The Application of Cannabidiol in Chronic Pain Management: A Narrative Review

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Abstract

Chronic pain is nociceptive or neuropathic pain that persists for three or more months. Some health issues that induce chronic neuropathic and nociceptive pain include, osteoarthritis, fibromyalgia, multiple sclerosis, irritable bowel syndrome, amongst others. Currently, pharmaceutical treatment options for chronic pain produce unwanted side effects, dependance, and/or tolerance. Cannabidiol is a non-psychoactive component of *Cannabis sativa* that has therapeutic potential against chronic pain. Cannabidiol has the ability to reduce chronic pain by suppressing inflammatory responses that cause hyperexcitability in pain receptors while inhibiting the transmission of pain signals. Cannabidiol directly interacts with GPR55 receptor to suppress nociception and inflammation. Cannabididiol indirectly interacts with CB2 and TRPV1 receptors to suppress nociception and inflammation. These direct and indirect interactions may also activate opioid receptors and peroxisome proliferator-activated receptors to assist in chronic pain relief. Cannabidiol inhibits psychoactive side effects by acting as a negative allosteric modulator of CB1. This narrative review thoroughly discusses receptors involved in the antinociceptive and anti-inflammatory effects of cannabidiol. In addition, this review discusses experimental studies pertaining to the effects of cannabidiol on chronic pain models.

1. What is Chronic Pain?

Estimates indicate that twenty percent of the United States population suffers from chronic pain[1]. Chronic pain is nociceptive or neuropathic pain persisting for three or more months and affects the quality of life [2,1]. Neuropathic pain is caused by damage to neurons, while nociceptive pain is caused by a harmful stimuli [3]. Chronic pain arises from harmful stimuli or nerve damage that induces functional changes to cells involved in the pain pathway. Central and peripheral neurons including microglia, astrocytes, oligodendrocytes, and Schwann cells modulate neuronal inflammation [4]. These central and peripheral neurons promote inflammation after injury, which causes pain receptors, called primary afferent nociceptors, to reach a state of hyperexcitability. The state of hyperexcitability causes transmission of pain signals to the dorsal horn of the spinal cord [5]. Within the dorsal horn, the neurons receiving the pain signals suppress the activity of inhibitory neurons [2, 3]. Inhibitory neurons are responsible for suppression of the pain sensation. When this process persists it can cause functional changes to the cells involved in the normal

pain pathway, especially inhibitory neurons [2]. This causes neuroimmune activation that will promote inflammation again [2]. If this loop becomes continuous for three or more months, the pain is considered chronic.

The *International Classification of Diseases* (*ICD*) of the World Health Organization divides chronic pain in seven categories: (1) Chronic primary pain, such as chronic back pain, fibromyalgia, irritable bowel syndrome, chronic pelvic pain; (2) Chronic cancer pain, including any pain from cancer treatment or cancer itself; (3) Chronic posttraumatic and postsurgical pain; (4) Chronic neuropathic pain, including any pain from a lesion or disease of the somatosensory nervous system (5) Chronic headache and orofacial pain, (6) Chronic visceral pain, including pain that originates from the internal organs of the head and neck region and the thoracic, abdominal, and pelvic cavities; and (7) Chronic musculoskeletal pain, including pain that is a result of joint, bone, or muscle diseases [1]. These categories consist of either nociceptive or neuropathic pain, however some categories include both types of pain.

With increasing chronic pain diagnoses, it is important for individuals to understand chronic pain treatment options. Opioid treatment is the most frequently used chronic pain treatment in the United States [10]. In 2012, the United States officially declared opioid abuse an epidemic due to the increase in prescriptions for chronic pain [10,11]. Since then, opioid prescriptions for chronic pain and opioid abuse have continued to increase. In 2015, more than 33,000 people lost their lives to an accidental opioid overdose in the United States alone [14]. In 2019, the U.S. Food and Drug Association stated that opioids are the cause of an extraordinary number of deaths [76]. In fact, overdoses from prescription opioids are reducing life expectancy in the United States [76]. Not only do opioids carry a risk of addiction and tolerance, but opioid treatment interferes with normal neurotransmission, resulting in harmful side effects, such as respiratory depression [11, 3]. Other treatment options include drugs that target glutamate receptors. Although drugs that target glutamate receptors indeed reduce pain, they also produce unwanted side effects by interfering with normal neurotransmission [6]. These side effects include hallucinations, ataxia and sedation [6]. Rodríguez-Muñoz et al. stated that a series of neurological disorders result from glutamate receptor dysfunction [9], this suggests that relief of chronic pain is not worth the side effects of tampering with glutamate receptors.

Cannabidiol is an effective alternative to the current chronic pain treatment options. The objective of this review is to understand the role of cannabidiol as a chronic pain treatment option. Research access was granted by the University of Montevallo, where keywords were submitted into the University of Montevallo Carmichael Library database. PubMed databases were also used. Studies were then selected by relevance to cannabidiol and chronic pain within the past twenty years, however the majority of studies have been performed within the past ten years. The results for each chosen study were interpreted with caution to reduce biased information.

3. What is cannabidiol?

Cannabidiol, CBD, is the primary non-psychoactive constituent of *Cannabis sativa* [15,16,17,18,19,20]. CBD may be isolated from the cannabis plant to yield an oil that is administered by oral consumption, parenteral and peritoneal injections, and/or topical application. Research shows that CBD has therapeutic potential for treatment of chronic pain like neuropathic pain, cancer pain, multiple sclerosis pain, and inflammation [18,21,22,20]. CBD interacts with the body's endocannabinoid system to produce chronic pain relief. The endocannabinoid system is comprised of endogenous cannabinoids, cannabinoid receptors, and enzymes involved in the synthesis, transport, and degradation of endogenous cannabinoids. These components work together to regulate neuronal and immune functions [23].

While CBD directly interacts with some receptors, CBD also indirectly interacts with the endocannabinoid system by increasing anandamide levels. Anandamide, AEA, is an endogenous cannabinoid acting as a lipid messenger [45,26]. This cannabinoid is a membrane lipid that is synthesized by N-arachidonoyl-phosphatidylethanolamine selective phospholipase D in response to high levels of calcium ions [24]. Once synthesized, AEA activates cannabinoid receptors then is quickly degraded into arachidonic acid. Though a short duration of action, AEA can modulate nociception, inflammation, and oxidative

stress by activating cannabinoid receptors [25]. In other words, high levels of calcium cause AEA to synthesize, signalling cannabinoid receptors to “turn on”. For a short period of time, AEA messages cannabinoid receptors to produce therapeutic effects. Once AEA is degraded, the cannabinoid receptors “turn off” and stop producing therapeutic effects.

CBD increases the concentration of AEA by inhibiting the degradation of AEA. Without the influence of CBD, AEA is transported from cannabinoid receptors to the endoplasmic reticulum by fatty acid binding protein transporters (FABPs) [26]. In the endoplasmic reticulum, fatty acid amide hydrolase (FAAH) is responsible for inactivating AEA via catabolism [26]. CBD binds to FABPs so AEA is not delivered to FAAH. With the influence of CBD, AEA is not degraded or inactivated, which increases the levels of endogenous AEA and prolongs the duration of its therapeutic effects.

Altogether, CBD exerts antinociceptive and anti-inflammatory effects by directly interacting with receptors. In addition, CBD prevents the degradation of AEA so that AEA may exert antinociceptive and anti-inflammatory effects by directly interacting with receptors. This means CBD affects multiple receptors within the endocannabinoid system and outside of the cannabinoid system, making it a multitarget drug [7]. Because CBD is a multitarget drug, it can produce antinociceptive, antioxidative, anti-inflammatory, and neuroprotective effects that may be utilized in the treatment of numerous medical disorders.

4. CBD Receptors:

Preclinical and clinical studies have shown CBD reduces nociception. The nociceptive effects of CBD are predominantly attributed to its indirect modulation of transient vanilloid receptor subfamily group member 1 (TRPV1) [27]. However CBD exerts antinociceptive effects from interactions with cannabinoid receptor-2 (CB2) and G protein-coupled receptor 55 (GPR55). CBD may also exert antinociceptive and anti-inflammatory effects through opioid receptors and peroxisome proliferator-activated receptors, but these are often in conjunction with activation of TRPV1, CB2, and GPR55. Because CBD is a multitarget drug, it affects many cannabinoid and non-cannabinoid receptors. The following will discuss the interactions and effects of CBD with CB1, CB2, TRPV1, GPR55, and 5-HT1A found in literature to date.

A. CB1

CB1 and CB2 are the most well-known cannabinoid receptors in the body. CB1 is expressed throughout the central nervous system, predominantly on presynaptic neurons in the brain, spinal cord, and dorsal root ganglia [2,19]. Presynaptic neurons are important in the pain process because they are responsible for the transmission of pain signals to the brain. CB1 regulates the release of pain signals from presynaptic neurons [19,28]. Activation of CB1 reduces the release of neurotransmitters like glutamatergic excitatory systems and GABAergic inhibitory systems in the brain and spinal cord, which results in antinociception [28]. In fact, research by Agarwal et al. showed that deletion of CB1 induces nociception [29,30]. Though activation of CB1 results in antinociception, activation of CB1 also results in unwanted side effects [31,29,28,27]. These side effects include the “high” feeling one gets from tetrahydrocannabinol, THC, like drowsiness, memory impairment, confusion, and heightened sensitivity to external experience [28, 29,32].

CBD is considered a negative allosteric modulator [28,9], or antagonist [32,27], of CB1. This means that CBD does not activate CB1 like THC. Instead, CBD indirectly inhibits the activation of CB1, thereby inhibiting of the “high” feeling side effects [32,28]. Ward et al. showed that the CB1 antagonist SR141716 did not hinder the antinociceptive effects of CBD [31]. This suggests that CBD exerts its antinociceptive effects through receptors other than CB1, while inhibiting the rise of psychoactive side effects.

As previously discussed, CBD increases levels of the endogenous cannabinoid, anandamide. Without the influence of CBD, anandamide will bind to CB1, which mediates the transmission of GABA inhibitory pain signals [19]. With the influence of CBD, anandamide is at high concentrations and becomes an agonist of TRPV1, as CBD becomes a negative allosteric modulator of CB1. Altogether, CB1 is important in the pain process and interacts with endogenous and exogenous cannabinoids, however CB1 has little to no role in the antinociceptive effects of CBD.

B. CB2

CB2 is an endocannabinoid receptor that does not cause psychoactive effects like those associated with CB1 [33,34,35,23,36,37]. CB2 plays a large role in the modulation of inflammatory responses. CB2 is expressed in areas of the brain and in immune cells, including myeloid, microglia, macrophage, lymphoid, and mast cells [2,35, 34,33]. Studies show that deletion of CB2 receptor caused an inflammatory phenotype to worsen in several models, due to an upregulation of immune cell functions [36,37]. These data prove that CB2 plays an important role in the body's inflammatory and pain processes.

After injury, like harmful stimuli or nerve damage, CB2 on microglia is activated by 2-arachidonoyl-glycerol [33,34]. 2-arachidonoyl-glycerol (2-AG) is an endogenous cannabinoid that promotes inflammatory responses when bound to CB2 [34]. These inflammatory responses include: proinflammatory cytokine recruitment, nitric oxide production, and leukocyte rolling. Inflammation causes pain receptors, called primary afferent nociceptors, to reach a state of hyperexcitability that sends out pain neurotransmitters [4, 3, 2]. Once the injury has healed, primary afferent nociceptors settle, inflammation subsides, and levels of 2-AG are reduced. In some cases of chronic pain, such as rheumatoid arthritis, CB2 and 2-AG are constantly promoting inflammation, which keeps primary afferent nociceptors in a state of hyperexcitability.

Activation of CB2 by AEA relays an opposite response [34]. AEA bound to CB2 negatively regulates inflammatory responses. In human and murine models, research shows that AEA downregulates inflammation by reducing cytokine release and nitric oxide production [23,38,39,40,41]. Cytokine release and nitric oxide production enable leukocyte rolling [33,29], therefore AEA reduces the proinflammatory responses that cause primary afferent nociceptors to reach their state of hyperexcitability.

Though there are mixed opinions about the interactions between CBD and CB2, it is certain that CBD acts to suppress inflammatory responses through CB2. Some literature says that CBD is an agonist of CB2 [33] and others say that CBD is an inverse agonist of CB2 [42,43,27]. Whether CBD directly interacts with CB2 is redundant because AEA's interactions with CB2 are the cause of CBD's anti-inflammatory effects. CBD increases AEA levels by inhibiting the degradation of AEA. This provides inflammatory and nociceptive relief because AEA binds to CB2 instead of 2-AG binding to CB2. Research by Turcotte et al. proved that in vivo models treated with CBD resulted in decreased T cell responses and inhibited inflammatory cytokine production [34].

C. TRPV1

Transient vanilloid receptor subfamily group member 1 (TRPV1) is an ion channel expressed on nociceptive neurons like astrocytes [44,45]. When TRPV1 is activated it allows transmission of pain signals from primary afferent nociceptors to the dorsal horn of the spinal cord to the brain [4,6]. Ion channels are important in the pain pathway because they change the charge gradient across neuron membranes, this allows the release of pain signals to the next neuron in the pain pathway. Without injury, the charge gradient across the cell membrane is very polar. TRPV1 has cation permeable pores that allow calcium ions inside of the cell membrane when an injury occurs and TRPV1 is activated [5]. An influx of calcium ions changes the charge gradient and allows the neuron to release glutamate, the main neurotransmitter involved in the pain sensation [6,8]. Philpott et al. stated that opening of TRPV1 ion channels not only relays pain signaling, but also causes the peripheral release of inflammatory neuropeptides which promote neurogenic inflammation and enhanced leukocyte trafficking in joints [27]. Unfortunately, expression of TRPV1 increases on primary afferent nociceptors after inflammation [18]. Simply put, TRPV1 is activated in response to inflammation which causes an increase in expression of TRPV1. Therefore, the more TRPV1 is activated, the more inflammation occurs, which causes more TRPV1 to be activated, which causes more inflammation. These data suggest that TRPV1 is closely related to chronic pain.

CBD indirectly modulates TRPV1 through AEA. CBD inhibits the degradation of AEA, thereby increasing the concentration of AEA. At nano (nM) concentrations AEA does not have an effect on TRPV1, however at micro (μM) concentrations AEA exerts a TRPV1-mediated stimulatory effect [29,46]. This

means, CBD can elevate AEA concentrations so that AEA mediates TRPV1's influx of calcium ions. An experiment by Fenwick et al. showed the differences between activation of TRPV1 via AEA versus capsaicin [45]. Capsaicin is a molecule in spicy food that binds to TRPV1 to induce glutamate release, which induces a pain sensation [45]. When capsaicin activated TRPV1, an immense influx of calcium ions caused vesicular release of glutamate. In contrast, when AEA activated TRPV1 it modulated normal calcium currents without mobilizing vesicular glutamate. Fenwick et al. concluded that AEA does not change spontaneous glutamate release, which is required for normal neurotransmission, while capsaicin increased glutamate release [45]. Research suggests that activation of TRPV1 via AEA simply modulates normal neurotransmission, which resists the increase transmission of pain signals without side effects of hindered glutamate receptors [29,18].

D. GPR55

G protein-coupled receptor 55 (GPR55) is another important cannabinoid receptor involved in the pain process. GPR55 is frequently expressed in dorsal root ganglia that convey pain signals from muscles, joints, and skin and is expressed in the brain [47,48]. Like TRPV1, GPR55 exerts its effects by changing the charge gradient across neuron membrane [49,50]. Unlike TRPV1, GPR55 is not an ion channel, but modulates the activity of ion channels. Deliu et al. described that activation of GPR55 induces neuronal membrane depolarization [49]. As previously stated, neurons involved in pain neurotransmission are polar until harmful stimuli or nerve damage induce depolarization. This means that activation of GPR55 is associated with the opening of ion channels, specifically calcium ion channels. These openings change the charge gradient and allow the transmission of pain signals after an injury [49,50,51]. Research by Staton et al. showed mice without GPR55 failed to develop mechanical hyperalgesia in a model of neuropathic hypersensitivity [51]. Moreover, deletion of GPR55 in mice regulated proinflammatory cytokines [51]. Other research confirmed GPR55 is not only involved in the transmission of pain signals, but also in the recruitment of inflammatory responses [49,52,18]. Based on the reaction to GPR55 activation, inhibition of GPR55 would result in anti-inflammatory and antinociceptive effects.

CBD is a full antagonist of GPR55 [27,7]. CBD binds to GPR55 to inhibit other GPR55 ligands from activating pronociceptive and proinflammatory responses. A study by Hammell et al. showed in vitro application of CBD inhibits pain signalling through GPR55 and TRPV1, and in vivo oral administration of CBD reduces proinflammatory cytokine release [18]. In other words, CBD reduces inflammation that leads to pain while preventing the transmission of pain signals by GPR55 antagonism. CBD can provide inflammatory, neuropathic, and nociceptive pain relief through its inhibition of GPR55. In fact, nerve damage increases the expression of GPR55 in the dorsal root ganglia, which suggests that GPR55 largely participates in neuropathic pain [53], so inhibition of GPR55 via CBD could significantly suppress neuropathic pain.

E. 5-HT1A

Some research proposes CBD may also produce antinociceptive effects through the serotonin receptor 5-HT1A [31,33,29]. 5-HT1A is responsible for the transmission of serotonin, a neurotransmitter involved in the signaling of pain, depression, and anxiety [32]. Indeed, studies show that pain and mood display comorbidity [54,55,56]. In addition, 5-HT1A in the rostral ventromedial medulla plays an important role in modulating the inhibitory pain pathway [31], however research suggests that activation of solely 5-HT1A does not produce antinociceptive effects. In fact, some studies have shown that when TRPV1 is blocked, CBD will bind to 5-HT1A to produce anxiolytic effects without antinociceptive effects [32,17]. In other words, 5-HT1A is predominantly responsible for the anti-anxiety effects of CBD while TRPV1 is predominantly responsible for the antinociceptive effects of CBD.

5. Pain specific trials:

Though research on CBD is limited, there have been several studies focused on the antinociceptive and anti-inflammatory effects of CBD. The following will discuss the therapeutic effects CBD provides in various chronic pain models.

A. Chronic Headache Pain

Though there is limited research on the effects of CBD on chronic headache pain, studies show AEA is directly related to headache management. Migraine is a type of headache disorder considered to be a form of chronic pain. There are multiple factors that can cause migraines including genetics [46,57]. Because there are multiple etiologies for migraines, it is difficult to find a drug target that will reduce the chronic pain associated with migraines. Sutherland et al. described that migraines occur when the brain loses control of homeostasis, which induces neuroinflammation and activates the trigeminovascular system [57,75]. The trigeminovascular system is the primary sensory nerve network in the brain. When activated, causes a cascade of events, including excessive pain signalling. CBD is a promising treatment for migraines due to endocannabinoids function to maintain homeostasis [46]. Indeed, preclinical studies have proposed that reduction of endocannabinoids such as AEA may be one of the mechanisms underlying migraines. A study by Knoller et al. showed that women who experience migraines have an increase in FAAH activity, which means reduced levels of AEA [58]. CBD inhibits the degradation of AEA, therefore has the ability to restore AEA levels.

AEA is important in managing migraine pain for multiple reasons. First, AEA inhibits the production of nitric oxide and calcitonin gene-related peptide [23,46,59]. Both nitric oxide and calcitonin gene-related peptide contribute to the cascade of pain signals that occur after neuroinflammation and activation of trigeminovascular system [23,46,59]. Malek et al. designed a study to observe the effect of AEA on neuroinflammatory diseases such as Alzheimer's disease and Parkinson's disease. Interestingly, they found that AEA decreases nitric oxide and calcitonin gene-related peptide, and interacts with CB2 to reduce neuroinflammation [23]. This data is also relevant to migraine treatment in that reducing nitric oxide, calcitonin gene-related peptide, and neuroinflammation will decrease pain signaling.

In addition, AEA manages migraine pain through TRPV1. Lochte et al. stated that excessive glutamate signalling followed by inhibition of NMDA receptors often precedes migraine pain [46,58]. As previously discussed, AEA modulates glutamate signaling by activation of TRPV1. Collectively, this data suggests that AEA prevents migraine pain by modulation of glutamate and inhibition of the production of nitric oxide and calcitonin gene-related peptide.

These experiments prove CBD has therapeutic potential as a drug alternative in chronic headache pain management.

B. Chronic Arthritis Pain

Arthritis is an inflammatory disease that affects joints. Rheumatoid arthritis consists of painful swelling of multiple joints including the hands and feet [60]. Similarly, osteoarthritis consists of painful swelling of joints, but is characterized by joint degeneration and in some patients, articular neuropathy [27]. CB2 and TRPV1 are abundant on neurons and microvasculature in joints affected by arthritis [27]. Oral consumption, parenteral injections, and topical application of CBD has shown to relieve inflammation related to arthritis in many studies [61,16,17]. As previously stated, CBD suppresses the inflammatory responses through CB2 and GPR55, which attenuates inflammation and glutamate pain signalling. In addition, CBD indirectly regulates glutamate pain signalling through TRPV1 found in arthritic joints. Many researchers suggest that anti-inflammatory effects arise from suppression of GPR55 instead of CB2 [60,62,18]. By reducing inflammatory responses and modulating pain signaling, CBD helps manage chronic pain associated with arthritis.

A study by Philpott et al. showed CBD injections into arthritic joint attenuating initial inflammation, thereby reducing end-stage arthritic pain and articular neuropathy in a sodium monoiodoacetate model of osteoarthritis [27]. The study concluded that locally injected CBD reduced inflammation and pain caused by osteoarthritis within 14 days [27]. Another study tested the effects of topically applied CBD gel on adjuvant-induced monoarthritis model [18]. Results showed that joint inflammation and pain-related behaviors significantly reduced after four days of topical application [18]. Many other studies that used oral administration of CBD further showed CBD decreasing serum inflammatory cytokine levels in arthritic models [61,16,17,27].

Studies have shown that CBD has therapeutic potential as a drug alternative in chronic arthritis pain

management. Oral consumption, topical application, and parenteral injections of CBD have produced beneficial effects in arthritis models. Shang et al. stated that endogenous cannabinoids like AEA are utilized in the area that they are synthesized, therefore local application of CBD is believed to be more effective than oral consumption [33]. Indeed, topical application and parenteral injections showed to produce benefits faster than oral consumption due to the first pass metabolism encountered by orally administered drugs [18,16]. Though oral consumption does produce benefits, higher dosing is required to relieve chronic pain.

C. Chronic Multiple Sclerosis Pain

Multiple sclerosis is a chronic autoimmune disease that causes inflammation of the central nervous system [15,63,64]. Chronic inflammation caused by multiple sclerosis constantly triggers pain. In addition, chronic inflammation in the central nervous system may lead to neurodegeneration [15,63]. Though the exact mechanism by which CBD relieves chronic pain of multiple sclerosis is not fully developed [15], studies show that CBD has therapeutic actions against inflammation and pain associated with multiple sclerosis [15,65,66,67]. One proposed mechanism is described by CBD's effect on astrocytes. Inflammation associated with multiple sclerosis begins by malfunction of astrocytes on the blood brain barrier [66,67,15]. Astrocytes are important in clearance of neuronal debris, maintaining ion and metabolic balance, and proper neuronal activity [67]. Astrocyte malfunction leads to activation of the innate immune system of the central nervous system, which recruits proinflammatory cytokines and T cells [63,64,15]. Interestingly, astrocytes express CB1 [15,67], CB2 [15,67], TRPV1 [44,45], and possibly GPR55 [68]. CBD may depress inflammatory responses by its direct interaction with GPR55 and its indirect interaction with CB2 on astrocytes. In addition, CBD may indirectly modulate pain signaling through TRPV1 on astrocytes.

A study by Elliot et al. tested the effects of CBD on a murine model with encephalomyelitis, autoimmune neuroinflammation comparable to multiple sclerosis [63]. They found CBD treatment induces action of myeloid-derived suppressor cells that reduce proinflammatory cytokines, T cells, and other proinflammatory responses [63]. Further research showed that CBD achieves anti-inflammatory effects in multiple sclerosis models by directly and indirectly interacting with astrocytes [69,15,65,66,67]. Based on CBD's interactions with cannabinoid receptors, anti-inflammatory effects of CBD are attributed to its indirect activation of CB2 and direct inactivation of GPR55. CBD alleviates chronic pain associated with multiple sclerosis by suppressing inflammatory responses while modulating pain signaling through TRPV1.

D. Chronic Primary Pain

There is limited research on the effects of CBD on chronic primary pain. However, there is extensive data indicating the relationship between the endocannabinoid system and chronic primary pain. Inflammatory bowel diseases are a type of chronic primary pain. Irritable bowel syndrome is an inflammatory disease of the gastrointestinal tract that causes pain in the abdomen [70]. The exact etiology is unknown, however irritable bowel syndrome has shown comorbidity with other chronic primary pain models such as fibromyalgia and chronic pelvic pain [70,71]. For this reason, this review will discuss the effect of CBD on chronic primary pain as a whole.

Studies show that the endocannabinoid system, specifically GPR55 and TRPV1, play key roles in chronic primary pain models [52,72,73,74]. Sumida et al. reported that GPR55 controls the immune homeostasis of the gastrointestinal tract by regulating the intraepithelial lymphocyte migration [73]. In addition, TRPV1 has a critical role in the pain sensation of all chronic primary pain models [72,74]. In fact, fibromyalgia is characterized by pain sensations caused by excessive calcium influx in dorsal root ganglion neurons and sciatic nerve neurons [72]. These data suggest control of GPR55 and TRPV1 will mediate pain sensations associated with chronic primary pain models. As previously discussed, CBD suppresses inflammatory responses by inhibiting GPR55, and CBD modulates TRPV1 calcium influxes for healthy glutamate signaling. Though research is limited on the subject, CBD is a promising treatment option to chronic primary pain because CBD has been proven to suppress inflammation and excessive glutamate signalling.

Conclusions

CBD has the ability to reduce chronic pain by suppressing inflammatory responses that cause hyperexcitability in pain receptors while inhibiting the transmission of pain signals. CBD directly interacts with GPR55 receptor to suppress nociception and inflammation. CBD indirectly interacts with CB2 and TRPV1 receptors to suppress nociception and inflammation. These direct and indirect interactions may also activate opioid receptors and peroxisome proliferator-activated receptors to assist in chronic pain relief. CBD inhibits psychoactive side effects by acting as a negative allosteric modulator of CB1. Studies on chronic headache pain, chronic multiple sclerosis pain, chronic primary pain, and chronic arthritis pain show that CBD attenuates chronic pain without side effects. Because of the short duration of the trials, no studies have shown dependence or tolerance issues with the use of CBD. Exponential research on the therapeutic effects of CBD is expected. CBD is a strong candidate for chronic pain treatment due to its natural mechanisms for maintaining immune and nervous homeostasis.

Declarations

Availability of Data and Materials: The datasets analyzed during the current study are available in the University of Montevallo Carmichael Library or PubMed repositories, https://www.ncbi.nlm.nih.gov/pubmed/ , http://libguides.montevallo.edu/index?group_id=15001

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