Polymers Containing Natural Plant Phenolic Compounds for Peripheral Nerve Injury

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Abstract: Peripheral nerve injury is a serious and disabling disease prevalent in the world. It caused by trauma is often accompanied with soft tissue injuries, fractures, infections, etc., and can cause permanent damage. The treatment methods of peripheral nerve injury mainly include traditional microsurgical repair, neurotrophic drug treatment, as well as cutting-edge nerve conduit treatment, nerve stimulation, cell therapy, etc. However, more than 30% of patients with peripheral nerve injury still have poor recovery, including partial loss or complete loss of motor and/or sensory function, muscle atrophy， chronic pain and severe disability, among can lead to permanent disease. Phenolic compounds are secondary metabolites which is the most abundant in plants, consisting of an aromatic ring and one or more hydroxyl substituents, the main groups including flavonoids, phenolic acids, tannins, stilbene and lignans. A lot of studies have shown that natural phenolic compounds have various properties, such as antioxidant, anti-infective, anticancer, anti-inflammatory, etc., and have broad applications in the prevention of heart disease, cancer, diabetes, oxidative stress-related diseases, and neuroprotection prospect. This review discusses the potential applications and molecular mechanisms of natural phenolic compounds its polymer derivatives in the treatment of peripheral nerve injury.

Keywords: Peripheral nerve injury; Natural phenolic compounds; Nerve regeneration; Polymeric materials; Anti-infective; Analgesia; Antioxidant; Anti-inflammatory.

1. Introduction

Peripheral nerve injury is a prevalent and disabling disease worldwide, with motor vehicle accidents, penetrating trauma, falls and workplace injuries being the most common causes [1]. Endogenous regeneration is possible if the nerve maintains continuity, but if the nerve loses its continuity, surgical splice is required to restore it[2]. For nerve injury in segmental defects, autologous nerve transplantation is considered as the gold standard[3]， but only 40%-50% of patients receiving peripheral nerve injury repair are able to regain function, and biological pathways are still needed to promote nerve regeneration and improve functional outcomes after injury. Phenols are the richest natural secondary metabolites in plants, which exist in many grains, fruits, vegetables, herbs, and spices. Phenolic compounds consist of an aromatic ring and one or more hydroxyl substituents, and the main groups include phenolic acids, tannins, flavonoids, lignans and stilbene, etc.[4]. A mass of studies have shown that phenols display various properties, such as antioxidant, antimicrobial, anti-cancer, anti-inflammatory, etc. [5]. The polymeric derivatives can maintain phenolic concentrations and slow down their metabolism, thereby enhancing their effects. In peripheral nerve injury, natural phenols and their polymeric derivatives may act through their antioxidant, antimicrobial, anti-inflammatory, pain-relieving, and neuroprotective abilities, with potential advantages such as easy availability, convenient implementation, and fewer complications.

2. Natural Phenolic Compounds and Peripheral Nerve Injury

2.1. Natural Phenolic Compounds

Polyphenols are natural secondary metabolites that are widely present in all higher plants. The basic structural feature of phenolic compounds is an aromatic ring containing one or more hydroxyl groups. According to the number of phenol units in the molecule, it is divided into simple phenols and polyphenols. Polyphenols include coumarin, lignin, lignans, tannins, phenolic acids and flavonoids, etc. [6] （Figure 1.）. Flavonoids are the most abundant class of plant phenolic compounds, and more than 4,000 flavonoids have been found[7]， divided into 6 subgroups based on composition: flavonols, flavonoids, flavonoids, anthocyanins, flavanols and isoflavones[8]. Phenolic acids are also the main type of phenols in plants, which can be divided into two subclasses: hydroxybenzoic acid (HBA) and hydroxycinnamic acid (HCA)[9]，such as catechin, caffeic acid, etc. Tannin is a kind of phenolic compound with relatively high molecular weight （500-3000Da）, which mainly exists in plant tissues as high molecular complex polymers composed of organic acids and glycosides[10]. It can be split into condensed and hydrolyzed tannins, which has the ability to form oxidative bonds with other plant molecules[11]. Lignans are cell wall phenolic compounds produced by the oxidative dimerization of two phenylpropane units. They are insoluble and have the effect of protecting plants. Cereals, oilseeds, especially flaxseed are important sources of lignans[12]. Stilbene derivatives are a class of phenolic compound with a small molecular weight composed of a 1,2diphenylethylene nucleus and some hydroxyl groups, mainly represented by resveratrol, which has antioxidant, anti-inflammatory, anti-cancer and other effects[13]. Natural phenolic compounds have the potential advantages of high content and easy availability. Its polymer derivatives can enhance their effect, has become the focus of current research. Methods for extracting phenols from plants include solid-liquid extraction, heating and reflux extraction, ultrasonic-assisted extraction，etc.[14]. For the quantitative analysis of phenolic compounds, gas chromatography ， spectrophotometry, high performance liquid chromatography and their combinations are commonly used [15].

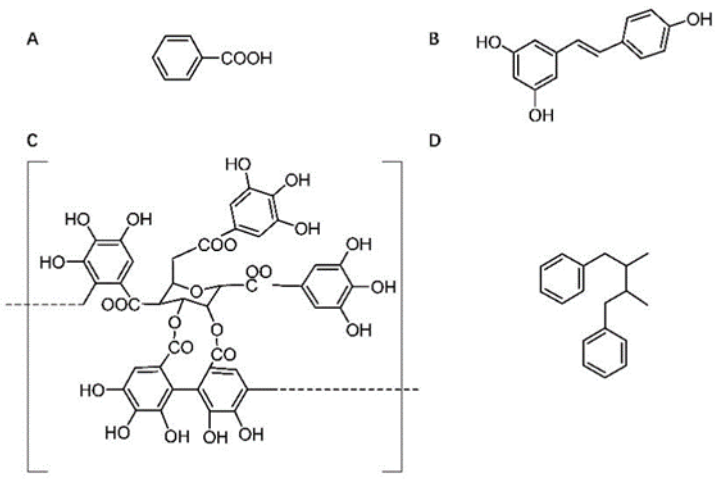

Figure 1. The chemical structure diagram of phenolic acids (A), resveratrol (B), the repeating unit of the ellagitannin of chestnut wood (C), classical lignan (D).

2.2. Peripheral Nerve Injury

Peripheral nerve injury is a general and disabling lesion in the world, which can cause lots of signs and symptoms, such as throbbing, tingling, numbness, dyskinesia, and burning pain. The sensory signals of the human body are transmitted to the central nervous system through sensory nerve fibers, and the resulting responses are transmitted to the target end by motor nerve fibers of the peripheral nervous system[16]. Peripheral nerve fibers are one of the most fragile structures in our body and are susceptible to damage, which affects motor activity and sensory loss in the areas they innervate. Damaged neurons in peripheral nerve injury are separated into distal and proximal parts, with Wallerian degeneration at the distal end and retrograde deformation at the proximal end[17]. In the hours following an injury, the ends of axons that have ceased to function seal off and swell, leading to the destruction of the myelin sheath. Subsequently, neurofilaments and cytoskeleton also disintegrate, fibroblasts proliferate, and dense fibrous tissue scars form at the injury site[18], further increasing inflammation. During peripheral nerve regeneration, macrophages are activated and myelin deposits are engulfed[19]. At the same time, macrophages and Schwann cells produce cytokines to promote axonal growth, form Bungner bands, connect endometrial tubes, and release growth factors to guide regenerated axons to reinnervate nerves[20]. Human axons regenerate with a rate of approximately 1 mm/day[21], most injuries often take months to years to heal. The damage of the endoneurium often leads to the retraction of the nerve fiber ends, coupled with the proliferation of fibroblasts, forms dense scars, which affect the regeneration of axons[22]. If there is no regenerated axon in the endoneurium, it will eventually be completely destroyed by fibrosis[23]. Therefore, peripheral nerve injury often requires surgical means to restore the continuity of the nerve, and nonsurgical means to reduce inflammation and proliferation, thereby promoting the recovery of the injury. The main purpose is to restore the continuity of the nerve[24]. Current research shows that phytochemicals also have a positive effect on accelerating the treatment of peripheral nerve injury.

3. Treatment of Peripheral Nerve Injury with Natural Plant Phenolic Compound

Studies have shown that natural phenolic

compounds can play a positive effect in neurodegenerative diseases and peripheral nerve damage. In the process of peripheral nerve injury, natural phenols and their polymer can work in pain management, neuroprotection and promotion of nerve regeneration, antioxidant, anti-inflammatory, anti-microbial and so on.

3.1. Pain Management

Pathological pain is the main clinical problem that plagues patients during the occurrence, recovery and sequelae of peripheral nerve injury, mainly manifested as continuous or intermittent spontaneous pain, such as burning, tingling, squeezing, etc.[25], which can be accompanied by evoked pain, inflammation and proinflammatory cytokines that may exacerbate pain after peripheral nerve injury[26, 27]. Neuropathic pain is often associated with oxidative stress, activation of proinflammatory cytokines, and proliferation and activity of microglia[28]. The current treatment of pathological pain is dominated by analgesic drugs, such as pregabalin, gabapentin, tricyclic antidepressants, and opioids, but their clinical use is often limited and there are many adverse reactions[29]. Studies have shown that some natural phenols, such as curcumin, rosmarinic acid, caffeic acid, quercetin, etc., and their polymer derivatives have a good effect on pain management.

Turmeric is one of the main ingredients in making curries and mustards, and curcumin (Figure 5.) is the main phenolic compound in turmeric. Studies have shown that its medicinal properties are related to pain relief, with strong anti-inflammatory activity and inhibition of inflammatory factors[30]. In studies, the stress response to neuropathic pain promotes the release of cortisol into the blood, and increased the content of 11βHSD1 leads to hyperalgesia, while curcumin can inhibit serum cortisol concentration and 11βHSD1 expression in dorsal root ganglia and spinal cord, thereby reducing thermal pain and mechanical hyperalgesia induced by CCI[31].

In experiments of peripheral neuralgia caused by drugs, such as oxaplatin, curcumin can reduce neuroinflammation by restraining the activation of NF-κB mediated by oxidative stress, thereby reducing peripheral neuropathic pain[32].At the same time, curcumin can effectively reverse the hyperalgesia caused by long-term application of morphine drugs by inhibiting spinal CaMKIIα, and the preparation of polymer PLGA-curcumin can improve the solubility and bioavailability of curcumin, and achieve better pain relief effect[33]. In the pain response caused by brachial plexus injury (BPA), curcumin can reduce the content of cFos protein and NGF protein, the number of GFAP positive cells and the expression of GFAP protein, at the same time, the content of TNF-α and IL-6 in the spinal cord of rats were significantly reduced. And its polymeric derivatives can significantly reduce the pain caused by brachial plexus injury by inhibiting the expression of proinflammatory cytokines and pain-related proteins, and inhibiting the activity of astrocytes [34]. (Figure 2.）

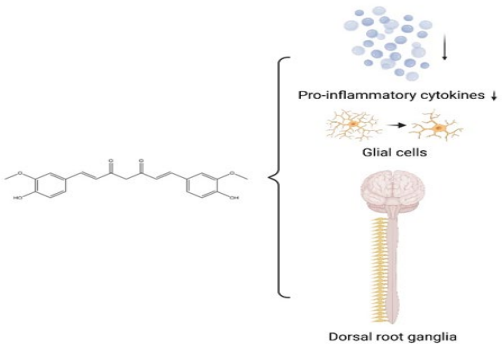

Figure 2. The mechanism of action of curcumin in reducing pain.

Rosmarinic acid and caffeic acid are the primary phenolic compounds in sage plants, which have certain anti-inflammatory and pain-relieving effects, and also have potential neuroprotective effects[35]. In animal experiments, rosmarinic acid showed a good pain relief effect, and its mechanism may be related to reducing the protein levels of GFAP, TLR-4 and Iba-1 in CCI mice, inhibiting the expression of TNF-α and iNOS enzymes（Figure 3.）, and resisting apoptotic factors (Bax, caspases 3, 9), thereby reducing pain response through anti-inflammatory, inhibiting glial cell activation and anti-apoptosis[36]. In vitro experiments, the formation of polymeric nanoparticles by encapsulating rosmarinic acid with chitosan can effectively protect the activity of rosmarinic acid, thereby increasing bioavailability, and may play a role in the treatment of nerve injury[37]. Caffeic acid and its derivatives also have a good analgesic effect. Studies have shown that in the behavioral experiments of CCI mice and the research on serum-related research indicators, the use of caffeic acid can effectively reduce serum CRP in mice, and in behavioral experiments shown to reduce pain, but the mechanism is unclear[38]. Phenethyl caffeate is a caffeic acid polymeric derivative, which is also a natural phenol, inhibited the p38 MAPK/NF-κB signaling pathway and TNF-α, IL-1β and the expression of inflammatory factors, for example IL-6, thereby restraining the activation of microglia and reducing pain[39].

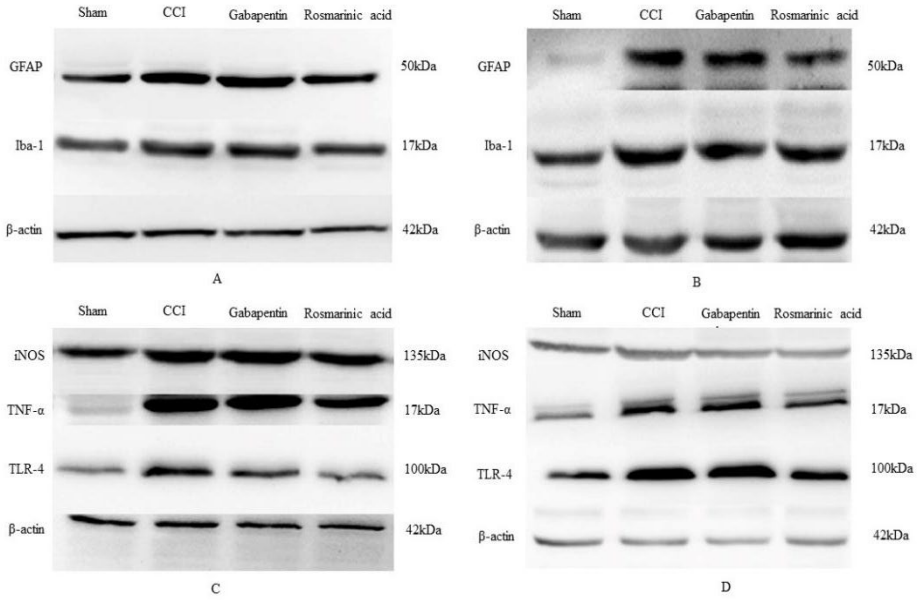

Figure 3. A. Immunoblot bands of GFAP and Iba-1 at 7 days B. Immunoblot bands of GFAP and Iba-1 at 14 days C. Immunoblot bands of iNOS, TNF-α and TLR-4 at 7 days D. Immunoblot bands of iNOS, TNF-α and TLR-4 at 14 days [36]. Used with permission from Elsevier and Nature America Publishing.

Quercetin, the most common flavonoid phenolic compound, is abundant in red grapes, kale, berries, apples, onions, broccoli and cherries, also in red wine and tea, and has strong antioxidant activity. Quercetin can activate the AMPK pathway and restrain the MAPK pathway and its downstream targets p-38, p-ERK and p-JNK, thereby relieving neuralgia in CCI rats [40]. In diabetic neuropathic pain, quercetin can inhibit the expression of P2X4 receptor in the dorsal root ganglion, thereby inhibiting the activation of p38MAPK and achieving the effect of alleviating pain [41]. Quercetin/chitosan-graft-alpha lipoic acid micelles is a versatile antioxidant water dispersion with high stability， can significantly enhance the antioxidant properties of quercetin, and play a slow-release quercetin effect [42]， may benefit quercetin for pain relief.

3.2. Neuroprotection and Promotion of Nerve

Regeneration

Peripheral nerve injury often leads to nerve defects, which can lead to injury or even rupture of nerve myelin sheaths and axons. Restoring the continuity of injured nerves and promoting nerve regeneration is crucial in the cure of peripheral nerve damage. Despite the increasing development of current microsurgical repair techniques, incomplete neurological recovery with sequelae often occurs [43]. The combined use of nerve regeneration drugs and microsurgery to treat peripheral nerve injury is one of the ideal treatment methods, but the neurotrophic drugs currently used are often unsatisfactory[44]. Finding an ideal drug to treat nerve injury is the current research direction. Phenolic compounds such as salidroside, green tea polyphenols, resveratrol, etc., have great potential in neuroprotection and neurorepair.

Salidroside is the main phenolic compound contained in rhodiola, which has antioxidative, antitumor, antiaging properties and other effects [45]. In peripheral nerve regeneration, the main exogenous mediators are the Schwann cells. In a rat experiment in which the continuity of the sciatic nerve stump was restored with autologous epimyal catheter and RSC96 Schwann cells, the application of salidroside generally improved the regeneration and functional rehabilitation of the rat sciatic nerve[46]. This mechanism may be related to that salidroside (Figure 4.) reduce the damage of oxygen free radicals to Schwann cells, and at the same time significantly upregulates the expressions of neurotrophic factors BDNF and GDNF, thereby inducing Schwann cell proliferation[47]. In the study of nerve damage induced by colistin treatment, salidroside can reduce Schwann cell damage by inhibiting oxidative stress, while regulating PI3K/Akt/mitochondrial signaling to increase Schwann cell tolerance, thereby reducing damage of Schwann[48]. The combination of salidroside and PLGA/Schwann cells to construct nerve conduits has improved treatment effect compared with the single application of PLGA/Schwann cells, which is conducive to orderly nerve arrangement and functional recovery, and significantly promotes nerve regeneration[49].

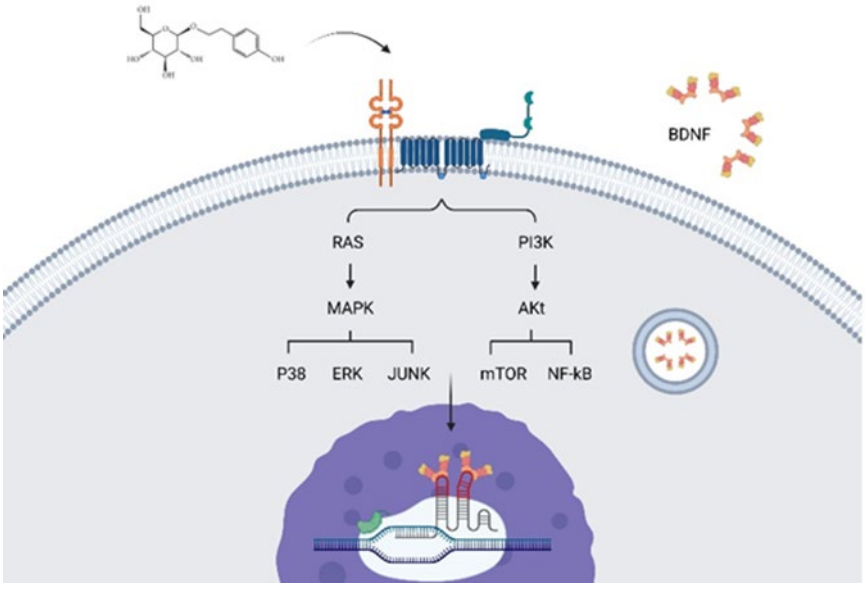

Figure 4. Salidroside can reduce the damage of oxygen free radicals to Schwann cells and upregulate the expression of neurotrophic factors such as BDNF

Green tea polyphenols (Figure 5.) are the dominating bioactive phenolic compounds in green tea, which have antioxidant, anti-inflammatory, and anticancer effects, and has a protective effect on the central nervous system in degenerative diseases of the central nervous system[50]. Experiments have

shown that green tea polyphenols also have a certain effect on the recovery of peripheral nerve damage. For rats with severed sciatic nerve, only the epineurium was sutured, and the application of green tea polyphenols could promote the mRNA and protein expressions of NGF, GAP-43, NF200 and MAG in sciatic nerve fibers. The adhesion between the nerve anastomosis and the surrounding tissue is relieved, and the nerve conduction velocity, the development of myelinated nerve fibers and the axonal regeneration are significantly improved, and the nerve regeneration is significantly promoted [51]. Green tea polyphenols and biodegradable poly (ε-caprolactone) (PCL) were made into polymeric implants, which can release green tea polyphenols for a long time, and may play a positive role in the clinical application of green tea polyphenols[52].

Resveratrol (Figure 5.), a nonflavonoid polyphenolic compound, is an antitoxin produced by many plants when they are irritated, and has antioxidant, anti-inflammatory, and cardiovascular protection effects[53]. Recent studies have shown that resveratrol is also effective in nerve protection and regeneration. Although surgery is often used to restore nerve continuity in nerve root avulsion injuries, but due to the retraction of the injured nerve stump and the slow regeneration of nerves, the curative effect is often poor [18]. The rat autologous nerve was used as a nerve graft to restore the continuity of the nerve, and the graft was pretreated with resveratrol，the results show that resveratrol can significantly increase the thickness of myelin sheath, the amount of nerve regeneration axons and motor neurons, at the same time, the expression of glial cell linederived neurotrophic factor (GDNF) and the number of dedifferentiated Schwann cells were significantly increased in neural grafts[54]. Resveratrol and its polymeric derivatives have a very strong potential in neuroprotection and regeneration. Experiments show that the complexation of resveratrol with cyclodextrin as an implantable polymer can stably release resveratrol and play a neuroprotective role. It can also reduce the oxidative stress and inflammatory response after intracortical microelectrode implantation through its antioxidant effect, thereby enhancing the therapeutic effect of intracortical microelectrodes on neurological diseases[55].

3.3. Antioxidant and Anti-inflammatory

After peripheral nerve injury, ischemia and inflammatory processes occur, and oxidative stress can disrupt peripheral nerve regeneration and repair processes after nerve injury. The production of oxygen free radicals can lead to lipid peroxidation, which can aggravate cell damage and lead to cell death [56]. Therefore, in the cure of peripheral nerve injury, antioxidant is also an indispensable part. Peripheral nerve damage is often associated with inflammation of nerves and surrounding tissues, and oxidative stress is also an important cause of inflammation. Many natural phenols have been proven to have antioxidant effects, which can be used as reducing agents, free radical quenchers and transition metal chelators [57]. It has broad application prospects in antioxidation, reducing inflammation, and promoting the recovery of peripheral nerve damage pharmaceuticals.

Prunus salicina lindl is a popular fruit that is widely used in food, pharmaceutical, cosmetic and other industries. It has antidiabetic and heart protection effects. Its biological activity is mainly related to its high content of phenolic compounds[58]. In an experiment, the antioxidant activity of Prunus salicina lindl extract was determined by DPPH method, ABTS method, FRAP method and ORAC method, the results showed that the higher the phenolic content of the extract, the stronger the antioxidant activity. Epicatechin, neochlorogenic acid, catechin, etc. contained in Prunus salicina lindl and their polymeric derivatives show good oxygen free radical scavenging ability, thus exerting antioxidant effect[59].

The curcumin mentioned above not only has a painrelieving effect, but also has a strong

antioxidant effect. Macrophages play a vital role in the immune system and are also vulnerable to reactive oxygen species. In vitro, curcumin can reduce reactive oxygen species (ROS) by enhancing the activities of superoxide dismutase (SOD), antioxidant enzymes such as catalase (CAT)and glutathione peroxidase (GSHPX), and activate the Nrf2-Keap1 pathway to resist oxidants and protect the activity of macrophages, thereby exerting an antioxidant effect[60]. It is also possible to control the release of curcumin by preparing curcumin-chitosan polymer, curcumin loaded poloxamer188based nanoparticles and curcumin-loaded shellac NPs, thereby regulating the antioxidant activity of curcumin[61-63].

The anti-inflammatory effects of phenols are not solely dependent on antioxidants, as their anti-inflammatory effects are also related to the regulation of cytokine production and the expression of proinflammatory genes. Resveratrol can prevent the production of IL-2 and IFN-γ by lymphocytes, and the production of TNF-α and IL-12 by macrophages, thereby inhibiting the occurrence of inflammation. Studies have also shown that resveratrol can inhibit microgliamediated neuroinflammation and protect neurons from inflammatory damage [64, 65]. In the inflammatory response stimulated by lipopolysaccharide, the addition of resveratrol can also reduce the levels of inflammatory factors such as TNF-α, PGE2, IL-1β, IL-8, COX-2 and monocyte chemoattractant protein-1[66]. Resveratrol cross-linked chitosan nanoparticles modified with phospholipids can protect resveratrol, reduce the degradation rate and improve the stability, which is an effective model for the application of resveratrol as a therapeutic drug[67].

3.4. Anti-infective Effect

Peripheral nerve injury caused by trauma, diabetes, postoperative infection, etc. is often accompanied by infection. The consequences of infection are often catastrophic and may result in a stronger inflammatory response, more severe pain, and delayed healing of the injury or not healed, which brings great challenges to the treatment of peripheral nerve injury[68]. The current treatment for infections is dominated by antibiotics, but due to the abuse of antibiotics, the current level of bacterial resistance is getting higher and higher[69]. Finding complementary medicines or substitutes for antibiotics has become an urgent and critical issue. Many natural phenolic compounds extracted from plants exhibit antibacterial, antiviral and antifungal activities in experimental or daily applications.

In studies, caffeic acid has antibacterial activity against Gram negative bacteria (such as Escherichia coli and Pseudomonas aeruginosa) and Gram positive bacteria (such as Staphylococcus aureus), and its antibacterial activity is stronger than traditional gentamicin and streptomycin [70]. Chitosan caffeic acid polymerization also showed good bacteriostatic effect on Staphylococcus epidermidis, Staphylococcus aureus and Staphylococcus, Pseudomonas aeruginosa, etc[71]. Catechin can display an antibacterial effect by inhibiting bacterial toxins and extracellular matrix, destroying bacterial cell walls and cell membranes, inhibiting enzymes in bacteria, oxidative stress, and damaging DNA. It plays a synergistic role with a variety of antibiotics, and can restore their sensitivity to antibiotics against drug-resistant bacteria such as Pseudomonas aeruginosa and methicillin resistant Staphylococcus aureus bacteria[72]. Polycatechin is obtained by reacting with glyceryl diglyceride ether cross-linking compound, which can obtain stronger antioxidant capacity, and its antibacterial activity against Staphylococcus aureus is stronger than that of monomer[73].

Curcumin has broadspectrum antibacterial activity against both Gram negative bacteria and Gram positive，it can inhibit bacterial growth by targeting bacterial cell membranes, cell walls, proteins, DNA and other cellular structures or by inhibiting quorum sensing (QS) systems [74].

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