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Pharmacotherapeutics role of Cannabinoid (CB1 & CB2) Receptor agonists modulator in chemotherapy-induced peripheral neuropathy: A Review

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ABSTRACT

The injury or illness of the somatosensory nerve system results in pain termed neuropathic pain. It often increases dependence on medication as well as the need to visit hospitals. Allodynia, hyperalgesia, and paresthesia are symptoms that are produced by this disorder. In animal studies,

“Chronic constriction injury (CCI), partial sciatic nerve ligation (Seltzer model), and spinal nerve ligation (SNL) are metho ds used to reproduce it. Chemotherapy

induced peripheral neuropathy (CIPN) is the most common kind of neuropathic pain among the wide range of manifestatio ns.It frequently results from the use of chemotherapeutic agents, which include but are not limited to ixabepilone, thalidom ide, taxanes, and platinum compounds.” While opioids are commonly prescribed for CIPN, these drugs cannot be safely used for prolonged periods due to the high potential for addiction. There has been increasing attention given to cannabinoid receptors, particularly CB2, because of their role in the modulation of inflammation and pain. This review analyzes the possible therapeutic effects of CB2-selective agonists on CIPN and other neuropathic disorders. More recently, itaconates and isatins have been discovered to be CB2 agonists and they show promise in preclinical studies. This article focuses on the neuropathic pain mechanisms associated with these agents’ analgesic effects..

Keywords: *Neuropathic pain, Cannabinoids, Itaconate, isatin, ABK5, allodynia*

1. INTRODUCTION

Neuropathic Pain

Unwanted mental and sensory experiences that are often linked to actual or potential damage to body tissues are the manifestation of discomfort. It usually occurs when harmful stimuli activate primary nociceptive afferents, which are then processed by the nociceptive system. In order to warn of possible danger, this communication relies on unique receptors and complex fiber networks that link peripheral tissues to the brain. However, neuropathic pain is a condition in which pain can occur even when peripheral sensory endings are not stimulated (Merskey & Bogduk, 1994 & Pertwee, 2006 & Dixon, 1899). The IASP defines neuropathic pain as "a sensation of distress stemming from damage or a condition impacting the somatosensory nervous system." This guideline omits scenarios such as Complex Regional Pain Syndrome type I (CRPS I), which fail to produce detectable damage to somatosensory areas, encompassing the cerebellum.

The Somatosensory System and Pain

The somatosensory system is responsible for detecting sensations such as touch, pressure, temperature, vibration, pain, and body position. Signals from thermoreceptors, mechanoreceptors, nociceptors, chemoreceptors, and pruriceptors originate in the skin, muscles, joints, and fascia. These impulses travel via peripheral nerves, "are relayed through the spinal cord, and ultimately reach the cerebral cortex via thalamic nuclei (Attal et al., 2011 & Torrance et al., 2006 & Finnerup et al., 2016)." Any disruption in this pathway due to disease or injury can lead to altered sensory processing and pain

Characteristics and Impact of Neuropathic Pain

Dejerine and Egger described neuropathic or central pain for the first time in 1903. It is now well acknowledged that neuropathic pain often leads in increased medication use and medical visits. Patients often report persistent burning or electric shock-like sensations, as well as discomfort from non-painful stimuli (such as light touch). These symptoms are often recurring and resistant to ordinary analgesics (Bouhassira et al., 2008 & Borsook, 2012 & Watson & Sandroni, 2016).

Neuropathic discomfort greatly diminishes overall well-being and frequently correlates with additional health issues like insomnia, unease, and melancholia. The characteristics that delineate it include:

• Allodynia: discomfort arising from triggers that are usually not associated with pain.

• Hyperalgesia: an intensified reaction to nocuous stimuli.

• Paresthesia: unusual feelings such as tingling, prickling, and numbness.

Prevalence and Associated Conditions

Epidemiological data, largely gathered from standardized screening questionnaires, indicate that chronic neuropathic pain commonly affects areas such as the lower back, neck, and limbs. It is more prevalent in women than men (8% vs. 5.7%) and increases with age, particularly in individuals over 50. Occupation and geographic location also play roles, with higher prevalence reported among manual laborers and rural populations. (Banach et al., 2016 & Seretny et al., 2014 & Areti et al., 2014)

The primary health issues"associated with neuropathic pain include postherpetic neuralgia, trigeminal neuralgia, radiculopathies, diabetic neuropathy, HIV-related neuropathy, leprosy, nerve pain post-amputation, and central pain resulting from a stroke. Central neuropathic discomfort originates from damage to the spinal cord or brain, influenced by various conditions including stroke, Parkinson's disease, multiple sclerosis, syringomyelia, transverse myelitis, and neuromyelitis optica (Windebank & Grisold, 2008 & Cleeland et al., 2010). Peripheral neuropathic pain is often linked to damage in small unmyelinated C fibres alongside myelinated Aδ fibres. Fundamental components in the foundational processes and expression of neuropathic discomfort include age-related decline, diabetes, cancer, and the neurotoxic effects of chemotherapy (affecting Aβ, Aδ, and C nerve fibres) (Kent et al., 2013 & Cioroiu & Weimer, 2017 & Hershman et al., 2014 & Fallon, 2013)."

Chemotherapy Induced Neuropathic Pain

Although cancer survival rates have increased significantly—by approximately 35% in the past decade—many survivors continue to face long-term complications that detract from their quality of life. A particularly troubling consequence is the damage to the nervous system caused by chemotherapeutic drugs. While these agents are effective in eradicating malignant cells, they can also induce various forms of neuropathy, including those affecting cranial and autonomic nerves, large and small fiber nerves, and both sensory and motor pathways. Additionally, they may contribute to demyelination and axonal degeneration (Brzeziński, 2012 & Polomano & Farrar, 2006 & Mantyh et al., 2002).

Amid the array of neurological consequences, chemotherapy-induced peripheral neuropathy (CIPN) emerges as the most prevalent and incapacitating disorder. The occurrence of its presentation fluctuates between 19% and 85%, shaped by the particular chemotherapeutic drug employed and the duration of the treatment protocol. Certain categories of pharmaceuticals demonstrate the highest frequency rates: "taxanes (11.87%), thalidomide and its analogues (20-60%), ixabepilone (60-65%), and therapies that include platinum (70-100%). Recent studies reveal that around 68.1% of people encounter signs of chemotherapy-induced peripheral neuropathy (CIPN) after the first month of treatment, with 60% impacted after three months, and nearly 30% suffering from these symptoms after six months or longer (Guindon et al., 2007 & Knotkova & Pappagallo, 2007 & Portenoy et al., 2012)."

CIPN is typically characterized by the following clinical features:

1. **Predominantly sensory symptoms**, although motor and autonomic impairments may also occur depending on the drug.
2. **Onset often correlates with chemotherapy administration**, with symptoms emerging during or even after treatment—a delayed manifestation referred to as *"coasting."*

3. **Symptoms are generally symmetrical**, though they may occasionally be more severe on one side.
4. **Sensory disturbances often follow a "stocking-and-glove" pattern**, initially affecting the distal extremities, particularly the feet.

In more severe cases, patients may experience simultaneous involvement of both hands and feet, with pain as a dominant symptom. Compared to other forms of neuropathy—such as diabetic polyneuropathy—CIPN often develops more rapidly and presents with heightened severity (Attal et al., 2010 & Dworkin et al., 2007).

The mechanisms behind CIPN are multifactorial and complex, involving:

- **Immune-mediated responses**
- **Neuroinflammation**
- **Disruption of microtubule dynamics**
- **Demyelination**
- **DNA damage**

These processes collectively contribute to the structural and functional impairment of peripheral nerves, leading to the characteristic pain and sensory disturbances associated with CIPN (Walker & Hohmann, 2005 & Rahn & Hohmann, 2009).

Neuropathic Pain Management and CIPN

Mitigating neuropathic pain (NP) is broadly acknowledged as the essential initial measure in the management of patients susceptible to its onset (Rahn et al., 2007 & Wallace et al., 2007 & Wallace et al., 2007 & Xiong et al., 2011). Nonetheless, the existing collection of data endorsing medicinal approaches explicitly designed to avert neuropathic cancer discomfort (NCP) remains somewhat constrained. Considering the complex and varied aspects of NCP, successful management requires a tailored and sustained strategy that takes into account the distinct clinical requirements of every cancer patient (Bambouskova et al., 2018 & Basu et al., 2022).

Recommendations for managing pain associated with cancer, particularly its neuropathic dimensions, are based on the most recent proposals from the World Health Organisation (WHO). The European Society for Medical Oncology (ESMO) alongside the National Comprehensive Cancer Network (NCCN) likewise endorses these recommendations. The World Health Organisation promotes a progressive strategy that begins with less potent analgesics and methodically increases in strength based on the severity of the symptoms. Throughout this process, careful monitoring is crucial to evaluate the efficacy of the intervention as well as any potential negative responses.

In cases of mild discomfort (scoring between 1 and 3 on a pain assessment scale), “the primary approach to treatment generally involves the use of non-opioid pain relievers, including paracetamol and non-steroidal anti-inflammatory medications (NSAIDs) (Cascão et al., 2017 & Li et al., 2018 & Fiorenzani et al., 2014 & Klauke et al., 2014).”

As discomfort escalates to a moderate or intense degree, opioids take on a pivotal role in the therapeutic strategy. When non-opioid medications fail to deliver sufficient alleviation, milder or short-duration opioids—like codeine, dihydrocodeine, or dextropropoxyphene—might be considered for use. Alternative feasible choices encompass dual-action pain relievers like tramadol and tapentadol, or partial opioid agonists including transdermal buprenorphine.

If opioid therapy alone proves insufficient or causes intolerable side effects at higher doses, combining opioids with adjuvant analgesics (coanalgesics) is recommended to improve symptom control while minimizing adverse reactions.

Commonly used coanalgesics include:

- **Cannabinoids**
- **Bisphosphonates**
- **Corticosteroids**
- **Gabapentinoids** (e.g., gabapentin, pregabalin)
- **Antidepressant medications** (such as tricyclic antidepressants, duloxetine, and venlafaxine)
- **N-methyl-D-aspartate** (NMDA) receptor blockers

These agents play a vital role in tackling both the neuropathic and inflammatory dimensions of pain associated with cancer, ultimately elevating patient comfort and enriching the overall quality of life.

Endocannabinoid System

The endocannabinoid (eCB) system is comprised of three essential elements: naturally occurring ligands, cannabinoid receptors, and the enzymes that facilitate the synthesis and degradation of these compounds. By engaging with these receptors and imitating the impacts of naturally present compounds, both synthetic and natural cannabinoids provoke a range of physiological responses, such as alleviating pain, enhancing appetite, and warding off nausea. Cannabinoids often act as a supplementary therapeutic option in healthcare settings, particularly when conventional medications do not produce the desired outcomes.

The primary cannabinoid receptors consist of CB1, "primarily located in the central nervous system (CNS), and CB2, which is mainly present in peripheral tissues. The primary psychoactive compound in cannabis, THC, interacts as a partial agonist with both CB1 and CB2 receptors. The analgesic attributes of cannabis have undergone thorough investigation, demonstrating its collaborative effects with opioids in the treatment of persistent pain disorders"(Sharma et al., 2016 & Berger et al., 2019 & Ceccarelli et al., 2020 & Huffman et al., 1999).

In scenarios such as peripheral non-cancer neuropathic distress and neuropathic agony associated with multiple sclerosis, oromucosal cannabis-based therapies have shown promise in clinical environments. For instance, nabiximols, a cannabinoid-infused oromucosal spray, was subjected to assessment in a randomised, placebo-controlled trial carried out in 2012, which involved participants diagnosed with cancer. Although it provided a certain level of discomfort relief, the study underscored various limitations, including persistent adverse effects and increased dropout rates. Consequently, while initial results appear encouraging, the effectiveness of cannabinoids in managing neuropathic cancer pain (NCP) remains to be fully validated (Eljaschewitsch et al., 2006 & Diaz et al., 2009).

The amygdala, globus pallidus, substantia nigra, cerebral cortex, putamen, caudate, and "cerebellum are among the most abundant regions in the brain for G protein-coupled receptors, with CB1 receptors notably abundant in these particular zones. In addition to the central nervous system, CB1 can be found in musculoskeletal tissues along with a range of non-neuronal cells, including adipocytes and hepatocytes. Although CB2 receptors are mainly linked to immune cells, they are also present in particular regions of the brain, contributing to the modulation of immune responses" (IASP, 2019 & McPartland et al., 2014 & Glass et al., 1997).

By obstructing calcium influx and amplifying inward rectifying potassium currents, CB1 receptors restrict neurotransmitter secretion and reduce neuronal excitability. 2-arachidonoylglycerol "(2-AG) and anandamide (N-arachidonylethanolamide, AEA) serve as the primary endogenous ligands within the endocannabinoid system. These are produced via the activity of enzymes, particularly 1,2-diacylglycerol lipase and phospholipase A. Their inactivation is chiefly regulated by the enzymes tasked with ligand degradation, notably fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL)."

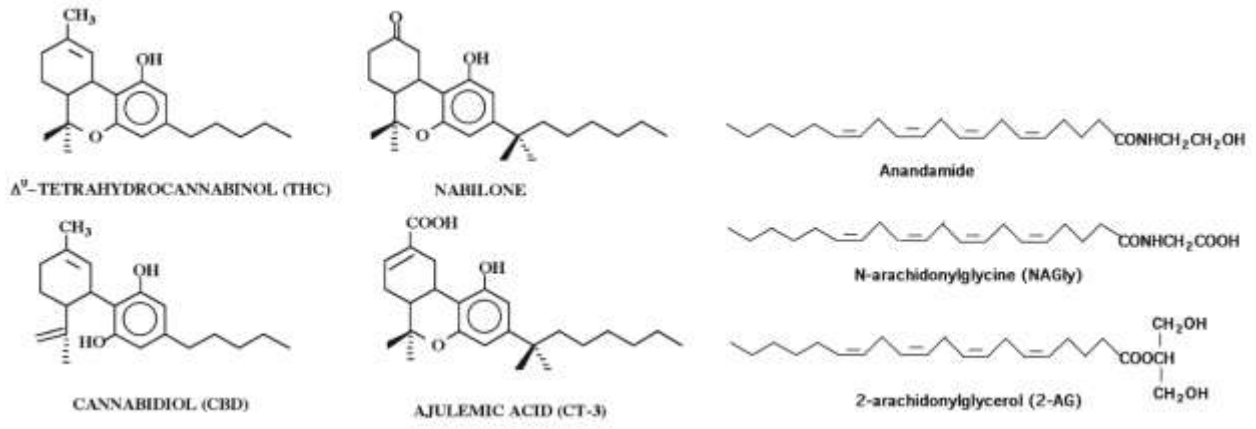


Figure 1 Chemical structure of endocannabinoids and some active components from *Cannanis sativa*

Cannabinoid Receptor in Neuropharmacology

The therapeutic application of Cannabis sativa for alleviating discomfort dates back to some of the most ancient human societies. An important breakthrough in our comprehension of its medicinal characteristics was achieved through the extraction of Δ^9-tetrahydrocannabinol (Δ^9-THC)—the main psychoactive element of the plant—by Gaoni and Mechoulam. This revelation was crucial in exposing the endocannabinoid system (ECS), an inherently existing communication network within the brain that plays a significant role in modulating pain perception, appetite, immune response, and various other bodily functions (Tang et al., 2021 & Diaz et al., 2008).

One of the pioneers in examining the analgesic characteristics of Cannabis sativa was W.E. Dixon, who noted that elevated quantities of cannabinoids produced effects including drowsiness, diminished motor skills, and ataxia, indicating an influence on the central nervous system (CNS). Expanding upon this foundation, Walker and associates presented preliminary scientific proof indicating that cannabinoids obstruct nociceptive signal transmission, thereby reinforcing longstanding assertions regarding the effectiveness of cannabis in alleviating pain (Hashiesh et al., 2021 & Çakır et al., 2020 & Jonsson et al., 2006).

These groundbreaking discoveries ignited a wave of exploratory studies examining the effects of cannabis on nerve-related pain. Utilising established methodologies for nerve injury, such as spinal nerve ligation (SNL), partial sciatic nerve ligation (Seltzer model), and chronic constriction injury (CCI), numerous preclinical studies have consistently shown that cannabinoid treatment significantly reduces pain-related behaviours. A multitude of investigations, totalling no fewer than nine, have revealed that cannabis displays a pain-relieving effect in instances of peripheral nerve injury, indicating its possible use as a remedy for neuropathic discomfort.

Table 1 "Cannabinoids studied in surgical models for Neuropathic pain[44]

Category	**Compound Evaluated**
Cannabinoid ligands	Δ^9-THC; Cannabidiol (CBD); Δ^9-THC:CBD; cannabis extract; Nabilone (synthetic analog of Δ^9-THC)
Endocannabinoids	Anandamide (AEA); 2-arachydonoylglycerol (2-AG)
Fatty Acids	N-arachidonoyl glycine (NaGly); Palmitoylethanolamine (PEA)
CB receptor stimulators	ACEA; Met-F-AEA; BAY59-3074; CP55,940; CT-3 (Ajulemic acid); HU-210; WIN55,212-2;
Endocannabinoid modulators	AM404 & VDM11 (Uptake inhibitors); OL135 & URB597 (FAHH inhibitors); JZL184 and JZL184 (MGL inhibitors)"

FAAH, known as fatty-acid amide hydrolase; MGL, which stands for monoacylglycerol lipase; and THC, referring to tetrahydrocannabinol.

Furthermore, evidence suggests that they can induce neuropathic pain in experimental models of nerve-associated distress triggered by chemotherapy, HIV/antiretroviral treatment, and diabetes (Table 2).

Table 2 Cannabinoids studied in preclinical models for disease induced neuropathic pain

Model Studied	**Compound Evaluated**
Diabetic Neuropathy[45,46]	Met-F-AEA; WIN55; 212-2; AM1241
Chemotherapy-induced Neuropathy (Cisplatin induced)[47]	WIN55; 212-2
Chemotherapy-induced Neuropathy (Paclitaxel induced)[48-50]	WIN55; 212-2; MDA7; (R,S)-AM1241; (R)-AM1241; (S)-AM1241; AM1714
Chemotherapy-induced Neuropathy (Vincristine induced)[51]	WIN55; 212-2; (R,S)-AM1241
HIV-SN[52,53]	WIN55; 212-2; L-29

HIV-SN - HIV sensory neuropathy

Recent research has broadened the comprehension of cannabinoid pharmacology, extending its reach beyond the traditional cannabinoid receptors. Significantly, glycine receptors (GlyRs), especially those featuring the α3 subunit, have surfaced as crucial players in the pain-relieving properties of cannabinoids. Investigations conducted by Xiong and associates uncovered that the stimulation of these receptors is crucial in alleviating neuropathic discomfort, establishing them as an innovative focus for cannabinoid-oriented treatment approaches (Hashiesh et al., 2021 & Çakır et al., 2020 & Jonsson et al., 2006).

Although CB1 receptor agonists have demonstrated their capacity to alleviate discomfort, unwanted adverse effects have hindered their effectiveness. As an illustration, the CB1 antagonist and inverse agonist Rimonabant (SR141716), initially sanctioned for obesity management, was withdrawn from circulation following reports of significant mental health side effects, such as depression and thoughts of self-harm. CB2 receptors, believed to play a role in pain relief and inflammation reduction without inducing the pleasurable sensations linked to CB1 activation, have gained prominence due to these obstacles. These receptors are chiefly stimulated by inflammatory circumstances. CB2-selective agonists have garnered heightened interest as more secure options for addressing neuropathic pain, "owing to their promising therapeutic capabilities and reduced likelihood of central side effects.[54, 55]

Selective CB2 agonists for neuropathic pain treatment

The CB2 receptor has garnered significant interest as a potential therapeutic target for addressing neurodegenerative conditions such as Alzheimer's disease and neuropathic pain. Research indicates that the activation of CB2 receptors diminishes neuroinflammatory signalling pathways and supports the restoration of microglial cells' homeostatic roles, transforming their pro-inflammatory characteristics into an anti-inflammatory state (Aly et al., 2019 & Gertsch et al., 2008).

Research findings reveal that the activation of CB2 receptors influences the functioning of extracellular signal-regulated kinases 1 and 2 (ERK1/2), which play vital roles within the mitogen-activated protein kinase (MAPK) signalling pathway. Additionally, laboratory investigations reveal that the endocannabinoid anandamide stimulates immune-related pathways within the central nervous system, encompassing the MAPK cascade, to suppress inflammatory reactions and safeguard against immune-induced neuronal damage (Seitz et al., 2007 & Jiang et al., 2011 & Ogawa et al., 2017 & Scott et al., 2019).

Among the innovative substances that engage CB2, MDA-7 (1-(3-benzyl-3-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonylpiperidine) has demonstrated promise. It modifies the expression of genes linked to neuroinflammation triggered by paclitaxel. CB2 agonists, including MDA-7, have shown efficacy in alleviating mechanical allodynia across various preclinical pain models. These include the spinal nerve ligation (SNL) model, paclitaxel-induced peripheral neuropathy, and the chronic post-ischemic pain framework, which simulates complex regional pain syndrome type I (Lin et al., 2018 & Iyer et al., 2020 & Lin et al., 2022).

CB2 agonists need to traverse the blood-brain barrier (BBB) to influence reactive microglia within the central nervous system. Consequently, to enhance the therapeutic benefits and efficacy of CB2-targeted therapies, careful patient categorisation and pharmacokinetic assessment are crucial.

Itaconates

Itaconate, a significant byproduct of the tricarboxylic acid (TCA) cycle, has demonstrated potential as a therapeutic agent due to its robust immunomodulatory and anti-inflammatory properties. The primary impacts involve suppressing the production of pro-inflammatory cytokines by activated macrophages while simultaneously promoting the activity of nuclear factor erythroid 2–related factor 2 (Nrf2), a crucial transcription factor that governs inflammation and the cellular defence against oxidative stress. In order to enhance the therapeutic capabilities of itaconate, various synthetic derivatives have been developed, such as dimethyl itaconate (DI), 4-octyl itaconate (4-OI), and ethyl itaconate (EI). DI has demonstrated significant anti-inflammatory characteristics, primarily through the stimulation of the Nrf2 pathway.

In experimental models of inflammatory discomfort triggered by spinal nerve ligation (SNL) and Complete Freund's Adjuvant (CFA), DI exhibited both protective effects on the nervous system and pain-relieving advantages, as highlighted in preclinical studies conducted by Ren et al. Within the cellular structures of the dorsal root ganglion (DRG), spinal cord, and hind paw, DI therapy significantly reduced the concentrations of inflammatory substances including interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α). Furthermore, it obstructed the phosphorylation of extracellular signal-regulated kinases 1/2 (ERK1/2), halted macrophage activation within the DRG, and diminished glial cell activity in the spinal dorsal horn. (Faust et al., 2009 & Yang et al., 2014 & Davenport et al., 2010)

The pain-relieving effects of DI were intricately linked to increased Nrf2 expression within the DRG and spinal cord. Significantly, the concurrent administration of ML385, a specific inhibitor of Nrf2, negated these analgesic effects and diminished Nrf2 expression, thereby reinforcing the crucial function of Nrf2 signalling in facilitating the therapeutic results of DI. Furthermore, DI demonstrated the ability to enhance Nrf2 expression in cultured microglia, resulting in a decrease in the release of pro-inflammatory cytokines (Dejerine & Egger, 1903 & Bujalska, 2008 & Welch & Stevens, 1992)."

In addition to its effects on neuropathic pain, DI has shown remarkable anti-tumor characteristics, including the inhibition of IL-1 secretion in intestinal epithelial cells, "which in turn hinders the advancement of colorectal cancer. An independent study conducted by Lin and colleagues revealed that DI provided safeguarding benefits in neuropathic pain by diminishing pro-inflammatory indicators (IL-1, TNF-α), boosting the anti-inflammatory cytokine IL-10, and obstructing the activation of the nod-like receptor protein 3 (NLRP3) inflammasome complex."

Collectively, these discoveries underscore the potential therapeutic benefits of DI and its associated itaconate derivatives as

innovative solutions for addressing neuropathic pain, functioning by influencing inflammation and stimulating protective cellular mechanisms like Nrf2 signalling.[59,60,61,62,63]

Celastrol

The promising results noted with CB2 receptor agonists such as (R)-AM1241 and AM1714, both sourced from Cannabis sativa, have ignited curiosity in exploring additional botanical compounds for addressing chemotherapy-induced peripheral neuropathy (CIPN). Among these, celastrol, a potent antioxidant derived from Tripterygium wilfordii Hook, has shown remarkable therapeutic potential in preliminary studies (Walker et al., 1988 & World Health Organization, 2012 & Swarm et al., 2013 & Ripamonti et al., 2012).

Research investigations have demonstrated that celastrol significantly and proportionally alleviates the swelling and heightened sensitivity induced by carrageenan. The mRNA levels of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β are notably reduced in mice that have been administered carrageenan. Significantly, the pain-relieving efficacy of celastrol was somewhat diminished by SR144528, a specific antagonist of the CB2 receptor, suggesting that its analgesic advantages could be at least partially facilitated through CB2 receptor mechanisms.

Alongside its properties that combat inflammation, celastrol has demonstrated potential in fighting cancer. Within leukaemia cells, it amplifies responsiveness to chemotherapy through the activation of caspase-3, prompting PARP cleavage, and diminishing the expression of the oncogenic protein Bcr-Abl. Additionally, in models of lung adenocarcinoma, celastrol has demonstrated the ability to enhance the expression of miR-33a-5p, a microRNA known for its tumor-suppressive properties. This miRNA interacts with the 3' untranslated region (3' UTR) of the mTOR gene, resulting in the inhibition of mTOR signalling, a pathway frequently linked to the advancement of cancer (Onaivi, 2011 & Atwood & Mackie, 2010 & Gaoni & Mechoulam, 1964).

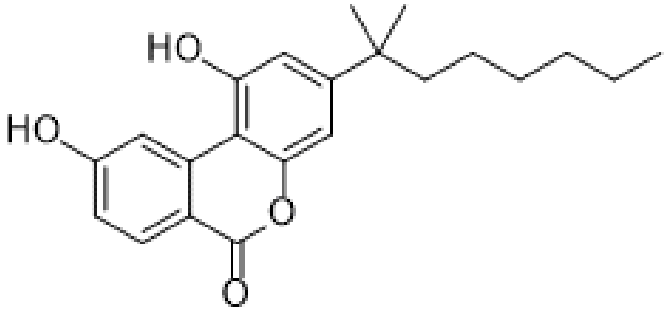
In summary, the results indicate that celastrol, by simultaneously influencing CB2 receptor function and addressing inflammatory and cancer-related pathways, presents significant promise as a potential treatment option for both CIPN and a range of cancers.[64,65, 66,67,68]

AM1714

AM1714 represents an innovative compound categorised as a CB2-selective cannabinoid receptor agonist, demonstrating encouraging outcomes in the treatment of mechanical allodynia induced by paclitaxel. Preclinical investigations have shown that AM1714 diminishes mechanical sensitivity in a manner that is dependent on the dosage after the administration of paclitaxel. In every dosage evaluated, subjects administered AM1714 demonstrated a notable decrease in mechanical allodynia when contrasted with those given a vehicle control (Pascual et al., 2005 & Naguib et al., 2008 & Rahn et al., 2008).

Furthermore, AM1714 demonstrated the ability to reinstate mechanical thresholds to levels that closely resemble baseline, which had been altered due to neuropathy induced by paclitaxel. Among the administered doses, the peak dosage (10 mg/kg, via intravenous route) markedly increased paw withdrawal thresholds surpassing the pre-treatment levels noted on day 21. Nonetheless, reduced dosages (5 mg/kg and 1 mg/kg, IV) failed to yield statistically meaningful alterations when compared to the baseline measurements (Ren et al., 2022 & Gautam et al., 2022 & Lin et al., 2022).

Significantly, the application of SR141716 (a CB1 receptor blocker) did not impede the anti-allodynic properties of AM1714, suggesting that its mode of action is chiefly facilitated through CB2 receptor activation rather than any engagement with CB1. The results bolster the significance of CB2 agonists such as AM1714 in mitigating neuropathic discomfort while avoiding the central side effects associated with CB1 activation.[50]



β-Caryophyllene

β-Caryophyllene (BCP), “a naturally occurring sesquiterpene, is present in significant amounts within the essential oils of various culinary and medicinal botanicals, including oregano, cinnamon, and black pepper. While it acts as a complete agonist for the CB2 cannabinoid receptor, it fails to produce the psychoactive effects typically linked to CB1 receptors.

Research indicates that both one-time and multiple doses of BCP can reduce discomfort in male rodents, including rats and mice. Models of discomfort, like the Formalin Test (FT)—a recognised technique for replicating chronic pain—have been employed to assess the effectiveness of BCP. When FT was given at weekly intervals, it effectively mirrored chronic pain scenarios akin to those seen in chemotherapy-induced peripheral neuropathy (CIPN) (Xiong et al., 2012 & Bermudez-Silva et al., 2010)."

Research findings indicate that BCP demonstrates safeguarding properties across various preclinical frameworks, encompassing models for inflammatory discomfort, neurological conditions, and interstitial cystitis. From a mechanistic perspective, BCP exhibits a strong affinity for the CP55,940 binding domain of the CB2 receptor (often identified as the THC binding site), where it triggers cellular activation and promotes anti-inflammatory responses (Maurer et al., 1990 & Vera et al., 2007).

Long-term use of BCP has been linked to a significant decrease in pain-related activities, highlighting its promise as a natural, non-psychoactive treatment option for addressing chronic and neuropathic discomfort.[69-75]

JWH133

The Δ-tetrahydrocannabinol group exhibits structural resemblances to the synthetic cannabinoid JWH133. Although it possesses similarities to Δ^9-THC, HU210, recognised as a non-selective agonist of cannabinoid receptors, undergoes a chemical transformation by the removal of the phenolic hydroxyl group. A multitude of investigations has been carried out regarding its pharmacological properties and specific affinity for CB2 receptors, "particularly highlighted in the review by Hashiesh et al. Investigations conducted prior to clinical trials have revealed the remarkable anti-inflammatory properties of JWH133, particularly in experimental setups like Cecal Ligation and Puncture (CLP)-induced polymicrobial sepsis in Sprague-Dawley rats and inflammation induced by Compound 48/80 in BALB/cJBom mice (van Hecke et al., 2014 & Bouhassira & Attal, 2011)."

Within the framework of the CLP model, JWH133 demonstrated its ability to diminish NF-κB signalling, an essential pathway governing inflammatory reactions, while also inhibiting apoptosis. Additionally, it enhanced the expression of crucial phagocytic receptors including Tyro3, Axl, and MerTK, which belong to the TAM receptor tyrosine kinase family. Through the application of both primary macrophages and RAW264.7 macrophage cell lines, JWH133 demonstrated an enhancement in the phagocytosis of apoptotic cells in a manner that was dependent on dosage, regardless of the presence of oxidised low-density lipoprotein (OxLDL) in the cells.

The results highlight the promising therapeutic capabilities of JWH133 as a CB2-focused compound that can influence immune reactions and alleviate inflammation, potentially impacting sepsis and various other inflammatory disorders.[76-81]

ABK5

ABK5 represents a one-of-a-kind agonist for the CB2 cannabinoid receptor, setting itself apart from conventional cannabinoid ligands such as THC and CP55940. Discovered via extensive high-throughput screening, ABK5 exhibited its functional efficacy by inhibiting the accumulation of cyclic AMP (cAMP) in cells expressing CB2, a mechanism facilitated by Gi protein coupling subsequent to receptor activation (Desroches et al., 2014 & Attal, 2012).

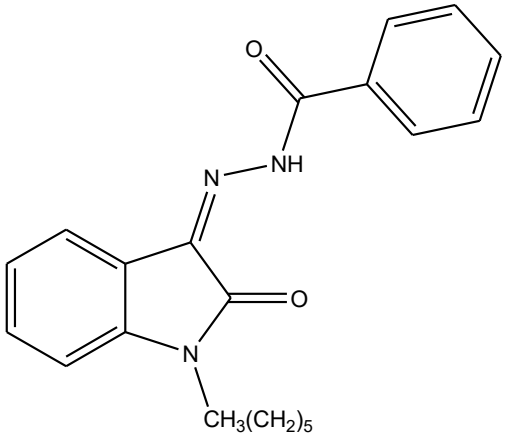
Earlier research has indicated that ABK5 demonstrates a strong binding affinity for CB2 receptors, with an inhibition constant (Ki) varying between 1 and 16 nM, while displaying minimal affinity for CB1 receptors, thereby confirming its selective action on CB2. "The binding specific to this receptor initiates a series of intracellular signalling cascades, notably the ERK1/2 and MEK pathways, which play a vital role in the regulation of cells and the modulation of the immune response."

In cellular investigations, ABK5 suppressed the growth of Jurkat cells, a human T-cell leukaemia lineage, suggesting its possible anti-inflammatory characteristics. Additionally, it diminished the expression of crucial inflammatory mediators—IL-2 and TNF-α—at both mRNA and protein levels, while also limiting cell migration in reaction to the chemokine CXCL12 (IASP, 2019 & McPartland et al., 2014 & Glass et al., 1997).

Moreover, in vivo studies demonstrated that ABK5 significantly diminished swelling and elevated mechanical pain thresholds in rats treated with Complete Freund's Adjuvant (CFA), reinforcing its dual role in analgesia and anti-inflammatory effects. The results indicate that ABK5 presents a potential therapeutic avenue for addressing inflammatory and neuropathic pain disorders via precise modulation of the CB2 receptor.[82-84]

Isatin

A novel series of N-alkyl isatin acylhydrazone derivatives has been discovered through [^{35}S]GTPγS binding assays, showcasing significant functional efficacy and specificity towards the human CB2 receptor. Within this group, Compound 33 demonstrated notable antiallodynic advantages in a lumbar 5/6 neuropathic pain spinal nerve ligation (SNL) model. Through a comprehensive exploration of structure–activity relationships (SAR) within this series, three additional compounds exhibiting remarkable selectivity and potency as CB2 receptor agonists were identified.[85]



LY2828360

LY2828360 serves as a G protein-biased agonist, specifically honing in on the CB2 cannabinoid receptor, exhibiting similar receptor affinity in human and rat cellular environments. In contrast to conventional CB2 agonists, LY2828360 triggers a gradual reduction in cyclic AMP (cAMP) levels and stimulates the ERK1/2 signalling pathway, all while avoiding the internalisation of CB2 receptors or the recruitment of β-arrestin. This indicates a unique, non-traditional mechanism of action (Dejerine & Egger, 1903 & Bujalska, 2008 & Welch & Stevens, 1992).

Preclinical investigations have underscored the compound's potential to alleviate opioid withdrawal manifestations in morphine-dependent rodent models. Moreover, LY2828360 has been discovered to mitigate neuropathic pain caused by chemotherapy and to hinder the development of morphine tolerance associated with its anti-allodynic properties. These discoveries bolster its prospective function in augmenting opioid-centered treatments while reducing related adverse effects (van Hecke et al., 2014 & Bouhassira & Attal, 2011).

Furthermore, in conditioned place preference (CPP) experiments, designed to assess drug-induced reward behaviours, LY2828360 markedly diminished the rewarding impacts of morphine. This phenomenon is thought to be facilitated by the activation of peripheral CB2 receptors, especially within keratinocytes, which subsequently triggers the secretion of β-endorphin, a naturally occurring opioid peptide that plays a crucial role in alleviating pain and modulating reward pathways (Walker et al., 1988 & World Health Organization, 2012 & Swarm et al., 2013 & Ripamonti et al., 2012).

Collectively, these results highlight the potential of LY2828360 as a dual-function therapeutic solution, providing both analgesic effects and opioid-sparing advantages while avoiding the central side effects linked to CB1 receptor activation.[86-90]

2. CONCLUSION

In contrast to the activation of CB1 receptors, frequently linked to undesirable euphoric sensations, focussing on CB2 cannabinoid receptors offers a promising and more secure option for traditional cannabinoid therapies. Owing to the minimal presence of CB2 receptors in normal central nervous system (CNS) tissue, CB2-selective agonists have demonstrated exceptional pain-relieving capabilities across diverse pain categories, such as acute, inflammatory, and neuropathic pain, while exerting negligible influence on the CNS.

A growing body of evidence illustrates the intricate mechanisms through which CB2 agonists elicit their pain-relieving properties. For example, through influencing microglial activation and modulating spinal immune responses, the intrathecal delivery of CB2 agonists has demonstrated a decrease in pain hypersensitivity within chronic pain frameworks.

A variety of preclinical studies have underscored the effectiveness of these substances in addressing peripheral neuropathic discomfort, especially showing significant potential in cases of chemotherapy-induced peripheral neuropathy (CIPN).

Despite the fact that a restricted selection of CB2 agonists has advanced to clinical trials, their strong preclinical results have sparked a growing enthusiasm for the creation of innovative CB2-focused therapies. These agents possess the promise of enhancing the management of neuropathic pain while simultaneously reducing central side effects, thus providing a more focused and acceptable treatment approach for patients

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