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USE OF CANNABINOIDS IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE: A REVIEW OF CLINICAL AND INTERVENTION STUDIES

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ABSTRACT

Introduction: Inflammatory bowel disease (IBD) is a general term used to describe a group of chronic inflammatory diseases of the gastrointestinal tract with complex etiologies. They mainly include Crohn's disease (CD) and ulcerative colitis (UC) .
Purpose of the work: The purpose of this paper is to present current knowledge on the use of cannabinoids in the treatment of inflammatory bowel disease, with a particular focus on their impact on patient well being.
Material and methods: The study is based on a review of the scientific literature, including clinical and experimental studies on the effects of cannabinoids on the gastrointestinal tract and their use in the treatment of IBD.
Results: The endocannabinoid system (ECS) plays an important role in modulating many physiological processes, including maintenance of intestinal homeostasis, regulation of intestinal function, visceral sensation, modulation of gastrointestinal motility and immunomodulation of inflammation in IBD. Studies have shown that their use leads to a reduction in abdominal pain, emotional distress, stool frequency and anorexia nervosa. They also found higher rates of depression, smoking and alcohol consumption among IBD patients who used cannabis. The long-term safety profile of cannabinoids in IBD patients has not been established.
Summary: Cannabinoids have the potential to be effective supportive therapies for inflammatory bowel disease, but more research is needed to determine their long-term safety and optimal dosage.

KEYWORDS

Cannabinoids, Inflammatory Bowel Disease, Endocannabinoids, Crohn's Disease, Ulcerative Colitis

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Literature review

Inflammatory bowel disease (IBD) is a general term used to describe a group of chronic inflammatory diseases of the gastrointestinal tract with complex etiologies. They mainly include Crohn's disease (CD) and ulcerative colitis (UC). [1] These are relapsing-remitting diseases characterized by chronic inflammation of the gastrointestinal tract, accompanied by impaired epithelial integrity, excessive macrophage intrusion and an increased risk of developing colorectal cancer in the future. These diseases affect millions of people around the world and are considered global diseases with increasing prevalence, generating high health costs and significantly reducing the quality of life of patients . [1][2]

IBD is a chronic disease that can reduce patients' quality of life and is correlated with comorbidities outside the gut, such as cardiovascular disease, osteoporosis, arthritis and increased risk of cancer. IBD symptoms can be further exacerbated by stress and psychiatric illnesses such as depression and anxiety. [3]

Although current medications significantly help control the disease, many people have begun to use complementary therapies because of the belief that they are natural and safe, and because of the side effects of current medications. Cannabinoids are among the most commonly used complementary medications incorporated into treatment somatically by IBD patients. However, these behaviors can have undesirable and toxic effects due to unintended interactions with drugs or enzymes that metabolize the drugs used. [2]

Materials and methods

An extensive literature review was conducted using PubMed, Google Scholar and Scopus to assess the potential benefits of cannabinoids in the treatment of inflammatory bowel disease. The research focused on both human and animal studies and included a range of sources, including meta-analyses, observational studies and randomized controlled trials.

Keywords such as "cannabinoids," "inflammatory bowel disease," "IBD," "endocannabinoids," and "Crohn's disease," "ulcerative colitis" were the target of the search process. The collected studies were analyzed on the basis of their results regarding efficacy, safety, effect on symptoms and improvement of patients' quality of life.

ESC basic information

The endocannabinoid system (ECS) plays an important role in modulating many physiological processes, including maintenance of intestinal homeostasis, regulation of intestinal function, visceral sensation, modulation of gastrointestinal motility, neuroprotection and immunomodulation of inflammation in IBD. [1]

The key role that the ECS plays in maintaining the integrity of the intestinal barrier is complex and multifaceted, as it responds to both internal (microbial) and external (diet, stress, etc.) environmental factors, while also serving as a homeostatic effector system. [4] The ESC is composed of cannabinoid receptors (CB1 and CB2), endogenous bioactive lipids (anandamide and 2-arachidonoylglycerol), enzymes responsible for their synthesis and degradation (fatty acid amide hydrolase and monoacylglycerol lipase) transporters for cellular uptake of endocannabinoid ligands, whose manipulation through antagonists and agonists of the system shows a potential therapeutic role for ECS in inflammatory bowel disease. [4] [5] [6] [7]

Cannabinoids can promote Th2-related IL-4 and IL-10 production by inhibiting the release of pro inflammatory factors such as IL-1, IL-12, TNFα and interferon (INF)-G from monocytes in peripheral blood and intestinal tissues. Moreover, they can inhibit interleukin-6, a pro inflammatory cytokine produced by many cell types, as well as inhibit the production of interleukin-8 by activated B lymphocytes, which may have anti-inflammatory effects and potential therapeutic value in many autoimmune disorders. [1]

Although the biological mechanisms still need to be thoroughly elucidated, these functions appear to be related to the ability of the ECS to inhibit immune cell proliferation, cytokine shedding, reactive oxygen species, and nitric oxide release. [1] [3] Cannabinoid receptors CB1 and CB2 have been shown to influence a wide range of physiological functions. Considering its role in regulating inflammation, pain, memory, mood and other functions. The endocannabinoid system has been extensively studied for its potential therapeutic applications in the treatment of various diseases. [8]

Inflammatory bowel disease and cannabinoids review of current research

It has been suggested that many factors are involved in the development of IBD, including environmental and immunological factors that interact to disrupt the gastrointestinal immune system, genetic susceptibility, and the microbiome. [6] [3]

The gut microbiota is a critical environmental factor influencing gut physiology.and gut neuron control mechanisms. Microbial dysbiosis is associated with disruption of epithelial barrier function and, as a result, with both local gastrointestinal diseases, such as IBD, and various systemic conditions, such as diabetes and obesity. Research into the regulation of the ECS by the gut microbiome is at an early stage, but results have emerged that support the general hypothesis that the ECS regulates gut homeostasis through interactions with the microbiota [3]. It has been shown that a dysregulated endocannabinoid system can lead to inflammatory bowel disease and colorectal cancer. [5]

Although pharmacological treatment with aminosalicylates, corticosteroids, immunosuppressants and biologic agents is now fairly well developed, all indications for each type of therapy are related to the individual course of the disease and how patients tolerate the treatment. [1] The current therapeutic goals in treating patients with IBD are to eliminate symptoms, improve quality of life, reduce inflammation and prevent complications. [9] [11]

The use of pharmacological agents is associated with unwanted side effects, which is particularly difficult and important due to the long-term use in the treatment of IBD. More than half of IBD patients qualify for long-term immunosuppressive therapy. Current immunosuppressive therapies are associated with a number of long-term risks, including increased cancer risk, loss of immune tolerance, decreased bone density and increased fracture risk. These negative consequences underscore the significant need for the development of highly innovative IBD therapies. [1]

A substantial body of evidence from in vitro and in vivo studies has shown that cannabinoids and endocannabinoid degradation inhibitors exhibit anti-inflammatory, anti-tumor antioxidant, and anti-fibrotic properties with potential beneficial effects. [8]

Cannabinoids exert immunosuppressive effects mainly by inhibiting cell proliferation, suppressing the production and activation of cytokines and chemokines, and inducing apoptosis. At the same time, they have been shown to activate T lymphocytes, induce Treg cells to suppress cytokine production and reduce B lymphocyte activity, and ultimately prevent the inflammatory response in vivo. [1] [3] [5] [10]

It has been shown through experimental animal models of colitis that cannabinoids can be used as alternative agents to prevent or minimize the severity of experimental colitis. [11]

Preclinical studies have shown that cannabinoids have a strong protective function. Several in vitro studies have shown that CB1 and CB2 receptor agonists reduce experimentally induced intestinal inflammation. At the same time, their antagonists exacerbated inflammatory processes. Stintzing et al. revealed that the CNR1 gene encoding the CB1 receptor showed significant up-regulation, especially in CD patients. Endocannabinoids have a high potential to repair cytokine-induced damage in colitis and most likely, other inflammatory conditions in the gastrointestinal tract. [10]

The most extensive and comprehensive study of the use of cannabinoids in IBD patients is that of Grill et al, who demonstrated altered plasma endocannabinoid levels in IBD and distinct transcript profiles in UC and CD. Clinical studies described by Carvalho et al. have investigated the effects of cannabinoid ligands and the impact of blocking their metabolizing enzymes on intestinal inflammation, and have shown considerable hope at the preclinical level in the treatment of IBD. [1]

Naftali and colleagues conducted a randomized, controlled trial evaluating objective and clinical disease outcomes in patients with Crohn's disease using cannabis. The primary outcome of this study was induction of clinical remission after 8 weeks of treatment, and there were several secondary endpoints with objective disease assessment. There were no significant differences in biochemical assessments, including CRP and hemoglobin levels. All patients were able to discontinue steroid therapy during the study. Cannabis use was associated in patients with a reduction in abdominal pain and improved quality of life scores. However, all patients experienced clinical relapse within 2 weeks of cannabinoid withdrawal. [12]

A randomized controlled trial of medical marijuana in the treatment of Crohn's disease in Israel showed a reduction in the need for other drugs and surgery in patients taking cannabinoids. 90% of patients taking cannabinoids showed a decrease in the rate of Crohn's disease activity. 25% of patients were able to discontinue corticosteroid treatment. In addition to significant improvements in quality of life, pain scores and appetite, there was no improvement in markers, i.e. C-reactive protein (CRP) . [11]

Lal et al. conducted a study on 100 patients with ulcerative colitis (UC) and 191 patients with Crohn's disease taking cannabis Patients cited relief of symptoms such as diarrhea and abdominal pain, as well as increased appetite as benefits of cannabinoids. [12] Storr et al. drew similar conclusions in their study. One potentially troubling finding from their study was that CD patients who consumed cannabis for more than 6 months were more likely to need surgery. One possible explanation is that cannabis use masks symptoms that may be early signs of worsening inflammatory processes in the disease, causing patients to delay treatment. [13] [14] [15]

In a population-based cohort study, Mbachi et al. showed that cannabinoid use of Canabis sativa in patients with UC was associated with a reduced incidence of constipation and length of hospital stay compared to non-users. [16]

Lahat and colleagues conducted an uncontrolled observational study of IBD patients refractory to conventional therapy. Patients reported significant improvements in general well-being, social functioning, ability to work, depression and pain levels. In addition, patients noted improvements in disease-specific symptoms as measured by the Harvey Bradshaw Index (HBI), including abdominal pain and loose stools. Although there was no improvement in objective measures of disease, such as C-reactive protein levels, patients were able to gain weight. [13] [16]

In the meta-analysis performed by Kang et al. no differences were observed in the analysis regarding endoscopic disease activity and inflammatory markers. The researchers suggested that cannabinoids are associated with improved quality of life in both CD and UC, as well as with improved disease activity, but not with reduced inflammation. [17]

A randomized controlled trial on ulcerative colitis, in which patients with various stages of ulcerative colitis were randomly assigned to a group receiving a once-daily oral capsule containing 50 mg of CBD from a plant extract or a placebo for 10 weeks, found that CBD extract was not well tolerated. Patients reported reductions in abdominal pain, emotional distress, bowel frequency and anorexia. However, higher rates of depression, smoking and alcohol consumption were found among IBD patients who used cannabinoids. [9] [11]

Clinical studies suggest that cannabinoid therapy may play a therapeutic role in the treatment of IBD, nausea, vomiting and gastrointestinal motility disorders, especially in patients with severe disease and refractory to traditional drugs. The therapeutic anti-inflammatory effects of cannabinoids in IBD have yet to be precisely defined. [10] [18] The long-term safety profile of cannabinoids in patients with IBD has not been established. Current studies, describe common side effects, including headache, drowsiness, nausea and dizziness. [9] It is believed that cannabinoids may also mask many other debilitating effects. Therefore, there is a need for double-blind, randomized, placebo-controlled trials using serial markers of inflammation, biopsy

results and endoscopic disease severity to demonstrate objective improvement in IBD. [11][12][19] It seems inevitable that research will be directed toward finding better synthetic cannabinoids with full agonist activity and increased affinity for both CB1 and CB2 receptors, as well as a higher therapeutic window. However, the rapidly increasing number of reported side effects and poisonings must be given special consideration and special emphasis must be placed on further research and registration of these compounds. [20]

Studies suggest a strong link between changes in endocannabinoid levels and gastrointestinal diseases. Elevated endocannabinoid levels and increased CB receptor expression raise the possibility of both diagnostic and therapeutic applications. Cannabinoids show promise in the treatment of a variety of gastrointestinal disorders; however, conflicting results in some clinical trials on their effects highlight the need for further research. [10]

Applications

Because of the role of ECS in modulating inflammation, there is considerable interest in the therapeutic potential of cannabinoids for the treatment of autoimmune diseases, including inflammatory bowel disease. [21]

Although the results of the study are optimistic, further research is needed to precisely determine the mechanisms of action of cannabinoids. Therefore, further research is also needed on the optimal dosage and long-term safety of its use in different patient groups. [21] [22] Given the various drawbacks and limitations of available treatments for IBD, it is important to develop new pharmacological alternatives for the treatment of UC and CD. In this context, cannabinoids may be a good pharmacological strategy for the treatment of IBD due to the various functions of the ECS in maintaining intestinal homeostasis and the anti-inflammatory effects observed by positive regulation of this system in animal and human models.

DISCLOSURE

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