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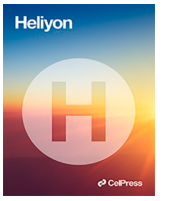

Review article

A comprehensive review of traditional Chinese medicine in treating neuropathic pain

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ABSTRACT

Neuropathic pain (NP) is a common, intractable chronic pain caused by nerve dysfunction and primary lesion of the nervous system. The etiology and pathogenesis of NP have not yet been clarified, so there is a lack of precise and effective clinical treatments. In recent years, traditional Chinese medicine (TCM) has shown increasing advantages in alleviating NP. Our review aimed to define the therapeutic effect of TCM (including TCM prescriptions, TCM extracts and natural products from TCM) on NP and reveal the underlying mechanisms. Literature from 2018 to 2024 was collected from databases including Web of Science, PubMed, ScienceDirect, Google academic and CNKI databases. Herbal medicine, Traditional Chinese medicines (TCM), neuropathic pain, neuralgia and peripheral neuropathy were used as the search terms. The anti-NP activity of TCM is clarified to propose strategies for discovering active compounds against NP, and provide reference to screen anti-NP drugs from TCM. We concluded that TCM has the characteristics of multi-level, multi-component, multi-target and multi-pathway, which can alleviate NP through various pathways such as anti-inflammation, anti-oxidant, anti-apoptotic pathway, regulating autophagy, regulating intestinal flora, and influencing ion channels. Based on the experimental study and anti-NP mechanism of TCM, this paper can offer analytical evidence to support the effectiveness in treating NP. These references will be helpful to the research and development of innovative TCM with multiple levels and multiple targets. TCM can be an effective treatment for NP and can serve as a treasure house for new drug development.

1. Introduction

Neuropathic pain (NP) is a common disease that afflicts many people. The etiology of NP is caused by damage to the sensory nervous system in the trunk or as a direct result of disease (e.g., cancer, trauma, and diabetes) [1]. According to the site of nerve injury, NP can be classified as peripheral NP (diabetic neuralgia pain, trigeminal neuralgia, etc.) and central NP (spinal cord injury, post-stroke pain, etc.). Most patients with NP have persistent burning, squeezing or compression pain, tingling or abnormal mechanical dynamics pain, and may be accompanied by precipitating pain, and are a common source of chronic pain [1]. If NP does not improve effectively, it can lead to depression, sleep disturbances, and a serious influence on life quality [2]. It is estimated that 7%–10 % of the

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Abbreviations

APC	antigen-presenting cell
BBB	Basso-Beattie-Bresnahan
STZ	streptozotocin
BDNF	brain-derived neurotrophic factor
BLA	basolateral amygdala
CCL2	chemokine ligand 2
CCI	chronic constriction injury
CIPN	chemotherapy-induced peripheral neuropathy
CNKI	China National Knowledge Infrastructure
SCI	spinal cord injury
CPSP	central post-stroke pain
DNP	diabetic neuropathic pain
DRD1	dopamine receptor D1
DRG	dorsal root ganglion
GPCR	G protein-coupled receptor
MWT	mechanical withdrawal threshold
NGF	nerve growth factor
NMDAR-2B,	N-methyl-D-aspartate receptor subunit 2B
NP	neuropathic pain
OIPN	oxaliplatin-induced peripheral neuropathy
PARP	poly ADP-ribose polymerase
pSNL,	partial sciatic nerve ligation
SNI	spared nerve injury
SCC	spinal cord compression
SGC	satellite glial cell
SNL,	spinal nerve ligation
SOD2	superoxide dismutase 2
STN	spinal trigeminal nucleus
TCM	traditional Chinese medicine;
TN	trigeminal neuralgia
TRPV1	transient receptor potential vanilloid
TTXr	tetrodotoxin-resistant
TTXs	tetrodotoxin-sensitive;
TWL,	thermal withdrawal latency
VGCC	voltage-gated calcium channels
VGSC	voltage-gated sodium channels

global population is suffering from NP [3]. The primary approach to treating NP is through medication. Currently, the use of painkillers is limited to opioids and non-steroidal drugs, which clinically has better pain-relieving effects, but at the same time have significant side effects. For example, they can cause nausea, vomiting, water and sodium retention, coagulation dysfunction, hepatic dysfunction and other side effects, so they cannot be used as widely used painkillers. In addition, opiate drugs can lead to addiction, respiratory depression, nausea and vomiting, and other serious side effects, which lead to a significant limitation of their use [4]. For this reason, we need to develop potential analgesic drugs and means with fewer side effects in pain treatment.

In recent years, traditional Chinese medicine (TCM) plays an indispensable role in anti-NP and it has lower side effects in treating the disease [5]. Many studies prove that TCM such as prescription treatments have a relieving effect on NP such as sciatica, trigeminal neuralgia, and cancerous pains [6–8]. Especially with the improvement of extraction and isolation techniques in TCM, many active molecules have been isolated and proved to be effective, such as tetrahydropalmatine [9] and berberine [10]. Currently, the pathogenesis of NP is relevant to many factors, such as inflammation, oxidative stress, ion channels and metabolic disorders, etc. Fortunately, TCM can treat NP through multi-pathway and multi-target treatment [11].

This review collected relevant literature on TCM for NP from 2018 to 2024 covering both domestic and international sources through Web of Science, Pubmed, ScienceDirect, Google academic and CNKI databases (herbal medicine, traditional Chinese medicine, neuropathic pain, neuralgia and peripheral neuropathy as search terms), excluding dissertations, conference papers, review articles, and excluding observation-only low-quality research articles. And the included literature was read one by one to organize useful information. Then reviewed the pathogenesis and classification of NP and its animal models, and reviewed the three aspects of TCM in terms of TCM prescriptions, TCM extracts, and monomer compounds extracted from TCM, respectively, to explore more potential biologically active TCM for the clinical application of NP disease and provide relevant reference for new drugs development.

2. Classification of NP and its animal models

Selecting and establishing appropriate animal models of pain is the key premise for NP research. According to etiology, NP can be divided into central nerve pain model, peripheral nerve injury model and disease-induced nerve pain model. Central nervous system pain is commonly seen in spinal cord injury (SCI), so it can be established by spinal cord compression, complete or partial spinal cord resection, photochemical ischemia, spinal cord compression, contusion or excitatory neurotoxin [12]. After SCI model was successfully established, motor dysfunction was evaluated by BBB (Basso Beattie Bresnahan) score and combined behavior score [13].

Peripheral nerve injury model is mainly constructed by injury and compression of spinal nerve and sciatic nerve, which can produce persistent pain to a large extent, so it has been widely used. Peripheral nerve injury can lead to dyskinesia, sensory disturbance, reflex disorder and autonomic nerve dysfunction in its innervation area, and can also induce hyperalgesia, allodynia and hyperalgesia. At present, the common models of peripheral nerve injury include chronic compression injury (CCI) model, spinal nerve ligation (SNL) model and spared nerve injury (SNI) model. CCI model is an animal pain model caused by peripheral single nerve injury [14]. The model was established by loosely ligating the sciatic nerve trunk of adult rats to produce peripheral mononeuropathy, followed by hyperalgesia and spontaneous pain (or sensory disturbance). SNL model could ligate L5 and L6 spinal nerves respectively, and mechanical hyperalgesia, thermal hyperalgesia and spontaneous pain appeared 1–2 days after operation and lasted for 4 months [15]. In addition, partial sciatic nerve ligation (PSNL) model was first reported by Seltzer [16]. In PSNL model, part of sciatic nerve was bluntly separated and deeply ligated. Within several hours to months after operation, rats showed ipsilateral hind limb protection and foot licking behavior, suggesting spontaneous pain. Von Frey test showed that rats produced allodynia and mechanical hyperalgesia, and thermal hyperalgesia at the same time. CCI model, SNL model and PSNL model can produce persistent and effective chronic pain. CCI model is more sensitive to pain, while SNL and PSNL models have longer pain duration. In addition, trigeminal neuralgia (TN) is a kind of NP in the face and mouth [17]. Pain is localized to one or more branches of the trigeminal nerve, may manifest as spontaneous pain, may be triggered by non-noxious stimuli, may recur, and is typically modeled in rodent strains such as Sprague-Dawley rats or C57BL/6 mice [18].

The NP models induced by diseases include diabetic neuralgia (DNP) model and chemotherapy-induced peripheral neuropathy model. DNP is the most common neuropathy worldwide [19], which can cause sensory loss, spontaneous pain, mechanical pain hypersensitivity and hyperalgesia symptoms. DNP model can be induced by drugs, diet, transgenic, etc., and the most common DNP model is established by streptozotocin (STZ) injection [20,21]. The STZ induced DNP model is simple, stable and successful, and DNP related peripheral neuropathy such as spontaneous pain, allodynia and hyperalgesia is accurate. Peripheral neuropathy after chemotherapy is one of the serious adverse reactions of chemotherapy, with an incidence of 30 %–40 % [22]. Drugs act on sensory

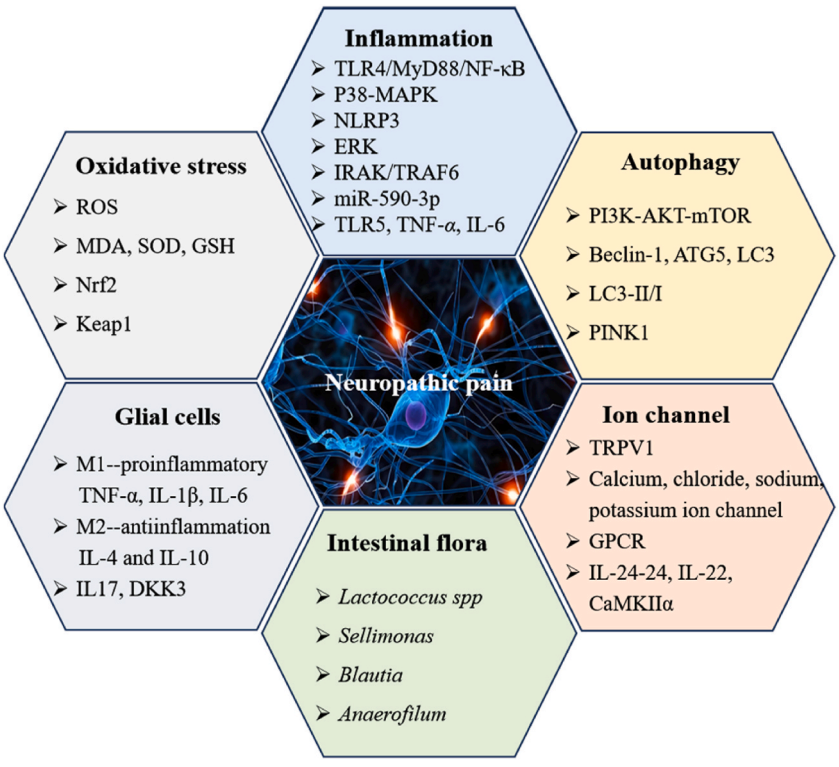

Fig. 1. Pathogenesis of NP. The pathogenesis of NP is mainly related to the development of inflammation, generation of oxidative stress, activation and transformation of glial cells, alteration of intestinal flora, occurrence of autophagy, and alteration of ion channels.

nerves, lowering action potentials and slowing conduction speeds, resulting in pain that persists long after chemotherapy is over. In addition, NP can lead to down-titration or premature discontinuation of chemotherapy, leading to cancer recurrence and reduced patient survival. Some chemotherapy drugs have neurotoxic effects and are easy to induce peripheral NP in the course of tumor treatment. At present, studies have been conducted to prepare peripheral neuropathy models by injecting antitumor chemotherapy drugs such as paclitaxel [23] and cisplatin [24] into tail vein or abdominal cavity of experimental animals. Chemotherapy-induced neuralgia lasts for a long time, even after the end of treatment, so it is helpful to propose treatment strategies for chemotherapy-induced neuralgia by studying animal models prepared with chemotherapy drugs.

3. Pathogenesis of NP

Many factors cause NP, including neuroinflammation, oxidative stress, activation of glial cells, autophagy, abnormal activation of ion channels, and changes in intestinal flora, as shown in Fig. 1.

3.1. Neuroinflammatory

The neuroinflammatory response is the key to the formation of peripheral sensitization. Peripheral sensitization mainly stems from the change of the chemical environment such as inflammatory response around the damaged nerve fibers. Another reason is relevant to the activation of immune cells accompanied by the secretion of inflammatory factors. Studies prove that NP symptoms of immunocompromised rats have significantly reduced compared to wild-type rats [25]. Immune cells (mast cell, neutrophil, macrophage, Schwann cell, and T cell) were activated and released many inflammatory cytokines after nerve injury. These cytokines include pro-inflammatory factors (TNF-α, IL-6, IL-1β), chemokines, inflammatory mediators, histamine, bradykinin, and nerve growth factor (NGF) [26]. These inflammatory factors activate or sensitize peripheral injury-sensing neurons, either directly or indirectly, to cause NP. In recent years, researchers have also found some new signal molecules in the role of neuroinflammation. Protein tyrosine phosphatase 1B (PTP1B) is a member of the protein tyrosine phosphatase family, mainly located in the cytoplasmic surface of the endoplasmic reticulum. After nerve injury, PTP1B will increase, causing endoplasmic reticulum stress, promoting the activation of NF-κB pathway and glial cell activation [27]. MicroRNA is distributed in central and peripheral nervous system and plays an important role in neuroinflammation. It has been reported that microRNA is involved in the development of NP [28]. In DNP, miR-590-3p was found to control immune cell entry into nerve tissue [29]. In addition, miRNAs can exert their role in NP by affecting multiple inflammatory signaling pathways, including TXNIP/NLRP3 inflammasome, MAP kinase, IRAK/TRAF6, TLR4/NF-κB, TLR5 and TNF-α signaling [30,31].

3.2. Oxidative stress

Oxidative stress is indispensable to the development of NP [32]. Many oxidative substances (oxygen radicals, superoxide nitroso and nitric oxide, etc.) are generated in the stress response after nerve injury. Overexpression of these oxidative products in cells can cause oxidative damage to cells, transforming normal highly regulated apoptosis into inflammatory necrosis. Poly ADP-ribose polymerase (PARP) is an enzyme that was widely distributed in cells participating in DNA repair and regulation of apoptosis. After nerve injury, oxidative products can over-activate PARP, rapidly depleting intracellular NAD^+ and ATP, leading to inactivation of the electron transport chain, interfering with mitochondrial energy metabolism and exacerbating nerve injury. PARP can also increase the secretion of MAPK, AP1, and NF-κB, to involve in the development of peripheral sensitization. Studies have shown that the neutralization of oxygen-free radicals and the use of PARP inhibitors can alleviate NP symptoms [33].

3.3. Glial cells

The glial cells are closely relevant to NP. The glial cells could be divided into microglial cells and central nervous system parenchyma or astroglial cells. Microglial cells mainly exist in perivascular. Central nervous system parenchyma or astroglial cells exist in neuroectoderm and synapse with nerve cells [34]. In CNS, microglia cells are the primary innate immune cells. Microglia cells are activated after stimulation when nerve injury results in NP. This is manifested as signal transmission following growing excitability in dorsal horn. This growing excitability derived from complicated signal transduction generated by communication among microglia, astrocytes, dorsal horn neurons and primary afferent nerves [35]. Glial cells will produce many growth cytokines, inflammatory factors and neuromodulators to induce neuroinflammation, and the secretion of cytokines further facilitates pain signaling and leads to neuropathic pain [35]. In addition, microglia cells can be divided into M1 and M2 types according to the activation. M1 microglia secrete pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. M2 microglia secrete anti-inflammatory cytokines including IL-4 and IL-10 [36], and M1 and M2 phenotypes can switch to each other. For example, anti-inflammatory or pro-inflammatory cytokines released by other cells can cause microglia to polarize. IL-17, a cytokine, produced mainly by T cells and NK cells, can trigger microglia production of inflammatory cytokines, while IL-4, an anti-inflammatory cytokine produced mainly by mature lymphocytes and mast cells, transforms microglia into an anti-inflammatory phenotype [37]. Other studies found that enhanced glycolysis could also promote microglial proliferation and proinflammatory phenotype transition by promoting nuclear translocation of IRF5 in the spinal dorsal horn, leading to neuropathic pain [38]. Zhang et al. [39] found that DKK 3 (a secretory glycoprotein) ameliorates neuropathic pain by preventing ASK1/JNK/p38-induced microglial polarisation and neuroinflammation. Therefore, changing the microglial phenotype is a viable approach to improve the NP.

Astrocytes also play a key role in NP by releasing a variety of factors such as cytokines, excitatory amino acids and adrenaline [40,41]. Connexin43 hemichannels in astrocytes are associated with maintenance of neuropathic pain after peripheral nerve injury [42]. In addition, CaMKII and CaV3.2 activate astrocytes by increasing intracellular Ca^{2+} levels, thereby participating in Cx43-based neuroinflammation, apoptosis, and mitochondrial damage in vincristine induced neuropathic pain [43]. Du et al. [44] found that astrocyte aging is also involved in NP, which may be related to clusterin protein. Overall, the mechanisms by which microglia and astrocytes are involved in NP are complex and involve multiple factors.

3.4. Autophagy

Autophagy is a self-digestive process which is dynamically adjusted by autophagosome induction and formation, and autophagosome-lysosome fusion. Recently, many studies have shown that autophagy is crucial for neuronal survival and homeostasis [45]. PI3K-AKT-mTOR signaling axis is a well-recognized autophagy-regulated signaling pathway [46]. mTOR, acts as a serine/threonine kinase, which can regulate cellular metabolism and and cell growth. mTOR signaling regulation is close to many human diseases, including diabetes mellitus, neurodegenerative disorders, and malignant tumors [47]. Researchers have found that regulating autophagy by modulating mammalian mTOR attenuates NP [48]. PINK1 can recruit autophagy receptors to initiate mitosis [49]. In SNL-induced NP rats, PINK1 expression is elevated and selectively localized to GABAergic interneurons, especially in autophagy mitochondria. Mitochondrial autophagy is associated with phagocytosis of damaged mitochondria [50]. During neuropathic pain, NLRP3 inflammatory bodies are activated in microglia, which can be inhibited by mitochondrial autophagy [51]. In general, NP can be reduced by regulating autophagy.

3.5. Ion channel

Ion channel is critical for the production and conduction of pain signals. Changes in the expression level and activity of pain-related ion channel is directly involved in peripheral sensitization. In the process of local inflammation caused by tissue injury, damaged primary afferent nerves, exudate immune cells, dilated blood vessels and excited sympathetic nerves can release a large number of inflammatory cytokines, which change the expression level and activity of pain-related ion channels, leading to peripheral sensitization [52]. A variety of ion channel abnormalities are involved in the development of NP, including calcium, sodium, chloride, potassium, TRPV1 channels, GPCR, etc. [53,54]. Recent studies have found that calcium ion channels are closely related to IL-24 [55]. IL-24 activates IL-22 receptor 1 and PKA signaling mediated by tyrosine protein kinase Lyn to enhance T-type calcium current, resulting in neuronal hyperexcitation and pain hypersensitivity. At the same time, excessive calcium influx may lead to increased mitochondrial membrane permeability, ATP depletion, cytochrome *c* (Cyt-c) release, free radicals and reactive oxygen species (ROS) production, thus activating apoptosis pathway [56]. CaMKIIα is particularly abundant in the central nervous system and is present in excitatory synapses [57]. SIRT1 is a member of the sirtuins family, and abnormal reduction of SIRT1 in the spinal cord after nerve injury increases Nav1.3 epigenetically, which subsequently activates CaMKIIα neurons and causes NP [58]. Yuan et al. [59] found that Kv1.3 channels in the spinal cord can participate in NP by promoting microglial M1 polarisation and activating NLRP3 inflammatory bodies.

3.6. Intestinal flora

Recent studies have shown that intestinal flora has the ability to influence the nervous system. Intestinal flora can modulate the activation of immune molecules by affecting the pro-inflammatory factors IL-8 and IL-1 and anti-inflammatory factors IL-10 and TGF-β [60,61], thereby affecting microglial activation. Studies have reported that NP is relevant to central nervous regulation disorder caused by gut-brain axis disorder [62]. In one study, it was found that the incidence of postherpetic neuralgia was significantly lower in patients with herpes zoster who had a strong cellular immune response than in those who had a weak response [63]. This suggests that postherpetic neuralgia is relevant to the body's immune system, and the intestine is the main organ for absorbing nutrients and the important immune organs. Zhong et al. [64] found that chemotherapy-induced disruption of the intestinal epithelial barrier can result in the displacement of intestinal flora and the release of harmful endogenous substances, which stimulate the host's antigen-presenting cell (APC), triggering the secretion of abundant pro-inflammatory mediators, which is a crucial cause for the development of Chemotherapy-induced peripheral neuropathy. Research showed that after sciatic nerve ligation, mice that were given oral antibiotics to alter the intestinal flora had far more regulatory T cells than pro-inflammatory Th1 cells, and their mechanical and thermal pain thresholds were significantly raised [65]. Bonomo et al. [66] demonstrated Western diet-induced NP could be ameliorated by transplanting the gut flora of normal-diet mice. The mechanism is related to a decrease in the hyperexcitability of neurons, macrophages, Schwann cells, and immune cells through their potential metabolites such as butyrate.

3.7. Others

With the further study of NP pathogenesis, some new viewpoints and mechanisms have been revealed gradually. Studies have found that drug destruction of blood vessel formation during chemotherapy in patients with cancer pain can cause NP [41]. Therefore, it is possible to alleviate pain by influencing angiogenic factors (VEGF, angiopoietin, fibroblast growth factor, etc.) to promote angiogenesis. Since iron apoptosis was first defined as a new iron-dependent cell death model in 2012, more and more studies have focused on the process and function of iron apoptosis [67]. Similarly, the role of iron death in NP has attracted attention and iron death

pathway was activated during NP [68]. Intracellular iron accumulation was observed in CCI or SNI-induced NP rat models, and iron accumulation induced lipid peroxidation and ROS production, resulting in mitochondrial damage, activated iron death [69,70]. Iron death enhances pain and hyperalgesia in NP rats by reducing neuronal and astrocyte activation [71]. The complement system is a key element of the innate immune response and works in concert with antibodies and phagocytes to clear pathogens [72]. Complement 5a (C5a) protein is one of the key components of the complement system and, when properly activated, C5a is essential for host defense and pathogen clearance; however, inappropriate activation can cause peripheral neuropathy [73]. The C5a/C5a receptor axis was found to promote leukocyte recruitment and proinflammatory cytokine production, driving inflammatory and NP [74]. In addition, up-regulation of C5a and C5a receptors was also found in spinal microglia of SNI model animals, and activation of C5a receptor 1 was also found to be associated with mechanical nociceptive sensitization in vivo models of postoperative pain [75]. In conclusion, the C5a/C5a receptor 1 axis is involved in various inflammatory and NP models, suggesting that targeting the C5a/C5aR1 axis may be a novel therapeutic target.

4. TCM prescription for NP

There is no neuropathic pain name in theory of traditional Chinese medicine, but it is attributed to the pain syndrome according to the symptoms. Although the causes of various neuropathic pain are different, the holistic view of TCM and the concept of treating different diseases provide a theoretical basis for the clinical treatment of such pain. In recent years, a lot of clinical data further confirmed that TCM prescriptions in a variety of NP have shown good therapeutic effect [76–80]. TCM prescriptions are a combination of various traditional Chinese medicines according to the theory of traditional Chinese medicine to regulate the body function and play a therapeutic role. In a retrospective study on the treatment of moderate to severe painful diabetic peripheral neuropathy with traditional Chinese medicine, 30 moderate or severe patients took Huangqi Guizhi Wuwu Decoction twice daily. After 6 months, the symptoms of limb pain, limb numbness and insomnia were significantly improved, and no serious adverse events occurred during the whole treatment period [76]. Gao et al. [80] found that Rongjin Tongbi Decoction could effectively relieve the pain of patients with sciatica caused by lumbar disc herniation due to deficiency of liver and kidney, improve the quality of life of patients, and there was no statistically significant difference in liver and kidney function related indicators before and after treatment, suggesting that the prescription was relatively safe. For postherpetic neuralgia, Buyang Huanwu Decoction and Shentong Zhuyu Decoction can improve pain score, sleep score and anxiety of patients [77,78]. Chinese medicines also has a good effect on patients with TN. Shi et al. [79] found that the number of headache attacks, duration and VAS score of patients after treatment with Longdan Xiegan Decoction were significantly lower than those before treatment, and the levels of inflammatory factors CRP, IL-6 and TFN-α of patients were significantly lower than those before treatment.

In the clinical observation of efficacy, adverse reactions can be seen. For example, in the study of Ni et al. [77], 17.64 % of patients in the traditional Chinese medicine treatment group experienced or partially experienced somnolence, dry mouth and dizziness, but the incidence rate was lower than that in the pregabalin treatment group. In addition, in a clinical observation of Tongqiao Huayu Decoction in treating TN, the incidence of dizziness, nausea, fatigue and other adverse reactions in Tongqiao Huayu Decoction group was 21.7 %, significantly lower than that in carbamazepine control group (50 %) [81]. Although Chinese medicines treatment showed some side effects, no serious adverse reactions were reported, and the side effects of Chinese medicines were lower than those of Western medicine, suggesting that Chinese medicines has higher safety.

For clinical studies, researchers pay more attention to the safety and effectiveness of drugs, while there are very few studies on the mechanism of action of drugs. Therefore, to deeply analyze the mechanism of TCM in treating neuropathic pain, researchers often carry out related studies in animal models. Chronic constriction injury (CCI) and spared nerve injury (SNI) are two commonly used animal models to study NP [14,82]. Duhuo Jisheng Decoction can regulate neuroinflammation and improve CCI-induced mechanical abnormal pain by suppressing microglia M1 polarisation and thus inhibiting IL-1β and IL-6 expression [83]. Wutou Decoction is a classic formula, which was found to be able to promote the secretion of NGF and BDNF through PI3K and PKA signaling pathways to exert the anti-NP effect [84]. In addition, Wutou Decoction can inhibit hippocampal microglia activation and restore the balance between glutamate and GABA neurons in the hippocampus to exert analgesia [85]. Yuanhu Zhitong Formula (YZF), can reduce the production of β-amyloid precursor protein, proto-oncogene tyrosine protein kinase, p-JNK1, and p-ERK1/2 when given continuously to alleviate NP in SNI rats [86].

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and serious adverse reaction after chemotherapy for tumors. CIPN can be manifested as pain, numbness and other sensory disorders, which seriously impact patients' life quality [87]. Both Huangqi Guizhi Wuwu Decoction and Danggui Sini Decoction can alleviate CIPN pain [88]. In addition, Huangqi Guizhi Wuwu Decoction can increase the threshold of mechanical pain, cold pain and thermal pain in CINP rats, and alleviate chemotherapy-induced NP through down-regulating TNFα/IL-1β/IL-6/MAPK/NF-κB pathway [89]. Siwei Jianbu Decoction could alleviate paclitaxel-induced peripheral pain and improve peripheral neuropathy by down-regulating NF-κB and MAPK pathways [23]. In pain induced by breast cancer bone metastasis, Yanghe Decoction could down-regulate the secretion of TRPA1, TNF-α, IL-1β, IL-6, and PEG2 [90].

Diabetic neuropathic pain (DNP) is one of the most common serious complications of diabetes mellitus. DNP manifests as unusual pain and sensory abnormalities in the limbs, often exacerbated at night, which extremely impact the patient's mood, sleep, and life quality, and even leads to depression [91]. It has been found that Yiqi Huoxue Tongluo Decoction could alleviate DNP through influencing the activity of spinal microglia. A further mechanism is associated with the down-regulation of ASK1-MKK3-p38 pathway and central sensitization induced [92]. Jinmaitong can alleviate DNP by modulating NLRP3 inflammatory vesicles and Gasdermin D. In addition, Jinmaitong would not impact the blood glucose level and body weight. But Jinmaitong could improve the pain threshold of mechanical withdrawal threshold (MWT) and thermal withdrawal latency (TWL), and attenuate morphological damage of dorsal

root ganglion (DRG) tissues [93]. In addition, further studies revealed that JMT could also improve DNP by regulating microglia activation through inhibition of the JAK 2/STAT 3 signaling pathway [94]. The TCM prescription for NP is summarized in Table 1.

5. TCM extracts for NP

Olibanum-Myrrha is a commonly used clinical pair capable of alleviating CCI-induced mechanical nociceptive hypersensitivity by down-regulating TLR4/MyD88 and TRPV1 signaling pathway [95]. Tetrapanacis Medulla alleviates sciatic nerve pain by decreasing inflammation levels, suppressing the phosphorylation of p38 MAPK, and down-regulating DRG protein levels [96]. Sedi Linearis Herba treatment could improve mechanical hypersensitivity in SNI rats whose mechanism is related to block microglia activation by down-regulating TLR4/NF-κB pathway [97]. *Boesenbergia rotunda* extract alleviated thermal nociceptive hypersensitivity, cold and mechanically abnormal pain responses in diabetic rats [98]. In addition, *Boesenbergia rotunda* extract significantly reduced injury perception responses in formalin and acetic acid tests and was able to reduce serum TNF-α and IL-1β levels [98].

Excitatory toxicity (ET) is an important factor in central sensitization triggering NP. Serum pannexin-1 (Panx1)-Src-N-methyl-D-aspartate receptor subunit 2B (NMDAR-2B) association is a new and crucial pathway for ET to initiate central sensitization [99]. DU et al. [100] showed that Chuanxiong Rhizoma extract has the effect of central analgesic. The mechanism was associated to inhibit the expression of glutamate, serine, and glycine from the extracellular fluid of the anterior cingulate cortex and spinal dorsal horn and to down-regulate the expression of the Panx1-Src-NMDAR-2B pathway in the spinal cord and brain in SNI rats. In male mice, the essential oil of Bupleuri Radix exerts antiabnormal pain effects through activation of the L-arginine-NO-cGMP-KATP pathway and opioid, PPA and cannabinoid receptors [101].

In a CCI- and cisplatin-induced mouse model, aqueous extracts of Notopterygii Rhizoma Et Radix were able to inhibit cold anomalous pain and mechanical anomalous pain, and reduced the response of DRG neurons to allyl isothiocyanate, which found to be related to modulation of TRPA1 [102]. In addition, *Corydalis Saxicola Bunting* total alkaloids could alleviate mechanical, thermal, and cold nociceptive hypersensitivity in CIPN rats and inhibit elevation of TNF-α, IL-1β, and PGE2, restoring p38 and TRPV1 expression in DRG, trigeminal ganglion and spinal cord [103]. In a streptozotocin injection-induced DPN model, *Lycium barbarum* polysaccharide (LBP) inhibited the activation of mTOR/p70S6K pathway and enhanced autophagy to exert analgesic effect [104].

Spinal nerve ligation (SNL) is also a model of NP. It was found that ginger root extract reduced pain and anxiety-like behavior in SNL rats [105]. In terms of intestinal flora, relative abundance of *Lactococcus* spp, *Sellimonas*, *Blautia*, Erysipelatoclostridiaceae and Anaerovoracaceae were increased after treatment with ginger root extract administration, while Prevotellaceae UCG-001, Rikenellaceae RC9, *Mucispirillum* and *Desulfovibrio*, *Desulfovibrio*, *Anaerofilum* and so on showed a decrease in relative abundance [105], suggesting that there is a link between these intestinal florae and the improvement of NP by ginger root extract. The TCM extracts for NP is summarized in Table 2.

Table 1
Summary of TCM prescription for NP.

Prescriptions	Prescriptions composition	Disease model	Action mechanism	Ref.
Duhuo Jisheng Decoction	Taxilli Herba, Eucommiae Cortex, Achyranthis Bidentatae Radix, Asari Radix Et Rhizoma, Angelicae Pubescentis Radix, Gentianae Macrophyllae Radix, Poria, Cinnamomi Cortex, Saposhnikoviae Radix, Chuanxiong Rhizoma, Ginseng Radix Et Rhizoma, Glycyrrhizae Radix Et Rhizoma, Angelicae Sinensis Radix, Paeoniae Radix Alba, Rehmanniae Radix	CCI rat model	ACHE, NOS2, MAPK3, PTGS2, AKT1↓, PPARG↑; IL-1, IL-6↓	[83]
Wutou Decoction	Aconiti Radix, Ephedrae Herba, Astragali Radix, Paeoniae Radix Alba, Glycyrrhizae Radix Et Rhizoma	primary glial cells; SNL mice	NGF, BDNF, GDNF↑; CCR5↓; PI3KPKA↑	[84, 85]
Yuanhu Zhitong Fomula	Corydalis Rhizoma, Angelicae Dahuricae Radix	SNI rat model	APP, SRC, JNK1, ERK1/2↓	[86]
Huangqi Guizhi Wuwu Decoction	Astragali Radix, Cinnamomi Ramulus, Paeoniae Radix Alba, Zingiberis Rhizoma Recens, Jujubae Fructus	CINP	TNF -α, IL-1β, IL-6↓, ERK1/2, p38, JNK, c-Fos, CREB, Nf-κB↓	[88, 89]
Siwei Jianbu Decoction	Salviae Miltiorrhizae Radix Et Rhizoma, Paeoniae Radix Rubra, Achyranthis Bidentatae Radix, Dendrobii Caulis	CIPN	p-JNK, p-ERK1/2, MAPKNF-kB↓, TNF-a, IL-1b, IL-6↓	[23]
Yanghe Decoction	Rehmanniae Radix Praeparata, Cervi Cornus Colla, Cinnamomi Cortex, Sinapis Semen, Ephedrae Herba, Rhizoma Zingiberis Carbonisatum, Glycyrrhizae Radix Et Rhizoma	Pain of bone metastasis of breast cancer	TNF-α, IL-1β, IL-6, PEG2↓	[90]
Yiqi Huoxue Tongluo Decoction	Astragalus, Angelica, Rehmannia glutinosa, Corydalis, Pueraria lobata, Caulis spatholobi, Weilingxian	DNP rat	IL-6, IL-1β, TNF-α↓, ASK1, MKK3, p38, OX42↓	[92]
Jinmaitong	Cuscutae Semen, Ligustri Lucidi Fructus, Corydalis Rhizoma, Hirudo, Cinnamomi Ramulus, Asari Radix Et Rhizoma	DNP rat	NLRP3, ASCcaspase-1↓, IL-1β, GSDMD↓, JAK 2/STAT 3↓	[93, 94]

Note: The table summarizes the names of TCM prescriptions and the specific drug composition, the research model used, the specific mechanism of action and the references.

Table 2
Summary of TCM extracts for NP.

TCM extracts	Disease model	Action mechanism	Ref.
Frankincense Myrrh water extract	CCI rat model	TRPV1↓, TLR4, MyD88, p-p65↓	[95]
Tetrapanax papyriferus	CCI rat model	IL-1β, IL6, TNF-α, TRPM8, TRPA1, TRPV1, TRPV4, p-p38 MAPK↓	[96]
Sedum Lineare	SNI rats	HMGB1, TLR4, MyD88, TRAF6, IKK, NF-κB p65↓	[97]
Boesenbergia rotunda Polyphenol Extract	DNP rats	Thermal hyperalgesia, cold and mechanical allodynic responses↓, TNF-α, IL-1β↓	[98]
Chuanxiong Rhizoma extract	SNI rats	Glu, D-Ser, Gly, NMDAR-2B, Src, Panx1↓	[100]
Bupleurum falcatum essential oil	Cervical spinal cord contusion	IL-1β, IL-2, TNF-α↓, L-arginine–NO–cGMP-KATP↑	[101]
Notopterygium incisum water extract	CIPN rat model	DRG, TRPA1↓	[102]
Corydalis saxicola alkaloids	CINP	TNF-α, IL-1β, PGE2↓, p-p38, TRPV1↓	[103]
Lycium barbarum polysaccharide	DPN	LC 3-II, Beclin 1↑, P62, mTOR, p-mTOR, p70 S6 K, p-p70 S6 K↓	[104]

Note: The table summarizes the source of TCM extracts, the research model used, the specific mechanism of action and the references.

6. Natural products from TCM for NP

6.1. Alkaloids

Alkaloids are a class of nitrogenous alkaline organic compounds present in nature. Most alkaloids have complicated ring structures, with nitrogen mostly contained in the rings. Usually, alkaloids possess significant biological activities, such as tetrahydropalmatine, levo-corydalmine, higenamine, neoline, isotalatizidine, evodiamine, berberine, strychnine, sinomenine, piperine, koumine, cyclovirobuxine D, etc., which are important active ingredients in Chinese medicine. These chemical composition structures are shown in Fig. 2. The position of hydroxyl group, delocalization degree of lone pair electron, steric condition, lipophilicity and hydration energy

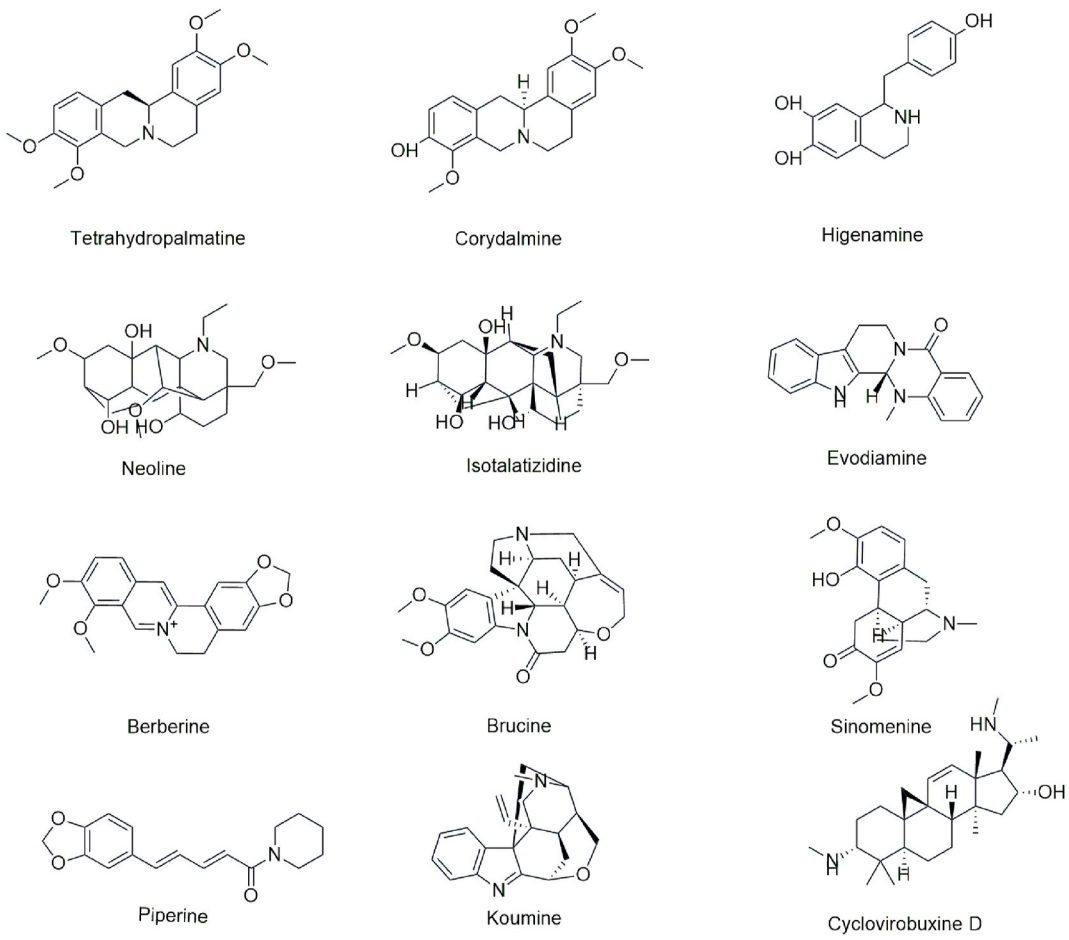

Fig. 2. The chemical structures of alkaloids showing anti-NP activity.

parameters of alkaloids can affect their biological activity [106]. Therefore, the study of structure-activity relationship is complex and needs further study.

CXCL1 can cause central sensitization and induce neuropathic pain via its receptor CXCR2 [107]. Levo-corydalmine could attenuate vincristine-induced NP through down-regulating NF-κB-dependent CXCL1/CXCR2 signaling pathway [108]. In cisplatin-induced peripheral neuropathy, berberine inhibits the neuroinflammatory response through down-regulating the over-expression of TRPV1 and NF-κB. Meanwhile, berberine could activate the JNK/p38 MAPK pathway at the early stage of injury [10]. Berberine significantly increased caudal flick and caudal cold anomalous pain latency, and suppressed oxidative stress by modulating the Nrf2 gene to reduce lipid peroxidation, increase superoxide dismutase, and decline glutathione content in the sciatic nerve, thereby ameliorating neuropathy [109]. For paclitaxel-induced NP, evodiamine can restore the expression of mitochondrial membrane potential abnormalities and peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α), uncoupling protein 2, and SOD2 [110]. Cyclovirobuxine D, a constituent of *Buxus microphylla* herbal medicine, attenuates inflammation and NP mainly by inhibiting voltage-gated Cav3.2 channels [111].

For CCI pain, Higenamine [112], Isotalatizidine [113], Guanfu base A [114], Koumine [115] and Tetrahydropalmatine [116] all exert anti-NP effects by inhibiting inflammatory signaling pathways. Higenamine can exert a neuroprotective effect by inhibiting NOX2/ROS/TRP/P38MAPK/NF-κB inflammatory signaling pathway and mitochondrial apoptosis pathway bcl-2/bax and cleaved caspase 3/caspase 3, thus alleviating NP [112]. Isotalatizidine attenuates chronic NP by stimulating the secretion of dynorphin A which is mediated by ERK/CREB signaling pathway [113]. P2Y12 receptors are associated with the onset and persistence of NP [117]. Guanfu base A alleviates mechanical and thermal hyperalgesia through decreasing P2Y12 receptors and p38 MAPK signal pathway [114]. Koumine is an active ingredient in *Gelsemium elegans* Benth. Koumine single or repeated treatment significantly reduced NP, and the treatment mechanism was related to inhibit the microglial activation, M1 polarisation, and astrocyte activation [115]. Tetrahydropalmatine may inhibit neuroinflammation in CCI rats through Clec 7a-MAPK/NF-κB-NLRP 3 inflammatory axis [116]. Bufalin, an active ingredient extracted from Bufonis Venenum, significantly decreased TRPV1 and P2X7 expression to relieve NP [118]. Brucine can directly inhibit the excitability of DRG neurons and reduce the number of action potentials. The further mechanism is related to the inhibition of tetrodotoxin-sensitive (TTXs) and tetrodotoxin-resistant (TTXr) sodium channels [119]. Glaucine, isolated from *Glaucium flavum* Crantz, reduces the expression of p-PKCγ, GFAP, and IBA1 through inhibition of dopamine D1 receptors, inhibits central sensitization of the spine, and alleviates NP [120].

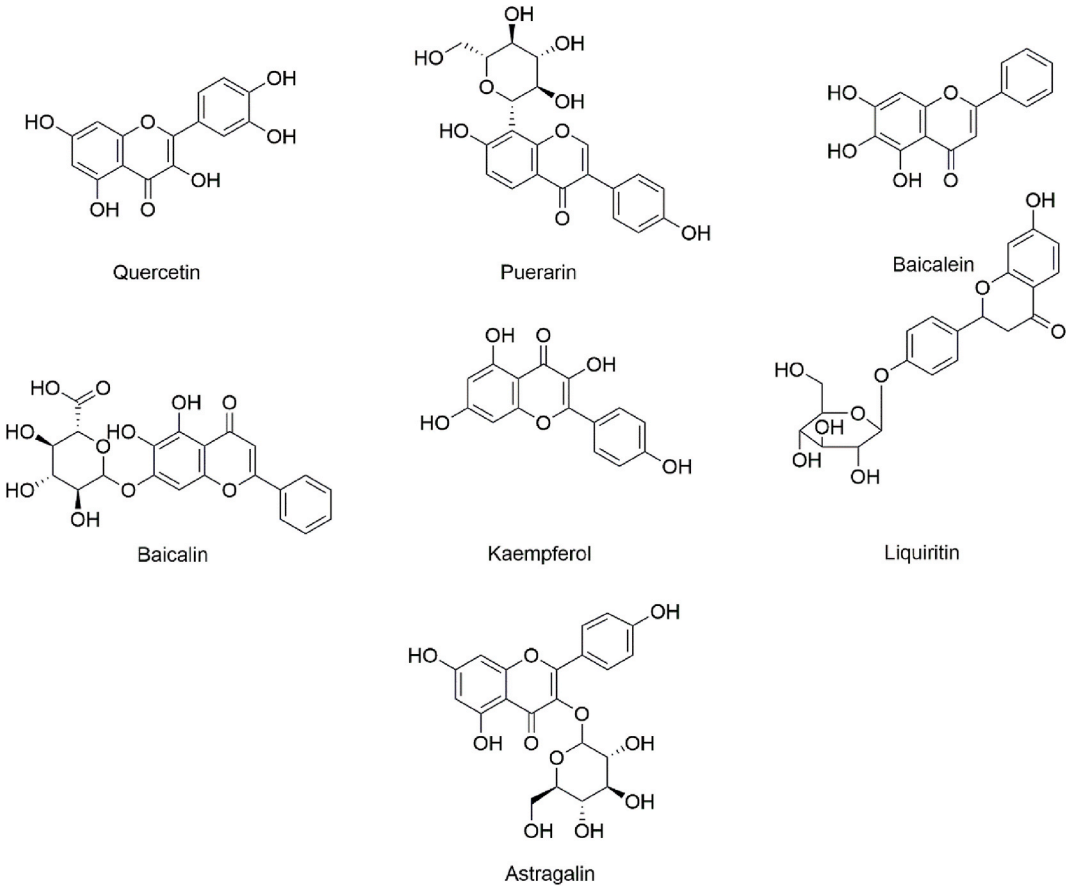

Fig. 3. The chemical structures of flavonoids showing anti-NP activity.

Cheng et al. [9] found that tetrahydropalmatine could improve the MWT and TWL in type 2 diabetic nephropathy induced via using high-sugar, high-fat chow diets and streptozotocin injection, whose mechanism is related to inhibit glial cell activation and p38 MAPK pathway [9]. *In vitro* model established by LPS-stimulating BV2 microglial cells, tetrahydropalmatine could facilitate the transition of BV2 cells from M1 to M2 phenotype, which significantly ameliorated the pain symptoms in DNP rats [9]. Moreover, berberine inhibits microglia and astrocytes activation in the spinal cord of diabetic mice [121]. And berberine ameliorates neonatal type 2 diabetic neuropathy through down-regulating the expression of BDNF, insulin-like growth factor, PPAR-gamma, and AMPK [122]. Neoline ameliorates diabetes-induced mechanical nociceptive hypersensitivity by inhibiting Nav1.7 VGSC currents [123]. Sinomenine, a natural bioactive ingredient extracted from Sinomenii Caulis, enhances the treatment of gabapentin or ligustrazine hydrochloride in peripheral or central neuropathic pain [124]. More importantly, it does not cause tolerance or significant side effects [124]. Palmatine is an alkaloid extracted from Fibraureae Caulis, which can alleviate DNP through decreasing P2X7 receptor and p-ERK1/2 [125].

Piperine, the active component of Piperis Longi Fructus, alleviates sciatica by decreasing the expression of PPARG and NF-κB [126]. Moreover, Hu et al. [127] further demonstrated that tetrahydropalmatine could improve NP through down-regulating p38 MAPK/NF-κB/iNOS signaling pathway.

6.2. Flavonoids

Flavonoids are widely found in plants in nature. Flavonoids are yellow pigments derived from 2-phenylchromone, which include the isomers of flavonoids and their hydrogenation and reduction products, including a range of compounds with C6-C3-C6 as the basic carbon framework. Most Chinese medicines contain flavonoids with many pharmacological activities, such as quercetin, puerarin, baicalein, baicalin, kaempferol, glycyrrhizin, Astragalin, and so on. These chemical composition structures are shown in Fig. 3. Due to their presence of multiple phenolic hydroxyl groups, flavonoids have significant anti-inflammatory and antioxidant effects [128]. And −OH at the C-5 and C-4′ positions enhance while −OH at the C-6, C-7, C-8, and C-3′ positions attenuate the activity [128]. In addition, the carbonyl group in the C3 structure of flavonoids reacts with sulfhydryl, hydroxyl and amino groups that constitute important functional groups of biological macromolecules such as enzymes and proteins, thus having neuroprotective effects [129].

Brachial plexus root avulsion injury (BPRAI) is a common clinical neurodegenerative lesion, which is manifested by impairment of sensory and motor functions of the affected upper limb, as well as neuropathic pain. Quercetin treatment significantly alleviates BPRAI and reduces neuroinflammatory infiltration and oxidative stress by inhibiting P2X receptors and suppressing PKC/MAPK/NOX signaling pathway [130]. Puerarin also ameliorated the death of α-motor neurons, inhibited iNOS protein expression, promoted CGRP proteins, and down-regulated PI3K/Akt signaling pathway to play neuroprotective roles in BPRAI rats [131]. In paclitaxel-induced peripheral neuropathy, puerarin could attenuate NP through decreasing TRPV1, calcitonin gene-related peptide and substance P [132,133]. Also, puerarin preferentially reduced the excitability of DRG neurons in paclitaxel-induced NP through blocking voltage-gated Nav 1.8 channels, and it was further demonstrated that puerarin blocked TTX-R Nav channels more strongly than TTX-S Nav channels [134].

Liquiritin, extracted from Glycyrrhizae Radix Et Rhizoma, can alleviate SNI-induced NP by modulating metabolism of sphingolipid, glycerophospholipid, glycerolipid, and calcium signaling pathway [135]. In addition, glycyrrhizin can alleviate SNL-induced NP through inhibiting neuroinflammation through inhibition of chemokine signaling pathways [136]. Diosmetin is a main component in Chrysanthemi Flos, which can decrease inflammatory reaction and down-regulate Keap1/Nrf2/NF-κB pathway to relieve SNL-induced NP [137]. Baicalein could reduce NP and improve sciatic nerve function through down-regulating the secretion of pro-inflammatory cytokines and attenuating astrocytes activation [138]. Moreover, baicalein can relieve anxiety-like behavior and NP in PTSD via the serotonergic system and spinal δ-opioid receptors [33]. Baicalein attenuated CCI-induced mechanical and thermal injurious responses and improved NP by inhibiting TRPV1 up-regulation and ERK phosphorylation [139]. Astragalin is isolated from Eucommiae Cortex reduces P2X4 expression in the DRG, which can inhibit satellite glial cell (SGC) activation, and attenuate pain in CCI rats [140]. Genistein, one of the most abundant isoflavones in *Sophora japonica* L., alleviated LPS-induced inflammatory injury in rat dorsal root ganglion neuron (DRGn). The treatment mechanism may be associated to decrease the HDAC6 expression and further inhibiting TLR4/MyD88/NF-κB signaling pathway [141]. Switching microglia polarisation from M1 to M2 phenotype is a prospective way for the treatment of NP [142]. A study [143] found that kaempferol inhibited the activation of BV2 cells, converting them from M1 to M2 phenotype, and attenuated NP by down-regulating TLR4/NF-κB signaling pathway.

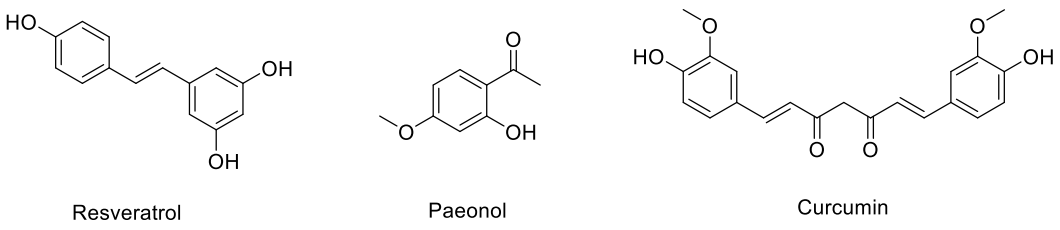

Fig. 4. The chemical structures of polyphenols showing anti-NP activity.

6.3. Polyphenols

Polyphenols are organic compounds formed by the direct attachment of hydroxyl groups (-OH) to aromatic nuclei (benzene or fused benzene ring) and are widely found in nature. Due to their more phenolic hydroxyl groups and unsaturated carbon bonds, phenolic compounds have strong anti-inflammatory and antioxidant activities [144]. Resveratrol (as shown in Fig. 4) is a polyphenolic component first isolated from the roots of Veratrum *grandiflorum*. By intrathecal injection, resveratrol could inhibit microglia-mediated neuroinflammation by modulating TREM2 autophagy axis in SNI rats, thus alleviating NP [145]. In the partial sciatic nerve ligation (pSNL) surgery NP model, resveratrol attenuated NP by inhibiting the upregulation of P2X3 and phosphorylation of ERK [146]. Skeletal nerve pain mechanism studies have found that ASIC3 is capable of causing pain by firing sensory neurons that innervate bones [147]. However, resveratrol can activate autophagy to reduce pain caused by bone cancer through down-regulating ASIC3 expression and up-regulating the p-AMPK, p-Sirt1 and p-LC3-II [148]. Trigeminal neuralgia (TN) is a common clinical neurologic disease, which is characterized by recurrent paroxysmal severe pain in the trigeminal nerve distribution area of one side of the face. Resveratrol reduces TN and improves cognitive deficiencies via modulating neural ultrastructure remodeling and CREB/BDNF signaling pathway [149].

Paeonol is extracted from Moutan Cortex, which could alleviate NP by regulating microglia M1 and M2 polarisation via RhoA/p38 MAPK signaling pathway [144]. Another research showed that paeonol inhibited calcium influx and uterine contraction via CB2R to alleviate dysmenorrhoea [150]. Curcumin, one of the main components in Curcumae Longae Rhizoma, can reduce mechanical and thermal nociceptive hypersensitivity induced by peripheral nerve injury [151]. Also, curcumin has a palliative effect on both cobra venom-induced TN and partial transection of the infraorbital nerve-induced TN. The further mechanism is associated to regulate synaptic plasticity in the hippocampal CA1 region [152,153]. Moreover, curcumin could relieve oxaliplatin-induced peripheral NP via down-regulating NF-κB expression [154].

6.4. Organic acids

Organic acids refer to some acidic organic compounds. Ferulic acid (as shown in Fig. 5), chemically known as 3-methoxy-4-hydroxycinnamic acid, is found in high levels in Chinese herbal medicines such as Ferulae Resina and Chuanxiong Rhizoma. Ferulic acid is one of the active ingredients in these herbs which could relieve sciatica [155]. On the one hand, ferulic acid was found to attenuate LPS-induced M32 polarisation by down-regulating the secretion of M1 polarisation markers (such as IL-1β, TNF-α, iNOS, and CD6) through RhoA/Rock pathway. On the other hand, ferulic acid could increase M1 polarisation through up-regulating the secretion of M2 polarisation markers (such as CD2 and Arg-206) [155]. Further study proved that ferulic acid also reduced inflammatory infiltration of GMI-R1 neuronal cells via TLR4/NF-κB pathway and increased Bcl-2 and Bcl-xl expression to inhibit apoptosis of GMI-R1 neuronal cells, finally promoting repair of injured sciatic nerve [156].

Salvianolic acid B is an active ingredient in Salviae Miltiorrhizae Radix Et Rhizoma, which could alleviate mechanical nociceptive hypersensitivity through decreasing the release of TNF-α and substance P by inhibiting TLR4/MyD88 pathway [157]. Gallic acid is present in traditional Chinese medicines such as Rhei Radix Et Rhizoma and Corni Fructus. Gallic acid could increase the MWT and TWL in CCI rats and alleviate NP through down-regulating the P2X7 receptor and activating TNF-α/STAT3 pathway [158]. In addition, gallic acid was able to reduce total calcium, TBARS, TNF-α, MPO activity, superoxide anion and GSH levels, exerting a neuroprotective effect [159]. Cinnamic acid is an active ingredient extracted from Cinnamomi Cortex. In the NP model induced by oxaliplatin injection, cinnamic acid was able to significantly attenuate the aberrant pain behavior, and the mechanism may be associated with inhibiting the

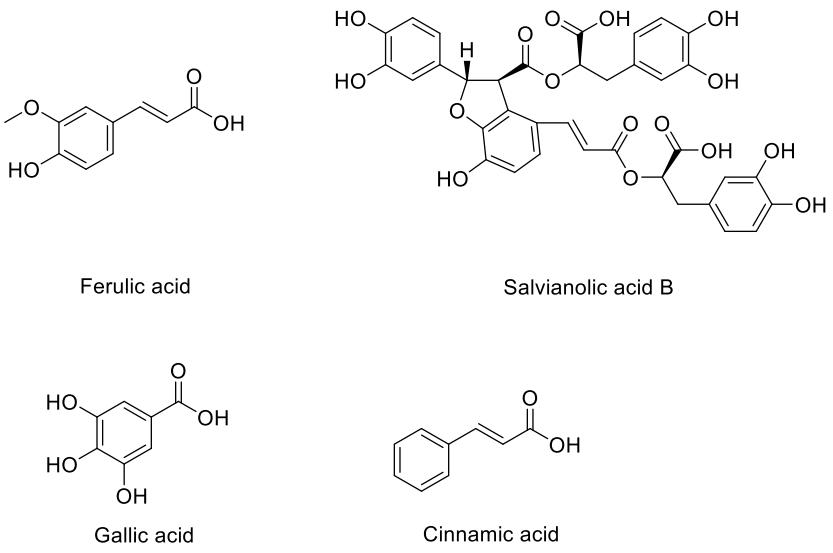

Fig. 5. The chemical structures of organic acids showing anti-NP activity.

spinal pain transmission [160].

6.5. Glycosides

Glycosides are components formed via linking the carbon atoms of the end groups of sugars or sugar derivatives with another class of non-sugar substances, including glycosides and saponins (as shown in Fig. 6). Gastrodin is a glycoside compound extracted from Gastrodiae Rhizoma. In the vincristine-established CIPN animal model, gastrodin mitigated CIPN via repressing spinal microglia activation through inhibiting CX3CL1 and its receptor CX3CR1, and inhibiting P38/MAPK pathway [161]. The underlying pathophysiological mechanism of NP involves the dysfunction of voltage-gated ion channels, particularly tetrodotoxin-sensitive voltage--gated sodium channels (VGSC) (Nav1.7) and presynaptic N-type voltage-gated calcium channels (VGCC) (Cav2.2), which results in increasing neuronal excitability [162]. It was found that gastrodin could down-regulate the current density of NaV1.7 and NaV1.8 channels. Also, gastrodin could speed up the inactivation process of NaV1.7 and NaV1.8 channels, thus relieving neuronal hyperexcitability and attenuating peripheral NP [163]. MiRNAs are indispensable to peripheral neuropathy, of which miR155 is associated with the regulation of diabetes and glucose [164]. Astragaloside IV can up-regulate miR155 expression and then inhibit the PI3K/Akt/mTOR signaling pathway to promote autophagy and inhibit apoptosis in Schwann cells, attenuating myelin damage in DPN [165]. Moreover, salidroside can alleviate DNP through down-regulating the P2X7 receptors and AMPK-NLRP3 inflammatory vesicle axis [166,167].

Albiflorin and paeoniflorin are monoterpene glycosides isolated from Chinese medicines Paeoniae Radix Alba and Paeoniae Radix Rubra. Albiflorin could inhibit hippocampal NLRP3 inflammasome to reduce CCI-induced NP [168]. Activation of NLRP3 inflammasome mediates the progress of NP after chronic compression injury of the sciatic nerve, and paeoniflorin attenuates NP via inhibiting the activation of NLRP3 inflammasome [169]. Integrated lipidomics and transcriptomics showed that paeoniflorin

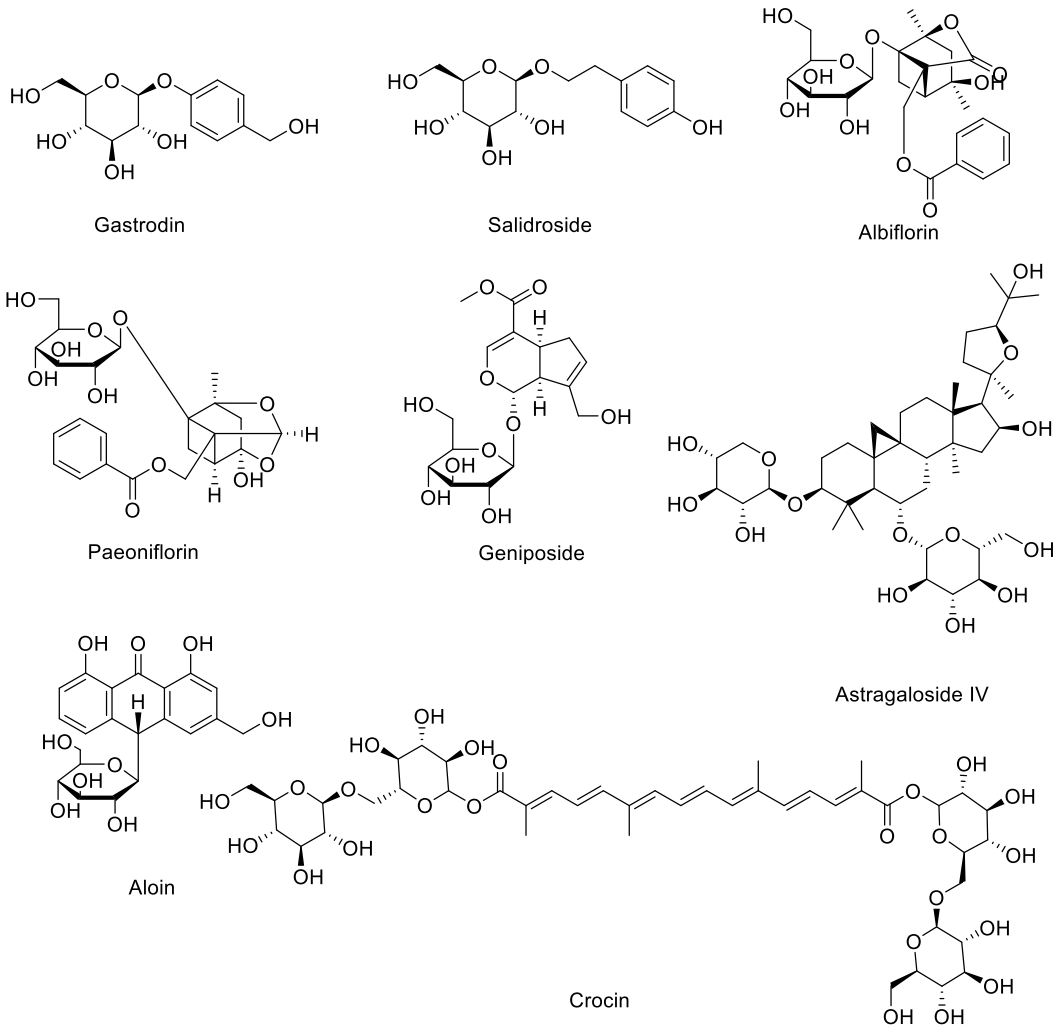

Fig. 6. The chemical structures of glycosides showing anti-NP activity.

alleviated NP by inhibiting neuroinflammation by influencing lipid metabolism and calcium signaling and chemokine signaling pathways [135,136]. Also, paeoniflorin could promote the repair of injured nerves and alleviate chronic sciatica by reducing apoptosis of Schwann cells through inhibiting TLR4/NF-κB pathway [170]. Geniposide, a compound isolated from Gardeniae Fructus, was able to alleviate NP via suppressing EGFR/PI3K/AKT pathway and the Ca^{2+} channel [171]. Astragaloside IV, an active ingredient extracted from Astragali Radix, significantly attenuated NP and inhibited spinal astrocyte excitation in CCI rats by modulating the KATP-JNK gap junction axis [172]. Glycosides is a principal constituent in Anoectochilus elatus Lindl., which could alleviate acute or chronic pains via inhibiting NO/cGMP and IRAK4/IRAK1/TAK1 pathway [173]. Aloin can regulate motor nerve conduction velocity, decrease MDA, TNF-α, IL-6 and IL-1β levels and increase GSH levels to prevent CCI-induced NP [174]. Crocin is a carotenoid derived from Croci Stigma. Studies proved that crocin could up-regulate the mechanical pain threshold in adjuvant-induced arthritis (AIA) through decreasing the expression of pain-associated molecules. The mechanism is associated to suppress Wnt 5a/β-catenin pathway [175].

6.6. *Terpenoids*

Terpenoids are derivatives with the general formula (C5H8)n which can be considered as a class of natural compounds formed by isoprene or isopentane linked in various ways. Diosgenin (as shown in Fig. 7), a compound in *Trigonella foenum-graecum* L., could exert analgesic effects by antagonizing TRPV1 and inhibiting inflammation in the DRG mouse model [176]. Celastrol, a pentacyclic triterpenoid, is a representative constituent of Triptergii Radix. Celastrol could up-regulate mechanical and thermal pain thresholds, inhibit the activation of spinal microglia and astrocytes, and inhibit TLR4/NF-κB signaling pathway to attenuate CCI-induced NP [177]. Rhodojaponin vi, a compound extracted from Rhodiolae Crenulatae Radix Et Rhizoma, can be used to alleviate NP through indirectly acting Cav2.2 channels by N-ethylmaleimide-sensitive fusion proteins to inhibit the increase in Ca^{2+} current strength [178]. Rhododendron III from Flos Rhododendri Simsii ameliorates CCI-induced nociceptive hypersensitivity and inhibits injury pain and peripheral neuralgia in rats, a mechanism associated with the blockade of voltage-gated sodium channels [179]. Epifriedelanol, a triterpenoid isolated from the root bark of *Ulmus davidiana*, ameliorates NP and restores spinal cord function through down-regulating neuronal apoptosis and NMDA receptors [180]. Dihydroartemisinin is derived from Artemisiae Annuae Herba and downregulates

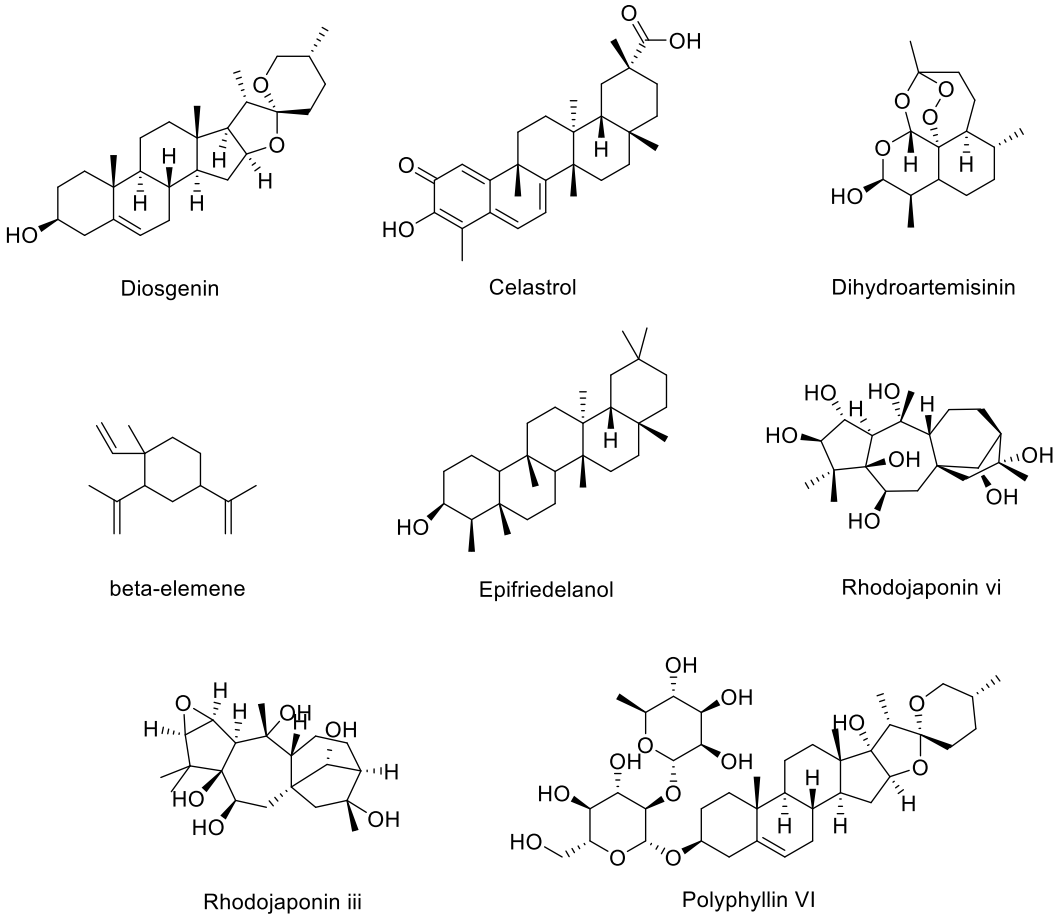

Fig. 7. The chemical structures of terpenoids showing anti-NP activity.

spinal cord and hippocampal HnRNPA1 to exert analgesic effects in SNL mice [181]. β-Elemene is a chemical constituent isolated from Curcumae Radix. In SNI rats, β-elemene could inhibit ERK pathway in spinal astrocytes and subsequently inhibit neuroinflammation [182]. Polyphyllin VI is a main component extracted from *Paris polyphylla*. PolyphyllinVI can inhibit P2X3 receptor and TNF-α, IL-1β, IL-6 through AMPK/NF-κB pathway, and increase MWT and TWL in SNI mice to play a neuroprotective role [183]. Furthermore, in oxaliplatin-induced peripheral neuropathy (OIPN), diosgenin not only protects PC12 from damage but also alleviates OIPN through down-regulating TLR4/NF-κB inflammatory signaling and intestinal microbiota [184].

6.7. Others

Emodin (as shown in Fig. 8) is an anthraquinone compound extracted from Rhei Radix Et Rhizoma. It was found that emodin can regulate the GABAergic and PI3K/AKT/NF-κB pathways [185], calcium signaling pathways [186], sphingolipid metabolism and arginine biosynthesis pathway [187] to alleviate CCI-induced NP. In addition, Wang et al. [188] found that emodin administration could alter the community structure of the intestinal flora, increasing the number of beneficial bacteria and metabolites. The metabolomics analyses showed that emodin increased S-adenosylmethanethionine and histamine levels to relieve NP [188]. Daphnetin, a coumarin constituent extracted from *Daphne giraldii* Nitsche, can decrease the secretion of inflammatory and chemokine factors and promote the polarisation of glial cells from M1 to M2 to ameliorate NP [189]. Daphnetin also can alleviate NP by inhibiting spinal cord inflammation and astrocyte activation via TLR4/NF-kB [190]. The scorpion venom peptide BmK AGAP is a protein peptide isolated from Scorpio. Intrathecal injection of BmK AGAP could decrease p-MAPKs and c-Fos expression to relieve CCI-induced NP behaviours and formalin-induced inflammation pain [191].

Corydecumine G, a phthaloisoquinoline derivative from *Corydalis decumbens* (Thunb.) pers., could decrease the expression of NO, iNOS, TNF-α and Pge2 in the dorsal horn of the L4-L6 spinal cord and inhibit LPS-induced BV2 microglia activation via inhibiting p38/ERK MAPK pathway [192]. Senkyunolide H, a natural compound derived from Chuanxiong Rhizoma, inhibits microglia activation and relieves LPS-induced neuroinflammation and oxidative stress in BV2 microglia via modulating ERK and NF-κB pathways [193]. Divanillyl sulfone is a novel structure in Gastrodiae Rhizoma. Divanillyl sulfone exerts its antinociceptive effects by inducing mitochondrial autophagy to inhibit NLRP3 inflammatory vesicles and promoting the improvement of mitochondrial autophagy-induced dysfunction by scavenging intracellular ROS and restoring the mitochondrial membrane potential [51]. Tanshinone IIA, derived from Salviae Miltiorrhizae Radix Et Rhizoma, alleviated DPN by inhibiting Nrf2/ARE and NF-κB pathways and inhibiting endoplasmic reticulum stress mediated by spinal dorsal horn neuronal circuits [194,195].

Hepatocellular carcinoma is a cancer with a complex pathogenesis. In the absence of an effectual remedy, hepatocellular carcinoma-induced pain can seriously affect patients' survival and life quality [196]. Muscone isolated from Moschus could activate the autophagy-related gene SESN2 to alleviate tumor growth. Meanwhile, muscone inhibited mTOR pathway to promote AMPK expression to alleviate tissue compression pain [197]. The natural products from TCM for NP is summarized in Table 3.

7. Discussion and prospect

NP, as one of the common types of chronic syndromes, has a large population, complex pathogenesis, and poor therapeutic effects. In contrast, Chinese medicine has been used in China for thousands of years, and based on human experience, many drugs have been discovered that can effectively treat NP and have lower side effects compared with Western drugs. Based on this, by searching the published research literature on TCM for NP from 2018 to 2024, this paper concluded that TCM can prevent and control NP through multiple pathways, including anti-inflammatory (inhibiting TLR4, MAPK, p38, NF-κB, and ERK signaling pathways, etc.), antioxidant (inhibiting the Nrf2 signaling pathway), regulating autophagy (PI3K/AKT signaling pathway), affecting ion channels (inhibiting

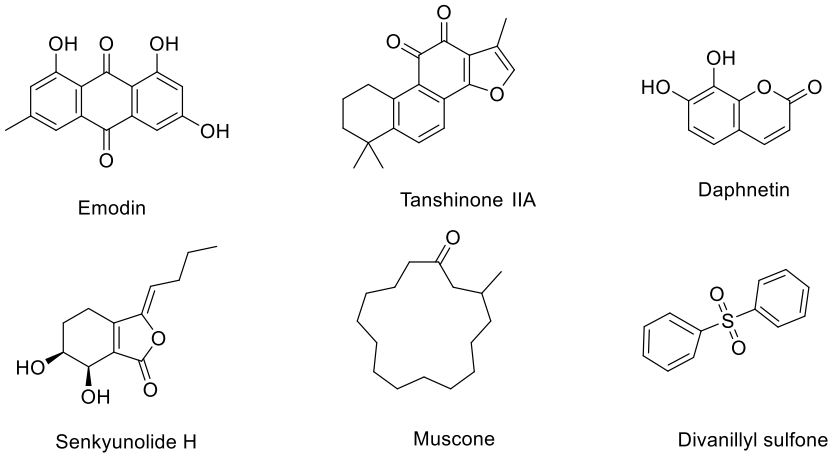

Fig. 8. Other chemical structures with anti-NP activity.

Table 3
Summary of natural product from TCM for NP.

Classification	Chemical composition	Source	Model	Action mechanism	Ref.
Alkaloids	Levo-Corydalmine	*Corydalis yanhusuo*	CINP mice	p-NF-κB, CXCL1, CXCR2↓	[108]
	Berberine	*Coptis chinensis*	CIPN rats, DNP rat	TRPV1, IL-1β, IL-6, TNF-α, JNK, p38↓, ERK 1/2p-p38↑; MDA, GSH, GPx, NF-κB, NGF,↓, SOD, Nrf2↑; BDNF, IGF-1, PPAR-γ, AMPK↓	[10,109,121,122]
	Evodiamine	*Euodia rutaecarpa*	CINP rats	IL-1β, IL-6, MCP-1, PGC-1 α, TNF-α, UCP2SOD2↓	[110]
	Cyclovirobuxine D	*Buxus microphylla*	CIPN mice	Cav3.2↓	[111]
	Higenamine	*Aconitum carmichaelii*	CCI rat; Schwann cell	TRPA1, TRPV1, ROS, MDA, TNF-αIL-6↓, SODGSH↑, p-p38 MAPK, p-NF-κB↓, bcl-2/bax↑, cyt-c, Nox2, cleaved caspase 3/caspase 3↓	[112]
	Isotalatizidine	*Aconitum carmichaelii*	CCI mice	CREB, dynorphin A, p-p38, p-ERK1/2↑	[113]
	Guanfu base a	*Aconitum carmichaelii*	CCI rats	P2Y12, p-p38 MAPK↓	[114]
	Koumine	*Gelsemium elegans* Benth.	CCI rats; microglia BV2 cells	Iba-1, GFAP, TNF-α, CD86, CD68, IL-6↓	[115]
	Bufalin	*Bufo gargarizans*	CCI rats	IL-1β, IL-18, IL-6, TNF-α, TRPV1P2X7↓	[118]
	Brucine	*Strychnos nux-vomica* L.	CCI mice	TTXs, TTXr sodium channel↓	[119]
	Glaucine	*Glaucium flavum* Crantz	CCI rats; PC12, C6 astrocyte cells, BV2 cells	p-PKCγ, GFAP, IBA1, p-ERK, p-JNK, p-p38, CCL2, CCL21, CX3CL1, TNF-α, IL-6↓	[120]
	Neoline	*Aconitum carmichaelii*	HEK293 cells	Nav1.7 VGSC peak current↓	[123]
	Palmatine	*Fibraurea recisa*	DNP rats	P2X7, GFAP, TNF-α, IL-1β, ERK1/2↓	[125]
	Piperine	*Piper longum* L.	Sciatica model of rats	TNF-α, NF-kB1↓, IL-10, TGF-β1, PPARG↑	[126]
	Tetrahydropalmatine	*Corydalis yanhusuo*	DNP rat; BV2 microglia; SNI	NO, IL-1β, IL-6, TNF-α↓, IL-10↑, p-p38, OX42↓, M1→M2↑, iNOS, p-MAPKs, p65↓	[9,127]
Flavonoids	Quercetin	*Sophora japonica* L.	BPRAI rats	CAT, GPx, SOD, TAC↑, P2X3, P2X4, GFAP↓, p-PKC, p-ERK, P-JNK, p-c-jun↓	[130]
	Puerarin	*Pueraria lobata*	BPRAI rats; SNL rats; CIPN rats	iNOS, CGRP, p-Akt, Trpv1, CGRP, $Na_v1.8$↓	[131–134]
	Diosmetin	Chrysanthemi Flos	SNL mice	TNF-a, IL-6, Keap1, NF-κB p65↓, HO-1, Nrf2↑	[137]
	Baicalein	*Scutellaria baicalensis* Georgi	PST rats; PTSD mice	TNF-a, IL-1β, IL-6↓, MAO-A↓, NE, 5-HT↑	[138,198]
	Baicalin	*Scutellaria baicalensis* Georgi	CCI rats	TRPV1, p-ERK↓	[139]
	Astragalin	*Eucommia ulmoides* Oliv.	CCI rats	P2X4, TNF-R1, p-ERK↓	[140]
	Genistein	*Sophora japonica* L.	DRGn rats	HDAC6, IL-1β, IL-6, TNF-α, TLR4, MyD88, NF-κB↓	[141]
	Kaempferol	*Bupleurum chinense* DC.	CCI rats; BV2 microglial cells	IL6, IL1β, PGE2, TLR4, NF-κB↓, IL10↑	[143]
Polyphenols	Paeonol	*Paeonia suffruticosa* r.	CCI rats; GMI-R1 cells	IL-1β, iNOS, CD32, IL6↓, IL10, CD206, ARG-1↑, IBA-1, RhoA, RhoAGTP, COX2, Rock1p-p38MAPK↓, PGE2, TNF-α↓	[144,150]
	Resveratrol	*Veratrum griflorum*	SNI rats; pSNL rats; BCP rats; TN rats	LC3II/LC3I↑, P62, IL-1β, IL-6, TNF-α↓, P2X3, p-ERK↓, ASIC3↓, AMPK, Sirt1, LC3-II, pCREB, BDNF↑, p38, ERK, JNK↓	[145,146,148,149]
	Curcumin	*Curcuma longa*	CCI rats; TN rats; CIPN rats	SOD, GSH-Px, CAT↑, MDA, p-NF-κB, TNF-α, IL-1β, IL-6↓	[152–154]
Organic acids	Ferulic acid	*Ferula sinkiangensis*	CCI rats	IL-6, TNF-α, TGF-β, TLR4, IBA-1, CD32, iNOS, nNOS, COX2, Myd88, p-NF-κB, p-p38MAPK, TRPV1, TRPA1↓, Bcl-2, Bcl-xl↑	[155,156]
	Salvianolic acid B	*Salvia miltiorrhiza*	SCI mice	TLR4, myD88↓	[157]
	Gallic acid	*Rheum palmatum* L.	CCI rats; CIPN mice	P2X7, TACE, TNF-α, NF-κB, STAT3↓, TBARS, GSH, MPO, TNF-α, total calcium↓	[158,159]
	Cinnamic acid	*Cinnamomum cassia*	CIPN rats	Cold and Mechanical Hypersensitivity↓	[160]
Glycosides	Gastrodin	*Gastrodia elata* Bl.	CIPN rats	TNF-α, IL-6, CX3CL1, CX3CR1, P38↓	[161,163]
	Astragaloside iv	*Astragalus membranaceus*	CCI rats; C6 cells; DPN rats; RCS96 cells	p-Cx43, p-JNK, PI3K, Akt, mTOR↓	[165,172]
	Salidroside	*Rhodiola rosea*	DPN rats; HEK293 Cells; DRG cells	TNF-α, IL-1β, P2X7 receptors↓, AMPK↑, NLRP3↓	[166,167]
	Albiflorin	*Paeoniae Alba*	CCI rats	NLRP3, ROS, NF-κB↓	[168]

(*continued on next page*)

Table 3 (*continued*)

Classification	Chemical composition	Source	Model	Action mechanism	Ref.
	Paeoniflorin	*Paeonia lactiflora*	CCI rats	NLRP3, IL1, IL6, TNF-α, CRP↓, IL10↑, TLR4, p-NF-kB, caspase3, cleaved-caspase3, cleaved-caspase7↓	[169,170]
	Geniposide	*Gardenia jasminoides*	CCI rats	IL-6, TNF-α, p-p53, p-p38, p-ERK, p-EGFR, PI3K, AKT, PKC, CaM, CaM KII α, CaM KII δ↓	[171]
	Gooderoside A	*Anoectochilus elatus*	CCI rats; BV 2 cells	IRAK4, IRAK1, TAK1, p38, JNK, ERK↓	[173]
	Aloin	*Aloe barbadensis*	CCI rats	MDA, TNF-α, IL-1β, IL-6↓, GSH↑	[174]
	Crocin	*Crocus sativus*	AIA rats	IL-1β, TNF-α, Wnt5a, β-Catenin, COX-2, iNOS, GFAP, Iba-1↓	[175]
Terpenoids	Diosgenin	*Trigonella foenum-graecum L.*	CCI rats; CIPN mice	IL-1β, IL-2, TNF-α, TLR4, NF-κB↓	[176,184]
	Celastrol	*Tripterygium wilfordii*	CCI rats	IL-6, TNF-α, IBA-1, GFAP, TLR4, p-NF-κB p65, p-p-IκB↓	[177]
	Rhodojaponin VI	*Rhododendron molle*	CCI rats; HEK-293 cells	Cav2.2↓	[178]
	Rhodojaponin iii	*Rhododendron molle* G. Don	CCI mice	$Na_V1.8$, $Na_V1.5$↓	[179]
	Epifriedelanol	*Ulmus davidiana*	SCI rats	TNF-α, IL-1β, IL-6, caspase 3, Bcl2, GluN1, NMDA↓	[180]
	Dihydroartemisinine	*Artemisia annua* L.	SNL mice; BV 2 cells	TNFα, NF-kB, HnRNPA1↓	[181]
	β-elemene	*Curcuma wenyujin*	SNI rats;	SOD, GSH-PX↑, TNF-α, IL-6, MDA, p-ERK↓	[182]
	PolyphyllinVI	*Paris polyphylla*	SNI mice	AMPK, NF-κB, P2 X3, TNF-α, IL-1β, IL-6↓	[183]
Others	Divanillyl sulfone	*Gastrodia elata*	CCI mice	LC3II, Beclin 1↑, p62, NLRP3, caspase-1 p10, IL-1β p17	[51]
	Emodin	*Rheum palmatum*	CCI rats	p-PI3K, p-AKT, NF-κB, CaMK II, PLC β1, PKC, PKA, TrkB↓, GABRβ2, GABRβ3↑	[185–188]
	Tanshinone ii	*Salvia miltiorrhiza* Bunge	DPN rats	ATF6, p-PERK, Keap1, NF-kB↓, Nrf2↑	[194,195]
	Daphnetin	*Daphne giraldii*	CCI rats; Rats with intrathecal injection of TNF-α; HMC3 cell, U251 cell	IL-6, TNF-α, GFAP, Iba-1, CD11b, CD86, CD80, CX3CL1, CX3CR1, CatS, TLR4, p-IKBa, NF-kB↓	[189,190]
	BmK AGAP	Scorpion	CCI mice	p-MAPKs, p-p38, p-ERK, p-JNK↓	[191]
	Corydecumine G	*Corydalis Decumbentis*	CCI rats; BV2 cells	Iba1, NO, iNOS, TNF-α, IL-6, Pge2, p38, ERK↓	[192]
	Senkyunolide H	*Ligusticum chuanxiong*	BV2 microglial cell	Iba1, IL-10, IL-6, IL-1β, NO↓, GSH, CAT, SOD↑, ERK, JNK, P38, IKB-α, NF-kB p65↓	[193]
	Muscone	Musk	HCC mice; HepG2 cell	Bcl-2↓, caspase-3, Bax, LC3 II, PERK, eIF2α, ATF4, DDIT3, AMPK↑, mTOR↓	[197]

Note: The table summarizes the classification and sources of natural products from TCM, the research model used, the specific mechanism of action and the references.

TRPV1, GPCR receptors), inhibiting microglia activation and regulating intestinal flora (as shown in Fig. 9). This coincides with the view that TCM can exert pharmacological effects through multi-targets, multi-pathways and multi-levels. As far as the current situation is concerned, ample studies have demonstrated the role of TCM in alleviating NP. However, most of the literature only focuses on the efficacy and mechanism of action of TCM therapy, but very few papers report the pharmacokinetic study of TCM in the treatment of NP. The biological processes of absorption, distribution, metabolism, and excretion of TCM in the body are more helpful to elucidate the action characteristics of TCM, and will also provide a reference for further research on new TCM anti-NP drugs. In addition, the research on efficacy and action mechanisms are relatively homogeneous, and there is a need to explore more new methods, such as the use of multi-omics analyses (metabolomics, proteomics, microbiomics) for comprehensive studies, to promote the progress of the research on Chinese medicine in treating NP diseases. In the future, with the in-depth study of the pathogenesis of NP, the discovery of more targets will provide more options for the treatment of NP.

Animal models are an important vehicle for the study of disease mechanisms, and an ideal animal model is a good basis for studying the potential mechanisms and therapeutic targets of NP. Currently, there is no single animal model that can encompass all aspects of NP. Animal models only simulate the possible final clinical manifestations of NP in humans and do not reflect the progression of the NP disease process. Secondly, animals are unable to communicate, and most tests assess pain through nerve reflexes, i.e., evoked pain assessment (which is susceptible to the subjective influence of the tester), whereas spontaneous pain assessment is often overlooked or not easily assessed. Finally, NP patients are often accompanied by anxiety, insomnia and even depression, which have a mutually reinforcing effect on pain and affect clinical diagnosis and treatment. Therefore, the development of valid and relevant assessments for NP model animals is also crucial for the study of models and is a direction for future NP research. In addition, the reproducibility and stability of the model still need to be considered in the selection. Compared with CCI, the SNI model is more reproducible, mainly because: the type and number of damaged nerve fibers in SNI are consistent, so the mechanical pain hypersensitivity and hot/cold pain allergy are stable; the key to the success of the CCI construction is the ligature tightness, however, it is difficult to quantify the ligature

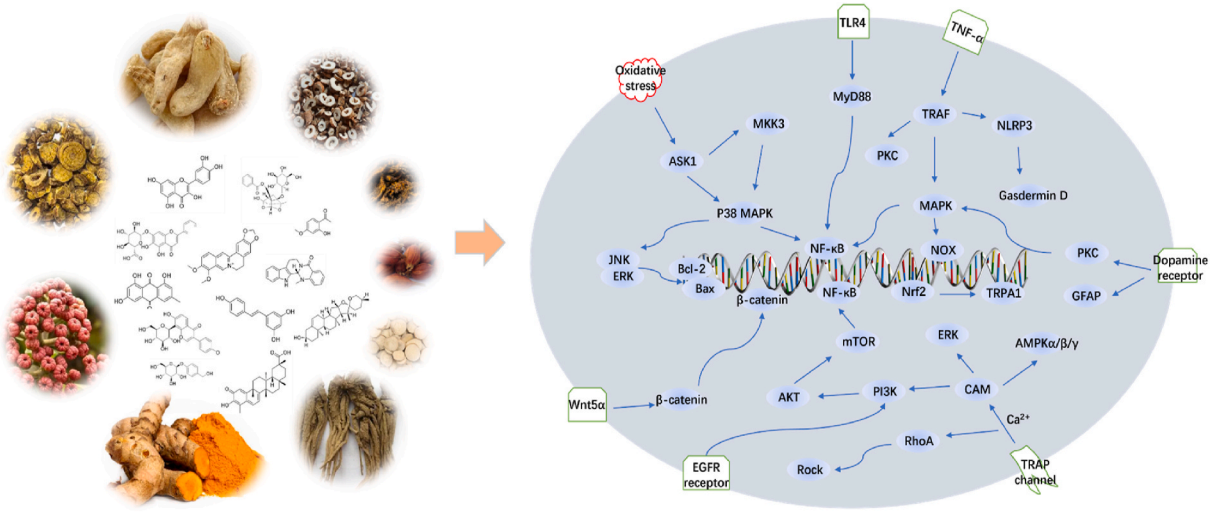

Fig. 9. Treatment mechanism of TCM for NP. The left figure shows some biologically active Chinese medicines and active ingredients, and the right figure shows the mechanism of action of Chinese medicines against NP. The signaling pathways and protein targets involved in the right figure are the possible pathways and sites of action of Chinese medicines.

technique of chromic bowel wire and the strength of the ligature, and the degree of nerve damage varies with different looseness, which leads to the difference in behavioral performance.

Currently, although Western drugs have better therapeutic effects in the treatment of NP, the side effects are equally obvious [4]. Because there are no options for high potency, low side effect medications, there are only a few conventional medications available at this time, such as lidocaine, tramadol, and pregabalin [199]. However, in recent years, more and more studies have found that traditional Chinese medicine can reduce the side effects of Western drugs and enhance the analgesic effect of Western drugs. For example, a recent paper reported that the combination of dihydroartemisinin and pregabalin can inhibit microglia activation and CCL3 expression to inhibit neuroinflammation, and can make up for the shortcomings of pregabalin in antidepressant and cognitive improvement, and enhance the analgesic effect of pregabalin in NP mice [200]. Another study found that the Chinese herb evodiamine was also able to enhance the analgesic effect of pregabalin in SNL rats [201]. In addition, Shaoyao Gancao Decoction combined with oxycodone can effectively alleviate the clinical symptoms of patients with neuropathic headaches, improve the quality of life of patients, and improve the therapeutic effect [202]. Therefore, the combination of Chinese and Western medicines may be a new research direction for the treatment of NP.

However, most studies have focused only on the efficacy and mechanism of action of TCM for NP, and high-quality clinical trials have not yet been conducted. Most clinical studies included low sample sizes and fewer subgroups in the trial design, and some studies did not have a control group, which did not result in high-quality clinical studies. In trials, due to their retrospective nature and reliance on past medical records, some important data are inevitably missed or difficult to obtain. In addition, due to limited follow-up, many trials failed to observe long-term medication outcomes and changes in patients' quality of life. Therefore, in future clinical trials, researchers should pay more attention to the rationality of the design of clinical trials and the reasonableness of the included samples. When conditions permit, multiple research groups can jointly conduct trials to include a larger sample size and improve the credibility of clinical trial results.

In conclusion, Traditional Chinese medicine (TCM), including TCM extracts, TCM prescriptions, and natural products from TCM, has shown well anti-NP effects and is essential for treating NP. This paper is a systematic summary of TCM and the purpose is to supply a scientific and effective reference for treating NP, to make good use of and develop TCM.

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CRediT authorship contribution statement

Naihua Hu: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Jie Liu:** Writing – original draft, Investigation, Formal analysis. **Yong Luo:** Resources, Formal analysis. **Yunxia Li:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] N.B. Finnerup, R. Kuner, T.S. Jensen, Neuropathic pain: from mechanisms to treatment, Physiological Reviews, American Physiological Society 101 (1) (2021) 259–301.
[2] G. Di Stefano, A. Di Lionardo, G. Di Pietro, et al., Neuropathic pain related to peripheral neuropathies according to the IASP grading system criteria, Brain Sci. 11 (1) (2020) 1.
[3] B.H. Smith, S.N. Raja, NeuPSIG: investing in solutions to the growing global challenge of neuropathic pain, British Journal of Anaesthesia, Elsevier 119 (4) (2017) 705–708.
[4] Y. Li, M. Yang, F. Wu, et al., Mechanism of electroacupuncture on inflammatory pain: neural-immune-endocrine interactions, Journal of Traditional Chinese Medicine = Chung I Tsa Chih Ying Wen Pan 39 (5) (2019) 740–749.
[5] A. Boyd, C. Bleakley, D.A. Hurley, et al., Herbal medicinal products or preparations for neuropathic pain, Cochrane Database Syst. Rev. 4 (4) (2019) CD010528.
[6] S.-H. Li, L. Li, R.-N. Yang, et al., Compounds of traditional Chinese medicine and neuropathic pain, Chin. J. Nat. Med. 18 (1) (2020) 28–35.
[7] F. Forouzanfar, H. Hosseinzadeh, Medicinal herbs in the treatment of neuropathic pain: a review, Iranian Journal of Basic Medical Sciences 21 (4) (2018) 347–358.
[8] Z.Y. Ju, K. Wang, H.S. Cui, et al., Acupuncture for neuropathic pain in adults, Cochrane Database Syst. Rev. 12 (12) (2017) CD012057.
[9] L.-Z. Cheng, J.-M. Zhou, J.-L. Ma, et al., Tetrahydropalmatine alleviated diabetic neuropathic pain by inhibiting activation of microglia via p38 MAPK signaling pathway, China J. Chin. Mater. Med. 47 (9) (2022) 2533–2540.
[10] J. Meng, S. Qiu, L. Zhang, et al., Berberine alleviate cisplatin-induced peripheral neuropathy by modulating inflammation signal via TRPV1, Front. Pharmacol. 12 (2021) 774795.
[11] B.-W. Zhang, H. Dong, Z. Wu, et al., An overview of the mechanisms involved in neuralgia, J. Inflamm. Res. 16 (2023) 4087–4101.
[12] S. El, H. Tj, B. P, et al., The integrated stress response contributes to tRNA synthetase-associated peripheral neuropathy[J]. Science (New York, N.Y.), Science 373 (6559) (2021).
[13] S.W. Scheff, D.A. Saucier, M.E. Cain, A statistical method for analyzing rating scale data: the BBB locomotor score, J. Neurotrauma 19 (10) (2002) 1251–1260.
[14] G.J. Bennett, Y.-K. Xie, A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man, Pain 33 (1) (1988) 87–107.
[15] S. Ho Kim, J. Mo Chung, An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat, Pain 50 (3) (1992) 355–363.
[16] Z. Seltzer, R. Dubner, Y. Shir, A novel behavioral model of neuropathic pain disorders produced in rats by partial sciatic nerve injury, Pain 43 (2) (1990) 205–218.
[17] J. Scholz, N.B. Finnerup, N. Attal, et al., The IASP classification of chronic pain for ICD-11: chronic neuropathic pain, Pain 160 (1) (2019) 53–59.
[18] P. Jinyi, L. Yihang, L. Zhengyiqi, et al., Progress in study on animal models of trigeminal neuralgia, J. Cent. S. Univ. 49 (1) (2024) 47–53.
[19] H. Cw, S. E, Epidemiology of peripheral neuropathy and lower extremity disease in diabetes[J]. Current diabetes reports, Curr Diab Rep 19 (10) (2019).
[20] H. Mj, K. Md, L. Me, et al., Peripheral neuropathy phenotyping in rat models of type 2 diabetes mellitus: evaluating uptake of the neurodiab guidelines and identifying future directions[J]. Diabetes & metabolism journal, Diabetes Metab. J 46 (2) (2022).
[21] B.-I. P, O.-C. Vh, E. L-A, et al., Evaluation of the neonatal streptozotocin model of diabetes in rats: evidence for a model of neuropathic pain[J]. Pharmacological reports : pr, Pharmacol. Rep. 70 (2) (2018).
[22] A.D. Desforges, C.M. Hebert, A.L. Spence, et al., Treatment and diagnosis of chemotherapy-induced peripheral neuropathy: an update, Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie 147 (2022) 112671.
[23] J. Suo, M. Wang, P. Zhang, et al., Siwei Jianbu decoction improves painful paclitaxel-induced peripheral neuropathy in mouse model by modulating the NF-κB and MAPK signaling pathways, Regenerative Medicine Research 8 (2020) 2.
[24] A. S, S. R, D. W, et al., Nicotinamide riboside alleviates cisplatin-induced peripheral neuropathy via SIRT2 activation[J]. Neuro-oncology advances, Neurooncol Adv 4 (1) (2022).
[25] E.Y. Lim, Y.T. Kim, Food-Derived Natural Compounds for Pain Relief in Neuropathic Pain[J], BioMed Research International, Hindawi, 2016, p. 2016.
[26] G. Descalzi, D. Ikegami, T. Ushijima, et al., Epigenetic mechanisms of chronic pain, Trends in Neurosciences, Elsevier Current Trends 38 (4) (2015) 237–246.
[27] B. Jiao, W. Zhang, C. Zhang, et al., Protein tyrosine phosphatase 1B contributes to neuropathic pain by aggravating NF-κB and glial cells activation-mediated neuroinflammation via promoting endoplasmic reticulum stress, CNS Neurosci. Ther. 30 (2) (2024) e14609.
[28] H. Golmakani, A. Azimian, E. Golmakani, Newly discovered functions of miRNAs in neuropathic pain: transitioning from recent discoveries to innovative underlying mechanisms, Mol. Pain 20 (2024) 17448069231225845.
[29] Y. Wu, Y. Gu, B. Shi, miR-590-3p Alleviates diabetic peripheral neuropathic pain by targeting RAP1A and suppressing infiltration by the T cells, Acta Biochim. Pol. 67 (4) (2020) 587–593.
[30] Y. Gada, A. Pandey, N. Jadhav, et al., New vistas in microRNA regulatory interactome in neuropathic pain, Front. Pharmacol. 12 (2022) 778014.
[31] Y. Liu, L. Wang, C. Zhou, et al., MiR-31-5p regulates the neuroinflammatory response via TRAF6 in neuropathic pain, Biol. Direct 19 (1) (2024) 10.
[32] P. Mukherjee, M.A. Cinelli, S. Kang, et al., Development of nitric oxide synthase inhibitors for neurodegeneration and neuropathic pain, Chemical Society Reviews, The Royal Society of Chemistry 43 (19) (2014) 6814–6838.
[33] P. Komirishetty, A. Areti, R. Gogoi, et al., Poly(ADP-ribose) polymerase inhibition reveals a potential mechanism to promote neuroprotection and treat neuropathic pain, Neural Regeneration Research 11 (10) (2016) 1545–1548.
[34] S.B. McMahon, M. Malcangio, Current challenges in glia-pain biology, Neuron 64 (1) (2009) 46–54.
[35] A. Ellis, D.L.H. Bennett, Neuroinflammation and the generation of neuropathic pain, Br. J. Anaesth. 111 (1) (2013) 26–37.
[36] J.S. Henkel, D.R. Beers, W. Zhao, et al., Microglia in ALS: the good, the bad, and the resting, J. Neuroimmune Pharmacol. 4 (4) (2009) 389–398.
[37] H. Zhu, Z. Wang, J. Yu, et al., Role and mechanisms of cytokines in the secondary brain injury after intracerebral hemorrhage, Prog. Neurobiol. 178 (2019) 101610.
[38] E. Kong, Y. Li, P. Ma, et al., Lyn-mediated glycolysis enhancement of microglia contributes to neuropathic pain through facilitating IRF5 nuclear translocation in spinal dorsal horn, J. Cell Mol. Med. 27 (12) (2023) 1664–1681.
[39] L.-Q. Zhang, S.-J. Gao, J. Sun, et al., DKK3 ameliorates neuropathic pain via inhibiting ASK-1/JNK/p-38-mediated microglia polarization and neuroinflammation, J. Neuroinflammation 19 (1) (2022) 129.
[40] J. Mika, M. Zychowska, K. Popiolek-Barczyk, et al., Importance of glial activation in neuropathic pain, Eur. J. Pharmacol. 716 (1) (2013) 106–119.
[41] A. Sharma, T. Behl, L. Sharma, et al., Exploring the molecular pathways and therapeutic implications of angiogenesis in neuropathic pain, Biomed. Pharmacother. 162 (2023) 114693.
[42] R.S. Tonkin, C. Bowles, C.J. Perera, et al., Attenuation of mechanical pain hypersensitivity by treatment with Peptide5, a connexin-43 mimetic peptide, involves inhibition of NLRP3 inflammasome in nerve-injured mice, Exp. Neurol. 300 (2018) 1–12.
[43] G.-Z. Li, Y.-H. Hu, Y.-N. Lu, et al., CaMKII and CaV3.2 T-type calcium channel mediate Connexin-43-dependent inflammation by activating astrocytes in vincristine-induced neuropathic pain, Cell Biol. Toxicol. 39 (3) (2023) 679–702.

[44] J. Du, N. Cheng, Y. Deng, et al., Astrocyte senescence-like response related to peripheral nerve injury-induced neuropathic pain, Cell. Mol. Biol. Lett. 28 (1) (2023) 65.
[45] H. Chen, Y. Hu, K. Xie, et al., Effect of autophagy on allodynia, hyperalgesia and astrocyte activation in a rat model of neuropathic pain, International Journal of Molecular Medicine, Spandidos Publications 42 (4) (2018) 2009–2019.
[46] J. Hu, X. Chen, J. Cheng, et al., Mammalian target of rapamycin signaling pathway is involved in synaptic plasticity of the spinal dorsal horn and neuropathic pain in rats by regulating autophagy, Neuroreport 32 (11) (2021) 925–935.
[47] M. Laplante, D.M. Sabatini, mTOR signaling in growth control and disease, Cell 149 (2) (2012) 274–293.
[48] L. Lisi, P. Aceto, P. Navarra, et al., mTOR Kinase: A Possible Pharmacological Target in the Management of Chronic Pain[J], BioMed Research International, Hindawi, 2015, p. 2015.
[49] M. Lazarou, D.A. Sliter, L.A. Kane, et al., The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy, Nature 524 (7565) (2015) 309–314.
[50] H. Katayama, H. Hama, K. Nagasawa, et al., Visualizing and modulating mitophagy for therapeutic studies of neurodegeneration, Cell 181 (5) (2020) 1176–1187.e16.
[51] S. Shao, C.-B. Xu, C.-J. Chen, et al., Divanillyl sulfone suppresses NLRP3 inflammasome activation via inducing mitophagy to ameliorate chronic neuropathic pain in mice, J. Neuroinflammation 18 (1) (2021) 142.
[52] A.I. Basbaum, D.M. Bautista, G. Scherrer, et al., Cellular and molecular mechanisms of pain, Cell 139 (2) (2009) 267–284.
[53] L. Basso, C. Altier, Transient receptor potential channels in neuropathic pain, Curr. Opin. Pharmacol. 32 (2017) 9–15.
[54] G.R. Tibbs, D.J. Posson, P.A. Goldstein, Voltage-gated ion channels in the PNS: novel therapies for neuropathic pain? Trends Pharmacol. Sci. 37 (7) (2016) 522–542.
[55] H. Cai, S. Chen, Y. Sun, et al., Interleukin-22 receptor 1-mediated stimulation of T-type Ca2+ channels enhances sensory neuronal excitability through the tyrosine-protein kinase Lyn-dependent PKA pathway, Cell Commun. Signal.: CCS 22 (1) (2024) 307.
[56] E. Palzur, D. Edelman, R. Sakas, et al., Etifoxine restores mitochondrial oxidative phosphorylation and improves cognitive recovery following traumatic brain injury, Int. J. Mol. Sci. 22 (23) (2021) 12881.
[57] Y. R, H. Y, H. Jw, CaMKII: a central molecular organizer of synaptic plasticity, learning and memory, Nature reviews. Neuroscience, Nat Rev Neurosci 23 (11) (2022).
[58] Y. Wang, Y. Zhang, N. Ma, et al., SIRT1 mediates the excitability of spinal CaMKIIα-positive neurons and participates in neuropathic pain by controlling Nav1.3, CNS Neurosci. Ther. 30 (6) (2024) e14764. John Wiley & Sons, Ltd.
[59] X. Yuan, S. Han, A. Manyande, et al., Spinal voltage-gated potassium channel Kv1.3 contributes to neuropathic pain via the promotion of microglial M1 polarization and activation of the NLRP3 inflammasome, Eur. J. Pain 27 (2) (2023) 289–302. London, England.
[60] H. Kayama, R. Okumura, K. Takeda, Interaction between the microbiota, epithelia, and immune cells in the intestine, Annu. Rev. Immunol. 38 (2020) 23–48.
[61] N. Shi, N. Li, X. Duan, et al., Interaction between the gut microbiome and mucosal immune system, Military Medical Research 4 (2017) 14.
[62] Eugenio Cavalli, Santa Mammana, Ferdinando Nicoletti, et al, The neuropathic pain: an overview of the current treatment and future therapeutic approaches, Int. J. Immunopathol. Pharmacol. 33 (2019) 1–10.
[63] H. Asada, VZV-specific cell-mediated immunity, but not humoral immunity, correlates inversely with the incidence of herpes zoster and the severity of skin symptoms and zoster-associated pain: the SHEZ study, Vaccine 37 (44) (2019) 6776–6781.
[64] S. Zhong, Z. Zhou, Y. Liang, et al., Targeting strategies for chemotherapy-induced peripheral neuropathy: does gut microbiota play a role? Crit. Rev. Microbiol. 45 (4) (2019) 369–393.
[65] W. Ding, Z. You, Q. Chen, et al., Gut microbiota influences neuropathic pain through modulating proinflammatory and anti-inflammatory T cells, Anesth. Analg. 132 (4) (2021) 1146–1155.
[66] R.R. Bonomo, T.M. Cook, C.K. Gavini, et al., Fecal transplantation and butyrate improve neuropathic pain, modify immune cell profile, and gene expression in the PNS of obese mice, Proc. Natl. Acad. Sci. USA 117 (42) (2020) 26482–26493.
[67] S.J. Dixon, K.M. Lemberg, M.R. Lamprecht, et al., Ferroptosis: an iron-dependent form of nonapoptotic cell death, Cell 149 (5) (2012) 1060–1072.
[68] K. Wan, M. Jia, H. Zhang, et al., Electroacupuncture alleviates neuropathic pain by suppressing ferroptosis in dorsal root ganglion via SAT1/ALOX15 signaling, Mol. Neurobiol. 60 (10) (2023) 6121–6132.
[69] Y. Guo, J. Du, C. Xiao, et al., Inhibition of ferroptosis-like cell death attenuates neuropathic pain reactions induced by peripheral nerve injury in rats, Eur. J. Pain 25 (6) (2021) 1227–1240.
[70] H. Wang, X. Huo, C. Han, et al., Ferroptosis is involved in the development of neuropathic pain and allodynia, Mol. Cell. Biochem. 476 (8) (2021) 3149–3161.
[71] L. Li, T. Li, X. Qu, et al., Stress/cell death pathways, neuroinflammation, and neuropathic pain, Immunol. Rev. 321 (1) (2024) 33–51.
[72] P.N. Nesargikar, B. Spiller, R. Chavez, The complement system: history, pathways, cascade and inhibitors, European Journal of Microbiology & Immunology 2 (2) (2012) 103–111.
[73] A.U. Quadros, T.M. Cunha, C5a and pain development: an old molecule, a new target, Pharmacol. Res. 112 (2016) 58–67.
[74] A.V. Wiese, F. Ender, K.M. Quell, et al., The C5a/C5aR1 axis controls the development of experimental allergic asthma independent of LysM-expressing pulmonary immune cells, PLoS One 12 (9) (2017) e0184956.
[75] C. Giorgio, M. Zippoli, P. Cocchiaro, et al., Emerging role of C5 complement pathway in peripheral neuropathies: current treatments and future perspectives, Biomedicines 9 (4) (2021) 399.
[76] Y. Zheng, F. Yang, L. Han, et al., Efficacy of Chinese herbal medicine in the treatment of moderate-severe painful diabetic peripheral neuropathy: a retrospective study, J. Diabetes Res. 2019 (2019) 4035861.
[77] G. Ni, X. Niu, fengxia Zhang, et al., Clinical observation on Shentong Zhuyu decoction in treating postherpetic neuralgia of qi stasis and blood stasis type, Guangming Traditional Chinese Medicine 38 (13) (2023) 2562–2565.
[78] T. Liu, Y. Tang, Y. Zeng, Clinical observation on treatment of post-herpes zoster neuralgia of qi deficiency and blood stasis type by fire needle combined with Buyang Huanwu decoction, Journal of Practical Traditional Chinese Medicine 39 (9) (2023) 1741–1742.
[79] H. Shi, Y. Li, W. Guo, et al., Intervention value of longdan xiegan decoction on patients with hepatogenous headaches after trigeminal neuralgia microvascular decompression, World Journal of Integrated Traditional and Western Medicine 18 (9) (2023) 1790–1794.
[80] Y. Gao, Z. Liang, J. Yang, et al., Clinical observation on Rongjin Tongbi decoction in treating sciatica caused by lumbar intervertebral disc herniation with liver and kidney deficiency type, Chin. J. Exp. Tradit. Med. Formulae 30 (8) (2024) 134–140.
[81] Y. Wen, Z. Chen, Clinical observation on treatment of trigeminal neuralgia with Tongqiao Huayu decoction, The Journal of Medical Theory and Practice 34 (5) (2021) 780–782.
[82] I. Decosterd, C.J. Woolf, Spared nerve injury: an animal model of persistent peripheral neuropathic pain, Pain 87 (2) (2000) 149–158.
[83] C. Gao, Y. Zhao, T. Yang, et al., Duhuo Jisheng decoction alleviates neuroinflammation and neuropathic pain by suppressing microglial M1 polarization: a network pharmacology research, J. Orthop. Surg. Res. 18 (2023) 629.
[84] Q. Guo, K. Mizuno, K. Okuyama, et al., Antineuropathic pain actions of Wu-tou decoction resulted from the increase of neurotrophic factor and decrease of CCR5 expression in primary rat glial cells, Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie 123 (2020) 109812.
[85] C. Zhu, Q. Xu, Z. Mao, et al., The Chinese medicine Wu-tou decoction relieves neuropathic pain by inhibiting hippocampal microglia activation, Sci. Rep. 8 (2018) 12292.
[86] T. Liu, T. Li, X. Chen, et al., A network-based analysis and experimental validation of traditional Chinese medicine Yuanhu Zhitong Formula in treating neuropathic pain, J. Ethnopharmacol. 274 (2021) 114037.
[87] C.L. Loprinzi, C. Lacchetti, J. Bleeker, et al., Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO guideline update, J. Clin. Oncol.: Official Journal of the American Society of Clinical Oncology 38 (28) (2020) 3325–3348.
[88] Y.-W. Liu, Y.-J. Chen, Y.-H. Chen, et al., Therapeutic efficacy of traditional Chinese medicine syndrome-based formulae to neuropathic pain caused by chemotherapy, Integr. Cancer Ther. 21 (2022) 15347354221121095.

[89] M. Li, Z. Li, X. Ma, et al., Huangqi Guizhi Wuwu Decoction can prevent and treat oxaliplatin-induced neuropathic pain by TNFα/IL-1β/IL-6/MAPK/NF-kB pathway, Aging 14 (12) (2022) 5013–5022.
[90] G. Hui, L.I. Yang, F. Lei, et al., Yanghe decoction attenuated pain hypersensitivity induced by Michigan cancer foundation-7 injection in rats with bone metastases from breast cancer by inhibiting transient receptor potential ankyrin 1, Journal of Traditional Chinese Medicine = Chung I Tsa Chih Ying Wen Pan 42 (6) (2022) 948–955.
[91] A.K. Schreiber, C.F. Nones, R.C. Reis, et al., Diabetic neuropathic pain: physiopathology and treatment, World J. Diabetes 6 (3) (2015) 432–444.
[92] F. Wang, H. Tang, J. Ma, et al., The effect of Yiqi Huoxue Tongluo decoction on spinal cord microglia activation and ASK1-MKK3-p38 signal pathway in rats with diabetic neuropathic pain, Evid. base Compl. Alternative Med.: eCAM 2022 (2022) 2408265.
[93] Q. Sun, R. Zhang, X. Xue, et al., Jinmaitong alleviates diabetic neuropathic pain through modulation of NLRP3 inflammasome and Gasdermin D in dorsal root ganglia of diabetic rats, Front. Pharmacol. 12 (2021) 679188.
[94] S. Wang, A. Taledaohan, M. Tuohan, et al., Jinmaitong alleviates diabetic neuropathic pain by inhibiting JAK2/STAT3 signaling in microglia of diabetic rats, J. Ethnopharmacol. 333 (2024) 118442.
[95] Y. Liao, C. Guo, A. Wen, et al., Frankincense-Myrrh treatment alleviates neuropathic pain via the inhibition of neuroglia activation mediated by the TLR4/MyD88 pathway and TRPV1 signaling, Phytomedicine: International Journal of Phytotherapy and Phytopharmacology 108 (2023) 154540.
[96] D. Zhang, J. Sun, B. Yang, et al., Therapeutic effect of tetrapanax papyriferus and hederagenin on chronic neuropathic pain of chronic constriction injury of sciatic nerve rats based on KEGG pathway prediction and experimental verification, Evid. base Compl. Alternative Med.: eCAM 2020 (2020) 2545806.
[97] X.-Y. Wang, H.-J. Ma, M. Xue, et al., Anti-nociceptive effects of Sedum Lineare Thunb. on spared nerve injury-induced neuropathic pain by inhibiting TLR4/NF-κB signaling in the spinal cord in rats, Biomed. Pharmacother. 135 (2021) 111215.
[98] P. Wang, C. Wen, O.J. Olatunji, Anti-inflammatory and antinociceptive effects of Boesenbergia rotunda polyphenol extract in diabetic peripheral neuropathic rats, J. Pain Res. 15 (2022) 779–788.
[99] O. van Hecke, S.K. Austin, R.A. Khan, et al., Neuropathic pain in the general population: a systematic review of epidemiological studies, Pain 155 (4) (2014) 654–662.
[100] D. Du, M. Zhang, Y. Liu, et al., Mechanism of Chuanxiong Rhizoma intervention on central sensitization of Panx1-Src-NMDAR-2B signaling pathway in neuropathic pain model rats, China J. Chin. Mater. Med. 46 (16) (2021) 4175–4186.
[101] D. Ahmadimoghaddam, M. Zarei, S. Mohammadi, et al., Bupleurum falcatum L. alleviates nociceptive and neuropathic pain: potential mechanisms of action, J. Ethnopharmacol. 273 (2021) 113990.
[102] Y. Ruan, X. Jin, H. Ji, et al., Water extract of Notopterygium incisum alleviates cold allodynia in neuropathic pain by regulation of TRPA1, J. Ethnopharmacol. 305 (2023) 116065.
[103] C.-P. Kuai, L.-J. Ju, P.-P. Hu, et al., Corydalis saxicola alkaloids attenuate cisplatin-induced neuropathic pain by reducing loss of IENF and blocking TRPV1 activation, Am. J. Chin. Med. 48 (2) (2020) 407–428.
[104] S.-Y. Liu, L. Chen, X.-C. Li, et al., Lycium barbarum polysaccharide protects diabetic peripheral neuropathy by enhancing autophagy via mTOR/p70S6K inhibition in Streptozotocin-induced diabetic rats, J. Chem. Neuroanat. 89 (2018) 37–42.
[105] C.-L. Shen, R. Wang, G. Ji, et al., Dietary supplementation of gingerols- and shogaols-enriched ginger root extract attenuate pain-associated behaviors while modulating gut microbiota and metabolites in rats with spinal nerve ligation, J. Nutr. Biochem. 100 (2022) 108904.
[106] X. Cheng, D. Wang, D. Yang, Advances in studies on biological activity and structure-activity relationships of isoquinoline alkaloids, Chin. Tradit. Herb. Drugs 37 (12) (2006) 1900–1904.
[107] R.L. Silva, A.H. Lopes, R.M. Guimarães, et al., CXCL1/CXCR2 signaling in pathological pain: role in peripheral and central sensitization, Neurobiol. Dis. 105 (2017) 109–116.
[108] L. Zhou, Y. Hu, C. Li, et al., Levo-corydalmine alleviates vincristine-induced neuropathic pain in mice by inhibiting an NF-kappa B-dependent CXCL1/CXCR2 signaling pathway, Neuropharmacology 135 (2018) 34–47.
[109] J. Singh, L. Saha, N. Singh, et al., Study of nuclear factor-2 erythroid related factor-2 activator, berberine, in paclitaxel induced peripheral neuropathy pain model in rats, J. Pharm. Pharmacol. 71 (5) (2019) 797–805.
[110] P. Wu, Y. Chen, Evodiamine ameliorates paclitaxel-induced neuropathic pain by inhibiting inflammation and maintaining mitochondrial anti-oxidant functions, Hum. Cell 32 (3) (2019) 251–259.
[111] D. Su, Y. Gong, S. Li, et al., Cyclovirobuxine D, a cardiovascular drug from traditional Chinese medicine, alleviates inflammatory and neuropathic pain mainly via inhibition of voltage-gated Cav3.2 channels, Front. Pharmacol. 13 (2022) 1081697.
[112] B. Yang, S. Ma, C. Zhang, et al., Higenamine attenuates neuropathic pain by inhibition of NOX2/ROS/TRP/P38 mitogen-activated protein kinase/NF-κB signaling pathway, Front. Pharmacol. 12 (2021) 716684.
[113] S. Shao, H. Xia, M. Hu, et al., Isotalatizidine, a C19-diterpenoid alkaloid, attenuates chronic neuropathic pain through stimulating ERK/CREB signaling pathway-mediated microglial dynorphin A expression, J. Neuroinflammation 17 (2020) 13.
[114] L. Zou, K. Yu, Y. Fan, et al., The inhibition by Guanfu base A of neuropathic pain mediated by P2Y12 receptor in dorsal root ganglia, ACS Chem. Neurosci. 10 (3) (2019) 1318–1325.
[115] G.-L. Jin, S.-D. He, S.-M. Lin, et al., Koumine attenuates neuroglia activation and inflammatory response to neuropathic pain, Neural Plast. 2018 (2018) 9347696.
[116] D. Wu, P. Wang, C. Zhao, et al., Levo-tetrahydropalmatine ameliorates neuropathic pain by inhibiting the activation of the Clec7a-MAPK/NF-κB-NLRP3 inflammasome axis, Phytomedicine: International Journal of Phytotherapy and Phytopharmacology 121 (2023) 155075.
[117] N. Gu, U.B. Eyo, M. Murugan, et al., Microglial P2Y12 receptors regulate microglial activation and surveillance during neuropathic pain, Brain Behav. Immun. 55 (2016) 82–92.
[118] L. Long, W. Zhong, L. Guo, et al., Effect of bufalin-PLGA microspheres in the alleviation of neuropathic pain via the CCI model, Front. Pharmacol. 13 (2022) 910885.
[119] G. Yu, L. Qian, J. Yu, et al., Brucine alleviates neuropathic pain in mice via reducing the current of the sodium channel, J. Ethnopharmacol. 233 (2019) 56–63.
[120] M. Zhou, C. Yao, Y. Yang, et al., Based on spinal central sensitization creating analgesic screening approach to excavate anti-neuropathic pain ingredients of Corydalis yanhusuo W.T.Wang, J. Ethnopharmacol. (2023) 117084.
[121] M. Liu, L. Gao, N. Zhang, Berberine reduces neuroglia activation and inflammation in streptozotocin-induced diabetic mice, Int. J. Immunopathol. Pharmacol. 33 (2019) 2058738419866379.
[122] G. Zhou, M. Yan, G. Guo, et al., Ameliorative effect of berberine on neonatally induced type 2 diabetic neuropathy via modulation of BDNF, IGF-1, PPAR-γ, and AMPK expressions, Dose Response 17 (3) (2019) 1559325819862449.
[123] Y. Nakatani, K. Negoro, M. Yamauchi, et al., Neoline, an active ingredient of the processed aconite root in Goshajinkigan formulation, targets Nav1.7 to ameliorate mechanical hyperalgesia in diabetic mice, J. Ethnopharmacol. 259 (2020) 112963.
[124] T. Gao, T. Shi, Z. Wiesenfeld-Hallin, et al., Sinomenine facilitates the efficacy of gabapentin or ligustrazine hydrochloride in animal models of neuropathic pain, Eur. J. Pharmacol. 854 (2019) 101–108.
[125] Y. Shen, S. Guan, H. Ge, et al., Effects of palmatine on rats with comorbidity of diabetic neuropathic pain and depression, Brain Res. Bull. 139 (2018) 56–66.
[126] J. Yu, H. Yuan, L. Bao, et al., Interaction between piperine and genes associated with sciatica and its mechanism based on molecular docking technology and network pharmacology, Mol. Divers. 25 (1) (2021) 233–248.
[127] C. Hu, M. He, M. Chen, et al., Amelioration of neuropathic pain and attenuation of neuroinflammation responses by tetrahydropalmatine through the p38MAPK/NF-κB/iNOS signaling pathways in animal and cellular models, Inflammation 45 (2) (2022) 891–903.
[128] X. Wang, Y. Cao, S. Chen, et al., Anti-inflammation activity of flavones and their structure-activity relationship, J. Agric. Food Chem. 69 (26) (2021) 7285–7302.

[129] J. Shi, H. Shi, Quantitative structure-activity relationship study of the neuroprotective activity of flavonoids, Journal of Nanning Normal University 40 (4) (2023) 75–80.
[130] Y. Huang, X. Zhang, Y. Zou, et al., Quercetin ameliorates neuropathic pain after brachial plexus avulsion via suppressing oxidative damage through inhibition of PKC/MAPK/NOX pathway, Curr. Neuropharmacol. 21 (11) (2023) 2343–2361.
[131] Y. Wang, C. Chen, W. Wang, et al., Effects of Puerarin on the expression of iNOS, CGRP, and PI3K/Akt signaling pathway in spinal cord anterior horn after brachial plexus root avulsion injury, Chinese Journal of Clinical Anatomy 37 (5) (2019) 517–522.
[132] H.-T. Xie, Z.-Y. Xia, X. Pan, et al., Puerarin ameliorates allodynia and hyperalgesia in rats with peripheral nerve injury, Neural Regeneration Research 13 (7) (2018) 1263–1268.
[133] Y. Wu, J. Chen, R. Wang, Puerarin suppresses TRPV1, calcitonin gene-related peptide and substance P to prevent paclitaxel-induced peripheral neuropathic pain in rats, Neuroreport 30 (4) (2019) 288–294.
[134] X. Zhang, X. Cao, R. Lai, et al., Puerarin relieves paclitaxel-induced neuropathic pain: the role of Nav1.8 β1 subunit of sensory neurons, Front. Pharmacol. 9 (2018) 1510.
[135] Y. Chen, L. Feng, D. Xu, et al., Combination of paeoniflorin and liquiritin alleviates neuropathic pain by lipid metabolism and calcium signaling coordination, Front. Pharmacol. 13 (2022) 944386.
[136] Q. Guo, W. Li, C. Wang, et al., Biomolecular network-based synergistic drug combination discovery: a combination of paeoniflorin and liquiritin alleviates neuropathic pain by inhibiting neuroinflammation via suppressing the chemokine signaling pathway, Signal Transduct. Targeted Ther. 5 (2020) 73.
[137] L. Zhao, X. Tao, Q. Wang, et al., Diosmetin alleviates neuropathic pain by regulating the Keap1/Nrf2/NF-κB signaling pathway, Biomed. Pharmacother. 170 (2024) 116067.
[138] H. Lai, C. Lu, C. Wong, et al., Baicalein attenuates neuropathic pain and improves sciatic nerve function recovery in rats with partial sciatic nerve transection, J. Chin. Med. Assoc. 81 (11) (2018) 955–963.
[139] Z. Wang, D. Ling, C. Wu, et al., Baicalin prevents the up-regulation of TRPV1 in dorsal root ganglion and attenuates chronic neuropathic pain, Veterinary Medicine and Science 6 (4) (2020) 1034–1040.
[140] M. Wang, X. Cai, Y. Wang, et al., Astragalin alleviates neuropathic pain by suppressing P2X4-mediated signaling in the dorsal root ganglia of rats, Front. Neurosci. 14 (2020) 570831.
[141] S. Zhou, J. Huang, K. Li, et al., Genistein attenuates LPS-induced inflammatory injury of rat dorsal root ganglion neuron via down-regulating HDAC6, J. Cent. S. Univ. 47 (6) (2022) 707–716.
[142] W. Dai, Y. Bao, J. Fan, et al., Levo-corydalmine attenuates microglia activation and neuropathic pain by suppressing ASK1-p38 MAPK/NF-κB signaling pathways in rat spinal cord, Reg. Anesth. Pain Med. 45 (3) (2020) 219–229.
[143] S. Chang, X. Li, Y. Zheng, et al., Kaempferol exerts a neuroprotective effect to reduce neuropathic pain through TLR4/NF-κB signaling pathway, Phytother Res.: PTR 36 (4) (2022) 1678–1691.
[144] X. Li, H. Shi, D. Zhang, et al., Paeonol alleviates neuropathic pain by modulating microglial M1 and M2 polarization via the RhoA/p38MAPK signaling pathway, CNS Neurosci. Ther. 29 (9) (2023) 2666–2679.
[145] Y. Wang, Y. Shi, Y. Huang, et al., Resveratrol mediates mechanical allodynia through modulating inflammatory response via the TREM2-autophagy axis in SNI rat model, J. Neuroinflammation 17 (1) (2020) 311.
[146] J. Guo, C. Wang, X. Niu, et al., Effects of resveratrol in the signaling of neuropathic pain involving P2X3 in the dorsal root ganglion of rats, Acta Neurol. Belg. 121 (2) (2021) 365–372.
[147] T. Yoneda, M. Hiasa, Y. Nagata, et al., Acidic microenvironment and bone pain in cancer-colonized bone, BoneKEy Rep. 4 (2015).
[148] H. Zhu, J. Ding, J. Wu, et al., Resveratrol attenuates bone cancer pain through regulating the expression levels of ASIC3 and activating cell autophagy, Acta Biochim. Biophys. Sin. 49 (11) (2018) 1008–1014.
[149] L. Zhang, B. Song, X. Zhang, et al., Resveratrol ameliorates trigeminal neuralgia-induced cognitive deficits by regulating neural ultrastructural remodelling and the CREB/BDNF pathway in rats, Oxid. Med. Cell. Longev. 2022 (2022) 4926678.
[150] Y. Peng, X. Zheng, Z. Fan, et al., Paeonol alleviates primary dysmenorrhea in mice via activating CB2R in the uterus, Phytomedicine: International Journal of Phytotherapy and Phytopharmacology 68 (2020) 153151.
[151] J. Du, Y. Deng, Z. Qiu, et al., Curcumin alleviates chronic pain and improves cognitive impairment via enhancing hippocampal neurogenesis in sciatic nerve constriction rats, J. Pain Res. 14 (2021) 1061–1070.
[152] L. Zhang, X. Ding, Z. Wu, et al., Curcumin alleviates pain and improves cognitive impairment in a rat model of cobra venom-induced trigeminal neuralgia, J. Pain Res. 11 (2018) 1095–1104.
[153] H. Zhi, Y.-Z. Jia, H. Bo, et al., Curcumin alleviates orofacial allodynia and improves cognitive impairment via regulating hippocampal synaptic plasticity in a mouse model of trigeminal neuralgia, Aging 15 (16) (2023) 8458–8470.
[154] X. Zhang, Z. Guan, X. Wang, et al., Curcumin alleviates oxaliplatin-induced peripheral neuropathic pain through inhibiting oxidative stress-mediated activation of NF-κB and mitigating inflammation, Biol. Pharmaceut. Bull. 43 (2) (2020) 348–355.
[155] D. Zhang, B. Jing, X. Li, et al., Ferulic Acid Alleviates Sciatica by Inhibiting Peripheral Sensitization through the RhoA/p38MAPK Signalling Pathway, Phytomedicine : international journal of phytotherapy and phytopharmacology, Phytomedicine, 2022, p. 106.
[156] D. Zhang, B. Jing, Z. Chen, et al., Ferulic acid alleviates sciatica by inhibiting neuroinflammation and promoting nerve repair via the TLR4/NF-κB pathway, CNS Neurosci. Ther. 29 (4) (2023) 1000–1011.
[157] Y. Wang, X. Xu, P. Hu, et al., Effect of toll-like receptor 4/myeloid differentiation factor 88 inhibition by salvianolic acid B on neuropathic pain after spinal cord injury in mice, World Neurosurgery 132 (2019) e529–e534.
[158] R. Yang, Z. Li, Y. Zou, et al., Gallic acid alleviates neuropathic pain behaviors in rats by inhibiting P2X7 receptor-mediated NF-κB/STAT3 signaling pathway, Front. Pharmacol. 12 (2021) 680139.
[159] S. Kaur, A. Muthuraman, Ameliorative effect of gallic acid in paclitaxel-induced neuropathic pain in mice, Toxicol Rep 6 (2019) 505–513.
[160] H.K. Chae, W. Kim, S.K. Kim, Phytochemicals of Cinnamomi cortex: cinnamic acid, but not cinnamaldehyde, attenuates oxaliplatin-induced cold and mechanical hypersensitivity in rats, Nutrients 11 (2) (2019) 432.
[161] B. Qin, N. Luo, Y. Li, et al., Protective effect of gastrodin on peripheral neuropathy induced by anti-tumor treatment with vincristine in rat models, Drug Chem. Toxicol. 44 (1) (2021) 84–91.
[162] L.A. Chew, R. Khanna, CRMP2 and voltage-gated ion channels: potential roles in neuropathic pain, Neuronal Signaling 2 (1) (2018) NS20170220.
[163] X. Wang, B. Zhang, X. Li, et al., Mechanisms underlying gastrodin alleviating vincristine-induced peripheral neuropathic pain, Front. Pharmacol. 12 (2021) 744663.
[164] X. Lin, Y. Qin, J. Jia, et al., MiR-155 enhances insulin sensitivity by coordinated regulation of multiple genes in mice, PLOS Genetics, Public Library of Science 12 (10) (2016) e1006308.
[165] Y. Yin, H. Qu, Q. Yang, et al., Astragaloside IV alleviates Schwann cell injury in diabetic peripheral neuropathy by regulating microRNA-155-mediated autophagy, Phytomedicine 92 (2021) 153749.
[166] G. Ni, R. Cui, A. Shao, et al., Salidroside ameliorates diabetic neuropathic pain in rats by inhibiting neuroinflammation, J. Mol. Neurosci. 63 (1) (2017) 9–16.
[167] T. Zheng, Q. Wang, F. Bian, et al., Salidroside alleviates diabetic neuropathic pain through regulation of the AMPK-NLRP3 inflammasome axis, Toxicol. Appl. Pharmacol. 416 (2021) 115468.
[168] P. Liu, J. Chen, S. Ma, et al., Albiflorin attenuates mood disorders under neuropathic pain state by suppressing the hippocampal NLRP3 inflammasome activation during chronic constriction injury, Int. J. Neuropsychopharmacol. 24 (1) (2020) 64–76.
[169] P. Liu, J. Cheng, S. Ma, et al., Paeoniflorin attenuates chronic constriction injury-induced neuropathic pain by suppressing spinal NLRP3 inflammasome activation, Inflammopharmacology 28 (6) (2020) 1495–1508.

[170] D. Zhang, S. Chang, X. Li, et al., Therapeutic effect of paeoniflorin on chronic constriction injury of the sciatic nerve via the inhibition of Schwann cell apoptosis, Phytother Res.: PTR 36 (6) (2022) 2572–2582.
[171] D. Zhang, Q. Chen, L. Yao, Geniposide alleviates neuropathic pain in CCI rats by inhibiting the EGFR/PI3K/AKT pathway and Ca2+ channels, Neurotox. Res. 40 (4) (2022) 1057–1069.
[172] W. Dai, L. Zhang, L. Han, et al., Regulation of the KATP-JNK gap junction signaling pathway by immunomodulator astragaloside IV attenuates neuropathic pain, Reg. Anesth. Pain Med. 45 (12) (2020) 955–963.
[173] Y. Shi, Y. Wu, L. Wang, et al., Gooderoside A from Anoectochilus elatus attenuates acute and chronic pains by inhibiting NO/cGMP and IRAK4/IRAK1/TAK1 signaling pathways, J. Ethnopharmacol. 324 (2024) 117767.
[174] A. Kale, A. Wadkar, U. Mahajan, et al., Aloin attenuates chronic constriction injury-induced neuropathic pain in rats by inhibiting inflammatory cytokines and oxidative stress, Asian Pac. J. Trop. Biomed. 11 (5) (2021) 205–213.
[175] J.-F. Wang, H.-J. Xu, Z.-L. He, et al., Crocin alleviates pain hyperalgesia in AIA rats by inhibiting the spinal wnt5a/β-catenin signaling pathway and glial activation, Neural Plast. 2020 (2020) 4297483.
[176] M.M. Rahman, H.J. Jo, C.-K. Park, et al., Diosgenin exerts analgesic effects by antagonizing the selective inhibition of transient receptor potential vanilloid 1 in a mouse model of neuropathic pain, Int. J. Mol. Sci. 23 (24) (2022) 15854.
[177] G.-J. Jin, X. Peng, Z.-G. Chen, et al., Celastrol attenuates chronic constrictive injury-induced neuropathic pain and inhibits the TLR4/NF-κB signaling pathway in the spinal cord, J. Nat. Med. 76 (1) (2022) 268–275.
[178] K. Chen, T. Wang, Y. Li, et al., Rhodojaponin VI indirectly targets Cav2.2 channels via N-ethylmaleimide-sensitive fusion protein to alleviate neuropathic pain, Acta Pharm. Sin. B 13 (3) (2023) 1326–1336.
[179] J. Yang, Q. Yang, J. Zhao, et al., Evaluation of Rhodojaponin III from Rhododendron molle G. Don on oral antinociceptive activity, mechanism of action, and subacute toxicity in rodents, J. Ethnopharmacol. 294 (2022) 115347.
[180] H. Guan, T. Yan, D. Wu, et al., Epifriedelinol ameliorates the neuropathic pain and recovers the function in spinal cord injury by downregulation of neuronal apoptosis and NMDA receptor, Tohoku J. Exp. Med. 258 (2) (2022) 143–148.
[181] C. Zhu, Y. Zhu, G. Zhang, et al., The analgesic and antidepressant properties of dihydroartemisinine in the neuropathic pain mice: by the downregulation of HnRNPA1 in the spinal cord and hippocampus, Clin. Transl. Med. 12 (2) (2022) e751.
[182] L.-T. Ma, Y. Bai, P. Cao, et al., The analgesic effects of β-elemene in rats with neuropathic pain by inhibition of spinal astrocytic ERK activation, Mol. Pain 18 (2022) 17448069221121562.
[183] M. Yi, Z. Zhang, Z. Luo, et al., PolyphyllinVI alleviates the spared nerve injury-induced neuropathic pain based on P2X3 receptor-mediated the release of inflammatory mediators, J. Ethnopharmacol. 325 (2024) 117886.
[184] S. Man, L. Xie, X. Liu, et al., Diosgenin relieves oxaliplatin-induced pain by affecting TLR4/NF-κB inflammatory signaling and the gut microbiota, Food Funct. 14 (1) (2023) 516–524.
[185] P. Chen, N.-Y. Huang, B. Pang, et al., Proteomic and metabolomic approaches elucidate the molecular mechanism of emodin against neuropathic pain through modulating the gamma-aminobutyric acid (GABA)-ergic pathway and PI3K/AKT/NF-κB pathway, Phytother Res.: PTR 37 (5) (2023) 1883–1899.
[186] P. Chen, D. Lin, C. Wang, et al., Proteomic analysis of emodin treatment in neuropathic pain reveals dysfunction of the calcium signaling pathway, J. Pain Res. 14 (2021) 613–622.
[187] P. Chen, C. Wang, R.-X. Luo, et al., Mechanism of emodin in relieving neuropathic pain by regulating serum metabolism, China J. Chin. Mater. Med. 47 (8) (2022) 2187–2194.
[188] C. Wang, L. Wu, R. Zhou, et al., Integration of microbiota and metabolomics reveals the analgesic mechanisms of emodin against neuropathic pain, Int. Immunopharm. 125 (Pt A) (2023) 111170.
[189] T. Zhang, W. Liang, M. Zhang, et al., Daphnetin improves neuropathic pain by inhibiting the expression of chemokines and inflammatory factors in the spinal cord and interfering with glial cell polarization, Pharmaceuticals 16 (2) (2023). Multidisciplinary Digital Publishing Institute (MDPI).
[190] T. Zhang, W. Liang, W. Ou, et al., Daphnetin alleviates neuropathic pain in chronic constrictive injury rats via regulating the NF-κB dependent CXCL1/CXCR2 signaling pathway, Pharmaceut. Biol. 61 (1) (2023) 746–754.
[191] J.-P. Ruan, Q.-H. Mao, W.-G. Lu, et al., Inhibition of spinal MAPKs by scorpion venom peptide BmK AGAP produces a sensory-specific analgesic effect, Mol. Pain 14 (2018) 1744806918761238.
[192] L. Tan, Y. Hu, X. Zhang, et al., Corydecumine G inhibits microglia activation via MAPK pathway in a rat model of neuropathic pain, J. Chem. Neuroanat. 124 (2022) 102124.
[193] J. Tan, W. Li, Z. Teng, et al., Senkyunolide H inhibits activation of microglia and attenuates lipopolysaccharide-mediated neuroinflammation and oxidative stress in BV2 microglia cells via regulating ERK and NF-κB pathway, Kaohsiung J. Med. Sci. 38 (4) (2022) 378–384.
[194] D. Kong, Z. Guo, W. Yang, et al., Tanshinone II A affects diabetic peripheral neuropathic pain via spinal dorsal horn neuronal circuitry by modulating endoplasmic reticulum stress pathways[J]. Experimental and clinical endocrinology & diabetes: official journal, German Society of Endocrinology [and] German Diabetes Association 128 (1) (2020) 59–65.
[195] F.-B. Feng, H.-Y. Qiu, Neuroprotective effect of tanshinone IIA against neuropathic pain in diabetic rats through the Nrf2/ARE and NF-κB signaling pathways, Kaohsiung J. Med. Sci. 34 (8) (2018) 428–437.
[196] H.-W. Sim, J. Knox, Hepatocellular carcinoma in the era of immunotherapy, Curr. Probl. Cancer 42 (1) (2018) 40–48.
[197] W. Qi, Z. Li, C. Yang, et al., Inhibitory mechanism of muscone in liver cancer involves the induction of apoptosis and autophagy, Oncology Reports, Spandidos Publications 43 (3) (2020) 839–850.
[198] L. Ruan, K. Guan, Y. Wang, et al., Baicalein exerts anxiolytic and antinociceptive effects in a mouse model of posttraumatic stress disorder: involvement of the serotonergic system and spinal delta-opioid receptors, Progress in Neuro-Psychopharmacology & Biological Psychiatry 122 (2023) 110689.
[199] S. Kankowski, C. Grothe, K. Haastert-Talini, Neuropathic pain: spotlighting anatomy, experimental models, mechanisms, and therapeutic aspects, Eur. J. Neurosci. 54 (2) (2021) 4475–4496.
[200] Y. Liu, W. Wang, G. Zhang, et al., Interventional effect and inflammatory regulation mechanism of dihydroartemisinin combined with pregabalin on neuropathic pain mice, China J. Chin. Mater. Med. 49 (6) (2024) 1570–1578.
[201] L. Zhan, C. Pan, X. Xu, et al., Effect of pregabalin capsule combined with evodiamine injection on inflammatory cytokines and pain behavior in rats with neuropathic pain, The Chinese Journal of Clinical Pharmacology 32 (20) (2016) 1890–1893.
[202] J. Yan, L. Zhu, M. Zhao, et al., Clinical observation on modified Shaoyao Gancao decoction combined with paracetamol and oxycodone in treating neuropathic headache, Modern Journal of Integrated Traditional Chinese and Western Medicine 28 (1) (2019) 69–71, 78.