



Pinostrobin- An Anti-Inflammatory Food Nutrient for Neuropathic Pain

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Abstract

Background: Pinostrobin, a bioactive flavonoid isolated from *Boesenbergia rotunda* (aka. fingerroot, Chinese-thai ginger, lesser galangal, widely used in Thai cuisine ingredients), has demonstrated multiple neuroprotective and anti-inflammatory properties. Also available in Indian pigeon pea, leaf and seeds (Arhar dal), with anti-inflammatory functional food potential, for target population in India.

Preclinical evidence suggests its potential in the management of neuropathic pain by modulating oxidative stress, neuroinflammation, and neuronal regeneration pathways.

Methods: Mechanistic and preclinical studies were reviewed, including those investigating pinostrobin in peripheral nerve injury, diabetic neuropathy, and neurotoxin-induced models. Experimental findings on oxidative status, motor recovery, nerve histopathology, and molecular signaling pathways were evaluated. Safety and pharmacokinetic data were compiled from rodent studies and limited human trials on *B. rotunda* extracts.

Results: Pinostrobin markedly reduced oxidative stress by restoring reduced glutathione and decreasing malondialdehyde concentrations in nerve tissues. It enhanced axonal regeneration and myelin repair, largely through activation of the Nrf2/ARE antioxidant pathway and suppression of apoptotic signaling (increased HO-1, GCLC, and Bcl-2/Bax ratio).

Antinociceptive responses were mediated via modulation of opioid, GABAergic, and serotonergic neurotransmission. Pinostrobin also maintained astrocytic function and reduced glial activation, mitigating neuroinflammation. Toxicological assessments in rats identified no adverse hepatic or renal effects at doses up to 500 mg/kg (LD₅₀ > 500 mg/kg). Although *B. rotunda* extracts are well-tolerated in human trials for other indications, no registered clinical or pharmacokinetic studies of purified pinostrobin were found for neuropathic pain as of 2025.

Conclusion: Comprehensive preclinical data indicate that pinostrobin exerts significant antioxidant, neuroprotective, and analgesic actions with a favorable safety profile. However, translation to clinical application remains pending due to the absence of human pharmacological or efficacy studies.

Future research should focus on Phase I safety evaluation and targeted clinical trials to confirm therapeutic relevance in neuropathic pain management.

Keywords: Pinostrobin (PN); *Boesenbergia rotunda* (*B. rotunda*); Neuropathic Pain; Oxidative Stress; Neuroinflammation; Nrf2/ARE Pathway; Neuroprotection

Introduction

Neuropathic pain is a complex and debilitating condition arising from injury or dysfunction of the somatosensory nervous system and remains inadequately managed by currently available therapies. Conventional treatments, including antidepressants, anticonvulsants, and opioids, often provide limited relief and are associated with significant adverse effects, highlighting the need for safer and more effective therapeutic alternatives [1, 2]. In this context, increasing attention has been directed toward naturally derived bioactive compounds with multimodal mechanisms of action that can simultaneously target oxidative stress, neuroinflammation, and neuronal dysfunction.

Pinostrobin is a naturally occurring flavonoid predominantly isolated from *Boesenbergia rotunda* (fingerroot), a medicinal plant widely used in traditional medicine across Southeast Asia. Accumulating preclinical evidence indicates that pinostrobin exhibits robust neuroprotective,

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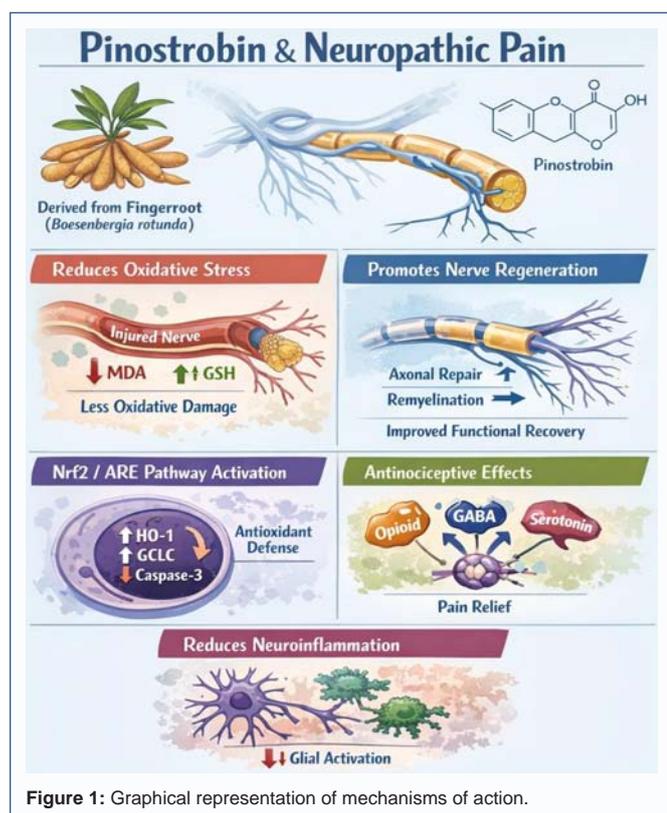


Figure 1: Graphical representation of mechanisms of action.

antioxidant, and antinociceptive properties, positioning it as a promising candidate for the management of neuropathic pain [1-5]. Experimental studies in animal models of peripheral nerve injury and metabolic neuropathy have demonstrated that pinostrobin reduces oxidative stress, attenuates inflammatory signaling, promotes axonal regeneration, and improves functional recovery following nerve damage [1, 3, 4]. In addition, its ability to modulate central neurotransmitter systems involved in pain processing further supports its analgesic potential in both neuropathic and inflammatory pain states [2, 5].

Despite these encouraging findings, the therapeutic potential of pinostrobin remains largely unexplored in the clinical setting. To date, evidence supporting its efficacy is limited to preclinical and mechanistic studies, with no published human clinical trials specifically evaluating pinostrobin for neuropathic pain [3, 5]. A systematic examination of its mechanisms of action, safety profile, and translational readiness is therefore warranted. This manuscript aims to synthesize current preclinical evidence on pinostrobin, highlight key mechanistic pathways relevant to neuropathic pain, and discuss critical gaps that must be addressed to advance this natural compound toward clinical application.

Mechanisms of Action in Neuropathic Pain

Reduction of Oxidative Stress

Studies on **sciatic nerve crush** (SNC) injury models in rats demonstrated that pinostrobin (20–40 mg/kg) significantly increased reduced glutathione (GSH) and decreased malondialdehyde (MDA) levels in peripheral nerves. This indicates decreased lipid peroxidation and attenuation of oxidative damage [1, 4].

Functional Recovery and Neuroprotection

Treated rats exhibited improved motor and sensory recovery

following nerve injury. These effects suggest that *pinostrobin enhances axonal regeneration and remyelination* following peripheral nerve damage [1, 4].

Activation of Nrf2/ARE Pathway

In neurotoxin-induced models of neurodegeneration, pinostrobin activated the Nrf2/ARE pathway, increasing the expression of antioxidant enzymes such as HO-1 and GCLC while suppressing apoptotic signaling (reduced caspase-3 activation, improved Bcl-2/Bax ratio). This antioxidant defense mechanism contributes to neuroprotection and possibly neuropathic pain relief [3].

Antinociceptive Effect

Pinostrobin, along with related flavonoids like pinocembrin and chrysin, shows antinociceptive (pain-suppressing) properties in animal models. The mechanism involves interaction with opioid, GABAergic, and serotonergic neurotransmission, supporting its analgesic potential in neuropathic and inflammatory pain [2].

Modulation of Neuroinflammation

Pinostrobin's anti-inflammatory effects, coupled with its ability to maintain astrocyte function (via GFAP and EAAT2 regulation in the hippocampus), help mitigate glial activation and neuroinflammatory processes commonly associated with chronic neuropathic conditions [5].

In summary, **pinostrobin** alleviates neuropathic pain through a combination of antioxidant, anti-inflammatory, and neuroprotective mechanisms, supported by both peripheral nerve repair and central modulation of oxidative stress and inflammation. These preclinical findings highlight its potential as a *natural therapeutic agent* for neuropathic pain management (Table 1 & 2).

Human Clinical Trials Testing Pinostrobin for Neuropathic Pain- Gap Analysis

No human clinical trials have yet tested pinostrobin specifically for neuropathic pain as of 2025. The available data are limited to preclinical animal and mechanistic studies, with no published or registered human trials found in the medical literature or clinical trial registries [2, 3, 5].

Current Research Status

Preclinical Findings: Pinostrobin, isolated mainly from *Boesenbergia rotunda*, has shown strong antinociceptive, antioxidant, and neuroprotective effects in animal models of **sciatic nerve crush** and **diabetic neuropathy**. These studies demonstrate improved nerve regeneration, decreased oxidative stress, and reduced inflammation [2, 5].

Pharmacokinetics and Safety: Studies in Sprague-Dawley rats have described the absorption, metabolism, and tissue distribution of orally administered pinostrobin, confirming its bioavailability and hepatic and neural accumulation. However, these experiments were exclusively animal-based and did not extend to human pharmacokinetics or toxicity testing [3].

No Registered Human Trials: A search of current biomedical databases and clinical trial platforms shows no registered or completed **Phase I–III clinical trials** evaluating pinostrobin in humans for neuropathic pain, diabetes-related nerve injury, or other neurological conditions [2, 3, 5].

In summary, *pinostrobin remains under preclinical evaluation,*

Table 1: Summary of neuropathic pain models.

Mechanism	Experimental Model	Outcome	Reference
Oxidative stress reduction	Sciatic nerve crush injury	Restored GSH, reduced MDA	[1, 4]
Nrf2/ARE pathway activation	MPP ⁺ -induced neurotoxicity	Increased HO-1, GSH-Px, SOD	[3]
Antinociceptive activity	Formalin & hot plate tests	Pain inhibition via GABA, opioid	[2]
Glial modulation	Chronic stress model	Improved astrocytic GFAP, EAAT2	[5]

Table 2: Summary of Pinostrobin bioactivity.

Compound	Study Type	Species/Subjects	Findings	Reference
<i>Boesenbergia rotunda</i> extract	Human clinical trial (FD)	Human (n=50)	Safe and well tolerated orally	[3]
<i>B. rotunda</i> ethanolic extract	Acute toxicity	Rat	No renal/liver damage at ≤2,000 mg/kg; minor effects at 4,000 mg/kg	[2]
Pinostrobin	Acute toxicity 14-day study	Rat	No abnormalities up to 500 mg/kg	[4]
Pinostrobin	General pharmacological review	Animal/ <i>in vitro</i>	Non-toxic at ≤100 mg/kg; safe in multiple organ systems	[1, 5]

Table 3: Summary of preclinical and clinical trials.

Research Stage	Species/Model	Purpose	Findings
Preclinical (<i>in vivo</i>)	Rat (sciatic nerve injury, diabetic model)	Neuropathic pain & nerve repair	Significant neuroprotective and antioxidant effects [2] [5]
Pharmacokinetics	Rat	Tissue distribution & metabolism	Detected in liver and nervous tissues; no human data [3]
Clinical (human)	—	Neuropathic pain	No published or ongoing trials* [2, 5]

with compelling animal data but no human trials yet assessing its safety or efficacy for neuropathic pain. Future clinical translation would require early-phase safety studies before therapeutic testing in humans can begin.

Human Safety Data for Pinostrobin or *B. rotunda* Extracts: Existing human safety data for pinostrobin and *Boesenbergia rotunda* (fingerroot) extracts are limited but indicate overall good tolerability and low toxicity in studies conducted so far [1-3]. Most evidence comes from animal toxicology assessments and a few human studies on *B. rotunda*, not purified pinostrobin.

Boesenbergia rotunda Extracts – Human Data

A 2021 Thai clinical study tested *Boesenbergia rotunda* extract for functional dyspepsia (FD) in humans and found the extract both *effective* and *safe* over the study period. Subjects tolerated daily dosing without reports of hepatotoxicity, nephrotoxicity, or serious adverse effects, suggesting good safety of the rhizome extract when standardized and consumed orally [3].

Additionally, *B. rotunda* ethanolic extract (BRE) was tested in preclinical safety studies showing no renal histopathological abnormalities at oral doses up to **2,000 mg/kg** in rats. Only at a very high dose (4,000 mg/kg) were minor renal irregularities observed, indicating a **wide therapeutic index** [2].

Pinostrobin – Preclinical and Toxicological Safety

Specific acute and subacute toxicity studies of purified pinostrobin (PN) in rodents reported no mortality or behavioral abnormalities at oral doses up to **500 mg/kg** for **14 days**. Biochemical markers for hepatic and renal function remained unchanged, and histopathology of liver and kidney tissues showed no damage, suggesting LD₅₀ > 500 mg/kg and general physiological safety [4] (Table 3).

Reviews of pharmacological studies confirm that pinostrobin

lacks significant systemic toxicity even at therapeutic or experimental levels (≤100 mg/kg in animal models) and does not affect normal tissue viability, further supporting its safety profile [1, 5].

Known Safety Mechanisms

- *Low cytotoxicity in non-malignant cells:* Cell-based assays demonstrate that while pinostrobin shows selective cytotoxicity against cancer cells, it spares healthy fibroblasts and hepatocytes, implying selective biochemical action [5].
- *Protective antioxidant properties:* Pinostrobin has repeatedly shown antioxidative protection in neuronal and renal cell models, further reducing toxicity risk [6].

Delivery Approaches for Pinostrobin

Oral delivery

Oral administration is the most practical and patient friendly route for pinostrobin. Preclinical pharmacokinetic studies show that pinostrobin is absorbed after oral dosing and can distribute to hepatic and neural tissues. This makes it suitable for chronic use in neuropathic pain. However, like many flavonoids, pinostrobin may have limited solubility and undergo first pass metabolism. These issues can be addressed through improved formulations such as lipid-based carriers, nano emulsions, or phytosome complexes to enhance bioavailability and maintain consistent systemic exposure.

Intranasal delivery

Intranasal delivery offers a non-invasive route to target the central nervous system more directly. By bypassing the blood brain barrier through olfactory and trigeminal pathways, this approach could increase brain exposure while reducing systemic dosing. This strategy is particularly relevant for neuropathic pain conditions with strong central sensitization and neuroinflammatory components, where central antioxidant and antinociceptive effects of pinostrobin may be critical.

Local or perineural delivery

For peripheral neuropathic pain, localized delivery near the site of nerve injury is an attractive option. Delivering pinostrobin directly to or around the injured nerve could achieve high local concentrations where oxidative stress, inflammation, and demyelination are most pronounced. This approach aligns well with preclinical evidence showing improved axonal regeneration, remyelination, and functional recovery, while limiting systemic exposure.

Sustained release biomaterial systems

Sustained release delivery systems can support long term therapeutic effects in chronic neuropathic pain. Incorporating pinostrobin into biodegradable hydrogels or polymer-based carriers allows gradual release over extended periods. This continuous exposure may better support nerve repair processes and long-lasting suppression of oxidative stress and inflammation, reducing the need for repeated dosing.

Nanoparticle based delivery

Nanoparticle based formulations provide an advanced strategy to improve pinostrobin delivery. These systems can enhance solubility, protect the compound from degradation, and promote cellular uptake in neurons or glial cells. With further development, nanoparticle platforms may also enable targeted delivery or combination therapy with other neuroprotective or analgesic agents.

Overall perspective Oral delivery remains the most immediately translatable approach for pinostrobin based on current safety and pharmacokinetic data. However, intranasal, local, sustained release, and nanoparticle-based strategies may substantially improve therapeutic precision and efficacy. Selection of the optimal delivery route will depend on the underlying pain mechanism, whether peripheral or central, and future human safety and pharmacokinetic studies.

Pinostrobin for Spinal Cord Injury-Induced Neuropathic Pain and Focal Subdural Hydrogel Delivery.

Pathophysiology of Neuropathic Pain after Spinal Cord Injury

Neuropathic pain is a pervasive and debilitating sequela of spinal cord injury (SCI) that emerges as a maladaptive response of the injured nervous system. Following SCI, a complex cascade of secondary processes including oxidative stress, neuroinflammation, and neuronal circuit remodeling contributes to chronic pain that is frequently refractory to standard therapies. Dysfunction within spinal dorsal horn circuits produces central sensitization characterized by enhanced excitatory transmission and loss of inhibitory control, leading to persistent nociceptive gain and spontaneous pain [1, 2]. Microglial and astrocytic activation further amplify pain signaling by releasing pro-inflammatory cytokines and neuromodulators, sustaining dorsal horn hyperexcitability and altering synaptic connectivity [3, 4]. Additionally, dorsal root ganglion neurons may develop ectopic activity and altered neurochemical phenotypes that feed aberrant sensory input into spinal circuits, exacerbating chronic pain [2]. Oxidative stress, manifested by reactive oxygen species (ROS) generation, lipid peroxidation, and depletion of endogenous antioxidants, further promotes neuronal injury, disrupts synaptic homeostasis, and reinforces neuroinflammatory signaling, creating a self-propagating pain microenvironment [5].

The dermatomal distribution and severity of neuropathic pain

may differ depending on the level of SCI. Cervical lesions often result in widespread pain involving both upper and lower limbs due to extensive involvement of ascending and descending pathways and broader disruption of neuromodulatory systems [1]. Thoracic injuries typically produce localized trunk dysesthesia and pronounced below-level pain in the lower extremities, reflecting spinothalamic tract dysfunction and dorsal horn reorganization below the lesion site [2]. In contrast, lumbar and conus medullaris injuries manifest predominant lower limb neuropathic pain with stronger peripheral dorsal root and ganglion contributions [2].

Therapeutic Rationale for Pinostrobin in SCI Neuropathic Pain

Pinostrobin is a flavonoid isolated from *Boesenbergia rotunda* with multimodal neuroprotective, antioxidant, and anti-inflammatory activity. In preclinical models of peripheral nerve injury, pinostrobin has been shown to reduce markers of oxidative stress, increase endogenous antioxidants, and promote functional nerve recovery [6]. It activates the Nrf2 antioxidant response pathway, upregulating cytoprotective enzymes and suppressing pro-apoptotic signaling, making it a mechanistically relevant candidate for mitigating oxidative and inflammatory drivers of neuropathic pain [5]. Furthermore, pinostrobin's ability to attenuate glial activation and modulate nociceptive neurotransmission supports its potential to counter both central sensitization and neuroimmune drivers of pain.

Engineered Hydrogel Conjugated Pinostrobin for Focal Subdural Delivery

A major translational challenge for natural pharmacologics like pinostrobin is achieving sustained therapeutic concentrations at the site of injury without systemic adverse effects or rapid metabolic clearance. Biomaterial-based delivery platforms such as hydrogels provide a strategic solution by enabling controlled, prolonged release of bioactive compounds near targeted neural tissue. Injectable hydrogels have been successfully utilized in SCI models to deliver neuroprotective and regenerative agents, demonstrating local retention, biocompatibility, and the potential to influence pain and repair processes within the spinal cord microenvironment [7, 8].

In the proposed approach, pinostrobin would be chemically conjugated or physically encapsulated within a biodegradable hydrogel engineered for slow and sustained release. This hydrogel-pinostrobin complex would be delivered focally into the subdural space adjacent to the injury site or spinal segments implicated in neuropathic pain generation (Figure 2). Placement in the subdural region ensures proximity to dorsal horn circuits, dorsal roots, and local glial populations that maintain chronic pain. Slow continuous release of pinostrobin is expected to reduce oxidative stress, suppress microglial and astrocyte activation, and stabilize neuronal excitability, thereby alleviating both below-level and at-level neuropathic pain phenomena. Sustained local exposure may provide a therapeutic advantage over intermittent systemic administration, reducing the need for high doses and minimizing systemic metabolism and adverse effects.

Conclusion

In summary, the current body of evidence supports pinostrobin as a promising natural compound for the management of neuropathic pain, with a safety profile that is encouraging but not yet fully defined in humans. Available human data are limited to clinical studies

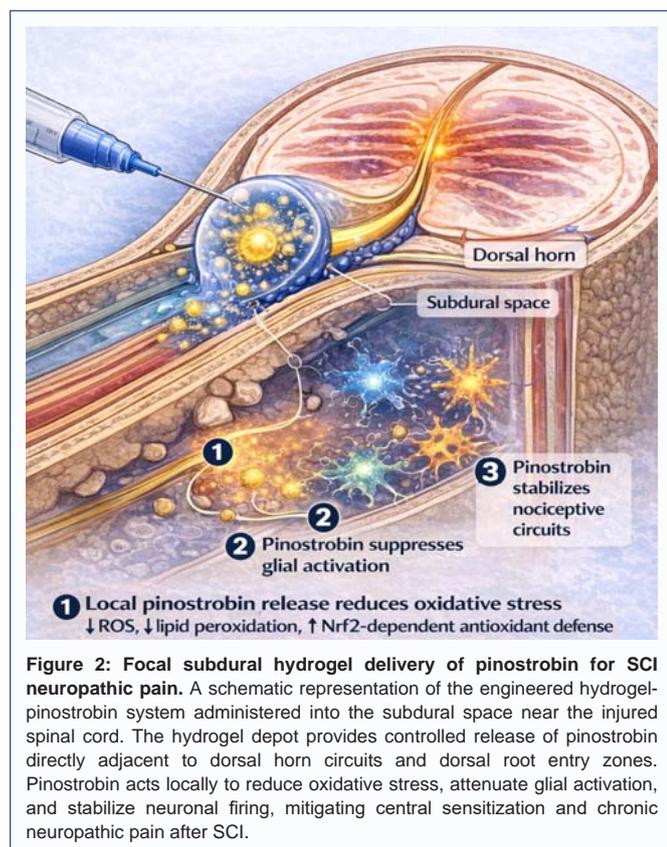


Figure 2: Focal subdural hydrogel delivery of pinostrobin for SCI neuropathic pain. A schematic representation of the engineered hydrogel-pinostrobin system administered into the subdural space near the injured spinal cord. The hydrogel depot provides controlled release of pinostrobin directly adjacent to dorsal horn circuits and dorsal root entry zones. Pinostrobin acts locally to reduce oxidative stress, attenuate glial activation, and stabilize neuronal firing, mitigating central sensitization and chronic neuropathic pain after SCI.

using *Boesenbergia rotunda* extracts, which have demonstrated good tolerability and an absence of serious adverse effects following oral administration. These findings suggest that bioactive constituents of the plant, including pinostrobin, can be safely consumed in standardized extract form. Complementing this, extensive preclinical toxicological studies of purified pinostrobin in rodent models consistently report low acute and subacute toxicity, with no significant behavioral abnormalities, organ damage, or alterations in hepatic and renal function at doses well above those shown to be pharmacologically effective.

Despite these reassuring observations, the safety evidence for pinostrobin itself remains indirect, as it has not yet been evaluated as a standalone compound in formal human studies. *Critical gaps* persist in our understanding of its human pharmacokinetics, bioavailability, metabolism, and dose-limiting toxicities. Notably, no Phase I clinical trials or toxicokinetic assessments of isolated pinostrobin have been reported to date, limiting confidence in its translational readiness. Addressing these gaps through well-designed early-phase clinical studies will be essential to establish safe dosing ranges, characterize systemic exposure, and identify any potential long-term safety concerns.

Looking forward, future studies are urgently needed to explore the therapeutic potential of pinostrobin in **spinal cord injury-induced neuropathic pain**, a condition with limited effective treatment options and complex underlying mechanisms. Advanced preclinical investigations integrating **SCI-specific pain models**, **biomaterial-based local delivery strategies**, and **long-term functional and behavioral outcomes** will be critical to determine whether pinostrobin can effectively modulate central sensitization, neuroinflammation, and oxidative stress within the injured spinal

cord. Such futuristic and translational studies may pave the way for first-in-human evaluation and ultimately position pinostrobin as a novel, multi-mechanistic, and disease-modifying therapeutic candidate for SCI-associated neuropathic pain.

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