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REVIEW

An overview of cannabis based treatment in Crohn's disease

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ABSTRACT

Introduction: Cannabis use among inflammatory bowel disease (IBD) patients is common. There are many studies of various laboratory models demonstrating the anti–inflammatory effect of cannabis, but their translation to human disease is still lacking.

Areas covered: The cannabis plant contains many cannabinoids, that activate the endocannabinoid system. The two most abundant phytocannabinoids are the psychoactive Tetrahydrocannabinol (THC), and the (mostly) anti–inflammatory cannabidiol (CBD). Approximately 15% of IBD patients use cannabis to ameliorate disease symptoms. Unfortunately, so far there are only three small placebo controlled study regarding the use of cannabis in active Crohns disease, combining altogether 93 subjects. Two of the studies showed significant clinical improvement but no improvement in markers of inflammation.

Expert opinion: Cannabis seems to have a therapeutic potential in IBD. This potential must not be neglected; however, cannabis research is still at a very early stage. The complexity of the plant and the diversity of different cannabis chemovars create an inherent difficulty in cannabis research. We need more studies investigating the effect of the various cannabis compounds. These effects can then be investigated in randomized placebo controlled clinical trials to fully explore the potential of cannabis treatment in IBD.

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Cannabis; marihuana; Crohn's disease; ulcerative colitis; inflammatory bowel disease

1. Introduction

Crohn's disease is a chronic idiopathic inflammatory bowel disease with an annual incidence ranging from 3 to 20 cases per 100,000 [1]. Unfortunately, there is no cure for CD, most patients require continuous medical treatment and about 50% of patients will require surgery within 10 years of diagnosis [2]. It is therefore of little wonder that patients with Crohns disease turn to alternative modes of treatment, including the use of cannabis to ameliorate disease symptoms. Cannabinoids, through their effect on the endocannabinoid system, have indeed been shown in various laboratory models to have an anti–inflammatory effect, but the question as to whether cannabis can reduce inflammation in the gut remains open.

1.1. Endocannabinoids and phytocannabinoids

The Cannabis plant contains dozens of different cannabinoids, terpenes, pinenes, flavonoids, and other compounds – nearly 500 different chemicals [3,4]. The main psychoactive compound is THC, first isolated by Gaoni and Mechoulam in 1964 [5]. Another compound of particular interest is cannabidiol (CBD) which is a compound lacking psychoactive effect but demonstrating an anti–inflammatory effect in various models of experimental colitis [6]. Other cannabinoids, such as cannabigerol (CBG), also demonstrated beneficial effect in murine models of colitis [7]. The cannabis plant also contains terpenes, pinenes and flavonoids which may have additional effects. Therefore, different cannabis plants are described as different chemovars rather than as different strains [8,9]. Three monoterpenes, limonene, β-myrcene, and α-pinene, and two sesquiterpenes, caryophyllene and humulene, are abundant in the majority of cannabis chemovars [10]. Some terpenes are more common in THC rich chemovar whereas others are more common in CBD rich chemovars [8]. As more knowledge about the medical use of cannabis is accumulating, it is becoming clearer that data should also be collected about the specific composition of the cannabis used.

Phytocannabinoids achieve their effect by activating the endogenous endocannabinoid system (ECS). This system exists in all mammals and in almost every organ. The system is comprised of the cannabinoid receptors CB1 and CB2, (and probably other receptors including TRPV1, GPR55 and GPR119) their ligands anandamide and 2-arachidonyl glycerol (2-AG) [11], and the enzymes that synthesize and degrade them [12]. In the nervous system, endocannabinoids are released by post-synaptic neurons and act as retrograde synaptic signals, which regulate neurotransmission [13], however, endocannabinoids are found in almost every organ, including gastrointestinal tract, heart, liver, adipose tissue, lungs, adrenal glands, smooth and skeletal muscle, male and female reproductive systems, bone and skin [14]. The actions of the ECS appear to be largely homeostatic. In the GI tract the ECS has an important role in peripheral regulation of visceral pain, nausea and vomiting, motility, permeability and inflammation [12]. Phytocannabinoids, by activating the ECS, lead to the same effects. Therefore, it is no wonder that they can bring symptomatic relief in IBD, and many animal models have shown also improvement in inflammation [15].

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Article Highlights

- The endocannabinoid system has an important role in the regulation of gastrointestinal function, including pain, motility, permeability and inflammation.
- Phytocannabinoids activate the endocannabinoid system. This activation may have a beneficial effect in inflammatory bowel disease.
- Anecdotal reports inform us that about 15% of IBD patients use cannabis to ameliorate their symptoms, but the large variation between different cannabis chemovars and different modes of cannabis consumption make cannabis studies inherently difficult.
- Randomized controlled studies regarding cannabis use in Crohns disease indicate a beneficial effect but they are still few and small. Larger studies are urgently needed.

1.2. Manipulations of the endocannabinoid system in models of inflammatory bowel disease

Many studies regarding the effect of cannabinoids using both in vitro and in vivo models of IBD have shown that cannabinoids have an anti–inflammatory effect.

In a model of DNBS to induced colitis CB1 knockout mice developed more sever and extensive colitis then wild type mice, colitis was worsened by pharmacological blockade of the CB1 receptor, and treatment of wild type mice with HU-210 (a synthetic CB1 and CB2 receptor agonist) improved DNBS colitis [16]. These findings were further supported by showing that mice with genetic deletion of either CB1 or CB2 or both CB1 and CB2, developed worse TNBS induced colitis then wild-type mice [17]. Intra-peritoneal injection of CBD (5–10 mg/kg) reduced colonic inflammation and weight loss in mice with DNBS colitis [18]. CBD was further tested in the same model of TNBS induced colitis comparing intra-peritoneal, intra-rectal and oral administration, showing improvement of colitis in the intraperitoneally or rectally treated mice but not in the orally treated mice [19]. In a study that compared CBD alone, THC alone, or both THC and CBD to sulfasalazine, a significant decrease in the extent of macroscopic damage to the colon was demonstrated [20].

In a different model of oil of mustard and dextran sulfate sodium induced colitis the synthetic cannabinoids agonists ACEA (a CB1 receptor agonist) and JWH-133 (a CB2 receptor agonist), were shown to have a protective effect [21].

Intra-peritoneal administration of Inhibitor to monoacylglycerol lipase (MAGL), the enzyme responsible for the degradation of 2-AG, was also associated with a reduction in both microscopic and histological inflammation in a model of TNBS colitis in mice. This effect was abolished when either CB1 or CB2 receptor antagonists were added [22].

Cholera toxin induced diarrhea in mice was improved by administration of the endogenous cannabinoid, Anandamide, as well as by selective CB1 receptor agonists. These agonists produced a significant dose-dependent inhibition of fluid accumulation in the small intestine [23].

In summary, these studies and many others have sown that activation of the endocannabinoid system, by either synthetic agonists, phytocannabinoids, or inhibition of endocannabinoid degradation, will ameliorate bowel inflammation. On the other hand, inhibition of the endocannabinoid system by knockout of cannabinoid receptors or by cannabinoid antagonists, will worsen bowel inflammation [13].

1.3. Observational trials of cannabis use in IBD

There are many anecdotal reports of cannabis use by patients with IBD [24,25] but most of them are limited to exploring the prevalence of cannabis use, with very little data about the dose of cannabis used, mode of consumption, and the effect, if any, of cannabis use on disease activity. Safety and side effects are also not addressed in most of the studies. Compared with the non-IBD population, patients with IBD report more Cannabis use, 74.4% (125/168) vs 48.3% (28/58) ($P < 0.001$) and improvement of pain, appetite and diarrhea [26]. A population based analysis of patterns of cannabis use among 2,084,895 subjects with IBD and 2,013,901 control subjects showed that subjects with IBD had a higher incidence of ever having used cannabis, started using at a younger age and used a heavier amount per day [27]. When questioning IBD patients about cannabis use, 17.6% of respondents were current users, and the use of Cannabis for more than 6 months was a strong predictor of requiring surgery (odds ratio = 5.03, 95% confidence interval = 1.45–17.46) [28]. Contrary to that, in two propensity matched retrospective cohort studies, Mbachi et al compared the prevalence of Crohn's and ulcerative colitis (UC) related complications amongst patients who were cannabis users and non-users. In the Crohns study they observed that Cannabis users were less likely to develop disease related complications such as intrabdominal abscess, active fistulizing disease, need for blood transfusion, colectomy and need for parenteral nutrition. Sadly, they also observed that concurrent psychiatric diseases were significantly higher among cannabis users [29]. In the UC study prevalence of partial or total colectomy was lower in cannabis users compared to nonusers (4.4% vs 9.7%, $P = .010$) [30]. These retrospective population based studies indicate that cannabis use may be beneficial in IBD, however they are limited by their retrospective nature and the lack of accurate information about disease activity response and the mode and dose of cannabis used by the patients.

In an observational study we reported the duration and dose of cannabis use as well as the influence on disease activity index. Crohn's disease patients (No 30) who were using licensed medical cannabis for an average period of 2.14 years participated in the study. The THC dose was between 0.5–1.5 mg/day, and we observed significant reduction in the Harvey Bradshaw index, from 14 ± 6.7 to 7 ± 4.7 ($P < 0.001$) [31].

An observational study of 127 IBD patients who were using medical cannabis by license from the ministry of health found that most patients were satisfied with a monthly dose of 30 grams of cannabis flowers and that 70% were consuming cannabis by smoking it [32]. The average Harvey Bradshaw index improved from 14 ± 6.7 to 7 ± 4.7 ($p < 0.001$) during a median follow up of 44 months (IQR 24–56 months). However, since patients are using many different varieties of cannabis, with different content of cannabinoids, obtaining more accurate information is difficult.

1.4. Randomized controlled trials of cannabis use in Crohns disease

A Cochrane review searching for randomized controlled trials comparing any form of cannabis or its cannabinoid derivatives

(natural or synthetic) to placebo or an active therapy for adults with Crohn's disease identified only 3 trials with 93 participants that matched the search criteria. The authors concluded that no firm evidence regarding the efficacy and safety of cannabis and cannabis oil in adults with active Crohn's disease was established [33].

The first trial included 20 patients with active Crohn's disease, 11 of whom received cigarettes containing 23% of THC (corresponding to 115 mg THC twice daily) and 10 placebo [34]. Crohn's disease activity index (CDAI) was reduced from 330 ± 105 to 152 ± 109 in the study group whereas in the placebo group the change was not significant – from 373 ± 94 to 306 ± 143; (p between groups< 0.005).

The second trial included in the Cochrane review inspected the use of CBD in active Crohn's disease. Forty per cent (4/10) of cannabis oil participants achieved remission at 8 weeks compared to 33% (3/9) of the placebo participants (p = non-significant). CRP at the end of the study was 2.2 ± 0.8 in the study group versus 3.9 ± 0.7 mg/dl in the placebo group (p = 0.3). These negative results could be due to the small dose that was used – 20 mg/day of CBD, or to the oral ingestion, or maybe CBD really does not have an effect in Crohn's disease [35].

The third trial investigated the efficacy of oral cannabinoid ingestion, aiming to investigate the efficacy of smaller doses of THC and higher doses of CBD. It was again a double blind placebo controlled study in which patients with active Crohn's disease were given cannabis oil with a ratio of CBD:THC of 4:1. The study included 46 patients, 23 in each group, 31 males (62%). Average age was 35 ± 12. CDAI before the treatment was 288.4 ± 78.0 and 298.5 ± 112.2. After eight weeks of treatment the CDAI was 143.1 ± 96.0 and 209.5 ± 113.0 in the cannabis and placebo groups, respectively (p < 0.05). Remission (CDAI <150) was achieved in 65% of the cannabis group and 35% of the placebo group. Median quality of life score after 8 weeks was 90.1(IQR 83–102) in the cannabis group and 76 (IQR 68–92) in the placebo group (p < 0.05). CRP before treatment was 3.1 ± 4.4 mg/dl and 3.6 ± 5.4 mg/dl, after treatment it was 2.4 ± 8 mg/dl and 4.1 ± 8.8 mg/dl in the cannabis and placebo groups, respectively (p = 0.40). Calprotectin before treatment was 182 ± 133 and 122 ± 91, after treatment it was 170 ± 115.6 and 137 ± 115 in the cannabis and placebo groups, respectively (p = 0.76). SES-CD was 9.5 ± 6.5 and 11.9 ± 6 before treatment and 7.17 ± 6 and 9.8 ± 5.4 after treatment in the cannabis and placebo groups, respectively (p = 0.17) [36,37].

1.5. Adverse effects

The popular opinion is that cannabis is a harmless substance, inducing pleasure and tranquility, and access to it should not be regulated or considered illegal. In reality, cannabis is not devoid of adverse effects. First and foremost, long-term cannabis use can lead to addiction. Indeed, approximately 9% of those who experiment with marijuana will become addicted [38] Cannabis withdrawal syndrome was indeed described, with symptoms that include irritability, sleeping difficulties, dysphoria, craving, and anxiety [39]. The regular use of cannabis in adolescents was shown to impaired neural connectivity in specific brain regions [40,41]. Imaging studies in persons who use cannabis regularly from an early age revealed decreased activity in prefrontal regions and reduced volumes in the hippocampus [42]. Exposure to cannabis impairs driving ability; and poor performance in controlled driving-simulation studies was correlated with blood THC levels [43].

Most cannabis users prefer to use it by smoking, and many mix it with tobacco. Although the effect of cannabis on lung cancer is difficult to separate from the effect of tobacco, there is ample evidence that cannabis smoking causes chronic bronchitis and increased rates of respiratory infections and pneumonia [44]. Cannabis use may also impair cognitive function; consequently, academic achievements of students who use cannabis regularly could deteriorate [45].

Cannabis can induce hyperemesis, producing the Cannabinoid hyperemesis syndrome (CHS) which presents with cyclical emetic episodes and compulsory hot bathing [46]. In a study examining hospital discharge data before and after the U.S. Department of Justice liberalization of cannabis use in 2009, the authors demonstrated a significant increase in the diagnosis of cannabis dependency (17.9%) and persistent vomiting (8%) [47]. This study illustrates how cannabis liberalization is proceeding without addressing the possible effect on public health.

2. Conclusion

Cannabis use among IBD patients is common and anecdotal evidence seems to demonstrate that it may be beneficial. However, good quality randomized controlled studies are needed to further explore the question as to whether the observed benefit of cannabis reflects symptomatic improvement or a real effect on inflammation. The results of these studies will determine whether cannabis will have a future role in the treatment of IBD.

3. Expert opinion

Current treatment of Crohns disease is unsatisfactory as only 40–60% of patients are responding [48]. If cannabis treatment has any potential, we simply cannot afford to ignore it.

The endocannabinoid system (ECS) has an important physiological role in modulating GI function, therefore, the possibility of developing treatment options that are based on ECS manipulation has a sound basis. Many studies in laboratory and animal models indicated that stimulating the ECS can ameliorate IBD. Randomized controlled studies are needed to provide the missing link between laboratory models and human disease. Unfortunately, the studies conducted thus far are small, and although they clearly indicate that cannabis induces clinical improvement in Crohns disease they do not demonstrate an objective improvement of markers of inflammation or endoscopic findings. It is paramount that well-designed RCTs with larger sample sizes be conducted to explore the therapeutic potential of cannabis based treatment.

Cannabis research is at a very early stage and there are still many questions to be answered. We need to better understand cannabis mode of action, to learn which cannabinoids or cannabinoids combinations are the most effective ones, and which doses are required. Since the smoking of cannabis is associated with chronic bronchitis symptoms and large airway inflammation [49] we need to develop modes of cannabis

consumption other than smoking. The current diversity and instability of cannabis products is not acceptable when providing medical treatment. Once we know which cannabinoids (or their combinations) are most effective, we will have to manufacture products at a pharmaceutical quality. Cannabis is a psychoactive drug that may induce addiction, but many cannabinoids such as CBD and CBG do not have a psychoactive effect. Research should focus on these cannabinoids in the hope that they will show anti–inflammatory activity without the undesirable central effect. Not less important is the monitoring of safety and side effects.

Cannabis research is blocked by many factors: cannabis is a schedule 1 drug and as such its use in clinical trials is limited. The medical community, quite rightly, refuses to adopt a treatment with so little evidence. Public opinion, on the other hand, regards the anecdotal data as a sound evidence of the efficacy of cannabis for the treatment of almost anything. The growing legitimacy of cannabis and the legalization of its use in many states created the current anomaly that, despite the lack of sound evidence, patients can get cannabis to treat their disease, but physicians cannot conduct proper research to investigate potential therapeutic uses.

Another inherent difficulty lies in the diversity of cannabis products. There are about 100 different cannabinoids, and they need to be tested for their possible effects. Other components of the cannabis plant also need to be tested, and then their various combinations with possible synergism between them will need to be investigated. This is obviously a huge task but if the effective cannabinoids will be identified and isolated, then we will be able to produce cannabis based medicine.

Cannabis research will continue, and hopefully will lead to the addition of another treatment option for Crohn's disease.

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Declaration of Interest

T Naftali is a consultant to STERO Biotechnology, a company that supplies CBD for medical use. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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