Cannabis in inflammatory bowel disease: a narrative summary

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Abstract

Introduction: Although cannabinoids have been used for several years, only recently have their mechanisms of action and therapeutic targets been described. Alterations in the endocannabinoid system have been observed in various diseases and conditions such as pain, inflammation, autoimmune diseases and various specific disorders. Inflammatory bowel disease groups two chronic idiopathic conditions with uncertain pathogeneses in which deregulation of the immune system plays an important role. Alternative treatments need to be developed for these patients since only a minority of patients achieve disease remission. Our goal is to review recent evidence related to the use of cannabis to treat ulcerative colitis and Crohn's disease. **Methods:** This is a focused narrative review based on searches of Pubmed and Embase. Relevant articles have been reviewed and summarized in narrative form. **Results:** The two main components of cannabis, CBD and THC, have been extensively studied, and their anti-inflammatory and antinociceptive effects have been tested. The effects of these components for control of the symptoms of ulcerative colitis and Crohn's disease have been widely described. However, high quality studies are needed to continue evaluating the efficacy and safety of cannabis use in patients with inflammatory bowel disease.

Keywords

Cannabis, medical marijuana, ulcerative colitis, Crohn's disease, inflammatory bowel disease.

INTRODUCTION

Cannabis has been used for decades for both its medicinal and psychotropic properties. The discovery of cannabinoids, key active components of Cannabis sativa, and research into their mechanisms of action and molecular targets are relatively recent. (1, 2)

The two main components of marijuana are tetrahydrocannabinol (THC), known for its psychoactive effects, and cannabidiol (CBD), a non-psychotropic substance found in high concentrations in the plant. (3) The molecular targets for cannabinoids have been described as G protein-coupled cannabinoid receptors. CB1 and CB2 have been identified as the two key receptors of their endogenous ligands, endocannabinoids. (1, 3)

Alterations in the endocannabinoid system have been observed in various diseases and conditions. They manifest with pain, inflammation, autoimmune diseases, allergic conditions, neurological and neuropsychiatric disorders, obesity, cancer, and cardiovascular and gastrointestinal diseases. (1)

Inflammatory bowel disease (IBD) includes two types of idiopathic conditions: ulcerative colitis (UC) and Crohn's disease (CD). (4) Neither condition's pathogenesis is yet certain, but dysregulation of the immune system in response to gut microbiota appears to be complicated and leads to inflammation of the gastrointestinal tract. (4, 5) The two diseases have peak incidences between the second and fourth decades of life without significant differences between genders. (4) Slight differences related to race or ethnicity have been identified. Western populations tend to have

higher prevalences of UC and CD, (4, 5) but the prevalence of IBD has increased markedly in developing countries. Indeed, recent evidence suggests that incidence is increasing in South America, Asia, Africa and Europe. (5, 6)

Identification of several inflammatory pathways in IBD has led to the use of immunomodulatory and anti-inflammatory agents. (7) Since IBD is considered to be an incurable chronic disease, treatment goals aim to minimize symptoms, improve quality of life and reduce the progression of the disease and associated complications. (4)

The main agents used to manage IBD include anti-inflammatories, immunomodulators, immunosuppressants, and biological compounds such as tumor necrosis factor inhibitors (Tumor Necrosis Factor, anti-TNF). In addition, new therapeutic options include biosimilars of the most widely used anti-TNF agents and Janus kinase inhibitors. (8)

Because about 40% of patients do not achieve remission surgery is often required. (5) Consequently, there is a need to develop alternative treatments which has led us to review recent evidence regarding the use of cannabis to manage UC and CD.

BACKGROUND

The Endocannabinoid System and Cannabis

The endocannabinoid system consists of endogenous cannabinoids, cannabinoid receptors, and enzymes responsible for synthesis or degradation of cannabinoids. (9) In contrast to classical neurotransmitters which are produced and stored in synaptic vesicles, endocannabinoids are produced and released immediately on demand. (1, 9, 10)

Several receptors have been described in the endocannabinoid system, but the effects of endocannabinoids are mainly mediated by CB1 and CB2 receptors which are coupled to the G protein. (1, 3, 9) CB1 receptors are present at high density in the central nervous system (CNS) especially in the cortex, basal ganglia, hippocampus, and cerebellum. (9, 10) Apparently, low concentrations of these receptors are found in the brain stem which explains the low toxicity of cannabinoids. (11)

In contrast, CB2 receptors are highly expressed on peripheral and immune cells, including mast cells, lymphocytes, macrophages, natural killer (NK) cells, mononuclear cells, and microglia. (9-11)

Lesions and tissue inflammation induce high levels of CB2 expression. Activation of the CB1 and CB2 receptors has consequences for synaptic functioning gene transcription and cell motility. (9) Other receptors described in the endocannabinoid system include the G protein-coupled receptor 55 (GPR55) and Transient receptor potential vanilloid subtype 1 (TRPV1).

Distribution of GPR55 varies since it occurs in the CNS and other organs, while TRVP1 is found predominantly in the nociceptive terminals of the peripheral nervous system (SNP) and, to some degree, in the CNS. (11) Acharya et al. have reviewed the role that endogenous cannabinoids play in maintaining immune homeostasis in the gut and found that anandamide, an endogenous cannabinoid, is an important promoter of regulatory T cell and macrophage differentiation since they promote expression of CB2 and TRVP1 receptors. (12)

Various studies have evaluated the function of the endocannabinoid system in gastrointestinal diseases such as IBD. A review by Hasenoehrl et al. described alterations in 5-hydroxytryptamine (5-HT) signaling that led to symptoms such as abdominal pain, altered intestinal peristalsis, and abdominal discomfort. (13) Similarly, a link between 5-HT and endocannabinoid levels has been identified suggesting a possible positive role for administration of cannabinoids or cannabinoid receptor agonists for management of these conditions.

IBD is characterized by dysregulation of the gut microbiota which can alter gut permeability. (14) The epithelial cells of the intestine express CB receptors which can regulate the permeability of the intestine. This occurs because 2-arachidonylglycerol and N-palmitoylethanolamide (PEA) appear to increase the intestinal barrier while anandamide apparently decreases it. (13) This suggests the existence of an important role for the endocannabinoid system in the regulation of the permeability of the intestine and in exposure of microbes to the immune system.

In addition, Pertwee's review of the pharmacology of the CB1 and CB2 receptors mediated by the two main components of Cannabis sativa, THC and CBD, showed that THC is capable of activating both receptors. (2) It suppresses locomotor activity, hypothermia and CB1 receptor mediated antinociception in vivo in healthy mice. Furthermore, it has been reported to help relieve symptomatic pain relief in patients with multiple sclerosis, cancer, chronic pain, and other conditions.

Given the presence of CB1 receptors in neurons, THC has been shown to inhibit the release of certain neurotransmitters and promote the release of others in specific regions of the brain suggesting that this is the mechanism that causes psychoactive effects. (2)

CBD also has the ability to activate both CB1 and CB2 receptors, although it shows a lower affinity for them than THC does. Lower concentrations of CBD are required for their interaction, and CBD has been reported to inhibit migration of immune cells and reduce clinical signs of inflammation. It appears to be an agonist for CB1 receptor agonists and an inverse agonist for CB2 receptors. This characteristic may explain its anti-inflammatory properties. (2, 3)

Capasso et al. wrote that CBD has been observed to have antioxidant, neuroprotective and antiproliferative, anxiolytic, hypnotic, anticonvulsant, anti-nausea and anti-inflammatory effects. (15)

Mechoulam et al. focus on CBD's powerful antioxidant effects which appear to inhibit the release of reactive oxygen species and production of nitric oxide by neutrophils. An increase in interleukin-12 (IL-12) and a decrease in interleukin-10 (IL-10) have also been documented after use of CBD. They also reported an immunosuppressive effect caused by inhibition of IL2 production. (3)

Endocannabinoid overexpression has been shown to have a protective role in intestinal inflammation in experimental models of colitis. These effects are thought to be mediated by CB1 and CB2 receptors, involved in visceral perception, intestinal motility, inflammation, and endothelial damage. (1) Activation of CB1 receptors inhibits the release of acetylcholine thereby decreasing intestinal smooth muscle contractility. Although CB2 receptors have been reported to be present in the enteric nervous system (ENS), their role in controlling peristalsis is believed to be minor. (13)

The Pathophysiology of IBD

The development of UC and CD involves the interaction of environmental factors, genetic factors, gut microbiota, and immune response. (14) Various environmental factors such as smoking, diet, lifestyle, and medications appear to alter the gut microbiota in genetically susceptible individuals. In the presence of a weakened intestinal barrier, these changes in the microbiota favor activation of the immune system and chronic intestinal inflammation. (5)

The role of environmental factors in various autoimmune diseases has been extensively studied within this context. In IBD, individuals who have been exposed to smoke, early use of antibiotics, consumption of food additives, and low levels of vitamin D appear to be at increased risk of developing these conditions. Similarly, improvements in such diverse issues as access to purified water and home health services, higher vaccination rates, and use of antimicrobials have clear correlations with lowering rates of IBD and other autoimmune diseases. (14, 16, 17)

Regarding genetic susceptibility, a number of studies have identified various genes with immune regulatory functions and others that mediate bacterial recognition associated with the development of CD and UC. (5, 14, 16)

Several enriched loci have been identified for genes involved in immunodeficiency, in proper functioning of T cells, and in modulation of cytokine production that are all related to IBD. (14) A recent study has found a significant association of the CB2-R63 variant with CD in children. (18) In addition, other genetic variants of components of the endocannabinoid system may be related to IBD (13).

Therefore, aggregation of the IBD family suggests genetic susceptibility. Many genes have been found to be associated with IBD, but this relationship only explains 25% of total IBD cases and only 7% of UC cases. (5, 16)

The immune system is mostly shaped by early contact with microbes and therefore depends on the environmental exposure of an individual through diet and hygiene practices. (5, 14) In this sense, the intestinal immune system is generally tolerant to high loads of microbes. Although the loss of immune tolerance has been described as an important step in the pathogenesis of IBD, the evidence is more consistent regarding the role of this loss of tolerance in the appearance of CD and UC. (6)

Decreased richness and alterations in the composition of the microbiota have been observed in patients with IBD. This generates defects in mucosal immunity and can also lead to development of illness. (6, 8, 16 , 17)

Thus, in IBD, infiltration of the intestinal mucosa by neutrophils which occurs early in the process of inflammation is responsible for disruption of the intestinal barrier, destruction of tissue and perpetuating inflammation. (14) Macrophages play an important role in the pathogenesis of CD, as they appear to produce large amounts of interleukin-6 (IL-6), interleukin-23 (IL-23), and TNF while also promoting production of interferons (IFN) by mononuclear cells.

In UC, neutrophils appear to accumulate in the blood and colonic tissue of patients. (16) Dendritic cells are responsible for mediating interference with B and T cells and for maintaining homeostasis. In IBD these cells appear to be conditioned to promote inflammation by expressing increased levels of TLR2 (Toll-like Receptor 2) and TLR4 (Toll-like Receptor 4) as well as producing more IL- 12 and IL-6. Apparently, they also express molecules that mediate their attraction and retention in the inflamed mucosa. (14, 16)

Increases in the production of interleukin-1 (IL-1), IL-6, TNF and other cytokines have been described without distinction between UC and CD. (6) So far, there is no clear evidence of dysregulation of innate immunity in UC while the opposite occurs in CD in which abnormalities in innate immunity are related to genetic variations. (6)

Although the role of antibodies in UC and CD has yet to be determined given that no antibodies have been found in either disease, they have been shown to have a pathogenic role and their presence supports altered humoral activity towards bacterial antigens. (6 , 14) Nevertheless, there is very little evidence that these conditions are antibody mediated diseases. (16)

Innate lymphoid cells play a central role in the pathogenesis of IBD, whereas cells isolated from UC patients have shown increased expression of interleukin-17A (IL-17A),

interleukin-22 (IL-22), transcription factors and various cytosine receptors. (16) Similarly, alterations in adaptive immunity have been described in UC since disproportionate increases in immunoglobulin levels have been detected during development of this disease. (6)

In addition to the role of innate and adaptive immunity in the pathogenesis of IBD, alterations in the mucosal barrier of the intestine have also been observed in patients with UC and CD. (14, 16) These alterations result in increased permeability of the mucosal barrier which allows bacteria to reach the epithelium and trigger an immune response. (14).

As inflammation occurs in the vicinity of the epithelium in UC, colonocytes become very involved in the pathogenesis of this disease. (6) Intestinal fibrosis is a common complication of IBD although it develops in different places on the intestinal in UC than it does in CD. Both lymphangiogenesis and angiogenesis occur in IBD and help perpetuate inflammation. These three processes are believed to occur in response to chronic inflammation and secretion of proliferation factors coupled with poor control mechanisms. (14)

Numerous alterations of the morphology and immunohistochemical composition of the ENS have been described in IBD. Neuropeptides such as substance P, corticotropin-releasing hormone, neurotensin, vasoactive intestinal peptide, opioid receptors, and galanin appear to be involved in the pathogenesis of IBD.

METHODS

This focused narrative literature review is based on searches of the Pubmed and Embase databases. For interventions with cannabis, the following medical subject headings (MeSH) and associated free terms were used through the Boolean operator "OR": "Marijuana", "Ganja", "Hashish", " Hemp "," Bhang "," Cannabis sativa "," Cannabinoids "," Cannabinol "," Dronabinol "," Tetrahydrocannabinol "," CBD "and" THC ".

For health conditions, the MeSH and free terms were "inflammatory bowel disease", "Crohn's disease" and "Ulcerative colitis". These terms were associated with the Boolean operator "OR". The intervention and the health condition of interest were associated with the Boolean operator "AND".

A total of 526 articles were obtained without language or date restrictions. One author (Paula Restrepo Jiménez) reviewed and selected those with the most recent or pertinent information.

RESULTS

Cannabis in IBD

Complementary and Alternative Medicine (CAM) is considered to be separate from conventional medical practice. (19) About 30 to 50% of IBD patients use CAM, and predictors of its use have been identified as side effects of conventional therapies, female gender, long progression of disease, and long-term use of steroids. (20)

Among the most common CAM treatments are herbs. Marijuana use is more common among patients with IBD than in the general population: about 15% of IBD patients use it to relieve symptoms such as nausea, abdominal pain, diarrhea, and increased appetite. (18, 20, 21)

A review of the current literature on the use of cannabis for managing experimental and human IBD by Ambrose and Simmons has described the presence of CB1 receptors in the colonic epithelium, in the plasma cells of the lamina propria, in the smooth muscle and in the submucosal myenteric plexus. (18) CB2 receptors have been identified in goblet cells of the epithelium, in Paneth cells, in macrophages, and in plasma cells of IBD patients.

Thus, changes in expression of CB1 and CB2 receptors have been observed in relation to the inflammatory process of the intestine. Endocannabinoid levels have also been found to be altered in IBD patients. An observational cross-sectional study conducted in Chile evaluated the use of CAM in 200 patients with IBD and found around 25% of those patients were then using CAM, close to 30% had previously used CAM, and 45% had never used CAM. (22)

A descriptive cross-sectional study of 99 adolescent and young adult patients in Colorado with UC, CD, or undetermined IBD found that 68% of reported not using cannabinoids, but 32% reported using cannabis on one or more occasions. Among those who had used cannabinoids, 52% reported weekly use, and 31% reported daily use. (23)

A recent study evaluated the profiles of patients who use marijuana to control IBD through a survey of 1,666 adults who self-identified as IBD patients. (24) Of those who used marijuana (114/1666), about 80.7% perceived benefits from its use. The principal symptoms that improved were pain, appetite, anxiety, fatigue, stool frequency, weight gain, bloody stool and nausea.

Another survey of 302 CD patients in Boston found that the rate of marijuana use has increased since 2012. (25) However, no significant increases in the medical use of cannabis were observed. Similarly, predictors of marijuana use were identified since a significant number of patients with previous hospitalizations and current biological therapy used marijuana.

The most common symptom for which marijuana was used was abdominal pain, and 35 out of 39 patients reported complete or moderate relief after treatment. Nausea, poor appetite, and diarrhea were also common symptoms treated by the participants and were mostly alleviated.

Phatak et al. (26) used a prospective questionnaire with 53 patients in a pediatric IBD clinic and found that 24 used marijuana for medicinal reasons. The 24 patients justified

the use of this substance was and little appetite, 21 consumed it to control nausea, and 20 used it to control diarrhea. Complete relief was reported for abdominal pain in 29%, for poor appetite in 37%, for nausea in 14%, and for diarrhea in 10% of cases.

Meanwhile, a summary of the results of several studies published by Cheifetz et al.) described the positive effects of cannabis use for IBD. Patients seemed to show reductions of disease activity although most controlled studies did not reach their primary end points. (18, 20)

A systematic review by Katchan et al. of the role of cannabinoids in autoimmune diseases has summarized many effects mediated by CB1 and CB2 receptors as well as various alterations described earlier in this article. (27) They highlighted the need for additional studies and clinical trials to clarify its action, safety and its efficacy for these patients even though there is evidence that treatment with cannabinoids can have a positive effect for IBD patients.

A systematic review and metaanalysis by Couch et al. that was updated in March 2017 found 105 experiments comparing cannabinoids with placebos or excipients. (28) Of these experiments, 63.8% favored cannabinoids, 32.3% showed no differences, and 3.8% were favorable to the excipient. Mice were used in 89 experiments of which 68.5% favored cannabinoids.

Cannabinoids were administered therapeutically in 37/104 experiments, prophylactically in 19/104 experiments, and prophylactically and therapeutically in 48/104 experiments. The results favored the cannabinoids in all of the last group.

Two other clinical trials have evaluated the effects of CBD and THC on CD.

In the first study, eleven patients were treated with 115 mg of inhaled THC and 10 patients received placebos. After 8 weeks, the group treated with THC had a non-significantly lower rate of remission than did the group that received placebos when evaluated by the Clinical Disease Activity Index (CDAI) ($p = 0.43$). (29)

However, a significant increase in the treatment group's quality of life found with the SF-36 questionnaire ($p = 0.04$). No significant differences were found between the groups' blood counts, C-reactive protein, liver and kidney function tests, or side effects.

The second study randomized patients to either receive 10 mg of CBD or placebos orally twice daily. There were 10 patients in the study group and 9 in the placebo group. A non-significant difference in CDAI was observed between groups after 8 weeks of treatment. Similarly, no significant differences were found between the groups in blood tests or in side effects. (30)

The metaanalysis of these studies showed that the two phytocannabinoids, CBD and THC, decreased severity scores below those of patients given placebos. Similarly, metaanalysis of 34 rat and mouse model studies found that cannabinoid drugs reduced CDAI with the excipient. However, a significant difference was observed among subtypes of the groups. (28)

Lahat et al. (31) analyzed the impact of cannabinoids on quality of life, weight, and disease activity in patients with IBD through a prospective pilot study that included 13 patients. After 3 months of inhaled cannabinoid treatment, patients showed a significant reduction in pain intensity and depression as well as in the Harvey-Bradshaw index. Similarly, these patients' perceptions of their own health, social functioning and ability to work improved.

A case-control pilot study that compared botanical extracts rich in cannabidiol to placebos for symptomatic treatment of UC randomized 60 patients into a treatment group of 29 patients and a control group of 31 patients. (32) It found that remission rates observed in the treatment group were higher than those of the placebo group (Odds ratio [OR] = 1.30; 90% confidence interval [CI]: 0.42 to 4.04). However, the difference was not statistically significant.

Similarly, the treatment group's disease severity lessened and quality of life scores improved, but differences were not significant. Adverse events were reported in 90% of the treatment group, compared to 48% of the placebo group. As expected, the most common adverse events, dizziness and drowsiness, were related to the nervous system.

In contrast, adverse events associated with possible disease progression were reported in 42% of the placebo group compared to only 10% of the treatment group.

The safety profile of cannabis has not been well established as few controlled studies have been conducted. Swaminath et al. reported results of a retrospective study in which the use of cannabis was associated with increased risk of surgery, but causality cannot be attributed given the nature of the study design. (21, 33)

In addition to the administration of cannabinoids, another potential therapeutic strategy may be to inhibit catabolism of endocannabinoids by blocking degradation enzymes. Anandamide degrades to arachidonic acid and fatty acid amide hydrolase while 2-acylglycerol,another cannabinoid, degrades to monoacylglycerol lipase. Pesce et al. suggest that inhibition of the enzymes responsible for these processes could increase the levels of endocannabinoids which act as indirect agonists and could reduce pain and inflammation. (34)

Experimental Models

Various studies have evaluated the effect of cannabis on experimental models of colitis. Borrelli et al. (35) investigated the effects of CBD on colitis induced by colonic admi-

nistration of 2,4,6-trinitrobenzenesulfonic acid in mice. Administration of CBD in doses containing 1 to 10 mg/kg significantly reduced the macroscopic damage associated with colitis. The maximum protective effect was achieved with the 5 mg/kg dose.

In addition to macroscopic findings, microscopic evaluation of mice treated with 5 mg/kg CBD found glandular regeneration and edema of the lower mucosa and submucosa. Thus, administration of 5 mg/kg to mice attenuated the expression of inducible Nitric-Oxide Synthase (iNOS) and the production of nitrites. An imbalance in the production of proinflammatory and anti-inflammatory interleukins has been shown to be a major event in intestinal inflammation. The authors described a CBD-counteracting effect on altered interleukin production. All the characteristics described above reaffirm the anti-inflammatory effects of CBD.

THC, the main component of marijuana, has been shown to produce various biological effects in humans and animals. In the gastrointestinal tract, stimulation of CB1 cannabinoid receptors appears to mediate inhibition of excitatory transmission in animals which reduces peristalsis. Several studies have evaluated the effect of CBD on hypermotility of inflamed intestines caused by administration of croton oil to mice.

Thus, Izzo et al. wrote that both natural and synthetic cannabinoid receptor agonists (cannabinol) reduced upper gastrointestinal motility in control mice and those treated with croton oil, with more noticeable effects when intestinal inflammation was present. (36)

It is important to mention effects were mediated by CB1 receptors became notorious, since the use of CB1 antagonists counteracted the effect, but this was not observed when CB2 antagonists were used.

Capasso et al. described similar results with the non-psychotropic component of marijuana, CBD. As in the study by Izzo et al., they found no changes in gastrointestinal motility in control mice. (15, 36)

For their part, Pagano et al. reported that oral or CBD provided orally or peritoneal administration reduced intestinal inflammation and damage in an experimental model of colitis. (37) Furthermore, it improved intestinal hypermotility in animals treated with croton oil. This suggests that these may components act on the basis of overreaction of receptors only under conditions of inflammation.

Some authors suggest that the effects observed may be mediated by stimulation of immune cells CB2 receptors. In an experimental model of colitis described by Leinwald et al., CB2 receptor upregulation occurred in response to inflammation and stimulation of these receptors induced pro-regulatory and anti-inflammatory effects. (38)

Similarly, Singh et al. (39) reported that the use of a selective CB2 agonist reduced experimental colitis and induced apoptosis of inactive T cells. This inhibited T cell production of inflammatory cytokines and inhibited migration and filtration of inflammatory cells in the colon.

However, Storr et al. (40) showed that drugs that target both CB1 and CB2 receptors could be more effective for protecting against colitis than selective drugs. Mice knocked out by CB1 receptors appeared to show an exacerbation of colitis, while those knocked out by CB2 did not. Nevertheless, targeting CB2 receptors has been shown to be effective for limiting colitis. (41)

Jamontt et al. evaluated the effects of CBD and THC alone or in combination in an experimental mouse model of colitis. (42) Treatment with these two components in doses of 10 mg/kg led to reductions in damage, neutrophil infiltration, and motility disturbances similar to those obtained with sulfasalazine, a standard treatment for IBD. In any case, the authors suggest that reduction of myeloperoxidase (MPO) activity could be an indirect effect of THC since it reduces the levels of cytokines involved in the recruitment of neutrophils.

Meanwhile, Schicho et al. evaluated the effect of an atypical cannabinoid (O-1602) in two experimental models of colitis. (43) This cannabinoid may act through the GPR55 receptor and inhibit neutrophil migration. The authors described that these atypical cannabinoids protected against experimental colitis by inhibiting recruitment of neutrophils, independent of CB1, CB2 and GPR55 which suggests the existence of other receptors that regulate this effect.

Cannabigerol (CBG), another non-psychotropic cannabinoid, has been shown to reduce generation of inflammatory cytokines, reduce production of reactive oxygen species, reduce the number of macrophages and reduce the number of mast cells in experimental models of IBD. (44)

Harvey et al. have studied the effect of anandamide and CBD on human colonic explant tissue treated with IL-17A, an interleukin known to be expressed in large numbers in UC, as well as being present in colonic mucosal tissue and serum from CD patients. (45)

Treatment with CBD significantly reduced both luminal and crypt epithelial damage, whereas anandamide treatment did not reduce crypt damage but reduced luminal epithelial damage. Thus, the protective effect of anandamide is thought to be caused by stimulation of CB2 receptors which reduces the production of IL-17A by T lymphocytes.

Consequently, the effect of CBD is not completely clear. It appears to activate PPAR-y receptors which mediates the anti-inflammatory response more than it activates CB1 or CB2. Couch et al. found that CBD represses phosphorylation of various intracellular proteins and represses production of proinflammatory cytokines in explant colonic tissue simulated with IFN and TNF. (47)

The authors also showed that CBD has anti-inflammatory effects on explant tissue of IBD patients and attributed this characteristic to the presence of immune cells in the tissue. Enteric cells are known to mediate acute and chronic inflammation through production of pro-inflammatory cytokines which amplify immune responses.

De Filippis et al. evaluated the effect of CBD on the brain-gut axis. Their findings suggest that CBD treatment results in protection from intestinal damage secondary to modulation of the glial-immune axis in cultured biopsies of UC patients. (46)

In addition to THC and CBD, other phytocannabinoids such as CBG, cannabinol (CBN), tetrahydrocannabivarin (THCV) and tetrahydrocannabinolic acid (THCA) have been shown to have beneficial effects although further studies are needed to establish their actions and dosages. (47)

CONCLUSIONS

Various preparations of cannabis sativa have been used for a number of years for treatment of different medical conditions. The two main components of cannabis, CBD and THC, have been extensively studied and proven to exert anti-inflammatory and antinociceptive effects, suggesting a possible role in symptomatic control of IBD.

Although symptom relief and quality of life improvements have been obtained in clinical studies, more high-quality research is required to assess the immediate and long-term efficacy and safety of cannabis use for treatment of UC and CD.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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REFERENCES

1. Di Marzo V. Targeting the endocannabinoid system: to enhance or reduce? Nat Rev Drug Discov. 2008;7(5):438-55. https://doi.org/10.1038/nrd2553
2. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta 9-tetrahydrocannabinol, cannabidiol and delta 9-tetrahydrocannabivarin. Br J Pharmacol 2008;153:199-215. https://doi.org/10.1038/sj.bjp.0707442
3. Mechoulam R, Peters M, Murillo-Rodriguez E, Hanus LO. Cannabidiol—recent advances. Chem Biodivers. 2007;4(8):1678-92. https://doi.org/10.1002/cbdv.200790147
4. Sairenji T, Collins KL, Evans DV. An Update on Inflammatory Bowel Disease. Prim Care. 2017;44(4):673-692. https://doi.org/10.1016/j.pop.2017.07.010
5. Ramos GP, Papadakis KA. Mechanisms of Disease: Inflammatory Bowel Diseases. Mayo Clin Proc. 2019;94(1):155-165. https://doi.org/10.1016/j.mayocp.2018.09.013
6. Danese S, Fiocchi C. Ulcerative colitis. N Engl J Med. 2011;365(18):1713-25. https://doi.org/10.1056/NEJMra1102942
7. Weisshof R, El Jurdi K, Zmeter N, Rubin DT. Emerging Therapies for Inflammatory Bowel Disease. Adv Ther. 2018;35(11):1746-1762. https://doi.org/10.1007/s12325-018-0795-9
8. Hindryckx P, Jairath V, D'Haens G. Acute severe ulcerative colitis: from pathophysiology to clinical management. Nat Rev Gastroenterol Hepatol. 2016;13(11):654-664. https://doi.org/10.1038/nrgastro.2016.116
9. Lu HC, Mackie K. An Introduction to the Endogenous Cannabinoid System. Biol Psychiatry. 2016;79(7):516-25. https://doi.org/10.1016/j.biopsych.2015.07.028
10. Battista N, Di Tommaso M, Bari M, Maccarrone M. The endocannabinoid system: an overview. Front Behav Neurosci. 2012;6:9. https://doi.org/10.3389/fnbeh.2012.00009
11. Katz D, Katz I, Porat-Katz BS, Shoenfeld Y. Medical cannabis: Another piece in the mosaic of autoimmunity? Clin Pharmacol Ther. 2017;101(2):230-238. https://doi.org/10.1002/cpt.568
12. Acharya N, Penukonda S, Shcheglova T, Hagymasi AT, Basu S, Srivastava PK. Endocannabinoid system acts as a regulator of immune homeostasis in the gut. Proc Natl Acad Sci U S A. 2017;114(19):5005-5010. https://doi.org/10.1073/pnas.1612177114
13. Hasenoehrl C, Taschler U, Storr M, Schicho R. The gastrointestinal tract – a central organ of cannabinoid signaling in health and disease. Neurogastroenterol Motil. 2016;28(12):1765-1780. https://doi.org/10.1111/nmo.12931
14. de Souza HS, Fiocchi C. Immunopathogenesis of IBD: current state of the art. Nat Rev Gastroenterol Hepatol. 2016;13(1):13-27. https://doi.org/10.1038/nrgastro.2015.186
15. Capasso R, Borrelli F, Aviello G, Romano B, Scalisi C, Capasso F, et al. Cannabidiol, extracted from Cannabis sativa, selectively inhibits inflammatory hypermotility in mice. Br J Pharmacol. 2008;154(5):1001–1008. https://doi.org/10.1038/bjp.2008.177
16. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. Lancet. 2017;389(10080):1756-1770. https://doi.org/10.1016/S0140-6736(16)32126-2
17. Gajendran M, Loganathan P, Catinella AP, Hashash JG. A comprehensive review and update on Crohn's disease. Dis Mon. 2018;64(2):20-57. https://doi.org/10.1016/j.disamonth.2017.07.001
18. Ambrose T, Simmons A. Cannabis, Cannabinoids, and the Endocannabinoid System-Is there Therapeutic Potential for Inflammatory Bowel Disease? J Crohns Colitis. 2019;13(4):525-535. https://doi.org/10.1093/ecco-jcc/jjy185

19. Quezada SM, Briscoe J, Cross RK. Complementary and Alternative Medicine. Inflamm Bowel Dis. 2016;22(6):1523-30. https://doi.org/10.1097/MIB.0000000000000761
20. Cheifetz AS, Gianotti R, Luber R, Gibson PR. Complementary and Alternative Medicines Used by Patients With Inflammatory Bowel Diseases. Gastroenterology. 2017;152(2):415-429.e15. https://doi.org/10.1053/j.gastro.2016.10.004
21. Swaminath A, Berlin EP, Cheifetz A, Hoffenberg E, Kinnucan J, Wingate L, et al. The Role of Cannabis in the Management of Inflammatory Bowel Disease: A Review of Clinical, Scientific, and Regulatory Information. Inflamm Bowel Dis. 2019;25(3):427-435. https://doi.org/10.1093/ibd/izy319
22. Fernández A, Simian D, Quera R, Flores L, Ibáñez P, Lubascher J, et al. Complementary and alternative medicine in patients with inflammatory bowel disease: A survey performed in a tertiary center in Chile. Complement Ther Med. 2018;40:77-82. https://doi.org/10.1016/j.ctim.2018.07.016
23. Hoffenberg EJ, McWilliams SK, Mikulich-Gilbertson SK, Murphy BV, Lagueux M, Robbins K, et al. Marijuana Use by Adolescents and Young Adults with Inflammatory Bowel Disease. J Pediatr. 2018;199:99-105. https://doi.org/10.1016/j.jpeds.2018.03.041
24. Kerlin AM, Long M, Kappelman M, Martin C, Sandler RS. Profiles of Patients Who Use Marijuana for Inflammatory Bowel Disease. Dig Dis Sci. 2018;63(6):1600-1604. https://doi.org/10.1007/s10620-018-5040-5
25. Merker AM, Riaz M, Friedman S, Allegretti JR, Korzenik J. Legalization of Medicinal Marijuana Has Minimal Impact on Use Patterns in Patients With Inflammatory Bowel Disease. Inflamm Bowel Dis. 2018;24(11):2309-2314. https://doi.org/10.1093/ibd/izy141
26. Phatak UP, Rojas-Velasquez D, Porto A, Pashankar DS. Prevalence and Patterns of Marijuana Use in Young Adults With Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr. 2017;64(2):261-264. https://doi.org/10.1097/MPG.0000000000001474
27. Katchan V, David P, Shoenfeld Y. Cannabinoids and autoimmune diseases: A systematic review. Autoimmun Rev. 2016;15(6):513-28. https://doi.org/10.1016/j.autrev.2016.02.008
28. Couch DG, Maudslay H, Doleman B, Lund JN, O'Sullivan SE. The Use of Cannabinoids in Colitis: A Systematic Review and Meta-Analysis. Inflamm Bowel Dis. 2018;24(4):680-697. https://doi.org/10.1093/ibd/izy014
29. Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. Clin Gastroenterol Hepatol. 2013;11(10):1276-1280.e1. https://doi.org/10.1016/j.cgh.2013.04.034
30. Naftali T, Mechulam R, Marii A, Gabay G, Stein A, Bronshtain M, et al. Low-Dose Cannabidiol Is Safe but Not Effective in the Treatment for Crohn's Disease, a Randomized Controlled Trial. Dig Dis Sci. 2017;62(6):1615-1620. https://doi.org/10.1007/s10620-017-4540-z
31. Lahat A, Lang A, Ben-Horin S. Impact of cannabis treatment on the quality of life, weight and clinical disease activity in inflammatory bowel disease patients: a pilot prospective study. Digestion. 2012;85(1):1-8. https://doi.org/10.1159/000332079
32. Irving PM, Iqbal T, Nwokolo C, Subramanian S, Bloom S, Prasad N, et al. A Randomized, Double-blind, Placebo-controlled, Parallel-group, Pilot Study of Cannabidiol-rich Botanical Extract in the Symptomatic Treatment of Ulcerative Colitis. Inflamm Bowel Dis. 2018;24(4):714-724. https://doi.org/10.1093/ibd/izy002
33. Storr M, Devlin S, Kaplan GG, Panaccione R, Andrews CN. Cannabis use provides symptom relief in patients with inflammatory bowel disease but is associated with worse disease prognosis in patients with Crohn's disease. Inflamm Bowel Dis. 2014;20(3):472-80. https://doi.org/10.1097/01.MIB.0000440982.79036.d6
34. Pesce M, Esposito G, Sarnelli G. Endocannabinoids in the treatment of gasytrointestinal inflammation and symptoms. Curr Opin Pharmacol. 2018;43:81-86. https://doi.org/10.1016/j.coph.2018.08.009
35. Borrelli F, Aviello G, Romano B, Orlando P, Capasso R, Maiello F, et al. Cannabidiol, a safe and non-psychotropic ingredient of the marijuana plant Cannabis sativa, is protective in a murine model of colitis. J Mol Med (Berl). 2009;87(11):1111-21. https://doi.org/10.1007/s00109-009-0512-x
36. Izzo AA, Fezza F, Capasso R, Bisogno T, Pinto L, Luvone T, et al. Cannabinoid CB1-receptor mediated regulation of gastrointestinal motility in mice in a model of intestinal inflammation. Br J Pharmacol. 2001;134(3):563–570. https://doi.org/10.1038/sj.bjp.0704293
37. Pagano E, Capasso R, Piscitelli F, Romano B, Parisi O, Finizio S, et al. An Orally Active Cannabis Extract with High Content in Cannabidiol attenuates Chemically-induced Intestinal Inflammation and Hypermotility in the Mouse. Front Pharmacol. 2016;7:341. https://doi.org/10.3389/fphar.2016.00341
38. Leinwand KL, Jones AA, Huang RH, Jedlicka P, Kao DJ, de Zoeten EF, et al. Cannabinoid Receptor-2 Ameliorates Inflammation in Murine Model of Crohn's Disease. J Crohns Colitis. 2017 27;11(11):1369-1380. https://doi.org/10.1093/ecco-jcc/jjx096
39. Singh UP, Singh NP, Singh B, Price RL, Nagarkatti M, Nagarkatti PS. Cannabinoid receptor-2 (CB2) agonist ameliorates colitis in IL-10(-/-) mice by attenuating the activation of T cells and promoting their apoptosis. Toxicol Appl Pharmacol. 2012;258(2):256-67. https://doi.org/10.1016/j.taap.2011.11.005
40. Storr MA, Keenan CM, Emmerdinger D, Zhang H, Yüce B, Sibaev A, et al. Targeting endocannabinoid degradation protects against experimental colitis in mice: involvement of CB1 and CB2 receptors. J Mol Med (Berl). 2008;86(8):925-36. https://doi.org/10.1007/s00109-008-0359-6

41. Storr MA, Keenan CM, Zhang H, Patel KD, Makriyannis A, Sharkey KA. Activation of the cannabinoid 2 receptor (CB2) protects against experimental colitis. Inflamm Bowel Dis. 2009;15(11):1678-85. https://doi.org/10.1002/ibd.20960
42. Jamontt JM, Molleman A, Pertwee RG, Parsons ME. The effects of Δ 9 tetrahydrocannabinol and cannabidiol alone and in combination on damage, inflammation and in vitro motility disturbances in rat colitis. Br J Pharmacol. 2010;160(3):712-723. https://doi.org/10.1111/j.1476-5381.2010.00791.x
43. Schicho R, Bashashati M, Bawa M, McHugh D, Saur D, Hu HM, et al. The atypical cannabinoid O-1602 protects against experimental colitis and inhibits neutrophil recruitment. Inflamm Bowel Dis. 2011;17(8):1651–1664. https://doi.org/10.1002/ibd.21538
44. Uranga JA, Vera G, Abalo R. Cannabinoid pharmacology and therapy in gut disorders. Biochem Pharmacol. 2018;157:134-147. https://doi.org/10.1016/j.bcp.2018.07.048
45. Harvey BS, Sia TC, Wattchow DA, Smid SD. Interleukin 17A evoked mucosal damage is attenuated by cannabidiol and anandamide in a human colonic explant model. Cytokine. 2014;65(2):236-44. https://doi.org/10.1016/j.cyto.2013.10.006
46. De Filippis D, Esposito G, Cirillo C, Cipriano M, De Winter BY, Scuderi C, et al. Cannabidiol reduces intestinal inflammation through the control of neuroimmune axis. PLoS One. 2011;6(12):e28159. https://doi.org/10.1371/journal.pone.0028159
47. Nallathambi R, Mazuz M, Ion A, Selvaraj G, Weininger S, Fridlender M, et al. Anti-Inflammatory Activity in Colon Models Is Derived from Δ9-Tetrahydrocannabinolic Acid That Interacts with Additional Compounds in Cannabis Extracts. Cannabis Cannabinoid Res. 2017;2(1):167–182. https://doi.org/10.1089/can.2017.0027