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Effects of Cannabidiol in Inflammation: A Review of Pre-clinical and Clinical Findings

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Abstract: Cannabidiol (CBD) is the second most abundant component of the plant *Cannabis sativa*. Currently, CBD is approved for Lennox-Gastaut and Dravet syndrome and newly for tuberous sclerosis complex. However, based on the available data, CBD migth have a broad spectrum of potential therapeutic uses. Therefore, the aim of this review was to summarize the evidence on the effects of CBD on pain and inflammation of various causes. PubMed and Web of Science databases were searched until January 2023. The medical keyword term "cannabidiol" was combined with "pain", "arthritis", and "inflammation". Based on the initial search for these terms, 9, 5, and 5 relevant publications have been selected. Based on the available data, it is not possible to draw a clear conclusion about the effect of CBD to releave pain, because each study used a different route of administration or treatment regimen. The studies also differed in etiopathogenesis of pain (chronic, neuropathic, and possibly inflammatory pain), and in general included only small number of subjects. In case of anti-inflammatory qualities of CBD, its effect on the intestinal system is negligible. On the other hand, positive treatment results were observed in all publications dealing with the effect of CBD on arthritis.

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Introduction

Cannabidiol (CBD) is the second most abundant component of the plant *Cannabis sativa* (Nahler et al., 2017). Nowadays, CBD substance is approved by regulatory authorities only for a few types of resistant epilepsies (Lennox-Gastaut and Dravet syndrome) and newly for tuberous sclerosis complex but is freely available in the form of food supplements. Typical oral forms (i.e., capsules) and parenteral forms can be encountered, but oral sublingual drops, sprays, or inhalation by aerosol, nebulizer, vapor, or cigarettes are also fairly common. The poor solubility of the compound in combination with significant first-pass effect cause low rate of gastrointestinal absorption (European Medicines Agency, 2023). On the other hand, CBD transport via the lymphatic system contributes significantly to the total drug exposure after peroral administration (Jelinek et al., 2022). Oral bioavailability has been described in range of 13–19% and can be notably increased by high-fat meal (Mechoulam et al., 2002; Lucas et al., 2018). The average bioavailability was 31% in 5 male participants after smoking (Ohlsson et al., 1986). CBD can be cumulated in adipose tissues. The metabolic pathways are mainly CYP2C19, CYP3A and uridine 5-diphosphate glucuronosyltransferase. The primary metabolite is the 7-OH-CBD metabolite, which is converted into 7-COOH-CBD metabolite (Lucas et al., 2018). It is not clear if CBD can convert to tetrahydrocannabinol (THC) in an acidic environment after dosing. There exists some evidence that acidic environments can support this transformation, but to date no *in vivo* experiments have confirmed this hypothesis (Wray et al., 2017). The elimination half-life (t1/2) was 56 h (European Medicines Agency, 2023). Intravenous administration, smoking or chronic oral administration results in a longer t1/2 of 24 hours, 31 hours, and 2–5 days, respectively (Ohlsson et al., 1986; Consroe et al., 1991). Major portion of CBD is excreted unchanged in the feces, while oxidized and glucuronidated metabolites are excreted via kidneys (Huestis, 2007; Ujvary and Hanus, 2016).

CBD influences a number of receptors. It is exogenous ligand that interact primarily with the endocannabinoid system, but the signaling is not completely understood (Pacher et al., 2020). CBD is negative allosteric modulator of cannabinoid receptors such as CB1 and CB2 (Laprairie et al., 2015; Cherkasova et al., 2022). CB1 receptors are primarily located in central nervous system compared to CB2 receptors (Ramirez et al., 2012). Some of the other most frequent targets of CBD include ligand-gated ion channels (NaV, GABAA), TRP channels (TRPV1, TRPV2, TRPA1, TRPM8), GPCRs (5-HT1A, α1A, CB1, CB2, GPR18, GPR55), CYP450 enzymes, and nuclear receptors (PPARγ) (Pertwee, 2005; Morales et al., 2017; Morales and Reggio, 2019). The complexity of CBD's interactions with its molecular targets suggests a very wide range of potential effects. Many of these have already been tested in various *in vitro*/*in vivo* and preclinical/clinical studies.

Because of that, this review aims to summarise the available evidence on the potential use of CBD in the treatment of inflammation and its symptoms.

Literature search

PubMed and Web of Science databases have been searched until January 2023. The medical subject headings term "cannabidiol" was combined with "pain", "arthritis" and "inflammation" using Boolean operators in order to identify relevant references. Searches were limited only to original articles written in English. The search results for the term "pain" were limited only to articles dealing with inflammation-related pain. Finaly, there were excluded studies testing the effects of CBD with combination with other medicine or using polycomponent mixtures of cannabinoids, except for mixtures in which the presence of substances with a majority of CBD was clearly declared.

There were 64, 68, and 481 results filtered based on the initial search for "pain", "arthritis" and "inflammation" terms, respectively. Out of which 9, 5, and 5 relevant publications have been subsequently selected.

Effects of cannabidiol

Although THC has a similar molecular structure and sufficient affinity for both cannabinoid receptors (CB1 and CB2), CBD has only limited affinity (Pacher et al., 2020). Some studies in animal and human subjects have shown that the CB2 expression is the primary receptor that regulates the immunosuppressive effect release of pro-inflammatory cytokines including TNFα and Th1 helper response (Malfait et al., 2000; James, 2020). Several publications have demonstrated the potential anti-inflammatory effect of cannabinoids (Nagarkatti et al., 2009). Their mechanisms of action include activating receptors, inhibiting cytokines and cell proliferation, inducing apoptosis, etc. (Zurier and Burstein, 2016; Nichols and Kaplan, 2020). Human B cells, NK cells, neutrophils, CD8+ T cells, monocytes, and CD4+ T cells are expressed by CB1 and CB2. CB2 expressed changes correlated with inflammation. Arachidonic acid derivatives (2-arachidonylglycerol and anandamide) play the immunomodulatory role of CB2. Typically, CB2 stimulation decreases immune cell functions via intracellular signaling mechanisms, such as activation of mitogen-activated protein kinases and inhibition of adenylate cyclase activity by Gi/o proteins. In fact, CB2 can suppress the release of TNF-, IL-2, and IFN- from activated human peripheral lymphocytes and the synthesis of proinflammatory cytokines including TNF-, IL-6, and IL-8 in human macrophages and monocytes. Also, endocannabinoid synthesis is increased by toll-like receptor (TLR) activation, and cannabinoids decrease the TLR-induced inflammatory response (Pellati et al., 2018). Recent preclinical evidence suggests that CBD has anti-inflammatory, analgesic and antioxidant effects (Soliman et al., 2021). The anti-inflammatory effects of cannabinoids have been demonstrated in animal models of arthritis (Selvi et al., 2008). In animal models of arthritis, CBD provided pain relief and reduced inflammatory cell infiltration into the joint (Hammell et al., 2016). The reduction of neuropathic and cancer pain is known indications for the use of cannabinoids, and three cannabis-based drugs (Nabilone, Sativex

and Marinol) are used clinically for this purpose (Russo et al., 2007; Mucke et al., 2018).

Effects of cannabidiol in inflammation

As the publications to date on the effect of CBD on inflammation are very promising, several research groups are conducting further studies to demonstrate its effect in different tissues. Couch et al. (2017) used Caco-2 cultures and colonic samples from patients (bowel cancer [n=13], inflammatory bowel disease [n=6] or emergency appendectomies [n=6]). They observed that CBD prevented increase of cytokines in colonic samples and this effect were diminished by CB2 and TRPV1 anatagonists (Couch et al., 2017).

The anti-inflammatory effect of CBD and dexamethasone was also comparedin another *in vitro* study. Inflammation was induced by lipopolysaccharide. Upon administering both substances, a similar effect was observed. However, the patterns of action differed substantially. CBD attenuated c-Jun N-terminal kinases phosphorylation levels, whereas dexamethazone attenuated only IκB kinase phosphorylation levels (Wang et al., 2022). According to a different, CBD has anti-arthritic activity and may help with joint inflammantion particularly by reaching synovial fibroblasts in inflammatory disorders (Lowin et al., 2020). A low dose of CBD impacts the activity of G-proteins, which act as molecular switches transmitting signals from other stimuli to cells (De Petrocellis et al., 2011).

Two research groups tried to describe anti-inflammantory properties of CBD *in vivo* – in Institute of Cancer Research male mice and in rats (Borrelli et al., 2009; Jamontt et al., 2010). In the first study, the experimental colitis was induced in mice by dinitrobenzenesulfonic acid (DNBS) (intracolonic administration). In the second study, acute colitis in rats was induced by 2,4,6-trinitrobenzenesulfonic acid (TNBS). Both of studies observed reduction of proinflmmantory interleukins. In rats, CBD not only reduced inflammation, but also reduced the incidence of functional disruptions.

The reduction of imune cell activaton with CBD in the pancreatic microcirculation as well as lowering the risk of developing type 1 diabetes (T1D) was also demonstrated. These experiments show that untreated non-obese diabetic (NOD) mice developed T1D earlier (19.5 weeks) whereas CBD treated mice (24 weeks) (Lehmann et al., 2016). However, it should be remembered that T1D is a very specific type of inflammation.

In a clinical study, CBD was examined as an adjuvant to ongoing treatment for inflammatory bowel diseases. During the experiment, the disease activity was monitored as well as laboratory parameters during 8 weeks of treatment and 2 weeks after. Standard therapy was not changed. Totally, 19 of 20 patients completed the study. The effects of CBD were insignificant for Crohn's disease, but that could be caused by a small dosage of CBD, limited number of patients, or the lack of the necessary synergism with other cannabinoids (Naftali et al., 2017).

Table 1 – A summary of studies investigate effects of CBD on intestinal inflammation

References	Study sample (patient population, sample size, gender and age)	Treatment schedule	Study design	Conclusion
Borrelli et al. (2009)	male ICR mice (35–40 g), colitis was induced by the intracolonic administration of DNBS	CBD (1–10 mg/kg and 5 mg/kg) was injected once a day for 6 consecutive days starting 3 days before induction	disease-induced animal model	CBD reduced proinflmmantiory interleukins and the wet weight/colon length ratio of the inflamed tissue.
Jamontt et al. (2010)	wistar rats male induced acute colitis by TNBS	CBD were i.p. applied: 5, 10, 15 and 20 mg/kg (n=4, 6, 5 and 5, respectively) for vehicle group (n=11) sulphasalazine (n=7) was administered at 300 mg/kg p.o. One dose was given every 24 h during 3 days	disease-induced animal model	CBD not only reduced inflammation, but it also reduced the incidence of functional disruptions.
Naftali et al. (2017)	19 patients (11 men) (average 39 ± 15 years) with a Crohn's disease	per oral (10 mg) CBD/placebo twice a day. Test – 8 weeks of treatment and 2 weeks thereafter	randomized controlled	After 8 weeks of treatment, the index was very similar in the CBD and placebo groups CBD had no beneficial effects.
Lehmann et al. (2016)	19 seven-week-old female NOD mice	administered daily 5 mg/kg CBD/ placebo i.p. 5 times a week for 10 weeks	disease-induced animal model	CBD-treated NOD mice exhibited substantially decreased leukocyte activation, and they also developed T1D later.
van Orten-Luiten et al. (2022)	32 female irritable bowel syndrome patients were randomized	chewing gum contain 50 mg CBD (max. 6 gums per day)	randomized, double-blinded, placebo-controlled cross-over	There were no group differences in pain scores or the number of gums used between CBD and placebo gum.

CBD – cannabidiol; ICR – Institute of Cancer Research; DNBS – dinitrobenzenesulfonic acid; TNBS – trinitrobenzenesulfonic acid; NOD – non-obese diabetic

Also, we found publication where they focused on changing in glycemic and lipids metabolizmus after dosing CBD and others cannabinoids compare to placebo (Jadoon et al., 2016). The details about avaible studies are summarized in Table 1.

Effects of cannabidiol in arthritsis

We evaluated 5 studies which met criteria for inclusion (Table 2). Two of these studies used a CBD extract, which included traceable amount of other substances. The study by Gamble et al. (2018) used extract contains low percentage of CBG, THC and other cannabinoids. The second research group – Heineman et al. (2022) – declared 99.07% pure isolate of CBD. Both these studies showed significant improvement in arthritis-related pain.

Similarly, to the previously mentioned studies, these groups administered CBD intraperitoneally and orally respectively. Based on Malfaits histological findings, we can confirm that optimal therapeutic effect has CBD at an i.p. dose of 5 mg/kg or an oral dose of 25 mg/kg. The therapeutic level of CBD is dose-dependent. According to their data, schematic administration can avoid the relapse of arthritis. Additionally, they examined the synovial cells, specifically before and after the administration of CBD. Synovial cell treated by CBD released significantly less TNF when cultivated *in vitro* (Malfait et al., 2000).

Effects of cannabidiol in inflammation-related pain

Pain management is a topic, where it is crucial to focus not only on the pain itself, but its origin. From the 64 found articles, we excluded cancer pain, palliative care, and pain caused by trauma. Due to these limitations, we were left with 9 publications, which we discuss below (Table 3).

In *in vitro* (human cells) and *in vivo* (mouse) models, CBD attenuated the production of proinflammatory cytokines IL-6 and TNF-α. These experiments were followed up by randomized, placebo-controlled veterinary study, when CBD significantly reduced pain and increased mobility in a dose-dependent manner in osteoarthritic dogs (Verrico et al., 2020).

Monosodium iodoacetate-induced osteoarthritis model in rats was used to assess the efficacy of CBD after intra-articular administration. CBD/placebo was administered in addition to using the CB1 receptor antagonist, the CB2 or the TRPV1 receptor antagonist. These three receptors are responsible for the anti-inflammatory and analgesic effects of CBD. The anti-inflammation effect of CBD arises from influencing only the CB2 and the TRPV1 receptor antagonist. Also, the binding of CBD to the TRPV1 receptor is responsible for the analgesic effect. Higher doses of CBD have only a local impact on secondary allodynia. Furthermore, in the acute phase of inflammation after CBD administration, a slowing of nerve demyelination versus placebo was observed on the 14th day after induction with monosodium iodoacetate (Philpott et al., 2017).

Table 2 – A summary of studies investigate effects of CBD on arthritis

References	Study sample (patient population, sample size, gender and age)	Treatment schedule	Study design	Conclusion
Malfait et al. (2000)	mices induced by model of murine CIA	p.o. applied – CBD doses were 10 mg/kg, 25 mg/kg, and 50 mg/kg (n=6 per group). Control group dose olive oil (n=6). Intraperitoneal administration – CBD – 20 mg/kg (n=12), 10 mg/kg (n=17), 5 mg/kg (n=15), and 2.5 mg/kg (n=9) and placebo (n=23)	disease-induced animal model	CBD was equally effective when administered i.p. or orally. The dose with an optimal effect at 5 mg/kg per day i.p. or 25 mg/kg per day orally. Clinical improvement was associated with the protection of the joints against severe damage.
Hammell et al. (2016)	54 rats were used in the experiments described here of which 21 were used as controls and 23 were subjected to adjuvant-induced arthritis	CBD gels (0.6, 3.1, 6.2 or 62.3 mg/day) were applied for 4 consecutive days after arthritis induction	paralel (control vs. disease-induced animal model)	Transdermal CBD gel with this dose significantly reduced joint swelling, limb posture scores as a rating of spontaneous pain, immune cell infiltration and thickening of the synovial membrane.
Jelinek et al. (2022)	14 rats with RA (induced by CIA)	7.5 mg of CBD per oral for 24 days	randomized, single-dose, laboratory-blinded	They observed the improvement of clinical parameters of RA after administration of CBD.
Gamble et al. (2018)	16 dogs diagnosed with osteoarthritis	CBD/placebo, 2 mg/kg every 12 h for 4 weeks. After 2-weeks of washouts period coss-over	randomized, placebo-controlled, owner and veterinarian double-blind, cross-over	Dogs were more comfortable and active when were treated by CBD.
Heineman et al. (2022)	18 participants with joint arthritis	treat by CBD twice a day 2 weeks (6.2 mg/ml CBD with shea butter) or placebo, followed by a 1-week washout period and then crossover	phase 2, double-blinded, randomized controlled	Topical CBD treatment showed a substantial reduction in associated disability and pain with specific joint arthritis.

CBD – cannabidiol; RA – rheumatoid arthritis; CIA – collagen-induced arthritis

CBD caused no clinical or statistically significant reduction of pain intensity in randomized, placebo-controlled study in 129 patients with osteoarthritis or psoriatic arthritis. For effect evaluation, primarily intensity of the pain (0–100 mm), but additionally Pittsburgh Sleep Quality Index, Hospital Anxiety and Depression Scale, Pain Catastrophizing Scale (PCS), and Health Assessment Questionnaire Disability Index were used. However, there are some notable limitations of this study. The patients absolved only 3 sessions with the doctors – first session where they were randomized, the second was made after 4 weeks via a phone call, and the last was made at the end of the study (after 12 weeks), and the dosage of CBD was 20–30 mg/day (Vela et al., 2022).

In contrast, Xu et al. (2020) reported that transdermal aplication of CBD can cause significant reduction in intense pain, sharp pain, and cold and itchy sensations in comparison with placebo. On the other hand, this study also has some limitations. The group of subjects is relatively small (n=29), and the pathology of examined diseases is heterogenous, which may affect the results. The final evaluation was done using a questionnaire and using the international scale for neuropatic pain (NPS) (Xu et al., 2020).

A balanced placebo design trial in healthy adults suggest that CBD and/or expectations for obtaining CBD can have a distinct effect on different pain outcomes. The notable limitations of this study are the fact that only a single dose of 50 mg CBD was used, and only a small group of young subjects were part of the trials (range 18–27 years) (De Vita et al., 2022).

Schneider et al. (2022) observed no significant effect of CBD on acute pain, hyperalgesia, and allodynia in comparison with placebo group. Similarly, to the previous study, the limitations include a single dose (although high), and relatively small sample of patients (Schneider et al., 2022).

Finally, CBD has not been shown to be superior to placebo as an adjunct medication for relief of acute non-traumatic back pain. Limitations of this study include application of only single dose of CBD, possible influence of analgesic medication used by patients before arrival, and also the verbal numerical pain scale may be biased by subjective evaluation (Bebee et al., 2021).

Limitation of Wades study is variable range of CBDs dose (2.5–120 mg/24 hours). They also applied CBD extract which is not detailly described (Wade et al., 2003).

Conclusion

This review provides a structured summarization of available and published evidence on the effects of CBD in a range of examined diseases. Each research group used different formulations, routes of administration, treatment regimens, as well as different groups of subjects. These inconsistencies make it difficult to draw objective conclusions. Finally, we would also like to note that our review focused on studies examining CBD's effect on pain, which also used different etiopathogenesis of pain (e.g., chronic, neuropathic, or inflammatory pain).

Table 3 – A summary of studies investigate effects of CBD on pain

References	Study sample (patient population, sample size, gender and age)	Treatment schedule	Study design	Conclusion
Verrico et al. (2020)	spontaneous canine model of OA on mice	4-week liposomal CBD (20 mg/day) and nonliposomal CBD (50 mg/day)	randomized, double-blind, placebo-controlled study	CBD significantly decreased pain and increased mobility in a dose-dependent among animals. Liposomal CBD (20 mg/day) was as effective as the highest dose of nonliposomal CBD (50 mg/day) in clinical outcomes.
Philpott et al. (2017)	17 rats induced osteoarthritis by monosodium iodoacetate	administreted i.artic.vehicle (50 ml) / CBD (100–300 mg/50 ml). In groups administred (s.c.) around joint the CB1 receptor antagonist (75 mg/50 ml) / the CB2 receptor antagonist (75 mg/50 ml) / the TRPV1 receptor antagonist (30 mg/50 ml)	disease-induced animal model	Local CBD therapy decreased acute, temporary joint inflammation. The early onset of pain and nerve damage in these OA joints was stopped by prophylactic CBD therapy. These results imply that CBD may be a secure and beneficial treatment for managing OA joint neuropathic pain.
Wade et al. (2003)	20 patient – 14 diagnoses of multiple sclerosis, 4 spinal cord injuries, 1 brachial plexus lesion with associated neuropathy, and 1 phantom limb pain following an amputation	2-week treatment periods range of 2.5–120 mg/24 hours	double-blinded, randomized placebo-controlled crossover study	Muscle spasms, spasticity, and bladder control did not improve statistically using CBD compared to placebo.
Vela et al. (2022)	129 patients randomized to CBD/placebo group	synthetic CBD 20 to 30 mg or placebo daily for 12 weeks	randomized, double-blind, placebo-controlled design	When compared to placebo, they found no clinically or statistically effects of CBD on pain intensity in individuals with hand osteoarthritis and psoriatic arthritis.
Xu et al. (2020)	29 patients (range 35–79 years, 37.9% females) with symptomatic peripheral neuropathy with different origin	250 mg of CBD per 3 fl. oz container, topical application 4 times a day during 4 weeks	double-blind, randomized placebo-controlled crossover	When compared to the placebo group, the CBD group saw a notable reduction in pain, cold, and itching feelings.

Haffar et al. (2022)	80 patients undergoing primary unilateral total knee arthroplasty applied topical CBD (CBD; n=19), essential oil (EO; n=21), CBD and essential oil (CBD + EO; n=21), or placebo (PLA; n=19) three times a day around the knee for two weeks postoperatively	CBD alone (group CBD), essential oils (group EO), CBD and essential oils (group CBD-EO), and placebo with no CBD or EO (group PLA)	randomized double-blinded placebo-controlled	No statistically significant differences existed for Visual Analogue Scale scores at other times.
De Vita et al. (2022)	15 healthy adults (between 18 and 27 years) each completed 4 separate experimental sessions	4 groups – control (told inactive-given inactive); expectancy (told active CBD-given inactive); drug (told inactive-given active CBD); and expectancy + drug (told active CBD-given active CBD). 50 mg of hemp-derived CBD isolate in a 0.3 ml oil solution administered sublingually via dropper	crossover, 2×2 factorial balanced placebo design	These results suggest that CBD and/or expectations for obtaining CBD can have a distinct effect on different pain outcomes.
Schneider et al. (2022)	20 healthy volunteers with acute pain model with intradermal electrical stimulation	single 800-mg orally administered CBD compared with placebo	randomized, placebo-controlled, double-blinded, crossover	When compared to a placebo, there was no significant difference in pain scores after CBD application. Also hyperalgesia and allodynia were not significantly different after CBD administration versus placebo.
Bebee et al. (2021)	100 patients with acute, non-traumatic low back pain (34–60 years), 56 men	400 mg of syntetic CBD or placebo	randomised, double blinded, placebo-controlled	The two-hour mean pain scores for both the CBD and placebo groups were comparable. The two groups reported adverse reactions and oxycodone use in the four hours before and after the four hours of administering CBD or a placebo were comparable.

CBD – cannabidiol; OA – osteoarthritis; EO – essential oil; PLA – placebo; s.c. – subcutaneously

After evaluating the effects of CBD on intestinal inflammation, it can be concluded that the positive effect is not proven beyond doubt. On the other hand, all available data suggest that CBD has a positive effect on joint inflammation (arthritis) and exihibits a reduction of pro-inflammatory markers.

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