# Role of cannabis in digestive disorders

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*Cannabis sativa*, a subspecies of the *Cannabis* plant, contains aromatic hydrocarbon compounds called cannabinoids. $\Delta^9$-Tetrahydrocannabinol is the most abundant cannabinoid and is the main psychotropic constituent. Cannabinoids activate two types of G-protein-coupled cannabinoid receptors: cannabinoid type 1 receptor and cannabinoid type 2 receptor. There has been ongoing interest and development in research to explore the therapeutic potential of cannabis. $\Delta^9$-Tetrahydrocannabinol exerts biological functions on the gastrointestinal (GI) tract. Cannabis has been used for the treatment of GI disorders such as abdominal pain and diarrhea. The endocannabinoid system (i.e. endogenous circulating cannabinoids) performs protective activities in the GI tract and presents a promising therapeutic target against various GI conditions such as inflammatory bowel disease (especially Crohn's disease), irritable bowel syndrome, and secretion and motility-related disorders. The present review sheds light on the role of cannabis in the gut, liver, and pancreas and also on other GI symptoms, such as nausea and vomiting, cannabinoid hyperemesis syndrome, anorexia, weight loss, and chronic abdominal pain. Although the current literature supports the use of marijuana for the treatment of digestive disorders, the clinical efficacy of cannabis and its constituents for various GI disorders remains unclear. Eur J Gastroenterol Hepatol 29:135–143


## Introduction

Cannabis or marijuana has been a part of folk pharmacopeia for several years. There has been continuous research to explore its therapeutic potential [1]. Molecular and cell culture research, case reports, surveys of individuals using cannabis, and prospective clinical trials of cannabis-based medicines have provided evidence that cannabis may play a role in the management of some medical conditions. The aim of this manuscript is to provide credible data to update clinicians treating gastrointestinal (GI) disorders.

The two main subspecies of the *Cannabis* plant are *Cannabis sativa* and *Cannabis indica* [1]. *C. sativa* contains around 60 aromatic hydrocarbon compounds, called cannabinoids. Of all cannabinoids, the most abundant cannabinoid is $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC), which is the main psychotropic constituent [2]. *C. sativa* strains contain a higher $\Delta^9$-THC content than indica strains [1].

Until 1944, cannabis was listed on the American pharmacopoeia, but was removed because of political pressure to ban its use in the USA [3,4]. In 1986, the Food and Drug Administration (FDA) authorized the use of its active element $\Delta^9$-THC for medical purposes, such as treatment of side effects such as nausea and vomiting in patients receiving chemotherapy [4].

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Cannabis has been used commonly in Chinese and traditional Ayurvedic medicines for centuries. As of 1 July 2016, a total of 25 states, the District of Columbia, and Guam allow for comprehensive public medical marijuana and cannabis programs (*http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx*). Consroe *et al.* [5], in an anonymous survey of 112 multiple sclerosis patients, found a large proportion reported improvements in bowel and bladder dysfunction from smoked cannabis, although to date there are no published clinical trials. Swift and colleagues conducted a survey of Australians who were using cannabis for medical purposes. This study recruited adults using media stories. Regular and long-term use of medical cannabis was reported for multiple medical conditions, such as chronic pain (57%), depression (56%), arthritis (35%), persistent nausea (27%), and weight loss (26%). Cannabis was perceived to provide great overall relief in 86% of patients, and considerable relief from pain, nausea, and insomnia [6].

Cannabis products are available in different edible forms, including brownies, barbeque sauce, soda, etc. However, the most common method of consumption is smoking through cigarettes (joints), pipes, or water pipes (bongs) [7]. Product labeling and testing are not yet standardized, but information on pesticides, contaminants, and $\Delta^9$-THC potency may be included on the label. The composition and content of $\Delta^9$-THC varies among different products, with a typical range of 0.5–5.0%; however, the concentration of $\Delta^9$-THC is increasing and, in the future, may reach over 50% [8,9]. The psychotropic effects of cannabis start within a minute following inhalation, peak within a half-hour, and begin to taper within 2–3 h. Physiological effects begin after 30–90 min following oral ingestion, peak after 2–3 h, and may last 4–12 h [10]. Anxiety and psychotic symptoms are acute adverse effects of cannabis. Other major side effects include increased risk of motor vehicle crashes, altered adolescent psychosocial

development, decreased fertility, mental health changes, and hyperemesis syndrome [11,12].

There has been scientific advancement in the understanding of the pharmacology of cannabis and its complex interactions within the central nervous system [1]. Various studies have indicated that cannabis has therapeutic potential for the treatment of various conditions, such as HIV-related and cancer-related wasting, nausea, and vomiting because of chemotherapy, and neurological disorders, including chronic pain and multiple sclerosis [10,13]. The use of cannabinoids as an antiemetic is well established. Dronabinol, a man-made form of $\Delta^9$-THC that was FDA approved in 1985, stimulates appetite and counters the emetic effect of cancer chemotherapy [14]. Cannabis has been used for the treatment of GI disorders such as abdominal pain, nausea, vomiting, and diarrhea in the past [15]. Cannabis controls bowel movements in multiple sclerosis, and provides relief from the symptoms of Crohn's disease, irritable bowel syndrome (IBS), as well as other inflammatory GI conditions [14]. Cannabinoids have immunomodulatory properties and influence every component of the immune-response machinery, but their role is still uncertain in normal immune homeostasis and development of immune system disorders [16,17].

### The endocannabinoids system and the gastrointestinal system – current understanding

$\Delta^9$-THC is an active component of cannabis as well as endogenous and synthetic cannabinoids that exert biological functions on the GI tract. Cannabinoids activate two types of G-protein-coupled cannabinoid receptors: (a) cannabinoid type 1 receptor (CB1 receptor), which is located in the enteric nervous system and sensory terminals of vagal and spinal neurons and regulates neurotransmitter release, and (b) cannabinoid type 2 receptor (CB2 receptor), which is mostly distributed in the immune system. Both CB1 and CB2 receptors act within the immune system and may regulate opposite or different immune targets [15].

CB1 receptors are expressed in the normal human colon. The colonic epithelium is biochemically and functionally responsive to cannabinoids. Increased expression of epithelial CB2 receptors in human inflammatory bowel disease (IBD) tissue implies an immunomodulatory role that may impact mucosal immunity [2]. CB2 receptors are found mainly on immune cells such as macrophages, neutrophils, and B and T cell subtypes [18]. Recently, the expression of CB2 was detected in the digestive tract in mRNA in guinea pig whole gut [19]. Another study has provided evidence that, in the rat intestines, CB2 receptors may contribute toward reducing the increase of intestinal motility induced by an endotoxin inflammation [20].

Anandamide and 2-arachidonoylglycerol (2-AG) are the two naturally occurring endogenous lipid endocannabinoidal ligands of CB1 and CB2 receptors. At physiologically relevant concentrations, they can bind both receptors. However, at low nanomolar concentrations, 2-AG is CB1-receptor specific [21–23]. The discovery of these endogenous ligands, that is, anandamide and 2-AG, which appear to bind cannabinoid receptors, supports the presence of a functional endogenous cannabinoid system in the GI tract [1].

Cannabinoid receptors, their endogenous ligands, and the enzymes involved in their inactivation altogether constitute the endocannabinoid system [2]. The endocannabinoid system serves protective functions in the GI tract and defends against inflammation and abnormally high gastric and enteric secretion under pathophysiological conditions [15]. The endocannabinoid system presents a promising therapeutic target for treating various abnormal GI conditions such as inflammatory bowel disease, functional bowel disease (IBS), and secretion and motility-related disorders [15].

$\Delta^9$-THC inhibits peristalsis, reduces gastric and intestinal secretions, and protects against ulcers in rodents [24, 25]. Shook and Burks [26] reported that $\Delta^9$-THC, $\Delta^{9,11}$-THC, and cannabinol exert an inhibitory effect on GI transit and motility in rats. Endocannabinoids' cellular uptake is through facilitated diffusion and transport by a specific protein, as yet unknown [27], and inactivation is mediated [23] by fatty acid amide hydrolase (FAAH) or monoacylglycerol lipase [2].

The activation of the CB1 receptor inhibits motility of the intestine and may be responsible for regulating intestinal smooth muscle tone and peristalsis. A study by Rosell *et al.* [28] reported for the first time that cannabinoids inhibit contractions of the small intestine in the rat. Pertwee *et al.* [29] recognized the presence of CB1 receptors within the intestine of guinea pigs.

### Effects on the gut

Endocannabinoids play a role in regulating the motor activity of the gut (Fig. 1). Vasoactive intestinal peptide is a gut neuropeptide that may modulate precursor conversion to anandamide, thereby activating cannabinoid CB1 receptors and regulating *N*-palmitoylethanolamine, which in turn activates a CB2-like receptor subtype [30].

Coutts *et al.* [31] carried out a study in guinea pigs and rats and reported that activation of cannabinoid CB1 receptors inhibits GI motility, propulsion, and transit, whereas selective antagonism of these receptors has the opposite effects, suggesting the presence of endocannabinoid tone. Cannabinoids inhibit fast cholinergic synaptic transmission that occurs by reversible activation of presynaptic and postsynaptic CB1 receptors, and cannabinoids can reversibly depress slow excitatory synaptic transmission [32].

Endogenous and exogenous CB1-receptor agonists reduce gut motility, and CB1-receptor antagonists increase motility [33]. SR 141716A is a potent and competitive antagonist of cannabinoid CB1 receptors naturally expressed in the human gut. In an experimental model in the rat, SR 141716A was found to enhance both tonic and phasic motor activities in the colonic longitudinal smooth muscle, which suggests that it could act either through antagonizing the effect of the endogenous CB1-receptor agonist or by an agonist effect on these receptors, indicating a neuromodulatory role of cannabinoids in the GI system [34]. There is a close regulation of endocannabinoid levels in the gut. The anandamide hydrolase and synthase activities were detected in various organs, with the liver showing the highest activity [35]. Croci *et al.* [36] reported the existence of prejunctional cannabinoid CB1 receptors in human ileum longitudinal smooth muscle. It has been

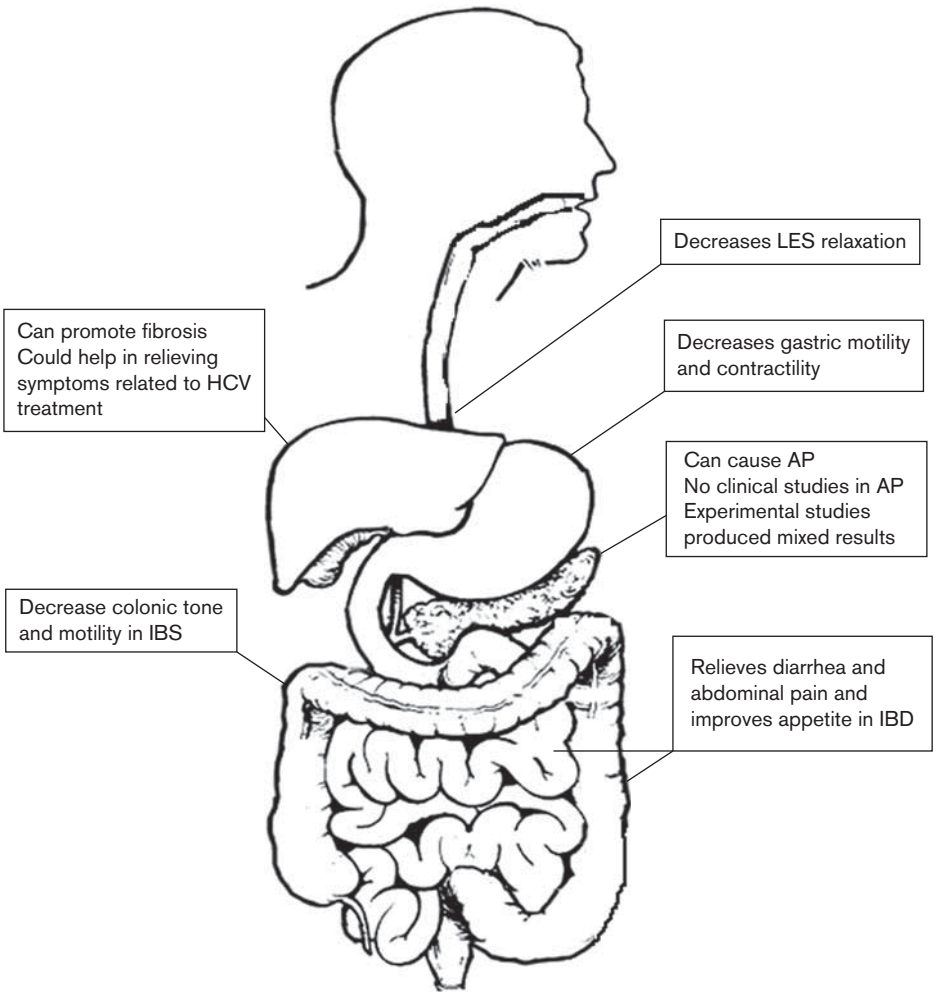


**Fig. 1.** Clinical effects of cannabis on the gastrointestinal system. AP, acute pancreatitis; HCV, hepatitis C virus; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; LES, lower esophageal sphincter.

shown that the CB1-receptor antagonist SR 141716A increased GI transit and fluid accumulation, whereas the CB1-receptor agonist WIN 55,212–2 decreased GI transit and fluid accumulation [37]. $\Delta^9$-THC has antihistaminic and anti-inflammatory activity in intestinal tissue [38]. The endogenous cannabinomimetic substance, 2-AG, has been isolated from gut homogenates, and CB1 receptor-binding sites have been identified in the small intestine [39].

### *Cannabis and inflammatory bowel diseases*

Cannabis preparations have been considered as promising pharmacological tools. They play an anti-inflammatory role in inflammatory bowel diseases. However, the use of cannabis in clinical therapy has been limited by its psychotropic effects. Cannabis has been used to treat anorexia, abdominal pain, emesis, gastroenteritis, intestinal inflammation diarrhea, and diabetic gastroparesis [37]. Cannabidiol (CBD), one of the more than 100 active cannabinoids identified in cannabis, shares the typical cannabinoid beneficial effects on the gut, without exerting any psychotropic effects. CBD acts at the extracannabinoid system receptor site peroxisome proliferator-activated receptor γ, and makes CBD a potential candidate for the development of IBD drugs. With low toxicity, even in humans, CBD slows the course of the disease and ameliorates symptoms of IBD such as abdominal pain, anorexia, and diarrhea [40].

The endogenous cannabinoid system protects against colonic inflammation and plays a therapeutic role in IBD. Lal and colleagues carried out a study to evaluate the use of cannabis in patients with IBD. Of all patients attending a tertiary-care outpatient clinic, 100 patients with ulcerative colitis and 191 patients with Crohn's disease completed a questionnaire on current and previous use of cannabis, disease history, medication use, and socioeconomic factors. A short IBD questionnaire was used to assess quality of life. A comparable proportion of ulcerative colitis and Crohn's disease patients reported lifetime or current cannabis use. Of lifetime users, 33% of ulcerative colitis and 50% Crohn's disease patients had used cannabis to relieve IBD-related symptoms such as diarrhea, abdominal pain, and reduced appetite. Patients were more likely to use cannabis for symptom relief because of abdominal surgery, use analgesic or alternative medicine options, and score lower on the IBD questionnaire [41].

Ravikoff Allegretti and colleagues carried out a prospective cohort survey study at an academic medical center to assess marijuana use patterns, including the prevalence, sociodemographic characteristics, and qualitative benefits of marijuana use among IBD patients. Of 292 patients

who completed the survey, 12.3% were active marijuana users, 39% were past users, and 48.6% had never used marijuana. Among current and past users, 32% reported that they used marijuana for disease symptoms. The majority of them found that marijuana was very helpful for completely relieving abdominal pain, nausea, and diarrhea [42].

Naftali and colleagues carried out a retrospective observational study in humans to examine disease activity, use of medication, surgery need, and hospitalization before and after cannabis use in 30 patients with Crohn's disease. The Harvey Bradshaw Index was used to assess disease activity for Crohn's disease. The results indicated a positive effect of cannabis on disease activity. Of 30 patients, significant improvement was observed in 21 patients after cannabis treatment. The authors concluded that cannabis might have a positive effect on Crohn's disease activity, as reflected by a reduction in Crohn's Disease Activity Index (CDAI) and in the need for other drugs and surgery. A significant improvement was observed in the average Harvey Bradshaw Index ($P < 0.001$). The need for other medication was reduced significantly. Only two patients required surgery during cannabis use for an average period of 3 years [43].

Naftali and colleagues next carried out a double-blind, placebo-controlled study to investigate the effects of cannabis on patients with active Crohn's disease, who did not respond to therapy with steroids, immunomodulators, or antitumor necrosis factor-α agents (i.e. CDAI > 200). These patients received cannabis cigarettes containing 115 mg of $\Delta^9$-THC twice daily versus placebo for 8 weeks. A clinical response was defined as a decrease in CDAI greater than 100, observed in 90% of patients in the cannabis group, and three patients were weaned off from steroids in this group. Improved appetite and sleep, with no significant side effects, were observed in patients receiving cannabis [44].

In an observational study, cannabis improved abdominal pain (83.9%), abdominal cramps (76.8%), joint pain (48.2%), and diarrhea (28.6%) in patients who were self-administering cannabis for either IBD-related symptoms and those who were not. However, use of cannabis for greater than 6 months for IBD symptoms was strongly associated with surgery in patients with Crohn's disease [45]. In addition, in a mouse model of colitis, cannabinoids were found to ameliorate inflammation [46].

### Cannabis and gastrointestinal motility

Cannabinoids reduce small intestinal, gastric, and colonic motility. Cannabinoid agonists act on prejunctional CB1 receptors and reduce contractility in smooth muscle, ascending neural contractions, and peristalsis in different areas of the GI tract [47]. Cannabinoids reduce GI transit through activation of CB1 receptors in rodents, as observed in various in-vivo studies, but not through CB2 receptor activation [33,47]. However, both CB1 and CB2 receptors could reduce the increased intestinal motility that is induced by inflammatory stimuli in pathophysiological states. Endogenous and synthetic cannabinoid receptor agonists have been shown to reduce gastric emptying, upper GI transit, and colonic propulsion in experimental models. Cannabinoids and their analogs have been found to reduce the electrically induced contractions in mice stomach, guinea pig ileum, and human colon. These effects are because of presynaptic inhibition of releases of acetylcholine and substance P in myenteric neurons [48]. A newly discovered third cannabinoid receptor, GPR55 (G-protein-coupled receptor 55), is found to be localized in myenteric neurons of mice and human colon. In in-vitro and in-vivo studies, GPR55 agonists reduced colonic muscle contractility and slowed whole-gut transit [49]. Bateman [50] showed that $\Delta^9$-THC does not significantly affect the gastric emptying of liquid meals in cannabis-naive volunteers, which was assessed in terms of initial adaptive relaxation of the stomach (5 min volume) and the subsequent rate of gastric emptying (half-life). In a randomized double-blind placebo-controlled trial, McCallum *et al.* [51] showed that prophylactic doses of $\Delta^9$-THC for chemotherapy-induced nausea and vomiting (CINV) increased the gastric transit time of radiolabeled solid food in healthy individuals who were experienced cannabis users. Recently, Abalo *et al.* [48] reported that the non-selective CB antagonist WIN 55,212–2 dose dependently reduced motility throughout the gut of the rat. Various other studies, including randomized clinical trials, have shown that cannabinoids reduce GI motility (Table 1) [47,52,57,58].

### Cannabis and irritable bowel syndrome

IBS is the most common GI disorder for which patients are referred to a gastroenterologist. It is a diagnosis of exclusion. The abdominal visceral pain of IBS is considered to be because of enhanced perception to colonic distension in about 70% of patients [58]. Considerable data suggest that visceral sensation in the abdomen may involve the cannabinoid system. In the past, multiple rat model experimental studies have identified the possible role of cannabis in visceral sensation in the abdomen [58]. In a randomized placebo-controlled trial, Esfandyari *et al.* [52] showed in healthy volunteers that dronabinol relaxes colonic tone and reduces postprandial colonic motility. However, another placebo-controlled study showed that dronabinol does not modify visceral perception to rectal distension and decrease visceral hypersensitivity in IBS patients compared with healthy volunteers [53]. Later, Wong and colleagues reported that in diarrhea-predominant and alternating IBS, a single 5 mg dose of dronabinol reduces fasting colonic motility and increases colonic compliance. They also noted that polymorphism in FAAH and CNR1 (gene for CB1 receptor) could influence the effects of dronabinol on colonic motility [54]. They further studied this effect and showed that a 2.5 or 5 mg dose of dronabinol selectively decreased gut transit in patients who had the *CNR1 rs806378* genotype [55]. Antinociceptive properties of FAAH inhibitors URB597 and PF-04457845 have also been evaluated for use in IBS [59].

The potential role of cannabis in IBS-diarrhea-predominant or the pain associated with IBS is supported by small numbers of patients in a few randomized trials. Additional high-quality method studies are needed before a clinical recommendation is indicated.

**Table 1.** Published randomized-controlled trials on effect of cannabis on various gastrointestinal functions and dysfunctions

| References | Number of patients | Study type | Intervention | Outcome measures | Results |
|---|---|---|---|---|---|
| Bateman [50] | 7 HV (all men) (cannabis naive) | Placebo controlled | $\Delta^9$-THC 0.5 and 1 mg in a random manner | Gastric emptying of liquid | NS |
| McCallum *et al.* [51] | 13 HV (cannabis users in past) (9 men, 4 women) | Double-blind placebo controlled | $\Delta^9$-THC at a dose of 10 mg/m$^2$ of the body surface area on 2 separate days | Gastric emptying of solid food | Significant delay in gastric emptying<br>No correlation between plasma $\Delta^9$-THC level and delay in gastric emptying |
| Esfandyari *et al.* [52] | 30 HV (16 women, 14 men) | Double-blind placebo controlled | DRO 5 mg, twice daily for three doses | GI transit<br>Fasting and postmeal gastric volumes<br>Satiation volume | Delay in gastric emptying of solid and liquid meal in women<br>NS in men |
| Klooker *et al.* [53] | 22 (10 IBS, 12 HV) | Placebo-controlled double-blind cross-over | DRO 5 and 10 mg in HV, 10 mg in IBS patients on 3 separate days at least 6 days apart | Rectal sensitivity to sigmoid stimulation<br>Before and after meal | Did not alter baseline perception to rectal distension both in HV or IBS patients<br>Increase colonic compliance |
| Wong *et al.* [54] | 75 (35 IBS-C, 35 IBS-D, 5 IBS-A) | Placebo-controlled double-blind parallel group | DRO 2.5 or 5.0 mg | Left colonic compliance<br>The motility index, tone, and sensation | Decrease colonic motility index<br>No effect on sensation and tone<br>FAAH and CNR1 variants could influence the effects of DRO colonic motility |
| Wong *et al.* [55] | 36 IBS-D | Placebo-controlled double-blinded parallel group | DRO 2.5 and 5 mg, twice daily for 2 days | Gastric, small bowel, and colonic transit | No effect on gut transit<br>DRO delays colonic transit in those with CNR1 variant |
| Naftali *et al.* [44] | 21 Crohn's disease patients (CDAI score > 200) | Placebo-controlled double blind | Cigarettes containing 115 mg of $\Delta^9$-THC, twice daily | Decrease in CDAI score of > 100 | Short course (8 weeks) of $\Delta^9$-THC produced significant steroid-free benefits to 10 of 11 patients with active Crohn's disease |
| de Vries *et al.* [56] | 24 chronic pancreatitis patients | Placebo-controlled double blind | Single 8 mg dose of namisol | Pain on Visual Analog Scale | NS |

CDAI, Crohn's Disease Activity Index; CNR1, gene coding for the CB1 receptor; DRO, dronabinol; FAAH, fatty acid amide hydrolase; GI, gastrointestinal; HV, healthy volunteers; IBS, irritable bowel syndrome; IBS-A, irritable bowel syndrome alternating; IBS-C, irritable bowel syndrome constipation predominant; IBS-D, irritable bowel syndrome diarrhea-predominant; $\Delta^9$-THC, $\Delta^9$-tetrahydrocannabinol.

### *Effects of cannabis on the liver*

Experimental evidence has shown that cannabinoids and their receptors play a role in various liver disorders, including liver fibrosis, hepatic encephalopathy, metabolic steatosis, and cirrhotic cardiomyopathy [60]. Multiple studies have suggested that activation of CB1 receptors is steatogenic, and their antagonism suppresses steatosis in hepatitis C. CB1 receptor activation increases de-novo lipogenesis, decreases fatty acid β-oxidation, and induces hyperphagia. CB2 receptor activation is mainly associated with insulin resistance, and protects against the development of liver fibrosis [61]. It has also been considered that this effect could indirectly cause progression of liver fibrosis in hepatitis C, thus reducing the rate of viral eradication [60,62]. Patsenker and colleagues showed that CB1 receptors are upregulated in hepatic tissue samples from patients with alcoholic liver fibrosis. They also showed in their in-vivo and in-vitro studies that inhibition of CB1 receptor expression either in $CB^{-/-}$ knockout mice or by CB1 receptor antagonist SR141716 protects against the development of alcohol-induced liver fibrosis [63]. In a prospective cohort study, daily cannabis use was found to be strongly associated with moderate-to-severe fibrosis in hepatitis C virus (HCV)-infected individuals [64]. On the basis of these results, the authors of these studies suggested that patients with HCV should be advised to refrain from regular cannabis use [60,64]. However, other clinical studies provide different results. In an observational study, Sylvestre *et al.* [65] found that modest cannabis use during HCV treatment could provide significant benefit to some patients in terms of increased treatment adherence because of non-specific improvements in the tolerability of the treatment regimen. The effectiveness of oral cannabinoids in decreasing the HCV treatment-related symptoms was also shown in a retrospective study by Costiniuk *et al.* [66]. In another study, Brunet *et al.* [67] could not find any significant effect of cannabis on liver disease progression among HIV-HCV-coinfected patients. On the basis of these interesting but disparate results, it is very difficult to come to a conclusion on the effect of cannabis on progression of hepatitis. However, given the potential for added insight and understanding, patients with liver diseases should be questioned on their use of cannabis, and they should be informed about its potential harmful effects on the liver.

### *Cannabis and its effects on the pancreas*

Both CB1 and CB2 receptors are present in the pancreas, with low-level expression with normal gland function. It has been shown that this expression is enhanced during inflammation of the pancreas. Activation of CB1 receptors is found to have a fibrogenic effect on the pancreas, whereas activation of CB2 receptors induces the opposite effect [1]. In experimental models, the effect of CB agonists and antagonists on the severity of acute pancreatitis has produced variable results, which could be because of variations in the dose, timing, and type of agent used [68–71]. Recently, multiple case reports of cannabis-induced acute pancreatitis [72–75] have been published. There are no randomized trials/studies on the effect of cannabis on acute pancreatitis. A survey study by National Surveys on Drug Use and Health showed that the lifetime risk of developing pancreatitis increases with the

use of marijuana, and it is directly related to the duration of use [76]. In a recent, randomized double-blind study, de Vries *et al*. [56] reported that a single 8 mg dose of namisol (pure $\Delta^9$-THC) did not result in pain relief in persistent abdominal pain because of chronic pancreatitis.

## Cannabis in specific gastrointestinal symptoms

### Chemotherapy-induced nausea and vomiting

Nausea and vomiting are the most stressful symptoms experienced by patients receiving chemotherapy, and chemotherapy-related emesis is experienced by up to 75% of all cancer patients [77,78]. CINV is associated with anxiety, depression, and helplessness, and may lead to discontinuation of therapy because of noncompliance [79,80]. CB1 receptors are found in almost all regions of the brain including the dorsal vagal complex of the brainstem, which is involved in vomiting [81]. In the animal model, the antiemetic effect of cannabinoids has been confirmed to be mediated by CB1 receptors in the dorsal vagal complex [58]. However, evidence of a role of CB2 receptors in nausea and vomiting is still lacking. In the ferret, CB2 receptors antagonism has been shown to block the antiemetic action of 2-AG, but not of anandamide [81].

Currently, dronabinol, nabilone, and levonantradol are the three synthetic $\Delta^9$-THC analogs that have been evaluated in various clinical trials for the treatment of CINV [4]. Machado Rocha and colleagues carried out a systematic review and meta-analysis to evaluate the efficacy of cannabinoids in CINV and found that dronabinol had a better acute antiemetic efficacy than conventional antiemetic drugs such as prochlorperazine and metoclopramide. $\Delta^9$-THC analogs nabilone and levonantradol were not found to have superior acute antiemetic efficacy compared with conventional antiemetics; however, they had a clinically significant outcome toward the intervention [82]. In another recent meta-analysis of 23 randomized-controlled trials comparing cannabinoids with either placebo or with a conventional antiemetic, Smith *et al.* [83] concluded that cannabinoids may be useful for treating refractory CINV, with moderate quality of evidence to support this hypothesis. Most of these studies have compared cannabinoids with conventional drugs such as prokinetics, neuroleptics, and dopamine antagonists. One study compared the efficacy of dronabinol alone and in combination with ondansetron (a 5-$HT_3$ receptor antagonist) versus ondansetron alone for delayed CINV. The authors found that, in CINV, both of the drugs were similarly effective and combination therapy was not more effective than either agent alone [84]. However, no randomized-controlled trial has been published comparing cannabinoids with neurokinin-1 receptor antagonists such as aprepitant.

Dronabinol and nabilone were FDA approved in 1985 for intractable CINV [85]. As per the American Society of Clinical Oncology and the European Society for Medical Oncology, cannabinoids should not be used as the first-line treatment for CINV and should only be used as reserved therapy if all other medical therapies have failed [85,86].

### Anorexia and weight loss

Cannabis also acts as an appetite stimulant. It is believed to increase appetite and food intake by activating CB1 receptors that are expressed in the hypothalamus, which regulate energy balance [87]. Cannabis smoking has been shown to increase the total daily caloric intake by up to 40% and body weight versus placebo. This increase in body weight during active cannabis use was more than predicted by caloric consumption [88]. In a randomized double-blind controlled trial, oral $\Delta^9$-THC-treated patients reported enhancement of food taste and increase in appetite and protein intake [89]. However, in another similarly conducted trial, no difference in participants' appetite and quality of life was found when comparing cannabis extract, $\Delta^9$-THC, and placebo [90]. In patients with advanced cancer, 800 mg/day liquid suspension of megestrol was found to be superior to 2.5 mg twice a day dronabinol in palliation for anorexia. Combination therapy of megestrol plus dronabinol did not provide additional benefit in weight gain and appetite stimulation compared with megestrol alone [91]. Many other trials have produced similar mixed results for anorexia and cachexia in cancer patients, with only a modest benefit from dronabinol [1]. A CB1 receptor antagonist, rimonabant, showed promising results as an antiobesity drug, but could not receive FDA approval because of its psychoactive profile [92].

In multiple studies, dronabinol was also found to improve anorexia and weight loss in patients with AIDS [93] and this effect has shown to be dose dependent, with higher doses associated with weight gain of more than 1 kg within 4 days [94]. The placebo-controlled studies by Haney and colleagues [94,95], showed that smoking 2–4% $\Delta^9$-THC three or four times per week increased food intake and body weight. However, in a recent meta-analysis, it was concluded that there is limited evidence of an association of dronabinol with weight gain, increase in appetite, and greater percentage of body fat [96].

## Cannabis paradox – cannabinoid hyperemesis syndrome

With increasing rates of cannabis abuse, a new clinical condition known as cannabinoid hyperemesis syndrome (CHS) has been identified as separate from cyclical vomiting syndrome. CHS is characterized by chronic cannabis use, cyclic episodes of nausea and vomiting, and learnt behavior of frequent hot bathing [97].

The mechanism of CHS is still unclear, but it has been suggested that chronic use coupled with long half-life of $\Delta^9$-THC may induce a 'drug reintoxication effect' during food deprivation or stress secondary to lipolysis [97]. In animal models, CBD has been shown to produce a biphasic response in lithium-induced and cisplatin-induced emesis. Low-dose CBD produces antiemetic effects and higher doses produce a proemetic effect [98,99]. Moreover, cannabigerol has been shown to reverse the antiemetic effects of CBD in rats and shrews, which are considered to occur through 5-$HT_{1A}$ receptors [100].

The clinical course of CHS involves three phases: prodromal, hyperemetic, and recovery phase. As the name suggests, the prodromal phase is characterized by early morning nausea, fear of vomiting, and abdominal discomfort that can last for months to years. Patients usually present to the emergency room in the hyperemetic phase, where they develop intense nausea, profuse vomiting, and mild generalized abdominal pain. The recovery phase is associated with improved symptoms, weight gain, and normal eating patterns [97]. During the hyperemetic phase, patients take numerous long hot baths/showers to

alleviate the symptoms. The mechanism of this phenomenon is still unclear. Darmani has proposed that cannabis tends to increase the core body temperature while concomitantly reducing skin temperature. Compulsive hot baths help to increase blood flow to skin to dissipate the elevated core body heat [101]. Another not so favored theory is that hot bathing might correct the disequilibrium of digestive and thermoregulatory systems within the hypothalamus [12,101].

Patients with this syndrome visit emergency rooms multiple times, undergo many batteries of tests, and the diagnosis may be missed with both economic and morbidity effects on the patients and hospitals. This delay could be because of lack of awareness and confusion of this entity by medical professionals. Patients often continue to consume cannabis with the misbelief of its benefit as an antiemetic, which in turn exacerbates the problem. CHS is a diagnosis of recognition and exclusion. The clinician should remain vigilant for this diagnosis if no organic cause of cyclic nausea and vomiting can be found in chronic cannabis users even after thorough laboratory tests and imaging studies.

### *Conclusion*

The recreational and medical use of cannabis is now increasingly being reported in various parts of the world. Scientific evidence is mounting that supports the use of cannabis for the treatment of digestive disorders such as nausea, vomiting, chronic abdominal pain, and inflammatory bowel diseases despite the caveat of product purity and legal challenges. The endocannabinoid system plays a complex role in diverse biological pathways that affect GI physiology and pathology. However, the clinical efficacy of cannabis or its constituent for various digestive disorders remains unexplored. This, in part, could be because of the fact that only a few $\Delta^9$-THC major constituents have been studied, leaving almost 100 of other constituents. Another way to possibly explain the mixed results of the effect of cannabis on digestive diseases could also be that we are still missing the other possible receptors with significant interactions. Some patients with GI disorders switch to cannabis for symptomatic relief, without a clear understanding of the risks and benefits involved. Long-term randomized-controlled trials are warranted in the future for an understanding of the role of cannabis in GI symptoms and diseases as well as to evaluate the efficacy and safety of cannabinoids in patients with GI disorders.

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### *Conflicts of interest*

There are no conflicts of interest.

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