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Phytotherapy for Post-Mastectomy Neuropathic Pain in Breast Cancer Survivors: Mechanistic Insights and Integrative Clinical Perspectives

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Abstract

Chronic neuropathic pain (CNP) after mastectomy remains a challenging and often refractory condition for many breast-cancer survivors, prompting growing interest in supportive therapies beyond standard pharmacologic options. Phytotherapy provides a scientifically grounded adjunct within integrative and quantum medicine, bridging traditional botanical practice with contemporary molecular research.

This review summarizes current evidence on the mechanistic and clinical roles of phytotherapeutic agents in post-mastectomy CNP. Botanicals such as *Curcuma longa*, *Zingiber officinale*, and *Piper nigrum* demonstrate broad activity, including modulation of TRP ion channels, suppression of pro-inflammatory mediators (TNF-α, IL-6, COX-2), activation of the Nrf2/ARE antioxidant pathway, and regulation of neuroimmune and glial processes involved in central sensitization. Comparisons with gabapentinoids and antidepressants suggest potential synergistic or opioid-sparing effects. Safety considerations—such as standardization, bioavailability, and herb–drug interactions—are also reviewed. When used under appropriate clinical supervision, phytotherapy may support improved analgesia, functional recovery, and quality of life for breast-cancer survivors. Continued research, particularly randomized trials and mechanistic studies, remains essential for responsible clinical integration.

Keywords: Phytotherapy, Integrative medicine, Neuropathic pain, Neuroinflammation

Abbreviations

AEA: Anandamide; BDNF: Brain-Derived Neurotrophic Factor; CB_1/CB_2: Cannabinoid Receptors 1 and 2; CCI: Chronic Constriction Injury; CGRP: Calcitonin Gene-Related Peptide; DRG: Dorsal Root Ganglion; ERK: Extracellular Signal-Regulated Kinase; GLP-1R: Glucagon-Like Peptide-1 Receptor; MAPK: Mitogen-Activated Protein Kinase; MMP-2/MMP-9: Matrix Metalloproteinases; NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells; SNRIs/SSRIs: Serotonin–Norepinephrine/Selective Serotonin Reuptake Inhibitors; TLR4: Toll-Like Receptor 4; TRP Channels: Transient Receptor Potential Channels; TRPV1/TRPA1/TRPM8: TRP Channel Subtypes

Introduction

Neuropathic pain (NP) arises from injury or dysfunction within the somatosensory system and presents as spontaneous pain, hyperalgesia, and allodynia, reflecting disturbances across both sensory and affective components of the central pain matrix [1]. Chronic neuropathic pain (CNP) develops when sustained neuroplastic changes activate glial and immune pathways, promoting neuroinflammation, oxidative stress, and disrupted neurotransmission [2]. Among cancer survivors, NP is especially common after breast surgery. Post-mastectomy pain syndrome (PMPS) can stem from intercostobrachial-nerve injury, radiation-induced neuropathy, or postoperative fibrosis [3], and reported incidence ranges from 20% to 68% depending on surgical technique and adjuvant therapy [4]. With the U.S. breast-cancer survivor population expected to exceed 26 million by 2040,

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the burden of persistent pain and its impact on quality of life will continue to grow [5].

Conventional treatments—including gabapentinoids, tricyclic antidepressants, and opioids—often yield only partial benefit and are limited by sedation, cognitive effects, tolerance, or dependence [6,7]. These constraints have intensified interest in safer, multimodal approaches. Phytotherapy has re-emerged as a clinically relevant adjunct because botanicals such as *Curcuma longa*, *Zingiber officinale*, *Crocus sativus*, and *Cannabis sativa* demonstrate anti-inflammatory, antioxidant, and neuromodulatory activity across peripheral and central pathways implicated in PMPS [2,8]. This review synthesizes the molecular and clinical evidence supporting phytotherapeutic strategies for post-mastectomy neuropathic pain, with attention to mechanisms of action, therapeutic potential, and opportunities for integration within contemporary oncology and pain-management frameworks.

Pathophysiology of neuropathic pain

Neuropathic pain (NP) arises when injury to the peripheral or central nervous system triggers maladaptive changes within the somatosensory pathway. Damaged neurons become hyperexcitable, generating ectopic discharges driven by altered expression of voltage-gated sodium channels (Nav1.7–1.9), calcium channels, and transient receptor potential (TRP) channels involved in thermal and mechanical sensing [9]. These channel-level changes lower pain thresholds and lead to spontaneous pain, hyperalgesia, and allodynia. Neuroinflammation is a key driver in the transition from acute to chronic NP. Activated microglia and astrocytes release TNF-α, IL-1β, and IL-6, which amplify excitatory neurotransmission and suppress inhibitory GABAergic signaling, reinforcing central sensitization [10]. Microglial pathways involving P2X4, MAPK, and NF-κB sustain a persistent cytokine feedback loop within the dorsal horn. Central networks also shape the lived experience of NP: neuroimaging demonstrates altered activity in the anterior cingulate cortex, insula, and prefrontal cortex, reflecting the sensory, emotional, and cognitive dimensions of chronic pain.

Emerging translational work highlights several of these mechanisms as viable phytotherapeutic targets. Terpenoids, alkaloids, and flavonoids can modulate TRPV1, Nav channels, and purinergic receptors while attenuating glial activation and oxidative stress [11]. Together, these multimodal actions provide a biologically plausible foundation for incorporating phytotherapy into chronic NP management, addressing the interconnected neuroimmune and redox pathways that sustain persistent pain [11].

Limitations of conventional management

Conventional management of CNP relies primarily on NSAIDs, tricyclic antidepressants (TCAs), SNRIs, and calcium-channel ligands such as gabapentin and pregabalin. Although these medications reduce neuronal excitability and modulate synaptic transmission, most patients achieve only 30–50% pain relief, and treatment is often limited by sedation, dizziness, cognitive slowing, or gastrointestinal and renal toxicity [6,7,12,13]. Among oncology survivors, these burdens are further compounded by polypharmacy, chemotherapy related neurotoxicity, and altered hepatic or renal metabolism, which heighten adverse effect and interaction risks. Opioids are now discouraged for long-term neuropathic pain because of tolerance, dependence, and opioid-induced hyperalgesia, rendering them unsuitable for routine chronic use [14,15].

Interventional therapies—such as nerve blocks, spinal-cord or dorsal-root-ganglion stimulation, and cryoneurolysis—may provide temporary relief but suffer from variable efficacy, procedural cost, and potential complications including infection, fibrosis, and sensory disturbances. Collectively, these limitations highlight the need for safer, mechanistically comprehensive adjuncts capable of addressing neuroinflammation, oxidative stress, and glial dysfunction—domains in which phytotherapeutic agents show growing translational promise.

Rationale for phytotherapy

Phytotherapy—the use of standardized plant-derived bioactive compounds—offers a multitarget therapeutic strategy well suited to CNP. Unlike single-target synthetic drugs, phytochemicals engage multiple processes central to neuropathic pathology, including neuroinflammation, oxidative stress, mitochondrial dysfunction, and disrupted neurotransmission [16-18]. Compounds such as curcumin, gingerols, and piperine modulate TRP channels (TRPV1, TRPA1, TRPM8) to reduce peripheral hyperexcitability while simultaneously suppressing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) through NF-κB, MAPK, and JAK/STAT inhibition [16]. They also down-regulate COX-2 and iNOS, limiting prostaglandin- and nitric-oxide–driven nociception, and activate Nrf2/ARE signaling to enhance SOD, CAT, and GPx activity, restoring redox balance [17].

Beyond these biochemical actions, phytochemicals modulate neuroimmune and glial pathways, decreasing astrocyte–microglial cytokine release, stabilizing mitochondrial function, and attenuating central sensitization [18]. Together, these convergent mechanisms produce broad neuroprotective and anti-hyperalgesic effects across peripheral and central circuits. This multimodal profile is particularly relevant for post-mastectomy breast cancer survivors, in whom oxidative injury, neuroinflammation, and mitochondrial impairment play major roles in CNP.

Integrative medicine context

In evidence-based integrative medicine, phytotherapy is viewed as a practical, science-supported adjunct to conventional neuropathic-pain care. Psychoneuroimmunology and neuroendocrine-stress research show that chronic neuropathic pain is not purely sensory but a biopsychosocial process shaped by interactions among the nervous, endocrine, and immune systems [19,20]. Persistent stress, HPA-axis disruption, and immune imbalance can elevate IL-6 and TNF-α and promote glial activation, which together heighten pain sensitization, fatigue, and emotional distress in breast-cancer survivors [21-23].

Integrative modalities such as phytotherapy, mindfulness practices, acupuncture, and nutrition-based interventions aim to address these overlapping biological and psychological drivers. This systems-level perspective aligns with modern frameworks that view physiological regulation as a dynamic network of molecular, neural, and bioelectromagnetic interactions. Within this context, phytotherapy offers tools to reduce oxidative stress, cytokine imbalance, mitochondrial dysfunction, and glial activation while also supporting stress regulation, sleep, and mood. Used alongside conventional care, these effects can help strengthen resilience and improve quality of life for breast-cancer survivors living with chronic neuropathic pain.

Scope of This Review

This review synthesizes preclinical, translational, and clinical evidence on phytotherapeutic approaches for post-mastectomy

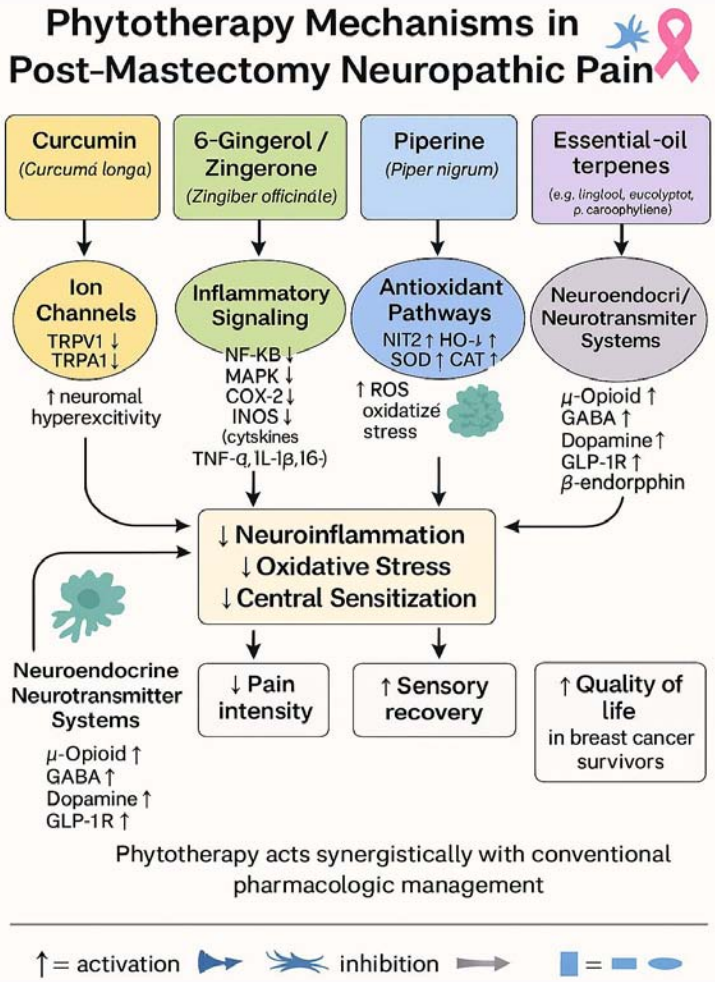

Figure 1: Phytotherapy Mechanisms in Post-Mastectomy Neuropathic Pain.

neuropathic pain (PMNP) in breast-cancer survivors, focusing on how botanical compounds modulate TRP channels, NF-κB and MAPK signaling, cytokine and oxidative-stress pathways, glial activation, and epigenetic regulation. It compares mechanisms across single-plant extracts as well as multi-herb systems highlighting shared targets and complementary actions. Safety considerations, including pharmacokinetic variability, herb–drug interactions, and the need for standardized extraction and dosing, are also reviewed. Summary tables and schematic figures outline core bioactive constituents, key mechanistic pathways, therapeutic outcomes, and levels of evidence to guide future randomized trials, pharmacovigilance efforts, and integrative protocols for chronic PMNP.

Methods

This narrative review assessed scientific evidence on phytotherapeutic agents for NP in breast cancer survivors following mastectomy. The primary aim was to synthesize molecular and cellular mechanisms through which medicinal plants and their bioactive constituents influence neuropathic-pain pathways; secondary aims included evaluating therapeutic outcomes, safety considerations, and translational implications. A structured search of PubMed, PubMed Central, MEDLINE, the Cochrane Library, ScienceDirect, Web of Science, and Google Scholar was conducted from database inception through May 2025. MeSH terms and free-text keywords—"phytotherapy," "medicinal plants," "neuropathic pain," "post-mastectomy pain," "breast cancer survivors," "neuroinflammation," "oxidative stress," "TRPV1," "NF-κB," "Nrf2," "MAPK," and "COX-2"—were combined with Boolean operators, and reference lists of included papers were screened for additional sources. Only peer-reviewed, English-language studies were considered.

Eligible evidence included in vitro and in vivo experiments, randomized controlled trials, observational studies, case series, and mechanistic or integrative reviews examining analgesic, anti-inflammatory, antioxidant, or neuroprotective effects of medicinal plants or isolated phytochemicals relevant to neuropathic pain. Data extracted from each study included botanical species, principal active constituents, study design, experimental model, mechanistic targets (TRPV1, NF-κB, MAPK, COX-2, Nrf2, cytokines), therapeutic outcomes, and safety findings. Evidence was categorized as preclinical or clinical, and mechanistic themes were synthesized around shared pathways—TRP-channel modulation; NF-κB, MAPK, and JAK/STAT inhibition; and Nrf2-mediated antioxidant responses—then compared with mechanisms of conventional agents such as gabapentinoids, SNRIs, and COX inhibitors to identify points of convergence. Because this review relied exclusively on previously published data, institutional review board approval and patient consent were not required, and all sources were documented according to established academic and ethical standards.

Integrative phytotherapy and aromatherapy in neuropathic pain management

Neuropathic pain is difficult to manage because of its multifactorial biology and the limited durability of standard drugs, which are often constrained by tolerance, cognitive and sedative side effects, and dependence [24,25]. Even with optimized therapy, up to 20% of cancer survivors continue to experience persistent or insufficiently controlled pain, underscoring the need for adjunctive modalities that address biological, psychological, and survivorship-related contributors [5,26,27]. Phytotherapy offers such a multimodal framework: standardized compounds including curcuminoids, gingerols, piperine, eugenol, and crocin inhibit NF-κB and COX-2, activate Nrf2/ARE antioxidant pathways, and desensitize TRP channels involved in peripheral and central sensitization [2,5,8,28]. Through these overlapping actions, botanical agents reduce neuroinflammation, restore redox balance, and help stabilize neuronal excitability—areas in which single-target analgesics often fall short.

Aromatherapy provides a complementary pathway, using inhaled or topical essential oils such as *Lavandula angustifolia*, *Mentha piperita*, and *Citrus bergamia* [8]. Their volatile terpenes, linalool, menthol, and limonene, modulate serotonergic, dopaminergic, and GABAergic signaling through olfactory limbic and hypothalamic circuits [29-31]. Psychoneuroimmunology studies demonstrate that this olfactory limbic engagement can downregulate HPA-axis activity and reduce IL-6 and TNF-α, linking emotional regulation with physiologic pain modulation [30,31]. Together, phytotherapy and aromatherapy offer non-opioid, well-tolerated approaches that act across neurochemical, immune, and psychological domains, aligning with integrative-oncology priorities of safety, personalization, and improved quality of life for post-mastectomy breast cancer survivors.

Molecular mechanisms of phytochemicals in neuropathic pain

Phytochemicals relieve neuropathic pain through a broad, interconnected network of molecular actions that extend well beyond the single-target effects of conventional drugs. Many plant-derived alkaloids, terpenoids, and phenolics modulate dopaminergic, GABAergic, cholinergic, and opioid pathways, helping restore the disrupted excitatory–inhibitory balance within central pain circuits [2,32-34]. Piperine enhances GABAergic tone and inhibits voltage-gated sodium channels, while curcumin up-regulates spinal μ-opioid receptors, supporting endogenous analgesia. These compounds also counter oxidative stress: curcuminoids, gingerols, and flavonoids scavenge ROS, increase glutathione, and activate Nrf2/ARE signaling to protect neurons from mitochondrial dysfunction and excitotoxicity [30,35,36].

Equally central is their capacity to suppress neuroinflammation. Botanical constituents inhibit NF-κB, iNOS, COX-2, and 5-LOX, lowering TNF-α, IL-1β, and IL-6 and limiting microglial activation [5,37]. Curcumin and piperine demonstrate synergistic inhibition of NF-κB and STAT3 in spinal microglia, reducing pain hypersensitivity. Flavonoids, lignans, and iridoids further regulate MAPK and PKC pathways, promote IL-10 and regulatory T-cell activity, and shift microglia from a pro-inflammatory M1 phenotype toward a reparative M2 state, supporting neural recovery [5,38]. Many phytochemicals also influence nociceptor excitability through actions on Nav1.7–1.9 sodium channels and TRP channels—capsaicin desensitizes TRPV1, while curcumin and piperine inhibit TRPA1 and TRPV1 to reduce neurogenic inflammation [35,39]. In addition, glycosides such as morroniside from *Cornus officinalis* activate spinal GLP-1 receptors, initiating cAMP/PKA/p38β/CREB and IL-10/STAT3 signaling, enhancing β-endorphin release and producing sustained, tolerance-free analgesia [40-43]. Together, these mechanisms illustrate the multimodal, pleiotropic basis of phytotherapeutic analgesia in chronic neuropathic pain.

A schematic representation of the principal molecular pathways through which key phytochemicals—*Curcuma longa* (curcumin), *Zingiber officinale* (6-gingerol / zingerone), *Piper nigrum* (piperine), and essential-oil terpenes (e.g., linalool, eucalyptol, β-caryophyllene)—alleviate post-mastectomy neuropathic pain in breast-cancer survivors.

These compounds converge on multiple regulatory targets, including ion-channel modulation (TRPV1 ↓, TRPA1 ↓), inflammatory-signaling inhibition (NF-κB ↓, MAPK ↓, COX-2 ↓, iNOS ↓; ↓ cytokines TNF-α, IL-1β, IL-6), antioxidant-pathway activation (Nrf2 ↑, HO-1 ↑, SOD ↑, CAT ↑), and neuroendocrine / neurotransmitter-system regulation (μ-opioid ↑, GABA ↑, dopamine ↑, GLP-1R ↑, β-endorphin ↑).

Collectively, these effects attenuate neuroinflammation, oxidative stress, and central sensitization, leading to reduced pain intensity, enhanced sensory recovery, and improved quality of life in breast-cancer survivors.

Phytotherapy thereby acts synergistically with conventional pharmacologic management as a safe, multi-target, non-opioid adjunct for chronic neuropathic pain. (↑ = activation / up-regulation; ↓ = inhibition / down-regulation.)

Comparative Efficacy of Phytotherapy and Conventional Pharmacologic Treatments

Neuropathic pain after mastectomy remains common and difficult to manage. Standard pharmacologic agents—gabapentinoids, tricyclic antidepressants, and SNRIs—provide meaningful relief in only 30–50% of patients and are often limited by sedation, dizziness, cognitive slowing, constipation, and weight gain, all of which can diminish adherence and overall quality of life for breast-cancer survivors [44]. These constraints have prompted increasing interest in adjunctive therapies that can reduce pain without adding to systemic burden.

Phytotherapeutic agents offer a broader, multi-target approach by acting simultaneously on pathways central to neuropathic pain. Compounds such as curcumin, gingerols, and piperine inhibit NF-κB and MAPK signaling; suppress TNF-α, IL-1β, and IL-6; modulate TRPV1/TRPA1 channels; and activate Nrf2/ARE antioxidant responses [16,28,45]. Through these pleiotropic effects, they mitigate peripheral and central sensitization while supporting endogenous inhibitory mechanisms, including μ-opioid-receptor modulation and restoration of GABAergic tone [27]. Translational and clinical studies from 2021–2024 report additive—or sometimes comparable—analgesic benefit: curcumin combined with pregabalin or duloxetine improves VAS scores and functional outcomes in chemotherapy-induced neuropathy [16,39], while ginger and piperine formulations enhance gabapentinoid efficacy and permit dose reduction [46]. These botanicals also cause fewer cognitive and gastrointestinal side effects, an important consideration for long-term survivorship. Beyond analgesia, phytochemicals modulate oxidative stress, neuroinflammation, and glial activation—mechanisms relevant to chemotherapy-related neurotoxicity and

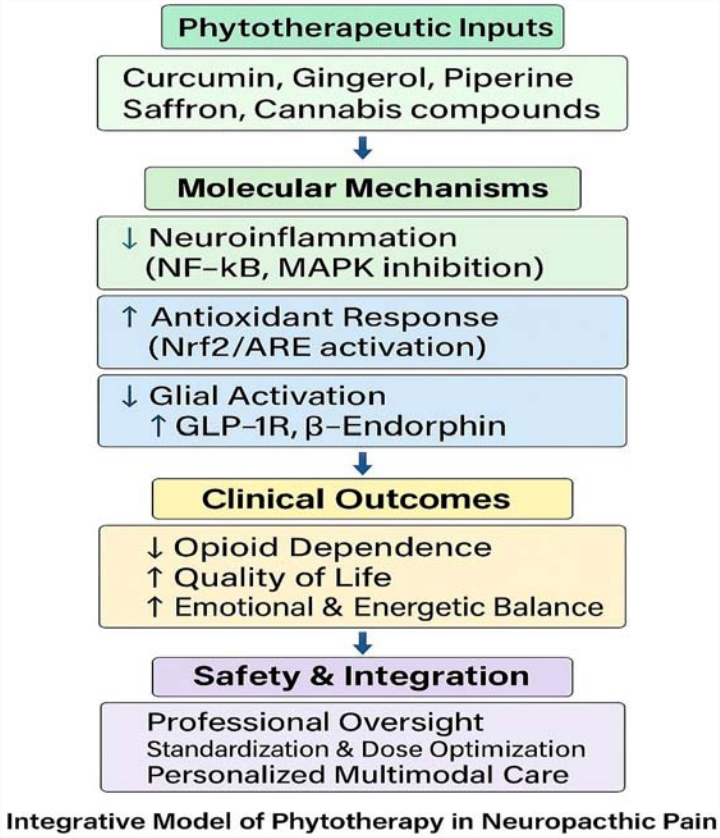

Figure 2: Integrative Model of Phytotherapy in Neuropathic Pain

broader quality-of-life outcomes [47]. Current evidence suggests that phytotherapy complements conventional pharmacologic treatment by addressing underlying biological drivers and reducing adverse effects. Randomized trials in post-mastectomy NP are still needed to confirm efficacy and guide integrative pain-management strategies.

Plants and Their Derivatives for Neuropathic Pain

Shinrin-Yoku (Forest Therapy) and Phytoncide Exposure

Shinrin-Yoku ("forest bathing") is an evidence-supported nature therapy practice that promotes psychological and physiological restoration through immersion in forest environments [48]. In the context of neuropathic-pain care, it can be viewed as an environmental extension of phytotherapy, as inhaled forest volatiles, phytoncides, exert measurable neuroimmune effects. Compounds such as α-pinene, limonene, and borneol possess anti-inflammatory, antioxidant, antimicrobial, and potential analgesic activity [49]. Experimental and clinical studies demonstrate that phytoncide inhalation enhances natural-killer (NK) cell activity, improves autonomic balance, and reduces stress hormone output [50], findings reinforced by a recent systematic review showing significant increases in NK-cell activation following forest volatile exposure [51]. Forest therapy trials further report reductions in salivary cortisol, improved heart-rate variability, and decreases in perceived stress and pain intensity, linking phytoncide-rich environments to neuroendocrine stability and broader psychoneuroimmune resilience [52]. These data suggest that immersive forest environments and inhaled plant volatiles offer a meaningful adjunct to pharmacologic and botanical strategies for chronic neuropathic pain. However, standardized dosing parameters, formal safety evaluation, and rigorously controlled clinical trials are still needed to support reproducibility and guide clinical integration.

Kampo Medicine in Neuropathic Pain Management

Kampo, Japan's traditional medical system, is now firmly integrated into contemporary clinical care for neuropathic and chemotherapy-induced pain [53]. The Japanese Ministry of Health, Labour, and Welfare approves Kampo formulas as ethical pharmaceuticals, and they are often co-prescribed when conventional analgesics provide only partial relief [53,54]. Although modernized to meet current pharmacologic and safety standards, Kampo retains its emphasis on restoring physiological balance rather than simply suppressing symptoms. Its multi-herb formulas, refined to remove toxic components, act synergistically across pathways central to neuropathic pain, including neuroinflammation, central sensitization, and microcirculatory dysfunction [53,54].

Kampo's diagnostic framework continues to draw from classical concepts such as Yin–Yang, Kyo–Jitsu, Netsu–Kan, and the vital substances Qi, Ketsu, and Sui, offering a holistic model that parallels modern integrative medicine and its recognition of somatic, emotional, and energetic influences on chronic pain [43]. Formulas such as Goshajinkigan (GJG) and Yokukansan (YKS) have shown promising effects in preclinical and clinical studies, including reduced glial activation, suppression of pro-inflammatory cytokines, and enhancement of endogenous opioid signaling [53,54]. As evidence grows, Kampo stands out as a biologically plausible adjunct to standard neuropathic-pain therapies. Future priorities include improved pharmacokinetic standardization, stringent quality control, and larger randomized trials to clarify its therapeutic role across

diverse patient populations.

Yokukansan (YKS)

Yokukansan is one of the most extensively studied Kampo formulations for neuropathic and chemotherapy-induced pain, with well-documented neuroprotective, anti-inflammatory, and neuromodulatory actions [43,53,54]. Composed of *Glycyrrhizae radix, Bupleuri radix, Uncariae uncis cum ramulus,* and *Cnidii rhizome*, YKS acts across several pathways central to neuropathic pain. It reduces excessive glutamatergic transmission by suppressing presynaptic glutamate release and enhancing astrocytic uptake, thereby limiting NMDA-receptor overactivation and central excitotoxicity [53,54]. At the same time, it strengthens inhibitory control by enhancing GABAergic tone and activating 5-HT_1A and 5-HT_2A/2C receptors—a serotonergic mechanism validated in paclitaxel-induced and postoperative pain models, where YKS increased withdrawal thresholds and reduced allodynia [55,56].

YKS also exerts robust neuroimmune effects: it suppresses microglial and astrocytic activation, inhibits NF-κB and MAPK pathways, and lowers IL-1β, IL-6, and TNF-α, protecting spinal and dorsal-root neurons from inflammatory and apoptotic injury [53,57]. Additional work shows modulation of opioid- and stress-related pathways, including stabilization of dopaminergic and GABAergic signaling and prevention of morphine tolerance [57]. Across chronic constriction injury, diabetic neuropathy, and chemotherapy-induced neuropathy models, YKS consistently reduces mechanical and thermal hypersensitivity [53,55,56]. Clinical and translational reviews confirm a favorable safety profile and support its role as a systems-based, multimodal therapy [43,54]. Future priorities include standardized extraction, bioavailability studies, and controlled clinical trials comparing YKS with first-line neuropathic-pain therapies.

Neuragen PN

Neuragen PN® is an FDA-registered topical homeopathic–phytotherapeutic formulation used for neuropathic pain. It combines six ultra-diluted homeopathic substances with essential oils designed to enhance dermal penetration and modulate neuroinflammatory and nociceptive signaling [29,58]. Studies from 2019–2025 show that its major botanicals—*Hypericum perforatum, Lavandula angustifolia, Citrus aurantium, Melaleuca alternifolia*, and *Eucalyptus globulus*—act synergistically on ion channels, neurotransmitter pathways, and cytokine networks. Hypericum perforatum supports serotonergic and dopaminergic tone while suppressing NF-κB–driven cytokine release, providing combined analgesic and anxiolytic effects. *Lavandula angustifolia* and *Citrus aurantium* modulate TRPV1 and NMDA receptor signaling and inhibit ERK/JNK phosphorylation, reducing nociceptor sensitization. *Melaleuca alternifolia* and *Eucalyptus globulus* further decrease TNF-α, IL-1β, and oxidative stress, helping protect peripheral nerves from inflammatory and redox injury [29,58]. The essential-oil matrix also facilitates dermal absorption of the ultra-diluted actives, producing local receptor engagement without systemic exposure.

These combined actions position Neuragen PN® as a multitarget, non-opioid adjunct for neuropathic pain. Its effects on TRP-channel desensitization, MAPK/NF-κB inhibition, monoamine regulation, and oxidative balance are supported by emerging preclinical and early clinical findings (2019–2025), including relevance to post-mastectomy and chemotherapy-related neuropathies. With a favorable safety profile and minimal systemic risk, Neuragen PN fits well within integrative pain-management approaches, though randomized controlled trials are still needed to define efficacy, dermal pharmacokinetics, and long-term tolerability in breast-cancer survivors.

Tibetree Cheezheng Pain-Relieving Plaster (PRP)

The Cheezheng Pain-Relieving Plaster (PRP) is a Tibetan–Chinese polyherbal transdermal formulation widely used for musculoskeletal and neuropathic pain. Systematic reviews from 2020–2024 report that PRP reduces C-fiber hyperexcitability, suppresses TNF-α and IL-1β, inhibits COX-2 and 5-LOX, and provides antioxidant and neuroprotective support across both peripheral and central pathways [59,26]. These effects reflect the diverse actions of its component herbs. Camphor from *Cinnamomum camphora* modulates TRP channels—activating TRPV1, TRPV3, and TRPM8 while inhibiting TRPA1—to desensitize nociceptors. *Zanthoxylum bungeanum* attenuates microglial and astrocytic activation through MAPK (p38/ERK/JNK) and TLR4 signaling while promoting IL-10 and β-endorphin release. *Lamiophlomis rotata* may further enhance analgesia through spinal GLP-1 receptor activation. Anti-inflammatory and antioxidant contributions from *Curcuma longa* (NF-κB, COX-2, Nrf2/HO-1 modulation) and flavonoid-rich species such as *Myricaria germanica, Carthamus tinctorius,* and *Oxytropis falcata* help reduce oxidative injury and support neural repair.

Overall, PRP functions as a multimodal, non-opioid topical therapy capable of modulating ion channels, cytokine networks, and redox pathways with minimal systemic exposure. Evidence from 2020–2024 supports its clinical utility as an adjunct or stand-alone treatment for chronic neuropathic pain, including post-mastectomy neuropathy in breast-cancer survivors [60]. Randomized, controlled studies incorporating mechanistic biomarkers are needed to refine dosing, assess transdermal bioavailability, and confirm long-term safety.

Aconitum Species and Their Active Compounds

Aconitum species (Ranunculaceae), historically used for neuralgias in both Asian and European traditions, contain a range of bioactive alkaloids—most notably lappaconitine (LA)—that exhibit potent analgesic, anti-inflammatory, and antioxidant effects. Although crude extracts have been limited clinically because of aconitine-related cardiotoxicity, recent preclinical and pharmacologic studies have renewed interest in detoxified preparations and purified LA as promising non-opioid options for refractory neuropathic pain [39,61]. LA exerts its primary antinociceptive effects through reversible inhibition of Nav1.7 and Nav1.8 sodium channels, stabilizing sensory-neuron excitability and reducing the repetitive firing that characterizes neuropathic signaling—producing analgesia comparable to opioids but without the same dependence risk [61,62]. These channel effects are reinforced by broader anti-inflammatory and redox mechanisms: LA and related Aconitum flavonoids suppress NF-κB and MAPK activity and scavenge reactive oxygen species, interrupting the oxidative–inflammatory cycle that drives pain chronification [61,63]. Polysaccharide fractions additionally down-regulate P2X3 and P2X7 receptors in dorsal-root–ganglion neurons, limiting ATP-mediated nociceptive signaling and microglial activation [63].

Despite these promising mechanisms, safety remains central to Aconitum therapeutics. Traditional preparations may retain diester alkaloids such as aconitine, which can trigger arrhythmias and neurologic toxicity, underscoring the need for rigorous processing and

clinical oversight. In contrast, modern detoxified extracts and purified LA demonstrate markedly improved safety profiles in controlled studies [61,62]. Together, these findings support detoxified Aconitum alkaloids—particularly LA—as mechanistically robust, multi-target candidates for neuropathic pain, including post-surgical and cancer-treatment–related syndromes, provided standardized formulations and appropriate monitoring are in place.

Sophora Species and Their Active Compounds

Sophora species (Fabaceae), long used in Traditional Chinese Medicine for pain and neurological disorders, contain a rich profile of quinolizidine alkaloids, flavonoids, and phenolic acids with demonstrated neuroprotective, anti-inflammatory, and analgesic activity [64]. Key constituents, including aloprine, oxysophocarpine, and matrine, act on several mechanisms central to neuropathic-pain biology. Aloprine inhibits NF-κB and MAPK pathways, reducing TNF-α, IL-1β, and IL-6 while enhancing SOD activity, thereby limiting glial activation and oxidative neuronal injury. Oxysophocarpine activates the Nrf2/ARE pathway to boost endogenous antioxidant defenses and counter cytokine-driven oxidative stress associated with pain hypersensitivity [65]. Matrine adds complementary central effects through κ- and μ-opioid receptor engagement and cholinergic modulation, along with NF-κB suppression, and has shown benefit in chemotherapy-induced neuropathy [66].

Together, these alkaloids provide a coherent mechanistic rationale for Sophora's traditional use in neuropathic-pain conditions. Their combined ability to suppress inflammatory cascades, enhance antioxidant and opioid pathways, and stabilize neuronal excitability positions Sophora species as promising phytotherapeutic candidates for chemotherapy-related or post-surgical neuropathic pain, including in breast cancer survivors who often require safer, multi-target alternatives to conventional analgesics.

Papaver somniferum and Its Derivatives

Papaver somniferum has shaped the history of analgesia, with its principal alkaloids—morphine, codeine, and thebaine—forming the foundation of modern opioid therapy. These compounds remain highly effective for severe neuropathic pain, acting as agonists at μ-, δ-, and κ-opioid receptors to dampen nociceptive transmission [67]. Presynaptic inhibition of calcium influx reduces excitatory neurotransmitter release, while postsynaptic potassium efflux promotes hyperpolarization, together limiting neuronal excitability. Beyond classical opioid activity, minor constituents of poppy-seed oil, including stigmasterol and related polyphenols, exert modest anti-inflammatory effects through down-regulation of IL-1β, TNF-α, and NF-κB signaling [68]. These peripheral actions have prompted interest in lower-risk derivatives and standardized preparations that may offer some benefit in milder neuropathic states.

In clinical practice, however, opioid safety remains the defining concern. Long-term morphine or codeine use carries risks of tolerance, dependence, respiratory depression, constipation, and opioid-induced hyperalgesia, requiring careful patient selection and monitoring. Regulatory bodies such as EFSA and the FDA continue to monitor contamination risks in culinary poppy products, which generally contain negligible opium latex but may vary by source. Clinicians must also remain alert to drug interactions, as co-administration with serotonergic or sedative medications can precipitate serotonin syndrome, cardiotoxicity, or respiratory suppression. Naloxone remains the established antidote for opioid toxicity. Taken together, Papaver somniferum illustrates the evolution from traditional botanical analgesics to contemporary opioid pharmacology: while indispensable for severe or refractory neuropathic pain, its therapeutic use must be situated within structured, closely supervised clinical frameworks [68].

Cannabis sativa and Cannabis indica

Cannabis sativa and *Cannabis indica* have long been used for analgesic, anti-inflammatory, anxiolytic, and neuroprotective purposes. Their principal phytocannabinoids, THC and CBD, act on the endocannabinoid system, which regulates nociception, immune signaling, and affective tone [69,70]. Variations in THC:CBD ratios.

Variations in THC:CBD ratios and terpene chemotypes help account for differences in sedation, mood effects, and analgesic potency among cultivars [48]. Mechanistically, phytocannabinoids engage CB_1 and CB_2 receptors, desensitize TRPV1 and TRPA1 channels, and modulate serotonergic and GABAergic circuits. These pathways converge to suppress NF-κB, COX-2, and iNOS activity and decrease pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [49]. CBD additionally activates PPAR-γ and adenosine A_2A receptors, contributing antioxidant and anti-glial effects without psychotropic activity [48]. Clinical formulations, including decarboxylated teas, standardized oils, oromucosal sprays, and topical preparations, produce meaningful antinociceptive and anti-inflammatory effects, with standardized products showing more predictable CB_2-mediated cytokine suppression and improvements in hyperalgesia and sleep [69,70,72].

Systematic reviews and meta-analyses support the use of cannabinoid-based therapies for neuropathic pain associated with chemotherapy, and cancer survivorship [69,73]. Patients who do not respond adequately to gabapentinoids, antidepressants, or opioids often report reductions in pain intensity with sublingual or topical THC/CBD preparations. CBD, in particular, is suitable for long-term use due to its minimal psychoactivity and broad anti-inflammatory, neuroprotective profile [71,72]. Taken together, the multimodal effects of *Cannabis sativa* and *Cannabis indica*, involving CB_1/CB_2 activation, TRP-channel desensitization, cytokine suppression, and serotonergic modulation, align with integrative-oncology goals emphasizing multi-target efficacy, and quality-of-life improvement. Evidence supports cannabinoid phytotherapy as an adjunct for post mastectomy cancer-related neuropathic pain.

Corydalis yanhusuo (YHS) and its active alkaloids

Corydalis yanhusuo (YHS), a Papaveraceae species used in TCM, has drawn growing interest as modern studies clarify the analgesic potential of its diverse alkaloids—including dehydrocorybulbine (DHCB), tetrahydropalmatine (THP), dehydrocorydaline (DHC), berberine, palmatine, magnoflorine, columbamine, corydine, and corydaline. Together, these compounds exert antinociceptive, anti-inflammatory, and neuroprotective effects through opioid, dopaminergic, cytokine, and oxidative-stress pathways [74-76]. DHCB and THP engage μ-opioid receptors to reduce ascending nociceptive signaling, while berberine supports endogenous opioid tone and dampens peripheral inflammation [74,77,78]. YHS also modulates dopaminergic circuits: THP and DHCB regulate D_1/D_2 receptor activity to restore dopaminergic balance [75], and corydine and corydaline act as partial D_1 antagonists that help limit spinal neuronal hyperexcitability [76]. Anti-inflammatory actions arise through suppression of TNF-α, IL-1β, and IL-6 via NF-κB, iNOS, and

Table 1: Comparative Mechanistic Summary of Phytotherapeutic and Polyherbal Agents.

Plant / Formulation	Key Active Compounds	Principal Mechanistic Targets	Therapeutic Actions	Supporting References
Polyherbal Formulations				
Kampo (Yokukansan – YKS)	*Atractylodes macrocephala* polysaccharides, Glycyrrhiza flavonoids	GABAergic / serotonergic modulation; microglial suppression	↓ Anxiety; ↓ Neuroinflammation; analgesia in neuropathic models	53, 54
Neuragen PN	Hyperforin, Linalool, Bergapten, Terpinene-4-ol	TRPV1/TRPA1 desensitization; NF-κB inhibition; μ-Opioid & CB1/CB2 agonism	↓ Pain sensitivity; ↓ Cytokines; ↑ Monoamines and β-endorphin	29, 58
PRP (CheeZheng Plaster)	Camphor, Sanshool, Iridoid glycosides, Curcumin	TRP activation; MAPK/TLR4/GLP-1 modulation; NF-κB/ COX-2 suppression	↓ inflammation; ↑ Nerve repair; non-opioid analgesia	38, 63
Single-Plants				
Aconitum spp.	Lappaconitine (LA)	Voltage-gated Na^+ channel blockade; P2X receptor modulation	↓ Neuronal excitability; analgesia (toxicity caution)	3
Sophora spp.	Matrine, Aloprine, Oxysophocarpine	NF-κB/Nrf2 regulation; Opioid & AChR activation	↓ Cytokines; ↓ ROS; analgesic/ neuroprotective	39
Papaver somniferum (Opium poppy)	Morphine, Codeine, Stigmasterol (seed oil)	μ/δ/κ-Opioid receptor agonism; muscarinic activation	Potent analgesia; benchmark comparator (toxicity risk)	121
Corydalis yanhusuo	Dehydrocorybulbine, Tetrahydropalmatine	μ-Opioid & Dopamine D1/D2 modulation; NF-κB suppression	↓ Pain perception; ↓ Inflammation; ↑ Monoamines	77
Cannabis sativa / indica	THC, CBD, β-Myrcene, Limonene	CB1/CB2 activation; TRPV1/GPR55 modulation; COX-2 inhibition	↓ inflammation; ↓ Pain; ↑ Sleep and mood	69, 70, 72, 73, 71
Tanacetum parthenium (Feverfew)	Parthenolide, Flavonoids	Phospholipase A / NF-κB inhibition	↓ Prostaglandins; ↓Chemo-neuropathy	83
Capsicum spp. (Capsaicin)	Capsaicin	TRPV1 activation / defunctionalization; NF-κB inhibition	↓ Nociceptor sensitivity; ↓ Pain transmit	86, 88
Zingiber officinale (Ginger)	6-Gingerol, 6-Shogaol, Zingerone	COX/LOX inhibition; TRPV1 activation; NF-κB suppression	↓ Cytokines; ↓ ROS; analgesia ≈ NSAIDs	90, 89
Allium sativum (Garlic)	Allicin, Ajoene, Organosulfides	TRPA1/TRPV1 modulation; COX2/5LOX inhibition; ↑ Antioxidant enzymes	↓ Pain; ↓ Cytokines; ↑ SOD, CAT, GPx	92, 93
Salvia officinalis / divinorum	Ursolic acid, Salvigenin, Salvinorin A	TRPA1 & KOR activation; NF-κB suppression	↓inflammation; non-addictive analgesia	96, 95, 94
Crocus sativus (Saffron)	Crocin, Crocetin, Safranal	NF-κB, COX-2, Cytokine / ROS modulation	↓ Allodynia & Hyperalgesia; ↑ Antioxidant enzymes	97, 98
Curcuma longa (Turmeric)	Curcumin	NF-κB, COX-2, JAK-STAT inhibition; Nrf2 activation	↓ IL-1β, TNF-α; ↑ Monoamines; Neuroprotection	99, 66, 100, 58
Syzygium aromaticum (Clove)	Eugenol, β-Caryophyllene	TRPV1 modulation; NF-κB/COX-2 inhibition; Opioid interaction	Analgesic; antispasmodic; anti-inflammatory	106, 104, 102
Harpagophytum procumbens (Devil's Claw)	Harpagoside, Harpagide	TNF-α / COX-2 inhibition; ↑ PRDX2 pathways	↓ Pain and oxidative stress; neuroprotection	111, 112, 80
Rosa damascena (Damask rose)	2-Phenylethyl alcohol, Quercetin	Olfactory–limbic pathway; autonomic modulation	↓ Stress-related pain; ↑ Parasympathetic tone	28, 114
Rosmarinus officinalis (Rosemary)	1,8-Cineole, Carnosic acid, Carnosol	COX-2/PGE inhibition; Ca^{2+}/K^+ channel blockade	↓ Inflammation; ↓ Spasm; ↑ Circulation	116, 112, 115, 118, 117
Mentha × piperita (Peppermint)	Menthol, Menthone	TRPM8/TRPA1 activation; Na^+/Ca^{2+} channel modulation	Cooling analgesia; ↓ Pain perception	119, 64, 120, 121, 122
Elaeagnus angustifolia (Senjed)	Flavonoids, Phenolic acids	Cytokine/PGE in inhibition; GABA/5-HT modulation	↓ Inflammation; ↑ Muscle relaxant analgesia	125, 124, 123
Ugni myricoides (Black Chilean Guava)	α-Pinene, 1,8-Cineole, β-Caryophyllene	CNS neurotransmitter modulation; ↓ Cytokines/PGE	↓ Hypernociception; analgesia ≈ gabapentin	127, 129, 128, 29
Cornus officinalis (Dogwood)	Morroniside, Ursolic acid	GLP-1R activation; ↑ IL-10; ↓ TNF-α/MMP	↓ inflammation; ↑ Mitochondrial stability	64, 134, 68, 94
Salix alba (White Willow Bark)	Salicin, Polyphenols	COX-2/NF-κB inhibition; ↓ PGE synthesis	↓ Pain and inflammation; natural NSAID alternative	137, 138, 58, 140, 136
Myristica fragrans (Nutmeg)	Myristicin, Elemicin	COX-2/cytokine inhibition; ↓ Substance P release	↓ Inflammation; analgesic; antioxidant	42, 29, 141, 143
Morinda citrifolia (Noni)	Iridoids, Scopoletin, Anthraquinones	COX-2/MMP-9 inhibition; GABA-A receptor binding	↓ Pain and inflammation; ↑ Anxiolytic effect	145, 103, 49, 147

Abbreviations: TRP: Transient Receptor Potential; CB: Cannabinoid Receptor; COX: Cyclooxygenase; MAPK: Mitogen-Activated Protein Kinase; NF-κB: Nuclear Factor κB; TNF: Tumor Necrosis Factor; IL: Interleukin; ROS: Reactive Oxygen Species; GLP-1: Glucagon-Like Peptide-1; KOR: Kappa Opioid Receptor; ↑: increase; ↓: decrease.

COX-2 inhibition, while palmatine and magnoflorine inhibit TLR4- and MAPK-mediated glial activation [74,79,80].

Additional mechanisms reinforce its relevance to neuropathic pain. Columbamine inhibits MAO-B, preserving dopamine and serotonin and strengthening descending inhibitory control [81,82]. THP and berberine enhance SOD activity and reduce ROS accumulation, protecting against mitochondrial dysfunction and apoptosis [75,76]. Importantly, both DHCB and berberine readily cross the blood–brain barrier, allowing direct central engagement of these pathways [74,76]. Taken together, this multitarget profile positions *Corydalis yanhusuo* as a promising non-opioid adjunct or alternative for refractory neuropathic pain, including post-mastectomy states. Preclinical evidence from 2019–2025 strongly supports further translational and clinical evaluation within integrative pain-management frameworks.

Tanacetum parthenium (Feverfew)

Tanacetum parthenium (feverfew), a GRAS-recognized

medicinal plant from the Asteraceae family, has long been used for pain and inflammation, and contemporary research now confirms its relevance to neuropathic pain. Its major constituents, sesquiterpene lactones such as parthenolide, along with flavonoids and pinenes, act across several neurobiological pathways that drive chronic neuropathic states [83,84]. Parthenolide inhibits glial activation and microglia-derived cytokine release through NF-κB, TLR4, and MAPK modulation, while also supporting mitochondrial stability and endogenous antioxidant defenses [85]. Feverfew further reduces prostaglandin synthesis via phospholipase A_2 and COX-2 inhibition, modulates calcium influx and glutamatergic transmission to lessen neuronal hyperexcitability, and suppresses TNF-α, IL-1β, and ROS, helping maintain neuronal integrity and counter oxidative stress [84]. Activation of the Nrf2/ARE pathway additionally boosts SOD, catalase, and glutathione peroxidase activity, restoring redox balance and enhancing neuroprotection [85].

Together, these mechanisms yield consistent anti-hyperalgesic and neuroprotective effects, with preclinical studies showing reductions in mechanical and thermal hypersensitivity comparable to first-line pharmacologic agents but with better tolerability [83,84]. In models of paclitaxel-induced and peripheral-nerve injury, feverfew extracts reduce pain behaviors without the sedation or cognitive side effects seen in gabapentinoids. These data support T. parthenium as a promising low-toxicity, non-opioid adjunct for chronic neuropathic pain, particularly in oncologic and post-surgical settings where long-term safety is crucial.

Capsaicin (Capsicum spp.) in neuropathic pain

Capsaicin, a vanilloid alkaloid derived from *Capsicum* species, is an FDA-approved topical phytochemical used for neuropathic pain, including post-mastectomy syndromes [86,87]. Its analgesic effect arises from selective activation of TRPV1-expressing nociceptive C-fibers, which produces an initial influx of Ca^{2+} and Na^{+} followed by functional desensitization of the channel and depletion of neuropeptides such as substance P and CGRP. This sustained reduction in nociceptor activity diminishes peripheral pain transmission without systemic toxicity [88]. At higher concentrations, capsaicin induces reversible "defunctionalization" of peripheral nerve endings through transient mitochondrial down-regulation and axonal retraction, after which reinnervation occurs with reduced excitability [88]. TRPV1 activation also engages anti-inflammatory pathways by suppressing NF-κB and COX-2 activity, lowering IL-1β and TNF-α, and enhancing local endocannabinoid signaling [86,87].

Clinically, low-dose topical creams (0.025–0.075%) applied daily over several weeks offer modest but meaningful analgesia, whereas the 8% capsaicin patch (Qutenza®) can provide pain relief lasting up to three months after a single 30–60-minute treatment [86]. Registry data show benefit across multiple neuropathic conditions, including post-mastectomy, and chemotherapy induced neuropathies, with side effects generally limited to transient erythema or burning at the application site [87]. Importantly, capsaicin does not cause systemic toxicity, tolerance, or dependence, even with repeated use [88]. Its combination of TRPV1 desensitization, neuroimmune modulation, and reversible peripheral-nerve remodeling makes capsaicin a practical non-opioid adjunct for chronic neuropathic pain, particularly in breast-cancer survivors.

Zingiber officinale (Ginger)

Zingiber officinale has been used in Traditional Chinese and Ayurvedic medicine for its analgesic, anti-inflammatory, and antioxidant properties [28]. Pharmacologic studies now confirm that its principal phenolics, 6-gingerol, 8-gingerol, 6-shogaol, and zingerone, act on multiple neuroinflammatory, oxidative, and nociceptive pathways relevant to chronic neuropathic pain [89,90]. These compounds suppress COX-1/COX-2 and 5-LOX activity, reducing prostaglandin and leukotriene synthesis, and down-regulate TNF-α, IL-1β and IL-6 through NF-κB/MAPK inhibition, limiting microglial activation and neuroimmune sensitization [89]. Gingerols and shogaols also modulate TRPV1 and TRPA1 channels, decreasing substance P release and dampening neuronal hyperexcitability, while activation of the Nrf2/ARE pathway enhances SOD, GSH, and GPx activity to support mitochondrial stability and protect neurons from oxidative injury [90]. These convergent actions explain the consistent antinociceptive and antiallodynic effects observed in experimental and clinical studies. Recent work also highlights improvements in mitochondrial resilience and gut–brain-axis regulation, suggesting broader neuroprotective benefits for Z. officinale beyond analgesia [89,90]. With its strong safety profile and multitarget mechanisms, ginger represents a practical non-opioid adjunct for chronic neuropathic pain, including cancer-related and post-mastectomy neuropathies.

Allium sativum (Garlic)

Allium sativum (garlic) has long been recognized for its antioxidant, anti-inflammatory, and neuroprotective properties. Its principal organosulfur compounds—allicin, ajoene, and S-allyl-cysteine—together with flavonoids and phenolic acids, act across several pathways relevant to neuropathic pain [91-93]. These constituents inhibit COX-2 and 5-LOX, lowering prostaglandin and leukotriene production, and they down-regulate TNF-α, IL-1β, and IL-6 while supporting IL-10, shifting the neuro-immune environment toward an anti-inflammatory state. Garlic also modulates TRPA1 and TRPV1 channels, reducing nociceptor excitability [91], and activates the Nrf2/ARE pathway, enhancing SOD, CAT, and GPx and improving mitochondrial redox stability [93]. Additional mitochondrial effects—including improved ATP generation and membrane-potential stabilization—contribute to its neuroprotective profile [92].

By acting simultaneously on inflammatory cascades, oxidative stress, and ion-channel activity, A. sativum offers analgesic support in neuropathic-pain models. Studies in chemotherapy induced neuropathy show reductions in hyperalgesia comparable to gabapentinoids but with a stronger safety margin [92,93]. Together, these findings position garlic as a practical, low-toxicity, non-opioid adjunct within integrative and oncologic pain-management settings.

Salvia officinalis and *Salvia divinorum*

The *Salvia* genus includes several plants with neuroprotective, anti-inflammatory, and antioxidant actions relevant to neuropathic pain [94]. *Salvia officinalis* (common sage) and *Salvia divinorum* (diviner's sage) are of particular interest because they act through complementary peripheral and central mechanisms [95,96]. In *S. officinalis*, triterpenoids such as ursolic acid, carnosol, and carnosic acid reduce TRPA1/TRPV1 hyperexcitability, inhibit NF-κB and COX-2 signaling, and suppress TNF-α, IL-1β, and IL-6 in dorsal-root ganglia (Boualam 2024). Sage flavonoids also enhance antioxidant defenses, including SOD and CAT, and help stabilize mitochondrial function in neuropathic-injury models (96). Essential oils rich in 1,8-cineole, camphor, and borneol add further peripheral benefit through NF-κB and COX-2 inhibition, reduced ROS production, and

blockade of voltage-gated calcium channels [95].

Salvia divinorum contributes a distinct central mechanism through salvinorin A, a highly selective κ-opioid receptor (KOR) agonist that partially modulates CB1 signaling and produces potent analgesia without euphoria, reward, or tolerance [96]. By activating spinal and supraspinal KOR pathways, salvinorin A decreases substance-P and glutamate release, reduces neuropathic hyperexcitability, and supports neuroimmune balance through IL-10/STAT3 activation and microglial M2 polarization [96]. Importantly, it does not stimulate mesolimbic dopamine pathways, lowering dependence risk compared with μ-opioid agonists [94]. Together, *S. officinalis* and *S. divinorum* provide a complementary phytotherapeutic profile—combining peripheral TRP-channel modulation, anti-inflammatory and antioxidant activity, and central KOR-mediated analgesia—making them non-addictive adjuncts for chronic neuropathic pain.

Crocus sativus (Saffron)

Crocus sativus L. (saffron) is a GRAS-designated botanical widely recognized for its analgesic, anti-inflammatory, and neuroprotective properties. Its major constituents—crocin, crocetin, safranal, and picrocrocin—work together to modulate oxidative stress, cytokine signaling, and neurotransmitter pathways, an effect increasingly supported by preclinical data and early clinical findings [97,98]. In chemotherapy-induced neuropathy models, crocin and crocetin reduce mechanical allodynia and thermal hyperalgesia by suppressing spinal TNF-α and IL-1β and by modulating serotonergic and dopaminergic transmission [98]. Saffron also enhances endogenous antioxidant defenses—boosting SOD, CAT, and GPx while lowering malondialdehyde—which helps protect peripheral and central neurons from oxidative and mitochondrial injury. Crocin and safranal inhibit NF-κB and COX-2, thereby decreasing TNF-α and IL-6 and limiting glial activation in dorsal-horn pain pathways.

Clinically, saffron has demonstrated additive benefit when used alongside agents such as α-lipoic acid or amitriptyline, improving analgesic outcomes with fewer adverse effects [97]. Taken together, *Crocus sativus* offers a multitarget approach to neuropathic-pain modulation through cytokine suppression, redox stabilization, and neurotransmitter regulation. Evidence from 2022–2023 supports saffron as a safe, well-tolerated adjunct for chronic neuropathic pain, particularly in oncology settings where low-toxicity, multimodal strategies are essential.

Curcuma longa (Turmeric)

Curcuma longa L. (turmeric) is a GRAS-recognized medicinal plant with well-established anti-inflammatory, antioxidant, and neuroprotective effects. Its principal polyphenol, curcumin, regulates several molecular pathways implicated in neuropathic pain, including cytokine cascades (IL-1β, IL-6, TNF-α), redox enzymes such as COX-2 and 5-LOX, and transcriptional regulators such as NF-κB, Nrf2, and JAK/STAT [66,99]. Through inhibition of NF-κB and JAK2/STAT3 signaling, curcumin reduces key pro-inflammatory cytokines and limits microglial and astrocytic activation, dampening spinal neuroinflammation [99]. It also enhances endogenous antioxidant defenses via Nrf2 activation—up-regulating SOD, CAT, and GPx and lowering ROS and malondialdehyde—thereby preserving mitochondrial stability in both chronic-constriction and chemotherapy-induced neuropathy models [58,66]. Curcumin modulates histone acetylation and BDNF-related gene expression and helps normalize monoaminergic signaling, targeting epigenetic and neurotransmitter pathways that often contribute to chronic pain states [66].

Translational studies show that nano-formulated and phytosomal curcumin markedly improve bioavailability and analgesic outcomes, and recent in-vivo work confirms reductions in thermal hyperalgesia and allodynia through combined antioxidant and neuroimmune mechanisms [100]. Together, these multitarget effects—cytokine suppression, antioxidant restoration, inflammasome inhibition, and epigenetic modulation—position *Curcuma longa* as a safe and versatile non-opioid adjunct for neuropathic pain. Evidence from 2023–2025 supports its relevance in chemotherapy-induced, post-surgical, and diabetic neuropathy, making curcumin a strong candidate for integrative pain-management approaches.

Syzygium aromaticum (Clove)

Syzygium aromaticum L. (clove) has a long record of medicinal use and is now recognized for its potent analgesic, anti-inflammatory, and antioxidant properties [83,101]. Its essential oil—dominated by eugenol and supported by β-caryophyllene and methyl salicylate—acts across several pathways central to neuropathic-pain physiology. Eugenol modulates TRPV1 and voltage-gated sodium channels, producing an initial excitatory response followed by sustained desensitization that lowers nociceptor excitability and dampens peripheral sensitization [102]. Evidence that naloxone reverses part of clove's analgesic effect suggests limited μ-opioid receptor cross-talk [103]. Clove extracts also inhibit NF-κB and reduce TNF-α, IL-1β, and IL-6, limiting glial activation and neuroinflammatory signaling [104]. At the synaptic level, eugenol suppresses NMDA-receptor currents and enhances GABA-A activity, helping restore the disrupted excitatory–inhibitory balance characteristic of neuropathic pain [105].

Clove's strong antioxidant profile further contributes to its neuroprotective activity: eugenol-rich extracts reduce lipid peroxidation and enhance endogenous antioxidant enzymes such as SOD, CAT, and GPx, thereby protecting neurons from ROS-driven mitochondrial dysfunction [104,106]. Regulation of intracellular Ca^{2+} flux adds smooth-muscle relaxation and antispasmodic effects [106], while studies in breast-cancer models showing eugenol-induced apoptosis [107] offer additional relevance for oncology-related neuropathic pain. Taken together, *Syzygium aromaticum* provides a robust, multitarget strategy for neuropathic-pain management through integrated ion-channel desensitization, cytokine suppression, neurotransmitter modulation, and antioxidant restoration. Recent findings (2024–2025) support its role as a safe, non-opioid adjunct for chronic, post-surgical, and cancer-associated neuropathic pain.

Harpagophytum procumbens (Devil's Claw)

Harpagophytum procumbens (Devil's Claw), has long been used for inflammatory, musculoskeletal, and neuropathic pain. Its therapeutic actions stem mainly from iridoid glycosides—harpagoside, harpagide, and procumbide—which exert anti-inflammatory, antioxidant, and antinociceptive effects. Contemporary studies confirm that these constituents modulate several pathways central to neuropathic pain. Harpagoside suppresses TNF-α, IL-1β, and COX-2, reducing prostaglandin-mediated neuroinflammation [108], while extracts enhance endogenous antioxidant defenses by up-regulating catalase, superoxide dismutase, glutathione reductase, and peroxiredoxin-2, thereby protecting neurons from ROS-driven injury [109]. Additional

work shows reductions in serotonin (5-HT), prostaglandin E_2, and 8-iso-prostaglandin $F_2\alpha$—mediators directly associated with hyperalgesia and allodynia [110]. Harpagide's suppression of inducible nitric-oxide synthase (iNOS) and nitric oxide offers an added neuroprotective effect without the renal or gastrointestinal risks associated with NSAIDs [110]. Together, these actions explain why Devil's Claw is considered a well-tolerated botanical alternative for chronic inflammatory and neuropathic conditions [111,112].

Overall, the combined effects of Devil's Claw on cytokine signaling, oxidative stress, and nociceptor sensitization support its role as a multitarget modulator of chronic neuropathic pain. Preclinical and translational studies [112] suggest benefit in post-surgical and chronic neuropathies, including post-mastectomy pain syndromes. Yet, despite extensive traditional use and evidence in musculoskeletal disorders, randomized controlled trials specifically evaluating neuropathic pain remain scarce. Further work is needed to clarify optimal dosing, bioavailability, and long-term safety [80,110]. Notably, no randomized controlled trials from 2023–2025 have examined *H. procumbens* in post-surgical or chemotherapy-induced neuropathic pain, highlighting a clear need for focused clinical investigation.

Rosa damascena (Damask Rose)

Rosa damascena Mill., long used in Persian, Greek, and Unani medicine for its calming and analgesic properties, contains flavonoids (kaempferol, quercetin), monoterpenes (β-citronellol, geraniol, myrcene), and 2-phenylethyl alcohol (PEA) that collectively provide anti-inflammatory, antioxidant, anxiolytic, and neuromodulatory effects relevant to neuropathic pain [28]. These constituents act on both central and peripheral pathways: inhaled or systemically absorbed volatiles modulate amygdalo-hippocampal–cortical circuits, reduce limbic hyperactivity, and enhance serotonergic and dopaminergic signaling, while protecting hippocampal neurons from oxidative injury (Xia 2024). Peripherally, rose-derived flavonoids and monoterpenes inhibit NF-κB and COX-2 and suppress TNF-α, IL-1β, and IL-6, limiting glial activation and restoring antioxidant defenses such as SOD, CAT, and GPx (28). Rose essential oil also improves autonomic balance by lowering sympathetic tone and enhancing vagal activity, helping reduce stress-driven amplification of pain [113]. Toxicologic studies confirm a favorable safety profile with no genotoxic or reproductive risks at therapeutic doses [114].

Through this combination of emotional regulation, neuroimmune modulation, and oxidative protection, R. damascena represents a plausible non-opioid adjunct for chronic and post-surgical neuropathic pain, including in breast-cancer survivors. Its capacity to dampen cytokine-driven inflammation, reduce central sensitization, and counteract stress-related hyperalgesia aligns well with integrative pain-management frameworks. However, no randomized controlled trials to date (2023–2025) have evaluated its efficacy specifically in post-mastectomy or chemotherapy induced neuropathy, underscoring the need for targeted clinical research.

Rosmarinus officinalis L. (Rosemary)

Rosmarinus officinalis L. has a long history of use for pain, inflammation, and muscle tension, and contemporary research supports its relevance to neuropathic-pain pathways. Its principal monoterpenes (1,8-cineole, camphor) and diterpenes (carnosic acid, carnosol) exert coordinated neuroprotective, anti-inflammatory, antioxidant, and vasomodulatory effects [115,116]. Carnosic acid and carnosol modulate voltage-gated calcium and potassium channels, reducing neuronal hyperexcitability while stabilizing mitochondrial function and limiting calcium-driven excitotoxicity [117,118]. Rosemary diterpenes further inhibit NF-κB, MAPK, and COX-2 signaling, lowering TNF-α, IL-1β, and PGE_2 and dampening glial activation associated with mechanical and thermal hyperalgesia [116]. Volatile constituents such as 1,8-cineole and camphor also act on α_1/α_2-adrenergic receptors to enhance microcirculatory perfusion, contributing to analgesic and muscle-relaxant effects [115]. Preclinical neuropathic-pain models consistently show reductions in microglial and astrocytic activation and restoration of antioxidant enzymes—including SOD, CAT, and GPx—helping re-establish redox balance [116,118]. Clinically, rosemary-containing formulations have improved pain and function in chronic musculoskeletal conditions, supporting its translational potential [112].

Taken together, rosemary offers a multidimensional profile—ion-channel regulation, cytokine and prostaglandin suppression, adrenergic modulation, and antioxidant support—that aligns well with the neurobiological features of chronic neuropathic pain, including in cancer survivors. While emerging evidence is encouraging, no randomized trials from 2023–2025 have specifically evaluated its use in post-mastectomy or chemotherapy-induced neuropathy, underscoring the need for targeted clinical investigation.

Mentha × piperita (Peppermint)

Mentha × piperita L. (peppermint), a GRAS-recognized hybrid of Mentha aquatica and Mentha spicata, has long been used for its analgesic, anti-inflammatory, and antispasmodic effects. Its principal monoterpene, menthol—along with menthone and peppermint flavonoids—shows broad neuromodulatory activity relevant to neuropathic pain. Recent studies report that both topical and inhaled preparations can reduce neuropathic-pain intensity and improve sensory tolerance in chemotherapy- and surgery-related models [64,119,120]. Menthol activates TRPM8 and modulates TRPA1 on peripheral nociceptors, producing a cooling-desensitization effect that reduces mechanical and thermal allodynia [64,121]. Peppermint essential oil also suppresses TNF-α, IL-1β, and IL-6 via NF-κB and COX-2 inhibition, limiting neuroinflammation and glial activation [119,122]. In parallel, menthol stabilizes voltage-gated sodium and calcium channels and enhances GABAergic tone, helping restore the disrupted excitatory–inhibitory balance characteristic of neuropathic circuits [64,121].

Clinical studies have shown that peppermint oil inhalation reduces postoperative pain and anxiety after lumbar discectomy in a randomized trial [120], while topical menthol improved pain thresholds and quality-of-life measures in chemotherapy-induced peripheral neuropathy [64,122]. Taken together, these data position Mentha × piperita as a multifaceted, non-opioid adjunct acting through TRPM8/TRPA1 desensitization, cytokine suppression, and ion-channel stabilization. Its strong safety profile supports its consideration for chronic neuropathic pain—including chemotherapy- and post-mastectomy-related syndromes—though dedicated trials in post-mastectomy neuropathic pain are still needed [64,119-122].

Elaeagnus angustifolia L. (Senjed, Russian Olive)

Elaeagnus angustifolia L. (Senjed, Russian Olive), long used in Persian and Central Asian medicine for nerve and musculoskeletal pain, has gained modern support for its relevance to neuropathic-

pain pathways. Its flavonoids, phenolic acids, and glycosides exert coordinated anti-inflammatory, antioxidant, and neuromodulatory effects [123-126]. Extracts consistently suppress TNF-α, IL-1β, and COX-2 via NF-κB and MAPK inhibition, reducing neurogenic inflammation and nociceptive signaling [123,126]. In parallel, its antioxidant constituents enhance SOD and catalase, limit ROS accumulation, and help preserve mitochondrial integrity in neuronal and glial cells—an important protective mechanism in chronic oxidative injury [123,126].

Evidence also suggests interactions with GABAergic and serotonergic systems, which may lessen central sensitization and modulate the emotional dimensions of neuropathic pain [125]. Phenolic glycosides demonstrate smooth-muscle–relaxant activity through calcium-channel blockade and may improve regional perfusion, easing tension that often accompanies neuropathic states. Together, these anti-inflammatory, antioxidant, neuromodulatory, and vascular actions position E. angustifolia as a biologically plausible non-opioid adjunct for post-surgical, diabetic, and chemotherapy-related neuropathic pain. However, no randomized controlled trials have yet evaluated its use specifically in post-mastectomy or chemotherapy induced neuropathy, highlighting the need for targeted clinical research [123,124].

Ugni myricoides (Black Chilean Guava)

Ugni myricoides, a South American species of the Myrtaceae family, produces an essential oil rich in terpenoids that exhibits analgesic, anti-inflammatory, and neuroprotective activity. Its dominant constituents, α-pinene (~52%), 1,8-cineole (~12%), and β-caryophyllene (~3%), act synergistically on central and peripheral pathways relevant to neuropathic pain [29,127]. Consistent with other Myrtaceae-derived oils, U. myricoides combines antinociceptive and antioxidant effects mediated through terpenoid signaling [128,129]. α-Pinene modulates glutamatergic and cholinergic transmission and reduces neuronal hyperexcitability [127,130], while 1,8-cineole and β-caryophyllene suppress TNF-α, IL-1β, and COX-2, limiting neuroinflammation and peripheral sensitization [8,129,131]. These constituents also strengthen endogenous antioxidant defenses by lowering ROS and enhancing SOD, CAT, and GPx activity, supporting mitochondrial and neuronal redox balance [28,31].

Together, this terpenoid profile produces a coherent multimodal effect, anti-inflammatory, antioxidant, and neuromodulatory, that translates into measurable analgesia. Preclinical studies report antinociceptive efficacy comparable to indomethacin and gabapentin, underscoring the translational potential of U. myricoides for refractory neuropathic pain [127,131]. However, no randomized clinical trials have yet examined its role in human neuropathic-pain populations, highlighting the need for focused research, particularly in post-surgical and chemotherapy-induced neuropathies.

Cornus officinalis (Shan Zhu Yu, *Fructus Corni*)

Cornus officinalis (Shan Zhu Yu), a core herb in TCM, contains secoiridoid glycosides, triterpenoids, flavonoids, and phenolic acids, with morroniside and loganin identified as its principal bioactive constituents [39,64]. Contemporary research shows that these compounds exert anti-inflammatory, antioxidant, neuroprotective, and antinociceptive effects relevant to neuropathic pain. A substantial body of work demonstrates that C. officinalis activates glucagon-like peptide-1 receptors (GLP-1R), modulates microglial cytokine balance, and stabilizes mitochondrial function—three mechanisms central to the persistence of neuropathic pain [26,132,133]. Morroniside and related secoiridoids function as GLP-1R agonists in both spinal and dorsal-root–ganglion tissues, reducing neuronal hyperexcitability and enhancing β-endorphin release [26,132]. GLP-1R activation also increases IL-10 and TGF-β, promoting a more anti-inflammatory milieu within central pain circuits [133].

C. officinalis additionally limits glial-driven neuroinflammation by suppressing microglial activation, reducing TNF-α and IL-1β, and increasing IL-10, thereby lowering central sensitization [64,134]. Its mitochondrial-stabilizing actions—preserving membrane integrity, reducing ROS, and up-regulating antioxidant enzymes such as SOD, CAT, and GPx—further support neuronal survival under neuropathic stress [132,135]. Taken together, these synergistic effects position Cornus officinalis as a promising non-opioid adjunct for neuropathic pain, especially in conditions marked by oxidative stress, glial activation, and central sensitization. Despite compelling mechanistic and preclinical evidence, randomized clinical trials have not yet evaluated its efficacy in post-mastectomy or chemotherapy-induced neuropathy, highlighting a clear need for future clinical investigation.

Salix alba L. (White Willow Bark)

Salix alba (white willow bark) has long been used as a natural analgesic, owing to its salicin content, which is metabolized to salicylic acid and suppresses COX-2–mediated prostaglandin production. The U.S. National Center for Complementary and Integrative Health recognizes it as a safe, evidence-supported botanical for inflammatory pain [136]. Recent pharmacologic data extend its relevance to neuropathic pain, showing that *S. alba* extracts inhibit NF-κB activation and reduce pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6—pathways central to both peripheral and central sensitization [58,137-140].

Beyond cytokine suppression, white willow bark demonstrates antioxidant and neuroprotective effects by enhancing SOD and GPx activity, reducing reactive oxygen species, and preserving mitochondrial integrity—mechanisms highly relevant to neuropathic pain associated with oxidative stress [137,138]. Although most randomized trials have focused on musculoskeletal conditions, the mechanistic overlap strongly supports investigating *S. alba* as a low-toxicity adjunct in neuropathic and post-surgical pain, particularly given its favorable safety profile and lower gastrointestinal risk compared with synthetic salicylates [58,136,140].

Myristica fragrans (Nutmeg)

Myristica fragrans Houtt. (Myristicaceae) has been used traditionally for its analgesic, anti-inflammatory, and antioxidant properties, and recent pharmacologic work supports its relevance to neuropathic pain. Its essential oil contains several phenylpropanoids—most notably myristicin—which exert neuroprotective and antinociceptive actions. Contemporary studies show that nutmeg extracts suppress key inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8), reduce chemokines such as MCP-1 and MIP-1α/β, and decrease myeloperoxidase activity, thereby limiting macrophage and neutrophil recruitment and dampening neuroinflammation central to neuropathic-pain sensitization [141,142]. Nutmeg constituents also inhibit COX-2, lowering PGE_2 synthesis and mitigating inflammatory hyperalgesia with gastrointestinal tolerability that may surpass that of traditional NSAIDs [29,143].

In addition to these anti-inflammatory effects, nutmeg influences

neurotransmission and neuropeptide signaling relevant to central sensitization. Its essential oil appears to reduce Substance P release and diminish neuronal hyperexcitability, mechanisms consistent with lowering pain transmission in chronic neuropathic states despite limited direct clinical trials [142,144]. Together, this combination of cytokine suppression, COX-2 inhibition, and neuromodulatory regulation provides a coherent mechanistic rationale for Myristica fragrans as a non-opioid adjunct for neuropathic pain. While human RCT evidence remains sparse, the pharmacologic foundation and favorable safety profile support further translational investigation and thoughtful incorporation alongside standard analgesic therapies.

Morinda citrifolia L. (Noni)

Morinda citrifolia L. (noni), a Rubiaceae species long used in Polynesian and Caribbean medicine for pain, inflammation, and oxidative stress, is traditionally known as the "pain-killer tree." Both oral and topical preparations have been used for chronic pain syndromes, and contemporary studies now support several mechanistic pathways through which noni may modulate neuropathic pain. Its extracts influence COX-2 activity, matrix metalloproteinase-9 (MMP-9) expression, and GABA-A receptor function, together forming a non-opioid, multitarget profile relevant to peripheral and central sensitization [103,145-147]. COX-2 inhibition reduces prostaglandin E_2 (PGE_2) synthesis and dampens inflammatory nociceptive signaling, while suppression of MMP-9 limits extracellular-matrix degradation and inflammatory infiltration—processes implicated in peripheral neuroinflammation.

At the neuronal level, noni's iridoids and alkaloids appear to modulate GABA-A receptors, stabilizing neuronal excitability and offering an additional anxiolytic component that may benefit chronic neuropathic-pain states. Through the combined effects of COX-2 suppression, MMP-9 reduction, and GABA-A receptor modulation, Morinda citrifolia provides both peripheral and central analgesic mechanisms without relying on opioid pathways. Although these mechanistic findings are well supported, formal randomized clinical trials in post-mastectomy or chemotherapy-induced neuropathy have not yet been conducted, underscoring the need for targeted translational research.

Conclusion

Medicinal plants—used for centuries to relieve pain and restore physiological balance—continue to provide valuable adjunctive options alongside conventional pharmacologic therapy. Their diverse phytochemicals, including polyphenols, terpenoids, alkaloids, and iridoids, act across anti-inflammatory, antioxidant, neuromodulatory, and epigenetic pathways that address both peripheral and central contributors to neuropathic pain. Many botanicals also influence mood, stress responses, and neuroimmune signaling, supporting the psychological dimensions of recovery [96,98,100].

Although generally safer than synthetic analgesics, the effectiveness and safety of plant-based therapies depend on proper species identification, standardized extraction, bioactive consistency, and attention to patient-specific factors. Certain constituents—such as aconitine from Aconitum spp., salicylates from Salix alba, and highly concentrated essential oils—carry risks when improperly dosed or combined with other medications, underscoring the need for professional oversight [58].

When appropriately standardized and integrated into multimodal care, botanicals can reduce reliance on opioids and NSAIDs and improve chronic neuropathic-pain outcomes. As summarized in Table 1, agents such as Zingiber officinale, Curcuma longa, Crocus sativus, Piper nigrum, Cannabis sativa, and composite formulations including Kampo, Yokukansan, Neuragen PN, and PRP share convergent mechanisms involving TRP-channel desensitization, NF-κB and MAPK inhibition, cytokine suppression, and redox stabilization [29,56,64,128,134]. These overlapping pathways provide a strong scientific basis for multi-target phytotherapy as a non-opioid strategy for neuropathic-pain management.

Recent integrative analyses further reinforce the translational relevance of these mechanisms across diverse botanicals [58]. Ultimately, the responsible incorporation of phytomedicine into conventional frameworks can support a patient-centered, evidence-based model of care that enhances analgesia while promoting systemic regulation and emotional well-being. Continued standardization, rigorous clinical validation, and trained practitioner guidance remain essential to ensure safety and therapeutic effectiveness [95,99].

Future Perspectives

Despite promising preclinical findings and early clinical signals, significant gaps remain before phytotherapeutics can be fully integrated into evidence-based neuropathic-pain management. A critical next step is the completion of rigorous randomized controlled trials evaluating efficacy, safety, dose–response profiles, and pharmacokinetic consistency for leading phytochemicals across diverse neuropathic-pain subtypes. Parallel mechanistic studies using multi-omics platforms (genomics, transcriptomics, proteomics, and metabolomics) will be essential for clarifying synergistic molecular networks and identifying biomarkers predictive of treatment response, ultimately supporting more personalized botanical interventions. Advancements in formulation science, particularly nanocarrier, liposomal, and phytosomal delivery systems, offer additional potential to improve bioavailability, tissue penetration, and CNS accessibility of key phytochemicals.

Equally important is the establishment of unified standards for botanical authentication, chemical consistency, and manufacturing quality. Globally harmonized regulatory frameworks—aligned with ISO and WHO guidelines—are needed to ensure reproducibility, safety, and cross-border regulatory credibility [35]. Strengthening pharmacovigilance through long-term registries and systematically updated herb–drug interaction databases will further support safe clinical integration and real-world monitoring. Looking ahead, interdisciplinary models that combine validated botanicals with nutritional, behavioral, and rehabilitative therapies may help achieve synergistic analgesic effects and improved functional outcomes.

Bridging traditional ethnobotanical knowledge with contemporary systems biology has the potential to position phytotherapy as a cornerstone of precision integrative pain medicine. As research infrastructure matures, collaborative efforts among clinicians, pharmacologists, and regulatory scientists will be essential to translate mechanistic promise into reproducible clinical benefit. Through standardized, ethically sustainable, and scientifically grounded approaches, botanical therapeutics may provide effective, low-toxicity, and holistic relief for individuals living with chronic neuropathic pain.

A hierarchical translational framework illustrating the role of

phytotherapy in post-mastectomy neuropathic pain among breast-cancer survivors.

Key phytotherapeutic inputs—Curcuma longa, Zingiber officinale, Piper nigrum, Crocus sativus, and Cannabis sativa—converge on shared molecular mechanisms including ↓ neuroinflammation (NF-κB and MAPK inhibition), ↑ antioxidant response (Nrf2/ARE activation), ↓ glial activation, and ↑ GLP-1 receptor and β-endorphin signaling.

These processes yield clinically relevant outcomes such as ↓ opioid dependence, ↑ quality of life, and ↑ emotional and energetic stability.

The model further emphasizes formulation standardization, safety monitoring, and clinician-guided integration within personalized multimodal care frameworks.

(↑ = activation/up-regulation; ↓ = inhibition/down-regulation.)

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