

# Cannabis and Cannabis Derivatives for Abdominal Pain Management in Inflammatory Bowel Disease

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## Keywords

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## Abstract

For centuries, cannabis and its components have been used to manage a wide variety of symptoms associated with many illnesses. Gastrointestinal (GI) diseases are no exception in this regard. Individuals suffering from inflammatory bowel disease (IBD) are among those who have sought out the ameliorating properties of this plant. As legal limitations of its use have eased, interest has grown from both patients and their providers regarding the potential of cannabis to be used in the clinical setting. Similarly, a growing number of animal and human studies have been undertaken to evaluate the impact of cannabis and cannabinoid signaling elements on the natural history of IBD and its associated complications. There is little clinical evidence supporting the ability of cannabis or related products to treat the GI inflammation underlying these disorders. However, 1 recurring theme from both animal and human studies is that these agents have a significant impact on several IBD-related

symptoms, including abdominal pain. In this review, we discuss the role of cannabis and cannabinoid signaling in visceral pain perception, what is currently known regarding the efficacy of cannabis and its derivatives for managing pain, related symptoms and inflammation in IBD, and what work remains to effectively utilize cannabis and its derivatives in the clinical setting.

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## Introduction

Cannabis, also known as marijuana, refers to the plant belonging to the family Cannabaceae, the genus *Cannabis*, and the species *Cannabis sativa* (hereafter referred to as Cannabis) [1]. Cannabis use for medicinal purposes has been described for thousands of years [1]. Over the centuries, numerous potential health-related applications of *Cannabis* have been identified. Due to legal restrictions and cultural and societal stigma associated with its use, *Cannabis* has been notoriously difficult to study in the USA, particularly for biomedical purposes. However, over the past few decades, *Cannabis* has enjoyed increasing mainstream cultural acceptance as well as legal-

ization in several countries around the world [2]. In the USA, as of February 2021, thirty-four states and the District of Columbia currently have passed laws broadly legalizing or decriminalizing *Cannabis* in some form [3, 4]. Several states have approved the use of so-called medical marijuana for a variety of conditions, including as an alternative or adjuvant therapy for the inflammatory bowel diseases (IBD), Crohn's disease (CD), and ulcerative colitis (UC) [3, 5]. Recent studies suggest that 10–12% of IBD patients utilize *Cannabis* at least intermittently to address their symptoms [6–10]. Due to increasing acceptance and availability of *Cannabis*, patients have expressed growing interest in the therapeutic potential of this agent and its derivatives. As a result, health-care providers are increasingly relied upon to provide advice about *Cannabis* and its promise as a treatment for IBD [11].

Developing a clear scientific understanding of the impact of *Cannabis* in the setting of IBD has been challenging, however. Multiple studies utilizing animal models of enterocolitis provide evidence that the endocannabinoid system (ECS) can have a powerful influence on gastrointestinal (GI) inflammation and proxy measures of motility and visceral sensitivity [12]. On the other hand, studies that have looked at *Cannabis* or cannabinoid derivatives (including inhaled and oral tetrahydrocannabinol (THC), *Cannabis* derivatives including synthetic THC (dronabinol) or endocannabinoid ligands (palmitoylethanolamide), and phytocannabinoids (cannabidiol [CBD] oil)) in the setting of human IBD have shown no objective evidence for modulation of disease-related inflammation [13–16].

However, multiple human studies have demonstrated that *Cannabis* has a positive impact on a variety of symptoms, including abdominal pain [13, 17]. Unsurprisingly, IBD patients who use *Cannabis* or related products frequently report taking it specifically for abdominal pain management, including approximately 90% of a cohort in 1 study [9]. Thus, while it is not clear that *Cannabis* helps IBD-associated inflammation, mounting evidence suggests that *Cannabis* may be an effective analgesic option for IBD-associated abdominal pain and many patients are already using for this purpose. Accordingly, it is critical for IBD providers to have a clear understanding of what the scientific literature can and cannot tell us about cannabinoid use in this setting.

The purpose of this review is to highlight recent developments relating to the use of *Cannabis* and its derivatives for the management of IBD and the abdominal pain associated with these conditions. We will present an overview of the ECS, focusing primarily on its role in the GI

tract and visceral nociceptive pathways. We will also review what is currently known about cannabinoid signaling in the context of IBD, IBD-associated pain, and conditions associated with altered abdominal pain perception. Finally, we will discuss the current gaps in knowledge on this subject as well as potential future research directions.

## Methods

We conducted a series of MEDLINE searches spanning 2001–2021 analyzing *Cannabis* (or any *Cannabis* derivative or synthetic cannabinoid) consumption among patients with IBD. Each study was classified by the study design, which included randomized controlled trials, retrospective and prospective clinical studies, and tolerance studies assembled using a combination of medical subject heading and free-text search terms. We also classified studies based on the dosage of *Cannabis* or cannabinoid derivative (or lack thereof) and the method of consumption (inhaled, oral, and oromucosal). The primary outcome variable was the modulation of IBD-related abdominal pain, with secondary outcome variables of IBD disease activity, quality of life, and influence of other IBD-related symptoms.

Medline searches included the following terms: *Cannabis* + IBD/Inflammatory bowel disease; *Cannabis* + IBD/Inflammatory bowel disease + RCT/Randomized controlled trial; *Cannabis* + IBD/Inflammatory bowel disease + abdominal pain; *Cannabis* + abdominal pain; THC/Tetrahydrocannabinol + IBD/Inflammatory Bowel Disease; CBD/Cannabidiol + IBD/Inflammatory Bowel Disease; marijuana + IBD/Inflammatory Bowel Disease; marijuana + IBD/Inflammatory bowel disease + RCT/Randomized controlled trial; marijuana + IBD/Inflammatory bowel disease + abdominal pain; PEA/palmitoylethanolamide + IBD/Inflammatory Bowel Disease; Anandamide + IBD/Inflammatory Bowel Disease; Anandamide + IBD/Inflammatory bowel disease + pain; 2-AG/2-Arachidonoylglycerol + IBD/Inflammatory Bowel Disease.

## Overview of ECS

The ECS encompasses structures and physiological processes within the body that mediate the effects of cannabinoids. The ECS includes cellular receptors, endogenous ligands of those receptors, termed endocannabinoids, and the enzyme regulators of endocannabinoid production and metabolism [18, 19]. There are at least 2 G-protein-coupled receptors, known as cannabinoid type-1 and type-2 receptors (CB<sub>1</sub>R and CB<sub>2</sub>R), linked to G<sub>i</sub> proteins that inhibit adenylate cyclase conversion of ATP to cyclic AMP and also inhibit neuronal firing [20]. There are additional cellular mediators involved in ECS modulation that we will not discuss in significant detail here. For example, in addition to CB<sub>1</sub>R and CB<sub>2</sub>R signaling in the gut, there are other receptors that respond to the endocannabinoids such as the G-protein-coupled receptor 55 (GPR55), the transient receptor potential cation channel subfamily V (vanilloid) member 1 (TRPV1), and peroxisome proliferator-activated receptors alpha and gamma (PPAR $\alpha$  and PPAR $\gamma$ ) [19]. Additional information regarding the general properties of those intracellular mediators of the ECS can be found in the reviews referenced here [19, 21, 22].

CB<sub>1</sub>Rs are distributed throughout the central nervous system and throughout peripheral tissues including the GI tract, liver, skeletal muscle, cardiovascular tissue, reproductive tissue, and adipose tissue [23]. CB<sub>2</sub>Rs are found on immune cells, as well as within the central nervous system, including microglia, and the GI tract [20]. The primary endocannabinoids are 2-arachidonoylglycerol (2-AG) [24], which binds CB<sub>1</sub>R and CB<sub>2</sub>R equally, and anandamide (arachidonylethanolamine [AEA]) [25], which binds CB<sub>1</sub>R with greater affinity than CB<sub>2</sub>R. The plant-derived phytocannabinoids delta-9-THC is a partial, nonselective agonist of CB<sub>1</sub>R and CB<sub>2</sub>R. Some synthetic cannabinoids are nonselective, full agonists of CB<sub>1</sub>R and CB<sub>2</sub>R (HU-210 [26], CP 55,940 [27], SAB378 [peripherally restricted] [26, 28]), while others are full agonists for both CB<sub>1</sub>R and CB<sub>2</sub>R with an increased selectivity for either CB<sub>1</sub>R (2-arachidonoyl glyceryl ether [noladine ether] [29]) or CB<sub>2</sub>R (WIN55,212-2) [27]. There are CB<sub>1</sub>R-selective agonists (arachidonyl-2'-chloroethylamide, ACEA [30]) and CB<sub>1</sub>R antagonists, which may be further classified as first-generation (SR141716A [Rimonabant] [31, 32] and AM251) for their generalized systemic effects or second-generation (TM38837, AM6545, and JD5037 [22]) for peripherally limited effects. Similarly, there are CB<sub>2</sub>R-selective agonists (JWH-133 [26, 33], JWH-015, AM1241, HU-308 [26], and GP1a [34]) and CB<sub>2</sub>R-specific antagonists (SR144528 [35] and AM630) [27]. Functional relationships between CB<sub>1</sub>Rs and CB<sub>2</sub>Rs are dependent on their location and local function, as they may work in unison, compete with, or oppose each other's actions [36].

Importantly, the ECS also includes the modulators of the endocannabinoids anandamide (AEA) and 2-AG [24, 25]. Both AEA and 2-AG are synthesized from unique membrane-bound arachidonic acid precursors and hydrolyzed by fatty acid amide hydrolase (FAAH) and monoglyceride lipase (MGL), respectively. Inhibition of FAAH (by specific inhibitors including PF-04457845 [37], URB597 [38], and PF-3845 [39]) or MGL (by antagonists JZL184 [40], KML29 [41], JW651 [42], JJKK-048 [43], and MJN110 [44]) increase levels of AEA and 2-AG, respectively. Additionally, there are nonselective inhibitors, such as JZL195 [40] that antagonize both FAAH and MGL, leading to an overall increase in ECS activity. This demonstrates that there are myriad pharmacological tools available to study the role of the ECS in IBD.

#### *Cannabinoid Signaling within the GI Tract*

The ECS plays a crucial role in every major aspect of GI function and physiology, including motility, mucosal secretion, visceral pain perception, and epithelial barrier function [19, 45]. A careful evaluation reveals how prevalent ECS components are within the gut. Immunohistochemistry of human colonic tissues identified CB<sub>1</sub>R within normal colonic epithelium, smooth muscle, and submucosal-myenteric plexus, with co-expression of CB<sub>2</sub>R on plasma cells and lamina propria [46]. CB<sub>1</sub>R is expressed throughout enteric nervous system cholinergic neurons, ascending and longitudinal muscle interneurons, and intrinsic primary afferent neurons [20, 45]. CB<sub>1</sub>R is also expressed within intestinal mucosa enteroendocrine cells and enterocytes [45, 47]. CB<sub>2</sub>R is also expressed on enterocytes as well as on neurons in the enteric nervous system [48, 49].

Functionally, both CB<sub>1</sub>R and CB<sub>2</sub>R are involved in the physiological control of the GI tract. Activation of CB<sub>1</sub>R generally leads to reduction of intestinal motility, inhibition of gastric acid secretion, and decreases the tone of the lower esophageal sphincter [20,

48]. CB<sub>1</sub>R has also been implicated in epithelial barrier control and interactions with the gut microbiome [22]. One proposed mechanism for the ECS-mediated increase in gut permeability is through the modulation of circulating levels of microbial lipopolysaccharide (LPS), a gram-negative bacteria endotoxin [50]. Support for this hypothesis is provided by examination of CB<sub>1</sub>R and CB<sub>2</sub>R in rodent models assessing gut barrier permeability [50]. Specifically, in the presence of a CB<sub>1</sub>R antagonist (SR141716A), LPS levels have been shown to be reduced in the context of improved gut barrier function and decreased gut permeability. Conversely, application of the CB<sub>1</sub>R agonist (HU-210) has been associated with increased levels of circulating plasma LPS [50]. Additionally, the administration of a CB<sub>2</sub>R agonist (JWH-133) reduces LPS-mediated GI effects (e.g., motility), suggesting that it works in opposition to CB<sub>1</sub>R, particularly during inflammatory states [51]. CB<sub>2</sub>R is also frequently expressed on immune cells, and their stimulation appears to facilitate suppression of immune system activity and inflammation [45]. Finally, there is evidence that activation of CB<sub>2</sub>R can reduce visceral sensitivity and pain [48, 52, 53]. Additionally, endocannabinoids AEA and 2-AG and the inhibition of their degradative enzymes FAAH and MGL, respectively, also enhance gut permeability and inhibit intestinal motility [54–60].

#### *Cannabinoid Signaling in Visceral Pain*

##### *Direct Impacts on Visceral Pain Perception*

Together, animal and human studies support the role of the ECS in the direct modulation of visceral pain pathways. As previously described, CB<sub>1</sub>R and CB<sub>2</sub>R are expressed on peripheral and central structures which influence sensory function, including extrinsic primary afferent neurons innervating the gut [61], neurons within the spinal cord [62], and regions of the brain directly associated with pain perception. This includes the periaqueductal gray and the rostral ventromedial medulla, which appear to provide key descending inhibitory input to nociceptive neurons within the spinal cord [62–65]. Of note, CB<sub>1</sub>R agonists in either the periaqueductal gray or the rostral ventromedial medulla induce analgesic effects [62]. In rodent models of visceral pain, CB<sub>1</sub>R and CB<sub>2</sub>R agonists usually induce analgesic effects [52, 53, 66]. Increasing availability of these endocannabinoid agonists, through genetic knockout or pharmacologic inhibition of FAAH and/or MAGL, also diminishes visceral pain perception in rodent models [67, 68], while antagonists and/or genetic knockouts of CB<sub>1</sub>R/CB<sub>2</sub>R tend to induce hyperalgesic states [66, 69]. For example, in human studies, synthetic THC (Dronabinol) generally induced analgesic effects and increased pain tolerance [70, 71]. However, the analgesic effects were dependent on the clinical scenario (i.e., not effective in irritable bowel syndrome [72, 73], pancreatitis [74, 75], or postoperative pain [75, 76]).

##### *Indirect Impacts on Visceral Pain Perception*

There are also numerous other pathways through which endocannabinoids have the potential to influence visceral pain sensation. The most obvious example of this in the setting of IBD relates to the impact that these agents have on gut inflammation (which we will discuss in following section). In a related manner, cannabinoid signaling elements have been shown to affect the GI microbiome (a significant potential determinant of IBD-associated inflammatory activity and abdominal pain) [12]. Interestingly, a rodent model treated with probiotic strains of *Lactobacillus* had a reduction in visceral sensitivity and an upregulation of CB<sub>2</sub>R and

$\mu$ -opioid receptors in intestinal epithelium [77]. These reductions in visceral sensation were likely mediated by the CB<sub>2</sub>R, given the analgesic effects were reversed in the setting of CB<sub>2</sub>R antagonists [77].

#### Influence of the ECS in IBD

In addition to the analgesic effects described above, there are several mechanisms through which CB<sub>1</sub>R and CB<sub>2</sub>R may serve a protective role and provide novel targets for pharmacologic modulation in IBD [54]. One report found elevated concentrations of CB<sub>1</sub>R but no significant difference in CB<sub>2</sub>R in inflamed mucosa compared to uninflamed mucosa in IBD patients [78]. However, there is no consensus regarding the relative changes in expression of CB<sub>1</sub>R and CB<sub>2</sub>R in the setting of IBD [7, 55]. The pathophysiology of IBD involves increased gut permeability, particularly in the setting of active disease inflammation [79]. As previously discussed, there is emerging evidence suggesting that gut epithelial permeability is under regulatory control by the ECS and microbiota, and thus a potential target for pharmaceutical therapy [55].

#### ECS Impact on Animal Models of IBD

In rodent models of IBD, CB<sub>1</sub>R and CB<sub>2</sub>R agonists reduced the gut mucosa inflammation and improved IBD-related symptoms [30, 80]. Similarly, increasing availability of the endogenous CB<sub>1</sub>R and CB<sub>2</sub>R agonist, through genetic knockout or pharmacologic-mediated inhibition of the metabolism of AEA, reduced gut mucosa inflammation in rodent models of IBD [81, 82]. Conversely, pretreatment with CB<sub>1</sub>R and CB<sub>2</sub>R antagonists and/or genetic knockouts of these receptors prevent their protective effects on disease inflammation and even induce colitis in rodent IBD models [80, 81]. However, although the data from IBD rodent models have been promising, this has not translated to modulation of disease-related inflammation in human clinical trials studies [13–16].

#### ECS Impact on Patients with IBD

The use of *Cannabis* or *Cannabis* derivatives is common among patients with IBD for symptomatic relief, often specifically for abdominal pain relief [6, 9, 83, 84]. The initial small cohort studies for *Cannabis* use (variable forms of consumption) in IBD were promising as its use was associated with symptom relief, improved health-related quality of life, and reduction of alternative analgesic medications in patients with IBD [8, 15]. However, although the subsequent larger studies also found that *Cannabis* use (variable forms of consumption) was associated with symptom improvement [9, 13], 1 report found an increased risk of surgery in those patients [13]. The clinical trials conducted thus far have not demonstrated any objective changes in disease markers of inflammation. Thus far, there have only been 3 relatively small placebo-controlled studies with *Cannabis* use in active CD. Notably, 2 of these reports demonstrated an improvement in IBD-related symptoms [13, 16]. A report on the effects of long-term *Cannabis* use (variable forms of consumption) in IBD found patients had an improvement in IBD-related symptoms, decreased use of alternative medications, and weight gain [17]. Interestingly, there were recommendations on the dosage of THC (21 mg) and CBD (170 mg) that induced a clinical response [17].

A randomized controlled trial of low-dose (10 mg provided twice per day) CBD in CD was reportedly well-tolerated but had no discernible impact on disease activity [14]. A follow-up randomized controlled trial in mild to moderate UC (refractory to

5-aminosalicylic acid) using a higher dose of CBD oil (50–250 mg twice per day) induced symptomatic improvement (including reduced abdominal pain) [85]. Notably, there was still no overt impact on CD inflammatory activity, and fewer patients were able to tolerate the increased dose of CBD [85]. Of note, there is an ongoing phase II placebo-controlled clinical trial in CD using an even higher dose of CBD (300 mg) [86]. A separate dose-escalation trial of CBD in Parkinson's disease (utilizing a maximum dose of 20–25 mg/kg/day for 10–15 days in 15 patients) found that it was associated with increased liver enzymes in this population [87]. In summary, at the present time, clinical data relating to use of *Cannabis* and its derivatives in IBD is still limited. However, the studies currently available demonstrate significant impacts on symptom perception (e.g., abdominal pain), but not on intestinal inflammation or disease course.

#### Indirect Influences on Visceral Pain Perception

In addition to the effects the ECS has on visceral pain perception described above, it also exerts indirect influences on pain perception, including within the GI system.

#### Psychiatric Effects of Endocannabinoids

*Cannabis* and many of its derivatives have been associated with a wide array of positive and negative psychiatric effects, many of which can influence abdominal pain perception. Patient responses to *Cannabis* consumption vary considerably depending on several factors, including the exact form and subtype consumed, the associated dosage and frequency, and clinical and epidemiological features of the individual [88]. In the acute setting, individuals consuming *Cannabis* may describe sensations of euphoria and relaxation or panic, anxiety, depression, and even psychosis [89, 90]. THC, a nonselective partial agonist of CB<sub>1</sub>R and CB<sub>2</sub>R, is the primary cannabinoid component that mediates these effects [27, 90]. In rodent models, the administration of THC induced dose-dependent catalepsy, which correlates with psychotropic effects in humans [90]. Additionally, quantitative bioassays of THC-induced sedation, ptosis, and body sag in monkeys and static ataxia in dogs, which in combination with human trials confirms THC mediates the psychotropic effects of *Cannabis* [91]. These symptoms all have the capability of influencing patient pain experience. Colorectal distension rodent models, widely accepted laboratory assessments of visceral pain, identified the CB<sub>1</sub>R and CB<sub>2</sub>R agonists reduce pain, while antagonism increases visceral pain sensation [92–94]. There were, however, mixed reports whether the effects were mediated with CB<sub>1</sub>R alone [66] or both CB<sub>1</sub>R and CB<sub>2</sub>R [92, 93]. Regardless of the promising data in animal models, THC showed no impact [72] or even increased pain sensation [95] after colorectal distension in patients with irritable bowel syndrome or chronic pancreatitis [75]. In the case of IBS, the psychotropic side effect of increased awareness was hypothesized to contribute to the worsened pain symptoms [95]. Similarly, the psychiatric effects of *Cannabis* may induce a paradoxical effect in the setting abdominal pain. THC has shown efficacy in pain reduction in other clinical scenarios, such as neuropathic pain in multiple sclerosis [96] or chronic cancer-related pain when combined with CBD [97]. With chronic *Cannabis* use, it is also possible to develop signs of dependency and withdrawal [98–100], and this has been associated with an increased risk of developing substance use disorders [101, 102], many of which may also influence pain perception.

### ECS Impact on GI Motility

Cannabinoid effects on gut motility may also have a significant influence on visceral pain perception. Altered states of gut motility can be associated with abdominal discomfort and other related symptoms [103]. Animal models demonstrate that *Cannabis* exposure generally leads to reductions in GI motility throughout the GI tract [104]. These effects appear to be primarily mediated by an inhibition of acetylcholine release, which leads to reduced peristalsis and smooth muscle contractility [105]. CB<sub>1</sub>R agonists have been found to reduce GI motility, while CB<sub>1</sub>R antagonists increased GI motility [106]. CB<sub>2</sub>R has also been implicated in the reduction of GI motility, particularly during inflammatory states [107]. In human studies, the administration of THC, a nonselective agonist of CB<sub>1</sub>R and CB<sub>2</sub>R, has been associated with a reduction in GI motility and constipation [108]. In a rodent model of croton oil-induced intestinal inflammation, the primary nonpsychoactive cannabinoid, CBD, also inhibited GI motility [109]. Importantly, CBD only reduced gut motility in the setting of gut inflammation and not under normal conditions [109]. Additionally, IBD patients have reported a *Cannabis*-mediated improvement in diarrhea and abdominal pain/discomfort in several studies [6, 9, 13]. Thus, *Cannabis*-mediated effects on GI motility could be an important influence on abdominal pain experience of these individuals.

### ECS Impact on Nausea

Perceptions of pain and nausea can be closely linked to 1 another [110, 111]. Cannabinoids have a complicated influence on perception of nausea and, in turn, may influence abdominal pain perception in a related manner. In animal (rodent) models, administration of cannabinoids or FAAH inhibitors reduce signs of nausea, while use of cannabinoid antagonists resulted in demonstration of nausea [112, 113]. Similarly, cannabinoids reduced symptoms of vomiting in several animal models of cisplatin or opioid-induced vomiting (e.g., cats [114], pigeons [115, 116], ferrets [117, 118], and least shrews [112], among others [119]). These antiemetic effects have been directly attributed to CB<sub>1</sub>Rs found in vomiting control centers in the dorsal vagal complex, including the area postrema, nucleus solitary tract, and dorsal motor nucleus of the vagus [112, 118, 120]. There are also peripheral mechanisms involved through THC-mediated inhibition of 5-hydroxytryptophan-induced emesis [120].

In the clinical setting, there is evidence that cannabinoids can be helpful for acute reduction of nausea associated with a variety of conditions [112, 121]. In a recent study, synthetic THC (Dronabinol) had similar efficacy for the treatment of chemotherapy-induced nausea and vomiting in comparison to ondansetron, 1 of the most commonly used antiemetic agents [122]. In a separate study in patients exhibiting chemotherapy-induced nausea and vomiting, there was reduction of delayed nausea and vomiting when combining THC/CBD with ondansetron [123]. There are also reports from human trials in which CB<sub>1</sub>R antagonists induced nausea and emesis [124, 125]. Alternatively, however, long-term users can develop a paradoxical and debilitating effect in which they experience recurrent or persistent nausea after exposure to cannabinoids called cannabis hyperemesis syndrome [126]. Although the mechanism is unknown, *Cannabis* cessation appears to help improve these symptoms in this circumstance.

## Current Considerations and Challenges

Providers need to keep in mind several significant issues when cannabinoids are utilized or are being considered for use in a clinical setting. First, there are a variety of potential legal hurdles that limit *Cannabis* and cannabinoid clinical use and research in the USA [127]. Although there is a trend in the USA toward increasing availability of medicinal *Cannabis* (an estimated 69% of residents reside within a state with either medicinal *Cannabis* or recreational marijuana as of November 2020 [4]), there is no federal legislation permitting its medicinal use at a national level [127]. *Cannabis* remains a Schedule I substance in the USA. Second, biomedical investigators face a variety of legal and administrative restrictions when considering research relating to *Cannabis*/cannabinoids [127]. There are currently significant limitations in regard to potential suppliers and on the amount and type of *Cannabis* and/or its derivatives that are available to investigators. As it is illegal at the federal level, *Cannabis* (medicinal or otherwise) also cannot be transported across state lines. Third, negative societal stigmatization of *Cannabis* and cannabinoid use remains a significant issue. Individuals perceive that their peers and/or potential employers view them negatively [128, 129] and may be less willing to utilize these agents.

Additionally, there are a variety of side effects that have been associated with *Cannabis* use. One primary limitation involves the psychoactive effects. *Cannabis* consumption has been associated with decreased motivation and reaction time, as well as alterations in executive function [130]. In certain circumstances, *Cannabis* may also induce auditory or visual hallucinations, and increase risk for a variety of psychiatric illnesses [131]. Adolescents are at increased risk for the negative side effects of chronic use, including increased risk of schizophrenia later in life and decreased intelligence quotient [131]. Chronic *Cannabis* use can also lead to problematic GI symptoms, such as nausea. These adverse issues are likely related to particular constituents of *Cannabis* (e.g., THC). As a result, for years there has been great interest in separating out and testing various cannabinoid elements.

One of the biggest barriers, however, is a current lack of knowledge relating to *Cannabis* and its derivatives. The legal and societal barriers described above have significantly limited the degree to these agents have been studied in the clinical setting in the USA. While *Cannabis* holds significant potential promise in a variety of clinical

applications, we clearly need to learn much more about it and its components in order to determine their true efficacy and safety in each setting.

## Conclusion and Future Considerations

*Cannabis* and its derivatives have great therapeutic potential in the setting of IBD, particularly as potential treatments for associated frequent and problematic symptoms, including abdominal pain, and pain-modifying issues such as diarrhea and nausea. An increasing number of patients have access to *Cannabis* and cannabinoid agents, and it is very common for individuals with IBD to inquire about the potential utility of these agents for managing their disease. As we have reviewed here, a wide variety and number of animal and human studies have demonstrated not only the positive impact that cannabinoids can have in this context but also the multitude of pathways these agents may work through to induce their analgesic effects. However, relatively few studies have been undertaken in humans to evaluate this potential, particularly when considering select cannabinoid signaling elements. It is also unclear whether cannabinoids will be helpful to mitigate intestinal inflammation in humans, though clinical studies assessing for this in IBD are still relatively scarce.

It is clear that further study is required (particularly in the clinical setting) in order to determine the true potential of *Cannabis* and its components to manage IBD and its symptoms. Future research considerations should focus more specifically on derivatives of *Cannabis* and elements of the endocannabinoid signaling system, with the goal of developing and testing therapies that minimize

psychotropic side effects, while optimizing analgesia. While evaluating separate cannabinoid components, investigators will also need to consider the potential interplay between these therapies and other medications that study subjects are receiving, as endocannabinoids mediate a variety of sensory pathways and signaling systems. Finally, given the myriad pathophysiological and clinical differences among them, there should also be careful consideration for evaluating these agents in different, carefully phenotyped forms of IBD, including in both CD and UC.

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## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

## Author Contributions

K.B. performed a comprehensive literature review and helped to write and edit the manuscript. W.R.-K. helped to write and review the manuscript. S.D. helped to write and edit the manuscript. K.V. helped to conceptualize this project, write, and review the manuscript. M.C. developed the primary concept behind this manuscript, performed a comprehensive literature review, and helped to write and review the manuscript.

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