/time in 1st week, 20 min/time in 2nd week, 30 min/time in 3rd week, 40 min/time in 4th week, 1 time/day, for 4 weeks	Laser: 8 s/time in 1st week, 16 s/time in 2nd week, 24 s/time in 3rd week, 24 s/time in 4th week, 1 time/day, for 4 weeks	Area, diameter, thickness, axons, and myelin sheaths of nerve fibers↑	[148]
Rat (sciatic nerve crush injury)	TR	Electroacupuncture	Neuroregeneration, myelin recovery, and function↑	[149]
Rat (sciatic nerve crush injury)	TR: 30 min/time/day, for 21 days	Gallic acid: 200 mg/kg weight/d, 21-day	Motor coordination↑; Conduction velocity and pain reflex latency↓	[150]
Rat (sciatic nerve crush injury)	TR: 14–16 m/min, 30 min/time/day, 5 time/week, for 3 weeks	Curcumin: 60 mg/kg/day, for 2 weeks (IP.)	Nerve conduction velocity↑; neuropathic pain↓	[151]
Rat (sciatic nerve crush injury)	TR: 14–16 m/min, 30 min/time, 1 time/day, 5 time/week, for 3 weeks	Curcumin: 60 mg/kg/day, for 2 weeks (IP.)	Neuropathic pain↓	[152]
Rat (surgery for sciatic nerve injury)	RE: 60% 1 RM and increased by 10%/week, 8 repetitions/time, 3 times/day, for 3 weeks	Bowdichia virgilioides hydroethanolic extract: 200 mg/kg (p.o.)	MDA↓	[110]
Rat (diabetes-induced sciatic nerve damage)	Swimming: 30 min/day, 5 days/week, for 5 weeks	Quercetin: 30 mg/kg/day, for 5 weeks (p.o.)	MDA, PC, nitrites, iNOS, and sciatic nerves injury↓; SOD, CAT↑	[153]
Human (sciatic nerve transection)	Pilates and exercises	Peripheral nerve from sural and autologous cultured Schwann cells	Sensory and motor recovery↑	[154]
Mice (sciatic nerve transection)	TR: 10 m/min, 30 min/time, 2 repetitions/time, 3 times/week, for 8 weeks	Schwann cell graft	Function and morphology↑	[155]

Abbreviations: CAT, catalase; ES, electrical stimulation; iNOS, inducible nitric oxide synthase; IP, intraperitoneal; LFES, low-frequency pulse electrical stimulation; LLLT, low-level laser therapy; MDA, malondialdehyde; p.o per os (by mouth); RE, resistance exercise; RM, repetition maximum; SOD, superoxide dismutase; tDCS, transcranial direct current stimulation; TR, treadmill; TU, therapeutic ultrasound; ↑, Promotion; ↓, Inhibition.
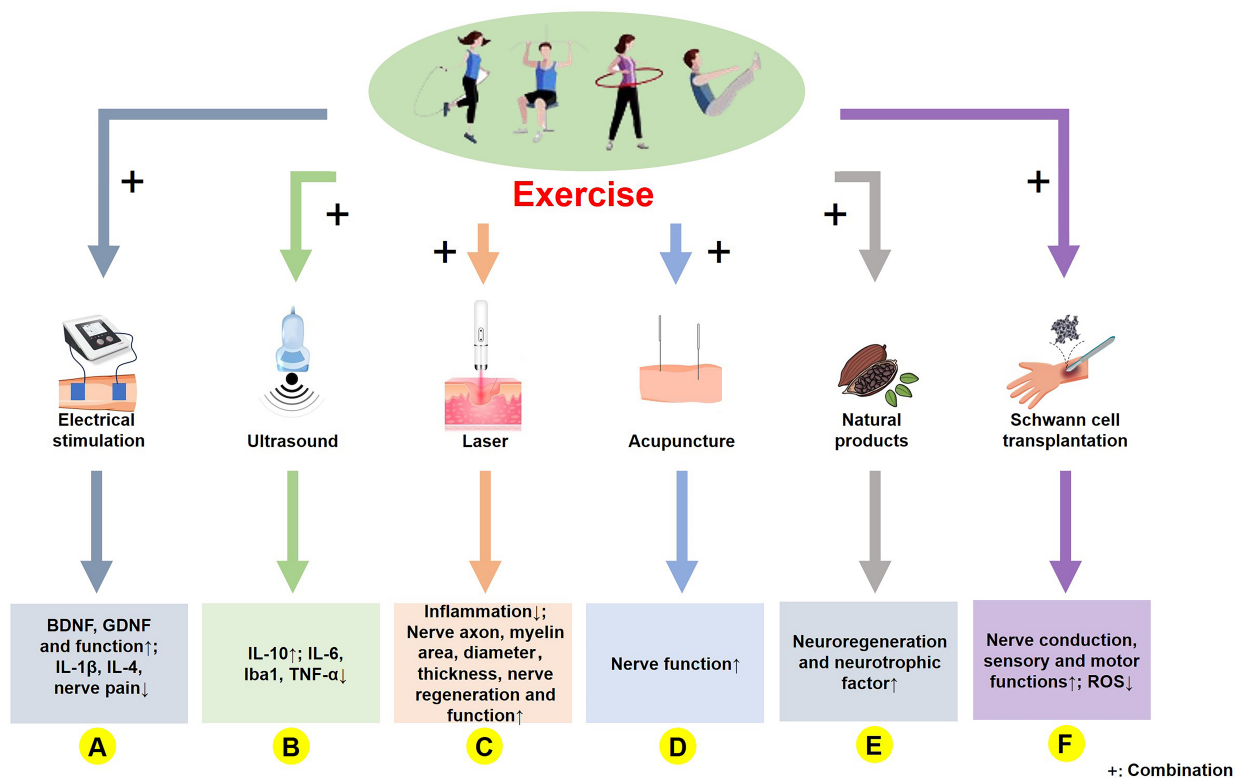
Fig. 3. Molecular mechanism of exercise combined with other treatments in PNI rehabilitation. (A) Exercise combined with electrical stimulation upregulates BDNF and GDNF levels, enhances motor function, and reduces IL-1β, IL-4, and neuropathic pain. (B) Exercise combined with ultrasound elevates IL-10 while suppressing IL-6, Iba1, and TNF-α. (C) Exercise combined with laser therapy attenuates inflammation, promotes axonal growth, increases myelin area, diameter, and thickness, and enhances nerve regeneration and functional recovery. (D) Exercise combined with acupuncture improves neurological function. (E) Exercise combined with natural products facilitates nerve regeneration and upregulates neurotrophic factors. (F) Exercise combined with Schwann cell transplantation enhances nerve conduction, sensory and motor functions, and reduces ROS. ↑, Promotion; ↓, Inhibition.

model in which laser therapy was combined with swimming exercises. The main findings showed that neither exercise nor laser therapy alone had significant effects on the morphology and function of the injured nerve, whereas the combined intervention significantly improved both nerve morphology and function (Fig. 3C) [148]. However, it has been reported that intervention using laser therapy does not significantly improve the PNI [160], whereas laser therapy combined with exercise leads to improvement. Overall, exercise combined with laser treatment may accelerate recovery from PNI.

6.2 Acupuncture

Acupuncture is a traditional Chinese therapy that is widely used to treat various diseases. In a rat model of sciatic nerve injury, the combination of combining electroacupuncture with exercise was more effective than either treatment alone. This combined therapy not only promoted better recovery of myelinated axons but also enhanced their innervation and muscle activity (Fig. 3D) [149]. In a rabbit model of sciatic nerve injury, combining electroacupuncture with treadmill exercise significantly

enhanced axonal regeneration compared to either treatment alone [161]. While exercise and acupuncture may positively affect PNI, relevant studies are scarce.

6.3 Natural Products

Natural products, which are biologically active substances found in nature, are widely used in disease management and healthcare. In a rat model of sciatic nerve crush injury, a 21-day regimen of gallic acid (200 mg/kg) combined with aerobic treadmill exercise significantly improved nerve conduction function [150]. Curcumin improved myelination and functional recovery in a sciatic nerve compression model by reducing oxidative stress [162]. In a chronic compression nerve injury model, a combination of curcumin and exercise effectively prevented electrophysiological disorders of the sciatic nerve [151]. Moreover, when comparing curcumin and exercise, a combination treatment was more effective in reducing pain [152]. A combined intervention of *Bowdichia virgilioides* hydroethanolic extract and resistance exercise reduced oxidative stress associated with PNI [110]. In diabetic nerve injury models, exercise improved nerve damage by reduc-

ing oxidative stress via interactions with quercetin (Fig. 3E) [153]. A combination of movement and natural products may have a synergistic effect on the PNI, and an in-depth exploration of this mechanism is a future research direction.

6.4 Schwann Cell Transplantation

Schwann cells are present in both myelinated and unmyelinated nerve fibers. They promote axonal regeneration and myelination by secreting neural factors. In 2016, Levi *et al.* [154] were the first to demonstrate that transplanting Schwann cells through autologous culture could accelerate recovery from PNI. After sciatic nerve transection and Schwann cell transplantation, there was a significant increase in the nerve function index and number of neurons (Fig. 3F) [155]. Exercise can improve nerve regeneration after nerve injury, which can also be improved by Schwann cell transplantation [100]. Therefore, combining exercise with Schwann cell transplantation may enhance PNI repair. Although research in this area is limited, this could offer a promising approach for neurosurgical and rehabilitation studies.

7. Conclusion

The rehabilitation process for a PNI caused by trauma or disease is complex and involves multiple physiological processes and molecular mechanisms. Exercise plays a critical role in accelerating recovery and reducing long-term complications. Current evidence suggests that non-weight-bearing aerobic exercise, early exercise intervention, temperature-modulated exercise, and a combination of exercise and other treatment modalities may enhance rehabilitation outcomes. However, clinical research on such combined therapeutic regimens remains limited, particularly regarding exercise combined with physical therapy, exercise environment optimization, and traditional Chinese medicine, all of which demonstrate substantial clinical potential. Therapeutic strategies targeting multiple pathological mechanisms, including inflammation suppression, oxidative stress reduction, neurotrophic factor upregulation, cellular autophagy modulation, vascular remodeling facilitation, and hormonal homeostasis regulation, may offer novel research avenues for PNI rehabilitation.

Author Contributions

ZWZ and JLH performed the literature search, wrote the manuscript and created the figures. JWS and HZ were responsible for the conception and design of the manuscript. All authors contributed to editorial changes in the manuscript and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Li NY, Onor GI, Lemme NJ, Gil JA. Epidemiology of peripheral nerve injuries in sports, exercise, and recreation in the United States, 2009 - 2018. The Physician and Sportsmedicine. 2021; 49: 355–362. https://doi.org/10.1080/00913847.2020.1850151.

[2] Tang W, Yin X, Liu K, Shao T, Gao Q, Shen H, *et al*. The reduction of imidazole propionate induced by intermittent fasting promotes recovery of peripheral nerve injury by enhancing migration of Schwann cells. Experimental Cell Research. 2024; 442: 114261. https://doi.org/10.1016/j.yexcr.2024.114261.

[3] Zeng Z, Zhang H, Wang X, Shen J, Chen D. Fasting, a potential intervention in Alzheimer's disease. Journal of Integrative Neuroscience. 2024; 23: 50. https://doi.org/10.31083/j.jin2303050.

[4] Svačina MKR, Gao T, Sprenger-Svačina A, Lin J, Ganesh BP, Lee J, *et al*. Rejuvenating fecal microbiota transplant enhances peripheral nerve repair in aged mice by modulating endoneurial inflammation. Experimental Neurology. 2024; 376: 114774. https://doi.org/10.1016/j.expneurol.2024.114774.

[5] Su Y, Huang M, Thomas AG, Maragakis J, Huizar KDJ, Zheng Y, *et al*. GCPII inhibition promotes remyelination after peripheral nerve injury in aged mice. International Journal of Molecular Sciences. 2024; 25: 6893. https://doi.org/10.3390/ijms25136893.

[6] Zhang T, Zhao J, Guan Y, Li X, Bai J, Song X, *et al*. Deferoxamine promotes peripheral nerve regeneration by enhancing schwann cell function and promoting axon regeneration of dorsal root ganglion. Neuroscience. 2023; 524: 149–157. https://doi.org/10.1016/j.neuroscience.2023.05.029.

[7] Wang G, Lu P, Qiao P, Zhang P, Cai X, Tang L, *et al*. Blood vessel remodeling in late stage of vascular network reconstruction is essential for peripheral nerve regeneration. Bioengineering & Translational Medicine. 2022; 7: e10361. https://doi.org/10.1002/btm2.10361.

[8] Gu D, Xia Y, Ding Z, Qian J, Gu X, Bai H, *et al*. Inflammation in the peripheral nervous system after injury. Biomedicines. 2024; 12: 1256. https://doi.org/10.3390/biomedicines12061256.

[9] Hervera A, De VF, Palmisano I, Zhou L, Tantardini E, Kong G, et al. Reactive oxygen species regulate axonal regeneration through the release of exosomal NADPH oxidase 2 complexes into injured axons. Nature Cell Biology. 2018; 20: 307–319. https://doi.org/10.1038/s41556-018-0039-x.

[10] He QR, Cong M, Yu FH, Ji YH, Yu S, Shi HY, *et al*. Peripheral nerve fibroblasts secrete neurotrophic factors to promote axon growth of motoneurons. Neural Regeneration Research. 2022; 17: 1833–1840. https://doi.org/10.4103/1673-5374.332159.

[11] Fletcher B, Phillips R, Faust A, Cook JL, Nuelle JAV. Physical exercise to promote regeneration after peripheral nerve injury in animal models: A systematic review. Journal of Orthopaedic Research: Official Publication of the Orthopaedic Research Society. 2024; 42: 1608–1622. https://doi.org/10.1002/jor.25792.

[12] Kaya Y, Sarikcioglu L. Sir Herbert Seddon (1903-1977) and his classification scheme for peripheral nerve injury. Child's Nervous System: ChNS: Official Journal of the International

Society for Pediatric Neurosurgery. 2015; 31: 177–180. https://doi.org/10.1007/s00381-014-2560-y.

[13] SUNDERLAND S. A classification of peripheral nerve injuries producing loss of function. Brain: A Journal of Neurology. 1951; 74: 491–516. https://doi.org/10.1093/brain/74.4.491.

[14] Balog BM, Sonti A, Zigmond RE. Neutrophil biology in injuries and diseases of the central and peripheral nervous systems. Progress in Neurobiology. 2023; 228: 102488. https://doi.org/10.1016/j.pneurobio.2023.102488.

[15] Tian R, Zhou Y, Ren Y, Zhang Y, Tang W. Wallerian degeneration: From mechanism to disease to imaging. Heliyon. 2024; 11: e40729. https://doi.org/10.1016/j.heliyon.2024.e40729.

[16] Seddon HJ, Medawar PB, Smith H. Rate of regeneration of peripheral nerves in man. The Journal of Physiology. 1943; 102: 191–215. https://doi.org/10.1113/jphysiol.1943.sp004027.

[17] Boyd KU, Nimigan AS, Mackinnon SE. Nerve reconstruction in the hand and upper extremity. Clinics in Plastic Surgery. 2011; 38: 643–660. https://doi.org/10.1016/j.cps.2011.07.008.

[18] Chen M, Zhao J, Cai X, Zhu S. Editorial: Growth factors and stem cells intervention in injury repair and regeneration of spinal cord and peripheral nerve. Frontiers in Pharmacology. 2023; 13: 1115470. https://doi.org/10.3389/fphar.2022.1115470.

[19] Zhang H, Wang S, Zhang Q, Du X, Xu D, Wen J, et al. Indole-3-propionic acid promotes Schwann cell proliferation following peripheral nerve injury by activating the PI3K/AKT pathway. Neurotherapeutics: the Journal of the American Society for Experimental NeuroTherapeutics. 2025; e00578. https://doi.org/10.1016/j.neurot.2025.e00578.

[20] Song J, Meng H, Deng G, Lin H. Sustainable release selenium laden with SiO_2 restoring peripheral nerve injury via modulating PI3K/AKT pathway signaling pathway. International Journal of Nanomedicine. 2024; 19: 7851–7870. https://doi.org/10.2147/IJN.S460397.

[21] Li L, Yao H, Mo R, Xu L, Chen P, Chen Y, et al. Blocking proteinase-activated receptor 2 signaling relieves pain, suppresses nerve sprouting, improves tissue repair, and enhances analgesic effect of B vitamins in rats with Achilles tendon injury. Pain. 2024; 165: 2055–2067. https://doi.org/10.1097/j.pain.0000000000003229.

[22] He R, Wei Y, Yan S, Chen J, Guan Y, Xiong X, et al. Wnt 3a-modified scaffolds improve nerve regeneration by boosting schwann cell function. ACS Applied Materials & Interfaces. 2024; 16: 63317–63332. https://doi.org/10.1021/acsami.4c15013.

[23] Wang M, Wu S, Wang J, Fan D, Li Z, Tian S, et al. MiRNA-206 affects the recovery of sciatic function by stimulating BDNF activity through the down-regulation of Notch3 expression. Journal of Musculoskeletal & Neuronal Interactions. 2023; 23: 109–121.

[24] Wu Q, Xie J, Zhu X, He J. Runt-related transcription factor 3, mediated by DNA-methyltransferase 1, regulated Schwann cell proliferation and myelination during peripheral nerve regeneration via JAK/STAT signaling pathway. Neuroscience Research. 2023; 192: 1–10. https://doi.org/10.1016/j.neures.2023.01.008.

[25] Rayner MLD, Healy J, Phillips JB. Repurposing small molecules to target PPAR-γ as new therapies for peripheral nerve injuries. Biomolecules. 2021; 11: 1301. https://doi.org/10.3390/biom11091301.

[26] Ding Z, Jiang M, Qian J, Gu D, Bai H, Cai M, et al. Role of transforming growth factor-β in peripheral nerve regeneration. Neural Regeneration Research. 2024; 19: 380–386. https://doi.org/10.4103/1673-5374.377588.

[27] Wariyar SS, Brown AD, Tian T, Pottorf TS, Ward PJ. Angiogenesis is critical for the exercise-mediated enhancement of axon regeneration following peripheral nerve injury. Experimental Neurology. 2022; 353: 114029. https://doi.org/10.1016/j.expneurol.2022.114029.

[28] Khan J, Wang Q, Korczeniewska OA, McNeil R, Ren Y, Benoliel R, et al. Response profile in a rat model of exercise-induced hypoalgesia is associated with duloxetine, pregabalin and diclofenac effect on constriction-induced neuropathy. European Journal of Pain (London, England). 2023; 27: 129–147. https://doi.org/10.1002/ejp.2044.

[29] Watanabe O, Mackinnon SE, Tarasidis G, Hunter DA, Ball DJ. Long-term observation of the effect of peripheral nerve injury in neonatal and young rats. Plastic and Reconstructive Surgery. 1998; 102: 2072–2072–81; discussion 2082–4. https://doi.org/10.1097/00006534-199811000-00039.

[30] Cunha NB, Ilha J, Centenaro LA, Lovatel GA, Balbinot LF, Achaval M. The effects of treadmill training on young and mature rats after traumatic peripheral nerve lesion. Neuroscience Letters. 2011; 501: 15–19. https://doi.org/10.1016/j.neulet.2011.06.030.

[31] Brandt J, Evans JT, Mildenhall T, Mulligan A, Konieczny A, Rose SJ, et al. Delaying the onset of treadmill exercise following peripheral nerve injury has different effects on axon regeneration and motoneuron synaptic plasticity. Journal of Neurophysiology. 2015; 113: 2390–2399. https://doi.org/10.1152/jn.00892.2014.

[32] Boeltz T, Ireland M, Mathis K, Nicolini J, Poplavski K, Rose SJ, et al. Effects of treadmill training on functional recovery following peripheral nerve injury in rats. Journal of Neurophysiology. 2013; 109: 2645–2657. https://doi.org/10.1152/jn.00946.2012.

[33] English AW, Cucoranu D, Mulligan A, Sabatier M. Treadmill training enhances axon regeneration in injured mouse peripheral nerves without increased loss of topographic specificity. The Journal of Comparative Neurology. 2009; 517: 245–255. https://doi.org/10.1002/cne.22149.

[34] Park JS. Different effect by different starting time point of exercise of the nerve regeneration after the peripheral nerve injury. International Journal of IT-based Public Health Management. 2018; 5: 39–41.

[35] Teodori RM, Betini J, de Oliveira LS, Sobral LL, Takeda SYM, de Lima Montebelo MI. Swimming exercise in the acute or late phase after sciatic nerve crush accelerates nerve regeneration. Neural Plasticity. 2011; 2011: 783901. https://doi.org/10.1155/2011/783901.

[36] Sarikcioglu L, Oguz N. Exercise training and axonal regeneration after sciatic nerve injury. The International Journal of Neuroscience. 2001; 109: 173–177. https://doi.org/10.3109/00207450108986533.

[37] Doi A, Oda K, Matsumoto M, Sakoguchi H, Honda M, Ogata Y, et al. Whole body vibration accelerates the functional recovery of motor nerve components in sciatic nerve-crush injury model rats. Journal of Exercise Rehabilitation. 2023; 19: 149–162. https://doi.org/10.12965/jer.2346178.089.

[38] Sleijser-Koehorst MLS, Koop MA, Coppieters MW, Lutke Schipholt IJ, Radisic N, Hooijmans CR, et al. The effects of aerobic exercise on neuroimmune responses in animals with traumatic peripheral nerve injury: a systematic review with meta-analyses. Journal of Neuroinflammation. 2023; 20: 104. https://doi.org/10.1186/s12974-023-02777-y.

[39] de Oliveira Marques C, Amaro Espindula I, Kwame Karikari Darko E, Viçosa Bonetti L, Sonza A, Aparecida Partata W, et al. Whole-body vibration therapy does not improve the peripheral nerve regeneration in experimental model. Journal of Musculoskeletal & Neuronal Interactions. 2021; 21: 68–78.

[40] Yin L, An Y, Chen X, Yan HX, Zhang T, Lu XG, et al. Local vibration therapy promotes the recovery of nerve function in rats with sciatic nerve injury. Journal of Integrative Medicine. 2022; 20: 265–273. https://doi.org/10.1016/j.joim.2022.02.001.

[41] Strömberg T, Lundborg G, Holmquist B, Dahlin LB. Impaired regeneration in rat sciatic nerves exposed to short-term vibra-

tion. Journal of Hand Surgery (Edinburgh, Scotland). 1996; 21: 746–749. https://doi.org/10.1016/s0266-7681(96)80178-1.

[42] Molteni R, Zheng JQ, Ying Z, Gómez-Pinilla F, Twiss JL. Voluntary exercise increases axonal regeneration from sensory neurons. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101: 8473–8478. https://doi.org/10.1073/pnas.0401443101.

[43] Udina E, Puigdemasa A, Navarro X. Passive and active exercise improve regeneration and muscle reinnervation after peripheral nerve injury in the rat. Muscle & Nerve. 2011; 43: 500–509. https://doi.org/10.1002/mus.21912.

[44] Sabatier MJ, Redmon N, Schwartz G, English AW. Treadmill training promotes axon regeneration in injured peripheral nerves. Experimental Neurology. 2008; 211: 489–493. https://doi.org/10.1016/j.expneurol.2008.02.013.

[45] Cho YH, Seo TB. The timing point of exercise intervention regulates neuropathic pain-related molecules in the ipsilateral dorsal root ganglion neurons after sciatic nerve injury. Journal of Exercise Rehabilitation. 2022; 18: 286–293. https://doi.org/10.12965/jer.2244382.191.

[46] Minegishi Y, Nishimoto J, Uto M, Ozone K, Oka Y, Kokubun T, et al. Effects of exercise on muscle reinnervation and plasticity of spinal circuits in rat sciatic nerve crush injury models with different numbers of crushes. Muscle & Nerve. 2022; 65: 612–620. https://doi.org/10.1002/mus.27512.

[47] Debastiani JC, Santana AJ, Ribeiro LDFC, Brancalhão RMC, Bertolini GRF. Sericin silk protein in peripheral nervous repair associated with the physical exercise of swimming in Wistar rats. Neurological Research. 2019; 41: 326–334. https://doi.org/10.1080/01616412.2018.1564187.

[48] de Moura JA, de Morais J, Barbosa SMN, Ferreira MC, de Sousa Neto IV, Leite HR, et al. Negative neuromuscular and functional repercussion of forced swimming after axonotmesis. Journal of Exercise Rehabilitation. 2022; 18: 179–186. https://doi.org/10.12965/jer.2244150.075.

[49] Cannoy J, Crowley S, Jarratt A, Werts KL, Osborne K, Park S, et al. Upslope treadmill exercise enhances motor axon regeneration but not functional recovery following peripheral nerve injury. Journal of Neurophysiology. 2016; 116: 1408–1417. https://doi.org/10.1152/jn.00129.2016.

[50] Di Palma M, Ambrogini P, Lattanzi D, Brocca L, Bottinelli R, Cuppini R, et al. The impact of different exercise protocols on rat soleus muscle reinnervation and recovery following peripheral nerve lesion and regeneration. Frontiers in Physiology. 2022; 13: 948985. https://doi.org/10.3389/fphys.2022.948985.

[51] Ilha J, Araujo RT, Malysz T, Hermel EES, Rigon P, Xavier LL, et al. Endurance and resistance exercise training programs elicit specific effects on sciatic nerve regeneration after experimental traumatic lesion in rats. Neurorehabilitation and Neural Repair. 2008; 22: 355–366. https://doi.org/10.1177/1545968307313502.

[52] Kim KH, Hwangbo G, Kim SG. The effect of weight-bearing exercise and non-weight-bearing exercise on gait in rats with sciatic nerve crush injury. Journal of Physical Therapy Science. 2015; 27: 1177–1179. https://doi.org/10.1589/jpts.27.1177.

[53] Lima PTMR. Influence of differenced physical exercises in ischiatic nerve regeneration in rats: Functional and morphological study. Arquivos de Neuro-Psiquiatria. 2009; 67: 955–956. https://doi.org/10.1590/S0004-282X2009000500042.

[54] Cobianchi S, Marinelli S, Florenzano F, Pavone F, Luvisetto S. Short- but not long-lasting treadmill running reduces allodynia and improves functional recovery after peripheral nerve injury. Neuroscience. 2010; 168: 273–287. https://doi.org/10.1016/j.neuroscience.2010.03.035.

[55] Bonetti LV, Korb A, Da Silva SA, Ilha J, Marcuzzo S, Achaval M, et al. Balance and coordination training after sciatic nerve in-

jury. Muscle & Nerve. 2011; 44: 55–62. https://doi.org/10.1002/mus.21996.

[56] Bonetti LV, Malysz T, Ilha J, Barbosa S, Achaval M, Faccioni-Heuser MC. The effects of two different exercise programs on the ultrastructural features of the sciatic nerve and soleus muscle after sciatic crush. Anatomical Record (Hoboken, N.J.: 2007). 2017; 300: 1654–1661. https://doi.org/10.1002/ar.23611.

[57] Feter N, Freitas M, Gonzales N, Umpierre D, Cardoso R, Rombaldi AJS, et al. Effects of physical exercise on myelin sheath regeneration: A systematic review and meta-analysis. Science and Sports. 2018; 33: 8–21. https://doi.org/10.1016/j.scispo.2017.06.009.

[58] van Meeteren NL, Brakkee JH, Hamers FP, Helders PJ, Gispen WH. Exercise training improves functional recovery and motor nerve conduction velocity after sciatic nerve crush lesion in the rat. Archives of Physical Medicine and Rehabilitation. 1997; 78: 70–77. https://doi.org/10.1016/s0003-9993(97)90013-7.

[59] English AW, Wilhelm JC, Sabatier MJ. Enhancing recovery from peripheral nerve injury using treadmill training. Annals of Anatomy = Anatomischer Anzeiger: Official Organ of the Anatomische Gesellschaft. 2011; 193: 354–361. https://doi.org/10.1016/j.aanat.2011.02.013.

[60] Kuphal KE, Fibuch EE, Taylor BK. Extended swimming exercise reduces inflammatory and peripheral neuropathic pain in rodents. The Journal of Pain. 2007; 8: 989–997. https://doi.org/10.1016/j.jpain.2007.08.001.

[61] Özocak O, Kestane S, Duran HH, Çoksevim B. The curative effect of swimming exercise on electrophysiological parameters after sciatic nerve injury. The Journal of Turkish Sport Science. 2023; 6: 37–50. https://doi.org/10.46385/tsbd.1325961.

[62] Ward P, Wariyar S, Tian T, Pottorf T, Brown A. HIF1a and angiogenesis are critical for the regenerative effects of exercise. The FASEB Journal. 2022; 36. https://doi.org/10.1096/fasebj.2022.36.s1.i2256.

[63] Seo TB, Oh MJ, You BG, Kwon KB, Chang IA, Yoon JH, et al. Erk1/2-mediated Schwann cell proliferation in the regenerating sciatic nerve by treadmill training. Journal of Neurotrauma. 2009; 26: 1733–1744. https://doi.org/10.1089/neu.2008.0711.

[64] Wood K, Wilhelm JC, Sabatier MJ, Liu K, Gu J, English AW. Sex differences in the effectiveness of treadmill training in enhancing axon regeneration in injured peripheral nerves. Developmental Neurobiology. 2012; 72: 688–698. https://doi.org/10.1002/dneu.20960.

[65] Hsieh YL, Yang NP, Chen SF, Lu YL, Yang CC. Early intervention of cold-water swimming on functional recovery and spinal pain modulation following brachial plexus avulsion in rats. International Journal of Molecular Sciences. 2022; 23: 1178. https://doi.org/10.3390/ijms23031178.

[66] Yang CC, Wang J, Chen SC, Jan YM, Hsieh YL. Enhanced functional recovery from sciatic nerve crush injury through a combined treatment of cold-water swimming and mesenchymal stem cell transplantation. Neurological Research. 2015; 37: 816–826. https://doi.org/10.1179/1743132815Y.0000000060.

[67] Jin HY, Lee KA, Park TS. The effect of exercise on the peripheral nerve in streptozotocin (STZ)-induced diabetic rats. Endocrine. 2015; 48: 826–833. https://doi.org/10.1007/s12020-014-0422-8.

[68] Singleton JR, Marcus RL, Jackson JE, K Lessard M, Graham TE, Smith AG. Exercise increases cutaneous nerve density in diabetic patients without neuropathy. Annals of Clinical and Translational Neurology. 2014; 1: 844–849. https://doi.org/10.1002/acn3.125.

[69] Balducci S, Iacobellis G, Parisi L, Di Biase N, Calandriello E, Leonetti F, et al. Exercise training can modify the natural history of diabetic peripheral neuropathy. Journal of Diabetes and its Complications. 2006; 20: 216–223. https://doi.org/10.1016/

j.jdiacomp.2005.07.005.

[70] Sharma J, Ahmad I, Singh AK. Effects of exercises and manual therapy on nerve conduction studies of lower limb in patients with diabetes and diabetic peripheral neuropathy: A systematic review. International Journal of Diabetes in Developing Countries. 2023; 44: 241–264. https://doi.org/10.1007/s13410-023-01258-5.

[71] Kim JO, Seo TB, Yoon JH. Effects of treadmill training on axonal regeneration, spinal cord motor neuron, GAP-43 and GLUT-4 protein expression after sciatic nerve injury in the streptozotocin-induced diabetic rats. International Journal of Applied Sports Sciences, 2007; 19: 117.

[72] Malysz T, Ilha J, Nascimento PSD, De Angelis K, Schaan BD, Achaval M. Beneficial effects of treadmill training in experimental diabetic nerve regeneration. Clinics (Sao Paulo, Brazil). 2010; 65: 1329–1337. https://doi.org/10.1590/s1807-59322010001200017.

[73] Gulsen I, Demiroglu M, Aycan A, Ucler R, Alaca I, Orhon ZN, et al. Effects of low-intensity treadmill exercise on sciatic nerve in experimental diabetic neuropathy. Analytical and Quantitative Cytopathology and Histopathology. 2016; 38: 95–102.

[74] Stubbs EB, Jr, Fisher MA, Miller CM, Jelinek C, Butler J, McBurney C, et al. Randomized controlled trial of physical exercise in diabetic veterans with length-dependent distal symmetric polyneuropathy. Frontiers in Neuroscience. 2019; 13: 51. https://doi.org/10.3389/fnins.2019.00051.

[75] Dixit S, Maiya AG, Shastry BA. Effect of aerobic exercise on peripheral nerve functions of population with diabetic peripheral neuropathy in type 2 diabetes: a single blind, parallel group randomized controlled trial. Journal of Diabetes and its Complications. 2014; 28: 332–339. https://doi.org/10.1016/j.jdiacomp.2013.12.006.

[76] Taheri A, Rohani H, Habibi AJ. The effect of endurance exercise training on the expression of brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF) genes of the cerebellum in diabetic rat. Iranian Journal of Diabetes and Obesity. 2020; 11: 233–240. https://doi.org/10.18502/ijdo.v11i4.2879.

[77] Gu Y, Dennis SM, Kiernan MC, Harmer AR. Aerobic exercise training may improve nerve function in type 2 diabetes and pre-diabetes: A systematic review. Diabetes/metabolism Research and Reviews. 2019; 35: e3099. https://doi.org/10.1002/dmrr.3099.

[78] Kluding PM, Pasnoor M, Singh R, Jernigan S, Farmer K, Rucker J, et al. The effect of exercise on neuropathic symptoms, nerve function, and cutaneous innervation in people with diabetic peripheral neuropathy. Journal of Diabetes and its Complications. 2012; 26: 424–429. https://doi.org/10.1016/j.jdiacomp.2012.05.007.

[79] Markvardsen LH, Overgaard K, Heje K, Sindrup SH, Christiansen I, Vissing J, et al. Resistance training and aerobic training improve muscle strength and aerobic capacity in chronic inflammatory demyelinating polyneuropathy. Muscle & Nerve. 2018; 57: 70–76. https://doi.org/10.1002/mus.25652.

[80] Hussein AA, Aziz YAA, Ahmed MJ. Effect of Russian current with exercise vs exercise alone on chronic inflammatory demyelinating polyneuropathy. The Medical Journal of Cairo University, 2021; 89: 2735–2742. https://doi.org/10.21608/mjcu.2021.225161.

[81] Janssen J, Bunce M, Nixon J, Dunbar M, Jones S, Benstead J, et al. A clinical case series investigating the effectiveness of an exercise intervention in chronic inflammatory demyelinating polyneuropathy. Physiotherapy Practice and Research. 2018; 39: 37–44. https://doi.org/10.3233/PPR-170100.

[82] Zimmer P, Trebing S, Timmers-Trebing U, Schenk A, Paust R, Bloch W, et al. Eight-week, multimodal exercise counteracts a progress of chemotherapy-induced peripheral neuropathy and improves balance and strength in metastasized colorectal cancer patients: a randomized controlled trial. Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer. 2018; 26: 615–624. https://doi.org/10.1007/s00520-017-3875-5.

[83] Lin WL, Wang RH, Chou FH, Feng IJ, Fang CJ, Wang HH. The effects of exercise on chemotherapy-induced peripheral neuropathy symptoms in cancer patients: a systematic review and meta-analysis. Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer. 2021; 29: 5303–5311. https://doi.org/10.1007/s00520-021-06082-3.

[84] Kleckner IR, Kamen C, Gewandter JS, Mohile NA, Heckler CE, Culakova E, et al. Effects of exercise during chemotherapy on chemotherapy-induced peripheral neuropathy: a multi-center, randomized controlled trial. Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer. 2018; 26: 1019–1028. https://doi.org/10.1007/s00520-017-4013-0.

[85] Kneis S, Wehrle A, Müller J, Maurer C, Ihorst G, Gollhofer A, et al. It's never too late - balance and endurance training improves functional performance, quality of life, and alleviates neuropathic symptoms in cancer survivors suffering from chemotherapy-induced peripheral neuropathy: results of a randomized controlled trial. BMC Cancer. 2019; 19: 414. https://doi.org/10.1186/s12885-019-5522-7.

[86] Sun L, Lv Y, Tian J, Yu T, Niu F, Zhang X, et al. Regular swimming exercise attenuated neuroma pain in rats: involvement of leptin and adiponectin. The Journal of Pain. 2019; 20: 1112–1124. https://doi.org/10.1016/j.jpain.2019.02.097.

[87] Kanzawa-Lee GA, Larson JL, Resnicow K, Smith EML. Exercise effects on chemotherapy-induced peripheral neuropathy: A comprehensive integrative review. Cancer Nursing. 2020; 43: E172–E185. https://doi.org/10.1097/NCC.0000000000000801.

[88] Guo S, Han W, Wang P, Wang X, Fang X. Effects of exercise on chemotherapy-induced peripheral neuropathy in cancer patients: a systematic review and meta-analysis. Journal of Cancer Survivorship: Research and Practice. 2023; 17: 318–331. https://doi.org/10.1007/s11764-022-01182-3.

[89] Shen J, Wang X, Wang M, Zhang H. Potential molecular mechanism of exercise reversing insulin resistance and improving neurodegenerative diseases. Frontiers in Physiology. 2024; 15: 1337442. https://doi.org/10.3389/fphys.2024.1337442.

[90] Kanda K, Hashizume K. Effects of long-term physical exercise on age-related changes of spinal motoneurons and peripheral nerves in rats. Neuroscience Research. 1998; 31: 69–75. https://doi.org/10.1016/s0168-0102(98)00026-1.

[91] Shokouhi G, Tubbs RS, Shoja MM, Roshangar L, Mesgari M, Ghorbanihaghjo A, et al. The effects of aerobic exercise training on the age-related lipid peroxidation, Schwann cell apoptosis and ultrastructural changes in the sciatic nerve of rats. Life Sciences. 2008; 82: 840–846. https://doi.org/10.1016/j.lfs.2008.01.018.

[92] Sakita M, Murakami S, Fujino H. The morphological changes in the capillary architecture of the tibial nerve associated with spontaneous aging and aerobic exercise intervention during aging in rats. Journal of Physical Therapy Science. 2014; 26: 263–267. https://doi.org/10.1589/jpts.26.263.

[93] Park JS, Höke A. Treadmill exercise induced functional recovery after peripheral nerve repair is associated with increased levels of neurotrophic factors. PloS One. 2014; 9: e90245. https://doi.org/10.1371/journal.pone.0090245.

[94] Gómez-Pinilla F, Ying Z, Roy RR, Molteni R, Edgerton VR. Voluntary exercise induces a BDNF-mediated mechanism that promotes neuroplasticity. Journal of Neurophysiology. 2002; 88: 2187–2195. https://doi.org/10.1152/jn.00152.2002.

[95] Almeida C, DeMaman A, Kusuda R, Cadetti F, Ravanelli MI, Queiroz AL, *et al*. Exercise therapy normalizes BDNF upregulation and glial hyperactivity in a mouse model of neuropathic pain. Pain. 2015; 156: 504–513. https://doi.org/10.1097/01.j.pain.0000460339.23976.12.

[96] Bai J, Geng B, Wang X, Wang S, Yi Q, Tang Y, *et al*. Exercise facilitates the M1-to-M2 polarization of microglia by enhancing autophagy via the BDNF/AKT/mTOR pathway in neuropathic pain. Pain Physician. 2022; 25: E1137–E1151.

[97] Lopez-Alvarez VM, Puigdomenech M, Navarro X, Cobianchi S. Monoaminergic descending pathways contribute to modulation of neuropathic pain by increasing-intensity treadmill exercise after peripheral nerve injury. Experimental Neurology. 2018; 299: 42–55. https://doi.org/10.1016/j.expneurol.2017.10.007.

[98] Krakowiak J, Liu C, Papudesu C, Ward PJ, Wilhelm JC, English AW. Neuronal BDNF signaling is necessary for the effects of treadmill exercise on synaptic stripping of axotomized motoneurons. Neural Plasticity. 2015; 2015: 392591. https://doi.org/10.1155/2015/392591.

[99] McGregor CE, Irwin AM, English AW. The Val66Met bdnf polymorphism and peripheral nerve injury: Enhanced regeneration in mouse met-carriers is not further improved with activity-dependent treatment. Neurorehabilitation and Neural Repair. 2019; 33: 407–418. https://doi.org/10.1177/1545968319846131.

[100] Wilhelm JC, Xu M, Cucoranu D, Chmielewski S, Holmes T, Lau KS, *et al*. Cooperative roles of BDNF expression in neurons and Schwann cells are modulated by exercise to facilitate nerve regeneration. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2012; 32: 5002–5009. https://doi.org/10.1523/JNEUROSCI.1411-11.2012.

[101] Arbat-Plana A, Cobianchi S, Herrando-Grabulosa M, Navarro X, Udina E. Endogenous modulation of TrkB signaling by treadmill exercise after peripheral nerve injury. Neuroscience. 2017; 340: 188–200. https://doi.org/10.1016/j.neuroscience.2016.10.057.

[102] Byun YH, Lee MH, Kim SS, Kim H, Chang HK, Lee TH, *et al*. Treadmill running promotes functional recovery and decreases brain-derived neurotrophic factor mRNA expression following sciatic crushed nerve injury in rats. The Journal of Sports Medicine and Physical Fitness. 2005; 45: 222–228.

[103] Fan LY, Wang ZC, Wang P, Lan YY, Tu L. Exogenous nerve growth factor protects the hypoglossal nerve against crush injury. Neural Regeneration Research. 2015; 10: 1982–1988. https://doi.org/10.4103/1673-5374.172316.

[104] Omura T, Sano M, Omura K, Hasegawa T, Doi M, Sawada T, *et al*. Different expressions of BDNF, NT3, and NT4 in muscle and nerve after various types of peripheral nerve injuries. Journal of the Peripheral Nervous System: JPNS. 2005; 10: 293–300. https://doi.org/10.1111/j.1085-9489.2005.10307.x.

[105] Daniela M, Catalina L, Ilie O, Paula M, Daniel-Andrei I, Ioana B. Effects of exercise training on the autonomic nervous system with a focus on anti-inflammatory and antioxidants effects. Antioxidants (Basel, Switzerland). 2022; 11: 350. https://doi.org/10.3390/antiox11020350.

[106] André-Lévigne D, Pignel R, Boet S, Jaquet V, Kalbermatten DF, Madduri S. Role of oxygen and its radicals in peripheral nerve regeneration: from hypoxia to physoxia to hyperoxia. International Journal of Molecular Sciences. 2024; 25: 2030. https://doi.org/10.3390/ijms25042030.

[107] Areti A, Yerra VG, Naidu V, Kumar A. Oxidative stress and nerve damage: role in chemotherapy induced peripheral neuropathy. Redox Biology. 2014; 2: 289–295. https://doi.org/10.1016/j.redox.2014.01.006.

[108] Green-Fulgham SM, Harland ME, Ball JB, Li J, Lacagnina MJ, D'Angelo H, *et al*. Preconditioning by voluntary wheel running attenuates later neuropathic pain via nuclear factor E2-related factor 2 antioxidant signaling in rats. Pain. 2022; 163: 1939–1951. https://doi.org/10.1097/j.pain.0000000000002589.

[109] Safakhah HA, Moradi Kor N, Bazargani A, Bandegi AR, Gholami Pourbadie H, Khoshkholgh-Sima B, *et al*. Forced exercise attenuates neuropathic pain in chronic constriction injury of male rat: an investigation of oxidative stress and inflammation. Journal of Pain Research. 2017; 10: 1457–1466. https://doi.org/10.2147/JPR.S135081.

[110] Costa LS, Aidar FJ, Matos DGD, Oliveira JUD, Santos JLD, Almeida-Neto PFD, *et al*. Effects of resistance training and *Bowdichia virgilioides* hydroethanolic extract on oxidative stress markers in rats submitted to peripheral nerve injury. Antioxidants (Basel, Switzerland). 2020; 9: 941. https://doi.org/10.3390/antiox9100941.

[111] Nonaka K, Akiyama J, Une S. Exercise may increase oxidative stress in the sciatic nerve in streptozotocin-induced diabetic rats. Medicina (Kaunas, Lithuania). 2024; 60: 480. https://doi.org/10.3390/medicina60030480.

[112] Little CM, Coons KD, Sengelaub DR. Neuroprotective effects of testosterone on the morphology and function of somatic motoneurons following the death of neighboring motoneurons. The Journal of Comparative Neurology. 2009; 512: 359–372. https://doi.org/10.1002/cne.21885.

[113] Chew C, Sengelaub DR. Neuroprotective effects of exercise on the morphology of somatic motoneurons following the death of neighboring motoneurons. Neurorehabilitation and Neural Repair. 2019; 33: 656–667. https://doi.org/10.1177/1545968319860485.

[114] Ward PJ, Davey RA, Zajac JD, English AW. Neuronal androgen receptor is required for activity dependent enhancement of peripheral nerve regeneration. Developmental Neurobiology. 2021; 81: 411–423. https://doi.org/10.1002/dneu.22826.

[115] Liu C, Ward PJ, English AW. The effects of exercise on synaptic stripping require androgen receptor signaling. PloS One. 2014; 9: e98633. https://doi.org/10.1371/journal.pone.0098633.

[116] Thompson NJ, Sengelaub DR, English AW. Enhancement of peripheral nerve regeneration due to treadmill training and electrical stimulation is dependent on androgen receptor signaling. Developmental Neurobiology. 2014; 74: 531–540. https://doi.org/10.1002/dneu.22147.

[117] Foecking EM, Fargo KN, Brown TJ, Sengelaub DR, Jones KJ. Gonadal steroids in regeneration and repair of neuromuscular systems. In So KF, Xu XM (eds.) Neural Regeneration (pp. 129–150). Elsevier: Amsterdam, Netherlands. 2015. https://doi.org/10.1016/B978-0-12-801732-6.00008-2.

[118] Verhovshek T, Rudolph LM, Sengelaub DR. Brain-derived neurotrophic factor and androgen interactions in spinal neuromuscular systems. Neuroscience. 2013; 239: 103–114. https://doi.org/10.1016/j.neuroscience.2012.10.028.

[119] Jaiswal PB, Tung JK, Gross RE, English AW. Motoneuron activity is required for enhancements in functional recovery after peripheral nerve injury in exercised female mice. Journal of Neuroscience Research. 2020; 98: 448–457. https://doi.org/10.1002/jnr.24109.

[120] Acosta MC, Copley PA, Harrell JR, Wilhelm JC. Estrogen signaling is necessary for exercise-mediated enhancement of motoneuron participation in axon regeneration after peripheral nerve injury in mice. Developmental Neurobiology. 2017; 77: 1133–1143. https://doi.org/10.1002/dneu.22501.

[121] Park JS. Treadmill exercise enhance the peripheral nerve regeneration by induce the macrophages. Information. 2017; 20: 7581–7588.

[122] Chen YW, Li YT, Chen YC, Li ZY, Hung CH. Exercise training attenuates neuropathic pain and cytokine expression after chronic constriction injury of rat sciatic nerve. Anesthesia and

Analgesia. 2012; 114: 1330–1337. https://doi.org/10.1213/ANE.0b013e31824c4ed4.

[123] Tsai KL, Huang PC, Wang LK, Hung CH, Chen YW. Incline treadmill exercise suppresses pain hypersensitivity associated with the modulation of pro-inflammatory cytokines and anti-inflammatory cytokine in rats with peripheral nerve injury. Neuroscience Letters. 2017; 643: 27–31. https://doi.org/10.1016/j.neulet.2017.02.021.

[124] Taguchi S, Kami K, Tajima F, Senba EJ. Increase of M2 macrophages in injured sciatic nerve by treadmill running may contribute to the relief of neuropathic pain. Pain Research. 2015; 30: 135–147.

[125] Calik MW, Shankarappa SA, Langert KA, Stubbs EB, Jr. Forced exercise preconditioning attenuates experimental autoimmune neuritis by altering Th1 lymphocyte composition and egress. ASN Neuro. 2015; 7: 1759091415595726. https://doi.org/10.1177/1759091415595726.

[126] Ashour H, Rashed L, Sabry MJ. IL-6/STAT3 growth signalling induced by exercise conditioning promotes regeneration of injured rat sciatic nerve: return to an old cytokine. Comparative Exercise Physiology. 2017; 13: 45–52. https://doi.org/10.3920/CEP160028.

[127] Hosseini Askarabadi S, Mirnasori R, Rahmati MJ. Effect of endurance training on peripheral neuropathic pain and inflammatory mediators in diabetic rats. Report of Health Care. 2018; 4: 77–87.

[128] Sakita M, Murakami S, Fujino H, Hayashi S, Kameyama K, Saito T, et al. Remodeling of myelinated fibers and internal capillaries in distal peripheral nerves following aerobic exercise in aged rats. Journal of Applied Physiology (Bethesda, Md.: 1985). 2018; 125: 1051–1061. https://doi.org/10.1152/japplphysiol.00257.2018.

[129] Huang YK, Chang CC, Lin PX, Lin BS, Yao-Kuang Huang, Chang-Cheng Chang, et al. Quantitative evaluation of rehabilitation effect on peripheral circulation of diabetic foot. IEEE Journal of Biomedical and Health Informatics. 2018; 22: 1019–1025. https://doi.org/10.1109/JBHI.2017.2726540.

[130] Gholami F, Khaki R, Mirzaei B, Howatson G. Resistance training improves nerve conduction and arterial stiffness in older adults with diabetic distal symmetrical polyneuropathy: A randomized controlled trial. Experimental Gerontology. 2021; 153: 111481. https://doi.org/10.1016/j.exger.2021.111481.

[131] Zanjani SB, Chodari L, Bavil FM, Sadeghzadeh P, Shahabi P. Effect of voluntary exercise on intracellular signalling pathways of angiogenesis in the sciatic nerve of type 1 diabetic castrated male rats. Physiology International. 2019; 106: 39–47. https://doi.org/10.1556/2060.106.2019.08.

[132] Gholami F, Nikookheslat S, Salekzamani Y, Boule N, Jafari A. Effect of aerobic training on nerve conduction in men with type 2 diabetes and peripheral neuropathy: A randomized controlled trial. Neurophysiologie Clinique Clinical Neurophysiology. 2018; 48: 195–202. https://doi.org/10.1016/j.neucli.2018.03.001.

[133] Romeo-Guitart D, Leiva-Rodriguez T, Forés J, Casas C. Improved motor nerve regeneration by SIRT1/Hif1a-mediated autophagy. Cells. 2019; 8: 1354. https://doi.org/10.3390/cells8111354.

[134] Huang HC, Chen L, Zhang HX, Li SF, Liu P, Zhao TY, et al. Autophagy promotes peripheral nerve regeneration and motor recovery following sciatic nerve crush injury in rats. Journal of Molecular Neuroscience: MN. 2016; 58: 416–423. https://doi.org/10.1007/s12031-015-0672-9.

[135] Kumar S, Behera S, Basu A, Dey S, Ghosh-Roy A. Swimming exercise promotes post-injury axon regeneration and functional restoration through AMPK. eNeuro. 2021; 8: ENEURO.0414–20.2021. https://doi.org/10.1523/ENEURO.0414-20.2021.

[136] Seo TB, Oh MJ, Yoon JH, Yoon SJ, Park HC, Kang KH. Effect of treadmill training on Erk-mediated Schwann cell proliferation and axonal regrowth in the regenerating sciatic nerves. International Journal of Human Movement Science. 2008; 2: 63–77.

[137] Kim JE, Cho YH, Seo TB. Treadmill exercise activates ATF3 and Erk1/2 downstream molecules to facilitate axonal regrowth after sciatic nerve injury. Journal of Exercise Rehabilitation. 2020; 16: 141–147. https://doi.org/10.12965/jer.2040188.094.

[138] Kim JE. The effect of treadmill exercise on axonal regrowth and muscle hypertrophy via activation of the Akt/mTOR signaling pathway after sciatic nerve injury. Journal of Converging Sport and Exercise Sciences. 2020; 18: 209–217. https://doi.org/10.22997/jcses.2020.18.2.209.

[139] Asensio-Pinilla E, Udina E, Jaramillo J, Navarro X. Electrical stimulation combined with exercise increase axonal regeneration after peripheral nerve injury. Experimental Neurology. 2009; 219: 258–265. https://doi.org/10.1016/j.expneurol.2009.05.034.

[140] Lopes BC, Medeiros LF, Silva de Souza V, Cioato SG, Medeiros HR, Regner GG, et al. Transcranial direct current stimulation combined with exercise modulates the inflammatory profile and hyperalgesic response in rats subjected to a neuropathic pain model: Long-term effects. Brain Stimulation. 2020; 13: 774–782. https://doi.org/10.1016/j.brs.2020.02.025.

[141] Cobianchi S, Casals-Diaz L, Jaramillo J, Navarro X. Differential effects of activity dependent treatments on axonal regeneration and neuropathic pain after peripheral nerve injury. Experimental Neurology. 2013; 240: 157–167. https://doi.org/10.1016/j.expneurol.2012.11.023.

[142] Huang X, Jiang Z, Sun H, Xie B, Lu F, Huang W, et al. The effect of a high-quality nursing model employing low-frequency pulse electrical stimulation combined with early systemic functional exercises on the function of the affected limb in brachial plexus injury patients. American Journal of Translational Research. 2021; 13: 4939–4948.

[143] Kim YE. Effects of pain and functional recovery when low frequency electrical stimulation and aqua-exercise applied to sciatic nerve injured rats. Journal of the Korean Academy of Clinical Electrophysiology. 2008; 6: 17–30.

[144] Park S, Liu CY, Ward PJ, Jaiswal PB, English AW. Effects of repeated 20-Hz electrical stimulation on functional recovery following peripheral nerve injury. Neurorehabilitation and Neural Repair. 2019; 33: 775–784. https://doi.org/10.1177/1545968319862563.

[145] Hung CH, Huang PC, Tzeng JI, Wang JJ, Chen YW. Therapeutic ultrasound and treadmill training suppress peripheral nerve injury-induced pain in rats. Physical Therapy. 2016; 96: 1545–1553. https://doi.org/10.2522/ptj.20140379.

[146] Huang PC, Tsai KL, Chen YW, Lin HT, Hung CH. Exercise combined with ultrasound attenuates neuropathic pain in rats associated with downregulation of IL-6 and TNF-α, but with upregulation of IL-10. Anesthesia and Analgesia. 2017; 124: 2038–2044. https://doi.org/10.1213/ANE.0000000000001600.

[147] Ha MS, Baek IH, Lee HO, Kim SY, Rho MH. The effects of exercise and low-power laser on the changes of CMAP and histologic factor in peripheral nerve injured rats. Korean Journal of Physical Therapy Science. 2005; 12: 43–55.

[148] Rosa Junior GM, Magalhães RMG, Rosa VC, Bueno CRdS, Simionato LH, Bortoluci CH. Effect of the laser therapy in association with swimming for a morphological nerve repair and functional recovery in rats submitted to sciatic axonotmesis. Fisioterapia e Pesquisa. 2016; 23: 12–20. https://doi.org/10.1590/1809-2950/13929623012016.

[149] Kim J-H, Sutradhar B, Choi SH, Kim G. Treadmill with electro-acupuncture promotes nerve fiber regeneration with retaining muscle activity after sciatic nerve injury in rat. Journal

of Biomedical Research. 2011; 12: 70–78.

[150] Hajimoradi M, Fazilati M, Gharib-Naseri MK, Sarkaki A. Gallic acid and exercise training improve motor function, nerve conduction velocity but not pain sense reflex after experimental sciatic nerve crush in male rats. Avicenna Journal of Phytomedicine. 2015; 5: 288–297.

[151] Baratzadeh H, Safakhah HA, Rashidy_Pour A, Jarrahi M. The effects of co-administration of curcumin and forced exercise on electrophysiological responses in the neuropathic pain model of chronic constriction injury of peripheral nerves in rats. Koomesh. 2023; 25: e154152.

[152] Baratzadeh H, Safakhah HA, Rashidy-Pour A, Talebi A, Jarrahi M. Effects of co-administration of chronic curcumin and forced exercise on behavioral pain responses in the neuropathic pain model of chronic constriction injury in rats. Koomesh. 2022; 24: 366–375.

[153] Chis IC, Clichici A, Nagy AL, Oros A, Catoi C, Clichici S. Quercetin in association with moderate exercise training attenuates injuries induced by experimental diabetes in sciatic nerves. Journal of Physiology and Pharmacology: an Official Journal of the Polish Physiological Society. 2017; 68: 877–886.

[154] Levi AD, Burks SS, Anderson KD, Dididze M, Khan A, Dietrich WD. The use of autologous schwann cells to supplement sciatic nerve repair with a large gap: first in human experience. Cell Transplantation. 2016; 25: 1395–1403. https://doi.org/10.3727/096368915X690198.

[155] Goulart CO, Jürgensen S, Souto A, Oliveira JT, de Lima S, Tonda-Turo C, et al. A combination of Schwann-cell grafts and aerobic exercise enhances sciatic nerve regeneration. PloS One. 2014; 9: e110090. https://doi.org/10.1371/journal.pone.0110090.

[156] Wariyar SS, Ward PJ. Application of electrical stimulation to enhance axon regeneration following peripheral nerve injury. Bio-protocol. 2023; 13: e4833. https://doi.org/10.21769/BioProtoc.4833.

[157] Marqueste T, Alliez JR, Alluin O, Jammes Y, Decherchi P. Neuromuscular rehabilitation by treadmill running or electrical stimulation after peripheral nerve injury and repair. Journal of Applied Physiology (Bethesda, Md.: 1985). 2004; 96: 1988–1995. https://doi.org/10.1152/japplphysiol.00775.2003.

[158] Chiaramonte R, Pavone V, Testa G, Pesce I, Scaturro D, Musumeci G, et al. The role of physical exercise and rehabilitative implications in the process of nerve repair in peripheral neuropathies: A systematic review. Diagnostics (Basel, Switzerland). 2023; 13: 364. https://doi.org/10.3390/diagnostics13030364.

[159] Oliveira FB, Pereira VMD, da Trindade APNT, Shimano AC, Gabriel RECD, Borges APO. Action of therapeutic laser and ultrasound in peripheral nerve regeneration. Acta Ortopedica Brasileira. 2012; 20: 98–103. https://doi.org/10.1590/S1413-78522012000200008.

[160] dos Reis FA, Belchior ACG, de Carvalho PDTC, da Silva BAK, Pereira DM, Silva IS, et al. Effect of laser therapy (660 nm) on recovery of the sciatic nerve in rats after injury through neurotmesis followed by epineural anastomosis. Lasers in Medical Science. 2009; 24: 741–747. https://doi.org/10.1007/s10103-008-0634-3.

[161] Wang Y, Tang Q, Zhu L, Huang R, Huang L, Koleini M, et al. Effects of treatment of treadmill combined with electroacupuncture on tibia bone mass and substance pexpression of rabbits with sciatic nerve injury. PloS One. 2016; 11: e0164652. https://doi.org/10.1371/journal.pone.0164652.

[162] Caillaud M, Chantemargue B, Richard L, Vignaud L, Favreau F, Faye PA, et al. Local low dose curcumin treatment improves functional recovery and remyelination in a rat model of sciatic nerve crush through inhibition of oxidative stress. Neuropharmacology. 2018; 139: 98–116. https://doi.org/10.1016/j.neuropharm.2018.07.001.