New Pharmacotherapies in Neuropathic Pain

Subjects: Neurosciences

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Neuropathic pain, which is characterized by abnormal sensory processing due to nerve damage or dysfunction, often poses challenges in finding effective and well-tolerated therapies. Traditional analgesics, such as opioids and non-steroidal anti-inflammatory drugs (NSAIDs), may provide limited relief or be associated with significant side effects. The investigation into new drug targets and emerging pharmacotherapies in neuropathic pain could be of great interest in enhancing pain management and improving patient outcomes. In the context of neuropathic pain, repurposing drugs gained attention as a promising strategy for discovering novel treatment options. Repurposing drugs for neuropathic pain offers several advantages in the drug development process.

neuropathic pain therapy ambroxol cannabidiol

1. Ambroxol

Ambroxol, which is an active metabolite of bromhexine, was safely utilized for many years in the management of acute respiratory conditions, like bronchitis and chronic respiratory diseases, as it acts as an expectorant and mucolytic agent [1][2]. Furthermore, ambroxol recently showed potential in the management of neuropathic pain due to its multiple mechanisms of action [3]. Ambroxol modulates the activity of voltage-gated sodium channels, specifically Nav1.8, which are involved in the generation and propagation of pain signals [4]. By inhibiting Nav1.8 channels, ambroxol may reduce the excitability of nociceptive neurons and dampen neuropathic pain transmission [4]. Several pre-clinical studies investigated the analgesic properties of ambroxol in various animal models of neuropathic pain. In animal models of chronic, neuropathic, and inflammatory pain, ambroxol was tested using the formalin paw model and two mononeuropathy models, as well as a monoarthritis model in rats [5]. At a dosage of 1 g/kg, which is equivalent to clinical use, ambroxol effectively reduced pain symptoms and even reversed pain behavior. Its efficacy surpassed that of gabapentin (at 100 mg/kg), suggesting that a Nav1.8-preferring Na^+ channel blocker, like ambroxol, can suppress chronic, neuropathic, and inflammatory pain at clinically achievable plasma levels [5]. The effectiveness of pregabalin and ambroxol, either alone or in combination, in alleviating oxaliplatin-induced cold allodynia was evaluated using the mouse cold plate test [6]. The combination of ambroxol and pregabalin demonstrated an antiallodynic effect, whereas ambroxol preferentially bound to mouse Na(v)1.6 and Na(v)1.9 channels [6]. Additionally, ambroxol demonstrated efficacy in alleviating neuropathic spinal cord injury pain in rats by reducing hypersensitivity below the injury level, possibly through inhibiting peripheral sodium channels [7]. Thus, in vivo data suggest that ambroxol might be useful as a therapeutic alternative for the treatment of neuropathic pain.

While there is limited clinical data available on the alternative uses of ambroxol, some studies explored its analgesic effects. Topical ambroxol cream (20%) was used for the treatment of severe neuropathic pain in seven patients unresponsive to standard therapies, e.g., lidocaine or capsaicin patches, in the retrospective study [8], providing individual pain reductions within a period lasting for several hours. The cream effectively reduced pain attacks and was well tolerated without any reported side effects or skin changes [8]. In a study involving eight patients with complex regional pain syndrome symptoms lasting for less than 12 months, topical 20% ambroxol cream was used in addition to standard therapy, i.e., lidocaine or capsaicin patches [9]. The results showed a reduction in spontaneous pain, pain on movement, edema, allodynia, hyperalgesia, and skin reddening, as well as improvement in motor dysfunction and skin temperature [9]. In a study involving patients with trigeminal neuralgia, topical ambroxol 20% cream was used in addition to standard treatment [10]. All patients experienced pain reduction, with attacks being reduced and pain intensity decreasing; the pain relief was observed within 15–30 min and lasted for 4–6 h [10]. No side effects or skin changes were reported, and oral medication was reduced in some cases [10].

Ambroxol is generally considered safe and well tolerated when used within the recommended dosage range [2]. Common side effects may include gastrointestinal disturbances, such as nausea and vomiting, though side effects are typically mild and transient [2]. The use of ambroxol in neuropathic pain management is an emerging area of research; therefore, further clinical studies are required to evaluate its efficacy, optimal dosing regimens, and long-term safety profile, as well as the effects of combining ambroxol with other analgesic agents [4].

2. Cannabidiol

Cannabidiol (CBD) is a naturally occurring non-psychoactive cannabinoid compound that is found in the cannabis plant (*Cannabis sativa* L.). CBD was previously explored for various medical conditions and gained significant attention in recent years for its potential analgesic [11][12], anti-inflammatory [13][14][15], neuroprotective [16], anticonvulsant [13], antiemetic [17], and spasmolytic [18] properties.

CBD emerged as a prospective candidate for the treatment of neuropathic pain due to its potential analgesic and anti-inflammatory effects [11][12][13][14][15]. CBD interacts with the endocannabinoid system (ECS) in the body, which plays a role in regulating various physiological processes, including pain perception [19][20][21]. CBD acts on cannabinoid receptors, particularly the CB1 and CB2 receptors, to modulate pain signaling and reduce inflammation [19][20][21]. The G protein-coupled receptors CB1 and CB2, which belong to the cannabinoid receptor family, play a crucial role in regulating various intracellular signaling pathways [19]. These pathways involve the activation of mitogen-activated protein kinases (MAPK), phosphorylation, and the modulation of potassium and calcium channels [19]. CB1 receptor activation leads to a decrease in neuronal excitability and the release of neurotransmitters, such as gamma-aminobutyric acid and glutamate, in regions of the brain involved in nociception [22]. On the other hand, CB2 receptors are primarily found in immune tissues (e.g., spleen and tonsils) and immune cells (e.g., monocytes, B and T cells), with some presence in the brain. Activation of peripheral CB2 receptors produces anti-inflammatory and immunomodulatory effects, contributing to the alleviation of inflammatory and neuropathic pain [23][24].

CBD could also interact with other receptors and ion channels involved in pain transmission, such as transient receptor potential (TRP) channels [19][25][26][27]. CBD mechanisms of action involved in the treatment of neuropathic pain are summarized in **Figure 1**.

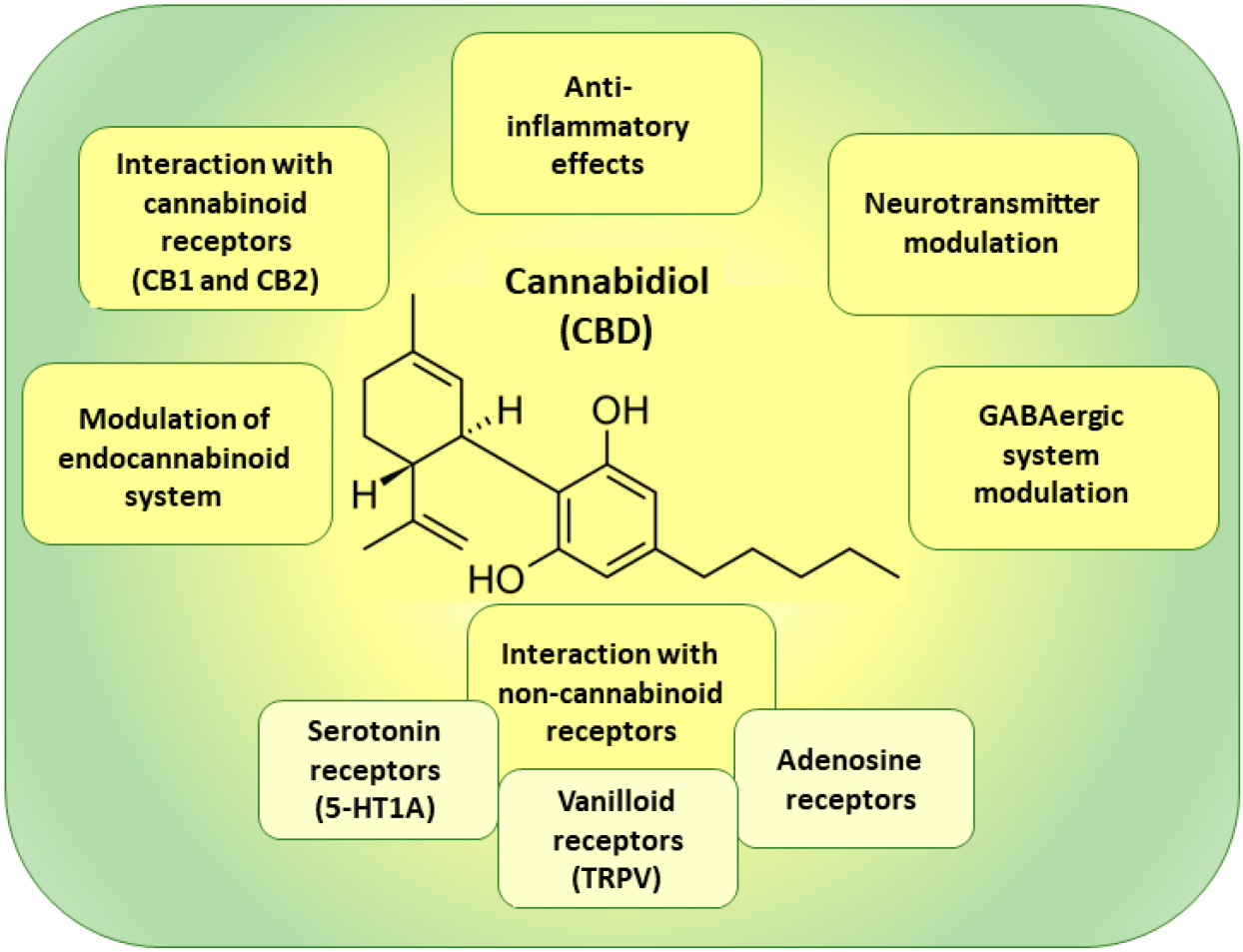

Figure 1. Mechanisms of action of cannabidiol (CBD) in pain relief.

Multiple pre-clinical and clinical studies demonstrated CBD's potential to alleviate neuropathic pain symptoms [28][29]. CBD could reduce pain, improve sleep quality, and enhance overall quality of life in individuals with multiple sclerosis (MS), diabetic neuropathy, and post-herpetic neuralgia [28][30].

In in vivo studies, the antinociceptive effect of cannabidiol (CBD) (from 2.5 to 20 mg/kg i.p.) as an acute treatment for neuropathic pain induced by spinal cord injury was investigated in female Wistar rats [31]. The results demonstrated a dose-dependent reduction in nociceptive behaviors, decreased lipid peroxidation levels, and increased GSH concentration, indicating the antioxidant effects of CBD [31]. The effects of cannabidiol (CBD) on neuropathic pain induced by paclitaxel were investigated using male C57BL6 mice [32]. CBD treatment effectively prevented paclitaxel-induced neuropathic pain and was associated with inhibition of type 4 Toll-like receptors (TLR4) and microglia activation [32]. CBD also increased the levels of endocannabinoids and reduced pro-inflammatory cytokine levels in the spinal cord [32]. The findings suggest that CBD's effects on neuropathic pain may involve modulation of the TLR4 pathway and activation of the endocannabinoid system [32]. CBD and β-

caryophyllene, which are two cannabis constituents, when acting individually and in combination, showed analgesic effects in a rat model of chronic spinal cord injury pain [33]. The combination produced enhanced pain reduction with minimal side effects, implying that the co-administration of CBD and β-caryophyllene could offer a promising treatment option for chronic spinal cord injury pain [33]. The interaction between these compounds involved CB1 receptors, highlighting a novel mechanism of action [33].

CBD is usually administered orally at a dosage range of 2–25 mg/kg/day, depending on the individual patient's response and tolerability. CBD is well tolerated and has relatively few serious adverse effects [34]; however, drug–drug interactions, diarrhea, fatigue, vomiting, somnolence and hepatic abnormalities were reported in several studies [35][36]. Due to adverse reactions, cannabinoid therapy should not be used for the patients with severe psychiatric, cardiac, renal, or hepatic disorders [37][38]

Despite CBD's potential for neuropathic pain management, additional research is necessary to better understand its mechanisms of action, optimal dosage, long-term safety, and possible drug–drug interactions. Additionally, regulatory frameworks that regulate the use of CBD can vary between countries and regions; therefore, it is important to be aware of the legal considerations.

3. Bromelain

Bromelain is an enzyme derived from the pineapple plant (*Ananas comosus* L. Merr.) and is primarily known for its therapeutic applications in the field of digestive health. Bromelain is commonly recognized for its proteolytic properties. It contains a mixture of enzymes, including proteases; therefore, it is widely used as a digestive aid, particularly to improve protein digestion and reduce digestive discomfort, especially in individuals experiencing pancreatic insufficiency or other digestive disorders. Bromelain is a safe-to-use nutraceutical that lacks side effects.

While the main application of bromelain is related to digestion, there is limited scientific evidence supporting its direct use for neuropathic pain management. Bromelain's potential anti-inflammatory properties and ability to modulate certain biological processes led to discussion about its potential use in neuropathic pain management.

In a rat model of neuropathic pain induced via sciatic nerve ligation, treatment with bromelain resulted in significant reductions in thermal hyperalgesia and mechanical allodynia [39]. It also facilitated the recovery of sciatic function and structural integrity [39]. Additionally, bromelain administration in another rat model of neuropathic pain showed a decrease in characteristic signs of neuropathic pain [40].

Bromelain was found to alleviate neuropathic pain and anxiety-like behaviors in a rat model of peripheral neuropathy [41]. It reduced pro-inflammatory cytokines, nitrate levels, and iNOS expression in the sciatic nerve, suggesting that bromelain's antinociceptive and anxiolytic effects are linked to its ability to reduce inflammation [41].

The efficacy and safety of OPERA®, which is a dietary supplement containing α-lipoic acid, Boswellia Serrata, methylsulfonylmethane, and bromelain, was evaluated in patients with chemotherapy-induced peripheral

neuropathy (CIPN) [42]. In total, 25 patients with CIPN were enrolled, and their neuropathy symptoms were evaluated over a 12-week period. The primary endpoint was the change in measured scores after 12 weeks of OPERA® therapy compared to the baseline. Secondary endpoints included the reduction in neuropathy symptoms after 12 weeks of treatment. The results showed a reduction in pain perceived by patients and improvement in sensor and motor neuropathic impairment. The OPERA® supplement was well tolerated, with no significant increase in toxicity or interactions with other therapies. Further research, including randomized controlled trials, is needed to confirm its potential benefits in a larger patient population [42]. Bromelain is administered orally, while the ideal dosage is not yet established and may vary depending on the specific product and its concentration, as well as the severity of neuropathic pain and the individual's response to treatment. In animal studies, dosages of 30–50 mg/kg per os were used [39].

Bromelain may help to reduce pain and inflammation by inhibiting inflammatory mediators, promoting tissue healing, and modulating immune responses. However, more research is needed to establish the efficacy and safety of bromelain specifically for neuropathic pain.

4. Melatonin

The endogenous hormone melatonin, also known as N-acetyl-5-methoxytryptamine, is primarily synthesized from the amino acid tryptophan. Tryptophan is converted into 5-hydroxytryptophan (5-HTP) by the enzyme tryptophan hydroxylase. Next, 5-HTP is further transformed into serotonin (5-hydroxytryptamine) by the enzyme aromatic L-amino acid decarboxylase. Serotonin serves as the precursor to melatonin synthesis. In the pineal gland, serotonin is converted into N-acetyl serotonin by the enzyme serotonin N-acetyltransferase, and is then methylated by the enzyme acetyl serotonin O-methyltransferase to form melatonin. However, it can also be produced in various organs and cells, including the brain, bone marrow, retina, skin, lens, and lymphocytes [43][44]. In adults, a constant secretion of approximately 30 µg/day of melatonin occurs, though its synthesis increases in the evening, reaching a peak concentration in the middle of the dark period [43][44]. Melatonin plays a crucial role in the regulation of circadian rhythms [43][44] and exhibits antioxidant properties, protecting against lipid peroxidation, inflammation, and tumor growth and promoting apoptosis and mitochondrial function [44][45]. Aging is associated with a decline in melatonin synthesis, leading to conditions such as insomnia, particularly in cases of Alzheimer's disease; cardiovascular disorders; and cancer [46].

The cellular effects of melatonin are mediated through interactions with specific receptors and intracellular targets, including transporters, ion binding proteins, enzymes, cytoskeletal components, and mitochondria [47][48][49][50]. Melatonin is capable of freely crossing cell membranes and the blood–brain barrier, allowing it to exert its actions in various tissues and organs [51]. These interactions enable melatonin to modulate the diverse cellular processes and signaling pathways involved in its beneficial effects.

Melatonin exhibits various mechanisms of action that contribute to its potential therapeutic effects in neuropathic pain [52][53], which are summarized in **Figure 2**.

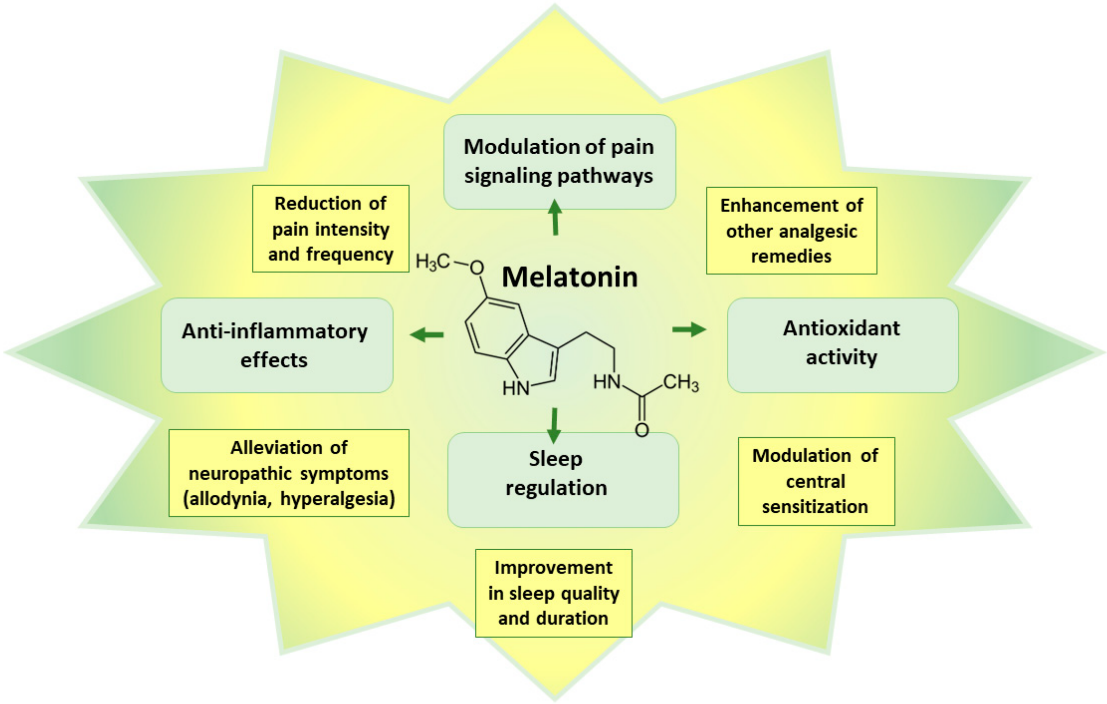

Figure 2. Main therapeutic effects of melatonin in neuropathic pain.

Firstly, it can modulate pain signaling pathways through interaction with receptors involved in pain regulation, such as opioid, adrenergic, and cannabinoid receptors [54][55]. The effects of melatonin also result from activation of MT1 and MT2 melatonin receptors, which leads to reduced cyclic AMP formation and reduced nociception [56]. Through these interactions, melatonin can effectively modulate pain perception and reduce pain transmission [56]. Secondly, melatonin possesses anti-inflammatory properties, suppressing the production of pro-inflammatory cytokines and molecules, like IL-1β, TNF-α, and NOS [56], which are associated with the inflammatory response observed in neuropathic pain. Additionally, melatonin acts as a powerful antioxidant, protecting cells from oxidative stress and minimizing neuronal damage and inflammation [56]. Melatonin is generally considered safe and non-toxic, with only mild side effects, such as dizziness, headache, nausea, and sleepiness, reported even at high doses [57].

In the context of neuropathic pain, melatonin demonstrated therapeutic effects in clinical and pre-clinical studies [52][58][59]. It could effectively reduce pain intensity and frequency; improve sleep quality and duration; alleviate neuropathic symptoms, like allodynia and hyperalgesia; and modulate central sensitization, which is a key mechanism underlying neuropathic pain [53][59]. Furthermore, when used in combination with conventional analgesic medications, melatonin showed the potential to enhance their efficacy [52].

The effects of melatonin in a mononeuropathy pain model on Sprague–Dawley rats were assessed in an in vivo study [60]. Administration of melatonin (5–10 mg/kg) on the 14th day after surgery reduced thermal hyperalgesia and modulated the nitroxidergic system in the dorsal root ganglia and skin [60]. Melatonin (37.5, 75, or 150 mg/kg once per day p.o. 30 min before lysophosphatidylcholine treatment for 3 days) also reduced neuropathic pain, behavior, and glial activation through MT2 melatonin receptor modulation in a rat model of lysophosphatidylcholine-induced demyelination neuropathy [61]. Intrathecal administration of melatonin ameliorated the neuroinflammation-

mediated sensory and motor dysfunction in a rat model with compression spinal cord injury [62]. Exogenous melatonin (10 mg/kg) alleviated neuropathic pain-induced affective disorders in rats by suppressing NF-κB/ NLRP3 pathway and apoptosis [63].

While preliminary studies suggested potential benefits of melatonin in neuropathic pain, it is important to note that further research is necessary to fully comprehend the precise mechanisms of action of melatonin and determine the optimal approach for its application as a pain reliever.

5. N-acetyl-L-cysteine

N-acetyl-L-cysteine (NAC) is a modified form of the amino acid cysteine. It is primarily recognized for its role as an antidote in cases of acetaminophen overdose [64][65]. It helps to replenish cellular levels of glutathione, which is a crucial antioxidant that protects the liver from the toxic effects of acetaminophen metabolites [64][65]. Additionally, NAC is used as a mucolytic agent to help break down and thin mucus in respiratory conditions, such as chronic bronchitis, cystic fibrosis, and chronic obstructive pulmonary disease [64][65].

N-acetyl-L-cysteine (NAC) was studied for its possible therapeutic effects in neuropathic pain in recent years [64][65]. The antioxidant and anti-inflammatory effects of NAC are hypothesized to play a role in its analgesic effects [64][65]. Oxidative stress and inflammation are known to contribute to nerve damage and the development of neuropathic pain. NAC, as a precursor of glutathione, can enhance the body's antioxidant defenses and help to reduce oxidative stress [65][66]. Moreover, it may modulate inflammatory responses and inhibit the release of pro-inflammatory molecules [67]. NAC could act as a neuroprotective agent by modulating the activity of various neurotransmitters and receptors involved in pain transmission [68][69]. It interacts with glutamatergic and GABAergic systems, influencing excitatory and inhibitory signaling in the central nervous system [68][69]. NAC can regulate the release and re-uptake of neurotransmitters, including glutamate, which plays a crucial role in neuropathic pain [68]. Additionally, NAC was found to modulate the activity of ion channels, such as voltage-gated sodium channels, which are involved in pain signaling [69].

NAC modulated Ca^{2+} influx through a TRPM2 channel in intracellular GSH-depleted rat dorsal root ganglions [69] or in the diabetic rat dorsal root ganglions in vitro [70]. NAC (100 mg/kg, i.p.) caused analgesia by reinforcing the endogenous activation of type-2 metabotropic glutamate receptors in mice in vivo [68]. Moreover, NAC (100 mg/kg, i.p., either single injection or daily injections for seven days) induced analgesia in a mouse model of painful diabetic neuropathy [71]. NAC (100 mg/kg/day, i.p. for 3 or 10 days) had no effect on the spinal cord glutathione system, but reduced nitric-oxide metabolites in rats with neuropathic pain [67]. Both the in vitro (0.1 mM) and in vivo (50, 100, and 200 mg/kg p.o.) applications of NAC significantly suppressed the activity of matrix metalloproteinases, thus alleviating the neuropathic pain in the chronic constrictive injury model in rats [72]. Furthermore, NAC (150 mg/kg/day i.p. for 1, 3, or 7 days) decreased spinal cord oxidative stress biomarkers in rats with neuropathic pain [66]. In the study on the role of astrocyte–neuron interactions in diabetic neuropathic pain, increased expression of chemokine CXC receptor 4 (CXCR4) and connexin 43 (CX43) were observed in the spinal cord dorsal horn of rats

with diabetic neuropathic pain, whereas the CXCR4 antagonist AMD3100 and the antioxidant NAC reversed nociceptive behavior [73].

While pre-clinical studies and some clinical trials showed promising results regarding the analgesic effects of NAC in neuropathic pain [65], further research is needed to establish its efficacy, optimal dosing, and long-term safety profile. Furthermore, the mechanisms through which NAC exerts its analgesic effects in neuropathic pain require additional investigation.

It is important to note that NAC is generally considered safe when used within recommended dosages (from 600 mg to 2400 mg per day) [65]. However, it may cause side effects, such as gastrointestinal symptoms (nausea, vomiting, diarrhea), allergic reactions, and potential interactions with certain medications [65].

6. Other Experimental Therapies

There are several non-traditional compounds that show potential for the management of neuropathic pain [74][75][76]. Acetyl-L-carnitine was investigated for its potential role in managing neuropathic pain [77][78]. It exerts its effects through multiple mechanisms, including modulation of neurotransmitters such as glutamate and GABA; promotion of nerve regeneration, antioxidant activity, and anti-inflammatory effects; and modulation of synaptic plasticity [78][79][80]. By influencing these processes, acetyl-L-carnitine may help to regulate pain signaling, repair damaged nerves, reduce oxidative stress and inflammation, and modulate abnormal neuronal activity associated with neuropathic pain [78][80]. Alpha–lipoic acid is an antioxidant that was previously studied for its neuroprotective and analgesic effects in suppressing neuropathic pain [81]. It is supposed to reduce oxidative stress and inflammation, thereby alleviating pain symptoms [81]. Palmitoylethanolamide is an endogenous fatty acid that acts as a modulator of inflammation and pain [82]. It was previously shown to exert analgesic effects by targeting various pathways involved in neuropathic pain, including the activation of cannabinoid receptors and the inhibition of inflammatory mediators [82]. Spermidine is a naturally occurring polyamine that plays essential roles in various cellular processes, including cell growth, differentiation, and neuronal function [83]. Studies indicate that spermidine may alleviate pain hypersensitivity, modulate neurotransmitter systems, and promote neuroprotection [83]. With its favorable safety profile, spermidine supplementation could offer a viable option for managing neuropathic pain, although further research is needed to determine its mechanisms of action and optimal usage in human subjects [83]. Resveratrol is a natural compound found in grapes, berries, and other plants [84][85]. Resveratrol demonstrated anti-inflammatory and analgesic properties in pre-clinical studies of neuropathic pain, modulating multiple signaling pathways associated with pain and inflammation [84][85]. Curcumin, which is a polyphenolic compound derived from turmeric [86][87], was previously investigated for its potential in neuropathic pain management due to its anti-inflammatory and anti-oxidant properties. Curcumin may modulate pain signaling pathways and inhibit the production of pro-inflammatory molecules [86][87]. While further research is needed to establish their efficacy and safety, these compounds hold promise as alternative approaches for alleviating neuropathic pain and improving the quality of life for individuals suffering from this challenging condition.

Non-coding RNA molecules play a significant role in the development and regulation of neuropathic pain [88]. These RNA molecules, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), were found to be involved in various aspects of neuropathic pain, such as neuronal plasticity, inflammation, and immune responses [88]. MiRNAs are small RNA molecules that regulate gene expression by binding to messenger RNAs (mRNAs) and inhibiting their translation or promoting their degradation [88]. In neuropathic pain, specific miRNAs were identified as key regulators of pain-related pathways. They can modulate the expression of genes involved in neuronal sensitization, synaptic plasticity, and inflammatory responses. By targeting these genes, miRNAs can influence the development and maintenance of neuropathic pain [88]. LncRNAs, on the other hand, are longer RNA molecules that do not encode proteins, but have important regulatory functions in cellular processes. Several lncRNAs are implicated in neuropathic pain by influencing gene expression, chromatin remodeling, and epigenetic modifications [88]. They can act as scaffolds, decoys, or guides to interact with proteins and other regulatory molecules, ultimately affecting the expression of pain-related genes [88]. Research into non-coding RNAs in neuropathic pain is still ongoing, and the specific mechanisms through which they contribute to pain pathology are being elucidated [88]. Understanding their roles may lead to the development of novel diagnostic markers and therapeutic targets for neuropathic pain management [88].

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