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# Review Article: The Potential of Terpenoids from Marine Organisms as Neuroprotective Agents in Peripheral Neuropathy

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**Abstract:** Peripheral neuropathy is a common neurological disorder, especially in individuals with diabetes mellitus and older adults, while current treatment options remain limited, encouraging the search for alternative therapies. This narrative review focuses on the potential role of terpenoids obtained from marine sources as neuroprotective agents in peripheral neuropathy. Terpenoids are involved in multiple mechanisms, such as reducing oxidative stress and inflammation, affecting ion channel activity, and regulating signaling pathways such as PI3K/Akt, MAPK, and Nrf2. These mechanisms are associated with lower oxidative stress, suppression of neuroinflammation, and improved neuronal survival. Compounds such as astaxanthin show promising effects in reducing neuropathic pain, although evidence remains largely preclinical. Clinical translation is limited by low bioavailability and insufficient long term safety data, and additional research is needed to clarify their therapeutic potential.

**Keywords:** peripheral neuropathy, marine terpenoid, neuroprotective agent, neuroinflammation

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## Introduction

Peripheral neuropathy is a disorder of the peripheral nervous system characterized by damage to sensory, motor, or autonomic nerves, leading to symptoms such as pain, paresthesia, muscle weakness, and organ dysfunction (Hammi et al., 2022). The prevalence of peripheral neuropathy ranges from 1% to 7% in the general population and increases with advancing age (Castelli et al., 2020). It occurs more frequently in individuals with chronic diseases, particularly diabetes mellitus, which accounts for approximately 66% of cases (Harsa et al., 2023). Other contributing factors include infections and exposure to toxic substances (Hammi et al., 2022). As a result, peripheral neuropathy significantly reduces patients' quality of life (Burhan et al., 2026).

The pathogenesis of peripheral neuropathy is multifactorial, involving oxidative stress, neuroinflammation, mitochondrial dysfunction, and neuronal apoptosis, which contribute to progressive nerve damage and persistent neuropathic pain (Yang et al., 2025). However, current treatments mainly focus on symptom relief, as first-line pharmacological therapies, including gabapentinoids, serotonin–norepinephrine reuptake inhibitors, and tricyclic antidepressants, are effective in reducing neuropathic pain but have limited

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effects on nerve regeneration and disease progression (Price et al., 2022). In addition, they are frequently linked to adverse effects that can decrease patient adherence and hinder long term use (Thouaye et al., 2023). Therefore, safer and more effective therapeutic approaches.

Over the past decades, bioactive compounds from marine organisms has rapidly expanded as a source of new drug candidates. The extreme marine environment drives organisms to produce unique secondary metabolites with complex molecular structures and diverse biological activities (Zeng et al., 2025). One important class of these compounds is terpenoids, which have been reported to possess diverse pharmacological properties, such as antiinflammatory, antioxidant, and neuroprotective activities (Xu et al., 2022). These biological activities directly target key mechanisms involved in peripheral neuropathy, including oxidative stress, neuroinflammation, and neuronal apoptosis, making marine derived terpenoids promising candidates for neuroprotective therapy.

Marine derived terpenoids have demonstrated potential in protecting neurons through multiple mechanisms, including decreasing oxidative stress, suppressing inflammatory responses, and preventing neuronal apoptosis. These mechanisms are relevant to the pathogenesis of peripheral neuropathy, which involves enhanced formation of reactive oxygen species (ROS), activation of inflammatory pathways, and mitochondrial dysfunction (Yang et al., 2025). Therefore, terpenoids may not only alleviate symptoms but also slow the progression of nerve damage. Although previous studies have reported their neuroprotective effects, the available evidence remains scattered and has not been comprehensively synthesized in the context of peripheral neuropathy. Accordingly, this review provides a comprehensive synthesis of current evidence on marine-derived terpenoids as neuroprotective agents in peripheral neuropathy by integrating their sources, mechanisms of action, and therapeutic prospects.

## Methods

This study was conducted as a review article by systematically searching the literature in PubMed, ScienceDirect, and Google Scholar databases. The search was performed using the keywords "peripheral neuropathy," "marine terpenoids," "neuroprotective," and "neuropathic pain" for publications from 2016 to 2026, limited to articles published in Indonesian or English. The retrieved data were analyzed descriptively by classifying the information based on the types of terpenoids, sources of marine organisms, mechanisms of action, and therapeutic roles in peripheral neuropathy.

## Results and Discussion

### Peripheral Neuropathy

This damage may be caused by various conditions, including systemic diseases, metabolic disorders, infections, toxin exposure, and complications of medical therapies, leading to impairments in sensory, motor, and autonomic functions (Hutapea et al., 2016; Gumkowska et al., 2024).

*Etiology*

1. Injury or Trauma

Trauma is a major cause of peripheral neuropathy, particularly in younger individuals. The incidence of peripheral nerve injury due to trauma is approximately 1.46%–2.8%, with the upper extremities being the most common site. Injuries may occur due to traffic accidents, sports activities, or direct trauma, leading to impaired nerve conduction, axonal degeneration, and structural alterations of nerves, which ultimately result in peripheral neuropathy (Lavorato et al., 2023).

2. Diabetes Mellitus

Diabetes mellitus is the primary cause of peripheral neuropathy, with the risk increasing with the duration of the disease. Chronic hyperglycemia causes damage to small blood vessels, impaired blood flow, oxidative stress, and the activation of metabolic pathways that damage peripheral nerves. As a result, neuropathy develops progressively and significantly reduces patients' quality of life (Nurjannah et al., 2023).

3. Infections

Several infections can lead to peripheral neuropathy, particularly Human Immunodeficiency Virus (HIV), which damages nerves through inflammatory processes, viral toxicity, and the effects of antiretroviral therapy. In addition, herpes viruses such as Varicella Zoster Virus, Herpes Simplex Virus type 1, and Herpes Simplex Virus type 2 are neurotropic, capable of remaining latent in nerve ganglia, and upon reactivation can cause radiculopathy, cranial neuropathy, and other peripheral nerve disorders (Kaku et al., 2018).

4. Alcohol

Chronic alcohol consumption is another important cause of peripheral neuropathy, affecting large, small, and autonomic nerve fibers. Its pathogenesis is multifactorial, including the direct toxic effects of alcohol, nutritional deficiencies (particularly vitamins B1 and B12), liver cirrhosis, toxin exposure, and impaired glucose metabolism. These factors collectively contribute to peripheral nerve damage with varied clinical manifestations (Julian et al., 2019).

**Pathophysiology**

Neuropathic pain arises from injury or dysfunction of the somatosensory nervous system, leading to abnormal pain signaling. Unlike nociceptive pain, it is caused by maladaptive changes in the peripheral and central nervous systems. Peripheral nerve injury increases neuronal excitability through sodium channel upregulation, generating spontaneous nerve impulses that cause chronic burning, stabbing, or electric shock-like pain (Sic et al., 2024).

In addition, peripheral sensitization develops as a result of inflammatory cytokine release and chemokines from damaged nerve tissues. These inflammatory mediators attract immune cells to the injured area and enhance neuronal sensitivity to pain stimuli. This sensitization increases pain perception and exacerbates neuropathic symptoms (Gu et al., 2024).

Central sensitization also contributes significantly to the pathophysiology of neuropathy. This process results from increased neuronal activity in the spinal cord and brain. Glutamate and other excitatory neurotransmitters activate NMDA and AMPA receptors, which enhances neuronal communication and strengthens pain signal transmission (Sic et al., 2024). Consequently, pain becomes persistent and challenging to manage.

Microglia and astrocytes, which are types of glial cells, are also critically involved in the development of neuropathic pain. Microglial activation stimulates the production of inflammatory cytokines, which further enhance central sensitization. Astrocytes contribute by increasing glutamate release and reducing its reuptake, thereby intensifying pain transmission and maintaining chronic pain states (Xie et al., 2022).

**Clinical Manifestations**

1. Sensory Symptoms

Sensory symptoms are the most common manifestations of peripheral neuropathy, including paresthesia characterized by tingling or burning sensations in the extremities, particularly in the feet. Patients may also experience neuropathic pain, which is often described as sharp, stabbing, or burning in nature. In addition, reduced sensation or numbness may occur, leading to impaired perception of temperature and pain. This condition increases the risk of unrecognized injuries in affected individuals (Putri et al., 2020; Sim et al., 2023).

2. Motor Symptoms

Motor symptoms in peripheral neuropathy include muscle weakness, particularly in distal muscles, which may progress proximally. Damage to motor nerves can also lead to muscle atrophy, foot deformities such as hammertoes and pes cavus, and reduced tendon reflexes. These conditions may result in impaired balance and a higher risk of falls (Putri et al., 2020; Sim et al., 2023).

3. Autonomic Symptoms

Peripheral neuropathy may also affect the autonomic nervous system. Clinical manifestations include orthostatic hypotension, impaired sweating regulation, gastrointestinal disturbances, and genitourinary dysfunction such as urinary retention and erectile dysfunction. These autonomic disturbances may have a substantial impact on patients' quality of life (Putri et al., 2020; Sim et al., 2023).

**Terpenoids**

Terpenoids, commonly referred to as terpenes, constitute one of the largest classes of natural compounds and exhibit highly diverse and complex chemical structures. These compounds are produced through biosynthetic processes and can be categorized according to the number of isoprene (C5) units they contain, including hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterterpenes (C25), triterpenes (C30), tetraterpenes (C40), and polyterpenes ($n > 8$) (Camara et al., 2024). In addition, numerous derivatives and modified forms of terpenoids have been identified.

Terpenoids have been reported to exhibit various biological activities, such as anti-inflammatory effects, anticarcinogenic, and neuroprotective effects (Xu et al., 2022). They have been used for centuries in traditional medicine to enhance memory and cognitive function, as well as for their anti-inflammatory, antibacterial, antiplasmodial, anticancer, and antioxidant properties. Moreover, terpenoids have demonstrated beneficial effects in the management of anxiety, mood disorders, and depression (Mony et al., 2022).

**Pharmacological Activities of Terpenoids**

1. Neuroprotective Effects on the Blood Brain Barrier (BBB)

BBB damage is triggered by neuroinflammation, oxidative stress, and the activation of signaling pathways, including PI3K, MAPK, and NF-κB. The integrity of the BBB is crucial in neuropharmacology, as it serves as the primary barrier regulating drug entry into the brain. Terpenoids exhibit multitarget neuroprotective properties by modulating these pathways, and provide neuroprotective effects. For example, ginkgolide B has been reported to enhance BBB permeability and decrease brain edema in animal models (Mony et al., 2022).

2. Inducing receptor protein binding

Modulation of the GABAergic system

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter that maintains neural

activity balance. Impairment of the GABAergic system is associated with various neuropsychiatric disorders. Terpenoids and other bioactive compounds are known to modulate this system, producing anxiolytic and antidepressant effects and offering potential as safer alternative to conventional therapies (Mony et al., 2022).
Blockade of dopamine D1 and D2 receptors

The dopaminergic system plays a key role in regulating neural function, where excessive dopamine activity is associated with psychotic disorders. Blocking dopamine D1 and D2 receptors is a therapeutic strategy to reduce these symptoms. Terpenoids such as limonene have been shown to modulate dopaminergic activity and provide neuroprotective effects (Mony et al., 2022).

**The PI3K/Akt Signaling Pathway in Neuroprotection**

The PI3K/Akt signaling cascade plays a key role in regulating neuronal growth, proliferation, and survival. PI3K activation triggers Akt phosphorylation, which in turn regulates various downstream proteins involved in metabolism and apoptosis (Putri et al., 2020). Terpenoids are known to exert neuroprotective effects through activation of this pathway (Yang et al., 2025). Akt enhances cell viability by downregulating pro-apoptotic factors such as Bax while upregulating anti-apoptotic mediators like Bcl-2, as well as activating Nrf2 and CREB (Putri et al., 2020). Nrf2 contributes to the upregulation of antioxidant genes, including HO-1 and suppressing the NF-κB inflammatory pathway, while CREB increases the expression of neuroprotective proteins (Lavorato et al., 2023; Putri et al., 2020). Additionally, Akt also influences the Wnt/β-catenin pathway and increases mTOR activity, which is involved in protein synthesis and cellular energy regulation (Putri et al., 2020).

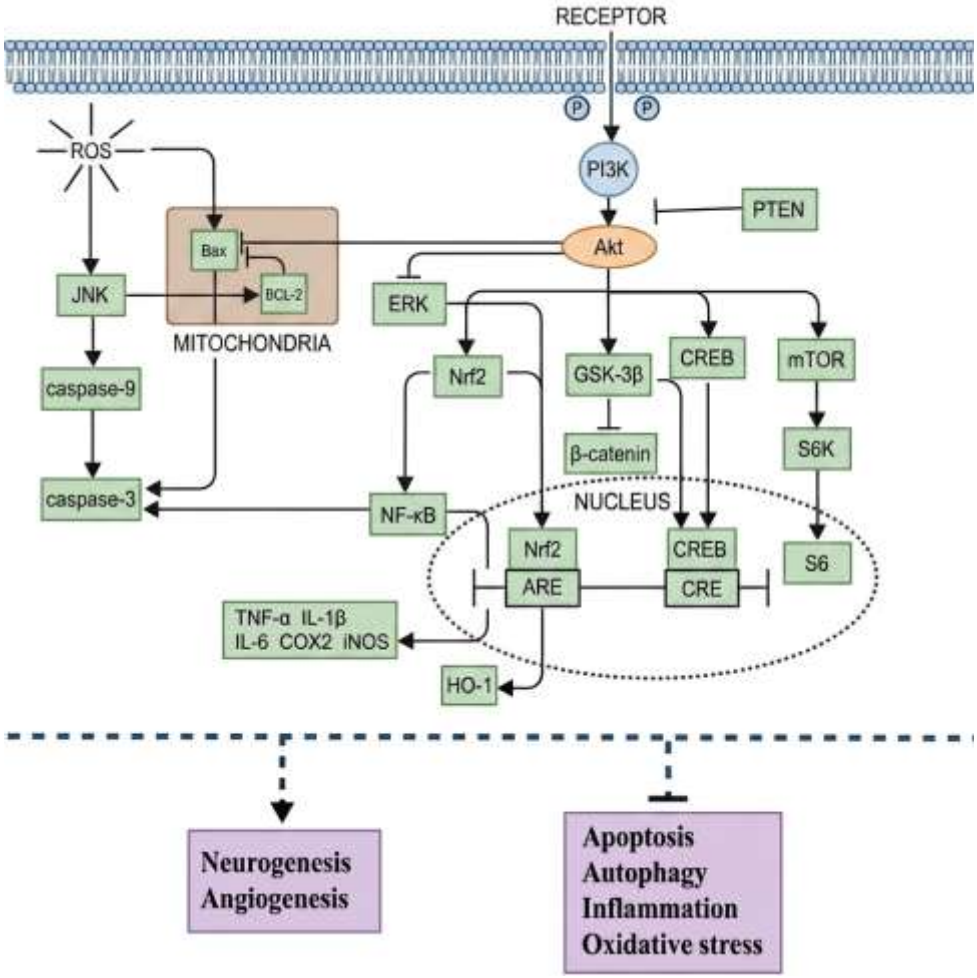


**Figure 2.** The PI3K/Akt Signaling Pathway in Neuroprotection

**Terpenoids from Marine Sources**

Terpenoids derived from marine sources possess unique chemical structures and exhibit higher pharmacological potential compared to terrestrial terpenoids or those from plant sources (Rampengan et al., 2025). The following table presents marine organisms that produce terpenoids along with their respective characteristics.

**Table 1.** Marine organisms producing terpenoids

| Marine Source | Terpenoid Class | Structural Features and Adaptations |
|---|---|---|
| Brown algae (*Sargassum*, *Ecklonia*) | Fucosterol (triterpenoid sterol); sargaquinoic acid (meroterpenoid); fucoxanthin (carotenoid) | Compounds frequently identified include halogenated and polycyclic diterpenes with highly oxygenated structures, including quinones and epoxide groups. Terpenoids can also interact with phenolic moieties to form meroterpenes (Saeed et al., 2021). Variations in chemical structure are affected by environmental conditions, such as salinity, light intensity, and predator-related stress. Furthermore, the extracts have demonstrated broad antioxidant capacity together with notable inhibitory effects on enzymes (Gowd et al., 2021). |
| Sponges (*Callyspongia*, *Aplysina*) & corals | Halimane diterpenoids; sesquiterpenes (e.g, scalane); sipholenol triterpenes | Characteristic features include halogenation, such as bromination (Br) and chlorination (Cl), on the ring (Vignaud et al., 2023). This enhances membrane permeability and the ability of to bind to target proteins. These compounds also exhibit antioxidant activity (Genovese et al., 2021). |
| Microalgae & plankton (*Haematococcus* microalgae) | Astaxanthin, β-karoten (tetraterpenoids) | Possess a conjugated polyene chain with a polar end group, enabling membrane integration and ROS scavenging. The keto carotenoid structure of astaxanthin further enhances antioxidant activity (Casertano et al., 2023). |
| Marine bacteria and fungi (symbiotic) | (A variety of terpenoids, including isoprenoids produced by symbiotic bacteria) | Marine microorganisms produce simple C20 diterpenes, often halogenated, that function in defense and influence the chemistry of host organisms. Although their antidiabetic potential remains limited, they offer promising prospects through fermentation. |

**Structure Activity Relationship of Marine Terpenoids**

The unique structural attributes of marine derived terpenoids specifically halogenation, polyene conjugation, and epoxide groups fundamentally dictate their neuroprotective efficacy against peripheral neuropathy. Halogenation, particularly bromination and chlorination which are highly prevalent in the marine environment, significantly enhances the lipophilicity of these compounds (Mandal et al., 2025). This increase in lipid solubility facilitates their penetration through BBB and neuronal membranes, allowing them to target intracellular pathways effectively while also establishing strong halogen-bonding interactions within specific receptor binding pockets (Diao et al., 2023).

Additionally, the conjugated polyene systems found in these terpenoids act as highly efficient electron delocalization networks. This configuration allows them to effectively quench reactive oxygen species (ROS) and reduce mitochondrial oxidative stress, a major driver of peripheral nerve injury (Rampengan et al., 2025). By inducing mild electrophilic stress, these systems can also activate the Nrf2 pathway, boosting endogenous antioxidant defenses (Lavorato et al., 2023**).** Furthermore, the presence of highly strained epoxide rings enables these compounds to undergo targeted nucleophilic attacks (such as with the thiol groups of cysteine residues on pro-inflammatory proteins), thereby covalently inhibiting chronic neuroinflammatory cascades, such as the NF-κB pathway, which are otherwise responsible for neuropathic pain (Mandal et al., 2025).

Consequently, the synergy between these distinct marine modifications and their precise structural interactions with neuronal targets highlights the promising therapeutic potential of marine terpenoids over their terrestrial counterparts. Understanding these structure activity relationships offers a clear rational design framework for optimizing marine-derived lead compounds into highly potent neuroprotective agents specifically tailored for peripheral neuropathy management (Diao et al., 2023).

**Table 2.** Differences in terpenoid compounds from marine and plant (terrestrial) sources

| Aspect | Marine Terpenoids | Terrestrial Terpenoids |
|---|---|---|
| Structural diversity | Terpenoids exhibit exceptionally high structural diversity, characterized by unique skeletons such as halimanes and sesterterpenes with frequent halogenation (Br, Cl) and oxygenation (Vignaud et al., *2023*). Many are meroterpenoids or possess a conjugated polyene system similar to carotenoids. It is also shaped by the MVA and MEP biosynthetic pathways (Li et al., 2021b). | The level of terpenoid diversity is relatively moderate because they generally originate from common biosynthetic pathways such as the MVA pathway, with structures limited to steroids or triterpene saponins. Halogenation and highly conjugated systems are rarely found, resulting in lower overall diversity (Li et al., 2021b). |
| Potential & bioactivity | Marine terpenoids exhibit potent antioxidant and antidiabetic activity, remaining effective even at very low concentrations through modulation of oxidative processes and metabolic enzymes (Panigrahy et al., 2021). Algal plastoquinones, for instance, have demonstrated inhibitory activity against enzymes such as PTP1B and α-glucosidase within specific concentration ranges (Panigrahy et al., 2021). In addition, these compounds may support glycemic balance and help reduce diabetes-related complications by attenuating inflammation and oxidative damage (Izbicka et al., 2023). | Plant-derived terpenoids generally require higher doses or combination with other compounds to achieve optimal effects. Monoterpenes found in essential oils possess antioxidant properties, but exhibit limited antidiabetic activity unless administered at high doses or in combination with other compounds. Some triterpenes, such as ginsenosides, show antioxidant potential but mainly act through a single pathway and lack broad-spectrum ROS scavenging capacity. Overall, marine terpenoids exhibit superior antioxidant activity compared with terrestrial terpenoids (Panigrahy et al., 2021). |
| Pharmacokinetics | The pharmacokinetics of marine terpenoids are generally characterized by high molecular weight, marked lipophilicity, and poor water solubility, contributing to low oral bioavailability. Without special formulation, these compounds are rapidly metabolized or eliminated, necessitating delivery systems such as lipid nanoparticles or cyclodextrin to enhance their bioavailability (Abdol et al., 2022). | Small terpenoids such as monoterpenoids (e.g., menthol) are generally easily absorbed due to their small size, although they are rapidly eliminated. In contrast, large terpenoids such as triterpenoid saponins (e.g., glycyrrhizin or ginsenosides) have low absorption and undergo extensive first-pass metabolism. Some plant terpenoids, such as taxol, also require special formulations to enhance their effectiveness. |

**Mechanism of Action of Terpenoids in Neuropathy Therapy**

1. Monoterpenoids

Monoterpenoids primarily exert neuroprotective effects by suppressing neuroinflammation and reducing neuronal hyperexcitability. Compared with other terpenoid classes, they predominantly regulate pro inflammatory cytokines such as TNF-α, IL-1β, IL-6 and CCL5/CCR5 (Li et al., 2021b). Furthermore, these compounds have been shown to modulate CB1 and CB2 cannabinoid receptors (Yang et al., 2025). In addition, monoterpenoids also inhibit voltage gated sodium channels (Nav) and improve mitochondrial function to reduce peripheral pain sensitization (Xu et al., 2023).

Representative monoterpenoids include vincamine, which reduces inflammation and oxidative stress by attenuating inflammatory responses, improving mitochondrial function, and limiting oxidative damage (Xu et al., 2023). γ-Terpinene exerts analgesic effects by activating cannabinoid receptor type 1 (CB1), whereas α-terpineol mediates analgesia through cannabinoid receptor type 2 (CB2) (Yang et al., 2025). Paeoniflorin alleviates hyperalgesia by suppressing astrocyte and microglial activation, whereas dexborneol enhances the therapeutic efficacy of pregabalin by increasing BBB permeability and inhibiting glial cell activity (Shen et al., 2024). In addition, carvacrol inhibits the activity of Nav1.2, Nav1.3, Nav1.6, Nav1.7, and Nav1.8 channels, thereby reducing neuronal excitability (Yang et al., 2025).

2. Sesquiterpenoids

Sesquiterpenoids primarily exert neuroprotective effects by regulating intracellular signaling pathways involved in neuropathic pain. Their mechanisms are mainly associated with the inhibition of MAPK/ERK signaling and the suppression of astrocyte and microglial activation (Yang et al., 2025). In addition, sesquiterpenoids enhance endogenous antioxidant defenses by increasing antioxidant enzyme activity and reducing oxidative stress (Ma et al., 2022). They also

modulate excitatory and inhibitory neurotransmission through NMDA and GABA_A receptors, thereby attenuating pain transmission (Dai et al., 2022).

Several sesquiterpenoids, including β-elemene, parthenolide, and kinerol, have demonstrated neuroprotective and analgesic activities through distinct molecular mechanisms. β-Elemene exerts analgesic effects by inhibiting ERK signaling and reducing NDRG2 expression, thereby suppressing astrocyte activation and decreasing the production of inflammatory mediators, including TNF-α, IL-1β, IL-6, and CXCR3 (Yang et al., 2025). In addition, β-elemene inhibits microglial activation and enhances antioxidant defenses by increasing superoxide dismutase (SOD) and glutathione peroxidase activities while reducing malondialdehyde (MDA) levels (Ma et al., 2022). Furthermore, β-elemene modulates pain transmission by inhibiting NMDAR-mediated excitatory signaling and enhancing GABA_A receptor-mediated inhibitory signaling (Dai et al., 2022). Parthenolide suppresses HCN2 and TRPA1 expression in the cerebral cortex, thereby reducing neuronal signal conduction (Yang et al., 2025). Meanwhile, kinerol inhibits the migration of RAW264.7 macrophages, contributing to its anti-inflammatory and antinociceptive activities (Li et al., 2021).

3. Diterpenoids

Diterpenoids mainly regulate key inflammatory signaling pathways involved in neuropathic pain, particularly the MAPK, NF-κB, and JNK pathways, while also modulating the endocannabinoid system through monoacylglycerol lipase (MAGL) inhibition (Yang et al., 2025). Several diterpenoids, including tanshinone IIA and cryptotanshinone, demonstrate these mechanisms through distinct molecular targets. Tanshinone IIA suppresses MAPK signaling, thereby reducing microglial activation and the production of inflammatory mediators, including TNF-α and IL-1β, in the spinal cord. It further attenuates inflammatory responses by targeting IRAK1, an upstream regulator of the NF-κB, p38, and JNK pathways. In addition, tanshinone IIA enhances antioxidant defenses by increasing superoxide dismutase (SOD) activity while reducing malondialdehyde (MDA) levels (Yang et al., 2025). Cryptotanshinone, meanwhile, alleviates oxaliplatin-induced neuropathic pain by inhibiting MAGL activity, increasing endocannabinoid concentrations, and reducing pain sensitivity (Yang et al., 2025).

4. Triterpenoids

Triterpenoids exhibit multimodal analgesic effects by simultaneously regulating immune responses, opioid signaling, endocannabinoid metabolism, and neuronal ion channels. This class modulates glucocorticoid and κ-opioid receptor pathways, activates potassium channels, and inhibits monoacylglycerol lipase (MAGL) to regulate endocannabinoid signaling (Yang et al., 2025). They also reduce neuronal excitability through the blockade of voltage-gated calcium channels, thereby attenuating both inflammatory and neuronal components of neuropathic pain (Calderon-Rivera et al., 2023).

Several triterpenoids, including ginsenosides and betulinic acid, demonstrate these mechanisms through distinct molecular targets. In a CCI model, ginsenoside Rf decreases IL-1β and IL-6 levels while increasing the anti-inflammatory cytokine IL-10 (Li et al., 2019). In addition, ginsenosides Rh2 and Rb1 suppress microglial and astrocytic activation and reduce the expression of TNF-α, IL-1β, and IL-6 in the spinal cord. Ginsenoside Rb1 also activates glucocorticoid receptors to increase dynorphin A expression, leading to κ-opioid receptor activation and attenuation of hyperalgesia. Furthermore, Rb1, together with notoginsenoside R1, enhances Kir3.1 phosphorylation, thereby increasing potassium channel activity and reducing neuronal excitability (Yang et al., 2025). Meanwhile, betulinic acid alleviates paclitaxel-induced mechanical allodynia by inhibiting MAGL activity and increasing endocannabinoid levels (Yang et al., 2025). Its derivative, betulinic acid analog 8, reduces hyperalgesia by blocking N- and T-type voltage-gated calcium channels in dorsal root ganglion neurons (Calderon-Rivera et al., 2023).

5. Tetraterpenoids

Tetraterpenoids are primarily distinguished by their ability to regulate oxidative stress through Nrf2 mediated antioxidant responses and modulate inflammasome-related neuroinflammation (Yang et al., 2025). These mechanisms contribute to the reduction of neuropathic pain by limiting oxidative damage, suppressing NLRP3 associated inflammatory responses, and enhancing opioid mediated analgesia (Zhao et al., 2024; Zhao et al., 2021).

Astaxanthin, a representative tetraterpenoid, demonstrates antinociceptive activity through these mechanisms. In the SNL model, astaxanthin attenuates neuroinflammation by regulating NLRP3-related inflammatory signaling pathways (Zhao et al., 2024; Zhao et al., 2021). It also reduces tactile and thermal hyperalgesia through Nrf2 activation, resulting in decreased oxidative stress and neuroinflammatory responses in the CCI model. Furthermore, astaxanthin potentiates opioid-mediated analgesic effects (Yang et al., 2025).

**Table 3.** Comparison table of terpenoid mechanisms of action in neuropathy

| Terpenoid Class | Primary Mechanism | Molecular Targets | Clinical Effects |
|---|---|---|---|
| Monoterpenoids | Anti-inflammatory, antioxidant, analgesic, reduces neuronal excitability, modulation of cannabinoid receptors and BBB permeability | Reduces pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, CCL5, CCR5, CRP), increases IL-10; modulates CB1 receptor signaling involved in pain regulation; mitochondrial function; BBB permeability; glial cells; modulates CB2 receptor activity involved in neuroinflammatory regulation; inhibits Nav1.2, Nav1.6, Nav1.3, Nav1.7, and Nav1.8 channels, reducing neuronal hyperexcitability | Reduces pain, reduces hyperalgesia, enhances drug efficacy (pregabalin), neuronal protection |
| Sesquiterpenoids | Anti-inflammatory, antioxidant, neurotransmission modulation | Inhibits ERK pathway and reduces TNF-α, IL-1β, IL-6 production; reduces microglial & astrocyte activation; increases SOD & GPx; reduces MDA levels to enhance antioxidant defense; modulates NMDAR, GABA_A receptors; modulates HCN2 & TRPA1 | Reduces pain transmission, reduces neuroinflammation, stabilizes neuronal activity |
| Diterpenoids | Anti-inflammatory, antioxidant, endocannabinoid modulation | Inhibits MAPK, NF-κB, and IRAK1 pathways; reduces TNF-α and IL-1β; increases SOD; reduces MDA; inhibits MAGL; thereby increasing endocannabinoids | Reduces neuropathic pain, reduces spinal inflammation, systemic analgesic effects |
| Triterpenoids | Anti-inflammatory, modulation of opioid receptors & ion channels | Reduces IL-1β, IL-6, TNF-α; increases IL-10; activates κ-opioid receptor; increases Dynorphin A; modulates $K^+$ channel (Kir3.1); inhibits MAGL; blocks N- and T-type $Ca^{2+}$ channels | Reduces hyperalgesia, reduces allodynia, reduces neuronal excitability |
| Tetraterpenoids | Anti-inflammatory, antioxidant, neuroprotective | Activates Nrf2; suppresses MAPK, NF-κB, and NLRP3 pathways; reduces oxidative stress; modulates opioid signaling system | Reduces pain, reduces neuroinflammation, enhances the efficacy of opioid analgesics. |

**Application of Terpenoids in Neuropathy Therapy**

One of the terpenoid compounds with promising potential for neuropathic pain management is astaxanthin, a marine derived carotenoid with potent anti-inflammatory and antioxidant activity. Recent experimental research using a streptozotocin (STZ)-induced diabetic neuropathy mouse model has demonstrated that astaxanthin treatment, administered either intrathecally or intraperitoneally, markedly alleviates mechanical and thermal hypersensitivity. Furthermore, long-term use of astaxanthin has been reported to produce a more stable analgesic effect compared to morphine. This compound also helps prevent opioid tolerance formation and attenuates opioid-induced hypersensitivity to pain. These neuroprotective effects are believed to occur via modulation of the MAPK pathway and activation of the Nrf2 signaling pathway (Ciapała et al., 2024).

The use of astaxanthin in alleviating symptoms of neuropathic pain has been further evaluated using a mouse model with induced diabetes. The study findings show that a single intrathecal injection effectively decreases sensitivity to mechanical and thermal stimuli in both male and female mice, with an optimal dose of 4 µg/5 µl producing a significant analgesic effect lasting approximately 1.5 to 5 hours post-administration. Although the available evidence is still limited to preclinical studies, astaxanthin holds great potential for clinical translation given its favorable safety profile without significant systemic side effects. Furthermore, its status as a dietary supplement approved for human use further supports its development as a candidate for pharmacological therapy, particularly through mechanisms involving MAPK pathway modulation, Nrf2 activation, and NMDA receptor inhibition in neuropathic conditions (Ciapała et al., 2024).

The use of astaxanthin as an adjunct therapy has also demonstrated significant clinical benefits in patients with *painful diabetic neuropathy* (PDN). Pathophysiologically, chronic hyperglycemia in diabetes triggers oxidative stress and an inflammatory response that contribute to nerve damage, including

through elevated accumulation of advanced glycation end products (AGEs) and reduced nerve growth factor (NGF) levels. In this context, NF-κB inflammatory pathway activation is suppressed by astaxanthin, leading to reduced production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, as well as inhibition of COX-2 enzymatic activity (Pinzon et al., 2021).

Clinical findings indicate that administering 6 mg of astaxanthin daily as an adjunct to standard therapy such as gabapentin, pregabalin, or amitriptyline can markedly reduce pain severity and enhance patients' quality of life, as measured using Brief Pain Inventory (BPI) ($p < 0.05$). These therapeutic effects are not only associated with increased endogenous antioxidant capacity and NGF levels but also with improved microvascular function by upregulating vascular endothelial growth factor (VEGF) expression. From a safety perspective, astaxanthin has an excellent profile with minimal side effects; only one case of a mild skin reaction was reported, requiring no specific intervention. This further supports the role of astaxanthin as a potential adjunct therapy in addressing both the underlying mechanisms and manifestations of pain in diabetic neuropathy (Pinzon et al., 2021).

Nevertheless, in general, the clinical development of marine derived terpenoids remains in an early stage. A number of marine bioactive compounds have entered Phase I through III clinical trials for different disease indications. However, in the context of type 2 diabetes mellitus and its associated complications, including neuropathy, clinical evidence remains limited and has not yet resulted in widespread therapeutic application. Several marine-based products, such as fucoidan and brown seaweed extract, have been evaluated in small-scale clinical studies in humans, although the results obtained are still variable and have not yet demonstrated strong consistency in efficacy (Sim et al., 2023).

In addition to astaxanthin, several bioactive compounds derived from marine organisms have also shown clinical potential in humans. One example is *Ecklonia cava* extract, which has been reported to lower blood glucose levels and improve insulin resistance without causing significant side effects. However, this evidence is derived from a crude extract containing multiple bioactive constituents rather than a purified terpenoid compound. Therefore, the specific contribution of terpenoids to the observed therapeutic effects remains uncertain. These findings should be interpreted as supportive evidence for the broader therapeutic potential of marine derived metabolites rather than direct evidence of individual marine terpenoid efficacy. Overall, although marine terpenoids demonstrate promising antioxidant, anti-inflammatory, and neuroprotective activities, their application in clinical practice remains limited due to insufficient clinical validation. Further studies are required to establish their efficacy, optimal dosage, long-term safety, and therapeutic relevance in neuropathy management (Sim et al., 2023).

**Advantages of Using Terpenoids in Neuropathy Therapy**

Marine terpenoids show promising potential in the treatment of neuropathy due to the adaptive ability of marine organisms to produce bioactive compounds through unique defense mechanisms. These compounds can interact with key molecular targets in the pathophysiology of neuropathy, such as inhibiting the aggregation of pathological proteins (amyloid-β and α-synuclein) and modulating the PI3K/Akt pathway, which plays a role in neuronal viability and protection. Some terpenoids from marine invertebrates have even been reported to have higher efficacy compared to conventional neuroprotective agents, thus holding potential for development as natural-product-based therapies (Rivai et al., 2023). In general, terpenoids have relatively low toxicity and are multitargeted, primarily through the activation of the PI3K/Akt pathway, which supports neuronal protein synthesis, axon regeneration, and the inhibition of neuronal apoptosis, thereby contributing to neuroprotective effects (Xu et al., 2022).

However, the clinical translation of marine-derived terpenoids is still limited by the low availability of natural resources and the low yield obtained from wild marine biomass. Future research should therefore explore sustainable strategies to improve the production of these bioactive compounds while minimizing ecological impacts. One potential approach is the use of marine tissue culture to produce marine biomass under controlled conditions (Urban-Gedamke et al., 2021). In addition, metabolic engineering of microalgae may enhance the biosynthesis of specific terpenoids by optimizing their metabolic pathways (Kang et al., 2020). Synthetic biology also represents a promising approach, particularly through the heterologous expression of marine biosynthetic gene clusters in microbial hosts, which may enable the sustainable and large-scale production of marine terpenoids for future pharmaceutical development (Li et al., 2021a).

**Limitations of Terpenoid Use in Neuropathy Therapy**

The development of marine terpenoids faces several key limitations, particularly in terms of pharmacokinetics. Their hydrophobic nature, high molecular weight, and low metabolic stability result in low oral bioavailability, suboptimal distribution, and rapid elimination, thereby reducing therapeutic efficacy (Rampengan et al., 2025). Additionally, because

persistent neuropathic pain involves central sensitization within the spinal cord and brain, limited penetration across the BBB may reduce the therapeutic efficacy of terpenoids that target these central mechanisms (Sic et al., 2024). Although various formulation strategies such as nanoparticles, lipid systems, and microencapsulation have been developed to improve stability and bioavailability, these approaches still require further validation (Rampengan et al., 2025).

In addition, there are challenges related to long-term safety, variability in individual responses, limitations in raw materials, and difficulties in standardizing and synthesizing complex compounds. To date, no marine terpenoids have become standard therapies, and clinical evidence remains limited and inconsistent. From a regulatory perspective, the lack of specific guidelines, along with challenges in standardizing natural products and ensuring resource sustainability, also pose significant barriers to clinical implementation; thus, further comprehensive research and clinical trials are still required (Rampengan et al., 2025; Rivai et al., 2023).

## Conclusion

Terpenoids, especially those obtained from marine organisms, demonstrate strong potential as therapeutic candidates for neuropathy treatment through multiple biological actions, including antioxidant and anti-inflammatory properties as well as broad neuroprotective effects targeting various pathways. Compounds such as astaxanthin have been shown to alleviate neuropathic pain and enhance quality of life by modulating signaling cascades such as MAPK and Nrf2 and suppressing inflammatory mediators. However, their use in clinical settings remains constrained due to pharmacokinetic limitations, poor oral bioavailability, insufficient safety profiles, limited evidence from human studies, regulatory challenges, and concerns regarding sustainable sourcing. Therefore, further investigations are required, including rigorous clinical trials, improved formulation strategies, and compound standardization to ensure their safe and effective application in neuropathy therapy.

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