Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Iridoids from Traditional Chinese Medicine for Neuropathic Pain: Therapeutic Potential and Molecular Mechanisms

Wenjun Wang[1,2], Tianlong Liu[3], Yi Ding[4], Xiaolong Liu[1], Ren Qingji[5], Yi Zhang[6], Zhengxiang Zhang[1]

[1]Yan'an Medical College, Yan'an University, Yan'an, Shaanxi, People's Republic of China; [2]Department of Traditional Chinese Medicine, Tangdu Hospital, Fourth Military Medical University, Xi'an, Shaanxi, People's Republic of China; [3]Department of Clinical Pharmacy, The 940th Hospital of Joint Logistics Support Force of Chinese PLA, Lanzhou, Gansu, People's Republic of China; [4]Department of Pharmacy, Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi, People's Republic of China; [5]Xizang University of Tibetan Medicine, Lhasa, Xizang, People's Republic of China; [6]State Key Laboratory of Southwestern Chinese Medicine Resources, School of Ethnic Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, People's Republic of China

Correspondence: Wenjun Wang; Zhengxiang Zhang, Yan'an Medical College, Yan'an University, No. 580 Shengdi Road, Baota District, Yan'an, Shaanxi, People's Republic of China, Email wenjunwang018@163.com; zhangzhengxiang168@163.com

Drug Design, Development and Therapy downloaded from https://www.dovepress.com/
For personal use only.

Abstract: Neuropathic pain (NP) affects global public health problem and remains inadequately controlled by existing drugs. A class of plant-derived iridoids, predominantly glycosides found in traditional Chinese medicine like *Lamiophlomis rotata* (Benth). Kudo, have recently emerged as promising neuroprotective substances. Here we systematically review pre-clinical efficacy and mechanisms of iridoids across various rodent models of NP. The studies selected for inclusion in this review were those that primarily focused on examining the phytochemical properties and the pharmacological mechanisms related to iridoids. Iridoid glycosides including loganin, catalpol, geniposide, gardenoside, shanzhiside methyl ester, 8-O-acetyl-shanzhiside methyl ester, picroside II and aucubin and seco-iridoid glycosides such as morroniside, gentiopicroside and oleuropein consistently reverse mechanical allodynia and thermal hyperalgesia with ED_{50} values ranging from 5 μg (intrathecal) to 130–250 mg/kg (oral), without tolerance after repeated dosing. Mechanistically, iridoid glycosides exert anti-neuropathic effects through a multifaceted mechanism involving anti-inflammatory, antioxidant, glial modulatory, neuroprotective, and potentially neurotransmitter-modulating actions. Additionally, compared with gabapentin, duloxetine or tramadol, iridoids achieve equivalent analgesia accompanied by favorable safety indices and ancillary anxiolytic and antidepressant effects. The main translational gap from the absence of chronic-progressive or primate validation studies, as well as the lack of large-scale clinical trials needed to establish their efficacy and safety in human populations. Collectively, plant-derived iridoids represent mechanistically novel, multi-target and safe candidate ingredients for NP, addressing the major unmet need for efficacy and tolerability beyond current standard of care. Future work should integrate high-quality clinical evidence to accelerate the development of iridoid-based therapeutics for NP.

Keywords: iridoids, iridoid glycosides, seco-iridoid glycosides, neuropathic pain, mechanism

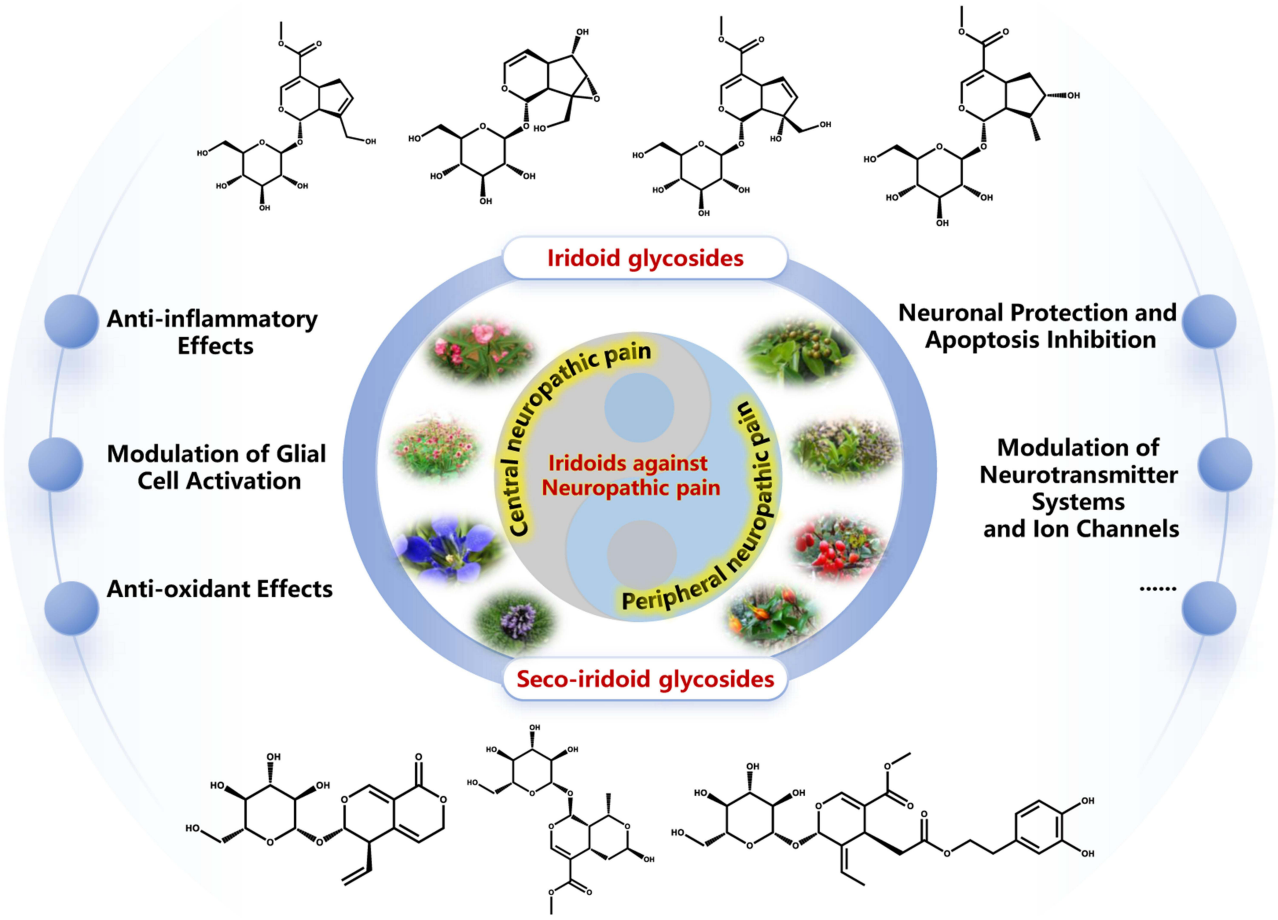
Introduction

Neuropathic pain (NP) is a crippling condition that arises from damage or pathological conditions affecting the somatosensory nervous system.[1] It is characterized by persistent or intermittent spontaneous pain, evoked pain, hyperalgesia, and paresthesia.[2] Chronic NP frequently leads to secondary complications such as sleep disturbances, anxiety, and depression, significantly impairing patients' overall quality of life.[3,4] Epidemiological studies indicated that NP affects approximately 7%-10% of the global population,[5] with a higher prevalence among individuals aged over 50 years.[6] Notably, it is estimated that one in every 20 individuals in western countries is affected by NP.[7] The substantial personal and socioeconomic burden associated with NP underscores the urgent need for more effective therapeutic strategies.[8] Although current therapeutic recommendations for NP, including pregabalin, gabapentin, duloxetine, and various tricyclic antidepressants, often provide inadequate relief (yet only 20% of patients achieve adequate pain relief

https://doi.org/10.2147/DDDT.S591283
Received: 23 December 2025
Accepted: 2 April 2026
Published: 8 April 2026

© 2026 Wang et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v4.0) License (http://creativecommons.org/licenses/by-nc/4.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

Graphical Abstract



with current treatments) and are associated with adverse reactions or considerable side effects,[9,10] highlighting the necessity of exploring other safe and effective treatment options.

In recent years, Chinese herbal medicine, especially plant-derived bioactive molecules, have gained increasing attention for their multifaceted pharmacological activities and favorable safety profiles.[11] Among them, iridoids are a class of naturally occurring monoterpene compounds, have recently attracted scientific interest due to their demonstrated bioactivities relevant to neurological disorders.[12] Indeed, iridoids are widely present in medicinal plants such as *Lamiophlomis rotata* (Benth). Kudo, *Gardenia jasminoides* J.Ellis, *Gentiana scabra* Bunge, *Strychnos nux-vomica* Linn., *Nerium oleander* Linn., *Eucommia ulmoides* Oliv., *and Ligustrum lucidum* Ait. *Lamiophlomis rotata* (Benth). Kudo, *Strychnos nux-vomica* Linn., and *Nerium oleander* Linn., in formulations of pills or capsules, have been traditionally used for relieving swelling and pain.[13,14] Prominently, several iridoids exhibit potent anti-inflammatory, antioxidant, anti-anxiety, antimicrobial and antiviral activities, and have shown promising results in protecting the nervous system (Figure 1). The structural diversity and modulatory effects on key pathways involved in pain perception make iridoids compelling candidates for NP drug development.

Despite growing preclinical evidence, the molecular mechanisms underlying NP remain incompletely elucidated, a complexity that highlights the need for multi-target therapeutic strategies. Iridoids, which can modulate neuroinflammation, oxidative stress, and glial activation, represent particularly promising candidates. This review presented a comprehensive examination of NP pathophysiology and a critical evaluation of the therapeutic potential of plant-

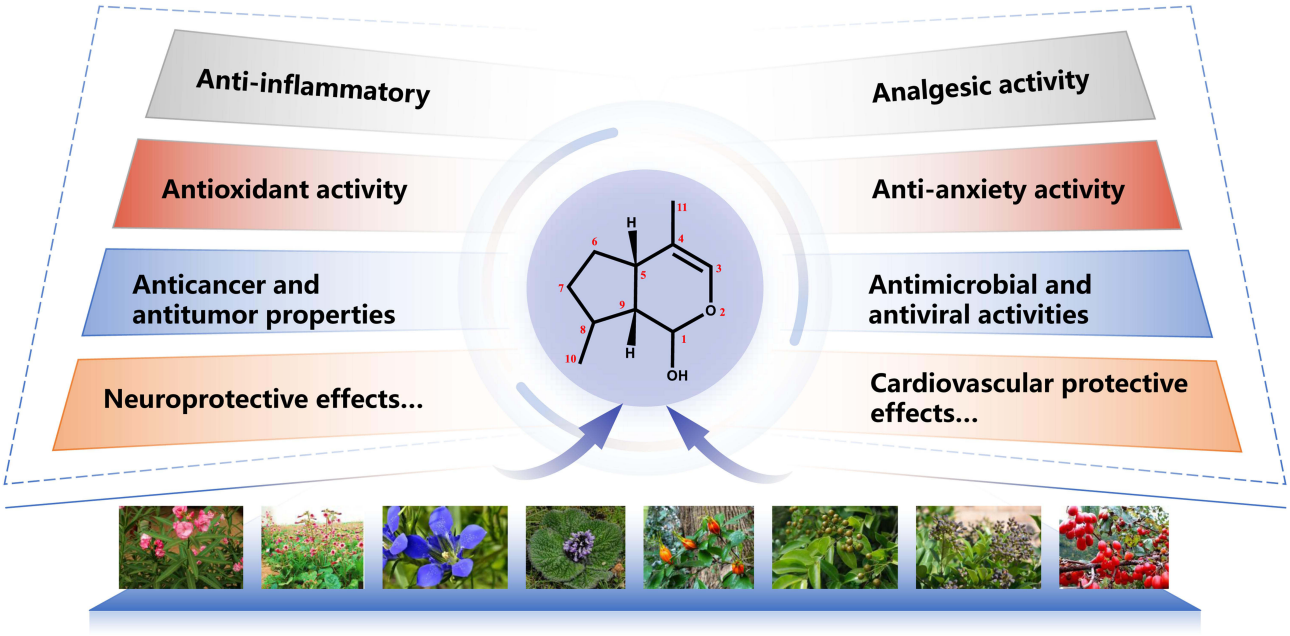


Figure 1 Overview of pharmacological action of iridoids. Iridoids possess many potent pharmacological activities, such as antioxidant, anti-inflammatory, analgesic, antidiabetic and neuroprotective properties.

derived iridoids, summarizing their purported efficacy and mechanisms of action. The overarching goal is to synthesize contemporary evidence to facilitate and inform the future development of iridoid-based therapies for NP.

Overview of Neuropathic Pain

NP represents a multifaceted and difficult-to-manage chronic condition that profoundly diminishes a patient's quality of life.[15] In particular, persistent or intermittent spontaneous pain can manifest independently of any specific stimulus, as observed in cases of painful polyneuropathy or complete spinal cord injury.[16] Conversely, stimulus-evoked pain might occasionally be present even in the absence of spontaneous discomfort.[17] The clinical distinction implies that separate or at least partially overlapping, underlying mechanisms are responsible for spontaneous and evoked pain.[18] The particular presence of evoked pain may be determined by whether specific afferent nerve fibers remain functional or have been damaged. Among the most frequent symptoms is a heightened sensitivity to both thermal and mechanical stimuli.[19] These manifestations serve as crucial clinical markers that aid healthcare professionals in the diagnostic process and the assessment of NP's severity.

The pathophysiology of NP involves peripheral and central sensitization, neuroimmune interactions, and glial cell activation. Peripheral sensitization results from inflammatory mediators acting on nociceptors, while central sensitization involves enhanced excitability of spinal and supraspinal neurons. Neuroimmune crosstalk, particularly microglial and astrocytic activation, plays a critical role in maintaining chronic pain states.

Classification of Neuropathic Pain

The traditional approach to classifying NP has been to base it on the associated underlying disease.[20] The newly introduced ICD-11 classification system establishes a more anatomically focused framework. And it initially categorizes NP as either peripheral neuropathic pain (PNP) or central neuropathic pain (CNP),[16] a distinction which depends on the anatomical site of the lesion or disease within the somatosensory nervous system (Figure 2). Following this primary anatomical division, each category is then further subdivided into specific neuropathic pain conditions according to their respective etiological causes.

PNP arises from a lesion or disease affecting the somatosensory nerves within the peripheral nervous system.[21] This category encompasses a wide spectrum of conditions, each characterized by pain that is often described as burning,

https://doi.org/10.2147/DDDT.S591283

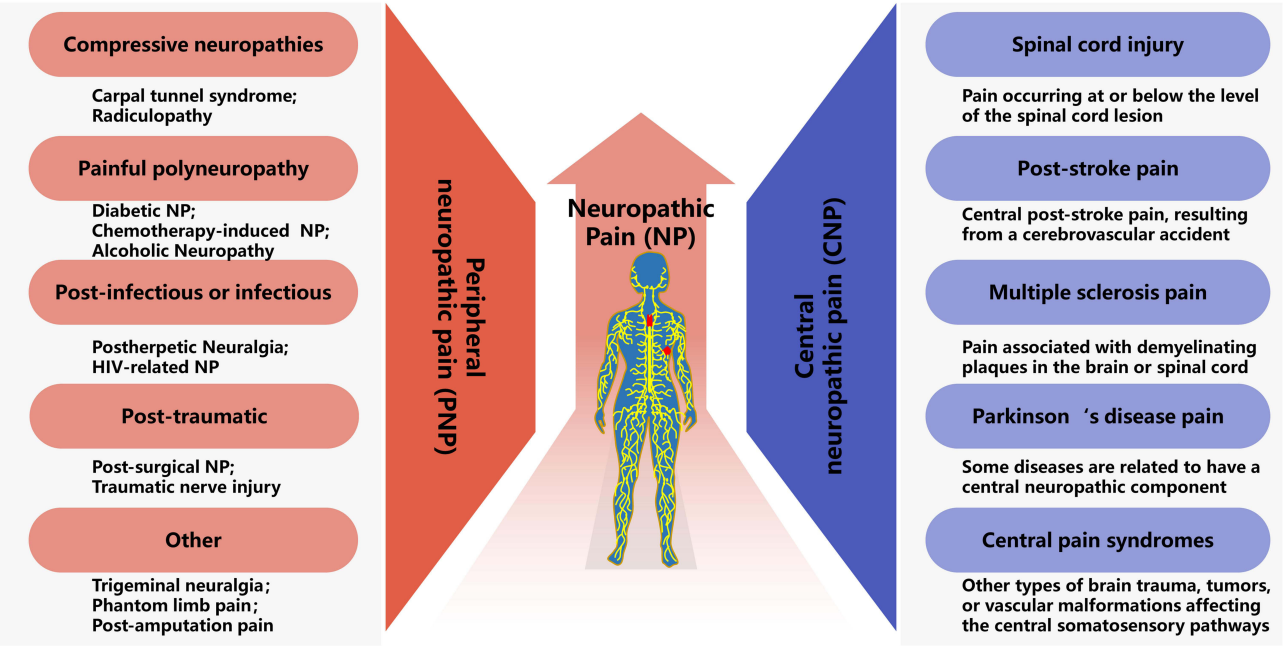


Figure 2 Classification of NP. The fundamental distinction between these two types of pain is based on the site of the primary lesion or disease: PNP and CNP.

shooting, stabbing, or electric shock-like.[22] A key diagnostic feature is the presence of positive sensory signs, such as allodynia (pain due to a non-painful stimulus) and hyperalgesia (increased pain from a painful stimulus), in the territory of the affected nerve(s).[23] The classification of PNP is primarily etiological and common underlying causes, including compressive neuropathies, painful polyneuropathy, post-infectious or infectious, post-traumatic, and other PNP like trigeminal neuralgia, phantom limb pain, post-amputation pain.

CNP is caused by a lesion or disease of the central somatosensory nervous system, affecting structures such as the brainstem, thalamus, or somatosensory cortex.[24] The clinical presentation of CNP can be heterogeneous but frequently includes constant burning pain, paroxysmal spontaneous pain, and evoked pain (allodynia and hyperalgesia). The CNP is typically located in body areas corresponding to the central nervous system lesion.[25,26] The classification of CNP based on the following primary etiologies, including spinal cord injury, post-stroke pain, multiple sclerosis pain, Parkinson's disease pain and central pain syndromes.

Animal Models

The selection and establishment of a suitable animal model serve as a fundamental prerequisite for conducting meaningful research on NP. Currently, the majority of these animal models are designed and modeled upon the underlying etiology of NP.[27]

Since CNP is frequently observed following spinal cord injury (SCI), common modeling techniques include inducing damage through methods such as spinal cord compression, contusion, complete or partial transection, photochemical ischemia, or the application of excitatory neurotoxins.[28] Subsequent to the successful induction of the SCI model, the resulting motor impairments are typically assessed using quantitative behavioral assessments, including the Basso Beattie Bresnahan locomotor rating scale and other combined behavioral scores.[29]

A number of established experimental paradigms are utilized to model peripheral neuropathic pain (PNP), which include the partial sciatic nerve ligation (PSNL), chronic constriction injury (CCI), spinal nerve ligation (SNL), spared nerve injury (SNI), and trigeminal neuralgia (TN) models.[30–32] All of these methods are recognized for their ability to induce a persistent and robust chronic pain state. Particularly, the CCI paradigm is often noted for producing a heightened pain sensitivity, whereas the SNL and PSNL models typically result in a pain response that is of longer duration.[16]

Additionally, diabetic neuropathic pain (DNP) and chemotherapy-induced PNP represent two other major categories within the framework of PNP. The diabetic model can be generated through various strategies, including drug induction, specialized dietary regimens, and transgenic technology.[33,34] Among these approaches, the streptozotocin-induced method is the most widely employed for establishing a diabetic NP condition, primarily due to its procedural simplicity, high model stability, and consistent success rate.[35]

Separately, chemotherapy-induced PNP is a severe and common adverse effect of cancer treatment, occurring in approximately 30%-40% of patients.[36] Chemotherapeutic agents such as oxaliplatin, vincristine, and paclitaxel can directly impair sensory nerve function.[37–39] This damage manifests as a reduction in action potential generation, a slowing of nerve conduction velocity, and the onset of PNP. Notably, these painful symptoms often persist long after the cessation of chemotherapy. Consequently, the development of animal models for chemotherapy-induced PNP provides an invaluable tool for investigating the underlying mechanisms and developing effective treatment strategies for this challenging condition.

While above models have greatly advanced our understanding of NP, each has limitations (Table 1). For instance, nerve ligation models primarily mimic traumatic neuropathic pain and may not fully capture the heterogeneity of human NP, which often involves comorbidities such as anxiety and depression. Moreover, most models focus on evoked pain behaviors, whereas spontaneous pain, a major complaint in patients, is less frequently assessed. The translational gap is also evident in the lack of affective and cognitive components in rodent models. In recent years, novel behavioral assays have been developed to better capture the complexity of NP, such as conditioned place preference for assessing spontaneous pain, grimace scales for evaluating pain-related affect, and tests for anxiety- and depression-like behaviors. Thus, future studies should incorporate behavioral assays for spontaneous pain and affective dimensions to improve clinical relevance.

From a translational perspective, non-human primates may be considered highly valuable models of NP due to their high degree of physiological and genetic similarity to humans, which allows for a more comprehensive simulation of the clinical disease process.[40] Nonetheless, the widespread use of primates is heavily constrained by practical limitations, including their limited availability, complex breeding requirements, substantial financial costs, and significant ethical considerations. Consequently, rodents have become the most prevalent and widely utilized species in contemporary NP research. Beyond the choice of species, intrinsic factors such as the animal's gender and genetic strain also exert a considerable influence on experimental outcomes.[41] For instance, in SCI models, both male and female mice develop CNP manifested as thermal hypersensitivity.[42] However, mechanical pain hypersensitivity is a phenotype observed predominantly in males, despite the fact that the overall likelihood of developing CNP post-

Table 1 Comparison of Common Animal Models of NP

Model	Mechanism	Advantages	Limitations	Translational Relevance
CCI	Chronic constriction of sciatic nerve	Robust and persistent pain; well-characterized	Variability; not specific to nerve injury type	Models traumatic nerve injury
SNL	Tight ligation of spinal nerves	Specific nerve injury; consistent allodynia	Requires microsurgery	Models radicular pain
SNI	Sparing of sural nerve; ligation of tibial and common peroneal nerves	Long-lasting pain; avoids autotomy	Complex surgery	Models partial nerve injury
PSNL	Partial ligation of sciatic nerve	Simple; reproducible	Not specific	Models partial nerve injury
STZ-induced DNP	Streptozotocin destroys pancreatic β-cells, causing diabetes	Easy to induce; mimics diabetic neuropathy	Hyperglycemia-related confounds	Models diabetic neuropathic pain
Chemotherapy-induced PNP	Systemic administration of chemotherapeutics	Clinically relevant; models CIPN	Systemic toxicity and variable pain behaviors	Models chemotherapy-induced peripheral neuropathy

https://doi.org/10.2147/DDDT.S591283

injury is nearly identical between sexes.[43] Similarly, the stability and manifestation of chemotherapy-induced PNP models can vary dramatically based on the animal's strain and gender. Research indicates that certain combinations, such as paclitaxel-induced PNP in C57BL/6 female mice or in CD1 male mice, as well as cisplatin-induced models in C57BL/6 male mice, demonstrated a relatively high and consistent incidence of NP, making them particularly stable for investigative purposes.[44]

The Sources and Classification of Iridoids

Natural iridoids, a group of monoterpene compounds consisting of cyclopentadiene and pyran ring structures, are predominantly found in plants and readily combine with sugars to form glycosides, primarily because of their inherent instability.[45] Therefore, iridoids are structurally categorized into two groups, iridoid glycosides and non-glycosidic iridoids, based on whether or not they contain intramolecular glycosidic bonds. Glycosidic iridoids are defined by the presence of a glycosidic bond, typically located at the aglycone C1-OH. In contrast, non-glycosidic iridoids are distinguished by an iridane skeleton or cyclopentane ring, consisting of iridoid lactones and iridodials.[46]

Meanwhile, iridoid glycosides can be primarily divided into two categories, carbocyclic iridoid glycosides and seco-iridoid glycosides.[47] Seco-iridoid glycosides are generated through the breaking of the cyclopentane ring. The variety of iridoids can be attributed, in part, to the variations in their biosynthetic processes, which involve several reactions, including phosphorylation, cyclization, oxidation, and glycosidation.[48] As shown in the Figure 3, the basic structure of iridoids was presented.

Iridoids are predominantly located in angiosperm dicotyledons in most plants, and, in certain instances, in monocotyledons. They are commonly found in various plant parts such as leaves, fruits, roots, and sprouts.[49] Iridoid compounds are widely present in medicinal plants such as *Lamiophlomis rotata* (Benth). Kudo, *Rehmannia glutinosa* (Gaertn). Libosch. ex Fisch. and C. A. Mey., *Gardenia jasminoides* J.Ellis, *Cornus officinalis* Sieb.et Zucc., *Gentiana scabra* Bunge, *Strychnos nux-vomica* Linn., *Nerium oleander* Linn., *Eucommia ulmoides* Oliv., and *Ligustrum lucidum* Ait., which belong to the Scrophulariaceae, Rubiaceae, Labiatae, Gentianaceae, Verbenaceae, and Myricaceae families (Figure 4). It is important to note that while *Strychnos nux-vomica* Linn. and *Nerium oleander* Linn. contain toxic components such as alkaloids and cardiac glycosides, the iridoid glycosides derived from these plants have been investigated at doses well below established toxicity thresholds, and their safety is further enhanced by traditional processing methods. The representative iridoid glycosides include shanzhiside methyl ester, 8-O-acetyl-shanzhiside methyl ester, catalpol, gardenoside, geniposide, picroside II and loganin, while the type of seco-iridoid glycosides include morroniside, oleuropein, and gentiopicroside (Figure 5).

Plant-Derived Iridoids on Neuropathic Pain

Neuropathic pain (NP) represents a complex and challenging clinical condition, yet plant-derived iridoids have emerged as promising candidates for its treatment. Numerous studies have specifically examined the analgesic properties of these iridoids, which are isolated from a diverse range of medicinal plants. The primary objective of this section is to consolidate and summarize the documented therapeutic efficacy of various plant-originated iridoids against NP, as systematically outlined in Table 2.

Iridoid Glycosides

Loganin, an iridoid glycoside isolated from *Strychnos nux-vomica* Linn., has exhibited various biological properties, including anti-inflammatory, antioxidant, and anti-apoptotic effects.[70] In the CCI model, 5 mg/kg loganin significantly improved pain behaviors, reducing both thermal hyperalgesia and mechanical allodynia from day 3 to day 14 post-injury, with the most pronounced effects observed at day 7.[51] In a follow-up CCI study focusing on the spinal cord, 5 mg/kg loganin similarly attenuated mechanical allodynia and thermal hyperalgesia. It reduced the expression of CXCL12/CXCR4 and downstream NLRP3 inflammasome components, along with inflammatory cytokines IL-1β and IL-18, in the spinal dorsal horn.[52] Additionally, in a model of painful diabetic neuropathy (PDN) induced by streptozotocin-nicotinamide, 5 mg/kg loganin ameliorated hyperalgesia and allodynia, improved insulin resistance (HOMA-IR), and enhanced antioxidant enzyme activities (SOD, CAT, GSH). It also reduced serum levels of TNF-α and IL-1β, and

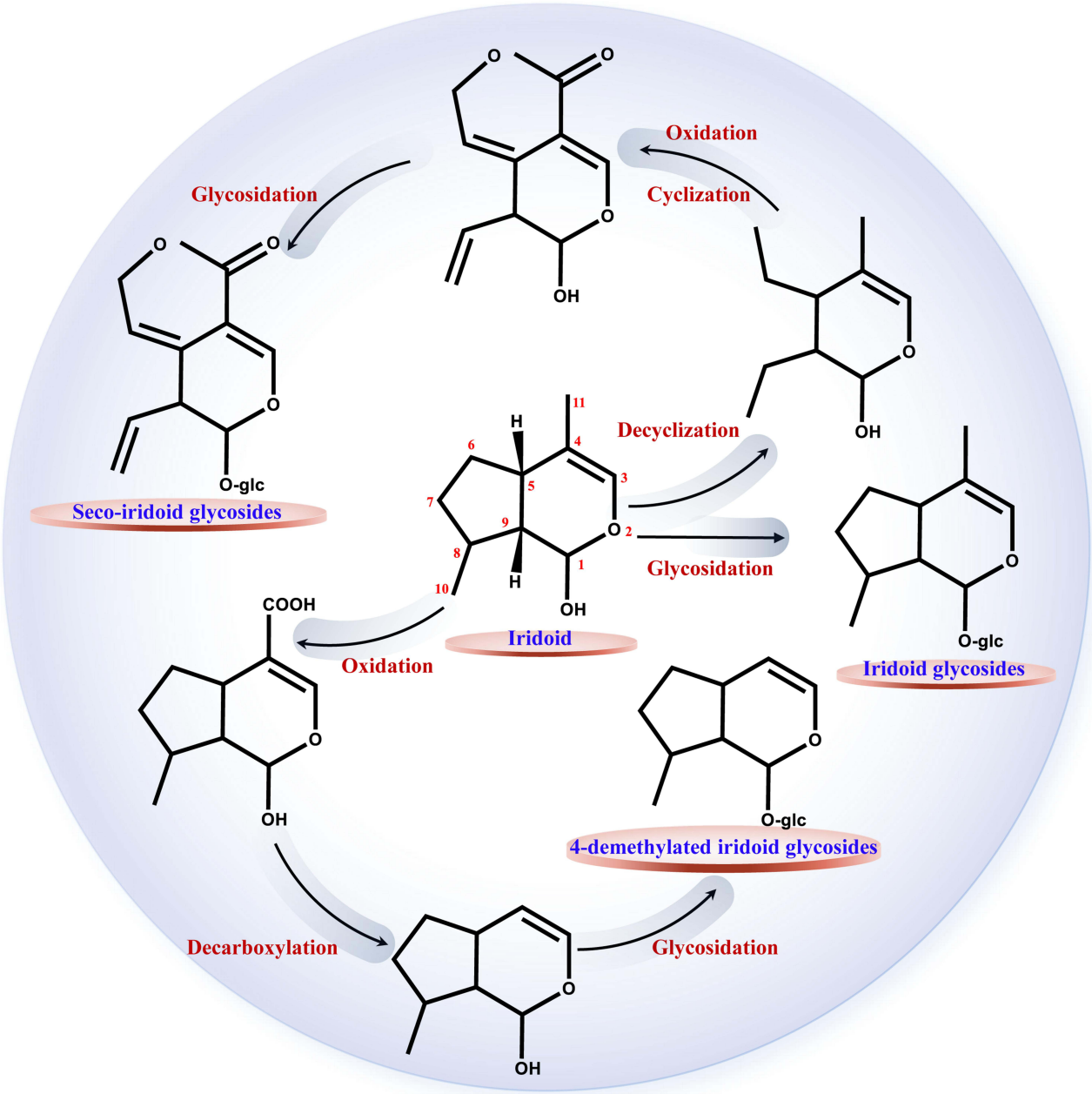


Figure 3 Chemical structure of iridoids. Iridoids are structurally classified into iridoid glycosides and non-glycosidic iridoids according to the presence or absence of intramolecular glycosidic bonds.

decreased expression of pain-related channels (Cav3.2) and neuropeptides (CGRP) in the spinal dorsal horn.[53] In the another CCI rat model, loganin was further shown to prevent Schwann cell demyelination and axonal damage in the sciatic nerve, indicating a protective effect on the structure of peripheral nerves.[54] It also modulated aberrant autophagic activity and reduced apoptosis in the spinal cord, as evidenced by decreased levels of cleaved caspase-3 and Bax, suggesting a broader neuroprotective role.

These findings collectively demonstrated the efficacy of loganin in various NP models. Importantly, although *Strychnos nux-vomica* Linn. contains toxic alkaloids such as strychnine, loganin—the iridoid glycoside derived from this plant—exhibited a much more favorable safety profile, with the doses used in preclinical studies (eg, 5 mg/kg) being well below established toxicity thresholds.

https://doi.org/10.2147/DDDT.S591283

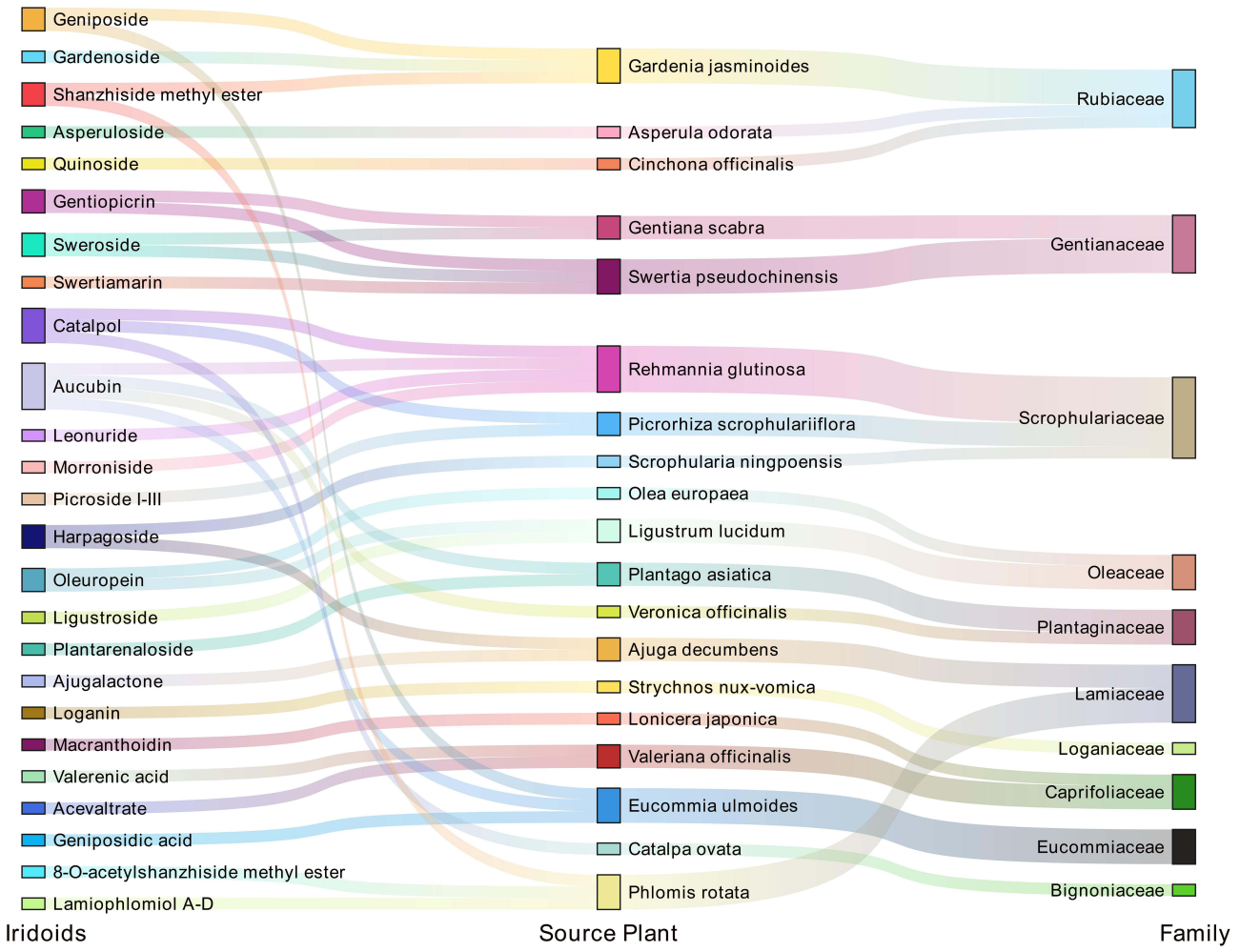


Figure 4 Various sources of iridoids. Plant-derived iridoids as major constituents of the Scrophulariaceae, Rubiaceae, Labiatae, Gentianaceae, Verbenaceae, and Myricaceae families.

Shanzhiside methyl ester, a principal iridoid glycoside derived from medicinal plants such as *Lamiophlomis rotata* (Benth). Kudo and *Gardenia jasminoides* J.Ellis,[71,72] has garnered significant attention for its potent anti-NP effects. In traditional Chinese medicine practice, *Lamiophlomis rotata* (Benth). Kudo-which enters the liver and spleen meridians with a bitter, pungent flavor and warm property-is traditionally used to promote blood circulation, relieve pain, and treat conditions such as rheumatic arthralgia and traumatic injuries.[73,74] *Gardenia jasminoides* J.Ellis, classified as entering the heart, lung, and triple burner meridians with a bitter flavor and cold property, is widely applied to clear heat, reduce swelling, and alleviate pain and inflammation.[75] These traditional applications provide a theoretical foundation for investigating iridoid glycosides derived from these medicinal plants as potential therapeutic agents for NP. In a model induced by SNL, intrathecal administration of shanzhiside methyl ester produced dose-dependent and long-lasting anti-allodynia, with an estimated ED_{50} of 40.4 μg.[57] Its anti-allodynic effect is completely abolished by glucagon-like peptide-1 (GLP-1) receptor antagonists, confirming the involvement of spinal GLP-1 receptors. Meanwhile, the iridoid glycoside extract of the *Lamiophlomis rotata* has been demonstrated to possess significant efficacy in alleviating NP. Zheng et al reported that oral administration of iridoid glycoside extract of *Lamiophlomis rotata* (200, 400, and 800 mg/kg) for 14 days effectively reversed mechanical allodynia in a dose-dependent manner in the SNI rat model.[59] Another study demonstrated that the iridoid glycoside extract of the *Lamiophlomis rotata* produced potent antinociceptive effects in rodent models of inflammatory, neuropathic, and bone cancer pain hypersensitivity, reducing pain behaviors by 50%-80% with half-effective doses close to human usage (130 mg/kg-250 mg/kg).[60] And activity-guided tracking identified

https://doi.org/10.2147/DDDT.S591283

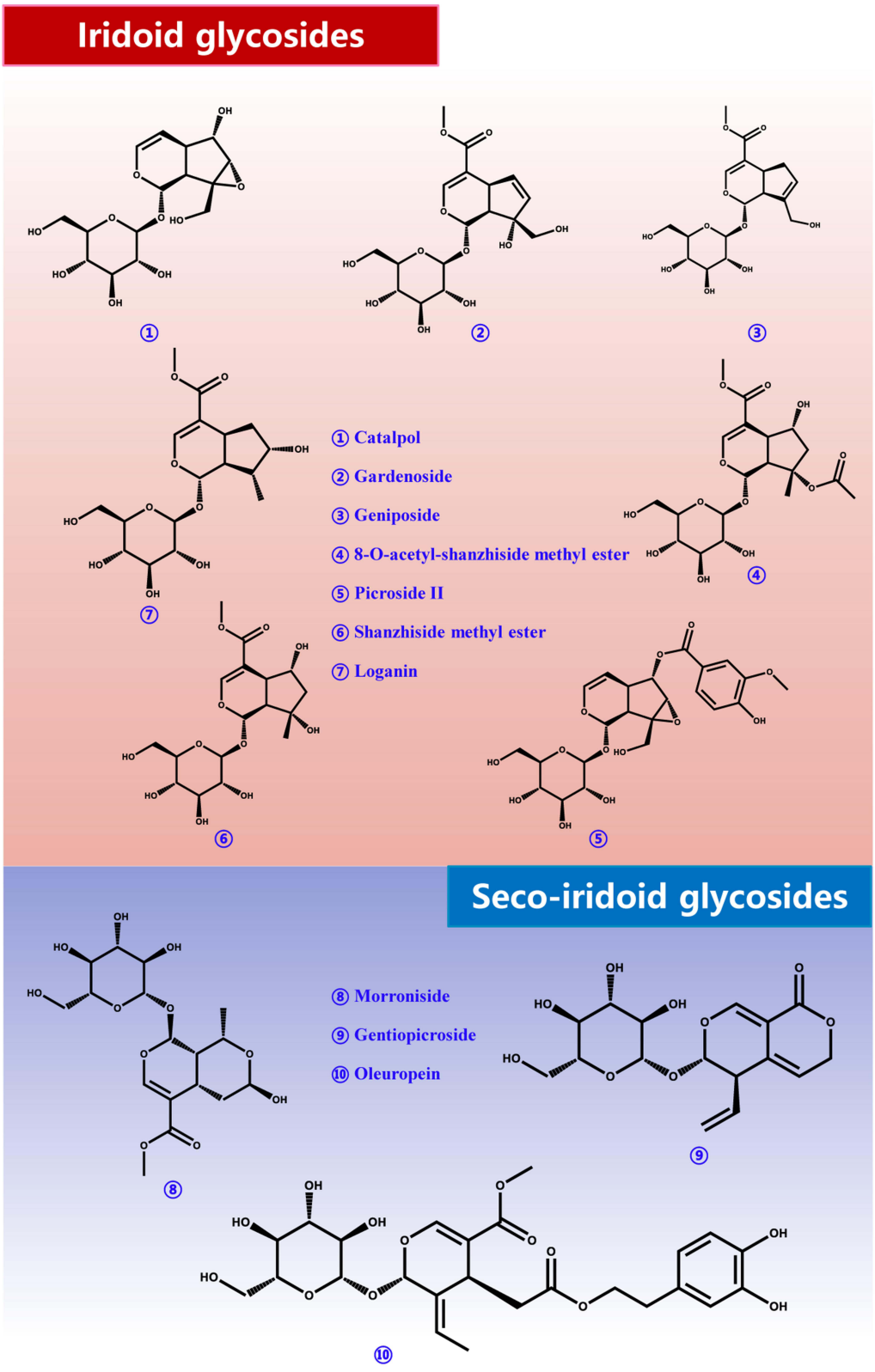


Figure 5 The representative iridoid glycosides include catalpol, gardenoside, geniposide, 8-O-acetyl-shanzhiside methyl ester, picroside II, shanzhiside methyl ester, and loganin, while the type of seco-iridoid glycosides include morroniside, gentiopicroside, and oleuropein.

https://doi.org/10.2147/DDDT.S591283

https://doi.org/10.2147/DDDT.S591283

Table 2 Plant-Derived Iridoids for the NP Treatment

Iridoids	Administration (Dosage and Duration)	Model	Effects and Mechanisms	References
Aucubin	10 mg/kg/day, 8 days, i.p.	Streptozotocin-induced DNP mice	↓ mechanical/thermal hypersensitivity; ↓ spinal TNF-α, IL-1β, IL-6; ↓ microglial activation; ↓ aerobic glycolysis via AKR1B1 inhibition	[50]
Loganin	5 mg/kg/day, 14 days, i.p.	CCI rat	↓mechanical/thermal hypersensitivity; ↓ sciatic TNF-α/IL-1β; ↓ NF-κB activation; ↓ Schwann-cell demyelination	[51]
Loganin	5 mg/kg/day, 14 days, i.p.	CCI rat	↓ PWT/PWL; ↓ spinal CXCL12/CXCR4, TXNIP, NLRP3 inflammasome, IL-1β/IL-18; inhibits neuronal/glial NLRP3 assembly	[52]
Loganin	5 mg/kg/day, 4 weeks, i.p.	Streptozotocin-nicotinamide-induced DNP rat	↓ blood glucose, HOMA-IR, thermal/mechanical hypersensitivity; ↑ SOD/CAT/GSH; ↓ spinal CaV3.2, CGRP, TNF-α, IL-1β; ↓ NF-κB and JNK-IRS1-Akt-GSK3β pathway	[53]
Loganin	5 mg/kg/day, 7 days, i.p.	CCI rat	↑ autophagic flux: ↓ LC3B-II, p62, Beclin-1, LAMP-2, pro-cathepsin D; ↓ Bax and cleaved caspase-3 in spinal neurons/microglia	[54]
Ligustrum vulgare aqueous extract (oleacein 23.48 mg/g, oleocanthal 8.44 mg/g, oleuropein 1.50 mg/g)	50–200 mg/kg/day, 21 days, i.p.	Streptozotocin-induced DNP rat	↓ mechanical hyperalgesia and allodynia; no change in blood glucose; antioxidant and anti-inflammatory actions (↓ TNF-α, NF-κB, MMP-9, COX-2/5-LOX)	[55]
Oleuropein	10–20 mg/kg/day, 14 days, p.o.	CCI and vincristine rat	↓ cold/mechanical allodynia and hyperalgesia; ↑ sciatic H_2S, CSE, CBS, orexin-A, Nrf2; anti-nociception reversed by orexin receptor antagonist suvorexant	[56]
Shanzhiside methylester	10–300 μg intrathecal (single bolus)	SNL rat	↓ Mechanical allodynia; stimulates spinal microglial β-endorphin expression via GLP-1R and p38 MAPK; no tolerance development	[57]
8-O-acetyl shanzhiside methylester	5–40 μg intrathecal daily, 14 days	SNL rat	↓ Mechanical hypersensitivity; inhibits astrocytic ERK activation and TNF-α expression; longer-lasting effect than lidocaine or ketamine	[58]
Total iridoid glycosides	200–800 mg/kg/day, 14 days, p.o.	SNI rat	↓ Mechanical allodynia; ↓ TNF-α, IL-1β, NO, NOS, cGMP; ↑ IL-10; inhibits NMDAR/PKC and NO/cGMP/PKG pathways	[59]
Total iridoid glycosides (aqueous extract)	30–3000 mg/kg/day, 7 days, p.o.	Mouse formalin test; SNL rat; bone cancer pain rat	↓ Tonic hyperalgesia and mechanical allodynia; no effect on acute pain; acts via spinal GLP-1R; no tolerance	[60]
Iridoid glycosides of *Paederia scandens*	70–280 mg/kg/day, 15 days, p.o.	SNI rat	↑ Mechanical withdrawal threshold; ↓ NOS activity, NO, cGMP; ↓ iNOS, PKG-Iα/β mRNA; inhibits NO/cGMP/PKG pathway	[61]
Gentiopicroside	100–300 mg/kg/day, 15 days, p.o. 1–100 μM pre-treatment in vitro, 24 h	6-OHDA -induced PD rat; MPP^+-induced SH-SY5Y cells	↓ Motor deficits; ↑ TH^+ neurons; ↓ microglial activation; ↓ NF-κB, TNF-α, IL-1β; ↓ iron accumulation via DMT1/FPN1; ↓ ROS, MDA; ↑ GPX4	[62]

Gardenoside+ozone	30 μg/mL ozone+300 μmol/L, gardenoside, intrathecal daily, 14 days	CCI rat	↑ MWT and TWL; ↓ P2X3/P2X7 mRNA and protein in L4-L5 DRG	[63]
Morroniside	30–600 mg/kg, p.o. 3–300 μg, intrathecal daily, 7 days	SNL rat; H_2O_2-induced human HEK293 cells	Dose-dependent anti-allodynia/-hyperalgesia; no tolerance; effect blocked by spinal GLP-1R antagonist exendin-(9-39); protects N9/HEK293 cells from H_2O_2 via GLP-1R	[64]
Morroniside	300 μg, intrathecal injection (single bolus)	SNL rat	↓ Mechanical allodynia via spinal microglial GLP-1R activation; ↑ IL-10; ↑ β-endorphin; m-opioid receptor activation; microglia depletion or IL-10/β-endorphin neutralization abolishes effect	[65]
Picroside II	10 mg/kg, day 3–14 post-operation, i.p.	CCI rat	Reverses mechanical allodynia and thermal hyperalgesia; ↓ spinal GFAP, IL-1β, IL-6, TNF-α; in LPS-astrocytes blocks NF-κB p65 phosphorylation and IκB-α degradation	[66]
Picroside II	3–100 μg, intrathecal (10 μL), single bolus	SNL; 5% formalin-induced acute pain	↓ Mechanical allodynia (ED_{50} 12.44 μg, Emax 55.7% MPE) and thermal hyperalgesia; ↓ phase-II formalin flinching; ↓ Iba-1^+ microglia density and spinal TNF-α, IL-1β, IL-6 mRNA; whole-cell patch-clamp shows dose-dependent reduction of mEPSC frequency/amplitude in lamina II, indicating suppressed glutamatergic transmission	[67]
Catalpol	1–125 mg/kg i.p., once daily for 7 days (CCI) or once daily for 5 days (SNL)	CCI and SNL rat	Dose-dependent reversal of mechanical allodynia (MPE up to 72%); ↓ spinal Iba-1, NF-κB p65, TNF-α, IL-1β, IL-6	[68]
Geniposide	10 mg/kg, 6 times a week, 4 weeks, i.p.	CCI rat	↑ MWT & TWL; ↓ spinal/DRG TNF-α, IL-1β, IL-6; ↓ EGFR/PI3K/AKT signalling and Ca^{2+}-pathway proteins (PKC, CaM, CaMKII); rescue reversed by NSC-228155	[69]

Notes: ↑ represents increase/improvement; ↓ represents decrease/reduction.

Abbreviations: AUC, area under the curve; CCI, chronic constriction injury; CGRP, calcitonin gene-related peptide; CNP, central neuropathic pain; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C chemokine receptor type 4; DNP, diabetic neuropathic pain; DRG, dorsal root ganglion; ED_{50}, median effective dose; fMRI, functional magnetic resonance imaging; GLP-1R, glucagon-like peptide-1 receptor; HOMA-IR, homeostasis model assessment of insulin resistance; ICD-11, International Classification of Diseases 11th Revision; IL, interleukin; iNOS, inducible nitric oxide synthase; LD_{50}, median lethal dose; LTP, long-term potentiation; MDA, malondialdehyde; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor family pyrin domain containing 3; NO, nitric oxide; NP, neuropathic pain; PD, Parkinson's disease; PNP, peripheral neuropathic pain; ROS, reactive oxygen species; RNS, reactive nitrogen species; SCI, spinal cord injury; SNI, spared nerve injury; SNL, spinal nerve ligation; TNF-α, tumour necrosis factor-alpha.

total iridoid glycosides, specifically the quality control markers shanzhiside methyl ester and 8-O-acetyl-shanzhiside methyl ester, as the principal effective components. Zhang et al found that consecutive intrathecal administration of 8-O-acetyl shanzhiside methyl ester significantly alleviated mechanical allodynia in a rat model of SNL-induced NP in a dose-dependent manner, and the analgesic effect of 8-O-acetyl shanzhiside methyl ester was comparable to that of lidocaine and ketamine but exhibited a longer duration.[58]

Geniposide and gardenoside, obtained from the dried and mature fruits of the *Rubiaceae* family, has been widely used in the treatment of chronic inflammatory diseases.[76] Geniposide treatment increased mechanical withdrawal threshold and thermal withdrawal latency in CCI rats, reduced inflammatory cytokines (TNF-α, IL-1β, IL-6), and improved neuropathology.[69] Its efficacy was comparable to gabapentin and was partially reversed by an EGFR agonist, suggesting a targeted analgesic role. Yu et al found that gardenoside can significantly improve CCI-induced sciatica by regulating the P2X3 and the P2X7 expression in rats.[63] Likewise, gardenoside combined with ozone significantly increased mechanical withdrawal threshold and thermal withdrawal latency in CCI rats, indicating potent analgesic effects, and behavioral tests confirmed reduced mechanical and thermal hyperalgesia after treatment.[77]

Additionally, repeated administration catalpol (1 mg/kg-125 mg/kg) dose-dependently reversed mechanical allodynia in both CCI and SNL models. The maximal possible effect reached up to 69.13% in CCI and 71.94% in SNL models, outperforming gabapentin in some doses.[68]

Picroside II, a major active component of *Picrorhiza scrophulariiflora* extracts, exerts many effects, such as antioxidant, anti-apoptosis, and anti-inflammatory activity.[78,79] A dose of 10 mg/kg picroside II effectively attenuated CCI-induced mechanical allodynia and thermal hyperalgesia. Pain behavioral tests showed significant improvements in paw withdrawal thresholds and tail flick latencies, confirming its analgesic properties.[66] Meanwhile, a latest study demonstrated that the analgesic effect of picroside II was significant in both pain models (SNL-induced NP model and formalin-induced tonic pain model), and the underlying mechanism may involve inflammatory signaling pathways.[67]

Aucubin was demonstrated significant efficacy in alleviating DNP. Recently, aucubin (10 mg/kg, i.p., 8 days) significantly reduced hyperglycemia, mechanical allodynia, and thermal hyperalgesia in a streptozotocin-induced DNP mouse model.[50] It also ameliorated anxiety-like behaviors, as evidenced by improved performance in open field and elevated plus maze tests.

Above studies collectively demonstrated that iridoid glycosides and related natural compounds such as loganin, gardenoside, picroside II, catalpol, aucubin, geniposide shanzhiside methyl ester, and 8-O-acetyl-shanzhiside methyl ester exhibit significant analgesic efficacy in standardized neuropathic pain models. These iridoid glycosides effectively ameliorated both mechanical and thermal hypersensitivity, often in a dose-dependent manner, and their effects are sustained over repeated administrations without apparent tolerance.

Seco-Iridoid Glycosides

Morroniside is an atypical secoiridoid with a broken double bond at C-7 and C-8 in the five-membered carbon ring and replaced by a six-membered cyclic inner ether fragment.[80] Likewise, morroniside demonstrated potent anti-neuropathic pain effects in a rat model induced by L5/L6 spinal nerve ligation. Oral (30–600 mg/kg) and intrathecal (3–300 μg) administration of morroniside dose-dependently attenuated mechanical allodynia, with ED_{50} values of 335 mg/kg and 7.1 μg, respectively, and completely blocked thermal hyperalgesia.[64] Notably, repeated intrathecal administration over 7 days did not induce analgesic tolerance. The anti-allodynic effects were completely abolished by intrathecal pretreatment with the GLP-1 receptor antagonist exendin, indicating a spinal site of action. Importantly, the analgesic effect of morroniside was demonstrated to be dependent on spinal microglia and the subsequent sequential upregulation of interleukin-10 (IL-10) and β-endorphin, as its anti-allodynia was abolished by microglial inhibition/depletion, or by neutralizing antibodies against IL-10 or β-endorphin, or by a μ-opioid receptor antagonist.[65]

Gentiopicroside is also a promising and important protective sec-oiridoid glycoside against pain. Beyond its classical role in Parkinson's disease (PD) research, the 6-hydroxydopamine (6-OHDA)-induced lesion model is also recognized as a model of CNP, as dopaminergic pathways originating from the substantia nigra are involved in pain modulation. In the 6-OHDA-induced unilateral rat model of PD,[62] gentiopicroside administration (100 and 300 mg/kg) not only improved motor functions (reducing apomorphine-induced rotations by 36%, prolonging rotarod latency, and increasing locomotor

activity), but also preserved dopaminergic neurons in the substantia nigra, as evidenced by increased tyrosine hydroxylase-positive cells compared to the 6-OHDA-only group. Similarly, in a mouse model of chronic constriction injury (CCI)-induced neuropathic pain,[81] gentiopicroside (50 and 100 mg/kg) administered over 8 days significantly alleviated nociceptive behaviors and improved sciatic functional index from day 8 onward. Electrophysiological recordings further confirmed that gentiopicroside restored nerve conduction velocity and compound action potential amplitudes impaired by CCI.

Oleuropein is a non-toxic seco-iridoid glycoside polyphenol compound that is widely present in plants of the Oleaceae family.[82] Daily oral administration of oleuropein (10 and 20 mg/kg) for 14 days markedly attenuated behavioral signs of CCI and vincristine-induced neuropathy in male rats, including cold allodynia, mechanical allodynia, and mechanical hyperalgesia.[56] Particularly, the higher dose (20 mg/kg) showed more pronounced effects and was selected for further comparative studies. Additionally, in a streptozotocin-induced diabetic neuropathy model, an aqueous extract of *Ligustrum vulgare leaves* (rich in oleuropein and its derivatives) was administered intraperitoneally for 21 days significantly alleviated mechanical hyperalgesia and allodynia in a dose-dependent manner.[55] Notably, the extract's analgesic effects were observed without affecting blood glucose levels, suggesting a direct action on pain pathways rather than through glycemic control, and the most effective dose (200 mg/kg) restored pain thresholds to near-normal levels, outperforming the positive control tramadol.

In conclusion, these results collectively highlighted the efficacy of seco-iridoid glycosides in attenuating behavioral impairments, neuronal damage, and pain hypersensitivity in various NP models, supporting their potential as therapeutic agents for further investigation. It is worth noting that some inconsistencies exist in the preclinical data. For instance, the same iridoid may show varying efficacy across different NP models, and effective doses can differ between studies, possibly due to differences in animal strain, gender, route of administration, or pain model characteristics. These factors should be considered when interpreting the results and designing future studies.

Mechanisms of Plant-Derived Iridoids on Neuropathic Pain

Plant-derived iridoids have shown potential therapeutic effects on NP. This part summarized the molecular and cellular mechanisms through which iridoids exert analgesic properties, including anti-inflammatory effects, modulation of glial cell activation, anti-oxidant effects, neuronal protection and apoptosis inhibition, and modulation of neurotransmitter systems and ion channels (Figure 6).

Anti-Inflammatory Effects

Chronic neuroinflammation is a hallmark of NP, characterized by the sustained activation of immune cells and the release of pro-inflammatory cytokines.[83] Iridoid glycosides, such as loganin, picroside II, and aucubin, have demonstrated significant anti-inflammatory properties in multiple NP models. In a CCI rat model, loganin significantly reduced the levels of TNF-α and IL-1β in the sciatic nerve and spinal dorsal horn, which was associated with the inhibition of NF-κB signaling, a key transcription factor in inflammatory responses.[51] A similar profile was reported that picroside II not only attenuated mechanical allodynia and thermal hyperalgesia, but also down-regulated spinal IL-1β, IL-6 and TNF-α at both mRNA and protein levels, confirming that inhibition of the NF-κB signalling cascade underlies its anti-neuroinflammatory action.[66] Similarly, Cheng et al reported that loganin mitigated CCI-induced NP by suppressing CXCL12/CXCR4-mediated NLRP3 inflammasome axis.[52] Aucubin mitigated STZ-induced DNP by suppressing microglial activation and inflammatory cytokine expression in the spinal cord. These findings suggest that iridoid glycosides exert their anti-nociceptive effects, at least in part, by attenuating neuroinflammation.[50] Moreover, gentiopicroside has been reported to suppress NF-κB activation and reduce the levels of pro-inflammatory mediators including iNOS, TNF-α, and IL-1β in both in vivo and in vitro models of PD-induced NP.[62] Taken together, these data demonstrated that iridoids exert analgesic effects, at least in part, by suppressing neuroinflammation via modulation of key inflammatory mediators and transcription factors.

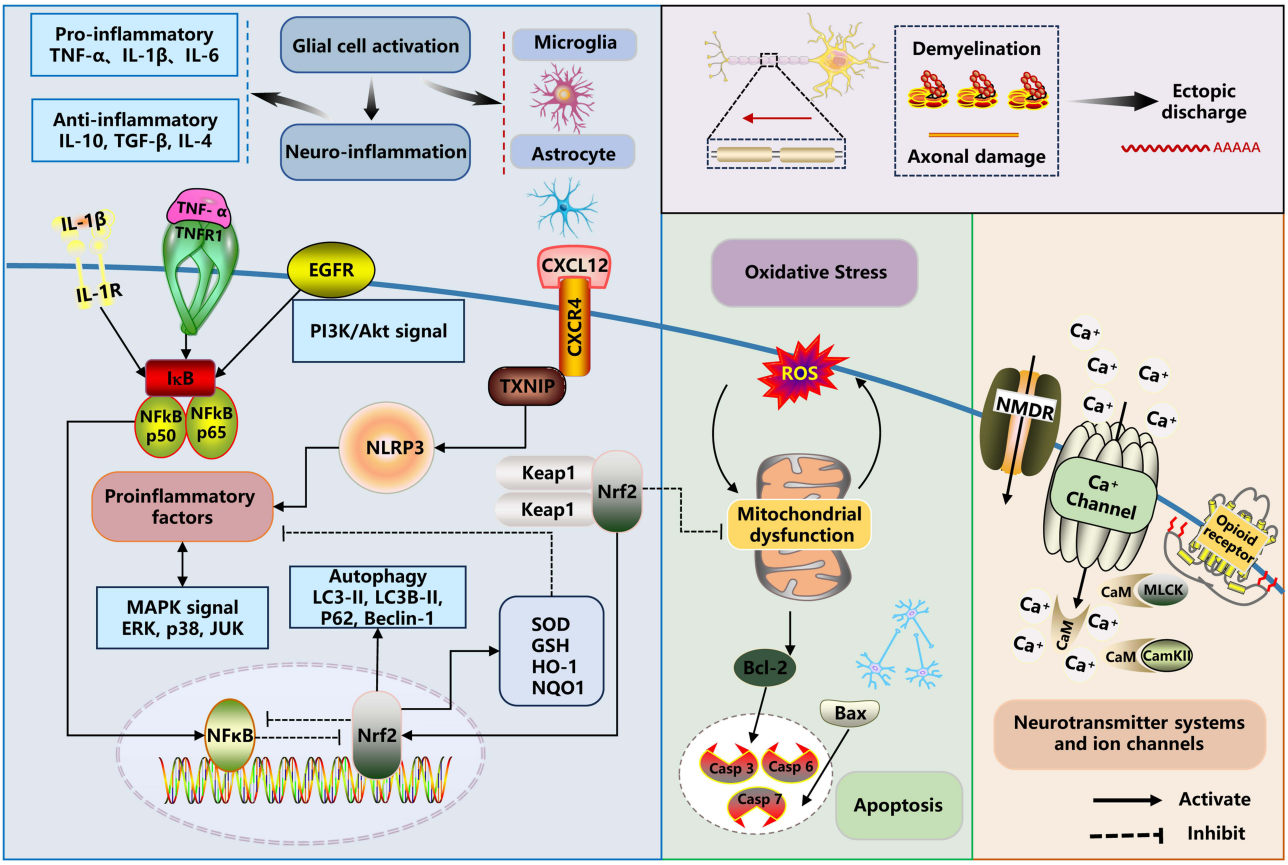


Figure 6 The main mechanisms that iridoids exert effects of NP. The underlying mechanisms that terpenoids exert analgesic effects in NPP are mainly related to the anti-inflammatory effects, modulation of glial cell activation, anti-oxidant effects, neuronal protection and apoptosis inhibition, and modulation of neurotransmitter systems and ion channels.

Modulation of Glial Cell Activation

Glial cells, particularly microglia and astrocytes, play a central role in the pathogenesis of NP.[26] Activated glial cells contribute to the development and maintenance of NP by releasing pro-inflammatory cytokines and sensitizing neurons.[84,85] Iridoid glycosides have been reported to modulate glial cell activation. Catalpol markedly reduced the number of Iba-1-immunoreactive microglia in the ipsilateral dorsal horn after CCI, paralleling decreases in pro-inflammatory cytokines.[68] Picroside II lowered CCI-evoked GFAP up-regulation and reversed the characteristic hypertrophic morphology of astrocytes, an effect correlated with suppression of NF-κB signalling.[66] Morroniside did not change microglial density, yet ex-vivo studies showed that it stimulated GLP-1-receptor-mediated β-endorphin release from cultured microglia, thereby shifting their phenotype toward an anti-nociceptive state.[64] In addition, shanzhiside methylester also promoted the activation of microglia in a beneficial manner by stimulating β-endorphin expression via the p38 MAPK pathway.[57] This dual modulation-suppressing harmful astrocytic activation while promoting protective microglial responses-highlights the complex and context-dependent effects of iridoid glycosides on glial cells. Collectively, iridoid glycosides restrain glial hyper-activation, either by blocking transcriptional programme that drive reactive phenotypes or by engaging receptor-mediated cascades that promote neuroprotective glial-neuronal communication.

Anti-Oxidant Effects

Oxidative stress plays a pivotal role in the pathogenesis of NP by promoting neuronal damage and sensitization.[86] Importantly, excessive reactive oxygen species (ROS) and reactive nitrogen species (RNS) can damage neurons and glial cells, exacerbating pain hypersensitivity. Iridoid glycosides have been shown to enhance antioxidant defenses and reduce

oxidative damage. Gentiopicroside significantly reduced ROS production and lipid peroxidation (measured by MDA levels) in MPP^+-treated SH-SY5Y cells, a cellular model of neurodegenerative pain.[62] Oxidative stress, a key pathological driver in PD models, also contributes to central sensitization and neuronal vulnerability in NP,[87] suggesting that the antioxidant effects of gentiopicroside may underlie its analgesic properties. It also upregulated GPX4, a key enzyme in the ferroptosis pathway, thereby enhancing cellular antioxidant defenses. In another study, the iridoid glycoside extract from *Paederia scandens* attenuated SNI-induced neuropathic pain by inhibiting the NO/cGMP/PKG signaling pathway.[61] Oleuropein, another iridoid glycoside, increased the expression of nuclear factor erythroid-2-related factor 2 (Nrf2), a master regulator of antioxidant responses, in the sciatic nerve of CCI and vincristine-treated rats.[56] These findings suggested that iridoid glycosides can mitigate oxidative stress by modulating both enzymatic and non-enzymatic antioxidant systems, thereby alleviating NP.

Neuronal Protection and Apoptosis Inhibition

Neuronal damage and apoptosis also are critical events in the pathophysiology of NP.[88,89] Iridoid glycosides have demonstrated neuroprotective effects by inhibiting apoptosis and promoting neuronal survival. Loganin reduced the expression of pro-apoptotic proteins such as Bax and cleaved caspase-3 in the spinal cord of CCI rats.[54] It also improved autophagic flux, as indicated by decreased accumulation of p62 and LC3B-II, suggesting a restoration of cellular homeostasis. Geniposide treatment attenuated neuronal loss in the L4-L5 spinal cord of CCI rats and restored the morphological integrity of sciatic-nerve bundles by inhibiting EGFR/PI3K/AKT pathway.[69] These results suggested that iridoid glycosides protect neurons from apoptosis, contributing to analgesic effects.

Modulation of Neurotransmitter Systems and Ion Channels

Dysregulation of neurotransmitter systems and ion channels is implicated in neuropathic hypersensitivity.[90,91] In a diabetic neuropathy model, loganin reduced the expression of CaV3.2 T-type calcium channels and calcitonin gene-related peptide (CGRP) in the superficial spinal dorsal horn.[53] Transcriptomic profiling revealed that geniposide down-regulates the expression of Ca^{2+} signalling proteins (including PKC, CaM, CaMKIIα and CaMKIIδ) in the CCI spinal cord, effects comparable to those achieved by the Ca^{2+} channel modulator gabapentin.[69] Gardenoside combined with ozone decreased the enhanced expression of P2X3 and P2X7 purinoceptors in DRG neurons after sciatic CCI, and the reduction coincided with alleviation of mechanical and thermal hypersensitivity, suggesting that dampening ATP-gated cation currents is another modality by which iridoids achieve analgesia.[77] Moreover, morroniside-induced activation of spinal GLP-1 receptors elevated β-endorphin release, functionally antagonising NMDA-receptor-mediated hyper-excitation.[64] Thus, iridoid glycosides modulate NP-relevant neurotransmission by limiting Ca^{2+} influx and downstream kinases, suppressing ATP-activated purinoceptor signaling, and recruiting endogenous opioid circuits, all of which converge to reduce neuronal hyper-excitability in the sensitized spinal cord. Thus, these findings indicated that iridoids modulate pain transmission by suppressing Ca^{2+} signaling, reducing excitatory neurotransmission, and enhancing endogenous inhibitory tone, thereby normalizing neuronal hyperexcitability in the spinal cord.

Taken together, iridoid glycosides exert anti-neuropathic effects through a multifaceted mechanism involving anti-inflammatory, antioxidant, glial modulatory, neuroprotective, and potentially neurotransmitter-modulating actions. The most robust evidence supports their role in suppressing neuroinflammation and oxidative stress, with emerging data highlighting their influence on glial cell activation and iron metabolism. Future research should focus on clarifying their effects on neurotransmitter systems and ion channels, as well as identifying their molecular targets and signaling pathways in specific pain contexts.

Conclusion and Future Directions

This review comprehensively summarized that plant-derived iridoids demonstrated consistent anti-allodynic or hyper-algesic efficacy in various rodent models of NP (CCI, SNL, SNI, DNP, and PD-PNP, etc.) without apparent tolerance after repeated administration. Both conventional iridoid glycosides and seco-iridoid glycosides have varying degrees of alleviating effects on different rat or mouse models of NP, indicating that the iridoids are expected to become potential candidates for anti-NP drugs. Mechanistically, iridoids exert anti-neuropathic effects through multifaceted actions,

including anti-inflammatory, antioxidant, glial modulatory, neuroprotective, and neurotransmitter-modulating activities. Notably, inhibition of NF-κB signaling and activation of the spinal GLP-1R/β-endorphin cascade are the two best-validated nodes and can serve as dual biomarkers for future lead optimization. Some iridoid glycosides or seco-iridoid glycosides showed equivalent efficacy comparison with first-line drugs (gabapentin, duloxetine, tramadol) at comparable doses, and additional improvement in comorbid anxiety, depression and sleep disturbance.

Despite the significant progress, there are several limitations and research gaps. First, the precise mechanisms of NP warrant further investigation using advanced technologies such as single-cell sequencing and cell-type-specific manipulation. Second, validation in chronic-progressive models and non-human primates, as well as incorporation of behavioral assays for spontaneous pain and affective comorbidities, is needed to enhance translational relevance. Third, large-scale, randomized controlled clinical trials are urgently required to establish human efficacy, safety, and optimal dosing. Fourth, medicinal chemistry efforts should focus on improving bioavailability, brain penetration, and metabolic stability through structural optimization and novel formulations. Fifth, systematic evaluation of long-term toxicity and drug interactions is necessary prior to clinical application.

Collectively, plant-derived iridoids represent mechanistically novel, multi-target candidates that have demonstrated safety for NP at the doses tested in animal models, addressing the major unmet need for efficacy and tolerability beyond current standard of care. Future efforts should prioritize clinical translation through rigorous trial design, formulation development, and mechanistic elucidation of their molecular targets.

AI Statement

ChatGPT has been used throughout the manuscript for grammar checks.

Acknowledgments

This work was funded by the National Natural Science Foundation of China (No. 82204761) and the National Key Research and Development Program of China (No. 2023YFC3504400).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Finnerup NB, Kuner R, Jensen TS. Neuropathic pain: from mechanisms to treatment. *Physiol Rev*. 2021;101(1):259–301. doi:10.1152/physrev.00045.2019
2. Ahmadi R, Kuner R, Weidner N, Kessler J, Bendszus M, Krieg SM. The diagnosis and treatment of neuropathic pain. *Deutsches Arzteblatt Int*. 2024;121(25):825–832. doi:10.3238/arztebl.m2024.0215
3. Kaplan CM, Kelleher E, Irani A, Schrepf A, Clauw DJ, Harte SE. Deciphering nociplastic pain: clinical features, risk factors and potential mechanisms. *Nat Rev Neurol*. 2024;20(6):347–363. doi:10.1038/s41582-024-00966-8
4. Raja SN, Carr DB, Cohen M, et al. The revised international association for the study of pain definition of pain: concepts, challenges, and compromises. *Pain*. 2020;161(9):1976–1982. doi:10.1097/j.pain.0000000000001939
5. Smith BH, Raja SN. NeuPSIG: investing in solutions to the growing global challenge of neuropathic pain. *Br J Anaesth*. 2017;119(4):705–708. doi:10.1093/bja/aex276
6. Klein NP, Bartlett J, Fireman B, et al. Effectiveness of the live zoster vaccine during the 10 years following vaccination: real world cohort study using electronic health records. *BMJ*. 2023;383:e076321.
7. Dangi A, Sharma SS. Pharmacological agents targeting transient receptor potential (TRP) channels in neuropathic pain: preclinical and clinical status. *Eur J Pharmacol*. 2024;980:176845. doi:10.1016/j.ejphar.2024.176845
8. Anttila S, Maatta J, Heikkala E, Arokoski J, Karppinen J, Oura P. Associations of socioeconomic and lifestyle characteristics, psychological symptoms, multimorbidity, and multisite pain with sciatica - a 15-year longitudinal study. *Spine J*. 2024;24(5):842–850. doi:10.1016/j.spinee.2023.12.013
9. Yongjun Z, Tingjie Z, Xiaoqiu Y, et al. A survey of chronic pain in China. *Libyan J Med*. 2020;15(1):1730550. doi:10.1080/19932820.2020.1730550
10. Petzke F, Tolle T, Fitzcharles MA, Hauser W. Cannabis-based medicines and medical cannabis for chronic neuropathic pain. *CNS Drugs*. 2022;36(1):31–44. doi:10.1007/s40263-021-00879-w
11. Chen YT, Chen PH, Chou FY, et al. The safety and efficacy of Chinese herbal medicine for pneumonia prevention in high-risk elder residents in the nursing home: a randomized, double-blind clinical trial. *J Ethnopharmacol*. 2024;318(Pt B):117017. doi:10.1016/j.jep.2023.117017
12. Dinda B, Dinda M, Kulsi G, Chakraborty A, Dinda S. Therapeutic potentials of plant iridoids in Alzheimer's and Parkinson's diseases: a review. *Eur J Med Chem*. 2019;169:185–199. doi:10.1016/j.ejmech.2019.03.009

13. Wei ZF, Zhou K, Dong J, et al. Efficacy of Lamiophlomis Rotata Capsule in the treatment of type IIIB prostatitis. *Zhonghua Nan Ke Xue*. 2017;23 (12):1107–1110.
14. Committee. *Committee for the Pharmacopoeia of PR China, (Part I)*. Beijing, PR China: People's Health Publishing House; 2020.
15. Di Stefano G, Di Lionardo A, Di Pietro G, Truini A. Neuropathic pain related to peripheral neuropathies according to the IASP grading system criteria. *Brain Sci*. 2020;11(1):1. doi:10.3390/brainsci11010001
16. Scholz J, Finnerup NB, Attal N, et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain*. 2019;160(1):53–59. doi:10.1097/j.pain.0000000000001365
17. Yam MF, Loh YC, Oo CW, Basir R. Overview of neurological mechanism of pain profile used for animal "pain-like" behavioral study with proposed analgesic pathways. *Int J Mol Sci*. 2020;21(12):4355. doi:10.3390/ijms21124355
18. Jensen TS, Finnerup NB. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. *Lancet Neurol*. 2014;13 (9):924–935. doi:10.1016/S1474-4422(14)70102-4
19. Bannister K, Sachau J, Baron R, Dickenson AH. Neuropathic pain: mechanism-based therapeutics. *Annu Rev Pharmacol Toxicol*. 2020;60 (1):257–274. doi:10.1146/annurev-pharmtox-010818-021524
20. Alles SRA, Smith PA. Etiology and pharmacology of neuropathic pain. *Pharmacol Rev*. 2018;70(2):315–347. doi:10.1124/pr.117.014399
21. Sommer C, Cruccu G. Topical treatment of peripheral neuropathic pain: applying the evidence. *J Pain Sympt Manag*. 2017;53(3):614–629. doi:10.1016/j.jpainsymman.2016.09.015
22. Jiang L, Cai S, Weng Z, Zhang S, Jiang SH. Peripheral, central, and chemotherapy-induced neuropathic changes in pancreatic cancer. *Trends Neurosci*. 2025;48(2):124–139. doi:10.1016/j.tins.2024.11.008
23. Moisset X. Neuropathic pain: evidence based recommendations. *La Presse Med*. 2024;53(2):104232. doi:10.1016/j.lpm.2024.104232
24. Watson JC, Sandroni P. Central neuropathic pain syndromes. *Mayo Clin Proc*. 2016;91(3):372–385. doi:10.1016/j.mayocp.2016.01.017
25. Rosner J, de Andrade DC, Davis KD, et al. Central neuropathic pain. *Nat Rev Dis Primers*. 2023;9(1):73. doi:10.1038/s41572-023-00484-9
26. Fiore NT, Debs SR, Hayes JP, Duffy SS, Moalem-Taylor G. Pain-resolving immune mechanisms in neuropathic pain. *Nat Rev Neurol*. 2023;19 (4):199–220. doi:10.1038/s41582-023-00777-3
27. Attal N, Bouhassira D. Translational neuropathic pain research. *Pain*. 2019;160 Suppl 1(1):S23–S28. doi:10.1097/j.pain.0000000000001522
28. Spaulding EL, Hines TJ, Bais P, et al. The integrated stress response contributes to tRNA synthetase-associated peripheral neuropathy. *Science*. 2021;373(6559):1156–1161. doi:10.1126/science.abb3414
29. Scheff SW, Saucier DA, Cain ME. A statistical method for analyzing rating scale data: the BBB locomotor score. *J Neurotrauma*. 2002;19 (10):1251–1260. doi:10.1089/08977150260338038
30. Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain*. 1988;33 (1):87–107. doi:10.1016/0304-3959(88)90209-6
31. Ho Kim S, Mo Chung J. An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. *Pain*. 1992;50 (3):355–363. doi:10.1016/0304-3959(92)90041-9
32. Seltzer Z, Dubner R, Shir Y. A novel behavioral model of neuropathic pain disorders produced in rats by partial sciatic nerve injury. *Pain*. 1990;43 (2):205–218. doi:10.1016/0304-3959(90)91074-S
33. Hicks CW, Selvin E. Epidemiology of peripheral neuropathy and lower extremity disease in diabetes. *Curr Diab Rep*. 2019;19(10):86. doi:10.1007/s11892-019-1212-8
34. Hossain MJ, Kendig MD, Letton ME, Morris MJ, Arnold R. Peripheral neuropathy phenotyping in rat models of type 2 diabetes mellitus: evaluating uptake of the neurodiab guidelines and identifying future directions. *Diabetes Metab J*. 2022;46(2):198–221. doi:10.4093/dmj.2021.0347
35. Barragan-Iglesias P, Oidor-Chan VH, Loeza-Alcocer E, et al. Evaluation of the neonatal streptozotocin model of diabetes in rats: evidence for a model of neuropathic pain. *Pharmacol Rep*. 2018;70(2):294–303. doi:10.1016/j.pharep.2017.09.002
36. Desforges AD, Hebert CM, Spence AL, et al. Treatment and diagnosis of chemotherapy-induced peripheral neuropathy: an update. *Biomed Pharmacother*. 2022;147:112671. doi:10.1016/j.biopha.2022.112671
37. Goel Y, Argueta DA, Peterson K, Lomeli N, Bota DA, Gupta K. Neuronal p38 MAPK signaling contributes to cisplatin-induced peripheral neuropathy. *Antioxidants*. 2025;14(4). doi:10.3390/antiox14040445
38. Yuan Y, Hu W, Chen C, et al. Pharmacokinetic, pharmacodynamic and pharmacogenetic studies related to vincristine-induced peripheral neuropathy in chinese pediatric ALL patients. *Clin Pharmacol Ther*. 2025;117(2):454–464. doi:10.1002/cpt.3462
39. Zhang J, Huang Y, Sun X, et al. Activating autophagy improves paclitaxel-induced peripheral neuropathy in chemotherapy. *Acta Pharm Sin B*. 2024;14(10):4632–4636. doi:10.1016/j.apsb.2024.08.010
40. Abboud C, Duveau A, Bouali-Benazzouz R, et al. Animal models of pain: diversity and benefits. *J Neurosci Methods*. 2021;348:108997. doi:10.1016/j.jneumeth.2020.108997
41. Mogil JS. Qualitative sex differences in pain processing: emerging evidence of a biased literature. *Nat Rev Neurosci*. 2020;21(7):353–365. doi:10.1038/s41583-020-0310-6
42. Gaudet AD, Ayala MT, Schleicher WE, et al. Exploring acute-to-chronic neuropathic pain in rats after contusion spinal cord injury. *Exp Neurol*. 2017;295:46–54. doi:10.1016/j.expneurol.2017.05.011
43. McFarlane K, Otto TE, Bailey WM, et al. Effect of sex on motor function, lesion size, and neuropathic pain after contusion spinal cord injury in mice. *J Neurotrauma*. 2020;37(18):1983–1990. doi:10.1089/neu.2019.6931
44. Gadgil S, Ergun M, van den Heuvel SA, van der Wal SE, Scheffer GJ, Hooijmans CR. A systematic summary and comparison of animal models for chemotherapy induced (peripheral) neuropathy (CIPN). *PLoS One*. 2019;14(8):e0221787. doi:10.1371/journal.pone.0221787
45. Bai M, Xiang H, Ding K, et al. Modification of iridoids in focus: bridging structural complexity with biological innovation. *Bioorg Chem*. 2025;161:108519. doi:10.1016/j.bioorg.2025.108519
46. Viljoen A, Mncwangi N, Vermaak I. Anti-inflammatory iridoids of botanical origin. *Curr Med Chem*. 2012;19(14):2104–2127. doi:10.2174/092986712800229005
47. Geu-Flores F, Sherden NH, Courdavault V, et al. An alternative route to cyclic terpenes by reductive cyclization in iridoid biosynthesis. *Nature*. 2012;492(7427):138–142. doi:10.1038/nature11692
48. Ndongwe T, Witika BA, Mncwangi NP, et al. Iridoid derivatives as anticancer agents: an updated review from 1970-2022. *Cancers*. 2023;15 (3):770. doi:10.3390/cancers15030770

49. Wang C, Gong X, Bo A, et al. Iridoids: research advances in their phytochemistry, biological activities, and pharmacokinetics. *Molecules*. 2020;25 (2):287.
50. Zheng XZ, Yu HY, Chen YR, Fang JS. Aucubin mitigates the elevation of microglial aerobic glycolysis and inflammation in diabetic neuropathic pain via aldose reductase. *World J Diabetes*. 2025;16(5):103915. doi:10.4239/wjd.v16.i5.103915
51. Chu LW, Cheng KI, Chen JY, et al. Loganin prevents chronic constriction injury-provoked neuropathic pain by reducing TNF-alpha/IL-1beta-mediated NF-kappaB activation and Schwann cell demyelination. *Phytomedicine*. 2020;67:153166. doi:10.1016/j.phymed.2019.153166
52. Cheng KI, Chen SL, Hsu JH, et al. Loganin prevents CXCL12/CXCR4-regulated neuropathic pain via the NLRP3 inflammasome axis in nerve-injured rats. *Phytomedicine*. 2021;92:153734. doi:10.1016/j.phymed.2021.153734
53. Cheng YC, Chiu YM, Dai ZK, Wu BN. Loganin ameliorates painful diabetic neuropathy by modulating oxidative stress, inflammation and insulin sensitivity in streptozotocin-nicotinamide-induced diabetic rats. *Cells*. 2021;10(10):2688. doi:10.3390/cells10102688
54. Cheng KI, Chang YC, Chu LW, et al. The iridoid glycoside loganin modulates autophagic flux following chronic constriction injury-induced neuropathic pain. *Int J Mol Sci*. 2022;23(24):15873. doi:10.3390/ijms232415873
55. Czerwinska ME, Gasinska E, Lesniak A, et al. Inhibitory effect of Ligustrum vulgare leaf extract on the development of neuropathic pain in a streptozotocin-induced rat model of diabetes. *Phytomedicine*. 2018;49:75–82. doi:10.1016/j.phymed.2018.06.006
56. Chen H, Ma D, Zhang H, et al. Antinociceptive effects of oleuropein in experimental models of neuropathic pain in male rats. *Korean J Pain*. 2021;34(1):35–46. doi:10.3344/kjp.2021.34.1.35
57. Fan H, Li TF, Gong N, Wang YX. Shanzhiside methylester, the principle effective iridoid glycoside from the analgesic herb Lamiophlomis rotata, reduces neuropathic pain by stimulating spinal microglial beta-endorphin expression. *Neuropharmacology*. 2016;101:98–109. doi:10.1016/j.neuropharm.2015.09.010
58. Zhang W, Bai Y, Qiao Y, et al. 8-O-Acetyl shanzhiside methylester from lamiophlomis rotata reduces neuropathic pain by inhibiting the ERK/TNF-alpha pathway in spinal astrocytes. *Front Cell Neurosci*. 2018;12:54. doi:10.3389/fncel.2018.00054
59. Zheng Y, Yin X, Huo F, Xiong H, Mei Z. Analgesic effects and possible mechanisms of iridoid glycosides from Lamiophlomis rotata (Benth.) Kudo in rats with spared nerve injury. *J Ethnopharmacol*. 2015;173:204–211. doi:10.1016/j.jep.2015.06.045
60. Zhu B, Gong N, Fan H, et al. Lamiophlomis rotata, an orally available Tibetan herbal painkiller, specifically reduces pain hypersensitivity states through the activation of spinal glucagon-like peptide-1 receptors. *Anesthesiology*. 2014;121(4):835–851. doi:10.1097/ALN.0000000000000320
61. Liu M, Zhou L, Chen Z, Hu C. Analgesic effect of iridoid glycosides from Paederia scandens (LOUR.) MERRILL (Rubiaceae) on spared nerve injury rat model of neuropathic pain. *Pharmacol Biochem Behav*. 2012;102(3):465–470. doi:10.1016/j.pbb.2012.06.007
62. Sun F, Ma Y, Li D, et al. Gentiopicroside attenuated dopaminergic neurodegeneration via inhibiting neuroinflammatory responses and ferroptosis in experimental models of Parkinson's disease. *Basic Clin Pharmacol Toxicol*. 2025;136(5):e70036. doi:10.1111/bcpt.70036
63. Yu M, Su B, Zhang X. Gardenoside suppresses the pain in rats model of chronic constriction injury by regulating the P2X3 and P2X7 receptors. *J Recept Signal Transduction Res*. 2018;38(3):198–203. doi:10.1080/10799893.2018.1468782
64. Xu M, Wu HY, Liu H, Gong N, Wang YR, Wang YX. Morroniside, a secoiridoid glycoside from Cornus officinalis, attenuates neuropathic pain by activation of spinal glucagon-like peptide-1 receptors. *Br J Pharmacol*. 2017;174(7):580–590. doi:10.1111/bph.13720
65. Tang X, Wu H, Mao X, Li X, Wang Y. The GLP-1 receptor herbal agonist morroniside attenuates neuropathic pain via spinal microglial expression of IL-10 and beta-endorphin. *Biochem Biophys Res Commun*. 2020;530(3):494–499. doi:10.1016/j.bbrc.2020.05.080
66. Nong X, Lan Y. Picroside II attenuates CCI-Induced neuropathic pain in rats by inhibiting spinal reactive astrocyte-mediated neuroinflammation through the NF-kappaB pathway. *Neurochem Res*. 2018;43(5):1058–1066. doi:10.1007/s11064-018-2518-7
67. Duan D, Wang L, Feng Y, Hu D, Cui D. Picroside II attenuates neuropathic pain by regulating inflammation and spinal excitatory synaptic transmission. *Can J Physiol Pharmacol*. 2024;102(4):281–292. doi:10.1139/cjpp-2023-0171
68. Wang Y, Zhang R, Xie J, Lu J, Yue Z. Analgesic activity of catalpol in rodent models of neuropathic pain, and its spinal mechanism. *Cell Biochem Biophys*. 2014;70(3):1565–1571. doi:10.1007/s12013-014-0096-0
69. Zhang DD, Chen QQ, Yao L. Geniposide alleviates neuropathic pain in CCI rats by inhibiting the EGFR/PI3K/AKT pathway and Ca(2+) channels. *Neurotox Res*. 2022;40(4):1057–1069. doi:10.1007/s12640-022-00531-5
70. Zhang F, Yan Y, Zhang J, et al. Phytochemistry, synthesis, analytical methods, pharmacological activity, and pharmacokinetics of loganin: a comprehensive review. *Phytother Res*. 2022;36(6):2272–2299. doi:10.1002/ptr.7347
71. Chen J, Ge J, Chen W, et al. UPLC-Q-TOF-MS based investigation into the bioactive compounds and molecular mechanisms of Lamiophlomis Herba against hepatic fibrosis. *Phytomedicine*. 2023;121:155085. doi:10.1016/j.phymed.2023.155085
72. Shan MQ, Wang TJ, Jiang YL, et al. Comparative analysis of sixteen active compounds and antioxidant and anti-influenza properties of Gardenia jasminoides fruits at different times and application to the determination of the appropriate harvest period with hierarchical cluster analysis. *J Ethnopharmacol*. 2019;233:169–178. doi:10.1016/j.jep.2019.01.004
73. Cui ZH, Qin SS, Zang EH, et al. Traditional uses, phytochemistry, pharmacology and toxicology of Lamiophlomis rotata (Benth.) Kudo: a review. *RSC Adv*. 2020;10(19):11463–11474. doi:10.1039/D0RA01050B
74. Li Y, Li F, Zheng TT, et al. Lamiophlomis herba: a comprehensive overview of its chemical constituents, pharmacology, clinical applications, and quality control. *Biomed Pharmacother*. 2021;144:112299. doi:10.1016/j.biopha.2021.112299
75. Wang L, Chen S, Liu S, et al. A comprehensive review of ethnopharmacology, chemical constituents, pharmacological effects, pharmacokinetics, toxicology, and quality control of gardeniae fructus. *J Ethnopharmacol*. 2024;320:117397. doi:10.1016/j.jep.2023.117397
76. Neri-Numa IA, Pessoa MG, Arruda HS, et al. Genipap (Genipa americana L.) fruit extract as a source of antioxidant and antiproliferative iridoids. *Food Res Int*. 2020;134:109252. doi:10.1016/j.foodres.2020.109252
77. Yu M, Zhao Y, Zhang X. Gardenoside combined with ozone inhibits the expression of P2X3 and P2X7 purine receptors in rats with sciatic nerve injury. *Mol Med Rep*. 2018;17(6):7980–7986. doi:10.3892/mmr.2018.8803
78. Ma S, Wang X, Lai F, Lou C. The beneficial pharmacological effects and potential mechanisms of picroside II: evidence of its benefits from in vitro and in vivo. *Biomed Pharmacother*. 2020;130:110421. doi:10.1016/j.biopha.2020.110421
79. Wu Q, Tang AL, Dong QQ, et al. Picroside II-encapsulated nanoformulations as pyroptosis inhibitor alleviate cytokine storms and remodel gut microbiota disturbances. *ACS Nano*. 2025;19(36):32569–32584. doi:10.1021/acsnano.5c09760
80. Shi P, Zheng B, Zhang S, Guo Q. A review of the sources and pharmacological research of morroniside. *Front Pharmacol*. 2024;15:1423062. doi:10.3389/fphar.2024.1423062

81. Liu N, Li YX, Gong SS, et al. Antinociceptive effects of gentiopicroside on neuropathic pain induced by chronic constriction injury in mice: a behavioral and electrophysiological study. *Can J Physiol Pharmacol*. 2016;94(7):769–778. doi:10.1139/cjpp-2015-0462
82. Khalil AA, Rahman MM, Rauf A, et al. Oleuropein: chemistry, extraction techniques and nutraceutical perspectives-An update. *Crit Rev Food Sci Nutr*. 2024;64(27):9933–9954. doi:10.1080/10408398.2023.2218495
83. Salvemini D, Doyle TM. Targeting neuroinflammation in neuropathic pain and opioid use. *J Exp Med*. 2023;220(2). doi:10.1084/jem.20221244
84. Ye Y, Su X, Tang J, Zhu C. Neuropathic pain induced by spinal cord injury from the glia perspective and its treatment. *Cell Mol Neurobiol*. 2024;44(1):81. doi:10.1007/s10571-024-01517-x
85. Malcangio M, Sideris-Lampretsas G. How microglia contribute to the induction and maintenance of neuropathic pain. *Nat Rev Neurosci*. 2025;26(5):263–275. doi:10.1038/s41583-025-00914-5
86. Shen Z, Guo YD, Tang MZ, et al. Dexborneol amplifies pregabalin's analgesic effect in mouse models of peripheral nerve injury and incisional pain. *Antioxidants*. 2024;13(7):803.
87. de Andrade DC, Mylius V, Perez-Lloret S, et al. Pain in Parkinson disease: mechanistic substrates, main classification systems, and how to make sense out of them. *Pain*. 2023;164(11):2425–2434. doi:10.1097/j.pain.0000000000002968
88. Zhou D, Zhang S, Hu L, et al. Inhibition of apoptosis signal-regulating kinase by paeoniflorin attenuates neuroinflammation and ameliorates neuropathic pain. *J Neuroinflammation*. 2019;16(1):83. doi:10.1186/s12974-019-1476-6
89. Duan YW, Chen SX, Li QY, Zang Y. Neuroimmune mechanisms underlying neuropathic pain: the potential role of TNF-alpha-necroptosis pathway. *Int J Mol Sci*. 2022;23(13):7191. doi:10.3390/ijms23137191
90. Thouaye M, Yalcin I. Neuropathic pain: from actual pharmacological treatments to new therapeutic horizons. *Pharmacol Ther*. 2023;251:108546. doi:10.1016/j.pharmthera.2023.108546
91. Sharma S, Rana P, Dhingra N, Kaur T. Insights into ion channels to identify drug target for neuropathic pain management. *Inflammopharmacology*. 2025;33(8):4455–4475. doi:10.1007/s10787-025-01899-4

Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/drug-design-development-and-therapy-journal