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Potential use of nanoencapsulated cannabinoids for the treatment of inflammatory bowel diseases: a systematic review

Uso potencial de canabinóides nanoencapsulados para o tratamento de doenças inflamatórias intestinais: uma revisão sistemática

Uso potencial de cannabinoides nanoencapsulados para el tratamiento de enfermedades inflamatorias del intestino: una revisión sistemática

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Abstract
Introduction: Inflammatory Bowel Disease (IBD) are diseases characterized by intestinal inflammation, divided into Crohn's Disease (CD) and Ulcerative Retrocolitis (UC). The cause is still unknown. There are a variety of studies that show the beneficial and potential effect of phytocannabinoids on Inflammatory Bowel Disease. Objective: To evaluate the beneficial effect of *Cannabis sativa*-derived metabolites in the treatment of IBD, associated with the use of nanotechnology in order to enhance this effect, through a systematic review study. Methodology: This systematic review of the literature of pre-clinical and clinical trials was carried out in the following databases: PUBMED, Science Direct and Scopus from 2012 to 2022. Some combinations of terms were used, such as inflammatory bowel diseases, cannabinoids, cannabidiol and nanotechnology. Results: A total of 418 articles were found in Pubmed, 80 articles in Science Direct and 443 in Scopus. In the end, 6 articles in Pubmed, 10 in Science Direct and 6 in Scopus were considered eligible for analysis according to the established inclusion and exclusion criteria. Discussion: In the analyzed studies, it was noticed that phytocannabinoids represent a promising alternative to treat IBD. Despite the great expectations surrounding these molecules, their physicochemical characteristics represent a significant limitation for their application in the treatment of IBD and other diseases. Therefore, nanotechnology proved to be a way to overcome these problems. Conclusion: In view of all the above, it can be inferred that metabolites derived from *Cannabis sativa* have great potential for the treatment of inflammatory bowel diseases.
Keywords: Inflammatory bowel disease; Cannabinoids; *Cannabis sativa*; Nanotechnology.

Resumo

Introdução: As Doenças Inflamatórias Intestinais (DII) são doenças caracterizadas por inflamação intestinal, dividida em Doença de Crohn (DC) e Retrocolite Ulcerativa (UC). A causa ainda é desconhecida. Há uma variedade de estudos que mostram o efeito benéfico e potencial dos fitocanabinoides na Doença Inflamatória Intestinal. Objetivo: Avaliar o efeito benéfico dos metabólitos derivados da *Cannabis sativa* no tratamento de DII, associado ao uso da nanotecnologia com o intuito de potencializar esse efeito, por meio de um estudo de revisão sistemática. Metodologia: Esta revisão sistemática da literatura de ensaios pré-clínicos e clínicos foi realizada nas seguintes bases de dados: PUBMED, Science Direct e Scopus de 2012 a 2022. Utilizou-se algumas combinações de termos como, doenças inflamatórias intestinais, canabinoides, canabidiol e nanotecnologia. Resultados: Foram encontrados um total de 418 artigos no Pubmed, 80 artigos no Science Direct e 443 no Scopus. Ao final, 6 artigos no Pubmed, 10 no Science Direct e 6 no Scopus foram considerados elegíveis para análise de acordo com a inclusão e exclusão critérios estabelecidos Discussão: Nos estudos analisados, percebeu-se que os fitocanabinóides representam uma alternativa promissora para tratar DII. Apesar das grandes expectativas em torno dessas moléculas, suas características físico-químicas representam uma limitação significativa para sua aplicação no tratamento de DII e outras doenças. Portanto, a nanotecnologia provou ser uma forma de superar esses problemas. Conclusão: Diante de todo o exposto, pode-se inferir que metabólitos derivados da Cannabis sativa possuem grande potencial para o tratamento de doenças inflamatórias intestinais.

Palavras-chave: Doenças inflamatórias intestinais; Canabinoides; *Cannabis sativa*; Nanotecnologia.

Resumen

Introducción: Las Enfermedades Inflamatorias Intestinales (EII) son enfermedades caracterizadas por inflamación intestinal, divididas en Enfermedad de Crohn (EC) y Retrocolitis Ulcerosa (CU). La causa aún se desconoce. Hay una variedad de estudios que muestran el efecto beneficioso y potencial de los fitocannabinoides en la enfermedad inflamatoria intestinal. Objetivo: Evaluar el efecto beneficioso de los metabolitos derivados del Cannabis sativa en el tratamiento de la EII, asociado al uso de nanotecnología para potenciar este efecto, a través de un estudio de revisión sistemática. Metodología: Esta revisión sistemática de la literatura de ensayos preclínicos y clínicos se realizó en las siguientes bases de datos: PUBMED, Science Direct y Scopus de 2012 a 2022. Se utilizaron algunas combinaciones de términos, como enfermedades inflamatorias del intestino, cannabinoides, cannabidiol y nanotecnología. Resultados: Se encontraron un total de 418 artículos en Pubmed, 80 artículos en Science Direct y 443 en Scopus. Al final, 6 artículos en Pubmed, 10 en Science Direct y 6 en Scopus fueron considerados elegibles para el análisis de acuerdo con los criterios de inclusión y exclusión establecidos Discusión: En los estudios analizados, se observó que los fitocannabinoides representan una alternativa prometedora para tratar la EII. A pesar de la gran expectativa que rodea a estas moléculas, sus características fisicoquímicas suponen una importante limitación para su aplicación en el tratamiento de la EII y otras enfermedades. Por lo tanto, la nanotecnología demostró ser una forma de superar estos problemas. Conclusión: Por todo lo anterior, se puede inferir que los metabolitos derivados del Cannabis sativa tienen un gran potencial para el tratamiento de enfermedades inflamatorias intestinales.

Palabras clave: Enfermedades inflamatorias intestinales; Cannabinoides; *Cannabis sativa*; Nanotecnología.

1. Introduction

Inflammatory Bowel Disease (IBD) is part of a group of autoimmune, chronic diseases whose etiology is unknown (Vasconcelos et al., 2018). IBD is a disease characterized by intestinal inflammation, divided into Crohn's Disease (CD), which presents a discontinuous transmural inflammation, affecting the gastrointestinal tract, and Ulcerative Colitis (UC), in which it is restricted to the intestinal mucosa (Fernandes & Gil, 2019).

The pathogenesis of CD and UC involves a dysregulated immune response to the commensal microbiota in genetically susceptible individuals (Kaplan; Ng, 2017). Both disorders are conditions that are characterized by histological chronic inflammation and compromised quality of life, as the symptoms of CD and UC include inflammation, diarrhea, abdominal pain, rectal bleeding, and weight loss, as well as can occur in adolescents and adults, in addition to affecting all sexes (Seyedian; Nokhostin, 2019; Hazel et al., 2020).

CD involves the terminal ileum, cecum, perianal area and colon, but it can affect other regions of the intestine. UC, in turn, affects the rectum and part of the colon or the entire colon. The cause of the disease is still unknown, however, recent studies present evidence that the pathogenesis is related to genetic susceptibility, intestinal microbiota, environmental factors and immunological abnormalities (Guan, 2019).

Regarding treatment, the literature suggests that the inflammatory pathway with the greatest number of studies is dependent on the pro-inflammatory tumor necrosis factor-alpha (TNF-α), through the action of TNF-α. However, currently, new drugs have been developed that include the agents that target leukocyte trafficking, Interleukin (IL) 23, Janus kinases (JAK), Sphingosine 1 phosphate (S1P) and Smad7, an inhibitor of Immunosuppressants cytokines transforming growth factor β1 (TGF-β1) (Argollo et al., 2017).

Furthermore, there are a variety of studies showing the beneficial effect and potential of cannabidiol in Inflammatory Bowel Disease (Picardo et al., 2019; Ambrose; Simmons, 2019; Hoffenberg et al., 2019; Carvalho et al., 2020; Perisetti et al., 2020; Kienzl et al., 2020; Bogale et al., 2021).

According to Picardo et al. (2019), several studies prove that cannabinoids improve intestinal inflammation through their interaction with the endocannabinoid system, being effective in symptomatic management. Carvalho et al. (2020) demonstrate that the use of Cannabis sativa leads to the improvement of symptoms of Crohn's disease and Ulcerative Colitis (UC) due to antioxidant and anti-inflammatory effects.

In this context, given that several studies have shown the potential for the use of cannabis as a potential drug for inflammatory conditions, this is study to evaluate the beneficial effect of *Cannabis sativa* derived metabolites in the treatment of IBD, associated with the possible role of nanotechnology in improving this effect, through a systematic review study.

2. Methodology

This systematic literature review of randomized controlled trials (RCTs) was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations (moher, 2019).

Was based on published research in the last ten years on the use of nanotechnology-based cannabinoid derivatives in inflammatory bowel disease. The electronic search strategy is using the following keywords inflammatory bowel disease and cannabidiol and nanoparticles Studies considered eligible were as follows: open-label or double-blind randomized controlled studies and including preclinical *in vivo* studies about on the use of nanotechnology-based cannabinoid derivatives in inflammatory bowel disease.

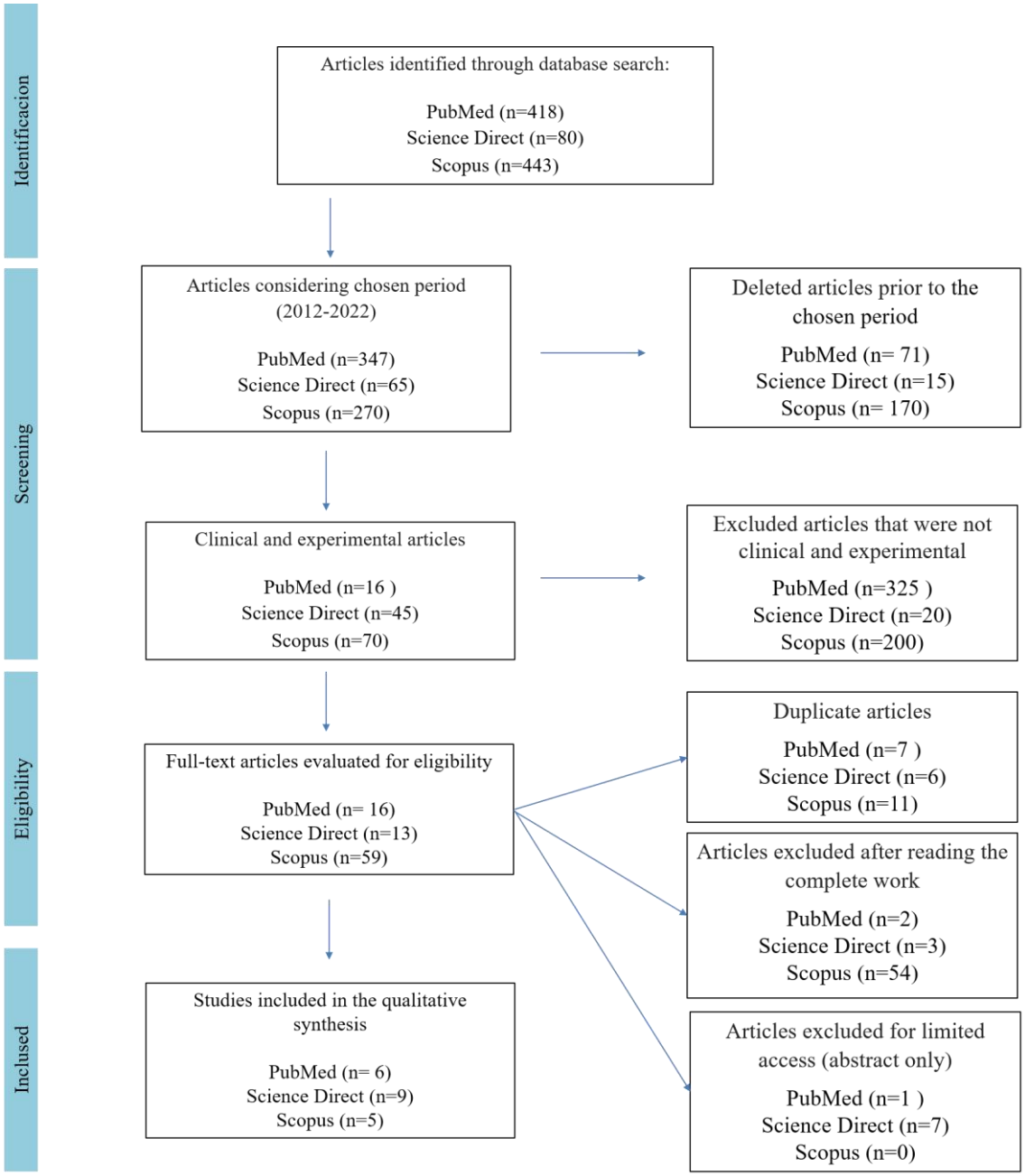
The following databases: PUBMED, Science Direct and Scopus from 2012 until 2022, in English.Original research papers and reviews were searched using combinations of the grouped search terms: (((cannabinoids) OR (cannabidiol)) OR (THC)) AND (nanoparticles OR nanotechnology) AND (inflammatory bowel disease) in diferents combinantion. A manual search based on references of the selected articles was performed.

A data extraction table was used to extract data of the eligible studies and to systematically describe study characteristics, such as study design. The articles were initially, by reading the titles and abstracts. After the initial screening, the studies were analyzed in their entirety, based on a reading of the complete studies, which were classified as a table of studies that met the eligibility criteria.

3. Results

A total of 418 articles in Pubmed, 80 articles in Science Direct and 443 in Scopus were found through a database search. Considering the exclusion criteria as articles prior to the year 2012, articles that were not clinical and experimental, the search resulted in 16 articles in PubMed, 13 articles in Science Direct and 59 articles in Scopus. Removing duplicate articles, those for which full access was not possible and those that were not part of the chosen theme, the search resulted in 6 articles for Pubmed, 9 for Science Direct and 5 for Scopus that were considered eligible for analysis according to the study inclusion and exclusion criteria chosen (Figure 1).

Figure 1. Flowchart of article selection (*Prisma Flow*).



Source: Prepared by the authors (2022).

In the flowchart represented above, you can first observe the total number of studies found in all databases, plus the different combinations of keywords. This total number of studies was filtered by year (2012-2022) and by those that fit as experimental or clinical research. Of this remaining number, duplicate articles were discarded, as well as those for which access could not be obtained. After a complete reading of the selected articles, some were also discarded because they did not fit the scope of the research. Finally, the actual number of articles selected for the production of this systematic review can be observed (Table 1).

Table 1. Main results of the studies found.

Author	Year	Main results
(Singh et al., 2018)	2018	This study demonstrated the applicability of *C. sativa* extracts for rapid and economical green synthesis of nanoparticles, some of which can be effectively used against biofilm formations: F-AuNPs, C-AuNPs, C-AgNPs.
(Silvestri et al., 2020)	2020	Fish oil and CBD co-administered at *per se* ineffective doses reduce colon inflammation, in a manner potentially strengthened by their independent elevation of *Akkermansia muciniphila*.
(Pagano et al., 2021)	2021	The combination of FO, CBD, and a per se inactive dose of CBG resulted in intestinal anti-inflammatory effects, and FO did not alter phytocannabinoid levels in the serum and in the colon.
(Nallathambi et al., 2017)	2017	The CBD shows dose dependent cytotoxic activity, anti-inflammatory activity was found only for the low concentration of CBD. Activity of the extract and active fraction was verified on colon tissues taken from IBD patients, and show suppress COX2 and MMP9 gene expression in both cell culture and colon tissue.
(Cocetta et al., 2021)	2021	The CBD as the most promising compound against intestinal inflammatory condition, is able to inhibit ROS production and restore epithelial permeability during inflammatory and oxidative stress conditions.
(Couch et al., 2019)	2019	Cannabidiol and palmitoylethanolamide reduce permeability in the human colon. These findings have implications in disorders associated with increased gut permeability, such as inflammatory bowel disease.
(Irving et al., 2018)	2018	This study suggested that CBD-rich botan- ical extract may have provided therapeutic benefit to those patients who tolerated it. These findings should be interpreted with caution given the multiple limitations of this study, but they encourage future studies to look at CBD-rich botanical extract.
(Tartakover Matalon et al., 2021)	2021	The study supports the notion that cannabis use affects eCB "tone" in UC patients and may have beneficial effects on disease symptoms in UC patients.
(Naftali et al., 2013)	2013	Complete remission was achieved by 5/11 subjects in the cannabis group and 1/10 in the placebo group. A clinical response was observed in 10/11 subjects in the cannabis group and 4/10 in the placebo group. Subjects receiving cannabis reported improved appetite and sleep, with no significant side effects.
(Naftali et al., 2017)	2017	This study failed to show a beneficial effect of low-dose cannabidiol in Crohn's disease. One should probably use higher doses of cannabidiol, use well-characterized plant extracts rather than isolated compounds, and look for objective measures of disease activity.
(Naftali et al., 2021)	2021	Short term treatment with THC rich cannabis induced clinical remission and improved quality of life in patients with mild to moderately active ulcerative colitis. However, these beneficial clinical effects were not associated with significant anti-inflammatory improvement in the Mayo endoscopic score or laboratory markers for inflammation.
(Wang et al., 2022)	2022	WP coating improved the encapsulation efficiency of CBD molecule and re-dispersibility of the lyophilized nanoparticles. Compared with zein nanoparticles, zein-WP nanoparticles were more effective in protecting CBD against UV and thermal treatment and during storage at 4 ◦C for 21 days. The antioxidant activity and in vitro release of CBD were improved by encapsulating in zein-WP nanoparticles.
(Becker et al., 2020)	2020	The study shows that delta-9-tetrahydrocannabinol (THC) attenuates colitis-associated colon cancer and anti-CD40-induced colitis. Working through the cannabinoid receptor 2 (CB2), THC increases CD103 expression on DCs and macrophages and up-regulates TGF-b1 to increase regulatory T cells (Tregs). By examining tissues from various sites, it was confirmed that THC affects DCs, especially at mucosal barrier sites in the colon and lungs, to reduce CD86 DC.
(Borelli et al., 2013)	2013	CBG attenuated murine colitis, reduced nitric oxide production in macrophages (effect being modulated by the CB2 receptor) and reduced ROS formation in intestinal epithelial cells. CBG could be considered for clinical experimentation in IBD patients.
(Martín-Banderas et al., 2014)	2014	He preparation procedure reported significant entrapment efficiencies along with slow drug release properties. In addition, surface functionalization of the NPs was satisfactorily accomplished with PEG moieties to assure the highest cellular uptake and to minimize protein adsorption. In fact, in vitro results confirmed the improved cell uptake of PEG-PLGA NPs and, interestingly, their antiproliferative (anticancer) efficacy over the free drug.
(Harvey et al., 2014)	2014	IL-17A has a widespread distribution in the human colon and the capacity to elicit mucosal damage which can be attenuated by cannabinoid ligands.
(Matarazzo et al., 2021)	2021	In-situ gelling hydrogels are not suitable vehicles for highly lipophilic drugs such as CBD, while cationic CBD-NLC dispersions are promising formulations for the nasal administration of CBD.
(Hoffenberg et al., 2018)	2018	Marijuana use by adolescents and young adults with IBD is common and perceived as beneficial. Guidelines for screening, testing, and counseling of marijuana use should be developed for patients with IBD.
(Pagano et al., 2019)	2019	CBDV lessens cytokine expression in colonic biopsies from pediatric patients with ulcerative colitis, a condition in which TRPA1 was up-regulated. This preclinical study shows that CBDV exerts intestinal anti-inflammatory effects in mice via TRPA1, and in children with active UC.

Dunfor and Morgan (2021)	2021	No antinociceptive effect of THC was evident when administered 1 day after TNBS. In fact, administration of THC prolonged TNBS-induced depression of wheel running for over 5 days in adolescent and adult rats. These results show that home cage wheel running is depressed by TNBS-induced IBD, making it a useful tool to evaluate the behavioral consequences of IBD, and that administration of THC, instead of producing antinociception, exacerbates TNBS- induced IBD.

Source: Prepared by the authors (2022).

4. Discussion

Current statistics suggest that there is an increase in the incidence and prevalence of IBD. Given the time scale, it is unlikely that the genetic factor is directly related. Thus, the interaction with external factors must be considered as the most likely. The environment, the interaction of the organism with commensal microorganisms and the immune system itself are some examples (Becker et al., 2020).

There are several therapeutic proposals for the treatment and relief of symptoms related to IBD. Phytocannabinoids, natural molecules derived from the botanical species *Cannabis sativa*, are some of the most studied alternatives currently to treat IBD. Modulation of the endocannabinoid system has shown great promise for IBD in preclinical models and small cohort studies in humans (Wang et al., 2022).

However, the current evidence is still superficial and requires greater robustness from the methodological point of view. Retrospective studies and some reports have shown that the use of cannabis in patients with IBD for symptom relief is common. In addition, there are also prospective studies that reported an improvement in the quality of life of patients with CD and UC after treatment with inhaled cannabis (Borreli et al., 2013).

The randomized, double-blind study by Irving et al. (2018) in patients with ulcerative colitis, 75 patients were recruited and 39 were able to complete the study. The efficacy and safety of the investigational drug of cannabidiol-rich botanical extract in patients with mild to moderate ulcerative colitis refractory to 5-amino-salicylic acid therapy for 10 weeks was evaluated. Despite the limitations of the study, mainly related to low tolerance and short treatment, the results indicated a potential beneficial effect for the symptoms of ulcerative colitis, the quality-of-life analysis showed a better response for patients who used the botanical extract rich in cannabidiol.

According to Couch et al., (2019) in a randomized, double-blind, controlled trial, healthy male patients (18-50 years) were treated with oral cannabidiol (CBD) and the change in intestinal permeability was measured by a test of absorption of lactulose and mannitol with 600 mg of aspirin. Aspirin increased the urinary lactulose mannitol ratio, suggesting an increase in intestinal permeability, which was avoided by CBD showing the potential role of clinical use in IBD.

Furthermore, samples of human colonic mucosa collected from intestinal resections were experimentally inflamed and the result indicated a decrease in claudin-5 mRNA expression in response to inflammation and that this change was prevented by CBD treatment. Inflammation caused an inflammation-induced drop in transient vanilloid receptor 1 (TRPV1) mRNA and increase in proliferator-activated receptor (PPARα) transcription prevented by CBD. In this way, potential anti-inflammatory, and permeability-reducing effects in the gastrointestinal tract by cannabidiol have been demonstrated, which is considered to hold significant promise for the development of future intestinal therapies such as IBD, requiring phase 1 and phase 2 clinical studies. Similar results from Tartakover Matalon et al., 2021 on blood samples and biopsies from patients with IBD showed that cannabis treatment influences endocannabinoid levels and presents possible beneficial effects for the pathology.

Naftali et al., 2013 in a prospective study with 21 patients with a mean age of 40±14 years, 13 males, 11 established Crohn's disease study group, Crohn's Disease Activity Index (CDAI) between 200 and 450 points and that do not respond to therapy with steroids, immunomodulators or anti-tumor necrosis factor agents and 10 placebo group. Patients received cannabis twice daily in the form of cigarettes (11.5 mg of tetrahydrocannabinol (THC)) or placebo (cannabis flowers). After 8 weeks of

treatment, we showed a clinical improvement in 10/11 patients, a significant decrease of 100 points in the CDAI in the group that used cannabis rich in THC, about 90%, 10 subjects. Individuals in the cannabis group showed improved quality of life assessed by the Health Survey in abbreviated format (SF-36) and also reported better appetite and sleep, with no adverse effects. A decrease in CRP of 0.5 mg/dl from week 0 to week 8 was observed in 3 patients in the study group. The authors suggest that further studies are needed aiming at both the clinical improvement and the potential anti-inflammatory effect of cannabis in these patients.

Similarly, the study by Naftali et al. (2021) recruited 32 patients and analyzed the effect of cigarettes containing 0.5 g of dried cannabis flowers with 80 mg of tetrahydrocannabinol (THC) or placebo cigarettes for 8 weeks and the results showed clinical remission with improvement of abdominal pain and number of bowel movements per day observed with the Lichtiger Index and better quality of life in patients, demonstrating a great potential to induce anti-inflammatory effects in this pathology.

In a randomized study, Naftali et al. (2017) evaluated the effects of using oral cannabidiol or placebo, 10 mg, twice daily in 19 Crohn's disease patients, mean age 39 ± 15 years, male presenting a Crohn's disease activity index (CDAI) of 200. There was a reduction in CDAI, after 8 weeks of treatment, the score of 337 ± 108 decreases to 220 ± 122 in the study group, four patients achieved complete remission. The use of cannabis proved to be safe, even though it did not present great prominent beneficial effects, providing guidance on the dose used, use of isolated compounds, sample size, among other important assessments.

Studied an Anti-Inflammatory Activity in Colon Models Is Derived from Δ9-Tetrahydrocannabinolic Acid. The anti-inflammatory activity of C. sativa extracts was studied on three lines of epithelial cells and on colon tissue. C. sativa flowers were extracted with ethanol, enzyme-linked immunosorbent assay was used to determine the level of interleukin-8 in colon cells and tissue biopsies, chemical analysis was performed using high-performance liquid chromatography, mass spectrometry and nuclear magnetic resonance and gene expression was determined by quantitative real-time PCR (Nallathambi et al., 2017).

Through the study he concluded that anti-inflammatory activity in the colon may be mediated by THC, at least partially, through the GPR55 receptor. However, the cytotoxic activity of the C. sativa extract was increased by combining all fractions, suggesting that in a non-psychoactive treatment for IBD, THCA should be used instead of CBB (Nallathambi et al., 2017).

In a study by Becker (2020) and colleagues, the numerous mechanisms of innate and adaptive immunity were analyzed and observed how THC can help in the prevention of colon cancer associated with colitis. An anti-CD40 model of colitis in mice with T and B cell deficiency was used to assess how THC acts on the innate and adaptive immune system.

As a result, it was found that, in the CD40 colitis model, THC was able to reduce inflammation by reducing the proinflammatory cytokines IFNγ, TNFα, IL-17A and IL-22. The possible mechanism demonstrated in this study would be the agonism between THC and the CB2 receptor. Through this signaling pathway, intestinal APCs undergo a phenotypic shift to a more anti-inflammatory phenotype that is characterized by increased expression of CD103 and decreased expression of CD86.

In another study (Cocetta et al., 2021) aimed to investigate the effects of different C. sativa isolated compounds in an in vitro model of intestinal epithelium. In this study the cannabinoids were characterized by HPLC. The effect of Cannabis extracts on ROS production is depicted in basal condition, THC decreased ROS levels by 25 and 30% at 0.1 and 1 μg/mL, respectively, though no effect was observed for THCA. CBD 1 μg/mL was able to reduce ROS levels by 25% compared to control, while CBDA resulted in more potent ROS production by 30% at 0.1 μg/mL. Data acquired in this work underline the role of CBD as a potential modulator of markers of gut inflammation such as ROS production, alterations in the paracellular permeability and transepithelial resistance.

The author concludes that CBD has the potential to modulate the expression of intestinal inflammation markers, such as ROS production, changes in paracellular permeability and transepithelial resistance. (Cocetta et al., 2021)

The combination of cannabinoids has also been an option among researchers as shown (Pagano et al., 2021) who investigated whether the combination of FO with cannabigerol (CBG) and cannabidiol (CBD) or a combination of all three treatments results in a more pronounced intestinal anti-inflammatory action compared to the effects achieved separately. The author concluded that the combination of low doses of CBG and CBD with fish oil allows a reduction in the dose of phytocannabinoids, resulting in a potentially improved safety profile, which may support a possible formulation.

Another study also investigated the combination of fish oil and CBD (Silvestri et al., 2020). The assessment took place through the DNBS increased colon weight/colon length ratio, myeloperoxidase activity, interleukin-1β, and intestinal permeability. CBG, but not CBD, given by oral gavage, ameliorated DNBS-induced colonic inflammation. FO pretreatment (at the inactive dose) increased the antiinflammatory action of CBG and rendered oral CBD effective while reducing endocannabinoid levels. Furthermore, the combination of FO, CBD, and a per se inactive dose of CBG resulted in intestinal anti-inflammatory effects.

In an experimental study of murine colitis, Borreli et al. (2013) characterized the action of cannabigerol (CBG) and evaluated the effect of this phytocannabinoid on peritoneal macrophages and on intestinal epithelial cells of mice. The non-psychotropic phytocannabinoid has been shown to exert preventive and curative effects in the DNBS model of colitis. Furthermore, CBG is able to attenuate both nitrite production in macrophages and ROS production in intestinal epithelial cells. CBG was also effective in reducing the colon weight/colon length ratio of inflamed tissue. This is a reliable method to assess the inflammatory response.

Another research aimed to determine the effects of the cannabinoid ligands anandamide and cannabidiol on the integrity of the human colonic mucosa either alone or linked to IL-17A (Harvey, Wattchow and Smid, 2014). Interleukin 17 A is known to play a role in protecting the mucosa from infection. In summary, the effects of IL-17A on epithelial damage were attenuated by treatment associated with the endocannabinoid anandamide.

Hoffenberg (2018) and colleagues conducted a cross-sectional study to assess marijuana use by adolescents and young adults with IBD. The research included patients aged 13 to 23 years, seen between December 2015 and June 2017 with IBD. A comparison was then made between marijuana users and those who had never used, clinical characteristics and risk perceptions with use were evaluated. Patients provided information about perceived benefits, patterns, and problems with use. It was observed that the most common reasons among user patients for using Cannabis in these clinical conditions were to relieve pain, relax and relieve tension.

Another phytocannabinoid studied in isolation was cannabidivarin (CBDV) (Pagano et al., 2019). This study started from the idea that CBDV is a potent agonist of TRP ankyrin type 1 (TRPA1), which has a fundamental role in intestinal inflammation. Thus, the researchers observed that oral CBDV exerts, via TRPA1, anti-inflammatory effects in addition to altering the composition of the intestinal microbiota in a murine model of DNBS-induced colitis.

Cannabis-derived psychoactive compounds, such as THC, may have advantages over the painful symptoms of IBD. This fact is related to its negative effects that can lead to deleterious effects such as depression, as discussed in the study by Dunfor and Morgan (2021). According to the author, it is possible that THC exacerbates IBD in the early stages of inflammation but is able to alleviate pain in response to inflammation. In addition, their negative effects can be offset or reversed when combined.

In fact, bioactives derived from Cannabis sativas show great promise for the treatment of IBD. Numerous experimental and human studies meet expectations. However, other studies, as demonstrated, lack more robustness and standardization of their methodologies. The appropriate choice of administration route and pharmaceutical form, considering the particularities and

physicochemistry of the molecules, are some of the parameters that must be considered when designing studies involving molecules derived from Cannabis.

As reported by Wang et al. (2022), the applications of molecules such as CBD are hampered due to its lipophilicity and low bioavailability. Not taking these characteristics into account directly affects the search results. Consequently, it is impossible to observe the real pharmacological power that the molecule has.

In this way, the author proposed new formulas that make it possible to improve the stability of CBD through nanoencapsulation, making it usable for numerous applications. Zein nanoparticles were presented as a good alternative, being able to form an effective barrier to protect CBD against the hostile environment of the stomach. Such a coating can improve the physicochemical properties, stability performance and contributing to the binding ability of this lipophilic compound.

Martín-Banderas (2014) and collaborators also brought new proposals to overcome difficulties when using cannabinoids. The researchers synthesized a delivery system of microparticles loaded with cannabinoids prepared by oil-in-water emulsion/solvent evaporation. The objective was to evaluate sustained antitumor activity in vitro and *in vivo*. However, due to the size of the particles on a micrometer scale, the delivery system was limited by the parenteral route. Because of this, a new system was proposed using 9-THC oral PLGA nanoparticles. In this scenario, in vitro studies confirmed a better cellular uptake of these nanoparticulate systems and their anticancer efficacies.

Another study went beyond conventional ideas by using a nasal delivery system for CBD (Matarazzo et al., 2021). The purpose of this route is for the application of drugs that act on the central nervous system, and the nasal route has numerous advantages, such as avoiding first-pass metabolism and the blood-brain barrier. However, its main limitation is mucociliary clearance, leading to low bioavailability. Because of this, drugs to be administered by this route must be designed to increase their residence time in the nasal cavity. In this sense, nanostructured lipid carriers (NLCs) are a strategy that can be used to overcome this limitation. When incorporated into NLCs, the bioavailability of the molecule is increased due to protection against degradation and efflux. In this study, nasal administration of CBD in NLC produced a significant antinociceptive effect in animals with neuropathic pain.

Singh et al. (2012) synthesized cannabis sativa nanoparticles through green synthesis of gold and silver nanoparticles. From there, he also carried out a test for the inhibition of biofilm formation of bacteria such as *Escherichia coli*, the results are significant and can demonstrate its applicability in other diseases such as IBD.

Therefore, the nanoencapsulation of phytocannabinoids as a strategy to evaluate their potential in the treatment of IBD is, in addition to being viable, a promising proposal. By developing a delivery system for nanostructured cannabinoids, it becomes possible to evaluate its real effectiveness for this treatment. Nanotechnology can transform unstable molecules, with low bioavailability and low water solubility, into substances with greater possibility of application for curing many diseases.

5. Conclusion

In this work, it can be inferred that metabolites derived from Cannabis sativa have great potential for the treatment of inflammatory bowel diseases. Molecules such as cannabidiol (CBD), Tetrahydrocannabinol (THC), cannabigerol (CBG) and cannabidivarin (CBDV) are with significant numbers of studies focused on the treatment of IBD with relevant results. However, it is necessary more robust and standardized research, in addition to improving the characteristics of these molecules to establish their potential to this issue. There are possibilities for improving these molecules for applications in the treatment of IBD. The nanoencapsulation of phytocannabinoids can contribute to the development of promising studies that aim to propose therapeutic alternatives for the treatment of diseases such as CD and UC can change the course of these diseases, enabling the development of new products based on cannabinoids and nanotechnology. Additional research is needed to improve the cost-effectiveness

and long-term safety of nanometer drug delivery systems involving cannabinoid derivatives, through the use of biocompatible materials and harmless delivery processes and rigorous safety assessment for future applications in medicine.

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