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Review Article

Advances in Peripheral Nerve Injury Repair with the Application of Nanomaterials

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Peripheral nerve injury (PNI) is a relatively common disease caused by various circumstances, ultimately affecting the life quality of patients. Although existing medications and surgical interventions have particular benefits for nerve repair, more effective therapeutic strategies are urgently needed for various types of nerve injuries. Increasing investigations of nanomaterials have demonstrated their excellent biological properties, such as biocompatibility, permeability, degradability, high medicine loading efficacy, suitable mechanical properties, and broad applications in the biomedical field. Concerning peripheral nerve (PN) repair, nanomaterials with outstanding biological properties can be fitted as nerve conduits to provide support and guidance for PN regeneration and loaded with functional cells, cytokines, or specific medications to promote regenerative outcomes further. Almost all existing studies have focused on the application of different nanomaterials in PN repair, while the application of nanomaterials in different PN injuries has not been taken into account. This article outlines the application of nanomaterials in the medical field and the prevalent therapeutic strategies for PN repair. Importantly, it focuses on the application of nanomaterials in various PNI diseases, covering injuries of the sciatic nerve, cavernous nerve, facial nerve, median nerve, and more.

1. Introduction

Peripheral nerve injury (PNI), which is commonly encountered in the clinic, accounting for approximately 2.8% of all trauma patients, can be caused by crushing, stretching, laceration, collision, and, in some cases, ischemia [1–3]. The severity of symptoms in patients suffering from PNI varies, ranging from mild discomfort to irreversible damage, and may be accompanied by neurological deficits or even life-long disabilities [4, 5]. Recovery from PNI requires the reconstruction of the injured nerve. However, the intrinsic regenerative capacity of injured nerves is insufficient to achieve the regrowth of the proximal axon in severe PNI [6]. Currently, autologous nerve transplantation is the gold standard for severe nerve defects in the clinic, but its application is restricted because of hypoaesthesia with the donor nerve distribution area and the limited availability of autologous donor tissue [7]. With an extensive understanding of the pathophysiology of PNI, it has become apparent that a purely surgical nerve repair method would not be able to deal with the complicated cellular and molecular events of PN regeneration [8]. Therefore, it is vital and urgent to find potential alternatives for the regeneration of injured nerves.

In recent decades, nanomaterials have been widely explored and applied in various areas [9, 10], especially in the field of biomedicine [11, 12]. The term "nanomaterials" typically refers to materials with nanostructure components and at least one dimension less than 100 nm in size. However, a material over 100 nm in size but displaying unique nanoproperties is also categorized as a nanomaterial in some

cases [13]. Materials at these scales exhibit novel nanoeffects including optical, electrical, magnetic, and photothermal properties [14, 15], possessing better performance than traditional materials. In the biomedical field, many medical nanomaterials exhibit low biotoxicity, good biocompatibility, excellent biodegradability, controllable modifiability, and high drug loading efficiency, which show good prospects in disease diagnosis, bioimaging, drug delivery, and tissue engineering [16, 17]. With the rapid development of regenerative medicine, a variety of nanomaterials are used in studies and clinical treatments of PNI and have shown great potential for PN regeneration. Several similar articles have summarized the applications and related mechanisms of different nanomaterials in nerve regeneration (summarized in Table 1), affirming the broad prospects of nanomaterials in PN repair and providing a systematic understanding and reference of nanomaterials applied in PNI. These articles mainly discussed different types of nanomaterials and their mechanisms in PNI repair, while the discussion of the application of nanomaterials in different PN injuries was not taken into account. In this review, we searched PubMed for articles about PNI regeneration in the past 10 years to reveal the prevalent therapeutic strategies for PNI repair and highlight the vital role of nanomaterials in the treatment of PNI. Importantly, we enumerate and summarize the clinical and preclinical application of nanomaterials for PNI management and focus on the application prospects and therapeutic efficacy of nanomaterials in different PNI diseases. This is the first paper to summarize the application of nanomaterials with the clue of different peripheral nerves and would provide a better understanding of medical nanomaterials applied in a specific injured PN.

2. Therapies for PNI Repair

Peripheral nervous tissue is composed of neurons (nerve cells) and glial cells. Neurons, the main components of neural tissues, can receive stimuli, transmit nerve impulses, and act as the basic functional units of neural activity, while glial cells perform supporting, protecting, and nourishing functions in neural tissues [22]. Researchers have been devoted to uncovering the mechanisms of PNI, especially in terms of axonal regeneration, to find the optimal way to repair damaged nerves. When a neuron is damaged, it receives a reverse electrical signal, thereby activating the calcium channel and the Jun kinase cascade and changing the transcription signals [23, 24]. Subsequently, the proximal axon experiences related reactions, while the distal axon and axonal membrane break down and the degradation products are engulfed by Schwann cells (SCs) and macrophages [25, 26]. In addition to neurons, SCs also play an indispensable role in neural regeneration. At the initial stage of the injury, SCs participate in the regenerative process by transforming their myelinated phenotype to repair SCs to meet the various needs of damaged neural tissues [27, 28]. With the support of repairing SCs, the axonal buds appear, and the columnar structure is formed around the injured area, called the Biingner zone, promoting axonal regeneration via preservation of epiphyseal growth factors (GFs). Later, regenerating proximal axons extend along this Biingner zone to reestablish contact with the distal muscles, and only one of the extended axons can grow into its distal organ to complete the nerve regeneration process [29]. Of note, besides the potential regeneration function of axons and SCs, the regeneration microenvironment at the distal end of the injury site and regeneration conditions of target tissues are also crucial for the regeneration of damaged SCs [30, 31].

Based on the current understanding of PNI and its regenerative mechanisms, numerous therapies have been developed for PNI treatment, the pattern of which is presented in Figure 1. There are six main therapeutic methods for PNI, including pharmacological treatment, tension-free sutures, suture of adjacent nerve transfer, nerve transplantation (autologous, allogeneic, and xenogeneic), biological catheter transplantation (artery, vein, muscles, and tendons), and neural tissue engineering (NTE). Autologous nerve transplantation has been used as the "gold standard" and is the predominant method of treating nerve injury. In contrast, as an emerging approach, NTE is a current research hotspot and is the most promising strategy for the future. However, applications of other treatment options are limited to different degrees due to their various shortcomings and intractable issues.

2.1. Pharmacological Treatment. Pharmacological neuroprotective treatment is an essential strategy for PN repair, and many pharmaceutical preparations have significant effects on protecting neuronal cells [32]. Acetyl-L-carnitine and N-acetylcysteine, possessing excellent antioxidant properties, have shown significant neuroprotective effects in rat nerve injury models. The safety of these two agents in clinical applications is currently being considered [33, 34]. Additionally, various agents have been investigated and demonstrated a good synergistic therapeutic efficacy for PNI repair, such as betamethasone, thyroid hormone, FK506, salidroside, and curcumin [35–39]. Although these agents positively affect the protection and regeneration of damaged nerves, their therapeutic efficacy is significantly limited for PN transection or defect injury. To yield better results, agents are delivered by nanomaterials in many cases.

2.2. Surgical Treatment. PN detachment often requires surgical intervention. Currently, meticulous microsurgical repair with tensionless sutures is a preferable method for surgical treatment of PNI; however, this method only applies to the severed nerve ends with no tension or minimal tension [8, 40]. Meanwhile, because of the limited potential of tensionless sutures, autologous nerve transplantation as the gold standard was adopted to treat PN defects with high tension on both sides of the stump [41, 42]. However, the application of autologous nerve transplantation in the clinic is restricted because of the hypoaesthesia with the donor nerve distribution area and the limited availability of autologous donor tissue [7]. Allografting is another technique applied to restore PN with devastating or segmental injuries and provide a neurotropic effect accompanying SCs to bridge a 7 cm nerve gap [43]. This method has an abundant supply of donor's nerves compared to that of autografting, but the

Table 1: Similar reviews on the application of nanomaterial in peripheral nerve injury.

Categories of nanomaterials	Involved PNs	Discussion thread	Main contents	Conclusions or future perspectives	Ref.
Electroconductive nanomaterials (pure metal, carbon-based materials, electroconductive polymers, etc.) Piezoelectric nanomaterials (crystalline, ceramics, and piezoelectric polymers)	Sciatic nerve	Categories of nanomaterials	(1) Systematical introduction of major electroconductive and piezoelectric nanomaterials in the field of NTE (2) Analysis of potential interaction between cellular biological activity and nanostructured electroactive materials	(1) Nanomaterials have greater versatility and flexibility to tailor for personalized PN regeneration (2) More research on biodegradation products, long-term in vivo effects, and underlying regenerative mechanism of electroactive nanomaterials is needed for moving electroactive nanomaterials from lab benches to the clinics	[6]
2D nanomaterials (graphene, graphene oxide, zinc oxide, boron nitride)	Sciatic nerve	Categories of nanomaterials	(1) Application of 2D nanomaterials for PN regeneration strategies by facilitating the formation of new vessels (2) Analysis of the mechanism that newly formed capillaries directionally and metabolically supporting neuronal regeneration	(1) 2D nanomaterials potentiate regenerative results of long-range PN defect (2) For better therapeutic effects of 2D nanomaterials, strategies reversing the energy deficiency after PNI could be a viable solution	[18]
Hollow NGCs, porous NGCs, matrix-loaded NGCs, multichannel NGCs, and patterned substrate, NGCs loaded with filaments, magnetically/cell aligned fibres	Sciatic nerve, tibial nerve, peroneal nerve, fibular nerve	Categories of nanomaterials	(1) Review of recent designs and fabrication techniques of NGCs for PN regeneration	(1) Nerve regeneration in vivo is a complicated process whereby axons grow by the combined effect of topographic, electric, chemotactic, and haptotactic cues that guide the directional growth of the axons (2) More investigations are needed to study the degradation, cytotoxicity, immunogenicity, and long-term effect of such NGCs in vivo	[19]
Carbon nanomaterials (carbon nanotubes, graphene, carbon nanofibers, nanodiamonds) Nanoparticles (inorganic NPs, organic NPs) Nanofibers (random nanofibers, aligned nanofibers, nanofibers combined with conductive materials)	Sciatic nerve, optic nerve, median nerve, auditory nerve	Categories of nanomaterials	(1) Review of the potential of nanotechnology-based therapies to deliver bioactive molecules in a controlled manner, to tune cellular behavior and ultimately guide tissue regeneration in an effective manner	(1) Poor vascularization, guided tissue regeneration, excessive fibrosis, and neuroinflammation are several significant challenges in PN regeneration	[20]
2D nanomaterials (graphene oxide, reduced graphene oxide, transition metal dichalcogenides, black phosphorus, layered double hydroxides, metal-organic frameworks, etc.)	Sciatic nerve	Main contents	(1) Supporting biological properties of 2D nanomaterials for neuroregeneration (2) 2D nanomaterial-based scaffolds for NTE (3) Application of 2D nanomaterials for CNS and PNS injury	(1) Wide exploration of other 2D nanomaterials apart from graphene and its derivatives is needed (2) Research on evaluating the in vivo toxicity of 2D nanomaterials, particularly in the nervous system, is also important (3) Besides the concentration and time of exposure, other parameters such as the number of layers, size, and shape are required to be investigated	[21]

NTE: neural tissue engineering; 2D: two-dimensional; PN: peripheral nerve; PNI: peripheral nerve injury; NGCs: nerve guidance conduits; NPs: nanoparticles; CNS: central nerve system; PNS: peripheral nerve system.

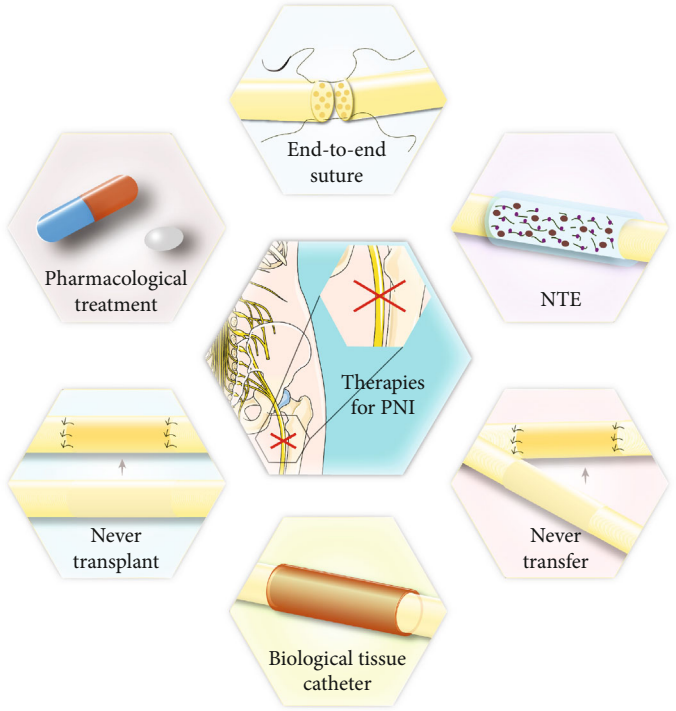

Figure 1: Therapies for PNI.

occurrence of an undesirable immune response and ethical issues could be the most critical drawback of allografts [44]. Thus, nonimmunogenic decellularized nerve allografts have been explored, and their abilities to support axonal guiding and PN regeneration have been illustrated [45]. In recent years, decellularized autologous tissue grafts derived from blood vessels, skeletal muscle, and tendons have also received much attention for the limited sources of autologous nerve transplantation. Studies have shown that compared with autologous nerve transplantation, different types of autologous tissue grafts show similar or even better effects on PNI [46, 47].

2.3. Neural Tissue Engineering. With an extensive understanding of the pathophysiology of PNI and more profound studies on neural regeneration mechanisms, it has become apparent that a purely surgical nerve repair method would not be able to deal with the complicated cellular and molecular events of PN regeneration [8]. Due to a shortage of proper biomaterials and the complexity of the body's injury environment, repairing and reconstructing largely crushed or segmented PN segments remain a challenge in regenerative medicine [46]. However, NTE technology, consisting of a supportive scaffold as a nerve guide conduit, bioactive molecules as nutritional and functional promotors, and responsive cells (seed cells), is being considered an emerging and promising strategy for PNI treatment [48, 49]. The schematic diagram of NTE is shown in Figure 2. NTE is one of the most popular strategies on PNI repair, with excellent prospects in nerve regeneration. As a fundamental part of tissue engineering, various scaffolds have been used in experiments, including different morphological nanostructures and different surface topography modifications of multiple structures, which are conducive to the survival and regeneration of nerve tissue. Furthermore, to better simulate the nerve regeneration environment in the body, various functional cells and nutritional factors have also been fully utilized. The most widely used cells are stem cells, SCs, and transfected cells with specific functions. Nutritional factors mainly include neurotrophic factors and other types of cytokines. The combination of various nanostructures, functional cells, and cytokines allows each component to exert its most significant advantages, making NTE a promising means to repair PN damage.

NTE involves the manufacturing and application of different biocompatible scaffolds for surgical transplantation to nourish and reconstruct damaged neural tissue [50]. Generally, NTE scaffolds can be divided into natural polymeric scaffolds and synthetic polymeric scaffolds [51, 52]. Among natural polymeric scaffolds, collagen, gelatin, silk fibroin (SF), fibrin, hyaluronic acid, alginates, and chitosan are being widely explored and have achieved notable outcomes in PN recovery [53, 54]. Meanwhile, polyester, such as polylactic acid (PLA) [55] and poly (lactic acid-co-glycolic acid) (PLGA), is the most common synthetic material explored in NTE [56]. However, the combined application of natural polymeric scaffolds and synthetic polymers for PN regeneration seems to be a better strategy to maximize its therapeutic efficacy where the complementary physical and biological properties of materials can be optimally used [52].

In NTE, SCs and stem cells are usually loaded on nerve scaffolds. Normal SCs transform into repairing SCs at the injured site, secreting trophic factors, and providing structural guidance for axonal growth, a vital physiological

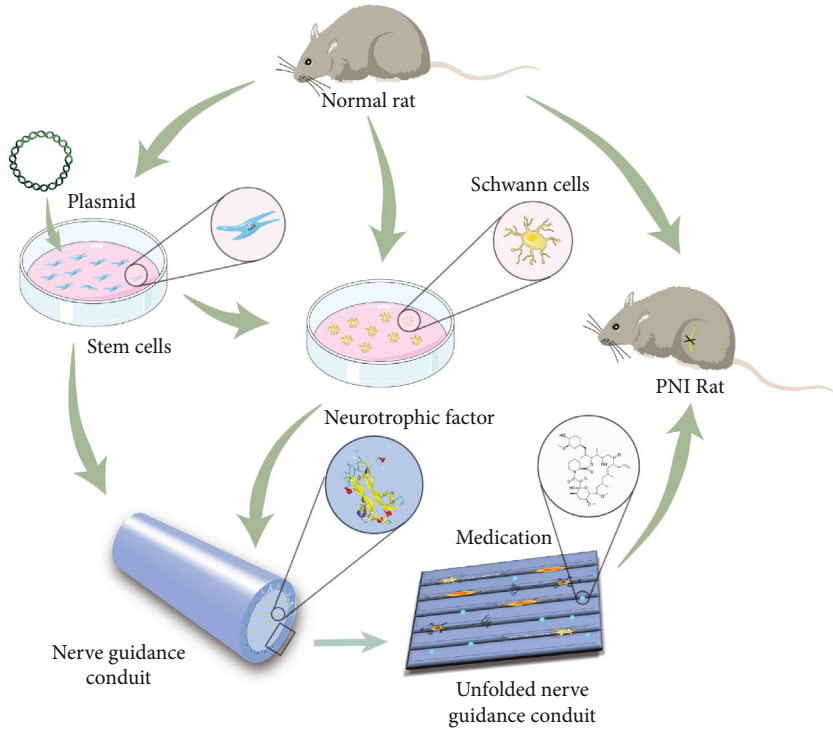

Figure 2: Applications of NTE in nerve injury repair.

process for PN regeneration [25, 57]. Meanwhile, stem cells including embryonic fetal stem cells [58], neural crest stem cells [59], adipose-derived stem cells [60], bone marrow mesenchymal stem cells [61], and induced pluripotent stem cells [62] can differentiate into multiple cell types and renew themselves with good proliferative abilities. What is more, multiple cytokines are also involved in forming regenerative phenotypes of neurons in injured PNs. They can indirectly affect seed cells and help achieve a better regenerative outcome in NTE. Neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell-derived neurotrophic factors (GDNF) are capable of promoting neuronal survival, synaptic plasticity, and neurogenesis [46, 63, 64]. Moreover, many other trophic factors have shown positive effects on axonal regeneration and remyelination with the support of tissue engineering, including vascular endothelial growth factor, ciliary neurotrophic factor, and insulin-like growth factor 1 [46, 65].

3. Applications of Nanomaterials in PNI Repair

3.1. Clinical Applications of Nanomaterials in PNI Repair. Although many nanomaterials have shown their potential value for PNI repair, only a minority of these materials have been comprehensively tested and approved for clinical use. Some devices with the approval of the Food and Drug Administration (FDA) have been successfully used for PNI repair in the clinic, which are summarized in Table 2 [66, 67]. Collagen, the most abundant ingredient in the extracellular matrix, has been extensively studied for NTE [53]. In addition to several potential properties such as excellent biocompatibility, mild immunogenicity, and sustaining nontoxic degradability [68], collagen can establish structural unity through secreting the extracellular matrix and sustaining the function of existing connective tissues and also promote cellular adhesion, proliferation, migration, and differentiation [69]. With the approval of the FDA, collagen has become one of the most promising natural scaffolds for nerve injury repair in the clinic. A 12-month follow-up of 20 patients who were implanted with Neuromaix, a collagen-based nerve guide, for the reconstruction of a sural nerve biopsy defect (20–40 mm), was summarized in a clinical study. All patients showed satisfactory wound recovery during the whole course of the study, and complete restoration of sensation was reported in two cases [54]. Similarly, collagen conduits filled with collagen filaments for patients with a sensory nerve defect at the wrist were evaluated in a multicenter, controlled, open-label study, showing that the treatment of nerve defects ≤ 30 mm via collagen conduits had a similar effect to that of autologous nerve grafts [70]. Moreover, bioabsorbable polyglycolic acid (PGA) nerve conduits were also used in clinical surgeries for PNI repair. Reconstruction of injured inferior alveolar nerves was performed with PGA nerve conduits for five patients, showing that PGA nerve conduits achieved diminution of pain and variable sensory recovery [71]. The caprolactone neurotube, another synthetic polymeric material, was designed for 12 patients with severed sensory nerves (gaps were less than 25 mm). The results of physical examination suggested that the use of a caprolactone neurotube as a synthetic bioabsorbable conduit for nerve repair is promising [72]. Besides the materials above, a polyglycolic acid-collagen (PGA-c) tube was used for 12 severe dysesthesia patients with surgical repair of the damaged lingual nerve or inferior alveolar nerve.

Table 2: Clinically approved nerve conduits from natural and synthetic sources [66, 67].

Materials	Products	Types	Degradation	Maximum length (mm)	Inner diameter (mm)
Processed human nerve allograft	Avance (AxoGen)	Conduit	3-4 months	70	1-5
Porcine small intestine submucosa (SIS)	AxoGuard Nerve Connector (AxoGen)	Conduit	3 months	10	1.5-7
	AxoGuard Nerve Protector (AxoGen)	Wrap	3 months	40	2-10
Collagen type I	NeuroMatrix/Neuroflex	Conduit	4-8 months	25	2-6
	NeuroMend	Wrap	4-8 months	50	4-12
	NeuraGen	Conduit	36-48 months	30	1.5-7
	NeuraWrap	Wrap	36-48 months	40	3-10
Poly (l-lactide-co-ε-caprolactone) (PLCL)	NeuroTube	Conduit	6 months	30	2-8
Poly (dl-lactide-co-caprolactone) (PDLLA-CL)	NeuroLac	Conduit	16 months	30	1.5-10
Poly (vinyl alcohol) (PVA)	SaluTunnel Nerve Protector	Conduit	Nondegradable	63.5	2-10
	SaluBridge	Wrap	Nondegradable	63.5	2-10
Polyglycolic acid (PGA)	NeuroTube	Conduit	3 months	40	2.3-8

Outcomes evaluated 2 months to 8 years postoperatively showed that the sensory impairment was alleviated with the help of PGA-c tubes in surgical treatment [73]. Recently, a chitosan membrane was applied to the neurovascular bundles after nerve-sparing robot-assisted radical prostatectomy for 140 patients, the safety and feasibility were evaluated, and the patients showed no signs of intolerance/allergy and achieved promising potency recovery [74]. The additional use of chitosan nerve tubes was assessed in primary sensory nerve repair. The results showed a relevant improvement in static two-point discrimination, which means that the additional use of chitosan nerve tubes can significantly improve peripheral sensory nerve regeneration [75].

3.2. Preclinic Applications of Nanomaterials in PNI Repair. Recently, preclinic investigations on nanomaterials used to promote regeneration of injured PN have mainly focused on the sciatic nerve. Meanwhile, considerable studies have also been designed for other types of PN repair, such as facial nerve, cavernous nerve, and median nerve repair. In this section, we spotlight the application status of nanomaterials in repairing different types of PNI. Additionally, the nanostructures applied for PNI in preclinic experiments are summarized in Figure 3, and different types of nanomaterials are designed into various forms, such as nanospheres, nanorods, nanofibers, nanofilms, nanosheets, matrix, and nanotubes (e.g., hollow, porous, multichannel, and multiwalled.)

3.2.1. Applications of Nanomaterials in Sciatic Nerve Injury. In the field of repairing PNs with nanomaterials, the sciatic nerve has been the most prevalent research object in the past decade. Nanoscaffolds explored on the sciatic nerve have mainly included collagen, polyester, and chitosan, while other relatively less used materials and their applications are summarized in Table 3.

(1) Collagen. Collagen is a key structural biopolymer and the most abundant protein in the human body. Collagen is a well-known biomaterial that provides the microenvironment with topographic cues to guide axon regeneration because of its different binding domains and properties for cell attachment and survival in NTE [76]. The use of a longitudinally oriented collagen conduit (LOCC) combined with human umbilical cord mesenchymal stem cells to improve regenerative efficacy after sciatic nerve transection was explored in dog models. This study uncovered that a LOCC could stimulate sciatic nerve regeneration by providing mechanical support for emerging nerves and cells. LOCC and umbilical cord mesenchymal stem cells synergistically boosted nerve regeneration and motor recovery in a dog model with a 35 mm sciatic nerve defect [77]. Similarly, NGF was also loaded on LOCC and synergistically achieved an ideal efficacy in the dog model with sciatic nerve defects (35 mm) [78]. Moreover, an oriented collagen tube implanted on the resected rat sciatic nerve promoted its recovery of sensory function; this finding suggested that nonmyelinated axons played a vital role in the recovery [79]. In another sciatic nerve injury model, a collagen sheet impregnated with basic fibroblast growth factor (b-FGF) was found to decrease allodynia and promote the recovery of damaged nerves in a chronic constriction injury rat model [80]. In addition to acting as an excellent vehicle for cell and drug delivery, collagen has been applied as a promising internal filler for neural conduits. An electrospun polycaprolactone (PCL) neural conduit filled with collagen-hyaluronic acid sponge was constructed to build a suitable microenvironment for the proliferation and maturation of SCs and boost axon growth [81], while a PGA-c was explored to accelerate recovery concerning electrophysiology, histomorphology, and sensory function with the combination of MeCbl sheets [82]. Additionally, collagen has also been applied in combination with other materials for nerve regeneration. A conduit made of poly (L-lactic acid)-co-poly(ϵ-caprolactone), polyaniline, and collagen was studied in a rat model to cover a nerve gap through decreasing muscle atrophy [83]. Except for the regeneration function for a nerve gap,

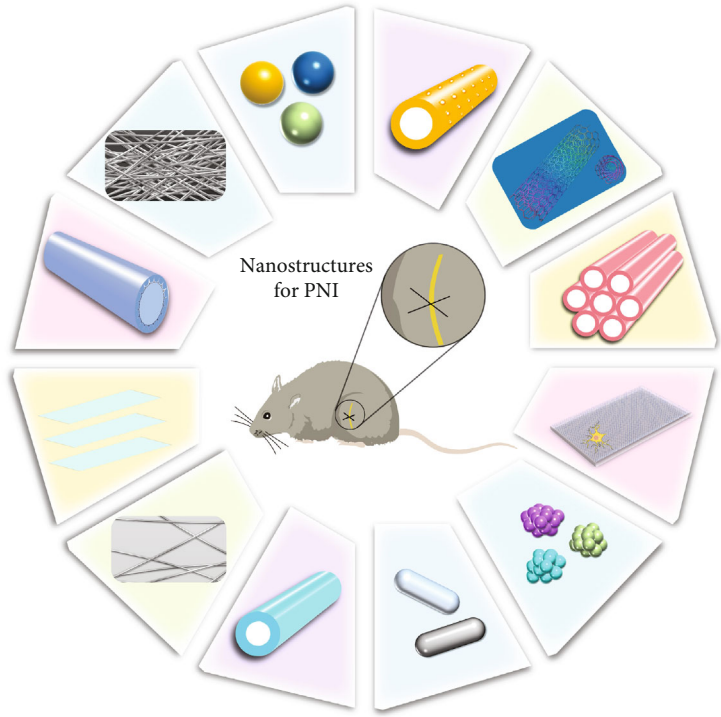

Figure 3: Nanostructures applied for PNI in preclinic experiments.

collagen type I hydrogel containing hydroxyapatite nanoparticles displayed a recovery function in rats with sciatic nerve crush injuries [84]. Like collagen catheters, a composite of collagen and other nanomaterials can also be combined with different seed cells or various neurotrophic factors to synergistically promote nerve regeneration and recovery [85, 86]. Meanwhile, an experiment involving SCs and stem cells coseeded on SF/collagen nerve scaffolds showed improvement of the regenerative microenvironment and promotion of nerve regrowth compared to plain SF/collagen [87]. However, the synergistic effects of collagen-based neurotrophic factors and seed cells have rarely been reported.

(2) PCL and Its Copolymers. Acting as a resolvable polyester, PCL is one of the most commonly used synthetic biomaterials in nerve injury repair because of its easy fabrication method, excellent biocompatibility, tailorable degradation, and mechanical properties [107]. 3D-printed multifunctionalized PCL conduits embedded with canine adipose tissue-derived multipotent mesenchymal stromal cells were found to exert promising neuroregenerative effects by supporting the trophic microenvironment in rats with critical sciatic nerve injury [108]. Additionally, PCL nerve conduits containing different materials, such as gelatin [109], reduced graphene oxide [109], and collagen VI [110], have been individually explored for nerve regeneration in rats with sciatic nerve defects and achieved beneficial efficacy for nerve regeneration. For example, collagen was locally delivered via a PCL conduit to promote recruitment and polarization for the prohealing (M2) phenotype of macrophages, which are beneficial to nerve regeneration [110]. Interestingly, aligned and random poly (l-lactic acid-co-ε-caprolactone) nanofibers seeded with macrophages were used in a rat sciatic nerve defect model. An *in vitro* experiment illustrated that aligned nanofibers dramatically stimulated elongation of macrophages and induced an M2 type of macrophages, while random nanofibers induced an M1 type. Notably, aligned nanofibers effectively polarized macrophages and potently boosted the proliferation and migration of SCs. Meanwhile, *in vivo* data demonstrated that nanofiber arrangement differentially activated macrophages, and those conduits made from aligned nanofibers dramatically promoted PN reconstruction partly by activating the M2 phenotype in macrophages [111]. Similarly, the surface topography of PCL and PLA blended films was modified into four different shapes: sloped walls (SL) and V-shaped, square-shaped, and nongrooved surfaces with micropits, which were tested *in vitro* by inducing ADSCs differentiated to SC-like cells and *in vivo* through evaluating nerve regeneration on SD rat sciatic nerve injury. The results showed that the SL-grooved nerve conduit had significantly enhanced therapeutic efficacy over the other groups both *in vitro* and *in vivo*, suggesting that different surface topographies of materials have different effects on nerve regeneration [112].

(3) Chitosan. Chitosan is a linear polysaccharide derived by chemical deacetylation of chitin, possessing promising properties, such as high adsorption capacity, suitable biodegradability, ideal biocompatibility, low cytotoxicity, and nonimmunogenicity [107]. Usually, chitosan is adopted as a scaffold to provide support and guidance for axial elongation in nerve regeneration. For example, a hollow chitosan conduit was applied to PN reconstruction in a rat with sciatic nerve injury, achieving positive benefits for nerve

Table 3: Other main nanomaterials applied for sciatic nerve injury in recent years.

Materials	Synergistic factors	Models	Animals	Gap (mm)	Results/conclusions	Ref.
MC/AN/NG	NGF and BDNF	A sciatic nerve transection model	Rabbit	15	NGF significantly promoted cell density, and BDNF significantly promoted myelination *in vitro*; MC/AN/NG scaffold showed superior nerve recovery and less muscle atrophy comparable to autograft *in vivo*	[88]
OCT	bFGF	A sciatic nerve defect model	Rat	25	OCT alone accelerated nerve repair in a large nerve defect rat, and the combination of bFGF and OCT was superior to OCT alone for nerve regeneration and functional recovery	[89]
Silk electrospun conduits	NGF and CNTF	A sciatic nerve crush injury model	Rat	\	Bioactive silk tubes represented a new and promising biocompatible nerve guidance conduit for nerve regeneration	[90]
Collagen-fibrin EngNT rods	\	A sciatic nerve defect model	Rat	8	The optimized collagen-fibrin blend provided a novel way to improve the capacity of EngNT to promote regeneration following peripheral nerve injury	[91]
Silk fibroin-based NGC	ChABC and GDNF	A sciatic nerve defect model	Rat	15	Conduit enhanced Schwann cell migration and proliferation and also fostered axonal regeneration; the outcomes were further enhanced when loaded with ChABC and GDNF	[92]
Sericin/silicone double conduits	\	A sciatic nerve transection model	Rat	5	The conduit supported SC proliferation and upregulated the transcription of GDNF and NGF and drastically improved nerve function and morphology comparable to that of autograft	[93]
PLA/MWCNTs/ GNFs/rhEpo-CNP conduit	EPO	A sciatic nerve defect model	Rat	10	The produced conduit had comparable nerve regeneration to the autograft, as the gold standard to bridge the nerve gaps	[94]
PLLA/MWCNTs/ chitosan NP conduit	SCs and curcumin	A sciatic nerve defect model	Rat	10	Controlled curcumin release decreased SC apoptosis and enhanced the regeneration and functional recovery; SCs and curcumin inside NGC had a significant role in sciatic nerve regeneration *in vivo*	[39]
PLA microporous hollow conduit	\	A sciatic nerve transection model	Mouse	\	PLA conduits showed increased myelinated fibers, blood vessels, regenerating nerve fibers, and functional recovery; PLA conduits could be a suitable substrate for cell survival and axonal growth becoming a potential alternative to autograft	[55]
EPO/PLGA-MS and NGF/B-PLGA-MS	NGF and EPO	A sciatic nerve injury model	Rat	\	Codelivery of EPO/PLGA-MS and NGF/B-PLGA-MS resulted in significant nerve recovery; this sequential system could provide a new therapeutic strategy for peripheral nerve injuries	[95]
PLGA scaffold	Stem cells	A sciatic nerve transection model	Rat	7	Acellular scaffold promoted functional recovery and nerve regeneration following nerve injury	[96]
Cellulose acetate/ PLA scaffold	Citalopram	A sciatic nerve defect model	Rat	\	The citalopram-containing scaffold could ameliorate functional recovery, making it a potential candidate for neural tissue engineering applications	[97]
CNT-PGFs/ PLDLA tubes	\	A sciatic nerve transection model	Rat	10	These tubes showed significantly increased regenerating axons and reinnervated muscles	[98]
PVDF-membrane cylinders	HAP stem cell spheres	A sciatic nerve severed injury model	Nude mouse	\	HAP stem cells might have greater potential than iPS or ES cells for regenerative medicine	[99]
PU NGC	\	A sciatic nerve transection model	Rat	10	PU NGC achieved a better efficacy on functional recovery than that of commercial conduits (NeuroTube) and could be a potential candidate for clinical peripheral nerve tissue engineering	[100]
PCL/collagen/ NBG conduits	hEnSCs	A sciatic nerve transection model	Rat	10	This PCL/collagen/NBG conduit filled with hEnSCs could be a suitable strategy to improve nerve regeneration in a nerve transaction rat	[85]

Table 3: Continued.

Materials	Synergistic factors	Models	Animals	Gap (mm)	Results/conclusions	Ref.
GFs-HP hydrogel	NGF and bFGF	A sciatic nerve crush injury in a diabetic model	Rat	\	GFs-HP hydrogel improved axonal regeneration, remyelination, and recovery of motor function, providing a promising therapy option for peripheral nerve regeneration in patients with DM	[101]
HA-based NGC	NGF and ONS cells	A sciatic nerve transection model	Rat	10	ONS-loaded NGCs improved functional, electrophysiological, and morphologic outcomes, and the addition of NGF further improved the outcomes of the repair	[102]
A porous keratin sponge	\	A sciatic nerve crush injury model	Rat	\	Keratin promoted cell adhesion, proliferation, migration, and the secretion of NFs and regulated the expression of macrophage inflammatory cytokines *in vitro*; keratin sponge could alleviate motor deficits *in vivo*, identifying as a valuable biomaterial to enhance peripheral nerve regeneration	[103]
PPY/Coll/n-Sr/BG composite	\	A sciatic nerve injury model	Rat	\	These biocomposite films had biomimetic morphology, bigger porosity, and higher surface territory than customary nerve channels. They accomplished fundamentally increasingly viable recovery of sciatic nerve wounds following 24 weeks of implantation *in vivo*	[104]
RGO-coated ApF/PLCL scaffold	\	A sciatic nerve defect model	Rat	10	This scaffold significantly enhanced SC migration, proliferation, and myelination including myelin-specific gene expression and neurotrophic factor secretion and exhibited a similar healing capacity to autograft *in vivo*	[105]
Nanosilver-collagen scaffold	\	A sciatic nerve transection model	Rat	10	Nanosilver scaffolds (2 mg/ml group) were effective in inhibiting bacteria both *in vitro* and *in vivo* and reduced the contamination-caused immune responses, which in turn promoted nerve regeneration and functional recovery	[106]

MC/AN/NG: multichanneled scaffold characterized with aligned electrospun nanofibers and neurotrophic gradient; NGF: nerve growth factor; BDNF: brain-derived neurotrophic factor; OCT: scaffold material-oriented collagen tubes; bFGF: basic fibroblast growth factor; CNTF: ciliary neurotrophic factor; EngNT: engineered neural tissue; NGC: neural guidance conduits; ChABC: chondroitinase ABC; GDNF: glial cell-derived neurotrophic factor; PLA: polylactic acid; MWCNTs: multiwalled carbon nanotubes; GNFs: gelatin nanofibrils; rhEpo: recombinant human erythropoietin; CNPs: chitosan nanoparticles; EPO: erythropoietin; PLLA: poly-L-lactic acid; SCs: Schwann cells; PLGA: poly-lactic-co-glycolic acid; MS: microspheres; B-PLGA: BSA-incorporated PLGA; CNT: carbon nanotubes; PGFs: phosphate glass microfibers; PLDLA: poly(L/D-lactic acid); PVDF: polyvinylidene fluoride; HAP: hair follicle-associated-pluripotent; PU: polyurethane; PCL: poly (e-caprolactone); NBG: nanobioglass; hEnSCs: human endometrial stem cells; GFs: growth factors; HP: heparin-poloxamer; HA: hyaluronic acid; ONS: olfactory derived stem; PPY/Coll/n-Sr/BG: polypyrrole/collagen/nanostrontium/bioactive glass; rGO: reduced graphene oxide; ApF: Antheraea pernyi silk fibroin; PLCL: poly(L-lactic acid-co-caprolactone).

regeneration [113]. Chitosan conduits combined with drugs, functional cells, or cell factors had a synergistic effect on morphological repair and showed potential for nerve regeneration [114–116]. Moreover, an ECM-modified chitosan nerve guidance conduit (NGC) filled with SF achieved regenerative outcomes for a 10 mm sciatic nerve gap in rats [117]. Meanwhile, chitosan/hyaluronic acid nerve conduit can reduce nerve adhesion and scar formation and increase the number of axons, nerve fiber diameter, and myelin thickness to achieve nerve regeneration [118]. A novel collagen-chitosan scaffold was developed to facilitate a 30 mm long nerve defect in beagles. The scaffold could achieve an equivalent efficacy for nerve reconstruction and functional restoration to that of an autograft [119]. In addition to tubes, chitosan can also be easily processed into nanofibers, membranes, nanoparticles, and sponges to suit different applications. For instance, a microporous chitin-based conduit filled with CM-chitosan fiber was explored and applied to cover a 10 mm sciatic nerve defect in SD rats. The results showed that a chitin/CM-chitosan nerve graft could promote the restoration of damaged neurons as effectively as an autograft [120]. Moreover, chitosan film associated with mesenchymal stem cells also achieved positive results in nerve regeneration by improving the functional and morphological properties of the damaged sciatic nerve [121]. Furthermore, thiolate-trimethyl chitosan- (TMCSH-) based polymeric nanoparticles containing a plasmid DNA encoding for BDNF and loaded with the nontoxic carboxylic fragment of tetanus neurotoxin (HC) for neuron targeting were constructed for targeted gene delivery to damaged neurons in a rat with a sciatic nerve crush injury. This TMCSH-HC/BDNF nanoparticle could effectively boost functional recovery by promoting the expression and release of BDNF in neural tissues [122]. However, chitosan also has its shortcomings, such as low mechanical properties under physiological conditions that limit its application in nerve regeneration to some extent. To make the most of its advantages, chitosan is usually cross-linked with other nanomaterials, for instance, PLA [94], to compensate for the lack of positive mechanical features [107].

Table 4: Nanomaterials applied to cavernous nerve injury in recent years.

Materials	Synergistic factors	Models	Animals	Results/conclusions	Ref.
PA nanofiber hydrogel vehicle	SHH protein	A CN resection rat model (5 mm)	Rat	SHH treatment by PA suppressed collagen induction and remodeling, an irreversible component of ED development; this vehicle might be widely applicable as an *in vivo* delivery tool	[131]
PA nanofiber hydrogel vehicle	SHH protein	A CN crush injury rat model	Rat	SHH protein could maintain CN architecture, promote CN regeneration, suppress penile apoptosis, and improve erectile function; this protein delivery had the potential for ED treatment	[124] [132]
Porous, silane-based curc-nanoparticles	Curcumin	A type II diabetes (T2D) rat model	Rat	Curc-NP group exhibited higher average ICP/BP and lower Nkap expression and heme oxygenase-1 expression than that of the control group; topical application of curc-NPs could systemically deliver curcumin, treat ED, and modulate inflammation	[126]
Gelatin microspheres	bFGF	A diabetic model	Rat	Erectile function was maintained because of the smooth muscle preservation caused by the long-term release of bFGF *in vivo*; this could be a novel therapeutic option for diabetes-induced erectile dysfunction	[127]
SPION-MSCs	\	A CN crush injury model	Rat	Transplanted SPION-MSCs existed for up to 4 weeks in the CN injured cavernosa of rats; erectile dysfunction recovered and could be monitored by MRI	[133]
Nanoshuttle magnetic nanoparticles	ADSCs	A CN crush injury model	Rat	Nanoshuttle magnetic nanoparticles kept ADSCs in the corpus cavernosum and improved ED therapeutic efficacy in an animal model	[134]
HP/GPT hydrogel	bFGF-loaded HP hydrogel and NGF-loaded GPT hydrogel	A CN injury model	Rat	The sequential and continuous release of growth factors from HP/GPT hydrogel prevented fibrosis and nerve damage induced by BCNI in the corpus cavernosum and promoted the recovery of erectile function	[128]
PLGA membrane	ADSCs, BDNF, and bFGF	A postprostatectomy ED model	Rat	Application of the BDNF-immobilized PLGA membrane with human ADSC and bFGF-incorporated hydrogel into the corpus cavernosum achieved nearly normal erectile function in a rat model of postprostatectomy ED	[135]
PLGA membrane	ADSCs and BDNF	A postprostatectomy ED model	Rat	ADSCs with BDNF-membrane on the CN could improve erectile function in this animal model, which may be used as a novel therapy for postprostatectomy ED	[129]
Hydrolyzed TMOS/PEG/chitosan nanoparticles	Tadalafil, sialorphin, and nitric oxide (NO)	An aging ED model	Rat	NPs encapsulating three different erectogenic agents increased erectile function *in vivo*, and the NPs represented a potential topical delivery of erectogenic agents for ED treatment	[136]

PA: peptide amphiphile; SHH: sonic hedgehog; CN: cavernous nerve; ED: erectile dysfunction; bFGF: basic fibroblast growth factor; SPION: superparamagnetic iron oxide nanoparticles; MSCs: human mesenchymal stem cells; ADSCs: adipose-derived stem cells; HP/GPT: heparin-pluronic/gelatin-poly(ethylene glycol)-tyramine; NGF: nerve growth factor; BCNI: bilateral cavernous nerve injury; PLGA: poly-lactic-co-glycolic acid; BDNF: brain-derived neurotrophic factor; TMOS: tetramethyl orthosilicate; PEG: polyethylene glycol; NPs: nanoparticles.

3.2.2. Applications of Nanomaterials in Cavernous Nerve Injury. Cavernous nerve injury is a common type of PNI, often associated with pelvic/retroperitoneal surgeries, diabetes, or aging. It can lead to erectile dysfunction (ED) by reducing morphological and functional reconstruction of the penile corpora cavernosa, including apoptosis and ensuing smooth muscle fibrosis and a lower response to normal signaling or treatments in erectile tissues [123]. For neurogenic ED, phosphodiesterase 5 inhibitors are the most widely used treatment in the clinic; however, they cannot effectively promote nerve regeneration and reverse the morphology and function of cavernous erectile tissues. Therefore, it is imperative to find an effective treatment for neurogenic ED.

With continuous comprehensive research on nanomaterials, their applications for topical delivery of drugs or nutritional factors to repair damaged nerves may become a novel therapeutic strategy for cavernous nerve injury; they are summarized in Table 4.

There is insufficient research on the repair of cavernous nerve injury than that of sciatic nerve injury. Recently, peptide amphiphile (PA) has been the focus of studies on cavernous nerve injury. As a delivery vehicle for sonic hedgehog protein, a vital regulator for neurite formation in peripheral neurons, PA had been applied in different cavernous nerve injury models. Under the synergy of PA, sonic hedgehog protein plays an essential role in maintaining the natural cavernous nerve structure and promoting cavernous nerve regeneration by boosting neurite formation in penile projecting neurons, suppressing smooth muscle apoptosis and fibrosis, and reducing collagen induction [124, 125]. Similar to PA, porous silane-based nanoparticles were also used in a rat model of type II diabetes to deliver curcumin and showed promising potential for ED treatment in preclinic studies. Compared with the control group, topical application of curc-NPs could effectively deliver curcumin, regulate the corporal expression level of inflammatory markers, and promote the recovery of ED [126]. Another therapeutic strategy using gelatin microspheres incorporated with b-FGF for ED achieved satisfactory results in diabetic rats [127]. Moreover, heparin-pluronic/gelatin-poly(ethylene glycol)-tyramine (HP/GPT) hydrogel decorated with b-FGF and NGF was designed to obtain a controllable release of these two GFs in rat models with bilateral cavernous nerve injury. A higher expression level of cyclic guanosine monophosphate, α-smooth muscle actin, and CD31 and a lower apoptotic level in the penile tissue were observed in rats treated with this decorated HP/GPT hydrogel than those treated with single growth factor alone, which contributed to the recovery of erectile function [128]. With the addition of ADSCs, a PLGA membrane incorporating with BDNF was designed and applied in cavernous nerve injuries and effectively improved erectile function in a rat model of post-prostatectomy ED [129]. Furthermore, 3D-printed hydrogel scaffolds seeded with muscle-derived stem cells with the hypoxia inducible factor-1α mutation were developed and showed great potential for penile reconstruction and reproductive capability restoration in a rabbit model [130].

3.2.3. Applications of Nanomaterials in Facial Nerve Injury. Facial nerve injury remains a tough clinical conundrum and may cause long-lasting disability and poor life quality [137]. Spontaneous regeneration of the defective nerve is incredibly slow, and it involves random axonal regeneration, obstructive scar formation, and possibly neuroma [138]. Many tissue-engineered nerve grafts have been designed and constructed in recent years, which have exhibited potential for facial nerve regeneration.

Recently, researchers have diverged on the issue of whether or not polyethylene glycol (PEG) fusion can play a positive role in facial nerve repair or not. Salomone et al. believed that PEG fusion can slow down demyelination in rats with facial nerve neurotmesis [139], while Brown et al. believe that using PEG for nerve suturing may not be a practical approach for the repair of facial nerve injury [140]. To solve this problem, more comprehensive and authoritative investigations of the role of PEG fusion in facial nerve injury repair should be conducted.

Compared to PEG, collagen is more prevalent in research on facial nerve injury repair. For sustainable delivery of GDNF, collagen conduits were applied to facial nerve defects (with an 8 mm gap) in rats. The results showed that a suitable concentration of GDNF was retained at the target site, and the efficacy of nerve regrowth and functional improvement was similar to that of an autograft [140]. Some other neurotrophic factors, such as neurotrophin-3 [141], ciliary neurotrophic factor [142], and b-FGF [143], were also bound with collagen conduits to boost the regrowth of facial nerves in rats, and all these combinations achieved good therapeutic efficacy. Interestingly, neural stem/progenitor cells loaded on collagen conduits with anchored b-FGF were found to play an indispensable role in facial nerve regeneration. This natural conduit accelerated functional recovery and nerve growth as effectively as an autograft [138]. In addition to various neurotrophic factors and seed cells, collagen can also work for nerve regeneration in the company of synthetic materials such as PGA [144] and PCL [145]. Moreover, the Nerbridge conduit, a new PGA-c nerve conduit, has been applied in the clinic. Two cases of Nerbridge successfully repairing the traumatic temporal branch of the facial nerve were reported, and these two patients achieved satisfactory results in the restoration of facial nerve function [146].

Besides collagen, a PGA tube was used as a carrier to deliver human exfoliated deciduous tooth stem cells, thereby assisting stem cells in differentiating into nerve cells in rats and promoting the regeneration of damaged facial nerves [147]. The chitosan-β-glycerophosphate hydrogel was also found to serve as an effective drug carrier and scaffold when filled in a specific vein conduit [148]. The joint application of autologous vein and C/GP-NGF hydrogel with a continuous release of NGF was able to boost the therapeutic efficacy of facial nerve defects (with a 5 mm gap) in rats with thicker myelin sheaths and larger regenerated axons than those in the NGF group [148]. Additionally, electro-spun SF nanofibers, PA nanofiber neurograft, silicone, and gelatin catheters are suitable materials for damaged facial nerve recovery, summarized in Table 5.

3.2.4. Applications of Nanomaterials in Median Nerve Injury. Injuries of upper extremities frequently occur in humans mainly on account of a motor vehicle collisions among young males, which may cause long-lasting disability and downgrade their life quality [149]. However, there are far fewer studies on the effect of nanomaterials on the median nerve than on the sciatic nerve, which are summarized in Table 6.

Chitosan, a novel natural nanomaterial, has received extensive attention in median nerve injury repair due to its excellent biocompatibility. A two-chambered chitosan nerve conduit was designed and tested in a 10 mm median nerve injury rat model. The designed nerve conduit provided better rigid support for nerve regrowth and further improved motor function of the upper limb [150].

In addition, a chitosan bioadhesive integrated with rose bengal (RB), a chemical for photochemical tissue bonding, is an alternative device for nerve regeneration that removes

Table 5: Nanomaterials applied to facial nerve injury in recent years.

Materials	Synergistic factors	Models	Animals	Gap (mm)	Results/conclusions	Ref.
PEG-fusion	Antioxidants	A facial nerve neurotmesis rat model	Rat	\	PEG-fusion achieved higher axonal diameter; although not providing a functional improvement, PEG-fusion slowed down demyelination	[139]
PEG-fusion	\	A facial nerve transection and neurorrhaphy rat model	Rat	\	PEG used for neurorrhaphy was not beneficial in a rat model of facial nerve injury; the addition of PEG to suturing might not be warranted in the surgical repair of facial nerve injury	[140]
Collagen nerve conduit	GDNF	A facial nerve defect rat model	Rat	8	The conduit effectively promoted the regeneration process by retaining a sufficient GDNF concentration at the target site; the efficacy on nerve regeneration and functional recovery was close to that of an autograft	[157]
Collagen	NT-3	A facial nerve crush injury rat model	Rat	\	CBD-NT-3 considerably enhanced facial nerve regeneration and functional recovery	[141]
Collagen nerve conduit	CNTF and BDNF	A facial nerve transection rat model	Rat	\	The combination of CNTF and BDNF greatly enhanced facial nerve regeneration and functional recovery	[158]
Collagen nerve conduit	CNTF and bFGF	A long facial nerve gap minipig models	Minipig	35	The number and arrangement of regenerated nerve fibers, myelination, and nerve function reconstruction were better in the CNTF+bFGF conduit group than in a single CNTF or bFGF conduit group; the functional composite conduit might promote facial nerve regeneration in minipigs effectively	[159]
Collagen nerve conduit	NS/PCs and bFGF	A facial nerve defect rat model	Rat	8	The conduit significantly promoted nerve growth and functional recovery, similar to those of an autograft; this conduit was valuable for facial nerve reconstruction	[138]
PGA-collagen tube	\	A facial nerve resection rat model	Rat	10	The tube achieved an inferior functional recovery obtained with an autograft. PGA-collagen tubes could be applied in facial nerve gap reconstruction, but further improvements were necessary to achieve results that are equivalent to those obtained with autografts	[160]
PGA-collagen conduits	ADSCs and SVF	A facial nerve defect rat model	Rat	7	The SVF conduit significantly achieved a higher amplitude of muscle action potential, larger axon diameter, and fiber diameter and had an easier construction process than ADSC conduit, indicating that SVF could be more suitable for nerve regeneration	[144]
PCL/collagen fibrous conduits	hUCS	A facial nerve defect rat model	Rat	4	The PCL/collagen/hUCS conduit provided more favorable microenvironmental conditions for facial nerve (FN) regeneration and had the more therapeutic potential for the regeneration of FN transectional damage than the autograft technique	[145]
PGA tube (PGAt)	BMSCs and Schwann-like cells differentiated from BMSC	A facial nerve defect autografted rat model	Rat	\	Regeneration of the facial nerve was improved by BMSC within PGAt in rats, yet Schwann-like cells were associated with superior effects	[161]

Table 5: Continued.

Materials	Synergistic factors	Models	Animals	Gap (mm)	Results/conclusions	Ref.
PLGA artificial nerve conduits	Containing rat DPC embedded collagen gel	A facial nerve defect rat model	Rat	7	PLGA tubes filled with DPCs promoted nerve regeneration and were readily resorbed *in vivo*	[162]
C/GP-hydrogel	MP	A facial nerve crush injury rat model	Rat	\	Locally injected MP delivered by C/GP-hydrogel effectively accelerated the facial functional recovery; the expression of GAP-43 protein was also improved by the MP, especially in the C/GP-MP group	[163]
C/GP hydrogel	Autologous vein conduit and NGF	A facial nerve defect rat model	Rat	5	NGF was continuously released from C/GP-NGF hydrogel *in vitro*; larger regenerated axons and thicker myelin sheaths were obtained in the C/GP-NGF group than those in the NGF group	[148]
Gore-Tex tubes	Polytetrafluoroethylene conduit filled with undifferentiated ADSCs encapsulated in alginate hydrogel	A facial nerve defect mongrel dog model	Mongrel dog	7	The addition of stem cells in the Gore-Tex tube enhanced the neural repair from a functional standpoint	[164]
Electrospun SF nanofiber conduits	\	A facial nerve defect rat model	Rat	5	Electrospun SF grafts promoted nerve regeneration after facial nerve injury and possibly became a potential NGC as an alternative to autografts for peripheral nerve regeneration	[165]
PA nanofiber neurograft	\	A facial nerve defect rat model	Rat	7.5	The neuroregenerative capability of these neurografts was similar to autograft	[166]
Bacterial cellulose (BC)	\	A facial nerve defect rat model	Rat	8	The numbers of regenerating myelinated fibers were significantly increased when BC tubes were used as a nerve conduit	[167]
Medgel	OSCs	A facial nerve palsy mouse model	Mouse	\	OSCs implanted with Medgel accelerated and enhanced recovery from facial palsy in mice	[168]
Acidic gelatin hydrogel microspheres	bFGF	A facial nerve defect rat model	Rat	7	A significantly increased rate of nerve regeneration and regenerating nerve axons	[169]
Silicone tube	Type I collagen gel containing dental pulp cells	A facial nerve defect rat model	Rat	7	Dental pulp cell facial palsy scores and amplitude and duration of compound muscle action potentials showed no significant difference from those of autograft	[170]
3D bioprinted scaffold-free neural constructs	GMSC spheroids	A facial nerve defect rat model	Rat	5	GMSC-laden nerve constructs promoted regeneration and functional recovery *in vivo* and possessed promising potential applications for the repair and regeneration of peripheral nerve defects	[171]

PEG: polyethylene glycol; GDNF: glial cell-derived neurotrophic factor; NT-3: neurotrophin-3; CNTF: ciliary neurotrophic factor; BDNF: brain-derived neurotrophic factor; bFGF: basic fibroblast growth factor; NS/PCs: neural stem/progenitor cells; PGA: polyglycolic acid; ADSCs: adipose-derived stem cells; SVF: the stromal vascular fraction; PCL: polycaprolactone; hUCS: human umbilical cord serum; BMSCs: bone mesenchymal stem cells; PLGA: poly-lactic-co-glycolic acid; DPCs: dental pulp cells; C/GP-hydrogel: chitosan-β-glycerophosphate hydrogel; MP: methylprednisolone; NGF: nerve growth factor; SF: silk fibroin; PA: peptide amphiphile; OSCs: olfactory stem cells; GMSCs: human gingiva-derived mesenchymal stem cells.

the requirement of sutures. Compared to the standard suture repair, RB-chitosan adhesive for median nerve repair showed comparable results based on histological and electrophysiological findings and yielded a faster and more notable functional recovery in a median nerve transection rat [151]. As an NGC, a chitosan hollow tube filled with fresh skeletal muscle fibers was developed to overcome the difficulty of muscle-in-vein preparation in rats with median nerve defects (8 mm). The results demonstrated that fresh skeletal muscles inside conduits could continuously produce endogenous soluble neuregulin 1 to promote the survival and dedifferentiation of SCs. Although the regenerative efficacy was similar to that of the hollow tube, the muscle-in-tube graft could serve as a promising option for nerve defect connection because it is more straightforward way to perform surgically [152]. Another natural nanostructure, a

Table 6: Nanomaterials applied to median nerve injury in recent years.

Materials	Synergistic factors	Models	Animals	Gap (mm)	Results/conclusions	Ref.
Chitosan bioadhesive	Integrated with RB responding to PTB technique	A median nerve transection rat model	Rat	\	RB-chitosan adhesive displayed comparable results on histological and electrophysiological findings and achieved quicker and more pronounced recovery of grip force when compared to the suture repair	[151]
Chitosan hollow tube	Skeletal muscle fibers	A median nerve defect rat model	Rat	8	The muscles provided endogenous soluble neuregulin 1 during the early regeneration; the muscle-in-tube graft might be a promising strategy to repair longer nerve gap or for secondary nerve repair	[152]
NeuraGen® collagen conduit	Human hair keratin biomaterial hydrogel	A median nerve transection NHP model	Macaca fascicularis NHP	10	An acellular biomaterial hydrogel conduit filler could be used to enhance peripheral nerve regeneration and motor recovery in an NHP model	[149]
PCL conduits	MSCs	A median nerve transection mouse model	Mouse	\	The PCL conduit filled with MSCs was capable of significantly improving the median nerve regeneration after a traumatic lesion	[172]
SilkBridge™ conduit	\	A median nerve transection rat model	Rat	10	SilkBridge™ conduit had an optimized balance of biomechanical and biological properties and led to a good functional and morphological recovery of the median nerve	[173]
Chitosan/PLGA-based nerve grafts	MSCs	A median nerve defect monkey model	Monkey	50	The recovery of nerve function was more efficient than that by chitosan/PLGA scaffolds alone, and morphological reconstruction was close to that by autografts	[174]
Iron oxide nanoparticles	Coated with PEI and loaded with VEGF and NGF	A median nerve defect rat model	Rat	5	The injection of VEGF and NGF functionalized MNPs with a biosecurity dose strongly accelerated the regeneration process and the motor function recovery compared to that obtained using the free factors	[156]

RB: rose bengal; PTB: photochemical tissue bonding; NHP: nonhuman primates; PCL: polycaprolactone; MSCs: mesenchymal stem cells; PLGA: poly-lactic-co-glycolic acid; PEI: polyethyleneimine; VEGF: vascular endothelial growth factor; NGF: nerve growth factor.

NeuraGen collagen conduit filled with human hair keratin biomaterial hydrogel, was also used in median nerve regeneration. This conduit can enhance nerve regrowth and motor restoration in an animal model with a 10 mm gap [149].

Among synthetic nanomaterials, PCL is the most attractive one in this field. PCL nanofiber wrap was developed and applied in NTE to repair median nerve damage. In a rat forelimb chronic denervation model, PCL wrap was able to promote nerve regeneration and subsequently slow down scar formation to improve the motor function of the upper limbs of rats [153]. Polymeric microspheres embedded in PCL conduits encapsulating GDNF were capable of providing a sustainable release of GDNF and bridging a 5 cm nerve gap in a rhesus macaque model [154]. PCL was also used as a nerve conduit to guide nerve regeneration and further boost nerve regeneration and functional restoration by loading with mesenchymal stem cells [155].

In addition, magnetic nanoparticles (MNPs) are also used for median nerve injury. MNPs immobilized with GFs inside an NGC were proposed to control the release of GFs over time and space. This exploration concluded that the injection of MNPs with a biosecurity dose potently promoted regeneration and motor function restoration [156].

In recent years, nanomaterials have also been widely applied in repairing other PNs, such as the trigeminal nerve, finger nerve, femoral nerve, phrenic nerve, and recurrent laryngeal nerve. The applications of nanomaterials for these nerve injuries are summarized in Table 7.

4. Prospects and Conclusion

PNI is a relatively common clinical disease and occurs mainly due to trauma or sometimes as a complication of surgeries. Patients with PNI may suffer from mild discomfort or even irreversible damage, which ultimately impairs body function and affects their work and life quality [4, 5, 175]. Currently, pharmacological treatment and surgical methods for PNI are severely limited, but recently tissue engineering therapy, mainly mediated by nanomaterials, has become the most promising choice. Tissue engineering therapy is supposed to mimic the native physiological environment and regulate cell behavior to promote the regeneration and functional recovery of injured nerve tissues. Many investigations on nanomaterials have shown adequate regenerative efficacy, demonstrating that tissue engineering therapy is feasible and effective in PNI treatment.

In this review, we enumerated the clinically approved nerve conduits, such as collagen and poly (l-lactide-co-ε-caprolactone) that can be used for PN regeneration. However, the therapeutic effect of these conduits is limited in clinical cases and more ideal nanomaterials need to be developed for PIN repair in the clinic. We also summarized the

Table 7: Nanomaterials applied for other peripheral nerve injuries in recent years.

Nerves	Materials	Synergistic factors	Models	Animals	Gap (mm)	Results/conclusions	Ref.
Fibular nerve	PGSm conduits	\	A common fibular nerve injury mouse model	Mouse	3	PGSm acted as a supporting substrate for both neuronal and glial cell growth *in vitro* and achieved regeneration of axons *in vivo*	[178]
Trigeminal, infraorbital nerve (ION)	fUBM-ECM nerve wraps	\	A trigeminal nerve transection rat model	Rat	\	fUB-ECM nerve wraps were biocompatible and bioactive and acted as good experimental and potentially clinical devices for treating epineural repairs	[179]
Cauda equina nerve	Collagen-laminin scaffolds	SCs	A cauda equina ventral root transected rat model	Rat	3	The findings demonstrated the feasibility of using CLSCs in cauda equina injury repair	[180]
Auditory nerve	Novel nanofibrous scaffolds	Neural precursor cells (NPCs)	A deafened guinea pig (Cavia porcellus) model	Guinea pig	\	The scaffolds showed partial recovery of electrically evoked auditory brainstem thresholds; this scaffold posed a promising strategy for auditory nerve regeneration	[181]
Laryngeal nerve (RLN)	Collagen tube	Loaded with laminin, LBD-BDNF, and LBD-GDNF	A rat RLN transection injury model	Rat	5	The collagen tube achieved an improved recovery in vocalization, arytenoid cartilage angles, compound muscle action potentials, and regenerated fiber area than that of autograft; the drug delivery system had superior efficacy than autograft in nerve regeneration of RLN transection injury.	[182]
Optic nerve	HSA-Br-NPs	Brimonidine	A rat optic nerve crush (ONC) model	Rat	\	Human serum albumin nanoparticles showed neuroprotective potential by inhibiting Aβ deposition and exerted a sustained therapeutic effect with the combined neuroprotective agent	[183]
Phrenic nerve	Chitosan nanofiber tube (C-tube)	\	A phrenic nerve injury beagle dog model	Beagle dog	5	C-tube group showed improvement of diaphragm movement with time, but no nerve fiber regeneration was found by histology	[184]
Femoral nerves	Silicon conduit	MABMC	A rabbit femoral nerve defect model	Rabbit	5	This cell therapy did not improve regeneration of the femoral nerve, but there was a tendency for better functional recovery	[185]

PGSm: poly(glycerol sebacate methacrylate); ION: fUBM-ECM: fetal porcine urinary bladder extracellular matrix; SCs: Schwann cells; NPCs: neural precursor cells; LBD: laminin-binding domains; BDNF: brain-derived neurotrophic factor; GDNF: glial cell-derived neurotrophic factor; HAS-Br-NPs: human serum albumin nanoparticles conjugated with brimonidine; MABMC: mononuclear autologous bone marrow cells.

preclinical strategies of nanomaterials in PNI and discussed the application prospects and therapeutic efficacy of nanomaterials in different PNI diseases. We found that nanomaterials have been extensively investigated and tested in defective sciatic nerves, while there are much fewer reports on other injured peripheral nerves, such as cavernous nerves, facial nerves, and median nerves. However, clinical studies have shown diverse regenerative potential in different types of PN damage [176], which was confirmed by the gene and protein expression levels of Wallerian degeneration brought by PN damage [177]. These studies suggest that more attention should be paid to different PNI diseases and more comprehensive and in-depth studies on the mechanisms of PN injury and regeneration, especially in different peripheral nerves, are urgently needed to provide a powerful guide for scaffold construction, cell loading, and cytokine regulation in NTE and even personalized treatments in the future. Moreover, only a few methods for PN regeneration can achieve therapeutic efficacy equal to or better than that of autologous nerve transplantation, the gold standard for PNI repair. Due to their limited therapeutic efficacy, novel nanomaterials or existing materials with optimal modification should urgently be developed to better simulate the regeneration environment *in vivo*, thereby rescuing more damaged nerves and accelerating the transformation of nanomaterials from laboratory research to clinical applications.

In conclusion, with the rapid development of nanotechnology and bioengineering, nanomaterials have shown ideal application prospects in PN regeneration. However, the limited properties of nanomaterials and incomplete understanding of the mechanisms of PN regeneration have hindered the application of nanomaterials in PNI diseases. To our knowledge, this was the first review to focus on different peripheral nerves and discuss the application of different

nanomaterials in specific peripheral nerves. This review also emphasized that more investigations are warranted to explore the regenerative mechanisms of different types of PNI and uncover the ideal application of nanomaterials in different injured nerves, which would provide a novel guidance for the study of PN regeneration and personalized treatments for PN repair.

Abbreviations

PNI: Peripheral nerve injury
PN: Peripheral nerve
SCs: Schwann cells
NTE: Neural tissue engineering
SF: Silk fibroin
PLA: Polylactic acid
PLGA: Poly (lactic acid-co-glycolic acid)
NGF: Nerve growth factor
BDNF: Brain-derived neurotrophic factor
GDNF: Glial cell-derived neurotrophic factors
PGA: Polyglycolic acid
PGA-c: Polyglycolic acid-collagen
LOCC: Longitudinally oriented collagen conduit
b-FGF: Basic fibroblast growth factor
PCL: Polycaprolactone
NGC: Nerve guidance conduit
ED: Erectile dysfunction
PA: Peptide amphiphile
PEG: Polyethylene glycol
MNPs: Magnetic nanoparticles
GFs: Growth factors.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

J.Z. and Z.Z. were responsible for the conceptualization. J.Z., Q.F., and L.L. were responsible for the original draft preparation. J.Z., Q.F., ZW.Z., and L.S. reviewed and edited the paper. Q.F., L.L., and ZW.Z. were responsible for the bibliographic search. J.Z., Z.Z., Y.X., and L.S. were responsible for the supervision. All authors have read and agreed to the published version of the manuscript. J.Z. and Q.F. are co-first authors. Jianqiang Zhu and Qingfeng Fu have contributed equally to the article.

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