

Review

Medicinal Plants and Phytochemicals in Neuropathic Pain: Mechanistic Insights and Therapeutic Potential

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Abstract

Neuropathic pain (NP) is a multifaceted condition with severe symptoms that have proven difficult to treat with conventional pharmacotherapies, which are hampered by partial efficacy and adverse effects. This review presents a comprehensive evaluation of the evolving scientific literature, demonstrating the pivotal role of medicinal plants and isolated phytochemicals as promising therapeutic alternatives for managing NP. This review also elucidates the complexity of NP pathophysiology, including peripheral and central sensitization, neuroinflammation, ion channel dysregulation, and oxidative stress. The article subsequently details a broad range of plant-derived compounds (e.g., curcumin, quercetin, and rosmarinic acid) and whole-plant extracts that have demonstrated efficacy in preclinical models, including chronic constriction injury (CCI), spared nerve injury (SNI), and chemotherapy-induced peripheral neuropathy (CIPN), through anti-inflammatory, antioxidant, ion channel modulatory, and neuroimmune mechanisms. In addition, we note that combining herbal therapeutics with conventional drugs yields synergistic effects that maximize analgesia and minimize side effects. Although there are good preclinical outcomes, further clinical research is required, including standardization, bioavailability issues, and the undeniable need for convincing human clinical studies. The review concludes that plant-based therapies can be considered a potential multi-target approach to NP. Further, the review underscores that the move to clinical practice requires advanced delivery platforms, well-designed clinical research, and a combination of strategies.

Keywords: neuropathic pain; chronic constriction injury; chemotherapy-induced peripheral neuropathy; spared nerve injury

1. Introduction

Neuropathic pain (NP) is a multifactorial, persistent condition that arises from dysfunction of the somatosensory nervous system, including peripheral nerves, the spinal cord, and the brain. However, unlike nociceptive pain, which results from tissue damage, somatic sensory pain, including NP, develops from nerve damage or altered pain processing. Fig. 1 depicts the multiple effects of oxidative stress in various parts of the brain [1,2]. Common symptoms include spontaneous pain, allodynia (pain in response to non-painful stimuli), and hyperalgesia (increased sensitivity to painful stimuli), all of which affect quality of life. Peripheral and central pathophysiological mechanisms include changes in ion channel expression, neuroinflammatory processes, glial cell activation, and the uneven distribution of excitatory and inhibitory neurotransmitters [3]. Since NP is a complex and heterogeneous disease, this condition is sometimes resistant to conventional pharmacotherapies. NP-related conditions include diabetic neuropathy, postherpetic neuralgia, spinal cord injury, chemotherapy-induced peripheral neuropathy (CIPN), and multiple sclerosis [4]. The signs and symptoms, and the level of severity, vary depending on the location and magnitude of the nerve damage.

The prevalence of NP affects approximately 7% to 10% of the global population and is especially high among patients with diabetes, cancer, and various neurological diseases [5]. The simultaneous drivers of both chronic diseases and longer life expectancy have led to a concomitant increase in the global effects of NP [6]. In addition to the logical somatic distress, NP is associated with substantial psychological morbidity, including anxiety, depression, and sleep disturbance. Socioeconomic implications are also significant, including high health expenditures, low productivity, and decreased quality of life [7,8]. Many NP cases remain undiagnosed or untreated, underscoring the need for more sensitive diagnostic tests and novel therapeutic approaches.

Conventional pharmacotherapies include antidepressants (e.g., duloxetine), anticonvulsants (e.g., gabapentin and pregabalin), opioids, and topical agents (e.g., lidocaine) [6]. Although these agents can help relieve some symptoms, they often provide only partial success. In addition, there are other negative side effects such as sedation, dizziness, and gastrointestinal disturbances, and dependence is possible [9]. These effects may compromise overall quality of life. Tolerance and high inter-individual variability in pharmacodynamic response also decrease long-term ef-

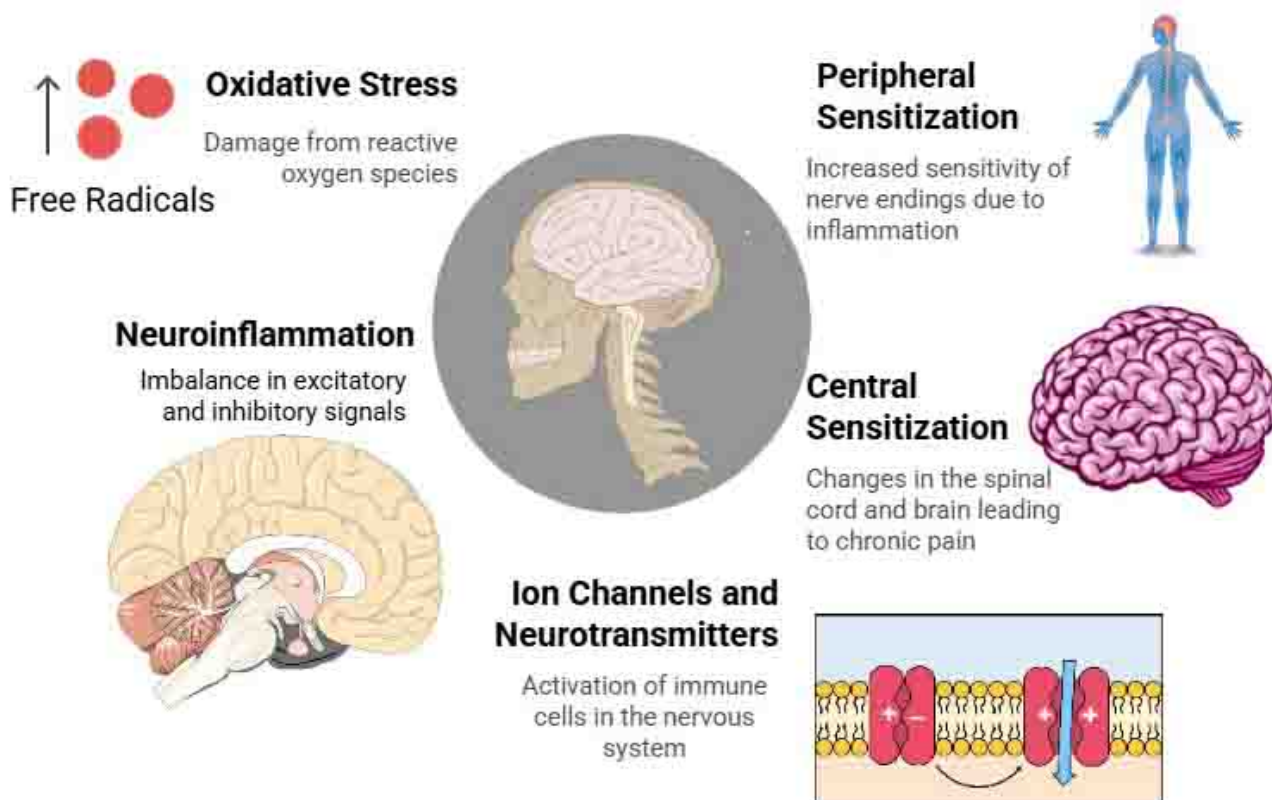


Fig. 1. Free radicals create oxidative stress, which has multiple phases of effects on the brain and nerves. Oxidative stress first causes neuroinflammation, which includes edema, aberrant signaling, and active immune cells. Next, oxidative stress promotes peripheral sensitization, which causes pain from light touch by making the nerves at the lesion site extremely sensitive to stimuli. Central sensitization, which is typified by elevated activity in the brain and spinal cord that intensifies pain signals, follows. Fig. 1 was generated from ChatGPT and then modified using Paint and Microsoft PowerPoint.

ficacy. Thus, considering these drawbacks, investigators are increasingly turning to other treatments, and specific modes of treatment using plant-derived and naturally occurring substances are of particular interest [10].

Isolation of natural compounds from plant-derived medicinal herbs has shown potential for managing NP because of their multi-target effects, antioxidant and anti-inflammatory actions, and relatively low toxicity [11]. Ayurvedic and traditional Chinese medicine (TCM) have long used formulations of herbal extracts to treat chronic pain disorders. Plant-derived agents such as curcumin, resveratrol, quercetin, and berberine have also shown efficacy in NP models in preclinical studies. These agents modulate ion channels, inhibit proinflammatory cytokines, and confer neuroprotection during oxidative stress [12]. Although numerous reviews discuss phytochemicals in NP, most remain descriptive compilations. The novelty of the present review lies in:

- Comparative assessment of strength and reproducibility of evidence.
- Integration of Ayurveda, TCM, Unani, and ethnomedicinal frameworks.

- Critical evaluation of safety, herb–drug interactions, and bioavailability challenges.
- Synthesis of mechanistic similarities across diverse plant families.

This review critically evaluates mechanistic, ethnopharmacological, and translational evidence for herbal and phytochemical interventions for NP, focusing on comparative efficacy, safety, and cultural context across global medical systems.

Literature Search Strategy and Selection Criteria

This narrative review summarizes current scientific evidence on medicinal plants, phytochemicals, molecular mechanisms, experimental models, and therapeutic outcomes for managing NP. A comprehensive literature search was performed using major scientific databases, including PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, Google Scholar, and SpringerLink. The literature search covered publications from approximately 2000 to 2026, with greater emphasis on studies published in the last decade to capture recent advances in phytochemical research and mechanistic understanding.

The search strategy included keyword combinations such as “neuropathic pain”, “medicinal plants”, “phytochemicals”, “plant extracts”, “bioactive compounds”, “anti-inflammatory mechanisms”, “oxidative stress”, “neuroprotection”, “microglial activation”, “transient receptor potential vanilloid 1 (TRPV1) modulation”, “nuclear factor kappa-B (NF- κ B) pathway”, “mitogen-activated protein kinase (MAPK) signaling”, “animal models of neuropathic pain”, “chronic constriction injury (CCI)”, “spared nerve injury (SNI)”, “chemotherapy-induced peripheral neuropathy”, and “diabetic neuropathy”. Boolean operators (AND/OR) were used to refine the search results.

The literature selection was based on predefined criteria. Studies that met the following criteria were included:

(i) investigated medicinal plants, plant extracts, isolated phytochemicals, or purified bioactive molecules with reported activity against NP; (ii) evaluated pharmacological effects using validated *in vitro*, *in vivo*, or mechanistic experimental models; (iii) provided information on molecular pathways, inflammatory mediators, modulation of oxidative stress, neuronal protection, or pain-related behavioral outcomes; (iv) were published as original research articles, relevant review articles, or authoritative scientific reports in peer-reviewed journals.

Studies that met any of the following criteria were excluded: (i) lacked experimental validation; (ii) focused exclusively on acute nociceptive pain and were not relevant to neuropathic mechanisms; (iii) did not provide sufficient information on plant identification, phytochemical constituents, or therapeutic outcomes; or (iv) were duplicate publications, conference abstracts, non-peer-reviewed sources, or articles unavailable in full text.

2. Pathophysiology of NP

NP results from a multifactorial interplay among peripheral nerve damage, central sensitization, neuroinflammation, and oxidative stress. Elucidating these processes provides a pathophysiological framework that guides treatment approaches, especially plant- or herb-based interventions [13]. Fig. 2 illustrates the general pathophysiology of NP.

2.1 Peripheral Sensitization Mechanisms

Peripheral sensitization is the heightened responsiveness of nociceptive afferent neurons after nerve injury. Damaged sensory axons release proinflammatory mediators, including prostaglandins, bradykinin, tumor necrosis factor- α (TNF- α), and interleukin-1 beta (IL-1 β), which lower the activation threshold of these neurons [14]. Concurrently, voltage-gated sodium channels (Nav1.7, Nav1.8), calcium channels, and transient receptor potential (TRP) channels are upregulated, further amplifying pain [15]. This shift in neurophysiological profile leads to spontaneous neuronal firing and heightened pain perception, even in response to benign stimuli [16].

2.2 Central Sensitization and Plasticity

Chronic pain leads to reorganization of spinal cord and cerebrum function, known as central sensitization. This reorganization is characterized by increased concentrations of excitatory neurotransmitters, particularly glutamate and substance P, a simultaneous decrease in the activity of inhibitory components using γ -aminobutyric acid (GABA) or glycine, and sustained synaptic excitation [17]. Microglial and astrocytic activation in the spinal cord, respectively, results in the release of cytokines and neurotrophic factors involved in persistent pain [18]. Collectively, these neuroplastic alterations can contribute to the prolonged duration of pain even after the initial tissue injury has healed and allow the pain chronification process and its possible extension to non-injured tissues to occur [19].

2.3 Neuroinflammation and Immune Crosstalk

Neuroinflammation is a primary pathogenic mechanism of NP and is facilitated by the activation of resident immune cells, most notably microglia, astrocytes, macrophages, and the many subtypes of T cells [20]. These immune effector cells secrete proinflammatory cytokines (e.g., interleukin-6 [IL-6], tumor necrosis factor- α (TNF- α), and interleukin-1) and chemokines, which, in turn, sensitize neurons and promote synaptic transmission [21]. Specifically, this crosstalk between the immune and nervous systems is mediated by Toll-like receptors (TLRs), particularly TLR4, and enhances pain perception. Persistent neuroinflammation remains central to the development and maintenance of NP. Therefore, inflammatory pathways are a promising therapeutic focus, and anti-inflammatory phytochemicals that have the potential to alter these mechanisms and, ultimately, decrease NP are being tested in preclinical trials [22].

2.4 Role of Ion Channels and Neurotransmitters

Pain signal generation and transmission are mediated by ion channels, including TRPV1, Nav1.7, Nav1.8, and Cav2.2 [23]. Pathological changes in the expression or function of these channels may trigger ectopic discharges, spontaneous pain, and hyperalgesia [24]. Excitatory effects are potentiated by neurotransmitters such as glutamate and substance P, which act as agonists, whereas GABA and glycine mediate inhibitory actions. In NP, the balance is strongly shifted toward the excitatory pathway, and inhibitory pathways are often downregulated [25]. These ion channels and the neurotransmitter systems that run through these pathways can be modulated by specific herbal mixtures, thereby restoring the system to its physiological state.

2.5 Oxidative Stress and Mitochondrial Dysfunction

Elevated reactive oxygen species (ROS) are linked to NP, subsequently leading to oxidative stress in the nervous system [26]. This hyperoxidative state causes mitochondrial dysfunction, DNA damage, and proinflammatory sig-

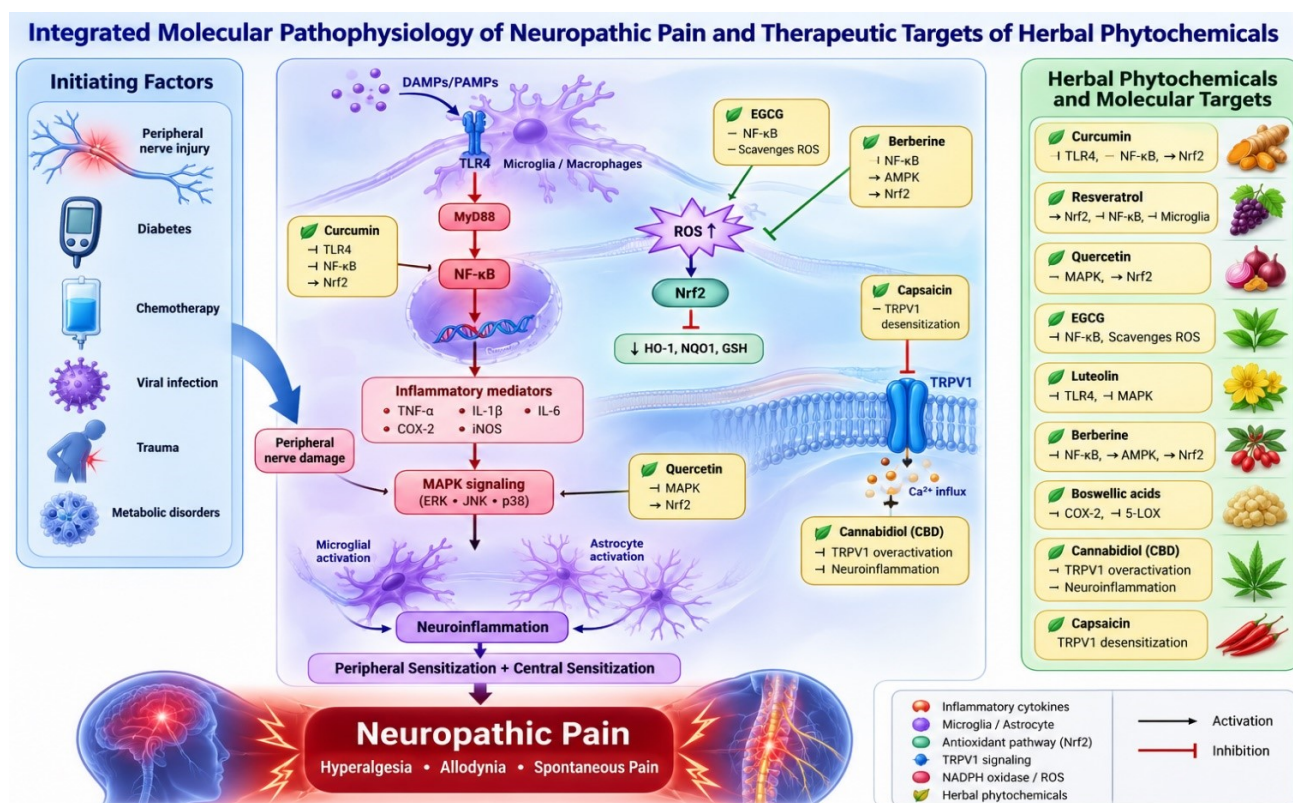


Fig. 2. General pathophysiology of neuropathic pain. DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; TLR4, Toll-like receptor 4; MyD88, myeloid differentiation primary response 88; ROS, reactive oxygen species; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; NQO1, NAD(P)H:quinone oxidoreductase 1; GSH, glutathione; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; IL-6, interleukin-6; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; AMPK, AMP-activated protein kinase; TRPV1, transient receptor potential vanilloid 1; NADPH, nicotinamide adenine dinucleotide phosphate; 5-LOX, 5-lipoxygenase; CBD, cannabidiol; EGCG, epigallocatechin gallate; CIPN, chemotherapy-induced peripheral neuropathy. Fig. 2 was generated from ChatGPT and then modified using Paint and Microsoft PowerPoint.

naling cascades. Mitochondrial impairment then decreases adenosine triphosphate in neuronal cells, increases energy metabolic deficits, and maintains chronic allodynia [27]. Therefore, the use of pharmacotherapies to boost ROS production and mitochondrial integrity, such as via the antioxidant effects of curcumin, quercetin, or resveratrol, holds potential as new treatment options in the management of NPs [28].

3. Diagnostic and Experimental Models of NP

NP remains a clinical enigma because of its multifactorial etiology, heterogeneous presentations, and poor response to treatment. Accurate diagnosis and modeling are critical for elucidating mechanisms and assessing novel therapies. This section outlines the available clinical diagnostic approaches and widely used experimental models for NP research [29].

Rodent NP models (CCI, SNI, partial sciatic nerve ligation [PSL], CIPN) provide essential mechanistic insights but do not fully capture the complexity of human NP.

Moreover, these models lack chronicity, emotional burden, drug-gene interactions, and comorbidity effects. Therefore, all findings herein should be interpreted as preclinical unless supported by human data.

3.1 Clinical Diagnostic Approaches

The diagnosis of NP in routine clinical practice relies on medical history, a thorough neurological examination, and validated pain estimation tools. Standardized questionnaires, including the Douleur Neuropathique 4 (DN4), Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), and PainDETECT [29,30], are frequently used to distinguish NP from other types of pain. Quantitative sensory testing (QST) is a relatively harmless procedure that determines magnitude thresholds for warmth, pressure, and vibration stimuli and provides functional data on sensory impairment [31]. Confirmation of peripheral nerve injury can be achieved through electrophysiological examinations such as nerve conduction studies and somatosensory evoked potentials [32]. When structural or metabolic abnormalities are suspected, imaging modalities, e.g., mag-

netic resonance imaging (MRI) and positron emission tomography (PET) scans, are used. Recently, researchers have stepped up efforts to develop composite biomarkers for NP [33]. Most interesting results show increased proinflammatory cytokines, glial markers, and particular microRNAs in both clinical and preclinical situations [34]. However, to date, no single gold-standard test or biomarker has been used, and the development of this area of research reminds us of the complexity of NP diagnosis [35,36].

3.2 Commonly Used Animal Models

NP uses experimental models, which are essential for studying pathophysiological mechanisms and assessing novel therapeutic regimens. Examples include physical, chemical, or disease-induced nerve injury, and all of these successfully model phenomena observed in human NP, such as allodynia and hyperalgesia, at both the central and peripheral levels.

3.3 Chronic Constriction Injury (CCI)

The Bennett and Xie CCI model. This model uses a loosely wrapped ligature around the sciatic nerve to cause partial nerve damage [37]. The occurrence of spontaneous nociceptive activity and tactile allodynia makes this protocol recapitulate the characteristics of human NP. The model also induces neuroinflammation and glial activation, allowing the evaluation of anti-inflammatory measures [38].

3.4 Spared Nerve Injury (SNI)

The SNI model involves two branches of the proximal sciatic nerve, which are restrained by sectioning and ligature of the nerve, and the third branch is left untouched. This procedure induces stable pain-like behaviors with only mild locomotor deficits in an experimental manner [39]. The SNI model has been indicated in the literature as one of the most reproducible and reliable preclinical models to investigate NP [40,41].

3.5 Chemotherapy-induced Peripheral Neuropathy (CIPN)

CIPN typically resembles the neuropathy caused by paclitaxel, oxaliplatin, vincristine, and other such agents [42]. These agents typically cause loss of sensation, spontaneous pain, and morphological damage to peripheral nerves. CIPN models have attracted increasing interest in recent years due to the growing clinical burden of NP associated with these agents [43,44]. These models elucidate mechanisms of drug-induced neurotoxicity, including oxidative stress, mitochondrial injury, and channel dysregulation [45].

3.5.1 Comparative Strength of Evidence

High-evidence compounds (multiple studies, mechanistic clarity):

- Curcumin, quercetin, epigallocatechin gallate (EGCG), rosmarinic acid, withanolides.

Moderate evidence:

- Diosgenin, bacosides, thymol. Low-evidence (single-study/single-mechanism):
- *Tabernaemontana catharinensis*, *Pterodon pubescens*, *Erythrina variegata*.

3.5.2 Mechanistic Similarities Across Plant Families

- Anti-inflammatory dominance: Curcumin, rosmarinic acid, boswellic acids, thymoquinone.
- Antioxidant dominance: EGCG, quercetin, bacosides, resveratrol.
- Ion channel modulation: Capsaicinoids (TRPV1), ginsenosides (Nav1.7), cannabinoids (CB1/CB2).
- Neuroregeneration: Withanolides, asiaticoside, hyperforin.

3.5.3 Critical Perspective

This comparative approach demonstrates that not all herbs possess equal translational potential. Plants supported by multiple independent laboratories using different models are more reliable than those with single-source data.

4. Overview of Medicinal Plants and Phytochemicals in NP

4.1 Selection Criteria and Literature Scope

Medicinal plants and phytochemicals were selected for demonstrated efficacy in preclinical or clinical models of NP. The literature included studies reporting apparent analgesic outcomes, replicable experimental protocols, and recognized active phytoconstituents. Most studies used rodent models of NP, such as CCI or CIPN, to assess the therapeutic activity of different plant-derived compounds. Only herbal products that showed reproducible results, mechanistic insight (e.g., anti-inflammatory or antioxidant effects), and low toxicity profiles were selected for this review (Table 1, Ref. [46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81]). The phytochemicals chosen ranged from polyphenols and alkaloids to terpenoids and glycosides, based on the quality of the evidence. Clinical trials were considered where available, particularly when they provided information on dose, tolerability, and mode of administration. Research on the synergistic action of plant extracts with standard analgesics was also considered useful for inclusion [46,47,48,82].

4.2 Classification: Whole Plants vs. Isolated Compounds

Extensive research has examined both crude plant extracts and identified phytochemicals for the management of NP. Whole plant extracts contain numerous active compounds that may interact to yield diverse therapeutic effects. These extracts contain terpenes, alkaloids, flavonoids, and saponins that synergistically modulate multiple pain signal-

ing systems. Conversely, certain substances can serve as distinct treatments. These extracts are easier to administer and investigate because each is typically standardized for purity. Conventional medicine typically employs whole plant extracts, often in the form of tinctures, powders, or decoctions. Medications derived from *Withania somnifera*, *Tinospora cordifolia*, or *Ocimum sanctum* may confer benefits in animal models of NP through mechanisms such as reducing oxidative stress or inhibiting proinflammatory cytokines.

In contrast to single-target medications, polypharmacology may also reduce the likelihood of tolerance development. The well-defined chemical components of pure substances make them common study tools in pharmacological investigations (e.g., quercetin in *Sophora japonica* or curcumin in *Curcuma longa*). These compounds exhibit reproducible pharmacodynamics and can be incorporated into innovative drug-delivery methods, such as liposomes or nanoparticles, to enhance bioavailability. To clarify the classification, Table 1 summarizes examples of both types used in NP models, and Table 2 presents their strengths and limitations.

4.3 Most Frequently Studied Families in NP

In herbal medicine and the management of NP, certain plant families are frequently examined for their high concentrations of phytochemicals and their historical application in medicinal practices. The families Lamiaceae, Zingiberaceae, Fabaceae, Solanaceae, and Asteraceae are most commonly used in experimental and clinical research. Examples of the Lamiaceae family include Rosemary (*Rosmarinus officinalis*), holy basil (*Ocimum sanctum*), and *Salvia miltiorrhiza*. These plants are abundant in essential oils, polyphenols, and flavonoids, exhibiting neuroprotective, antioxidant, and anti-inflammatory properties. Rosmarinic acid and carnosic acid from *Rosmarinus officinalis* have shown the capacity to inhibit microglial activation, subsequently leading to behavioral enhancements in NP models [48]. Likewise, *Salvia miltiorrhiza* is abundant in tanshinones and suppresses MAPK pathways and neuroinflammation [63].

The *Curcuma longa* (turmeric) and *Zingiber officinale* (ginger) family has been extensively studied for its potent anti-inflammatory and antioxidant properties. Curcumin, the main active compound in turmeric, has been reported to suppress NF- κ B activation and proinflammatory cytokines such as TNF- α and IL-6, thereby reducing neuropathic symptoms in CCI and SNI models [49,50,56]. Gingerols from *Zingiber officinale* target suppression of neuroinflammation receptors and exert analgesic effects, further supporting the extensive research on this family in NP studies [46,52].

Fabaceae, another significant family, includes *Glycyrrhiza glabra* (licorice) and *Mucuna pruriens*. The bioactive constituents glycyrrhizin and L-3,4-

Dihydroxyphenylalanine (L-DOPA) mediate anti-neuroinflammatory and dopaminergic mechanisms, respectively, thereby modulating the sensory and emotional aspects of pain [47,82]. *Licorice* extracts have been shown to alleviate pain behavior and reduce oxidative stress in neuropathic animals [47,82]. Capsaicin, a TRPV1 agonist derived from *Capsicum annuum*, a member of the Solanaceae family, initially induces a burning sensation and ultimately desensitizes the receptor, thereby diminishing afferent transmission of pain through peripheral nerve fibers [83]. Meanwhile, topical capsaicin preparations have also been clinically used to manage postherpetic neuralgia and diabetic neuropathy [84,85].

Furthermore, the Asteraceae family includes a significant presence of sesquiterpene lactones and flavonoids in *Arnica montana* and *Matricaria chamomilla*. These compounds are promising due to their neurosedative and anti-inflammatory activities. *Arnica montana* reduces inflammatory cytokines and provides neuroprotection in rodent models of neuropathy [86,87].

5. Pharmacological Mechanisms of Herbal Therapies in NP

5.1 Anti-inflammatory Actions

Inflammation is a major driver of the induction and maintenance of NP. Following peripheral nerve injury, the immune system is activated, releasing proinflammatory cytokines such as TNF- α , IL-1 β , and IL-6. These sensitized nociceptors result in persistent excitation of pain pathways even without reinjury. Sensitization mechanisms lead to chronic pain, characterized by both peripheral and central sensitization. Notably, numerous plant compounds have been shown to block inflammatory mediators, thereby alleviating pain in NP models. Curcumin, a key active component of *Curcuma longa*, has been extensively studied for its potential anti-inflammatory activity. Curcumin suppresses the NF- κ B signaling cascade, resulting in inhibition of TNF- α and IL-1 β production. Moreover, curcumin has demonstrated efficacy in considerably reducing hyperalgesia by suppressing the pain pathway in animal models of NP and by alleviating the post-inflammatory process through reduced inflammatory cytokines. Resveratrol, a stilbene present in grapes and berries, inhibits NF- κ B pathways and demonstrates substantial anti-inflammatory effects in pharmacological studies involving sciatic nerve injury, resulting in enhanced behavior and decreased glial activation [54].

Flavonoid-derived baicalin from *Scutellaria baicalensis* significantly reduces inflammation by inhibiting the TLR4/NF- κ B pathway. Notably, intraperitoneal administration of baicalin in CCI models lowered nerve edema, reduced cytokine expression, and enhanced nociceptive thresholds [55]. Another popular herbal medicine, *Withania somnifera* (ashwagandha) root extract, has shown significant neuroprotection in neuropathic models. Indeed, ashwagandha decreases spinal cord levels of TNF- α and

Table 1. Medicinal plants and phytochemicals investigated for neuropathic pain: classification, mechanisms, experimental models, and therapeutic outcomes.

Type	Plant/pure compound (source)	Experimental model	Mechanism of action	Therapeutic outcome	Ref.
Pure compound	Curcumin (<i>Curcuma longa</i>)	CCI, diabetic neuropathy	↓ TNF- α , ↓ IL-1 β , antioxidant activity	↓ allodynia and hyperalgesia	[49,50,51]
Extract	<i>Zingiber officinale</i> (Ginger)	SNI	COX inhibition, suppression of neuroinflammation	↓ pain sensitivity, ↓ inflammation	[46,52,53]
Extract	<i>Glycyrrhiza glabra</i>	CCI	NF- κ B inhibition, antioxidant	Nerve protection, ↓ oxidative stress	[47,54,55]
Extract	<i>Rosmarinus officinalis</i>	CIPN	ROS scavenging, cytokine suppression	Neuroprotection, ↓ neuroinflammation	[48,56,57]
Pure compound	Quercetin	CCI, other NP models	Microglial suppression, antioxidant activity	Reversal of neuropathic pain behavior	[58,59,60]
Pure compound	Diosgenin	CCI	↓ TNF- α , anti-inflammatory activity	↓ mechanical allodynia	[61,62]
Pure compound	Tanshinone IIA (<i>Salvia multi-orrhiza</i>)	SNL	MAPK inhibition, cytokine suppression	Reduced pain response	[63]
Extract	<i>Tabernaemontana catharinensis</i>	Mouse pain models	TRPA1 modulation, anti-inflammatory activity	Antinociceptive effect	[64]
Pure compound	Betanin (<i>Beta vulgaris</i>)	Cerebral ischemia-reperfusion injury; STZ-induced diabetes	Antioxidant activity; activation of Nrf2 signaling	Neuroprotective effects; ↓ oxidative stress	[65,66]
Extract	<i>Withania somnifera</i>	LPS/ β -amyloid-stimulated microglial cells; restraint-stress mice	↓ microglial activation and pro-inflammatory mediators; neuroprotective activity	↓ neuroinflammation; neuroprotection	[67,68]
Pure compound	Thymoquinone (<i>Nigella sativa</i>)	Diabetic neuropathy	Antioxidant and neuroprotective activity	Neuroprotection in diabetic neuropathy	[69]
Pure compound	EGCG (<i>Camellia sinensis</i>)	Dorsal root crush injury	↑ KAT6A, inhibition of pyroptosis	Improved sensory function recovery	[70]
Extract	<i>Bacopa monnieri</i>	CCI	Neuroprotective and antinociceptive effects	↓ allodynia and hyperalgesia	[71]
Extract	<i>Piper nigrum</i> / <i>Piper longum</i>	Paclitaxel-induced CIPN	↓ inflammatory and oxidative stress markers	↓ thermal hyperalgesia and neuropathic pain	[72]
Extract	<i>Tinospora cordifolia</i>	Paclitaxel-induced CIPN	Soluble epoxide hydrolase inhibition; antioxidant activity	↓ cold allodynia and mechanical hyperalgesia	[73]
Extract	<i>Boswellia serrata</i>	Oxaliplatin-induced CIPN	5-LOX and NF- κ B inhibition	↓ inflammatory neuropathic pain	[74,75]
Extract	<i>Hypericum perforatum</i>	Mouse CNS behavioral models	Modulation of central nervous system activity	CNS and antidepressant effects	[76]
Extract	<i>Centella asiatica</i>	A β 1–40-induced neurotoxicity in neuronal cells	Activation of antioxidative defence system	Neuroprotection against A β -induced neuronal toxicity	[77]
Pure compound	Cannabidiol (CBD) (<i>Cannabis sativa</i>)	CIPN	CB1/CB2 receptor modulation, microglial suppression	↓ pain scores, neuroprotection	[78,79]
Extract	<i>Pterodon pubescens</i>	PSNL	Vouacapan derivatives, cytokine modulation	↓ inflammation and pain	[80]
Extract	<i>Ocimum sanctum</i> (Tulsi)	Inflammatory and nociceptive animal models	Anti-inflammatory and analgesic activity	↓ inflammation and nociceptive pain	[81]

CCI, chronic constriction injury; SNI, spared nerve injury; CIPN, chemotherapy-induced peripheral neuropathy; ER, endoplasmic reticulum; HPA, hypothalamic-pituitary-adrenal; MAO, monoamine oxidase; CB1/CB2, cannabinoid receptor type 1/cannabinoid receptor type 2. ↓ = decrease and ↑ = increase.

Table 2. Medicinal plants and phytochemicals investigated for neuropathic pain: strengths, limitations, and relative translational potential.

Medicinal plant/source	Major phytochemical(s)	Mechanism(s) relevant to neuropathic pain management	Strengths	Limitations/challenges	Relative translational potential
<i>Curcuma longa</i> L. (turmeric)	Curcumin, desmethoxy-curcumin, and bis-desmethoxycurcumin	Modulation of NF- κ B, COX-2, TNF- α , IL-1 β , oxidative stress reduction, and inhibition of microglial activation	Extensive preclinical evidence; strong anti-inflammatory and antioxidant activity; good safety profile; multitarget action	Poor aqueous solubility, low oral bioavailability, and rapid metabolism; inconsistent clinical outcomes	High: promising with nanocarriers, liposomes, phospholipid complexes, and enhanced bioavailability systems
<i>Withania somnifera</i> (L.) Dunal (ashwagandha)	Withanolides (Withaferin A, Withanoid IV, Withanoid V)	Regulation of oxidative stress, neuroinflammation, GABAergic modulation, and neuronal regeneration	Neuroprotective activity; adaptogenic properties; improves nerve function and stress-related pain pathways	Limited neuropathic pain-specific clinical trials; dose standardization issues	Moderate–high: suitable for standardized extracts and combination therapies
<i>Boswellia serrata</i> Roxb.	Boswellic acids (AKBA)	5-lipoxygenase inhibition, reduction of inflammatory mediators, and inhibition of leukotriene synthesis	Strong anti-inflammatory profile; established use in inflammatory disorders	Limited direct evidence in neuropathic pain; poor water solubility	Moderate: potential in inflammatory neuropathy and adjunct therapy
<i>Cannabis sativa</i> L.	Cannabinoids (CBD, THC, CBG)	Activation of CB1/CB2 receptors, modulation of neurotransmitter release, and reduction in neuroinflammation	Demonstrated analgesic effects; clinical evidence available for some neuropathic pain conditions	Psych activity (THC), regulatory issues, tolerance, and adverse effects	High but regulated: strong clinical translation potential with controlled cannabinoid formulations
<i>Glycyrrhiza glabra</i> L. (licorice)	Glycyrrhizin, liquiritin, and glabridin	Antioxidant activity, inhibition of inflammatory cytokines, modulation of oxidative injury	Neuroprotective and anti-inflammatory properties; good traditional acceptance	Excessive use may cause mineralocorticoid-related adverse effects; limited neuropathic pain studies	Moderate: requires dose optimization and safety evaluation
<i>Ginkgo biloba</i> L.	Flavonoids (quercetin derivatives) and terpenoids (ginkgolides, bilobalide)	Antioxidant activity, mitochondrial protection, modulation of neuronal apoptosis	Evidence for neuroprotection and peripheral nerve function improvement	Complex extract composition; variable standardization	Moderate: potential for diabetic neuropathy and nerve regeneration approaches
<i>Camellia sinensis</i> (L.) Kuntze (green tea)	Epigallocatechin gallate (EGCG)	Antioxidant action, suppression of inflammatory pathways, and inhibition of oxidative neuronal damage	Strong antioxidant capacity; neuroprotective effects established	Low bioavailability; limited neuropathic pain clinical validation	Moderate: promising when combined with delivery enhancement strategies
<i>Zingiber officinale</i> Roscoe (ginger)	Gingerols and shogaols	TRPV1 modulation, COX/LOX inhibition, and antioxidant and anti-inflammatory effects	Natural analgesic potential; multiple pain-related pathways targeted	Limited neuropathic pain-specific evidence; pharmacokinetic limitations	Moderate: suitable as supportive therapy
<i>Piper nigrum</i> L. (black pepper)	Piperine	Enhances bioavailability of other phytochemicals; anti-inflammatory and antioxidant activity	Improves absorption of co-administered compounds; synergistic potential	Limited independent analgesic evidence; possible gastrointestinal irritation	Moderate–high: valuable as a bioavailability enhancer in phytopharmaceutical combinations
<i>Tinospora cordifolia</i> (Willd.) Hook.f. & Thomson (Guduchi)	Tinosporaside, alkaloids, and diterpenoids	Immunomodulation, antioxidant effects, and suppression of inflammatory cytokines	Traditional importance; immunoprotective and neuroprotective effects	Limited molecular evidence in neuropathic pain; quality variation	Moderate: requires standardized extracts and mechanistic studies
<i>Mucuna pruriens</i> (L.) DC.	L-DOPA, flavonoids, and phenolics	Dopaminergic modulation, antioxidant activity, and neuroprotection	Established neurological relevance; antioxidant protection	Mainly studied in Parkinson's disease; neuropathic pain evidence limited	Moderate: possible role in neuropathic pain associated with neurodegeneration
<i>Centella asiatica</i> (L.) Urban	Asiaticoside, madecassoside, and asiatic acid	Neuroregeneration, antioxidant activity, and enhancement of neuronal growth factors	Promotes nerve repair and cognitive/neural protection	Limited controlled neuropathic pain studies	Moderate–high: attractive candidate for nerve regeneration-based therapy

Table 2. Continued.

Medicinal plant/source	Major phytochemical(s)	Mechanism(s) relevant to neuropathic pain management	Strengths	Limitations/challenges	Relative translational potential
<i>Aloe vera</i> (L.) Burm.f.	Aloin, aloe-emodin, and polysaccharides	Anti-inflammatory, antioxidant, and modulation of cytokine pathways	Good safety profile; wound-healing and anti-inflammatory benefits	Limited systemic neuropathic pain evidence	Low–moderate: more suitable for topical neuropathic pain-associated conditions
<i>Salvia officinalis</i> L. (sage)	Rosmarinic acid, flavonoids, and essential oils	Antioxidant activity, modulation of inflammatory mediators, and ion channels	Strong phytochemical profile; antioxidant neuroprotection	Limited <i>in vivo</i> neuropathic pain validation	Moderate: requires further pharmacological evaluation
<i>Nigella sativa</i> L. (black cumin)	Thymoquinone	Suppression of NF- κ B, antioxidant effects, modulation of opioid pathways	Strong anti-inflammatory and neuroprotective activity; multiple animal studies	Limited human neuropathic pain trials; bioavailability concerns	Moderate–high: promising candidate for standardized formulations
<i>Hypericum perforatum</i> L. (St. John's Wort)	Hypericin, hyperforin, and flavonoids	Modulation of serotonin, dopamine, and inflammatory pathways	Evidence of neuropathic pain and mood-associated pain disorders	Drug interactions; variable active constituent levels	Moderate: potential but requires strict standardization
<i>Vitis vinifera</i> L. (grape seed)	Proanthocyanidins and resveratrol	Antioxidant activity, inhibition of oxidative nerve damage, and anti-inflammatory effects	Strong free radical scavenging ability; vascular protective effects	Limited direct neuropathic pain studies	Moderate: potential in diabetic neuropathy management
<i>Berberis aristata</i> DC./berberine-containing plants	Berberine	AMPK activation, inhibition of inflammatory cytokines, and antioxidant activity	Broad pharmacological activity; emerging evidence in diabetic neuropathy	Poor absorption; gastrointestinal effects	Moderate–high: suitable for nanoformulation-based approaches
AKBA, 3-O-Acetyl-11-keto- β -boswellic acid; THC, Δ^9 -Tetrahydrocannabinol (Delta-9-tetrahydrocannabinol); CBG, Cannabigerol; L-DOPA, Levodopa (L-3,4-dihydroxyphenylalanine); GABAergic, Gamma-Aminobutyric Acid (GABA)-ergic.					

IL-6 and abolishes pain-like behaviors [83]. Quercetin, a plant flavonoid found in onions and apples, inhibits proinflammatory signaling pathways such as MAPK and NF- κ B, thereby reducing the release of pain-causing cytokines. Intraperitoneal administration of quercetin in rat models of sciatic nerve injury alleviated pain responses and inflammation [84]. Analogously, *Glycyrrhiza glabra* (licorice root) extract produced significant reductions in IL-1 β and TNF- α levels in animals with peripheral nerve injury, thereby supporting the use of licorice root extract in inflammatory neuropathies [86].

Boswellia serrata, or Indian frankincense, contains boswellic acids that suppress COX-2, an enzyme central to inflammation. Animal studies have demonstrated the effectiveness of Indian frankincense against thermal hyperalgesia and inflammatory markers after nerve injury [87]. Combining herbal substances with traditional drugs has also been effective.

5.2 Antioxidant and Free Radical Scavenging

Oxidative stress is a process involved in the pathophysiology of NP. Oxidative stress is initiated by elevated formation of ROS and the inability of the body to neutralize ROS through internal antioxidants. Overproduction of ROS can lead to oxidative damage to neuronal membranes, proteins, and DNA, resulting in neuroinflammation, ion channel dysfunction, and neuronal hyperexcitability. Herbal molecules with antioxidant action are critical in protecting neurons and preventing NP by scavenging free radicals and augmenting the action of antioxidant enzymes [56,88,89].

The antioxidant effects of curcumin have significantly reduced ROS and increased antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). A study utilizing a rat CCI animal model showed that curcumin improved neuronal structure and increased malondialdehyde (MDA), a significant marker of lipid peroxidation [90]. Quercetin demonstrated efficacy as a neuroprotective drug by decreasing MDA levels and enhancing SOD enzyme activity in spinal cord tissue, while also alleviating neuropathic symptoms in sciatic nerve ligation models [59].

Rosmarinic acid, a polyphenol in *Rosmarinus officinalis*, exhibited antioxidant effects in rats with neuropathy by lowering nitrosative stress and increasing glutathione, thereby reducing allodynia and hyperalgesia [56].

Diosgenin, a steroidal saponin derived from *Dioscorea* spp., has demonstrated efficacy in restoring mitochondrial function and diminishing oxidative stress in damaged nerve tissues [88]. Flavonoids such as baicalein and kaempferol safeguard neurocells from oxidative stress by directly neutralizing intracellular radicals and indirectly by promoting Nrf2-mediated activation of intrinsic antioxidant defense mechanisms [91,92]. *Withania somnifera* extract improved levels of endogenous antioxidants in dorsal root ganglion neurons and spinal

cord tissue, thereby inhibiting ROS-induced apoptosis and enhancing pain thresholds [67,68].

5.3 Modulation of Ion Channels and Receptors (e.g., TRPV1, Nav1.7)

Modulation of ion channels and receptors is essential to the pathogenesis and management of NP. Nociceptive transmission is mediated by the activation of voltage-gated sodium channels (e.g., Nav1.7), voltage-gated calcium channels, and TRPV1 receptors in peripheral and central neurons. Herbal remedies have been shown to modulate these targets, thereby reducing pain [85,89,93,94].

TRPV1 is a non-selective cation channel primarily expressed in nociceptive neurons. TRPV1 is stimulated by heat, protons, and vanilloids such as capsaicin, leading to depolarization and pain transmission. Various herbal constituents have been demonstrated to activate TRPV1. Capsaicin, a naturally occurring compound in *Capsicum annum*, activates and desensitizes TRPV1 and is a commonly used topical agent for local NP [83,85]. Similarly, eugenol, obtained from *Syzygium aromaticum*, is a TRPV1 antagonist that exhibits analgesic effects in animal models [93].

Voltage-gated sodium channels, especially Na1.7, Na1.8, and Na1.9, are essential for generating action potentials in sensory neurons. Components of herbal medicines, such as ligustilide from *Angelica sinensis*, have been shown to inhibit NF- κ B-mediated chemokine production in spinal astrocytes, thereby decreasing neuronal excitability and NP characteristics in spinal nerve ligation models [95]. Diosgenin has also been reported to reduce oxidative stress and inflammatory responses in diabetic neuropathy, which is associated with antinociception [88].

Cannabinoids from *Cannabis sativa*, especially cannabidiol (CBD), also modulate TRPV1 and voltage-gated channels. CBD suppresses TRPV1 activation and the influx of sodium and calcium ions in nociceptor nerve cells, providing pain relief without intoxicating effects [79]. Berberine derivatives are protoberberine alkaloids from Berberis plants that downregulate TRPV1 expression and block calcium channels, thereby producing pain relief [94].

Moreover, herbals such as paeoniflorin from *Paeonia lactiflora* attenuate neuroinflammatory responses and suppress microglial activation, thereby alleviating mechanical allodynia [96]. Salidroside from *Rhodiola rosea* L. alleviates pain by regulating Th17/Treg imbalance through the AMPK/SIRT1 signaling pathway [97].

5.4 Inhibition of Cytokines and Microglial Activation

Neuroinflammation is a hallmark of NP, characterized by upregulation of proinflammatory cytokines and activation of microglia and astrocytes in the spinal cord and dorsal root ganglia. It is reasonable to expect that plant constituents could inhibit neuroimmune pathways, especially by preventing cytokine secretion and glial activation,

thereby offering a highly promising therapeutic intervention for the management of NP.

The effects of certain herbs are mediated by inhibiting the secretion of the major proinflammatory cytokines, TNF- α , IL-1 β , and IL-6. For example, in neuropathic models, curcumin robustly attenuated TNF- α and IL-1 β expression by inhibiting the NF- κ B signaling pathway, thereby reducing thermal hyperalgesia and mechanical allodynia [51]. Similarly, quercetin, a flavonoid abundant in most plants, prevents the release of proinflammatory cytokines and instead induces the production of anti-inflammatory cytokines, including IL-10, which contributes to the analgesic profile [59].

Resveratrol, a phenol isolated from *Polygonum cuspidatum*, has been shown to inhibit NP by preventing microglial activation and the generation of IL-1 β and TNF- α in the spinal cord by inhibiting the TLR4/NF- κ B signaling pathway [98]. Likewise, baicalin from *Scutellaria baicalensis* was observed to inhibit pain behavior in animal models by regulating the IRF4/CCL17 signaling pathway, thereby mitigating the release of proinflammatory mediators [99].

Paeoniflorin, an active constituent of *Paeonia lactiflora*, has potent neuroimmune modulatory effects that reduce microglial and astrocytic activation in the spinal cord by suppressing p38 MAPK/NF- κ B signaling and reducing the production of proinflammatory cytokines such as TNF- α and IL-1 β , thereby lowering IL-6 levels and increasing pain thresholds [96]. Similarly, tanshinone IIA, isolated from *Salvia miltiorrhiza*, exhibits strong anti-inflammatory effects by inhibiting astrocytic and microglial activation and NF- κ B and MAPK signaling, and by modulating transcription [63].

In diabetic neuropathy models, RA reduced expression of the inflammatory markers COX-2 and IL-6 and suppressed glial cell activity in the spinal cord, implicating RA in the inhibition of neuroinflammation [56,57].

Some plant-derived molecules regulate glial cell phenotypes, shifting the phenotypes from a proinflammatory (M1) to an anti-inflammatory (M2) state. EGCG, found in green tea, exerts neuroprotective effects by upregulating KAT6A and inhibiting pyroptosis, thereby promoting sensory functional recovery [70]. Berberine also reportedly alleviates diabetic neuropathic pain by modulating TRPV1 through the PKC signaling pathway [94].

5.5 Synergistic Effects With Conventional Drugs

Combining herbal compositions with conventional medications can enhance drug efficacy and reduce harmful side effects in the treatment of NP. When combined with drugs such as gabapentin, pregabalin, or non-steroidal anti-inflammatory drugs (NSAIDs), phytochemicals have been reported to exert synergistic effects through multiple pain pathways [100,101].

Quercetin, a flavonoid found in apples and onions, increases the effect of carbamazepine by suppressing inflammatory cytokines and modulating GABA-dominated transmission [100]. Combining morphine with curcumin, thymoquinone, CBD, and resveratrol enhances the analgesic efficacy of morphine and potentiates its pain-relieving effects. While morphine alone may suppress glial activation and delay the development of opioid tolerance, curcumin exerts similar effects by inhibiting microglial and astrocytic activation, reducing neuroinflammation, and attenuating oxidative stress. Consequently, co-administration of curcumin with morphine may produce synergistic analgesia while delaying the onset of opioid tolerance [102].

The drug combination (NSAID)/(hesperidin and/or diclofenac) caused greater pain inhibition with fewer gastrointestinal side effects, a characteristic of NSAIDs [103].

Panax ginseng active principles, ginsenosides, potentiate the analgesic effects of amitriptyline in diabetic neuropathy, possibly by modulating the levels of norepinephrine and serotonin [104]. Combinatorial effects of rosmarinic acid in co-treatment with pregabalin in reducing pain behaviors have also been described, due to its modulatory effects on voltage-gated calcium channels [57].

Notably, such combinations may also reduce the required dose of standard drugs, thereby lowering systemic toxicity. Combinations such as mangiferin with low-dose gabapentin have shown efficacy comparable to high-dose monotherapy and improved safety [101].

5.6 Safety and Herb–Drug Interaction Risks

While medicinal plants and phytochemicals are promising drug candidates for NP management, clinical applications should be evaluated to determine toxicity, pharmacokinetics, dosing, and phytochemical composition. Unlike standard drugs, herbal preparations may contain multiple bioactive components that can interact with physiological pathways or other drugs (e.g., antibiotics). Safety, standardization, and herb–drug interactions should be investigated for long-term NP therapy with herbs and phytochemicals.

A major safety concern with herbal medicines is organ-specific toxicity, particularly hepatotoxicity. Some commonly used medicinal plants for anti-inflammatory and analgesic purposes have been linked to liver injury when ingested at high doses or for prolonged periods. *Polygonum multiflorum* (He Shou Wu) is traditionally used for neuroprotective and anti-inflammatory purposes but has been associated with idiosyncratic hepatotoxicity, possibly related to anthraquinone derivatives and individual genetic risk factors that affect hepatic metabolism. *Boswellia serrata*, which has anti-inflammatory activity by inhibiting 5-lipoxygenase (5-LOX) and NF- κ B signaling, should be used with caution, as concentrated extracts can cause gastrointestinal disturbances and, in some cases, liver enzyme changes. These findings highlight the need for standardized

extracts, quality control of raw materials, and monitoring of hepatic biomarkers during long-term use.

Cardiovascular safety concerns have also been reported with some herbal agents. *Glycyrrhiza glabra* (licorice), which contains the bioactive compound glycyrrhizin, may induce mineralocorticoid-like effects by inhibiting 11 β -hydroxysteroid dehydrogenase type 2, resulting in sodium retention, potassium loss, hypertension, and fluid imbalance. These effects may be clinically relevant in NP patients who frequently receive concomitant medications for diabetes, cardiovascular disorders, or hypertension. Thus, excessive consumption of licorice-containing formulations should be avoided in individuals with cardiovascular risk factors.

Herbal agents may pose risks due to:

- Hepatotoxicity (*Polygonum multiflorum*, *Boswellia serrata*)
- Cardiovascular effects (*Glycyrrhiza glabra*)
- Sedation/cognitive effects (CBD)
- Cytochrome P450 (CYP450)/P-glycoprotein (P-gp) modulation:
 - Curcumin $\rightarrow$ CYP3A4 inhibition
 - Quercetin $\rightarrow$ CYP2C9 inhibition
 - Berberine $\rightarrow$ CYP2D6 inhibition

Potential interactions:

- $\uparrow$ opioid and benzodiazepine toxicity
- $\downarrow$ effectiveness of antidepressants
- $\uparrow$ bleeding risk with NSAIDs and warfarin

While medicinal plants and phytochemicals are significant therapeutic agents, their long-term clinical translation will be affected by their pharmacokinetic profiles and safety. A key mechanism of herb–drug interactions is the modulation of CYP450 enzymes (CYP3A4, CYP2C9, CYP2D6, and CYP2C19), which are responsible for the metabolism of most drugs studied in clinical practice. Several phytoconstituents can affect or interfere with these enzymes, altering plasma drug levels and influencing human drug response. Studies on curcumin have shown that it can inhibit CYP3A4, CYP2C9, and P-gp and, thus, may increase exposure to co-administered drugs with very short therapeutic windows. Piperine, as a common bioenhancer, inhibits CYP3A4 and intestinal P-gp in the blood and increases the bioavailability of several drugs, but it also increases the risk of adverse interactions. Herbal medicines can also interact with enzymes by activating their metabolism, which can alter drug clearance and reduce therapeutic effect. In NP management, we see the potential for interactions between these drugs since patients often receive multiple drugs such as opioids, antidepressants, anticonvulsants, and anti-inflammatory drugs. In addition, drug exposure due to interaction with phytochemicals at the same time may result in high rates of sedation or bleeding, hepatotoxicity, or a decrease in analgesic response. Other safety issues related to medicinal plants in-

clude pharmacokinetic effects in addition to toxicity. Some botanicals have organ-specific toxicity in some cases. *Polygonum multiflorum* has been associated with hepatotoxicity in susceptible individuals, and sustained *Glycyrrhiza glabra* (licorice) use may lead to mineralocorticoid-like effects with high blood pressure, hypokalemia, and cardiovascular complications due to glycyrrhizin-mediated inhibition of 11 β -hydroxysteroid dehydrogenase. CBD is studied and has been shown to have analgesic and neuroprotective effects but also has sedation and cognitive disorders, gastrointestinal disturbances, and significant CYP3A4 and CYP2C19 interactions.

Furthermore, adulteration, variability in phytochemical composition, and extraction methods pose significant risks to the safety and reproducibility of herbal products. Thus, future research on phytochemicals for NP should include pharmacokinetic profiling, CYP450 interaction studies, transporter assays, toxicity assessments, and well-designed clinical trials. Additionally, network pharmacology, molecular docking, and physiologically based pharmacokinetic (PBPK) modeling could help predict herb–drug interactions and support the development of safer plant-derived therapeutics [105,106,107].

6. Highlighted Medicinal Plants and Compounds

This section discusses plants and phytochemicals that have frequently been reported to be useful in alleviating NP. These compounds have been examined in preclinical models to elucidate their mechanisms of action, including anti-inflammatory, antioxidant, pro-nociceptive inhibition, and neuroprotective effects. The subsequent subsections will delineate the most promising among them. Table 3 (Ref. [47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,88,108,109]) represents the medicinal plants and phytocompounds used in the management of NP.

7. Challenges and Limitations

7.1 Standardization and Dosing Issues

The major issue with plant remedies used to treat NP is a lack of standardization. Herbal products usually vary in composition due to differences in cultivation, harvesting, and processing methods. This variability reduces reproducibility and effectiveness. Moreover, most herbal preparations do not quantify bioactive constituents, making it difficult to determine an appropriate dosage for clinical use [110].

For example, the therapeutic efficacy of curcumin is dose-dependent, yet curcumin concentrations can vary widely across turmeric preparations, resulting in differences in efficacy in experimental and clinical settings [111]. Gingerols in *Zingiber officinale* take different forms depending on the conditions during drying and storage, which in turn affect their anti-inflammatory activity [112].

Table 3. Key medicinal plants and phytochemicals in neuropathic pain management.

Plant/compound	Key bioactive components	Mechanism of action	Model/outcome	Ref.
<i>Curcuma longa</i> (turmeric)	Curcumin	Downregulates NF- κ B; reduces TNF- α and IL-1 β ; anti-inflammatory and antioxidant	CCI model; reduced pain hypersensitivity	[49,50,51,108]
<i>Zingiber officinale</i> (ginger)	Gingerols, shogaols	Inhibits COX/LOX; suppresses neuroinflammation	SNI model; reduced mechanical/thermal hypersensitivity and neuroinflammation	[52,53]
<i>Glycyrrhiza glabra</i> (licorice)	Glycyrrhizin, flavonoids	Anti-inflammatory and antioxidant effects; reduces pro-inflammatory cytokines	CCI model; reduced allodynia and inflammatory markers	[47,54,55]
<i>Rosmarinus officinalis</i>	Rosmarinic acid	Antioxidant; reduces oxidative stress and microglial activation	NP models; improved neurobehavioral outcomes	[48,56,57]
<i>Salvia miltiorrhiza</i>	Tanshinone IIA	Inhibits MAPK signaling; suppresses glial activation and inflammation	SNL model; reduced mechanical hyperalgesia	[63]
<i>Beta vulgaris</i> (beetroot)	Betanin	Antioxidant activity; activation of Nrf2 signaling; neuroprotective effects	Cerebral ischemia-reperfusion injury and STZ-induced diabetes models; reduced oxidative stress and neuronal injury	[65,109]
Quercetin	Quercetin	Inhibits IL-1 β and TNF- α ; modulates AMPK/MAPK; antioxidant	CCI and other NP models; improves pain symptoms	[58,59,60]
Diosgenin	Diosgenin	Suppresses cytokines; modulates oxidative stress	CCI and diabetic neuropathy models; reduces mechanical and thermal hyperalgesia	[61,62,88]
<i>Tabernaemontana catharinensis</i>	Voacangine-like alkaloids	TRPA1 modulation; anti-inflammatory and antinociceptive activity	Mouse pain models; analgesic effect	[64]

HMGB1, high-mobility group box 1; NP, neuropathic pain.

7.2 Lack of Human Trials and Translational Research

Despite strong evidence from preclinical models, many herbal interventions have not advanced to human clinical trials. The so-called translational gap prevents the integration of phytotherapy into conventional medical practice. Research is limited to rodent models of neuropathy, usually CCI or SNI, which do not adequately capture the complexity of neuropathic disease in humans [113].

There is also the challenge posed by metabolic differences between humans and rodents. Plant extracts, including resveratrol and diosgenin, show activity in rodents but lack pharmacokinetic and safety data in humans [114]. Ethical, logistical, and government policy considerations also hinder the conduct of large randomized controlled trials [64].

7.3 Regulatory and Quality Control Barriers

Herbal products also tend to evade strict pharmaceutical regulations, resulting in inconsistent purity and potency and an increased risk of safety issues. The clinical validity of these products is also lacking due to inconsistent labeling, heavy metal or adulterant contamination, and a lack of Good Manufacturing Practices (GMP) [115].

Regulatory systems differ around the world. Indeed, clinical confirmation is mandatory in some countries, whereas unstandardized herbal supplements are allowed to be sold over the counter in others. The international ad-

vancement of evidence-based phytotherapy has not been well unified in terms of policy [116].

7.4 Bioavailability and Pharmacokinetics Challenges

Many plant-derived compounds possess limited bioavailability, undergo extensive first-pass metabolism, and are poorly absorbed, which impedes their therapeutic applications. Examples of foods with seemingly beneficial compounds that undergo extensive first-pass metabolism include curcumin, which requires considerable formulation work to enhance its systemic availability (e.g., liposomes, nanoparticles, or the inclusion of adjuvants such as piperine) [117].

Similarly, quercetin and genistein are rapidly conjugated in the liver, and intact molecules are largely converted into inactive metabolites before reaching their target tissues. Without comprehensive pharmacokinetic profiling, their observed pharmacological efficacy may be overestimated, leading to an inaccurate assessment of their therapeutic potential.

7.5 Implications for Future Research

While substantial evidence supports animal studies, there is a paucity of information from human clinical studies. Moreover, standardized clinical trials are needed to ascertain the efficacy, dosage, safety, and long-term effects of these herbal compounds. Many of these phytochemicals

exhibit low bioavailability and high metabolic rates. Innovative formulations, including nano-carriers, patches, and liposomes, have the potential to improve outcomes. Research should also focus on understanding drug–herb interactions, genetic responses in pharmacology, and the principles of personalized herbal therapy. Consistent extraction methods, validated biomarkers, and standardized pharmacological protocols will be essential for translating laboratory models of herbal medicines into clinical practice.

Finally, determining an appropriate dosing regimen and assessing long-term safety in people are challenging.

8. Clinical Evidence, Randomized Controlled Trials, and Meta-Analyses

The clinical translation of medicinal plants and phytochemicals for NP management is an emerging and rapidly expanding field of research. While animal studies have extensively demonstrated the ability of plant-derived compounds to modulate neuroinflammation, oxidative stress, ion channels, and neuroimmune signaling pathways, clinical evidence remains comparatively limited. Among the investigated phytochemicals, capsaicin, CBD, curcumin, palmitoylethanolamide (PEA), *Boswellia serrata* derivatives, alpha-lipoic acid (ALA), and botanical preparations containing *Withania somnifera*, *Crocus sativus*, and other medicinal plants have demonstrated promising outcomes in patients with peripheral neuropathies [53,118].

Capsaicin, a bioactive alkaloid derived from *Cap-sicum annuum* that primarily acts by activating and desensitizing TRPV1 on nociceptive fibers, has been extensively validated in clinical settings. Moreover, high-concentration capsaicin (8% patch) has been extensively evaluated in patients with peripheral NP, including diabetic peripheral neuropathy and post-herpetic neuralgia. Randomized controlled trials have demonstrated significant reductions in pain intensity, improved quality of life, and prolonged analgesic effects after a single topical application compared with placebo [89].

CBD, derived from *Cannabis sativa*, has also attracted clinical interest for its interactions with cannabinoid receptors (CB1/CB2), modulation of microglial activation, and suppression of inflammatory cytokines. Preliminary clinical studies suggest benefits for NP conditions; however, variations in formulations and dosing, along with regulatory limitations, have limited definitive conclusions.

PEA, a naturally occurring lipid mediator found in several plant and animal sources, has demonstrated promising clinical efficacy in NP by activating peroxisome proliferator-activated receptor- α (PPAR- α), stabilizing mast cells, and reducing neuroinflammation. Multiple clinical trials and observational studies have reported improved pain scores and reduced need for conventional analgesics, particularly for diabetic neuropathy and sciatic pain.

Clinical investigations of curcumin (*Curcuma longa*) have demonstrated potential benefits due to inhibition of

NF- κ B signaling, reduction of TNF- α and IL-1 β , and antioxidant activity. However, most clinical studies have focused on inflammatory pain conditions rather than NP specifically. Limited human studies suggest improved pain outcomes when curcumin is used as an adjunct therapy, although poor bioavailability remains a major challenge.

ALA, although not strictly a phytochemical, is a naturally occurring antioxidant found in plants and has attracted considerable attention for diabetic neuropathy. Several randomized controlled trials and meta-analyses have reported improvements in neuropathic symptoms, including burning sensation, paresthesia, and pain severity, particularly after intravenous administration [119].

Extracts of *Withania somnifera* (ashwagandha), *Boswellia serrata*, *Crocus sativus* (saffron), and other medicinal plants have shown preliminary clinical benefits through antioxidant, anti-inflammatory, and neuroprotective mechanisms. However, most available studies have small sample sizes, short follow-up periods, and heterogeneous formulations, underscoring the need for large-scale, multicenter randomized trials [119].

Overall, available clinical evidence supports the therapeutic promise of medicinal plants and phytochemicals as complementary approaches to NP management. Nevertheless, compared with conventional pharmacotherapy, clinical validation remains limited. Therefore, future studies should prioritize standardized extracts, pharmacokinetic evaluation, dose optimization, long-term safety assessment, and well-designed randomized controlled trials. Details of clinical studies and human evidence on medicinal plants are presented in Table 4 (Ref. [51,52,59,60,75,120,121,122,123,124,125,126]).

9. Conclusion

NP is a complex condition characterized by multiple pathogenic processes, including oxidative stress, ion channel dysfunction, mitochondrial damage, and neuroinflammation. Conventional medications may offer limited therapeutic benefit and cause adverse effects. In recent years, numerous medicinal plants and phytochemicals have exhibited potential neuroprotective, anti-inflammatory, and antioxidant benefits in various preclinical NP models. Compounds such as curcumin, quercetin, diosgenin, and rosmarinic acid have demonstrated efficacy in modulating critical molecular targets, including NF- κ B, TRPV1, Nrf2, and proinflammatory cytokines, thereby helping to alleviate pain and promote nerve restoration.

Herbal remedies are multifaceted and, therefore, suitable for the complex condition of NP. In contrast to synthetically manufactured single-target pharmaceuticals, phytochemicals can modulate multiple processes, including glial cell inhibition, the restoration of neurotrophic factors, and calcium channel regulation. This multimodal approach is more effective for symptom management and may confer disease-modifying benefits. The management of NP with

Table 4. Clinical studies and human evidence of medicinal plants and phytochemicals in neuropathic pain.

Phytochemical/plant source	Clinical condition studied	Study design	Mechanism relevant to neuropathic pain	Major clinical findings	Translational potential	Limitations
Capsaicin (<i>Capsicum annuum</i>)	Diabetic peripheral neuropathy, post-herpetic neuralgia	Randomized controlled trials; systematic reviews/meta-analyses [120,121]	TRPV1 activation followed by nociceptor desensitization; reduced peripheral nerve excitability	Significant reduction in pain intensity and improved patient-reported outcomes after 8% capsaicin patch application	High	Local burning sensation, repeated application requirement, limited effect on central sensitization
Cannabidiol (CBD) (<i>Cannabis sativa</i>)	Peripheral neuropathic pain, chronic pain syndromes	Clinical trials, observational studies	CB1/CB2 receptor modulation, microglial suppression, reduced inflammatory cytokines	Reduction in pain scores and improved sleep quality reported in some studies	Moderate–high	Dose variability, psychoactive concerns with THC-containing preparations, limited large RCTs
Palmitoylethanolamide (PEA)	Diabetic neuropathy, sciatica, peripheral neuropathic pain	Randomized trials, prospective clinical studies, meta-analyses	PPAR- α activation, mast cell stabilization, inhibition of neuroinflammation	Significant reduction in pain intensity and analgesic requirement	Moderate–high	Limited long-term safety data; variability in formulations
Curcumin (<i>Curcuma longa</i>)	Neuropathic symptoms associated with chronic inflammatory disorders and diabetes	Small clinical trials; adjunctive studies [51]	NF- κ B inhibition, $\downarrow$ TNF- α , $\downarrow$ IL-1 β , and antioxidant activity	Improvement in pain-related symptoms when combined with conventional therapy	Moderate	Poor bioavailability; limited neuropathic pain-specific trials
Alpha-lipoic acid (ALA)	Diabetic peripheral neuropathy	Multiple RCTs and meta-analyses [122,123,124,125,126]	Antioxidant activity, mitochondrial protection, and improved nerve blood flow	Reduced neuropathic symptoms, including pain, burning, and paresthesia	High	Intravenous administration required for maximal efficacy; adverse gastrointestinal effects
<i>Boswellia serrata</i> (boswellic acids)	Inflammatory pain and neuropathic pain-associated conditions	Pilot clinical studies [75]	5-LOX inhibition, NF- κ B suppression, and reduced inflammatory mediators	Reduction in inflammatory pain symptoms and improved mobility	Moderate	Limited neuropathic pain-specific clinical evidence
<i>Withania somnifera</i> (ashwagandha)	Chronic pain, stress-associated pain conditions	Clinical trials and observational studies	HPA axis modulation, antioxidant and anti-inflammatory effects	Improvement in pain perception and stress-related symptoms	Moderate	Lack of neuropathy-focused RCTs
<i>Crocus sativus</i> (saffron)	Neuropathic symptoms and mood-associated chronic pain	Small clinical studies	Antioxidant, serotonergic modulation, and anti-inflammatory activity	Possible improvement in pain scores and associated depression/anxiety	Moderate	Small sample sizes and short study duration
Ginger (<i>Zingiber officinale</i>)	Musculoskeletal and inflammatory pain	Human trials; limited neuropathic studies [52]	COX inhibition, antioxidant effects, and TRPV modulation	Reduced inflammatory pain symptoms	Low–moderate	Insufficient neuropathic pain clinical trials
Quercetin (plant flavonoid)	Limited human neuropathy studies	Preliminary clinical investigations [59,60]	Microglial inhibition, antioxidant activity, and cytokine suppression	Potential neuroprotective effects	Moderate potential	Mostly preclinical evidence
EGCG (<i>Camellia sinensis</i>)	Neuropathy-related oxidative stress conditions	Limited clinical evidence	Mitochondrial protection, antioxidant activity, and reduced neuroinflammation	Potential improvement in oxidative stress markers	Moderate potential	Lack of neuropathic pain-specific RCTs

PPAR- α , peroxisome proliferator-activated receptor- α ; RCTs, Randomized Controlled Trials. $\downarrow$ = decrease.

medicinal plants is no longer regarded solely as a traditional practice; it has evolved into a scientifically grounded field. An herbal remedy is safer and more holistic in addressing the root cause of a condition rather than merely masking or alleviating symptoms. Plant-based therapies may be regarded as a feasible and sustainable treatment for NP in the future, contingent upon regulatory oversight, technological assistance, and evidence-based advancement.

Author Contributions

SD and PC: writing the original draft; SD, PC, SSK and VKJ: analyzed the data; PKS, GND: Conception or design and final analysis of content; GND: Supervision. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGPT-5.6 Luna in order to get recent findings on the topic. After using this tool/service, the authors reviewed and edited the content and modified figures as needed and take full responsibility for the content of the published article.

References

- [1] Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. *Nature Reviews. Disease Primers*. 2017; 3: 17002. <https://doi.org/10.1038/nrdp.2017.2>
- [2] Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain*. 2019; 160: 53–59. <https://doi.org/10.1097/j.pain.0000000000001365>
- [3] Gazerani P. The neuroplastic brain: current breakthroughs and emerging frontiers. *Brain Research*. 2025; 1858: 149643. <https://doi.org/10.1016/j.brainres.2025.149643>
- [4] Finnerup NB, Kuner R, Jensen TS. Neuropathic Pain: From Mechanisms to Treatment. *Physiological Reviews*. 2021; 101: 259–301. <https://doi.org/10.1152/physrev.00045.2019>
- [5] van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. *Pain*. 2014; 155: 654–662. <https://doi.org/10.1016/j.pain.2013.11.013>
- [6] Bouhassira D, Attal N. Diagnosis and assessment of neuropathic pain: the saga of clinical tools. *Pain*. 2011; 152: S74–S83. <https://doi.org/10.1016/j.pain.2010.11.027>
- [7] Scholz J, Woolf CJ. Can we conquer pain? *Nature Neuroscience*. 2002; 5: 1062–1067. <https://doi.org/10.1038/nn942>
- [8] Ahmadi R, Kuner R, Weidner N, Keßler J, Bendszus M, Krieg SM. The Diagnosis and Treatment of Neuropathic Pain. *Deutsches Arzteblatt International*. 2024; 121: 825–832. <https://doi.org/10.3238/arztebl.m2024.0215>
- [9] Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain*. 2007; 132: 237–251. <https://doi.org/10.1016/j.pain.2007.08.033>
- [10] Freeman R. Newer agents for the treatment of painful diabetic peripheral neuropathy. *Current Diabetes Reports*. 2005; 5: 409–416. <https://doi.org/10.1007/s11892-005-0047-7>
- [11] Forouzanfar F, Hosseinzadeh H. Medicinal herbs in the treatment of neuropathic pain: a review. *Iranian Journal of Basic Medical Sciences*. 2018; 21: 347–358. <https://doi.org/10.22038/IJBMS.2018.24026.6021>
- [12] Thouaye M, Yalcin I. Neuropathic pain: From actual pharmacological treatments to new therapeutic horizons. *Pharmacology & Therapeutics*. 2023; 251: 108546. <https://doi.org/10.1016/j.pharmthera.2023.108546>
- [13] Aggarwal S, Barnwal RP, Singh G, Pandey AG. Navigating through Neuropathic Pain: From Pathophysiology to Present and Future Treatments. *Current Topics in Medicinal Chemistry*. 2026. <https://doi.org/10.2174/0115680266417188251106114042> (Online ahead of print)
- [14] Matsuoka Y, Yamashita A, Matsuda M, Kawai K, Sawa T, Amaya F. NLRP2 inflammasome in dorsal root ganglion as a novel molecular platform that produces inflammatory pain hypersensitivity. *Pain*. 2019; 160: 2149–2160. <https://doi.org/10.1097/j.pain.0000000000001611>
- [15] Dib-Hajj SD, Yang Y, Black JA, Waxman SG. The Na(V)1.7 sodium channel: from molecule to man. *Nature Reviews. Neuroscience*. 2013; 14: 49–62. <https://doi.org/10.1038/nrn3404>
- [16] Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell*. 2009; 139: 267–284. <https://doi.org/10.1016/j.cell.2009.09.028>
- [17] Ji RR, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and Central Sensitization in Chronic and Widespread Pain. *Anesthesiology*. 2018; 129: 343–366. <https://doi.org/10.1097/ALN.0000000000002130>
- [18] Grace PM, Hutchinson MR, Maier SF, Watkins LR. Pathological pain and the neuroimmune interface. *Nature Reviews. Immunology*. 2014; 14: 217–231. <https://doi.org/10.1038/nri3621>
- [19] Price TJ, Basbaum AI, Bresnahan J, Chambers JF, De Koninck Y, Edwards RR, et al. Transition to chronic pain: opportunities for novel therapeutics. *Nature Reviews. Neuroscience*. 2018; 19: 383–384. <https://doi.org/10.1038/s41583-018-0012-5>
- [20] Chen O, Luo X, Ji RR. Macrophages and microglia in inflammation and neuroinflammation underlying different pain states. *Medical Review* (2021). 2023; 3: 381–407. <https://doi.org/10.1515/mr-2023-0034>
- [21] Inoue K, Tsuda M. Microglia and neuropathic pain. *Glia*. 2009; 57: 1469–1479. <https://doi.org/10.1002/glia.20871>

- [22] Lucas K, Maes M. Role of the Toll Like receptor (TLR) radical cycle in chronic inflammation: possible treatments targeting the TLR4 pathway. *Molecular Neurobiology*. 2013; 48: 190–204. <https://doi.org/10.1007/s12035-013-8425-7>
- [23] Dib-Hajj SD, Cummins TR, Black JA, Waxman SG. From genes to pain: Na v 1.7 and human pain disorders. *Trends in Neurosciences*. 2007; 30: 555–563. <https://doi.org/10.1016/j.tins.2007.08.004>
- [24] Stevens EB, Stephens GJ. Recent advances in targeting ion channels to treat chronic pain. *British Journal of Pharmacology*. 2018; 175: 2133–2137. <https://doi.org/10.1111/bph.14215>
- [25] Zeilhofer HU, Wildner H, Yévenes GE. Fast synaptic inhibition in spinal sensory processing and pain control. *Physiological Reviews*. 2012; 92: 193–235. <https://doi.org/10.1152/physrev.00043.2010>
- [26] García-Sánchez A, Miranda-Díaz AG, Cardona-Muñoz EG. The Role of Oxidative Stress in Physiopathology and Pharmacological Treatment with Pro- and Antioxidant Properties in Chronic Diseases. *Oxidative Medicine and Cellular Longevity*. 2020; 2020: 2082145. <https://doi.org/10.1155/2020/2082145>
- [27] Doyle TM, Salvemini D. Mini-Review: Mitochondrial dysfunction and chemotherapy-induced neuropathic pain. *Neuroscience Letters*. 2021; 760: 136087. <https://doi.org/10.1016/j.neulet.2021.136087>
- [28] Sic A, Manzar A, Knezevic NN. The Role of Phytochemicals in Managing Neuropathic Pain: How Much Progress Have We Made? *Nutrients*. 2024; 16: 4342. <https://doi.org/10.3390/nu16244342>
- [29] Sykioti P, Zis P, Vadalouca A, Siafaka I, Argyra E, Bouhassira D, et al. Validation of the Greek Version of the DN4 Diagnostic Questionnaire for Neuropathic Pain. *Pain Practice: the Official Journal of World Institute of Pain*. 2015; 15: 627–632. <https://doi.org/10.1111/papr.12221>
- [30] Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, et al. Development and validation of the Neuropathic Pain Symptom Inventory. *Pain*. 2004; 108: 248–257. <https://doi.org/10.1016/j.pain.2003.12.024>
- [31] Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. *European Journal of Pain (London, England)*. 2006; 10: 77–88. <https://doi.org/10.1016/j.ejpa.2005.02.003>
- [32] Zhang Z, Gewandter JS, Geha P. Brain Imaging Biomarkers for Chronic Pain. *Frontiers in Neurology*. 2022; 12: 734821. <https://doi.org/10.3389/fneur.2021.734821>
- [33] Moisset X, Bouhassira D. Brain imaging of neuropathic pain. *NeuroImage*. 2007; 37 Suppl 1: S80–S88. <https://doi.org/10.1016/j.neuroimage.2007.03.054>
- [34] Mi S, Zhang J, Zhang W, Huang RS. Circulating microRNAs as biomarkers for inflammatory diseases. *MicroRNA (Sharjah, United Arab Emirates)*. 2013; 2: 63–71. <https://doi.org/10.2174/2211536611302010007>
- [35] Clark AK, Old EA, Malcangio M. Neuropathic pain and cytokines: current perspectives. *Journal of Pain Research*. 2013; 6: 803–814. <https://doi.org/10.2147/JPR.S53660>
- [36] Mouraux A, Iannetti GD. The search for pain biomarkers in the human brain. *Brain: a Journal of Neurology*. 2018; 141: 3290–3307. <https://doi.org/10.1093/brain/awy281>
- [37] Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain*. 1988; 33: 87–107. [https://doi.org/10.1016/0304-3959\(88\)90209-6](https://doi.org/10.1016/0304-3959(88)90209-6)
- [38] Horvath RJ, Romero-Sandoval EA, De Leo JA. In Kruger L, Light AR (eds.) *Translational Pain Research: From Mouse to Man*. CRC Press/Taylor & Francis: Boca Raton (FL). 2010.
- [39] Decosterd I, Woolf CJ. Spared nerve injury: an animal model of persistent peripheral neuropathic pain. *Pain*. 2000; 87: 149–158. [https://doi.org/10.1016/S0304-3959\(00\)00276-1](https://doi.org/10.1016/S0304-3959(00)00276-1)
- [40] Pertin M, Gosselin RD, Decosterd I. The spared nerve injury model of neuropathic pain. *Methods in Molecular Biology (Clifton, N.J.)*. 2012; 851: 205–212. https://doi.org/10.1007/978-1-61779-561-9_15
- [41] Guida F, Iannotta M, Misso G, Ricciardi F, Boccella S, Tirino V, et al. Long-term neuropathic pain behaviors correlate with synaptic plasticity and limbic circuit alteration: a comparative observational study in mice. *Pain*. 2022; 163: 1590–1602. <https://doi.org/10.1097/j.pain.0000000000002549>
- [42] Zajaczkowska R, Kocot-Kępska M, Leppert W, Wrzosek A, Mika J, Wordliczek J. Mechanisms of Chemotherapy-Induced Peripheral Neuropathy. *International Journal of Molecular Sciences*. 2019; 20: 1451. <https://doi.org/10.3390/ijms20061451>
- [43] Cavaletti G, Marmiroli P. Management of Oxaliplatin-Induced Peripheral Sensory Neuropathy. *Cancers*. 2020; 12: 1370. <https://doi.org/10.3390/cancers12061370>
- [44] Schroyen G, Blommaert J, van Weehaeghe D, Sleurs C, Vandenbulcke M, Dedoncker N, et al. Neuroinflammation and Its Association with Cognition, Neuronal Markers and Peripheral Inflammation after Chemotherapy for Breast Cancer. *Cancers*. 2021; 13: 4198. <https://doi.org/10.3390/cancers13164198>
- [45] Canta A, Pozzi E, Carozzi VA. Mitochondrial Dysfunction in Chemotherapy-Induced Peripheral Neuropathy (CIPN). *Toxics*. 2015; 3: 198–223. <https://doi.org/10.3390/toxics3020198>
- [46] Shen CL, Wang R, Yakhnitsa V, Santos J, Watson C, Kiritoshi T, et al. Ginger Root Extract Mitigates Neuropathic Pain via Suppressing Neuroinflammation: Gut-Brain Connection. *Current Developments in Nutrition*. 2022; 6: 808. <https://doi.org/10.1093/cdn/nzac064.027>
- [47] Pandey D, Dubey V, Singh A. Therapeutic potential of Glycyrrhiza glabra L. in managing oxidative stress-induced disorders. *Journal of Drug Research in Ayurvedic Sciences*. 2024; 9(Suppl 2): S149–S159.
- [48] Areti A, Komirishetty P, Kalvala AK, Nellaiappan K, Kumar A. Rosmarinic Acid Mitigates Mitochondrial Dysfunction and Spinal Glial Activation in Oxaliplatin-induced Peripheral Neuropathy. *Molecular Neurobiology*. 2018; 55: 7463–7475. <https://doi.org/10.1007/s12035-018-0920-4>
- [49] Zhu X, Li Q, Chang R, Yang D, Song Z, Guo Q, et al. Curcumin alleviates neuropathic pain by inhibiting p300/CBP histone acetyltransferase activity-regulated expression of BDNF and cox-2 in a rat model. *PLoS One*. 2014; 9: e91303. <https://doi.org/10.1371/journal.pone.0091303>
- [50] Aggarwal BB, Gupta SC, Sung B. Curcumin: an orally bioavailable blocker of TNF and other pro-inflammatory biomarkers. *British Journal of Pharmacology*. 2013; 169: 1672–1692. <https://doi.org/10.1111/bph.12131>
- [51] Li Y, Zhang Y, Liu DB, Liu HY, Hou WG, Dong YS. Curcumin attenuates diabetic neuropathic pain by downregulating TNF-α in a rat model. *International Journal of Medical Sciences*. 2013; 10: 377–381. <https://doi.org/10.7150/ijms.5224>
- [52] Borgonetti V, Governa P, Biagi M, Pellati F, Galeotti N. Zingiber officinale Roscoe rhizome extract alleviates neuropathic pain by inhibiting neuroinflammation in mice. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*. 2020; 78: 153307. <https://doi.org/10.1016/j.phymed.2020.153307>
- [53] Mao QQ, Xu XY, Cao SY, Gan RY, Corke H, Beta T, et al. Bioactive Compounds and Bioactivities of Ginger (Zingiber officinale Roscoe). *Foods (Basel, Switzerland)*. 2019; 8: 185. <https://doi.org/10.3390/foods8060185>
- [54] Liu M, Wang J, Song Z, Pei Y. Regulation mechanism of curcumin mediated inflammatory pathway and its clinical application: a review. *Frontiers in Pharmacology*. 2025; 16–1642248.

- <https://doi.org/10.3389/fphar.2025.1642248>
- [55] Pastorino G, Cornara L, Soares S, Rodrigues F, Oliveira MBPP. Liquorice (*Glycyrrhiza glabra*): A phytochemical and pharmacological review. *Phytotherapy Research: PTR*. 2018; 32: 2323–2339. <https://doi.org/10.1002/ptr.6178>
 - [56] Rahbardar MG, Amin B, Mehri S, Mirnajafi-Zadeh SJ, Hosseinzadeh H. Rosmarinic acid attenuates development and existing pain in a rat model of neuropathic pain: An evidence of anti-oxidative and anti-inflammatory effects. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*. 2018; 40: 59–67. <https://doi.org/10.1016/j.phymed.2018.01.001>
 - [57] Ghasemzadeh Rahbardar M, Amin B, Mehri S, Mirnajafi-Zadeh SJ, Hosseinzadeh H. Anti-inflammatory effects of ethanolic extract of *Rosmarinus officinalis* L. and rosmarinic acid in a rat model of neuropathic pain. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*. 2017; 86: 441–449. <https://doi.org/10.1016/j.biopha.2016.12.049>
 - [58] Han X, Xu T, Fang Q, Zhang H, Yue L, Hu G, et al. Quercetin hinders microglial activation to alleviate neurotoxicity via the interplay between NLRP3 inflammasome and mitophagy. *Redox Biology*. 2021; 44: 102010. <https://doi.org/10.1016/j.redox.2021.102010>
 - [59] Ye G, Lin C, Zhang Y, Ma Z, Chen Y, Kong L, et al. Quercetin Alleviates Neuropathic Pain in the Rat CCI Model by Mediating AMPK/MAPK Pathway. *Journal of Pain Research*. 2021; 14: 1289–1301. <https://doi.org/10.2147/JPR.S298727>
 - [60] Takeda M, Sashide Y, Toyota R, Ito H. The Phytochemical, Quercetin, Attenuates Nociceptive and Pathological Pain: Neurophysiological Mechanisms and Therapeutic Potential. *Molecules (Basel, Switzerland)*. 2024; 29: 3957. <https://doi.org/10.3390/molecules29163957>
 - [61] Man S, Xie L, Liu X, Wang G, Liu C, Gao W. Diosgenin relieves oxaliplatin-induced pain by affecting TLR4/NF- κ B inflammatory signaling and the gut microbiota. *Food & function*. 2023; 14: 516–524. <https://doi.org/10.1039/d2fo02877h>
 - [62] Zhao WX, Wang PF, Song HG, Sun N. Diosgenin attenuates neuropathic pain in a rat model of chronic constriction injury. *Molecular Medicine Reports*. 2017; 16: 1559–1564. <https://doi.org/10.3892/mmr.2017.6723>
 - [63] Cao FL, Xu M, Wang Y, Gong KR, Zhang JT. Tanshinone IIA attenuates neuropathic pain via inhibiting glial activation and immune response. *Pharmacology, Biochemistry, and Behavior*. 2015; 128: 1–7. <https://doi.org/10.1016/j.pbb.2014.11.004>
 - [64] Brum EDS, Becker G, Fialho MFP, Casoti R, Trevisan G, Oliveira SM. TRPA1 involvement in analgesia induced by *Tabernaemontana catharinensis* ethyl acetate fraction in mice. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*. 2019; 54: 248–258. <https://doi.org/10.1016/j.phymed.2018.09.201>
 - [65] Thong-Asa W, Puenpha K, Lairaksa T, Saengjinda S. Neuroprotective effects of betanin in mice with cerebral ischemia-reperfusion injury. *Experimental Animals*. 2023; 72: 336–345. <https://doi.org/10.1538/expanim.22-0176>
 - [66] Mousavi M, Abedimanesh N, Mohammadnejad K, Sharini E, Nikkhah M, Eskandari MR, et al. Betanin alleviates oxidative stress through the Nrf2 signaling pathway in the liver of STZ-induced diabetic rats. *Molecular Biology Reports*. 2022; 49: 9345–9354. <https://doi.org/10.1007/s11033-022-07781-8>
 - [67] Gupta M, Kaur G. Aqueous extract from the *Withania somnifera* leaves as a potential anti-neuroinflammatory agent: a mechanistic study. *Journal of Neuroinflammation*. 2016; 13: 193. <https://doi.org/10.1186/s12974-016-0650-3>
 - [68] Bhatnagar M, Sharma D, Salvi M. Neuroprotective effects of *Withania somnifera* dunal.: A possible mechanism. *Neurochemical Research*. 2009; 34: 1975–1983. <https://doi.org/10.1007/s11064-009-9987-7>
 - [69] Kanter M. Effects of *Nigella sativa* and its major constituent, thymoquinone on sciatic nerves in experimental diabetic neuropathy. *Neurochemical Research*. 2008; 33: 87–96. <https://doi.org/10.1007/s11064-007-9419-5>
 - [70] Wang J, Yu Z, Hu Y, Li F, Huang X, Zhao X, et al. EGCG promotes the sensory function recovery in rats after dorsal root crush injury by upregulating KAT6A and inhibiting pyroptosis. *Translational Neuroscience*. 2023; 14: 20220326. <https://doi.org/10.1515/tnsci-2022-0326>
 - [71] Shahid M, Subhan F, Ahmad N, Ullah I. A bacosides containing *Bacopa monnieri* extract alleviates allodynia and hyperalgesia in the chronic constriction injury model of neuropathic pain in rats. *BMC Complementary and Alternative Medicine*. 2017; 17: 293. <https://doi.org/10.1186/s12906-017-1807-z>
 - [72] Sahranavard T, Ghorani V, Forouzanfar F, Asadi Kakhki SS, Nikfar Dastaki E, Golmakani E, et al. Piperine relieves neuropathic pain induced by paclitaxel in mice. *Acta Neurobiologiae Experimentalis*. 2025; 84: 332–340. <https://doi.org/10.55782/ane-2024-2590>
 - [73] Joshi P, Patel S, Paliwal A, Jain S, Verma K, Dwivedi J, et al. *Tinospora cordifolia* ameliorates paclitaxel-induced neuropathic pain in albino rats. *Journal of Ethnopharmacology*. 2024; 321: 117559. <https://doi.org/10.1016/j.jep.2023.117559>
 - [74] Siddiqui MZ. *Boswellia serrata*, a potential antiinflammatory agent: an overview. *Indian Journal of Pharmaceutical Sciences*. 2011; 73: 255–261. <https://doi.org/10.4103/0250-474X.93507>
 - [75] Mahajan S, Sureja V, Kheni D, Dubey V, Bhupathiraju K, Al-luri VK, et al. Protective effects of *Boswellia* and *Curcuma* extract on oxaliplatin-induced neuropathy via modulation of NF- κ B signaling. *Toxicology Reports*. 2024; 13: 101781. <https://doi.org/10.1016/j.toxrep.2024.101781>
 - [76] Öztürk Y, Aydın S, Beis R, Başer KH, Berberoğlu H. Effects of *Hypericum perforatum* L. and *Hypericum calycinum* L. extracts on the central nervous system in mice. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*. 1996; 3: 139–146. [https://doi.org/10.1016/S0944-7113\(96\)80027-4](https://doi.org/10.1016/S0944-7113(96)80027-4)
 - [77] Chen CL, Tsai WH, Chen CJ, Pan TM. *Centella asiatica* extract protects against amyloid β 1–40-induced neurotoxicity in neuronal cells by activating the antioxidative defence system. *Journal of Traditional and Complementary Medicine*. 2016; 6: 362–369. <https://doi.org/10.1016/j.jtcme.2015.07.002>
 - [78] Baron EP. Medicinal Properties of Cannabinoids, Terpenes, and Flavonoids in Cannabis, and Benefits in Migraine, Headache, and Pain: An Update on Current Evidence and Cannabis Science. *Headache*. 2018; 58: 1139–1186. <https://doi.org/10.1111/head.13345>
 - [79] Ward SJ, Ramirez MD, Neelakantan H, Walker EA. Cannabidiol prevents the development of cold and mechanical allodynia in paclitaxel-treated female C57Bl6 mice. *Anesthesia and Analgesia*. 2011; 113: 947–950. <https://doi.org/10.1213/ANE.0b013e3182283486>
 - [80] Nucci-Martins C, Martins DF, Nascimento LF, Venzke D, Oliveira AS, Frederico MJS, et al. Ameliorative potential of standardized fruit extract of *Pterodon pubescens* Benth on neuropathic pain in mice: Evidence for the mechanisms of action. *Journal of Ethnopharmacology*. 2015; 175: 273–286. <https://doi.org/10.1016/j.jep.2015.09.005>
 - [81] Umamageswari A., Kudagi B. Anti-inflammatory and analgesic properties of *Ocimum sanctum*: a comparative study using animal models. *International Journal of Basic and Clinical Pharmacology*. 2016; 981–986. <https://doi.org/10.18203/2319-2003.ijbcp20150878>
 - [82] Akintoye O., Fabunmi O., Olaseinde O., Ajibare A., Ayilara G., Owoyele B. *Glycyrrhiza glabra* (licorice) reduced neuropathic pain perception by reducing cortisol, brain nitric oxide and brain lactic dehydrogenase levels in experimental animals. *IBRO Re-*

- ports. 2019; 7: 44. <https://doi.org/10.1016/j.ibror.2019.09.089>
- [83] Chaudhary A, Arora D, Devi P. A Review on the role of Capsaicin in Neuropathic Pain. *Asian Journal of Research in Chemistry*. 2022; 495–498. <https://doi.org/10.52711/0974-4150.2022.00084>
- [84] Wagner T, Poole C, Roth-Daniek A. The capsaicin 8% patch for neuropathic pain in clinical practice: a retrospective analysis. *Pain Medicine (Malden, Mass.)*. 2013; 14: 1202–1211. <https://doi.org/10.1111/pme.12143>
- [85] Simpson DM, Robinson-Papp J, Van J, Stoker M, Jacobs H, Snijder RJ, et al. Capsaicin 8% Patch in Painful Diabetic Peripheral Neuropathy: A Randomized, Double-Blind, Placebo-Controlled Study. *The Journal of Pain*. 2017; 18: 42–53. <https://doi.org/10.1016/j.jpain.2016.09.008>
- [86] Verre J, Boisson M, Paumier A, Tribolo S, Boujedaini N. Anti-inflammatory effects of Arnica montana (mother tincture and homeopathic dilutions) in various cell models. *Journal of Ethnopharmacology*. 2024; 318: 117064. <https://doi.org/10.1016/j.jep.2023.117064>
- [87] Sepp J, Koshovy O, Jakstas V, Žvikas V, Botsula I, Kireyev I, et al. Phytochemical, Technological, and Pharmacological Study on the Galenic Dry Extracts Prepared from German Chamomile (*Matricaria chamomilla* L.) Flowers. *Plants (Basel, Switzerland)*. 2024; 13: 350. <https://doi.org/10.3390/plants13030350>
- [88] Kiasalari Z, Rahmani T, Mahmoudi N, Baluchnejadmojarad T, Roghani M. Diosgenin ameliorates development of neuropathic pain in diabetic rats: Involvement of oxidative stress and inflammation. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*. 2017; 86: 654–661. <https://doi.org/10.1016/j.biopha.2016.12.068>
- [89] Ahmad I, Kothawade S, Mim TJ, Jindal D, Paromita P, Khan A. Bioactive compounds for neuroinflammation and neuropathic pain management: molecular and cellular mechanisms. *Inflammopharmacology*. 2026; 34: 4383–4413. <https://doi.org/10.1007/s10787-026-02278-3>
- [90] Barati S, Yadegari A, Shahmohammadi M, Azami F, Tahmasebi F, Rouhani MR, et al. Curcumin as a promising therapeutic agent for diabetic neuropathy: from molecular mechanisms to functional recovery. *Diabetology & Metabolic Syndrome*. 2025; 17: 314. <https://doi.org/10.1186/s13098-025-01884-5>
- [91] Boyd A, Bleakley C, Hurley DA, Gill C, Hannon-Fletcher M, Bell P, et al. Herbal medicinal products or preparations for neuropathic pain. *The Cochrane Database of Systematic Reviews*. 2019; 4: CD010528. <https://doi.org/10.1002/14651858.CD010528.pub4>
- [92] Al-Numair KS, Chandramohan G, Veeramani C, Alsaif MA. Ameliorative effect of kaempferol, a flavonoid, on oxidative stress in streptozotocin-induced diabetic rats. *Redox Report: Communications in Free Radical Research*. 2015; 20: 198–209. <https://doi.org/10.1179/1351000214Y.0000000117>
- [93] Takahashi K, Yoshida T, Wakamori M. Mode-selective inhibitory effects of eugenol on the mouse TRPV1 channel. *Biochemical and Biophysical Research Communications*. 2021; 556: 156–162. <https://doi.org/10.1016/j.bbrc.2021.03.126>
- [94] Zan Y, Kuai CX, Qiu ZX, Huang F. Berberine Ameliorates Diabetic Neuropathy: TRPV1 Modulation by PKC Pathway. *The American Journal of Chinese Medicine*. 2017; 45: 1709–1723. <https://doi.org/10.1142/S0192415X17500926>
- [95] Zhao LX, Jiang BC, Wu XB, Cao DL, Gao YJ. Ligustilide attenuates inflammatory pain via inhibition of NFκB-mediated chemokines production in spinal astrocytes. *The European Journal of Neuroscience*. 2014; 39: 1391–1402. <https://doi.org/10.1111/ejn.12502>
- [96] Zhou J, Wang J, Li W, Wang C, Wu L, Zhang J. Paeoniflorin attenuates the neuroinflammatory response in a rat model of chronic constriction injury. *Molecular Medicine Reports*. 2017; 15: 3179–3185. <https://doi.org/10.3892/mmr.2017.6371>
- [97] Zheng K, Yang C, Han M, Kang F, Li J. Salidroside alleviates bone cancer pain by inhibiting Th17/Treg imbalance through the AMPK/SIRT1 pathway. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*. 2025; 145: 157000. <https://doi.org/10.1016/j.phymed.2025.157000>
- [98] Pan PT, Lin HY, Chuang CW, Wang PK, Wan HC, Lee MC, et al. Resveratrol alleviates nuclear factor-κB-mediated neuroinflammation in vasculitic peripheral neuropathy induced by ischaemia-reperfusion via suppressing endoplasmic reticulum stress. *Clinical and Experimental Pharmacology & Physiology*. 2019; 46: 770–779. <https://doi.org/10.1111/1440-1681.13105>
- [99] Wu YL, Jiang YT, Ou XJ, Peng JY, Zhou ZY, Wen XJ. Baicalin Alleviates Neuropathic Pain in Chronic Constriction Injury of the Sciatic Nerve in Mice by the Interferon Regulatory Factor 4/CCL17 Pathway. *World Journal of Traditional Chinese Medicine*. 2025; 11: 584–591. https://doi.org/10.4103/wjtc.wjtc_m_12_25
- [100] Karabacak E, Eken H, Dallali I, Arslan R. Use of kersetin and fisetin flavonoids in combination with pregabalin and gabapentin in the treatment of neuropathic pain. *The Journal of Pharmacy and Pharmacology*. 2024; 76: 824–833. <https://doi.org/10.1093/jpp/rgae034>
- [101] Godínez-Chaparro B, Quiñonez-Bastidas GN, Rojas-Hernández IR, Austrich-Olivares AM, Mata-Bermudez A. Synergistic Interaction of a Gabapentin- Mangiferin Combination in Formalin-Induced Secondary Mechanical Allodynia and Hyperalgesia in Rats Is Mediated by Activation of NO-Cyclic GMP-ATP-Sensitive K⁺ Channel Pathway. *Drug Development Research*. 2017; 78: 390–402. <https://doi.org/10.1002/ddr.21411>
- [102] Shi R, Jin T, Xu W, Liang Y. The therapeutic potential of phytochemicals in morphine tolerance: targeting microglia-mediated neuroinflammation. *Frontiers in Pharmacology*. 2025; 16: 1669257. <https://doi.org/10.3389/fphar.2025.1669257>
- [103] Martínez AL, González-Trujano ME, Chávez M, Pellicer F, Moreno J, López-Muñoz FJ. Hesperidin produces antinociceptive response and synergistic interaction with ketorolac in an arthritic gout-type pain in rats. *Pharmacology, Biochemistry, and Behavior*. 2011; 97: 683–689. <https://doi.org/10.1016/j.pbb.2010.11.010>
- [104] Hou W, Wang Y, Zheng P, Cui R. Effects of Ginseng on Neurological Disorders. *Frontiers in Cellular Neuroscience*. 2020; 14: 55. <https://doi.org/10.3389/fncel.2020.00055>
- [105] Arora D, Arora A, Sharma A. Quality control and standardization of herbal drugs: current status and future prospects. *J Pharmacogn Phytochem*. 2022; 11: 124–130. <https://doi.org/10.22271/phyto.2022.v11.i3b.14275>
- [106] Jo HG, Kim H, Baek E, Lee D, Hwang JH. Efficacy and Key Materials of East Asian Herbal Medicine Combined with Conventional Medicine on Inflammatory Skin Lesion in Patients with Psoriasis Vulgaris: A Meta-Analysis, Integrated Data Mining, and Network Pharmacology. *Pharmaceuticals (Basel)*. 2023; 16: 1160. <https://doi.org/10.3390/ph16081160>
- [107] Hewlings SJ, Kalman DS. Curcumin: A Review of Its Effects on Human Health. *Foods (Basel, Switzerland)*. 2017; 6: 92. <http://doi.org/10.3390/foods6100092>
- [108] Peng Y, Ao M, Dong B, Jiang Y, Yu L, Chen Z, et al. Anti-Inflammatory Effects of Curcumin in the Inflammatory Diseases: Status, Limitations and Countermeasures. *Drug Design, Development and Therapy*. 2021; 15: 4503–4525. <https://doi.org/10.2147/DDDT.S327378>
- [109] Shen CL, Wang R, Santos JM, Elmassry MM, Stephens E, Kim N, et al. Ginger alleviates mechanical hypersensitivity and anxiety-depressive behavior in rats with diabetic neuropathy through beneficial actions on gut microbiome composition, mi-

- mitochondria, and neuroimmune cells of colon and spinal cord. *Nutrition Research* (New York, N.Y.). 2024; 124: 73–84. <https://doi.org/10.1016/j.nutres.2024.01.014>
- [110] Ma Z, Lu Y, Yang F, Li S, He X, Gao Y, et al. Rosmarinic acid exerts a neuroprotective effect on spinal cord injury by suppressing oxidative stress and inflammation via modulating the Nrf2/HO-1 and TLR4/NF- κ B pathways. *Toxicology and Applied Pharmacology*. 2020; 397: 115014. <https://doi.org/10.1016/j.taap.2020.115014>
- [111] Song Z, Feng J, Zhang Q, Deng S, Yu D, Zhang Y, et al. Tanshinone IIA Protects Against Cerebral Ischemia Reperfusion Injury by Regulating Microglial Activation and Polarization via NF- κ B Pathway. *Frontiers in Pharmacology*. 2021; 12: 641848. <https://doi.org/10.3389/fphar.2021.641848>
- [112] Krishna SS, Shaji N, Kumar NV, Das A, Mangalath S, Biswas L, et al. Emerging targets and translational challenges in treating paclitaxel-induced peripheral neuropathy. *Molecular Biology Reports*. 2025; 52: 833. <https://doi.org/10.1007/s11033-025-10938-w>
- [113] Wang Y, Jiang B, Luo W. Memantine ameliorates oxaliplatin-induced neurotoxicity via mitochondrial protection. *Bioengineered*. 2022; 13: 6688–6697. <https://doi.org/10.1080/21655979.2022.2026553>
- [114] Man S, Zhou Y, Zhang X, Tang X, Xie L, Ma L, et al. Diosgenin alleviates neuropathic pain based on the enhancement of autophagy and promotion of M2 polarization. *International Immunopharmacology*. 2025; 159: 114936. <https://doi.org/10.1016/j.intimp.2025.114936>
- [115] Kang C, Sang Q, Liu D, Wang L, Li J, Liu X. Polyphyllin I alleviates neuroinflammation after cerebral ischemia-reperfusion injury via facilitating autophagy-mediated M2 microglial polarization. *Molecular Medicine (Cambridge, Mass.)*. 2024; 30: 59. <https://doi.org/10.1186/s10020-024-00828-5>
- [116] Ghasemzadeh A, Jaafar HZ, Rahmat A. Identification and concentration of some flavonoid components in Malaysian young ginger (*Zingiber officinale* Roscoe) varieties by a high performance liquid chromatography method. *Molecules*. 2010; 15: 6231–6243. <https://doi.org/10.3390/molecules15096231>
- [117] Basnet P, Skalko-Basnet N. Curcumin: an anti-inflammatory molecule from a curry spice on the path to cancer treatment. *Molecules* (Basel, Switzerland). 2011; 16: 4567–4598. <https://doi.org/10.3390/molecules16064567>
- [118] Mogil JS. Animal models of pain: progress and challenges. *Nature Reviews. Neuroscience*. 2009; 10: 283–294. <https://doi.org/10.1038/nrn2606>
- [119] Dwivedi S, Chaturvedi P. From Tradition to Biochemical Innovation: Phytobioactive Compounds in Modern Neuropharmacology. *International Journal of Pharmacology*. 2026; 22.
- [120] Anand P, Privitera R, Donatien P, Fadavi H, Tesfaye S, Bravis V, et al. Reversing painful and non-painful diabetic neuropathy with the capsaicin 8% patch: Clinical evidence for pain relief and restoration of function via nerve fiber regeneration. *Frontiers in Neurology*. 2022; 13: 998904. <https://doi.org/10.3389/fneur.2022.998904>
- [121] Olusanya A, Yearsley A, Brown N, Braun S, Hayes C, Rose E, et al. Capsaicin 8% Patch for Spinal Cord Injury Focal Neuropathic Pain, a Randomized Controlled Trial. *Pain Medicine (Malden, Mass.)*. 2023; 24: 71–78. <https://doi.org/10.1093/pm/pnac104>
- [122] Abubaker SA, Alonazy AM, Abdulrahman A. Effect of Alpha-Lipoic Acid in the Treatment of Diabetic Neuropathy: A Systematic Review. *Cureus*. 2022; 14: e25750. <https://doi.org/10.7759/cureus.25750>
- [123] Prado MB, Jr, Adiao KJB. Ranking Alpha Lipoic Acid and Gamma Linolenic Acid in Terms of Efficacy and Safety in the Management of Adults With Diabetic Peripheral Neuropathy: A Systematic Review and Network Meta-analysis. *Canadian Journal of Diabetes*. 2024; 48: 233–243.e10. <https://doi.org/10.1016/j.jcjd.2024.01.007>
- [124] Albeladi KE, Alwayili SKA, Kofi M. Efficacy of Using Alpha-Lipoic Acid Supplement in Patients with Diabetic Neuropathy: A Meta-Analysis and Systematic Review. *European Journal of Medical and Health Research*. 2024; 2: 248–253. [https://doi.org/10.59324/ejmr.2024.2\(3\).28](https://doi.org/10.59324/ejmr.2024.2(3).28)
- [125] Wanwimolruk S, Prachayasittikul V. Cytochrome P450 enzyme mediated herbal drug interactions (Part 1). *EXCLI Journal*. 2014; 13: 347–391.
- [126] Delgoda R, Westlake AC. Herbal interactions involving cytochrome p450 enzymes: a mini review. *Toxicological Reviews*. 2004; 23: 239–249. <https://doi.org/10.2165/00139709-200423040-00004>