

REVIEW

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A review of botanical interventions for neuropathy and neuropathic pain

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Abstract

Neuropathy is a complex condition characterized by nerve damage and a wide range of symptoms, creating significant challenges in clinical management. Traditional pharmacological treatments often present partial efficacy and adverse side effects, prompting increasing interest in botanical interventions. This review evaluates the effectiveness of various plants in treating neuropathy and neuropathic pain, focusing on their pharmacological properties, mechanisms of action, clinical studies, dosage, and safety profiles. Notable plants include *Crocus sativus* (saffron), *Citrullus colocynthis* (bitter apple), *Curcuma longa* (turmeric), *Lavandula angustifolia* (lavender), and *Cannabis sativa*. These botanicals demonstrate anti-inflammatory, antioxidative, and analgesic effects, highlighting their potential to reduce neuropathic pain and improve patients' quality of life. Future research should focus on optimizing dosages, clarifying long-term effects, and integrating botanicals into broader treatment protocols for neuropathic care.

Keywords Neuropathy, Neuropathic pain, Botanical interventions, Antioxidant, Anti-inflammatory, Analgesic

Introduction

Pain, whether present or not, is an unpleasant emotional and sensory experience that is associated with or described in terms of tissue damage [1]. Pain could be acute or chronic depending on the duration of the pain. There are estimates that pain affects 28% of people worldwide [2]. In 2019, among adults in the United States alone, 20.4% experienced chronic pain, while 7.4% suffered from high-impact chronic pain [3]. In light of the growing comprehension that persistent, pathological

alterations in the peripheral and/or central nervous systems (CNS) cause chronic pain, the International Classification of Diseases of the World Health Organization has classified chronic pain into a series of disease categories [4]. The most resistant form of chronic pain is neuropathic pain (pain caused by damage or disease to the somatosensory system), which occurs in approximately 7–10% of the general population [5]. Factors such as genetics, sex, prior injury, age, culture, and environmental influences all contribute to the diverse symptoms observed in patients with neuropathic pain [6]. Common clinical signs include sensory loss, spontaneous pain, and hypersensitivity, manifested as allodynia (pain from non-painful stimuli) and hyperalgesia (exaggerated pain responses) [7].

The pathophysiology of neuropathic pain involves both peripheral and CNS alterations. In the peripheral nervous system (PNS), nerve injury disrupts normal sensory signal transmission to the spinal cord, with ion channel

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dysregulation playing a key role as depicted in Fig. 1. Increased sodium channel activity leads to heightened neuronal excitability, while reduced potassium channel function impairs the modulation of this activity, ultimately contributing to ectopic nerve firing and ongoing pain [8]. At the site of injury, inflammation and altered gene expression further exacerbate the condition. Central sensitization occurs at the spinal and cortical levels, primarily driven by the overactivation of N-methyl-D-aspartate (NMDA) receptors for glutamate, resulting in amplified pain perception. The role of central pathways, particularly the involvement of the limbic system, explains the frequent comorbidities of anxiety, depression, and sleep disturbances in patients with chronic neuropathic pain [8].

Neuropathic pain is not easily treated since it has multiple etiologies, is difficult to diagnose objectively, and is resistant to traditional analgesic medications. Consequently, the primary goal of neuropathic pain management techniques is to address symptoms [9]. Neuropathy, characterized by damage or dysfunction of one or more nerves, leads to numbness, tingling, muscle weakness, and discomfort. Conventional pharmaceutical therapies

often come with side effects and limited efficacy [9]. Consequently, there is growing interest in plant-based treatments due to their potential therapeutic benefits with fewer side effects [10–17]. This review aims to explore plant-based treatments for neuropathic pain, focusing on botanicals with promising clinical and preclinical evidence. Current studies suggest that these plants can modulate inflammation, oxidative stress, and pain pathways, offering potential therapeutic benefits with fewer side effects than conventional drugs.

Materials and methods

A comprehensive literature search was conducted using databases such as PubMed and Google Scholar. The search terms included “neuropathy,” “neuropathic pain,” “plant-based treatments,” and specific botanical names like *Crocus sativus* and *Cannabis sativa*. Only peer-reviewed articles published between 2020 and 2023 were included. Preclinical and clinical studies were reviewed, with the exclusion of studies lacking pharmacological or clinical relevance.

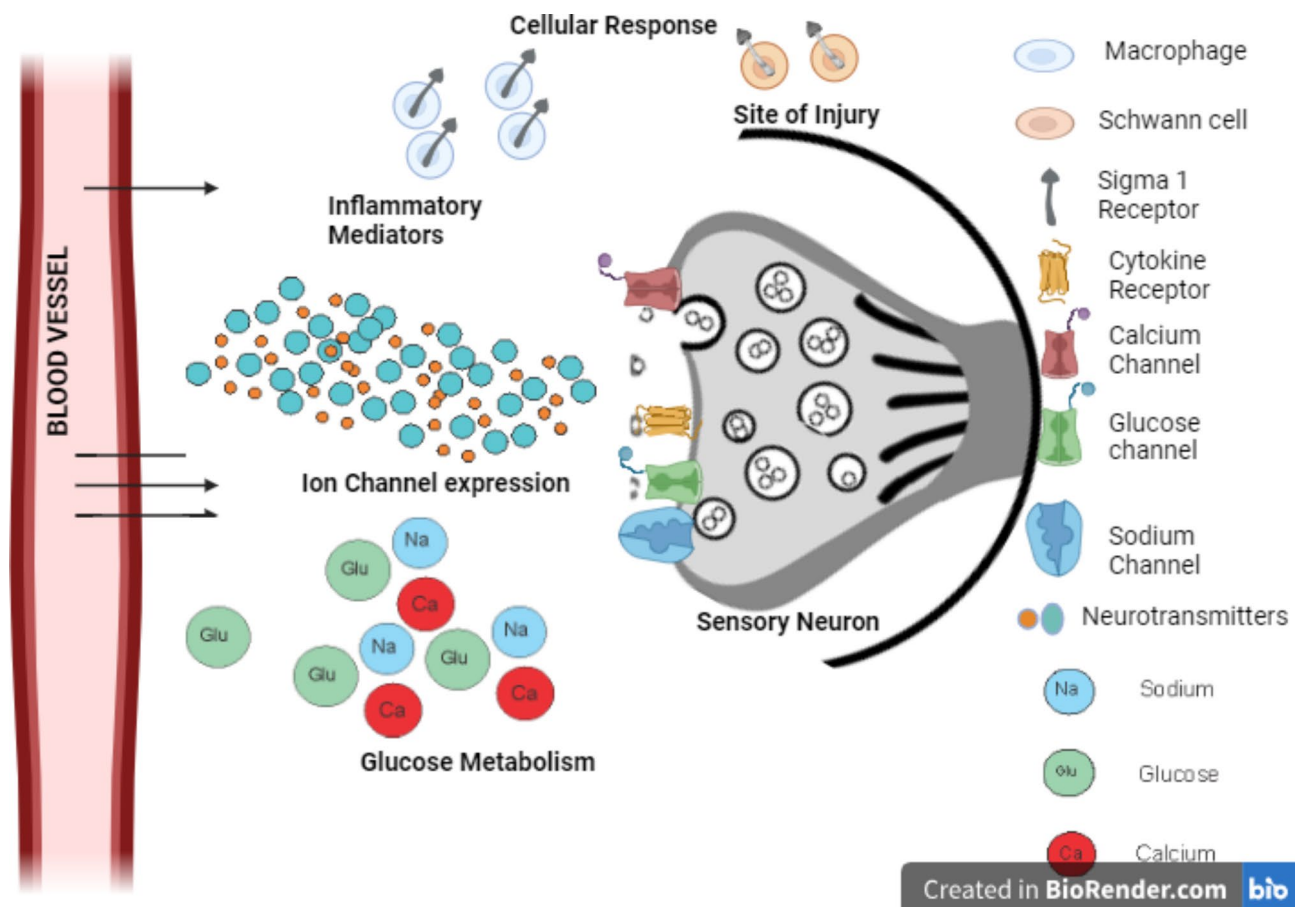


Fig. 1 Illustrative diagram of neuropathic pain pathophysiology

Plants employed in the treatment of neuropathy and neuropathic pain

The management of neuropathy and neuropathic pain presents a substantial challenge due to the complexity of its symptoms and the often inadequate response to standard pharmacological treatments. Recent studies have explored the efficacy of various plants in providing relief from neuropathic symptoms, showcasing their potential as alternative or complementary therapies. This section discusses several key plants that have been investigated for their therapeutic properties in treating different types of neuropathies and neuropathic pain. Table 1 summarizes various preclinical studies investigating the use of plant-based therapies in treating neuropathy and neuropathic pain. Each plant or plant-derived compound has been studied in different animal models of neuropathy, demonstrating varying degrees of efficacy. Numerous clinical studies have shown that compounds derived from plants, such as *Crocus sativus* and Capsaicin, can significantly alleviate symptoms of neuropathic pain, demonstrating their potential as viable treatment options. The evidence suggests that these plant-based therapies not only provide symptomatic relief but also operate through various biological mechanisms, such as antioxidative properties and interactions with pain receptors as summarized in Table 2.

Preclinical studies on plants used in treating neuropathy and neuropathic pain

Preclinical studies serve as a foundational step in this research, providing critical insights into the mechanisms of action, efficacy, and safety profiles of various phytotherapeutics. This section reviews key preclinical investigations that have evaluated the therapeutic potential of several plants traditionally used in managing neuropathic conditions. By synthesizing findings from these studies, we aim to highlight the promise of these natural compounds in alleviating neuropathic pain and enhancing nerve function, paving the way for future clinical applications.

Citrullus colocynthis

Citrullus colocynthis, also known as bitter apple, has been studied for its potential therapeutic effects on diabetic neuropathy, a prevalent complication of diabetes characterized by nerve damage due to high blood sugar levels. A study conducted by Ostovar et al., explored the efficacy of different preparations of *Citrullus colocynthis* in a rat model of diabetic neuropathy [18].

The study by Ostovar et al. evaluated multiple administration forms of *Citrullus colocynthis*, involving oral ingestion of fruit pulp powder at doses of 100 and 300 mg/kg daily, topical formulations (oil-based solution and salve), and comparison with gabapentin, a commonly

prescribed medication for neuropathy. The active compounds identified in the *Citrullus colocynthis* used in the study were cucurbitacin, flavonoids, alkaloids, and phenolic acids, which are known for their anti-inflammatory and antioxidant properties [18].

The positive outcomes of the study highlighted that *Citrullus colocynthis* was effective in treating symptoms of diabetic neuropathy in rats. The study provided evidence suggesting that both oral and topical applications could significantly reduce neuropathic pain, potentially linked to the anti-inflammatory and analgesic properties of the active compounds [18].

Interestingly, no negative outcomes were reported in this study, indicating that *Citrullus colocynthis* might be a well-tolerated treatment option.

Curcuma longa

Curcuma longa, commonly known as turmeric, has garnered attention for its potential in alleviating neuropathic pain. Studies investigating its efficacy in neuropathy treatment consistently report positive outcomes, indicating its promise as a therapeutic agent for neuropathic conditions.

Park et al., investigated curcumin's efficacy in a diabetic neuropathic pain model, administering doses spanning from 10 to 50 mg/kg daily. After four weeks, they observed improvements in behavioral reactions to mechanical, chilly, and thermal stimuli, highlighting curcumin's potential in alleviating neuropathic pain symptoms [19].

Overall, this study supports the notion that curcumin holds promise as a therapeutic agent for neuropathic pain management. However, further research, particularly in clinical settings, is warranted to elucidate the optimal dosage and treatment duration for maximizing curcumin's efficacy in neuropathy treatment.

Rhodiola rosea

Rhodiola rosea, a medicinal plant recognized for its adaptogenic properties, has been studied extensively for its potential therapeutic effects on neuropathic pain. The active compounds in *Rhodiola rosea*, primarily rosavin and salidroside, have been the focus of several research studies exploring their efficacy in different models of neuropathy. This literature review examines these studies, comparing their methodologies, dosages, outcomes, and active compounds to assess the effectiveness of *Rhodiola rosea* in neuropathic pain management.

Li et al. investigated the pain-relieving effects of rosavin in a mouse model simulating oxaliplatin-induced peripheral neuropathic pain. The study utilized an intraperitoneal dosage of 10 mg/kg and found that rosavin effectively alleviated cold allodynia, a common symptom of neuropathy, by interacting with 5-HT_{1A} receptors.

Table 1 Preclinical studies on plants used in treating neuropathy and neuropathic pain

Plant/Plant-based Therapy	Type/Model of Neuropathy/Pain	Dosage and Administration	Efficacy	Mechanism of Action	Future Considerations	Reference(s)
Citrullus colocynthis	Diabetic Neuropathy	100 and 300 mg/kg/day, oral and topical	Effective in treating symptoms of diabetic neuropathy	Anti-inflammatory and analgesic properties from cucurbitacin, flavonoids, alkaloids, phenolic acids	Evaluate efficacy in human trials	[18]
Curcuma longa	Diabetic Neuropathic Pain	10 to 50 mg/kg/day	Improved responses to mechanical, cold, and thermal stimuli	Anti-inflammatory properties of curcumin	Optimize dosage and treatment duration	[19]
Rhodiola rosea	Diabetic Peripheral Neuropathy	10 to 150 mg/kg/day	Alleviated cold allodynia and neuropathic pain symptoms	Antioxidative and anti-inflammatory effects of rosin and salidroside	Further clinical trials to validate findings	[20]; [21]; [22]
Licorice root	General neuropathic conditions	500 mg/day	Significant decrease in neuropathic pain symptoms	Anti-inflammatory and analgesic effects	Further research to explore full therapeutic potential	[23]
Allium sativum	Chronic Constriction Injury (CCI)-induced Neuropathic Pain	25–50 mg/kg for disulfide and 20–40 mg/kg for trisulfide	Attenuation of neuropathic pain through biochemical modulation	Activation of H2S-BDNF-Nrf2 signaling pathway	Determine optimal dosages and formulations	[24]
Brucine (from Strychnos nux-vomica)	Neuropathic Pain (CCI-induced Neuropathic pain)	Not specified (mice model)	Alleviates thermal hypersensitivity and mechanical allodynia	Inhibits tetrodotoxin-sensitive and tetrodotoxin-resistant sodium channels, reducing neuronal excitability	Further exploration into clinical applications	[25]
Licochalcone A (from Licorice)	Neuropathic pain (Formalin-induced pain model)	Not specified (animal model)	Inhibits pain responses in phases 1 and 2 of formalin test	Inhibits voltage-gated sodium (Nav) currents and Nav1.7 channel in DRG neurons	Develop Nav channel inhibitors as analgesic drugs	[26]
Cyclovirobuxine D (from Buxus microphylla)	Neuropathic pain (Paclitaxel-induced neuropathy)	Intraplantar or intraperitoneal (dose not specified)	Reduces pain via inhibition of Cav3.2 channels	Blocks voltage-gated calcium channels (Cav3.2 and Cav2.2) but mainly relies on Cav3.2	Explore clinical repurposing for pain management	[27]
Zerumbone (from Zingiber zerumbet)	Neuropathic pain (CCI-induced neuropathy)	10 mg/kg (intraperitoneal) in mice	Alleviates mechanical allodynia and thermal hyperalgesia	Modulates potassium channels and opioid receptors	Potential development of potassium channel-targeted drugs	[28]
Cuminic alcohol (Cuminum cyminum)	Noceptive and neuropathic pain (CCI-induced neuropathy)	200–400 mg/kg, i.p.	Significant analgesic effects	Involvement of opioid receptors and L-arginine/NO/cGMP pathway	Further exploration of long-term effects	[29]
Solanum virginianum	Neuropathic pain (CCI model)	100–200 mg/kg, p.o.	Reduces hyperalgesia and allodynia	Inhibition of calcium channels and restoration of antioxidant levels	Validation of extract components in clinical settings	[30]

This study provided mechanistic insights, suggesting that the serotonin pathway might be a critical target for rosavin's analgesic effects, with no adverse outcomes reported [20].

In a different approach, Yaping et al. studied the effects of *Rhodiola rosea* extract administered at 150 mg/kg/day on diabetic peripheral neuropathy in rats. The study observed several physiological changes, including decreased body weight, elevated blood glucose levels, and improved gastric functions. While the primary focus was not directly on pain, the improvements in peripheral symptoms associated with diabetes could indirectly influence neuropathic conditions [21].

Zheng et al. analyzed the effects of salidroside, another active compound, in dosages of 50 and 100 mg/kg/day. The research revealed that salidroside not only ameliorated hyperglycemia and insulin resistance but also notably alleviated neuropathic pain in diabetic rats. This purportedly occurred via the modulation of the AMPK-NLRP3 inflammation axis, suggesting that salidroside could be a crucial compound for addressing underlying inflammatory processes in diabetic neuropathy [22].

These studies collectively highlight the diverse therapeutic potential of *Rhodiola rosea* and its active compounds in treating neuropathic pain. The consistent observation of positive outcomes across various studies and models of neuropathy, coupled with the absence of significant negative effects, underscores *Rhodiola rosea*'s safety and efficacy. Future research could benefit from further clinical trials to validate these findings in human populations and to optimize dosages and treatment regimens, enhancing *Rhodiola rosea*'s application in neuropathic pain management.

Licorice root

Licorice root has garnered attention in the treatment of neuropathic pain due to its promising pharmacological properties. Particularly relevant to neuropathy are studies focusing specifically on its effects in alleviating symptoms of this condition.

One such study by Joshi & Tatke, explored the neuroprotective effects of licorice extracts in a rat model where neuropathic pain was induced through tibial and sural transection. The study administered 500 mg of licorice extract per day, observing a significant decrease in pain symptoms. This suggests that licorice extract might have potent analgesic and anti-inflammatory effects suitable for neuropathic pain management [23].

Allium sativum

Garlic (*Allium sativum*) has been the subject of numerous investigations exploring its potential therapeutic benefits in treating neuropathy, mainly leveraging its bioactive constituents like diallyl disulfide and diallyl

trisulfide. These studies collectively demonstrate promising outcomes regarding garlic's capacity to mitigate and potentially address symptoms linked with neuropathic pain.

Additionally, the investigations conducted by Wang et al. delved into the distinct components of garlic oil—diallyl disulfide and diallyl trisulfide—at different dosages (25 and 50 mg/kg for disulfide and 20 and 40 mg/kg for trisulfide) in chronic constriction-induced neuropathic pain models in rats. These studies indicated that both compounds could alleviate neuropathic pain by activating the H2S-BDNF-Nrf2 signaling pathway. The positive outcomes observed in these studies reinforce the notion that specific components of garlic oil can be highly effective in modulating neuropathic pain through biochemical pathways that promote neuronal health and pain reduction, without any noted negative effects [24].

In summary, garlic, particularly through its potent compounds diallyl disulfide and diallyl trisulfide, shows significant promise in treating neuropathic pain. The studies collectively suggest that garlic not only has potential as a pain management therapy but also might offer neuroprotective benefits in neuropathy treatment. However, the variance in efficacy related to different neuropathic models and garlic compounds underscores the complexity of its pharmacological effects and the need for further research to determine optimal dosages and formulations for specific types of neuropathic conditions.

Brucine (*Strychnos nux-vomica*)

Brucine, an alkaloid derived from the seeds of *Strychnos nux-vomica*, has shown promising results in alleviating neuropathic pain. In a study utilizing a chronic constriction injury (CCI) model in mice, brucine was observed to reduce both thermal hypersensitivity and mechanical allodynia. The specific mechanism involves the inhibition of tetrodotoxin-sensitive and tetrodotoxin-resistant sodium channels, which decreases neuronal excitability [25]. These findings highlight brucine's potential as a therapeutic agent for neuropathic pain management.

Future research should focus on further elucidating the clinical applications of brucine, particularly its efficacy in human subjects. Given its mechanism of action, exploring combination therapies with other analgesics may enhance its pain-relieving properties. Additionally, long-term safety studies are necessary to establish a comprehensive understanding of its therapeutic potential.

Licochalcone A (licorice)

Licochalcone A, a flavonoid found in licorice, has garnered attention for its analgesic properties in various pain models. In a study involving the formalin-induced pain model, this compound demonstrated a significant ability to inhibit pain responses in both phases of the formalin

Table 2 Clinical studies on plants used in treating neuropathy and neuropathic pain

Plant/ Plant-based Therapy	Type of Neuropathy/Pain	Dosage and Administration	Efficacy	Mechanism of Action	Future Considerations	Reference(s)
Crocus sativus	Chemotherapy-induced Peripheral Neuropathy; Carpal tunnel syndrome (CTS)	30 mg/day in two 15 mg doses; 30 mg of Crocus sativus + 600 mg of alpha-lipoic acid for 90 days (CTS)	Effective in relieving symptoms associated with CIPN and CTS	Antioxidative properties from safranal, crocin, crocetin, and picrocrocin	Further research on long-term effects and broader applications	(31,32)
Lavandula angustifolia	Diabetic Neuropathy	2.5 cc of 3% oil for massage	Significant reductions in neuropathic pain and improvements in QoL	Anti-inflammatory and analgesic properties from linalool and linalyl acetate	Explore additional chronic pain conditions	[33]
Capsaicin	Diabetic Peripheral Neuropathy	High-dose 8% patch	Effective pain relief in managing chronic neuropathic pain	Desensitization of pain receptors and depletion of substance P	Manage treatment regimens carefully due to potential adverse effects	[34]
Cannabis	Various neuropathic conditions	250 mg of cannabinoids per 3 fl. oz, topical	Significant reduction in intense, sharp, cold, and itchy pain	Interaction with cannabinoid receptors	Optimize dosage and administration	[35]

test [26]. The efficacy of licochalcone A is attributed to its action on voltage-gated sodium (NaV) channels, particularly NaV1.7, in dorsal root ganglion neurons.

The potential for developing NaV channel inhibitors as analgesic drugs based on licochalcone A is promising. Future studies should investigate the pharmacokinetics and safety profile of licochalcone A in clinical settings, as well as its interaction with other pain management therapies. This research could pave the way for novel therapeutic strategies in treating neuropathic pain.

Cyclovirobuxine D (*Buxus microphylla*)

Cyclovirobuxine D, extracted from *Buxus microphylla*, has been studied for its analgesic effects in neuropathic pain models, particularly in the context of paclitaxel-induced neuropathy [27]. This compound effectively reduces pain by primarily inhibiting Cav3.2 voltage-gated calcium channels, which play a critical role in pain signaling pathways. Studies have shown that cyclovirobuxine D significantly alleviates pain, providing a potential avenue for its use in pain management.

Further exploration into the clinical repurposing of cyclovirobuxine D could lead to innovative pain management options. Investigating the optimal dosing strategies and evaluating its efficacy in human trials will be crucial steps in assessing its viability as a therapeutic agent. Additionally, understanding its long-term effects and safety profile will enhance its clinical application.

Zerumbone (*Zingiber zerumbet*)

Zerumbone, a natural compound derived from *Zingiber zerumbet*, has shown significant analgesic properties in neuropathic pain models. In studies employing the CCI model in mice, zerumbone demonstrated the ability to alleviate mechanical allodynia and thermal hyperalgesia [28]. The compound’s mechanism of action involves modulation of potassium channels and interaction with opioid receptors, contributing to its pain-relieving effects.

Future research should focus on the development of zerumbone-based therapies targeting specific pain pathways. Investigating its pharmacological properties and potential side effects will be vital for its clinical application. Additionally, exploring combination therapies with other analgesics may enhance its effectiveness in managing neuropathic pain.

Cuminic Alcohol (*Cuminum cyminum*)

Cuminic alcohol, extracted from cumin seeds, has been explored for its analgesic effects in both nociceptive and neuropathic pain models [29]. It demonstrated significant analgesic effects, likely through the involvement of opioid receptors and the L-arginine/NO/cGMP signaling pathway. These findings suggest that cuminic alcohol

could serve as a promising candidate for developing new pain management therapies.

Further studies are necessary to explore the long-term effects and safety profile of cuminic alcohol in clinical settings. Investigating its efficacy in combination with other pain-relief strategies could enhance its therapeutic potential, paving the way for innovative treatments for various pain conditions.

Solanum virginianum

Solanum virginianum has been studied for its analgesic effects in neuropathic pain, demonstrating efficacy in reducing hyperalgesia and allodynia. With a dosage of 100–200 mg/kg administered orally, this plant-based therapy exhibits a mechanism involving the inhibition of calcium channels and the restoration of antioxidant levels [30]. These properties contribute to its potential as a natural analgesic.

Future studies should focus on validating the extract components in clinical settings to establish *Solanum virginianum*'s safety and effectiveness. Additionally, exploring its potential in combination therapies may enhance its overall analgesic effects, paving the way for novel treatment strategies in neuropathic pain management.

Clinical studies on plants used in treating neuropathy and neuropathic pain

Clinical studies are essential for validating the efficacy of plant-based therapies in human populations. These studies assess the safety, tolerability, and clinical outcomes of various plant extracts and their active components in treating neuropathic pain. Recent clinical trials have highlighted the promising effects of specific plants, such as *Crocus sativus* and *Lavandula angustifolia*, in managing conditions like carpal tunnel syndrome and diabetic neuropathy. The results indicate significant pain relief and improved patient quality of life, paving the way for further research into their long-term effectiveness and potential integration into standard treatment protocols for neuropathic pain management.

Crocus sativus

The utilization of *Crocus sativus* (saffron) for the treatment of neuropathy, particularly chemotherapy-induced peripheral neuropathy (CIPN), presents a compelling area of phytotherapeutic research. A study by [31], which examined the potency of crocin, a key active component of saffron, in managing CIPN symptoms.

Bozorgi et al. [31], carried out a randomized, double-masked, placebo-controlled clinical study targeting the usefulness of crocin on patients experiencing neuropathic pain due to chemotherapy. Patients were administered a daily dose of 30 mg of crocin, delivered in two 15 mg doses. The study demonstrated that crocin was

significantly effective in relieving the symptoms associated with CIPN. This effect is attributed to the pharmacological properties of the active compounds in saffron, namely safranal, crocin, crocetin, and picrocrocin. Notably, the study highlighted the lower adverse effects of crocin compared to conventional chemical agents, suggesting a favorable safety profile.

The potential of *Crocus sativus* (saffron) as a therapeutic agent extends beyond CIPN and into the management of conditions like carpal tunnel syndrome (CTS). Another study conducted by Passiatore et al. investigated the combined effects of alpha-lipoic acid (ALA) and saffron on patients with mild to moderate CTS, revealing a significant reduction in pain among those treated with the combination therapy [32]. These studies emphasize saffron's neuroprotective properties and its ability to provide symptomatic relief with minimal adverse effects. These findings underscore the potential for incorporating *Crocus sativus* into broader therapeutic strategies for various neuropathies, including CTS, highlighting the need for further research into its efficacy and applications in clinical settings.

Lavandula angustifolia

Lavandula angustifolia, commonly known as lavender, is renowned for its calming and therapeutic properties, especially in the form of essential oil. This review focuses specifically on studies that evaluate the efficacy of lavender oil in managing neuropathic pain among other conditions, highlighting the outcomes, dosage, and active compounds involved.

Rivaz et al. prominently examined the application of lavender oil for managing neuropathic pain. They explored the impact of aromatherapy massage with lavender essential oil on diabetic individuals experiencing neuropathic pain. The study employed a dosage of 2.5 cc of 3% lavender oil for the massage, reporting significant reductions in neuropathic pain and improvements in quality of life (QoL) two to four weeks post-intervention, with no side effects noted. The active compounds, linalool and linalyl acetate, known for their anti-inflammatory and analgesic properties, likely contributed to these outcomes [33].

These results indicate that the anti-inflammatory and calming attributes of lavender might be advantageous in diverse chronic pain situations, encompassing neuropathic pain.

Capsaicin

Capsaicin, the active compound in chili peppers known as 8-methyl-N-vanillyl-6-nonenamide, has been studied for its potential to alleviate neuropathic pain, particularly in conditions such as diabetic peripheral neuropathy and chemotherapy-induced neuropathy. This literature

review examines various studies focused on the application of capsaicin in different formulations and dosages, highlighting their outcomes and implications for treatment.

In a study by Leavell et al., a high-dose 8% capsaicin patch was evaluated for its effectiveness in treating painful diabetic peripheral neuropathy. The study reported that the patch provided effective pain relief, representing a significant step forward in managing chronic neuropathic pain. However, the authors noted potential adverse effects not directly from the patch but related to oral medication and polypharmacy, indicating a need for careful management of overall treatment regimens in these patients [34].

Cannabis

In recent research investigating plant-based treatments for neuropathy, Cannabis, particularly in its diverse extracts and formulations, emerges as a prominent subject of study. The effectiveness of Cannabis and its derivatives in alleviating symptoms of neuropathy has been investigated in several studies, focusing on different extracts such as cannabidiol (CBD) oil, inhaled cannabis, and plasma tetrahydrocannabinol (THC).

Xu et al. investigated the efficacy of topical cannabidiol (CBD) oil in managing peripheral neuropathy of the lower extremities. The dosage utilized was 250 mg of cannabinoids per 3 fluid ounces, with a specific emphasis on the cannabinoid compound group. The results demonstrated a notable decrease in severe pain, sharp pain, cold sensations, and itching, with no reported adverse effects, underscoring the potential safety and effectiveness of topical CBD oil for neuropathic pain [35].

Expanding on the exploration of THC, Wallace et al. conducted a secondary analysis derived from a randomized trial, concentrating on plasma tetrahydrocannabinol (THC) levels and their influence on pain alleviation in individuals with painful diabetic peripheral neuropathy. Here, a specific dosage of 50 mg/day of plasma THC was used. The study found that maintaining THC levels within a particular therapeutic window was positively associated with pain reduction, whereas deviations outside this window (both low and high levels) were associated with a lack of pain relief, underscoring the importance of dosage precision in the use of THC for therapeutic purposes [36].

Collectively, these studies underscore the therapeutic potential of cannabis-derived products in treating neuropathic pain, highlighting the importance of careful dosage adjustment and the choice of cannabis extract. While positive outcomes in pain reduction are well-documented, the studies also call attention to potential negative effects at inappropriate dosages, indicating the need for well-controlled treatment protocols and further

investigation into optimal therapeutic windows for cannabis use in neuropathy treatment.

Conclusion

These studies demonstrate that plant-based treatments can offer significant benefits in managing neuropathy and neuropathic pain. Plants like *Crocus sativus* have shown effectiveness in chemotherapy-induced neuropathy, while others like Cannabis have been effective across various neuropathic conditions. Most plants discussed have shown promising safety profiles and efficacy in both animal models and human clinical trials. However, while the results are encouraging, most studies call for further research to establish standardized dosages, long-term safety, and clearer mechanisms of action. There is indeed a necessity for larger, meticulously designed clinical trials to validate the findings from preliminary studies and to guarantee the reproducibility of results across diverse populations. Also, comparing the efficacy and safety of plant-based treatments against standard pharmacological therapies could help position these alternatives within current treatment paradigms.

Abbreviations

CIPN	Chemotherapy-induced Peripheral Neuropathy
CNS	Central Nervous System
QoL	Quality of Life
AMPK	AMP-activated Protein Kinase
NLRP3	NOD-, LRR- and pyrin domain-containing protein 3
THC	Tetrahydrocannabinol
CBD	Cannabidiol
H ₂ S	Hydrogen Sulfide
BDNF	Brain-Derived Neurotrophic Factor
Nrf2	Nuclear Factor Erythroid 2-related Factor 2

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Author contributions

S.O.O. and P.G.O. conceptualized the study and wrote the manuscript. S.O.O., P.G.O., I.O.O. and M.M.A. edited and checked the manuscript. All authors contributed to the article and approved the submitted version. All authors have read and agreed to the published version of the manuscript.

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Competing interests

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