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REVIEW ARTICLE

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Can cannabidiol have an analgesic effect?

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Abstract

Background: Cannabis, more commonly known as marijuana or hemp, has been used for centuries to treat various conditions. Cannabis contains two main components cannabidiol (CBD) and tetrahydrocannabinol (THC). CBD, unlike THC, is devoid of psychoactive effects and is well tolerated by the human body but has no direct effect on the receptors of the endocannabid system, despite the lack of action on the receptors of the endocannabid system.

Objectives and methods: We have prepared a literature review based on the latest available literature regarding the analgesic effects of CBD. CBD has a wide range of effects on the human body. In this study, we will present the potential mechanisms responsible for the analgesic effect of CBD. To the best of our knowledge, this is the first review to explore the analgesic mechanisms of CBD.

Results and conclusion: The analgesic effect of CBD is complex and still being researched. CBD models the perception of pain by acting on G protein-coupled receptors. Another group of receptors that CBD acts on are serotonergic receptors. The effect of CBD on an enzyme of potential importance in the production of inflammatory factors such as cyclooxygenases and lipoxygenases has also been confirmed. The presented potential mechanisms of CBD's analgesic effect are currently being extensively studied.

KEYWORDS
analgesic effect, analgesic mechanism, cannabidiol, cannabis, CBD

1 | INTRODUCTION

Cannabis, more commonly known as marijuana or hemp, has been used for centuries to treat various conditions. The Chinese are believed to have first used cannabis for medicinal purposes around 2900 BC. Cannabis root decoctions were used to treat arthritis and gout, among other things, as described by the Roman historian Pliny the Elder.[1,2] Currently, the use of marijuana for medicinal purposes is constantly increasing. The number of countries legalizing marijuana is increasing, and the Food and Drug Administration (FDA) has approved four cannabis-based drugs.[3,4] Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two phytocannabinols found in the highest concentrations in Cannabis sp.[5] The endocannabinoid system affects the broadly understood hemostasis of the body. Within the endocannabinoid system, CB1 and CB2 receptors are distinguished, which act via a G protein-coupled receptor (GPCR). THC is the main psychoactive component of cannabis with partial agonist activity at both cannabinoid receptors. Cannabidiol, unlike THC, is devoid of psychoactive effects and is well tolerated by the human body, but has no direct effect on the CB1 and CB2 receptors.[6–8] Observations to date have shown that CBD exerts a range of actions on the

Abbreviations: CBD, cannabidiol; COX, cyclooxygenase; dlPAG, dorsolateral periaqueductal gray; DRG, dorsal root ganglia; DRN, dorsal raphe nucleus; ECS, endocannabinoid system; FDA, Food and Drug Administration; GPCR, G Protein-Coupled Receptor; LOX, lipoxygenase; NAM, negative allosteric modulation; Nav, sodium channels; NSAID, nonsteroidal anti-inflammatory drug; THC, tetrahydrocannabinol; TRP, transient receptor potentials; TRPA, transient receptor potential of ankyrin; TRPM, transient receptor potential channels of melastatin; TRPV, transient receptor potential of vanilloid; VDAC, voltage-dependent anion channel.

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human body, Table 1.[9–14] Such a comprehensive interaction is associated with the involvement of a number of signaling pathways; however, these have not yet been fully identified. Many hypotheses and potential relationships through which cannabinoids may act on the body are available in the literature. In this study, we will present the potential mechanisms responsible for the analgesic effect of CBD. To the best of our knowledge, this is the first review to explore the analgesic mechanisms of cannabidiol.

1.1 | Endocannabinoid system

Studies on the "endocannabinoid system (ECS)" were initiated by the identification of anandamide in the pig brain in 1992.[15] Endocannabinoids (eCB) are lipid mediators located in the brain and peripheral tissues. Endogenous cannabinoids are endogenous lipids that include amides, esters, and ethers of long chain polyunsaturated fatty acid. They mimic the action of tetrahydrocannabinol (THC) in different biological processes.[6,7] The best characterized endocannabinoids are anandamide (arachidonoyl ethanolamide) and 2-arachidonoyl glycerol (2-AG), their precursors are present in lipid membranes. In most cells, transport across the plasma membrane is associated with GPCRs or by depolarization. Anandamide is a partial agonist for CB1 and CB2 receptors. In contrast, 2-AG is a full agonist for both CB1 and CB2 receptors.[7,16,17] The endocannabinoid system affects the broadly understood hemostasis of the body. It is also important for pain perception. Distributions and functions of cannabinoid receptors are shown in Figure 1.[18]

1.2 | Cannabinoid receptors

The obvious mechanism of analgesic action would seem to be an effect on cannabinoid receptors. THC

TABLE 1 Action of CBD on the human body.

CBD-action	Analgesic	Antidepressant	Immune-modulatory
	Antinausea	Neuroprotective	Antioxidant
	Anticancer	Anticonvulsant	Anti-inflammatory

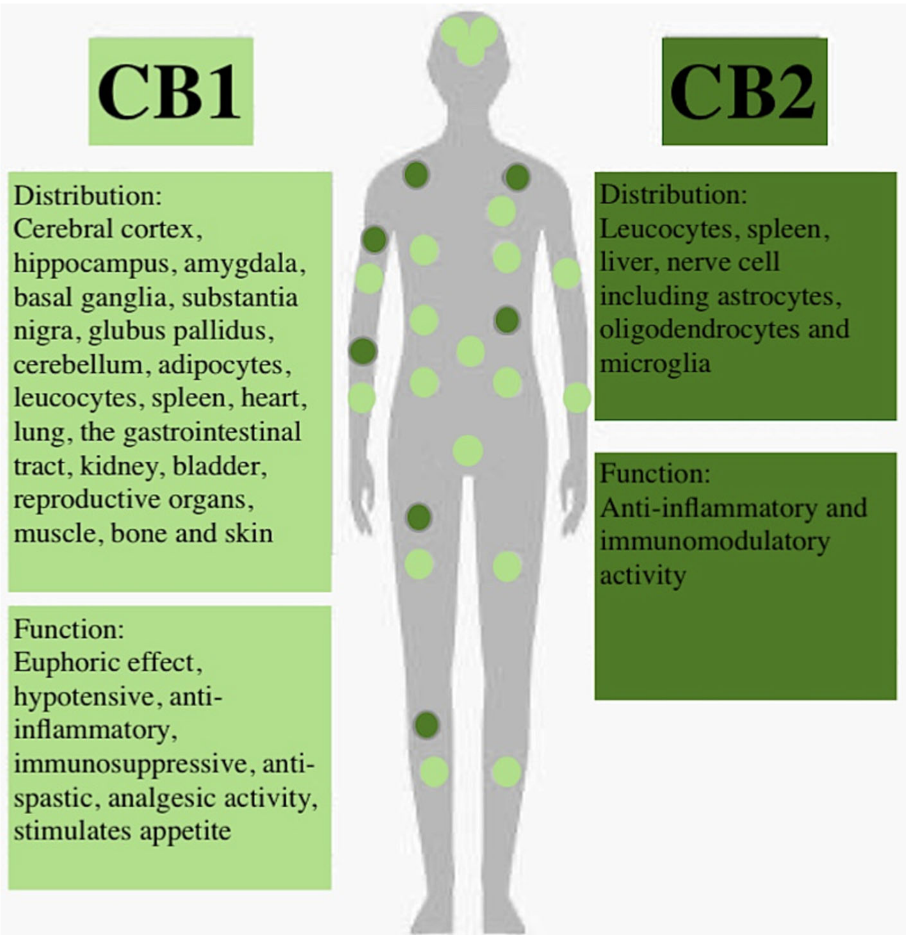

FIGURE 1 Distributions and functions of cannabinoid receptors.

acts on cells primarily by binding to cannabionoid receptors CB1 and CB2 belonging to a class of cell membrane receptors in the GPCR.[19–21] CB1 receptors are characterized by a high prevalence in the presynaptic membranes of neurons within the spinal cord, midbrain, and basal ganglia.[22–28] CB2 receptors are primarily located within the peripheral nervous system and the immune system, Figure 1. Interestingly, they have also been shown to increase their expression in tissues following peripheral nerve damage.[26,27,29] This localization seems to explain the association of the receptors with the effects of cannabinoids on pain perception, thinking, memory, pleasure, coordination and movement. The mechanism of action of both types of receptors is to negatively regulate adenylate cyclase activity through their Gi/Goα, which results in a decrease in intracellular cAMP concentration.[30–32] cAMP interacts physiologically with a variety of ion channels, including the positively influenced inwardly rectifying potassium channels and calcium channels. Therefore, a decrease in the concentration of cAMP in the intracellular space causes the prolongation of presynaptic action potentials.[31,33,34]

However, in contrast to THC, observations by most authors show that CBD has relatively low activity toward cannabinoid receptors.[24,35–38] An exception is the results of Tham et al. where the authors demonstrated partial CBD agonism toward human CB2 receptors in HEK293A cells.[39] Interestingly, the study by Thomas et al. showed that much lower doses of CBD resulted in antagonistic effects induced by CB1 and CB2 agonists, probably by negative allosteric modulation (NAM) of the cannabinoid receptors.[37–39] This was also confirmed by the observations of Pertwee et al. The authors showed a strongly antagonistic effect on CB1/CB2 receptor agonists. Furthermore, they suggested that, by affecting CB2 receptors, CBD influences the immune system by inhibiting the ability of immune cells to migrate.[40] This relationship was also apparent in the work of other authors.[25] Similarly, Laprairie et al. showed that CBD can act as a negative allosteric modulator of this receptor by inhibiting the effect of cannabinoid agonists.[41] Data on the effect of CBD on the signaling pathways of other cannabinoid ligands are also available in the literature.[42,43] The above results necessitate the search for other mechanisms explaining the analgesic effects of CBD Figure 2.

2 | MECHANISMS OF ANALGESIC ACTION

2.1 | GPCR

As previously mentioned, cannabinoid receptors belong to a large group of membrane receptors in eukaryotes which are GPCRs.[49] Data available in the literature show that, CBD can also interact with other receptors of this class. An example is the GPR55 receptor widely distributed within the brain.[50] It was characterized by John et al. who hypothesized that it was responsible for the blood pressure lowering properties of cannabinoids. However, this thesis was not supported by their findings.[51] In 2007, Ryberg et al. reported CBD activity on GPR55.[52] However, Lauckner et al. showed that this activation was not associated with an increase in

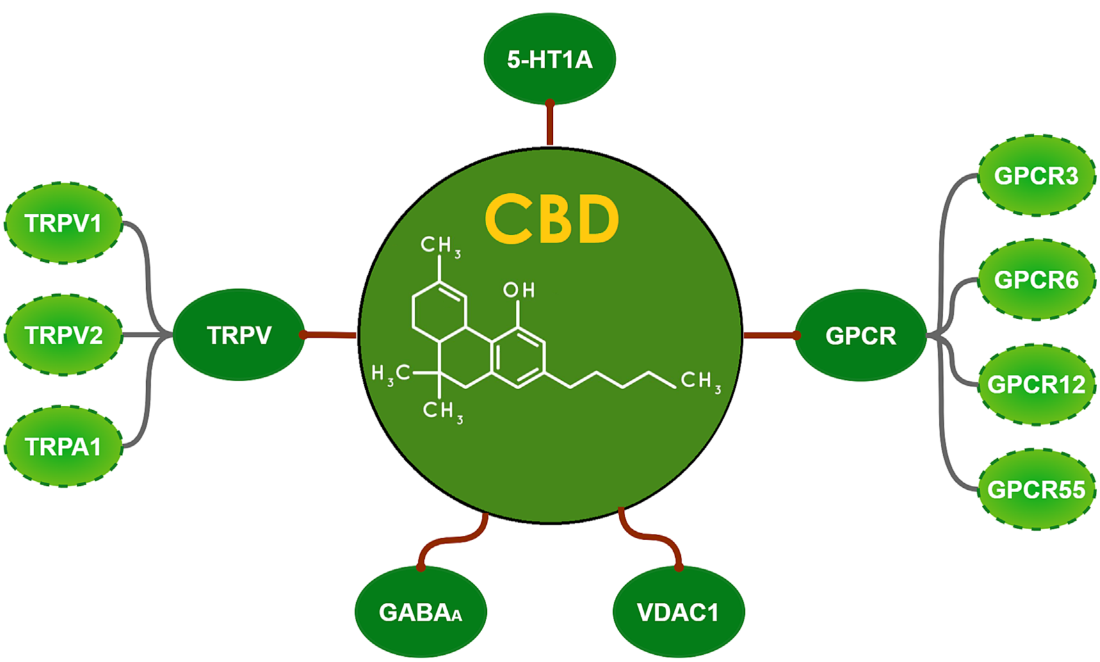

FIGURE 2 Receptors responsible for the analgesic effect of cannabidiol.[44–48]

intracellular calcium levels and activation of G(q), G(12), RhoA, actin, phospholipase C, and calcium release from IP(3)R-gated stores in contrast to the effect of THC.[53] A direct effect of CBD on rec GPR55 was not confirmed by Kapur et al. in their observations.[54] The exact role of GPR55 in the human body still remains a mystery, but its importance for its activation in inflammatory processes and pain modeling has been suggested.[55,56]

Other receptors in this group, which are GPR3, GPR6, and GPR12, also have an important affinity for CBD. As previous observations have shown, they are phylogenetically related to cannabinoid receptors.[44,45] The GPR3 receptor was the first of this family to be cloned from a mouse cDNA library in 1993.[57] Its expression is closely associated with the central nervous system including the cortex, cerebellum, hippocampus, amygdala, thalamus, hypothalamus, and pituitary.[58–60] The GPR6 receptor is widely distributed in the brain (primarily in the striatum, but also in the retrosplenial cortex, hippocampus, amygdala, and hypothalamus.[61,62] Both receptors have been the subject of observations by Loan et al. The authors showed that CBD significantly reduced β-arrestin 2 recruitment to both receptors suggesting a role as their inverse agonist.[63] They also analyzed another receptor, which is GPR12. Originally, its expression was associated with the pituitary gland, but in subsequent years it was also shown to be present in neurons located in the frontal cortex, piriform cortex, thalamus, hypothalamus, hippocampus, amygdala, and olfactory bulb.[64,65] In their work, Brown et al. showed that GPR12 is able to interact with CBD as an inverse agonist leading to inhibition of cAMP accumulation stimulated by the constitutively active GPR12.[66] The exact role of the aforementioned receptors has not yet been determined. Their role in the pathogenesis of neurodegenerative diseases is suspected. However, their role in pain modulation cannot be ruled out.[67]

2.2 | Serotonergic receptors

Another group of receptors associated with pain sensation are the serotonergic receptors. One of them is the 5HT1 receptor. In their work, Rock el. demonstrated that this type of receptor can also be affected by CBD. Its administration allowed for an antiemetic effect via indirect activation of the somatodendritic 5-HT1A autoreceptors in the dorsal raphe nucleus (DRN) in rats model.[46] Interesting observations on the interaction of serotonergic receptors with CBD were made by Campos et al. The authors analyzed the effects of CBD supply on 5-HT1A receptors present in the dorsolateral periaqueductal gray (dlPAG) of male Wistar rats—a midbrain structure responsible for, among other things, the sensation of anxiety. The rats were then subjected to rat tests of anxiety and pain perception by the rodents. The tail-flick test showed that CBD induced an antinociceptive effect 15 min after administration. This was weaker than for morphine however, significant compared to the control group. The injections were even more significant in the effect on anxiety levels of the observed rats. CBD supply to dlPAG increased exploration of the open arms without changing the number of entries into the enclosed arms in the elevated plus maze (EPM) test. The anxiolytic effect of CBD was equally confirmed in the Vogel conflict test (VCT). Furthermore, the researchers were able to reverse the aforementioned effect by supplying WAY100635, which is a 5HT1A receptor antagonist, but not in the presence of AM251 which is an antagonist of CB1 receptors, suggesting an effect of CBD specifically on serotonergic receptors.[68]

The importance of cannabinoids in the modulation of serotonergic transmission has also been the subject of observations by Jesus et al. The authors tested the effect of CBD supply on mechanical allodynia in streptozotocin-induced diabetic (DBT) rats. Using the Von Frey test, CBD was shown to cause a significant antiallodynic effect mediated by 5HT1A receptors. This action could be reversed by the supply of WAY100135 (which is an antagonist of 5HT1A receptors), confirming the role of serotinergic transmission in this aspect. The supply of CB1, CB2 or glycine antagonists did not induce such effect.[69] In another study by De Gregorio et al. using in vivo single-unit extracellular recordings in rats, they analyzed the firing rate of 5-HT neurons in dorsal raphe nucleus. The administration of acute intravenous increasing doses of CBD was shown to reduce the firing rate of 5-HT neurons. Moreover, also in this case, this effect could be neutralized by the administration of WAY100635 and capsazepine (which is a TRPV1 receptor antagonist), but not AM251 (a CB1 receptor antagonist). This confirms the importance of 5HT1 and TRPV1 receptors in the modulatory effects of CBD on serotonergic transmission.[70] In a second stage of the experiment, the authors also tested the effects of repeated subcutaneous administration of CBD for 7 days in healthy rats. The effect was a significant increase in the mean firing rate of DRN 5-HT neurons probably as a result of desensitisation of 5-HT1A autoreceptors.[70] Furthermore, in a spared nerve injury rat model, repeated CBD injections for 24 days resulted in decreased mechanical allodynia, decreased 5-HT firing activity and increased anxiety-like behavior. In contrast, the effect of a 7-day supply of the compound was a decrease in mechanical allodynia, decreased anxiety-like behavior, and normalized 5-HT activity.[70] Again, the antiallodynic effect was reversed with 5-HT antagonists and, in a partial way, TRPV1 antagonists. Moreover, the antianxiolytic effect was only affected by WAY100635.[70] Conclusions from the observations of de Gregorio et al. showed that 5-HT1A receptors significantly mediate the anxiolytic properties of CBD, but are only partly responsible for the analgesic effect.[70] In addition, the effect of capsazepine in reversing the antiallodynic effect of CBD indicates a dominant role for TRPV1 receptors in this aspect.[70]

2.3 | Opioid and dopamine receptors

The search for new receptors on which CBD interacts is also ongoing. Among others, CBD has been shown to interact with opioid receptors. Furthermore, computational analyses suggest the dopamine D3 receptor as a new potential target for this compound. However, further observations are needed to experimentally confirm this thesis.[71,72]

2.4 | Ionic channels

The result presented earlier shows that CBD can also exert analgesic effects through its action on ion channels. These include the transient receptor potential of vanilloid type 1 and 2 (TRPV1 and TRPV2) controlling the passage of Na+, K+, and Ca2+ across cell membranes. Transient receptor potentials (TRPs) belong to a larger group of cationic ion channels primarily present on the cell membranes of animal cells.[73] Their activation occurs primarily under the influence of capsaicin or heat above temperatures of 40°C (TRPV1) or ~50°C (TRPV2).[47,74] Both receptors are located within the central nervous system. TRPV1 are located, among others, in basal ganglia, hippocampus, cerebellum, diencephalon and DRG neurons while TRPV2 have been described in sensory neurons of the DRG, trigeminal ganglia, spinal cord and also within the cerebellum.[48,75–77] Another ion channel susceptible to cannabinoids is the transient receptor potential of ankyrin type 1 (TRPA1) which is often localized together with TRV1 in sensory neurons.[47,78–80] Activation of these receptors leads to depolarization of the cell membrane. In addition, TRPV1 and TRPA1 receptor-mediated functional desensitization, which manifests itself as a lack of receptor sensitivity to ligands after activation, is also observed.[5]

These mechanisms and the action on the aforementioned channels may be important in the antinociception effect. In their study, Maione et al. showed that CBD and CBC (cannabichromene) reduced electrical activity of ON and OFF neurons of the rostral ventromedial medulla in anaesthetized rat. This effect was dose-dependent. Moreover, it was reversible after treatment with selective antagonists of cannabinoid CB1, adenosine A1 and TRPA1 receptors, but not of TRPV1.[81] De Petrocellis et al. analyzed the effects of different phytocannabinoids on the activity of both vanilloid type 1 (TRPV1) and ankyrin type 1 (TRPA1) and the menthol- and icilin-sensitive transient receptor potential channels of melastatin type 8 (TRPM8). CBD was shown to induce TRPA1-mediated Ca2 + elevation in HEK-293 cells. However, this action was weaker than with cannabichromene (CBC). Interestingly, they also observed an antagonistic effect of CBD on TRPM8 receptor activity.[82] In a subsequent study, the authors showed that CBD stimulate and desensitize human TRPV1 which was consistent with data previously available in the literature.[83–85] Furthermore, they showed that THC and CBD increase activity at TRPV2 channels.[83] An analogous agonistic effect of CBD on TRPV2 was also previously described by Qin et al.[86]

However, CBD can also affect the activity of other types of receptors. The result of the study by Ghovanloo et al. suggests that CBD can inhibit the activity of sodium channels (Nav) at therapeutically relevant concentrations. Interestingly, this effect was temperature dependent.[87] The observations of Ross et al. showed that CBD and THC can also inhibit low-voltage-activated T-type calcium Ca(V)3 channels located, among others, in neurons involved in nociceptive processing.[88] There are also data in the literature suggesting a modulatory effect of CBD on GABAA ionotropic receptors and voltage-dependent anion channel 1 (VDAC1).[78,89]

2.5 | Effects on transporters and enzymatic systems

However, the action of CBD on pain modulation is not necessarily through a direct receptor-mediated mechanism. Data available in the literature suggest an effect of endocannabinoids on the activity of transporters and enzymes involved in the metabolism of drugs used to treat pain which may potentiate their effects. Observations by Wheal et al. conducted on a rat model sought a mechanism for the anti-inflammatory and analgesic properties of CBD in preclinical models of diabetes. The authors showed that this action is mediated by an increase in the activity of both cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) which are major targets of non-steroidal anti-inflammatory drugs (NSAIDs).[90,91] In addition, CBD is an inhibitor of lipoxygenase (LOX), which is potentially involved in the production of inflammatory factors..[92] The anti-inflammatory effects of CBD have been repeatedly confirmed in preclinical observations.[93–97]

An inhibitory effect on the cytochrome P450 superfamily (CYPs) constituting major enzymes involved in many drug metabolisms, including NSAIDs commonly used in pain management, has also been described.[19,73] Studies in rats also demonstrated an inhibitory effect of CBD on fatty acid amide hydrolase (FAAH), but observations conducted on the human isoform of the enzyme did not confirm the physiological significance of this relationship.[83,84] Results of analogous relevance were also obtained for mitochondrial complex I, II and IV, as well as testosterone hydroxylase and acyl-CoA cholesterin acyltransferase (ACAT), which are enzymes involved in steroid metabolism.[98–100] Studies by Carrier et al. have also shown the importance of CBD in reducing adenosine uptake suggesting its immunosuppressive effect by increasing endogenous adenosine signalling.[101] Similar observations were also made by Mijangos-Moreno et al. Additionally, the authors suggested that this relationship may be crucial in the sleep promoting effects of CBD.[102]

CBD also affects the activity of intracellular transporters of endocannabinoids such as fatty acid binding proteins 1, 3, 5, and 7.[102–104] There are reports of modulation of the activity of transporters of multidrug resistance proteins (multidrug resistance-associated protein 1 (ABCC1), ATP-binding cassette super-family G member 2 (ABCG2) or P-glycoprotein). However, this occurred at high concentrations of the substance, suggesting a lack of physiological relevance of this phenomenon.[5]

3 | LIMITATIONS

The limitations of this review are mainly due to the limitations of the available studies in the literature. Most of the available research in the literature has focused on cannabidiol and tetrahydrocannabinol. The premise of this study was to present the potential analgesic mechanisms of CBD itself. To the best of our knowledge, we have presented all the potential analgesic mechanisms of cannabidiol that have been studied. However, the presented mechanisms require confirmation in further studies.

4 | CONCLUSIONS

The analgesic effect of CBD is complex and still being researched. Unlike THC, CBD does not affect CB1 and CB2 receptors, but it can affect other cannabinoid receptors such as GPR55. Other GPCRs that can participate in pain modeling under the influence of CBD are GPR3, GPR6 and GPR12. The serotonergic receptors are another group of pain receptors.

The analgesic effect of CBD through the 5HT1A receptors has been demonstrated. 5HT1A receptors, along with TRPV1 receptors, participate in the modulating effect of CBD on serotonergic transmission. CBD also affects transient receptor potentials such as TRPV1 and TRPV2 and Ankyrin Type 1 Receptor Transient Potential (TRPA1). In addition, CBD may inhibit the activity of sodium channels (Nav) and inhibit low-voltage-activated T-type calcium Ca(V)3 channels involved in nociceptive processing. However, the effects of CBD on pain modulation are not necessarily only through a direct receptor-mediated mechanism. The effect of CBD on an enzyme of potential importance in the production of inflammatory factors such as cyclooxygenases and lipoxygenases has been confirmed. An inhibitory effect on the cytochrome P450 superfamily, which are the main enzymes involved in the metabolism of many drugs, including NSAIDs, has also been described. The presented potential mechanisms of CBD's analgesic effect are currently being extensively studied.

AUTHOR CONTRIBUTIONS

Research concept and design: Bartłomiej Kulesza and Jacek Kurzepa. *Collection and/or assembly of data*: Bartłomiej Kulesza and Marek Mazurek. *Data analysis and interpretation*: Marek Mazurek. *Writing the article*: Bartłomiej Kulesza and Marek Mazurek. *Critical revision of the article*: Bartłomiej Kulesza and Jacek Kurzepa. *Final approval of the article*: Bartłomiej Kulesza, Marek Mazurek, and Jacek Kurzepa. All authors reviewed the results and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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