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Effects of physiotherapy-based interventions on functional neural recovery following peripheral nerve injury in rodent models - a systematic review

Efectos de las intervenciones fisioterapéuticas en la recuperación neuronal funcional tras una lesión nerviosa periférica en modelos de roedores: una revisión sistemática

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SUMMARY

Peripheral nerve injuries often lead to significant motor and sensory impairments and seldom achieve complete functional recovery following surgical reconstruction; thus, it is crucial to integrate rehabilitation methods that promote peripheral nerve regeneration. A systematic review analyzed 22 preclinical studies examining the impact of physiotherapy interventions on neural recovery following peripheral nerve injury; the research covered a wide variety of physiotherapy interventions and outcomes. The search adhered to PRISMA guidelines. Research articles on various physiotherapy methods, such as exercise, neuromodulation techniques, and electrotherapy, for the rehabilitation of neural functions were retrieved from electronic databases. Overall trends indicated consistent enhancements in functional recovery and nerve regeneration with exercise-based and neuromodulatory approaches compared to electrotherapeutic methods. Certain electrotherapy modalities have shown variable and inconsistent outcomes, with treatment success frequently linked to the dosage and duration of application. Many studies were not comparable due to the existing variability in injury models, physiotherapy intervention methods, and outcome measures used across the research. The existing evidence suggests that physiotherapy is crucial for restoring function and regenerating peripheral nerves, underscoring the need for standardized rehabilitation protocols and additional research to inform clinical rehabilitation strategies for peripheral nerve injuries.

Keywords: *Peripheral nerve injuries, nerve regeneration, physical therapy modalities, exercise therapy, quality of life, well-being*

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RESUMEN

Las lesiones de nervios periféricos suelen provocar importantes deterioros motores y sensoriales y rara vez logran una recuperación funcional completa tras la reconstrucción quirúrgica. Por lo tanto, es crucial integrar métodos de rehabilitación que promuevan la regeneración de los nervios periféricos. Esta revisión sistemática analizó 22 estudios preclínicos que examinaron el impacto de las intervenciones de fisioterapia en la recuperación neural tras una lesión de nervios periféricos; la investigación abarcó una amplia variedad de intervenciones y resultados de fisioterapia. La búsqueda se ajustó a las directrices PRISMA. Se exploraron artículos de investigación sobre diferentes métodos de fisioterapia, como el ejercicio, las técnicas de neuromodulación y la electroterapia, para la rehabilitación de las funciones neurales en bases de datos electrónicas. Las tendencias generales indicaron mejoras consistentes en la recuperación funcional y la regeneración nerviosa con enfoques basados en el ejercicio y la neuromodulación, en comparación con los métodos electroterapéuticos. Ciertas modalidades de electroterapia han mostrado resultados variables e inconsistentes, y el éxito del tratamiento se ha relacionado con frecuencia con la dosis y la duración de la aplicación. Muchos estudios resultaron incomparables debido a las variaciones en los modelos de lesión, los métodos de intervención fisioterapéutica y las medidas de resultado empleadas en la investigación. La evidencia existente sugiere que la fisioterapia es crucial para restaurar la función y regenerar los nervios periféricos, lo que resalta la necesidad de protocolos de rehabilitación estandarizados y de investigación adicional para contribuir al desarrollo de estrategias clínicas de rehabilitación para las lesiones de nervios periféricos.

Palabras clave: *Lesiones de nervios periféricos, regeneración nerviosa, modalidades de fisioterapia, terapia con ejercicios, plasticidad neuronal, modelos animales, calidad de vida, bienestar*

INTRODUCTION

The peripheral nervous system (PNS) is a highly complex and multifunctional structure. Its primary role is to transmit information from the central nervous system (CNS) to peripheral target organs, ensuring that effector tissues receive and interpret neural commands appropriately. Additionally, the PNS collects sensory information from the periphery, transduces it into nerve impulses, processes it, and relays it back to the CNS for integration and response (1). Peripheral nerve injuries (PNIs) comprise a broad spectrum of conditions that damage one or more peripheral nerves, potentially resulting in partial or complete loss of motor, sensory, or autonomic function. Trauma remains one of the most common etiologies of PNI. In the upper limb, the radial nerve is the most frequently affected, followed by the median and ulnar nerves. In the lower limb, the sciatic nerve is the most commonly injured, with the peroneal nerve representing the second most frequently involved structure (2). The annual incidence is approximately 45 cases per 100,000 population. About 5% of polytrauma cases are complicated by severe peripheral nerve injury (3). Nerve injuries may result from crush, laceration, stretching, or prolonged compression. The two most commonly used classification systems are those of Seddon and Sunderland. Seddon (1943) classified nerve injuries into neurapraxia, axonotmesis, and neurotmesis. Sunderland later expanded this into a five-degree classification based on the extent of structural damage, with neurapraxia corresponding to first-degree injury, axonotmesis to second-degree injury, and neurotmesis to fifth-degree injury (4). Nerve repair can occur through remyelination, collateral sprouting from intact axons, or true axonal regeneration. In partial nerve injuries, collateral sprouting is an effective compensatory mechanism as long as a sufficient proportion of axons remains intact. When less than 20–30% of axons are damaged, functional recovery is achieved predominantly through collateral sprouting, typically within 2–6 months. In contrast, injuries involving more than 90% axonal loss depend primarily on axonal regeneration from the proximal stump, a process whose success is strongly influenced by the distance to the target tissue (5).

These outcomes may include complete loss or only partial recovery of motor and/or sensory function, along with persistent pain, muscle atrophy, and significant weakness, all of which can ultimately lead to permanent disability. One of the principal factors limiting successful nerve healing is the development of perineural scarring and fibrosis at the site of injury or repair (6). Electromyography (EMG) is the preferred diagnostic modality for assessing the location and severity of peripheral nerve injuries (PNIs).

Magnetic resonance imaging provides valuable complementary information, particularly for identifying root avulsion. Electrodiagnostic evaluation within the first 6 months after a PNI is essential to determine the extent of axonal degeneration (7). The surgical management of PNIs aims to restore functional reinnervation through several established techniques, including neurorrhaphy, autologous nerve grafting, conduit-assisted nerve repair, neurotization, and other reconstructive approaches (8). The advent of microsurgical nerve repair has marked a significant advancement in the field. Nevertheless, despite meticulous surgical technique and the availability of multiple repair strategies, complete functional recovery—especially regarding motor outcomes—remains uncommon (9,10).

Rehabilitation strategies play a crucial role after PNI to reduce lasting physical impairments, encourage functional adjustments, and enhance quality of life and overall well-being. Range of motion, stretching routines, and biofeedback are effective in preventing contractures and additional deformities. Techniques for sensory re-education have been created to enhance sensory function following reinnervation and to preserve cortical sensory organization, although current evidence regarding their effectiveness is limited. These strategies might improve the chances of nerve regeneration and functional recovery, contributing to innovation in rehabilitation (11).

Research has historically relied on experimental animals, and the findings produced have certainly enhanced the quality and effectiveness of medicine and health (12). A perfect translational animal model should replicate the mechanisms underlying human peripheral nerve injuries (13). Rodent models have been crucial in enhancing our understanding of peripheral nerve regeneration. These models are preferred for their ability to evaluate sensorimotor function, electrophysiological responses, immunohistological alterations, and radiographic findings following nerve injury. Rodent models are suitable for conducting nerve procedures and accurately replicating peripheral nerve injuries. They serve as a dependable research model for investigating nerve regeneration and assessing novel therapies for peripheral nerve injury (14,15). Thus, this systematic review aims to comprehensively evaluate and synthesize preclinical evidence on the effectiveness of physiotherapy interventions in promoting neural regeneration and functional improvement following peripheral nerve injury in rodent models, with particular attention to functional, electrophysiological, and histological outcomes.

METHODOLOGY

A systematic literature search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic and well-defined search strategy was developed to identify experimental studies evaluating physiotherapy interventions aimed at enhancing functional recovery following peripheral nerve injuries in rodent models. A comprehensive literature search was conducted across the following electronic databases: PubMed, ScienceDirect, Google Scholar, PEDro, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Library. All databases were searched from their inception through December 2025, with the final search performed on 20 December 2025. The search strategy involved three main domains: 1) peripheral nerve injury and its recovery; 2) physiotherapy intervention techniques; 3) experimental rodent models in preclinical studies. A comprehensive search strategy was developed using a combination of Medical Subject Headings (MeSH) and relevant keywords related to physiotherapy interventions for peripheral nerve injury and nerve regeneration. The list of MeSH keywords was elaborated and checked for their equivalent free-text terms, which were combined with Boolean operators (AND, OR) to ensure an effective approach while yielding adequate results. Several keyword combinations pertinent to peripheral nerve injuries and recovery, as well as to their rehabilitation, were combined with their MeSH numbers in the selected electronic databases. The following Boolean search strategy

was applied across the databases: ("peripheral nerve injury" OR "nerve transection" OR "nerve crush" OR "nerve regeneration" OR "peripheral nerve repair") AND ("physiotherapy" OR "physical therapy" OR "exercise therapy" OR "treadmill exercise" OR "swimming exercise" OR "strength training" OR "massage therapy" OR "nerve manipulation" OR "electrotherapy" OR "laser therapy" OR "infrared therapy" OR "ultrasound therapy" OR "extracorporeal shockwave therapy") AND ("rodent" OR "rat" OR "rats" OR "mouse" OR "murine model"). In addition, reference lists of relevant articles were manually screened to identify any additional eligible studies.

Data collection criteria

The studies included in this systematic review were selected according to predefined eligibility criteria encompassing study design, animal characteristics, type of peripheral nerve injury, intervention modality, and relevant outcome measures. Experimental studies published between 2015 and 2025 were screened for inclusion. Eligible studies employed rodent models of peripheral nerve injury, including crush, transection, compression, and reconstruction paradigms. The review focused on physiotherapeutic rehabilitation interventions administered following nerve injury, such as exercise therapy, neuromodulatory techniques, and electrotherapeutic modalities; studies comparing pharmacological interventions with physical activity–based approaches were also considered. Studies were included only if they reported at least one outcome measure pertinent to nerve regeneration or functional recovery, including functional performance assessments, electrophysiological indices, histological or histomorphometric analyses, and measures of neuromuscular function, thereby enabling evaluation from both biological and functional perspectives. Only full-text articles published in English were included. Non-rodent studies, non-randomized designs, review articles, conference abstracts, and studies lacking appropriate outcome measures were excluded. For each included study, data were systematically extracted regarding the author(s), year of publication, methodological design, animal characteristics, nerve injury model, intervention protocol, outcome measures, and principal findings.

Methodological quality

The quality of the methodology was evaluated using the SYRCLE Risk of Bias Assessment Tool for Animal Studies (38), as per Hooijmans et al. (38), to assess internal validity across all preclinical rodent studies measuring physiotherapy intervention following peripheral nerve injury. Each of the 22 studies was evaluated independently using the 10 SYRCLE Risk of Bias domains, with predefined criteria applied to assess methodological quality and report transparency, thereby assigning each domain a low, high, or uncertain risk rating.

The SYRCLE risk of bias evaluation tool comprises ten methodological areas that address the six main forms of biases that can occur, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and additional potential biases. A significant risk of bias was reported when clear methodological flaws were evident. In contrast, an unclear risk of bias was concluded when insufficient methodological details were available to make a decision. A low risk of bias occurred when clear methods were detailed and adhered to. Two separate reviewers assessed the qualifying studies to minimize bias and personal opinions.

RESULTS

Study selection criteria

A total of 700 records were identified through extensive search of the following electronic databases. After removing duplicate records, 435 records remained, which were assessed by title and abstract. After reviewing records by title and abstract, 365 studies were eliminated for not meeting the inclusion selection criteria.

Upon completion of the screening phase, 70 full-text articles were evaluated for their eligibility. After reviewing the full-text articles, 48 were excluded due to improper research methodologies and results outside the specific research parameters. Excluded studies included those without rodent models of experimentation, did not report peripheral nerve injury or physiotherapy interventions, did not relate to the research question, focused only on pharmacological interventions, were non-randomized or observational study designs, or lacked functional, electrophysiological, or neural regeneration outcome data for assessment. Articles that were duplicates or had no text available in full were also excluded. The final number of studies meeting eligibility criteria for inclusion in the systematic review was 22. Figure 1 shows a PRISMA flowchart illustrating the study selection process at each review phase. The study screening and assessment for eligibility were conducted independently by two reviewers, and both reviewers followed the same established inclusion/exclusion criteria. Differences of opinion or doubts were resolved through discussion, and if consensus was not achieved, a third reviewer was brought in after repeated full-text evaluation.

Study Characteristics

Table 1 summarizes the key characteristics of the 22 studies included in this review.

This systematic review synthesizes findings from 22 experimental studies evaluating the effects of physiotherapy interventions on functional recovery in rodent models of peripheral nerve injury. The primary objective was to describe the physiotherapy techniques employed to facilitate nerve regeneration and to classify these interventions into two major categories for structured comparison: exercise-based strategies and electrotherapeutic modalities.

Exercise-related interventions included treadmill training, swimming, and resistance-based protocols. Task-specific strengthening approaches incorporated both concentric and eccentric exercises. Additional neurostimulation-related

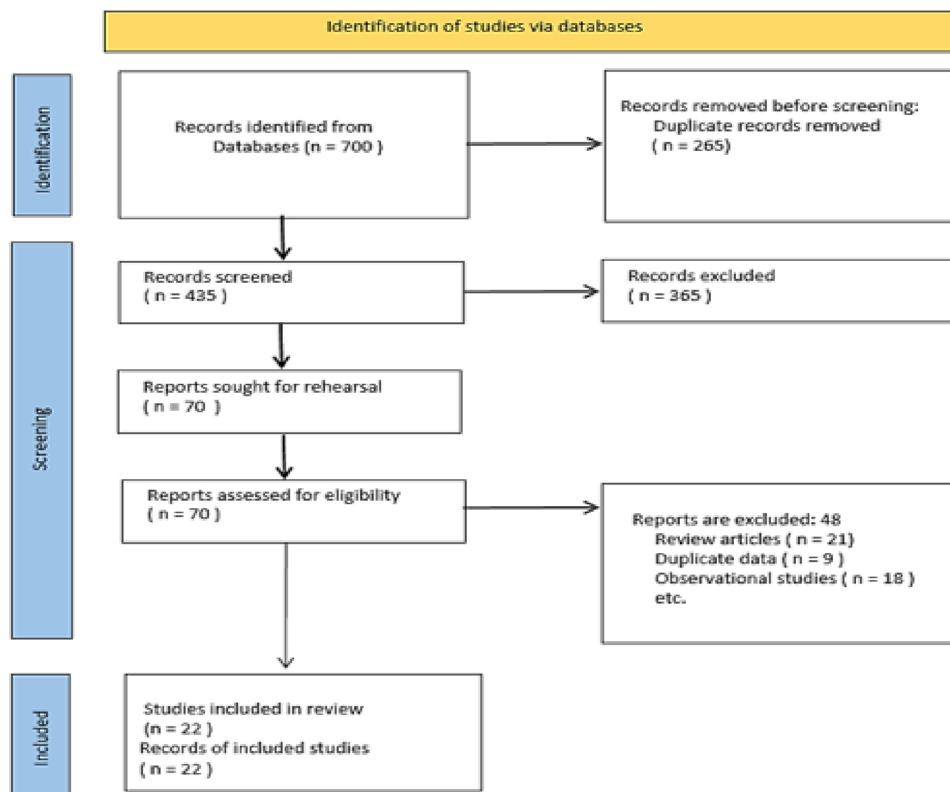

Figure 1. PRISMA Flowchart

Table 1. Study characteristics

Author name and year of publication	Study Title	Rodent Model	Gender	Surgical Intervention	Intervention	Intervention Characteristics	Outcome Measure	Reflection
Eftekari et al., 2025 (16)	Combined Central and Peripheral Nerve Stimulation Improves Functional Recovery of Mixed Peripheral nerve injury in a rat forelimb model	Lewis rats	Male (12)	Median and Ulnar nerve transection	Central and peripheral nerve stimulation	Low-intensity electrical nerve stimulation – Single-session peripheral nerve stimulation applied at low intensity to the injured nerve	Skilled forelimb reaching task (Montoya staircase test) Histological evaluation	**Functional recovery:** Combined central and peripheral nerve stimulation resulted in significantly better forelimb functional recovery compared to control and peripheral stimulation alone. Animals demonstrated improved skilled grasping performance. **Neural outcomes:** Histological analysis showed enhanced axonal regeneration and reinnervation in the combined stimulation group, indicating a synergistic neuromodulatory effect.
Bayburt et al., 2025 (17)	The effect of high-intensity versus photobiomodulation therapy on the regeneration of the sciatic nerve following crush injury: an animal study	Wistar Albino rats	Male (33)	Left sciatic nerve crush injury	Laser therapy	High-intensity laser therapy (HILT) and photobiomodulation (PBMT) – HILT (120 J, 1064 nm) and PBM (2.4 J, 650 nm) administered every 3 days for 10 sessions; compared with control.	Sciatic functional index (SFI) Electromyographic evaluation Histomorphometric evaluation	**Functional Recovery (SFI):** HILT significantly improved functional recovery, showing better SFI scores at postoperative days 21 and 28 compared to PBMT and control. PBMT showed no significant functional improvement over control. **Electrophysiological Outcomes (EMG):** HILT demonstrated significantly better latency and duration values, indicating improved nerve conduction. EMG amplitude showed no significant difference between groups. PBMT did not differ significantly from control.

Table 1. Study characteristics continuation…

Al-Sarraf et al., 2025 (18)	Resistance exercise promotes functional recovery from peripheral nerve injury	Sprague Dawley rats	Male (30)	Moderate sciatic crush injury (SCI) and sciatic nerve compression (SNC)	Resistance exercise	Progressive resistance exercise – Tunnel and pulley-based resistance training with graded load progression; performed 3 times/ week for 10 weeks.	Toe spread reflex (TSR) Foot positioning Extensor postural thrust (EPT) CatWalk tests	**<u>Functional Motor Outcomes:</u>** SNC and SCI significantly reduced Toe spread reflex, Foot positioning, and Extensor postural thrust scores. Resistance exercise enhanced recovery after SCI, improving TSR and EPT at later time points, but had no added benefit after SNC. **<u>Gait Analysis:</u>** Both injuries impaired paw contact area, print area, and step intensity, with prolonged swing phase. Resistance exercise did not significantly improve gait parameters following SNC or SCI.
Karakoç et al., 2025 (19)	Evaluation of Dexamethasone and Swimming Exercise as Complementary Interventions in a Rat Sciatic Nerve Injury Model	Wistar albino rats	Male (40)	Sciatic nerve dissection	Swimming exercise	Swimming exercise ± pharmacological support – Swimming training (20 min/session, 3 times/week for 21 days) applied alone or combined with dexamethasone following nerve injury.	Sciatic functional index Biochemical analysis Histological evaluation	**<u>Functional recovery:</u>** Dexamethasone and swimming exercise each improved SFI, with the combined treatment showing the greatest motor recovery. **<u>Nerve regeneration:</u>** Combination therapy resulted in better axonal regeneration and remyelination, with higher myelinated fiber density and improved g-ratio.

Table 1. Study characteristics continuation…

Taboada et al., 2025 (20)	Combination of Treadmill Training and Inosine Enhance Nerve Regeneration and Functional Recovery in Mice Sciatic Nerve Transection	C57/Bl6 mice	Male (24)	Sciatic nerve transection	Treadmill training	Treadmill exercise with inosine supplementation – Moderate-intensity treadmill walking (6–12 m/min, 10 min/session, 3 times/week for 8 weeks) with or without inosine administration.	Sciatic functional index Von Frey test Pinprick test Morphometric assessment Histological assessment	**Functional recovery:** Inosine + treadmill training produced the best gait and sensory recovery (SFI, pinprick, von Frey) compared with control or single treatments. **Nerve regeneration:** Combined therapy showed greater axonal regeneration and remyelination, with improved CMAP amplitudes and better nerve structure than control
Kawai et al., 2023 (21)	Ultrasound therapy for a week promotes regeneration and reduces proinflammatory macrophages in a rat sciatic nerve autograft model	Lewis rats	Male (39)	Sciatic nerve autograft surgery	Ultrasound therapy	Therapeutic ultrasound stimulation (UST) – Pulsed ultrasound (1 MHz, 140 mW/cm², 20% duty cycle) applied for 5 min/day, 5 days/week for 1 or 4 weeks.	Sciatic functional index Histological evaluation Electrophysiological evaluation	**Functional recovery:** Ultrasound-treated rats showed significant improvement in SFI compared to controls. **Nerve regeneration:** Increased axon number, axon diameter, and myelin thickness, with a more optimal g-ratio, indicating enhanced regeneration across the autograft

Table 1. Study characteristics continuation…

Santiago de Lima Figueiredo et al., 2022 (22)	Use of aerobic treadmill exercises on nerve regeneration after the sciatic nerve injury in spontaneously hypertensive rats	Isogenic rats	Male (30)	Sciatic nerve dissection	Treadmill training	Post-graft treadmill rehabilitation – Progressive treadmill training (5–20 m/min, 10–20 min/session) initiated after nerve grafting and continued for 6 weeks.	Sciatic Functional Index Nerve Morphometry and Morphological nerve analysis Motor neuron counts - Fluoro Gold	Functional Recovery (Sciatic Functional Index): Aerobic treadmill exercise did not significantly improve functional recovery after sciatic nerve injury in spontaneously hypertensive rats. Sciatic Functional Index values were similar between treadmill-trained and non-trained grafted groups, indicating no additional benefit of exercise on gait and functional nerve repair. Nerve Morphometry and Histological Regeneration: Morphometric analysis showed no significant differences between exercised and non-exercised groups in axonal diameter, fiber diameter, myelin sheath thickness, or G-ratio. Both groups exhibited inferior structural regeneration compared to sham controls, suggesting that treadmill exercise did not enhance axonal or myelin recovery. Motor Neuron Regeneration: Retrograde labeling demonstrated comparable numbers of regenerated motor neurons in the exercised and non-exercised groups. This indicates that aerobic treadmill training did not promote additional motor neuron reinnervation following sciatic nerve graft repair.

Table 1. Study characteristics continuation…

Kong et al., 2022 (23)	Exercise facilitates regeneration after severe nerve transection and further modulates neural plasticity	Sprague-Dawley rats	Female (16)	Sciatic nerve transection followed by an autograft surgery	Treadmill training	Incremental treadmill training – Low-to-moderate intensity treadmill exercise with gradual speed increments up to 8 m/min; 5 days/week for 6 weeks.	Von frey test Hargreaves heat latency Walking track analysis Histological evaluation Electrophysiological evaluation	**Sensory & Motor Recovery:** Treadmill exercise significantly improved sensory function and locomotor performance following severe nerve transection, with better withdrawal thresholds and gait parameters than in non-exercise controls. **Neural & Plasticity Outcome:** Exercise enhanced axonal regeneration and remyelination, reduced inflammation and muscle atrophy, and partially reversed maladaptive central and peripheral neural plasticity.
Heinzel et al., 2022 (24)	ESWT Diminishes Axonal Regeneration following Repair of the Rat Median Nerve with Muscle-In-Vein Conduits but not after Autologous nerve grafting	Lewis rats	Male (56)	Median nerve reconstruction with autologous nerve grafts (ANG) or with Muscle-In-Vein Conduits (MVC)	Extracorporeal shockwave therapy (ESWT)	Extracorporeal shockwave therapy (ESWT) post-surgery – Single ESWT session (300 impulses, 3 Hz, 0.1 mJ/mm²) applied following nerve reconstruction procedures.	Computerized gait analysis Grasping test Electrophysiological evaluation Histological evaluation	**Functional outcomes:** ESWT did not significantly improve functional recovery compared to non-ESWT controls in either autologous nerve graft or muscle-in-vein conduit groups over the 12-week follow-up. **Grasp test:** ESWT did not significantly improve grasp strength compared to non-ESWT controls in either repair model. Grasp performance remained inferior in the muscle-in-vein conduit + ESWT group. **Gait analysis:** No significant gait improvement was observed with ESWT in either repair model. Muscle-in-vein conduit + ESWT showed poorer gait recovery, while autologous graft groups showed no ESWT-related difference.

Table 1. Study characteristics continuation…

de Oliveira Marques et al., 2021 (25)	Whole-body vibration therapy does not improve the peripheral nerve regeneration in an experimental model	Wistar rats	Male (53)	Right Sciatic nerve crush injury	Whole-body vibration therapy	Whole-body vibration (WBV) therapy – WBV protocol combining low- and high-frequency exposure (15–30 Hz) for 15 min/session; 5 days/week for 5 weeks.	Sciatic Functional Index Horizontal Ladder Rung Walking Test Narrow Beam Test Histomorphometric analysis	**Functional recovery:** Whole-body vibration therapy did not produce significant improvement in peripheral nerve regeneration in the experimental model. Functional recovery, electrophysiological measures, and histological indicators of nerve repair showed no meaningful differences between the vibration-treated group and the control group, indicating that WBV offered no additional benefit for peripheral nerve regeneration under the study conditions
Li et al., 2021 (26)	Low-intensity extracorporeal shock wave therapy promotes recovery of sciatic nerve injury and the role of mechanically sensitive YAP/TAZ signaling pathway for nerve regeneration	Sprague-Dawley rats	Male (40)	Sciatic nerve crush injury	Extracorporeal shock-wave therapy (ESWT)	Repeated ESWT for nerve injury – ESWT (0–0.15 mJ/mm², 500 shocks, 3 Hz) was delivered 3 times/week for 3 weeks in sciatic nerve injury models.	Sciatic functional Index Von frey test Histological evaluation	**Functional recovery:** Li-ESWT significantly improved motor (SFI) and sensory (von Frey) recovery after sciatic nerve injury compared to untreated injury. **Overall:** Li-ESWT accelerates sciatic nerve regeneration and functional recovery via mechanosensitive YAP/TAZ pathway activation.

Table 1. Study characteristics continuation…

Seo et al., 2021 (27)	Effect of Botulinum Toxin Injection and Extracorporeal Shock Wave Therapy on Nerve Regeneration in Rats with Experimentally Induced Sciatic Nerve Injury	Sprague-Dawley rats	Not defined (45)	Right sciatic nerve crush injury	Extracorporeal shock-wave therapy (ESWT)	Single-dose ESWT intervention – One-time ESWT application (400 pulses, 0.098 mJ/mm², 4 Hz) compared with the botulinum toxin group (administered botulinum toxin after nerve injury) and the control groups.	Sciatic functional index analysis Electro-physiological studies	**Nerve regeneration:** Rats treated with botulinum toxin (BoNT) and/or extracorporeal shock wave therapy (ESWT) showed significantly enhanced sciatic nerve regeneration compared to injured, untreated control rats. **Functional recovery:** BoNT-treated rats and ESWT-treated rats demonstrated improved motor function and earlier functional recovery on gait/walking track assessments. **Comparative effects:** ESWT-treated rats showed more pronounced axonal regeneration, while BoNT-treated rats showed improved neuromuscular conditions that supported functional recovery.

Table 1. Study characteristics continuation…

Ito et al., 2020 (28)	Ultrasound therapy with optimal intensity facilitates peripheral nerve regeneration in rats through suppression of pro-inflammatory and nerve growth inhibitor gene expression	Lewis rats	Male (46)	Sciatic nerve crush injury (Axonotomesis)	Ultrasound therapy	Pulsed therapeutic ultrasound – Ultrasound therapy (1 MHz, 20% duty cycle) applied for 5 min/day, 5 days/week; compared with sham stimulation.	Sciatic functional Index Histomorphometric analyses	<u>**Functional Recovery:**</u> Rats receiving optimal-intensity ultrasound therapy showed significantly improved motor, sensory and functional recovery compared to untreated or sub-optimal intensity groups. Functional tests (such as walking track analysis / sciatic functional index) indicated earlier onset and greater magnitude of recovery in the ultrasound-treated group.
Xing et al., 2020 (29)	Brain plasticity after peripheral nerve injury treatment with massage therapy based on resting-state functional magnetic resonance imaging	Sprague-Dawley rats	Female (32)	Sciatic nerve transection and direct anastomosis	Massage therapy	Instrument-assisted soft tissue massage – Mechanical massage applied at controlled force and frequency (10 min/day for 4 weeks) following nerve injury.	Functional MRI	<u>**Sensory & Functional Recovery:**</u> Massage therapy following peripheral nerve injury was associated with improved functional recovery, supporting restoration of sensorimotor-related cortical activity compared to injury and sham groups. <u>**Neural & Brain Plasticity Outcome:**</u> Resting-state fMRI showed increased spontaneous brain activity (ALFF) in the somatosensory cortex after massage therapy, indicating enhanced adaptive brain plasticity and cortical reorganization following peripheral nerve injury

Table 1. Study characteristics continuation…

Marcilio et al., 2019 (30)	Effects of two intensities of treadmill exercise on neuromuscular recovery after median nerve crush injury in Wistar rats	Wistar rats	Female (24)	Median nerve crush	Treadmill training	Intensity-based treadmill running – Moderate- and high-intensity treadmill protocols (10–17 m/min), performed 5 days/week for 2 weeks.	Grasping test	**Functional recovery:** Moderate-intensity treadmill group showed significantly greater improvement in forelimb motor function compared to high-intensity and sedentary groups. High-intensity group demonstrated delayed and less consistent functional recovery. **Muscle strength / neuromuscular performance:** Grip strength and muscle activation were higher in the moderate-intensity exercise group. High-intensity exercise resulted in lower neuromuscular performance compared with moderate-intensity exercise.
Sung et al., 2017 (31)	Effects of Nerve Regeneration Therapy on SFI in Nerve-Injured Rats	Sprague-Dawley rats	Male (45)	Sciatic nerve crush injury	Treadmill training and Constraint-Induced Movement Therapy (CIMT)	Constraint-induced movement therapy (CIMT) with treadmill – Treadmill training (8 m/min, 30 min/session) combined with immobilization of the unaffected limb; 5 days/week for 2 weeks.	Sciatic functional index	**Functional recovery:** CIMT + treadmill group showed the greatest improvement in SFI across all time points, indicating superior functional motor recovery. The treadmill-only group demonstrated moderate improvement in SFI compared to the control group. The control group showed minimal spontaneous recovery, with persistently poor SFI values.

Table 1. Study characteristics continuation…

Martins et al., 2017 (32)	Long-Term Regular Eccentric Exercise Decreases Neuropathic Pain-like Behavior and Improves Motor Functional Recovery in an Axonotmesis Mouse Model: The Role of Insulin-like Growth Factor-1	Swiss mice	Male (40)	Right sciatic nerve crush injury	Eccentric exercise	Eccentric treadmill exercise – Downhill treadmill running (−16° slope, 6–14 m/min, 30 min/session), performed 5 days/week for 8 weeks, with or without IGF-1 inhibition.	Sciatic functional index Sciatic static index Grip strength Triceps Surae Muscle Weight Histomorphological analysis	**Neuropathic Pain:** Long-term eccentric exercise reduced mechanical and cold hypersensitivity, with greater effects at moderate-to-high intensities. **Motor Function:** Eccentric exercise improved motor functional recovery, including walking pattern and grip strength. **Muscle Atrophy:** Eccentric exercise reduced denervation-related muscle atrophy, helping preserve muscle fiber size and mass. **Nerve Regeneration:** Increased myelinated fiber density and improved nerve morphology were observed with eccentric exercise. **Inflammation:** Exercise reduced pro-inflammatory cytokine expression in muscle tissue.
Liao et al., 2017 (33)	Effects of swimming exercise on nerve regeneration in a rat sciatic nerve transection model	Not defined	Not defined (40)	Sciatic nerve transection	Swimming exercise	Duration-based swimming exercise – Swimming sessions of varying durations (10–30 min), conducted 3 times/week for 4 weeks.	Electro-physiological evaluation Histological evaluation	**Nerve regeneration:** Swimming groups showed dramatically higher successful nerve regeneration across 10-mm gaps compared to the sedentary control group

Table 1. Study characteristics continuation…

Hun et al., 2016 (34)	Therapeutic Ultrasound and Treadmill Training Suppress Peripheral Nerve Injury–Induced Pain in Rats	Sprague-Dawley rats	Male (60)	Chronic constriction injury of the sciatic nerve	Treadmill training (TT) Therapeutic ultrasound (TU)	Combined ultrasound and treadmill therapy – Pulsed ultrasound and inclined treadmill training applied independently to compare neuromodulator effects; 5 days/week for 4 weeks.	Heat and Mechanical sensitivity Histochemical analyses	**<u>Nerve Regeneration:</u>** Therapeutic ultrasound combined with treadmill training promoted peripheral nerve regeneration, leading to improved structural and functional recovery of the injured nerve compared with untreated controls. **<u>Sensitivity:</u>** The combined intervention reduced sensory hypersensitivity by decreasing mechanical allodynia and thermal hyperalgesia, with sensory thresholds shifting toward normal values, indicating restoration of sensory nerve function.
Cannoy et al., 2016 (35)	Upslope treadmill exercise enhances motor axon regeneration but not functional recovery following peripheral nerve injury	Lewis rats	Female (11)	Sciatic nerve transection	Treadmill exercise	Inclined and declined treadmill training – High-intensity treadmill walking on positive and negative slopes (±20°), 1 h/day for 2 weeks.	Muscle reinnervation timing Locomotor muscle activity Gait mechanics	**<u>Muscle Reinnervation:</u>** Upslope training (ST) produced the earliest muscle reinnervation, occurring significantly earlier than in the Level-trained (LT) and Untrained (UT) groups. **<u>Motor Axon Regeneration:</u>** Both ST and LT increased motor axon regeneration compared to UT, with LT showing a greater rate of recovery over time. **<u>Locomotor Muscle Activity:</u>** Slope-dependent EMG modulation was restored only partially in LT rats and remained impaired in ST and UT groups. **<u>Hindlimb Kinematics:</u>** LT rats showed improved gait mechanics, whereas ST rats adopted a crouched posture with impaired kinematic adaptation.

Table 1. Study characteristics continuation…

Chen et al., 2015 (36)	Far-Infrared Therapy Promotes Nerve Repair following End-to-End Neurorrhaphy in Rat Models of Sciatic Nerve Injury	Sprague-Dawley rats	Not defined (18)	Right sciatic nerve transaction followed by an end-to-end neurorrhaphy	Far Infrared radiation therapy	Far-infrared heat therapy – Thermal stimulation using far-infrared radiation (38–39°C) applied 5 times/week for 2 weeks.	Nerve function analysis (Sciatic functional index) Histological Assessment	**Functional recovery:** Rats treated with far-infrared (FIR) therapy showed significantly faster and greater improvement in sciatic functional index (SFI) compared to control groups.
Coradini et al., 2015 (37)	Evaluation of grip strength in normal and obese Wistar rats submitted to swimming with overload after median nerve compression	Wistar rats	Not defined (48)	Compression of the right median nerve	Swimming exercise	Progressive overload swimming protocol – Swimming exercise with added external load (5–10% body weight), 15–20 min/day, 5 days/ week for 3 weeks.	Grip strength meter	**Grip Strength:** Swimming with overload led to significant improvement in grip strength after median nerve compression in both normal and obese Wistar rats. However, normal rats showed faster and greater recovery compared to obese rats. **Comparative Outcome:** Obesity negatively influenced nerve recovery, with reduced gains in grip strength and delayed functional improvement despite participation in the swimming exercise protocol.

techniques, such as constraint-induced movement therapy and massage therapy, were also reported.

Electrotherapeutic modalities identified across the included studies comprised laser therapy, therapeutic ultrasound, shockwave therapy, infrared therapy, whole-body vibration therapy, and various forms of nerve stimulation. Collectively, these modalities were assessed for their potential to enhance neural regeneration and functional outcomes following peripheral nerve injury.

Substantial heterogeneity was observed across studies in injury models, physiotherapy protocols, intervention duration, and outcome assessment methods. Due to this variability, quantitative synthesis through meta-analysis was deemed inappropriate, and the results were therefore integrated using a narrative synthesis approach.

Risk of Bias Analysis

As shown in Figure 2, most of the studies reviewed exhibited moderate methodological quality and a reasonable level of bias risk. Several of the studies reviewed were methodologically weak in their use of allocation concealment and blinding methods, as shown in Figure 3. Insufficient use of these methods may increase the risk of selection, performance, and detection bias in the studies, reducing the overall quality of the evidence obtained, regardless of the severity of the peripheral nerve injury. The results indicate that most studies exhibited low bias in baseline characteristics, randomization of animals to groups, handling of incomplete outcome data, and selective outcome reporting, indicating that few studies had limitations in the performance of experiments in these areas. However, many studies were unclear in the areas of sequence generation, allocation concealment, blinding of participants or outcome assessors, and randomization of animal outcomes, primarily due to inadequate reporting rather than inherent methodological flaws. The areas of allocation concealment and blinding had the highest levels of bias compared to other areas of physiotherapy interventions.

Effects of Intervention

Exercise Interventions

In the studies analyzed, exercise-based interventions were explored as methods to improve neuromuscular and functional recovery after peripheral nerve injury. Resistance training primarily served as a strength-focused method. It showed positive effects on reflexes and muscle power in later recovery phases, although its impact on walking and coordinated movement appeared limited. In contrast, swimming, as a low-impact aerobic exercise, consistently demonstrated beneficial effects on functional recovery, axonal regeneration, and nerve fiber

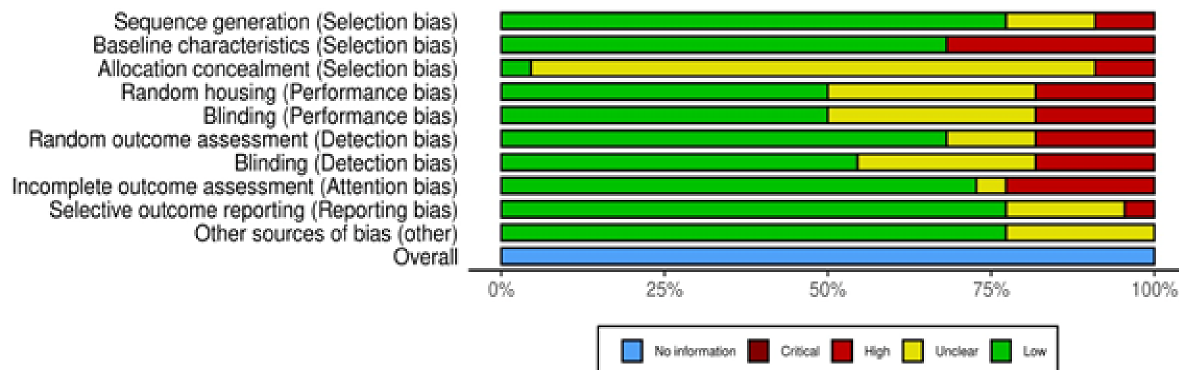

Figure 2. Risk of Bias Summary

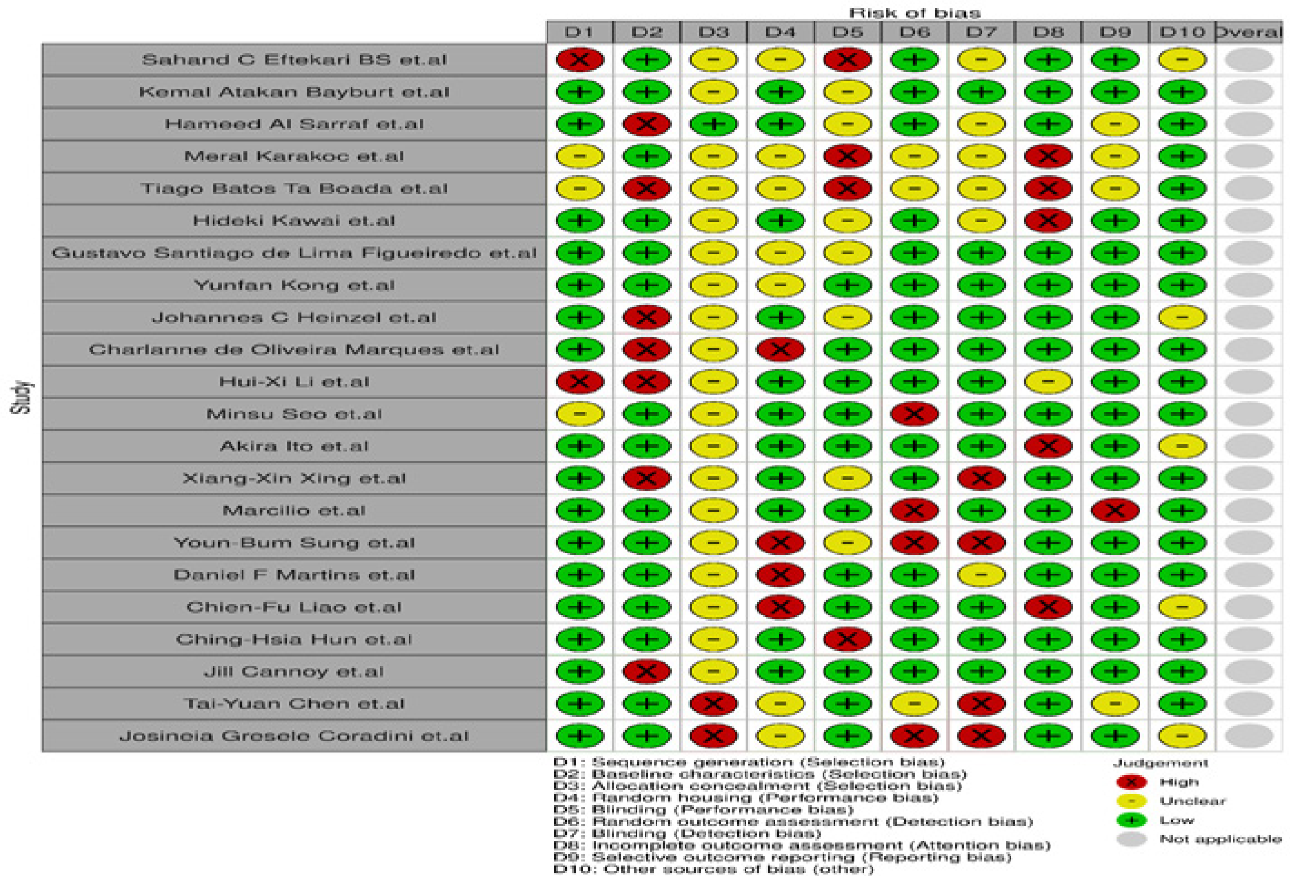

Figure 3. Risk of Bias of individual studies

reorganization, with greater improvements when paired with pharmacological or anti-inflammatory interventions.

Treadmill training has become the most researched method and has demonstrated considerable functional and neural advantages, including improved walking ability, sensory and motor recovery, axonal regeneration, remyelination, and electrophysiological enhancements. Significantly, moderate-intensity protocols yielded better outcomes than high-intensity regimens, which sometimes caused adverse effects. Therapeutic massage was linked to improved regeneration, corroborated by neuroimaging and peripheral mechanistic evidence. Constraint-induced movement therapy (CIMT) facilitated use-dependent plasticity, achieving better results when paired with aerobic exercise. Furthermore, eccentric exercise was associated with decreases in neuropathic pain, increases in myelinated fibers, improved nerve structure, and reduced inflammation, indicating mechanical, metabolic, and anti-inflammatory roles in neural recovery. Overall, these results underscore the importance of organized, goal-directed activities in promoting peripheral nerve regeneration and functional recovery.

Electrotherapeutic Interventions

Electrotherapy modalities were investigated for their ability to enhance neural regeneration and functional recovery following peripheral nerve injury. Nerve stimulation showed neuromodulatory advantages, as simultaneous central and peripheral stimulation resulted in enhanced sensorimotor and functional gains compared to peripheral stimulation by itself, indicating a supportive influence on reinnervation and

recovery speed. Laser treatment, comprising photobiomodulation and high-intensity laser therapy, demonstrated dose-dependent advantages, with higher intensities yielding improved motor, sensory, electrophysiological, and histological outcomes, underscoring the importance of proper dosing.

Therapeutic ultrasound consistently demonstrated pro-regenerative and anti-inflammatory properties, as evidenced by enhanced motor performance, higher axonal counts, thicker myelin, and normalized g-ratios. Conversely, extracorporeal shockwave therapy (ESWT) yielded varied results; although low-intensity approaches facilitated sensory and functional recovery, outcomes were unpredictable in complicated injury models and heavily reliant on specific parameters. Whole-body vibration therapy demonstrated limited restorative or functional advantages under the examined protocols. On the other hand, infrared radiation therapy showed encouraging results, including faster functional recovery, improved axonal alignment, and increased vascularization. In summary, these results show that electrotherapy techniques can aid peripheral nerve regeneration, but their efficacy is significantly affected by dosage, timing of application, and injury severity.

DISCUSSION

This systematic review evaluated 22 preclinical studies using rodent models of peripheral nerve injury that employed physiotherapy interventions. Of the included interventions, both exercises and electrotherapeutic modalities yielded positive results when administered at appropriate dosages and initiated early. Few interventions showed notably superior outcomes compared with other interventions, including treadmill training, swimming exercise, electrical stimulation, and photo-biomodulation therapy. Among these studies, exercise-based interventions had greater impacts on functional recovery, neural regeneration, neuroplasticity, and neuromuscular recovery than electrotherapeutic interventions. These findings suggest that activity-dependent intervention may play a crucial role in functional reinnervation. However, variability exists in interventional protocols, injury models, and outcome measures. The studies included in this review used different experimental models of peripheral nerve injury, most commonly nerve crush and nerve transection, which can affect both the pattern and speed of axonal regeneration. Variability was also observed in the timing of intervention initiation and in the duration and intensity of physiotherapy protocols, which may contribute to differences in functional and histological findings reported across studies. In addition, the use of different rodent species, particularly rats and mice, may influence regenerative responses and the overall effectiveness of rehabilitation strategies. This highlights the need for more standardized clinical studies to support further clinical applications.

Exercise-Based Interventions

Exercise interventions represented the largest category of treatment. These interventions reported strong regenerative and neuroprotective effects. Treadmill training was the most studied intervention, with multiple studies reporting enhanced axonal regeneration, remyelination, electrophysiological neural recovery, and functional motor performance (20,22,23,30,31,34,35,39). However, high-intensity treadmill training resulted in reduced functional performance and neural recovery compared to moderate-intensity regimens. This demonstrates a dose-response relationship where excessive mechanical or metabolic stress may reduce regeneration. Additionally, a few studies reported that faster axonal growth did not correlate with functional gains, suggesting that targeted reinnervation is as essential as axonal growth speed. Clinically, this highlights the need for graded, task-specific training rather than aggressive, high-intensity regimens (35,40).

Furthermore, swimming exercise has consistently demonstrated benefits such as low-impact aerobic exercise, with improvements in

axonal regeneration, nerve fiber organization, and motor recovery (19,33,37). Swimming exercises also reduce mechanical allodynia and modulate neurotrophic factors within the dorsal root ganglia. These beneficial effects suggest that aquatic exercises can support both sensory and motor recovery, with added benefits of hydrotherapy exhibiting its importance in early rehabilitation (41).

Similarly, resistance and eccentric exercises enhanced targeted neuromuscular stimulation. Resistance exercises demonstrated additional benefits, including improved strength and reflex-related outcomes, but with reduced effect on gait coordination (18). Eccentric exercises were associated with reduced neuropathic pain, increased myelinated fiber density, and reduced inflammation.

Despite this, constraint-induced movement therapy improved use-dependent plasticity with greater improvements when combined with aerobic exercise (31). Therapeutic massage has also promoted enhanced regeneration rate and has shown notable central neuroplastic changes on neuroimaging (29). Collectively, these findings emphasize the significance of sensory input and cortical reorganization in rehabilitation. Key evidence across exercise interventional studies is that early, repeated, and task-specific activation enhances neural plasticity and functional reinnervation (39,42). However, controversies still exist regarding optimal intensity, timing, and progression, as functional improvements remain inconsistent despite histological improvements.

Altogether, exercise-based interventions demonstrate substantial neuroregenerative and neuroprotective potential, particularly when delivered in an early, graded, and task-specific protocol. Moderate-intensity aerobic and resistance training consistently facilitates axonal regeneration, remyelination, and functional restoration, whereas excessive intensity may attenuate recovery. In summary, evidence supports precise dosing, and progression maximizes neural plasticity and functional reinnervation.

Electrotherapy Interventions

Electrotherapy interventions are adjuncts to exercise and exhibit specific positive effects for each modality. Electrical stimulation is one among the categories with stronger evidence for promoting axonal regrowth and accurate motor reinnervation (43-45). At the same time, brief stimulation was effective in maintaining neuronal excitability and accelerating regeneration. Combined central and peripheral stimulation produced greater outcomes than in peripheral stimulation alone (16). Clinically, this suggests that focused stimulation early after repair accelerates recovery.

Whereas photo-biomodulation (PBMT) or laser therapy demonstrated promising bioenergetics and neurotrophic effects. Higher-intensity protocols resulted in greater functional and electrophysiological improvements than low-intensity protocols (17, 46). The "triple site" strategy, which focused on the nerve, spinal cord, and denervated muscle, enhanced regeneration and reduced muscle atrophy (47). It also had modulatory effects on inflammation and neurotrophic signaling.

In addition, therapeutic ultrasound showed anti-inflammatory and pro-regenerative effects, with increased axon counts, thicker myelin, and normalized g-ratios. This suppressive mechanism of pro-inflammatory pathways provides a biological basis (21,28,34). In contrast, extracorporeal shockwave therapy (ESWT) illustrated mixed findings. Few studies have reported sensory and functional recovery through mechanosensitive signaling pathways, whereas other studies have reported equal or negative effects, particularly in severe injury models (24,26,27). These effects are highly dose and duration-dependent and limited to early stages (48,49). However, other adjunct modalities, such as whole-body vibration and infrared radiation therapy, have been shown to positively affect vascularization and axonal alignment (25,36).

Taken together, electrotherapy modalities function as valuable adjuncts that promote axonal regrowth, neurotrophic modulation, and electrophysiological recovery. Electrical stimulation and photo-biomodulation exhibit the

most robust and consistent therapeutic effects, especially when applied early and targeted. Nevertheless, therapeutic efficacy remains contingent upon optimal dosage, timing, and injury severity.

Overall Impact of Physiotherapy

Collectively, physiotherapy interventions enhance peripheral nerve regeneration through various complementary mechanisms, including activity-dependent neural plasticity, modulation of neurotrophic factors, improved vascularization, control of inflammation, prevention of muscle atrophy, and facilitation of specific functional reinnervation (50). These mechanisms create a biological and functional environment that supports nerve repair and neuromuscular recovery. The current evidence supports the cumulative effects of exercise-based and therapeutic modality-based interventions, with exercise as the main determinant of neuroplastic and functional gains. At the same time, electrotherapeutic modalities function as biological enhancers, supporting and accelerating regenerative processes. This interventional strategy aligns with modern neurorehabilitation principles that emphasize early activation, task specificity, and combined therapeutic approaches to optimize recovery outcomes, making it essential for promoting healthy lives and improving universal health coverage.

Translational Considerations and Limitations

Despite the encouraging evidence, there is considerable variability in injury models, intervention methods, and outcome assessments. In addition, most of the included preclinical studies used male rodents, and limited information was available regarding sex-specific responses or the influence of comorbid conditions, which may affect the generalizability of the findings. Evidence from rodent models, which regenerate more rapidly, also shows anatomical differences compared with humans. Therefore, applying evidence directly to clinical practice necessitates caution. Human nerves exhibit slower rates of regeneration, greater functional complexity, and greater variability in injury patterns.

The biological principles mentioned – use-dependent plasticity, neurotrophic support, and early activation align with contemporary clinical neurorehabilitation concepts. Tailored doses of treadmill exercise, task-oriented training, and additional methods such as electrical stimulation and photo-biomodulation therapy appear to have the greatest clinical significance.

CONCLUSION

This systematic review has analyzed the findings of 22 preclinical studies investigating the effects of physiotherapy interventions on peripheral nerve regeneration and functional recovery in rodent models. The analyzed results suggest that rehabilitation techniques involving consistent, organized physical exercise and specific therapeutic approaches showed a meaningful effect on neural recovery mechanisms after peripheral nerve damage. These interventions seem to encourage recovery by directly triggering regenerative processes, rather than serving as supplementary or additional methods. Despite significant variations in animal model research, intervention methods, and outcome assessments, this study provides evidence of the benefits of physiotherapy in nerve regeneration. However, as the evidence is derived from preclinical animal studies, further well-designed clinical research is required to determine the extent to which these findings can be translated into human rehabilitation. Additional research, following a standardized protocol, is necessary to identify the most effective methods.

INFORMATION DISCLOSURE STATEMENT

Conflict of Interest. The authors declare that there is no conflict of interest regarding the publication of this systematic review.

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