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Endocannabinoid system in irritable bowel syndrome and cannabis as a therapy

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ABSTRACT

Irritable bowel syndrome (IBS) global burden is underestimated despite its high prevalence. It's a gastrointestinal disease having obscure pathophysiology with multiple therapies yet unsatisfactory remedies. The Endocannabinoid system (ECS) of our body plays a key role in maintaining normal physiology of the gastrointestinal tract as well as involves abnormalities including functional diseases like IBS. This review highlights the importance of the Endocannabinoid system, its connections with the normal gastrointestinal functions and abnormalities like IBS. It also discusses the role of cannabis as medical therapy in IBS patients. A literature search for articles related to endocannabinoids in IBS and medical cannabis in PubMed and Google Scholar was conducted. The studies highlighted the significant participation of ECS in IBS. However, the breach in obtaining the promising therapeutic model for IBS needed further investigation in ECS and uncover other treatments for IBS. This review summarizes ECS, highlights the relationship of ECS with IBS and explores cannabis as a potential therapy to treat IBS.

1. Introduction

Irritable bowel syndrome (IBS) is a highly prevalent 7–16% gastrointestinal disease in the Western World [1] and is the frequent diagnosis in gastroenterology practice of the United States. [2] IBS is a chronic disease and patients present with abdominal pain with either constipation (IBS-C) or diarrhea (IBS-D), or mixed pattern of alternating symptoms of constipation and diarrhea (IBS-M) [3] and unsubtyped IBS (IBS-U) according to Rome IV. The abdominal pain should be present for at least 1 day per week for the last 3 months and the origin of symptoms should be at least 6 months before. Also, the symptoms should be related to at least two of the following; associated with defecation, a change in the stool frequency and the form of the stool. The most common symptoms in IBS patients are bloating and abdominal distention as in other functional bowel diseases. [4]

A high number of patients of IBS is returning to the physician (up to 50 %) due to the chronic relapsing course of the disease out marking the number of prevalent patients of IBS in Western Countries. [5] Notwithstanding its prevalence being elusive, IBS has made a huge weight in the health care system. IBS has many etiological factors and no clear pathophysiology with a different range of symptoms. Major etiologies are GI motility, increase in the visceral sensitivity which is abnormally processed by the central nervous system, psychological changes, alteration in mucosal immune activation, change intestinal permeability or gut flora [6] or neurohormonal mechanism. The heterogenous symptoms of IBS could be due to the interactions among these different etiologies.

The endocannabinoid system comprises locally synthesized endocannabinoids with its receptors and ligands. The gastrointestinal tract also has this endocannabinoid system with CB ligands, anandamide, and 2-arachidonoylglcerol (2-AG) and different cannabinoid receptors like cannabinoid 1 receptor (CB1), cannabinoid 2 receptor (CB2) causing a variety of function in the human body [7–9] in both physiological and pathophysiological conditions. Activation of CB1 and CB2 receptors decreases gastrointestinal motility, secretions, and hypersensitivity. [10] So, the alteration of this endocannabinoid system might play a major role in IBS. There are studies in IBS patients that show low-grade inflammations with immune cells and mast cells in the gastrointestinal tract. An increase in microbiota in the gastrointestinal tract of IBS patients might cause a breach of epithelial barrier leading to inflammation. Also, the involvement of the gut-brain axis could be related to visceral hyperalgesia and motility disturbance in IBS patients. [11] This seems in contrast to the earlier views of no histopathological and biochemical changes in functional gastrointestinal disorder.

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In the ancient period, Cannabis sativa was used to treat many gastrointestinal diseases. Now with few pieces of evidence, cannabis extracts are used for the study of the endocannabinoid system (ECS). [11] A recent study [12] suggested the potential therapeutic use of Cannabis containing THCA in Inflammatory Bowel Disease (IBD) for its anti-inflammatory activity on the colon epithelial cells with less psychoactive side effects. Some studies do highlight the overlap of pathophysiology between IBS and IBD. Though we hardly find the studies for the use of cannabis in IBS, the question still rises "What if cannabis is the better treatment for IBS than the existing treatment?" However, some alteration of the ECS by cannabinoids or by raising the level of endogenous cannabinoids pharmacologically, we have evidenced the valuable changes in GI pathophysiology. [13] In addition to that, it is proposed to be extremely safe and effective medication showing many beneficial effects, especially in patients with chronic pain. [14]

To better understand ECS including its component, CB receptors, and its signaling by endocannabinoids, the relationship of ECS with IBS and cannabis in a therapeutic role, it is our goal to learn more about the known and so far unknown components. This review gives an introduction to ECS and its role in the GI tract points out the relation of ECS in IBS and also addresses marijuana (cannabis) as a potential therapy.

2. Methods

2.1. Design protocol and eligibility criteria

This review study was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and was used to report the present systematic review. This review protocol followed PRISMA guidelines. All studies included in the review were selected without the restriction of study type, including investigation of Clinical trials, systematic review, and meta-analysiss. Studies were not selected based on gender, age, and ethnicity. Selection of studies and data extraction were reviewed according to the PRISMA protocol. There was no geographical restriction in the search.

2.2. Information, source, search strategy

The electronic databases were searched internationally using (PubMed, and Google Scholar). The search was performed for articles on the Endocannabinoid system for IBS and Medical Marijuana (Cannabis). The search yielded many articles including case reports, editorials, review articles, met-analysis. From the articles on Role of Endocannabinoid system for Irritable bowel syndrome and Cannabis as therapy was searched meticulously and ultimately only the articles on the association between endocannabinoid system, IBS and medical cannabis were included. Exclusion criteria were the reviews having a higher possibility for bias and research with confusing data. Only articles written in the English language were selected. The keywords used for the search were, Endocannabinoid system, cannabinoid receptor, medical marijuana, IBS, which yielded, 1) 4910 peer-reviewed published articles listed for endocannabinoid system, 2) 13,414 peer-reviewed published articles for irritable bowel syndrome, 3) 4889 peer-reviewed published articles for medical marijuana, 4) 10 articles for combined keywords, Irritable Bowel Syndrome and medical marijuana and,5) 31 listing for combined keywords endocannabinoid system and irritable bowel syndrome.

3. Discussion

3.1. Endocannabinoid system

The endocannabinoid system (ECS) is present throughout the body and plays the main role in homeostasis. It has an important role in the central nervous system as well as the peripheral system. The receptors and ligands are the main constituents of this ECS system. [11] These endogenous receptors give signals and change the function of the body as it is the pharmacologic target of cannabinoids drugs. [15] The endocannabinoids act on the receptors: cannabinoid type 1 (CB1) and cannabinoid type 2 (CB2) which are two different seven-transmembrane G-protein-coupled receptors. [16] The endocannabinoid system along with its intercellular signaling was identified as a result of the study of the mechanism of action of cannabinoids. The endocannabinoids are the lipid mediators that have different biological processes but similar actions to Δ9- tetrahydrocannabinol (THC). These lipid compounds are synthesized as per need from membrane phospholipids which then releases promptly from the cells to act on CB receptors. Then, the activation of the receptors and signal induction yields diverse biological responses. Ultimately, these endogenous endocannabinoids are inactivated by reuptake with the help of putative endocannabinoid membrane (EMT) and enzyme degradation.[17] Anandamide (arachidonylethalnolamide; AES), is inactivated by Fatty acid amide hydrolase (FAAH) and 2-AG mainly by monoacylglycerol lipase (MAGL). Endocannabinoids activates not only cannabinoid receptors but also non-cannabinoid receptors like transient receptor potential vanilloid type 1 (TRPV1), mainly depicted by primary afferent neurons and the orphan G protein-coupled receptor GPR55. [18] Endocannabinoids in intestine activates CB1 receptors in both physiological and pathological states, CB2 receptors in only pathophysiological states and TRPV1 receptor in some inflammatory conditions. [18]

3.2. Endocannabinoids in the GI tract

CB1 and CB2 are present broadly in all layers of the gastrointestinal tract. [18,19] CB1 is also culpable for the typical psychotropic effects of cannabis as it is expressed in CNS. [20] However, CB2 mainly present in the periphery helps in immunomodulation as it is expressed on immune cells. [21] Regional variation in receptor distribution influences regulations of gastrointestinal functions like sensation, motility, secretion, inflammation. [22]

According to the DiPatrizio NV, [23] single-nucleotide polymorphisms in genes of endocannabinoid family including fatty acid amide hydrolase (FAAH), anandamide, cannabinoid receptors, endocannabinoid metabolizing enzymes, and others, increase colonic transport and may result in irritable bowel syndrome. The cannabinoid receptor agonist, Dronabinol, showed reduced post-prandial colonic motility. However, subjects having a gene variant of FAAH or CB1R had altered the efficacy of this treatment. Another study demonstrated the influence of cannabinoid on overall motor, sensory and immune functions in the development of irritable bowel syndrome. [6]

3.3. Endocannabinoid and its potential role in IBS

There is a substantial amount of evidence stating the vital role of the endocannabinoid system in modulating the motility of the gastrointestinal system. According to Capasso R et al, [24] in vivo use of EMT inhibitors or FAAH blockers decreased the gastrointestinal motility. Other studies in animals, where they were treated with CB1 receptor antagonists increased motility. These studies notion tonic suppression of gastrointestinal motility by endocannabinoid system. [25–27] In a pharmacological trial done by Wong BS et al. [28] at Mayo Clinic, dronabinol, a non- selective cannabinoid agonist decreased fasting left colonic proximal and distal motility index and increased colonic compliance showing highest effect among the IBS-D and IBS-M patient. However, there was no tone or sensation alteration. This results in further favors modulation of cannabinoid receptor as a potential target for the treatment of IBS.

Clinical Endocannabinoid Deficiency (ECD) is a theory that advocates the deficient tone of endocannabinoid and production causes different pathophysiological syndromes including migraine, post traumatic stress disorder(PTSD), IBS etc. The levels of the

endocannabinoids, anandamide and 2-AE and the state of cannabinoid receptors reflects the Endocannabinoid tone. [2] Recent study have illuminated this theory with statistically significant differences in CSF anandamide levels in migraine patients and hypofunction of ECS in PTSD demonstrated with advanced imaging. [2] More objective finding is needed for ECD in IBS patients. In a randomized controlled trial with the THC and placebo, THC reduced post prandial colonic tone demonstrating relaxation of colon with the THC. However to ensure therapeutic benefit of cannabis objectically, studies using whole cannabis extract should be performed. [2] Different clinical data have shown cannabinoids treatment affecting the ECS with beneficial effects. In a study with subjects harboring the CNRI rs806378 CT/TT genotype, dronabinol treatment decreased the transit time in the colon. This effect was statistically significant ($p = 0.014$) in IBS-D Caucasian patients. [29] This supports modulation of the colonic transit time and sensation with the CB1 receptor-related mechanism and hence can influence the IBS related symptoms. [30]

There are hardly been any clinical trials with cannabinoids agents in IBS patients. Concerning the alteration of motility, cannabinoids seem to have a vital role and demand further large scale clinical study of cannabinoids in IBS patients. Since activation of CB1 receptors has shown undesirable psychomimetic effects [31,32] and with CB1 antagonist other effects like depression and anxiety have been evidenced, maximum caution is needed during the conduction of study with cannabinoids. [33] However, it's interesting that cannabinoids acting on the CB2 receptor can cause intestinal peristalsis without causing undesirable central side effects. It is hypothesized that this effect of intestinal peristalsis is to inhibition of the release of inflammatory mediators expressed by inflammatory, immune or epithelial cells. [34] The drugs inhibiting endocannabinoids, like FAAH inhibitors, increase the levels of endogenous cannabinoids by different pathways stimulating CB1 receptors. [35] Some studies suggest targeting the degradation pathway of cannabinoids intracellularly or obstructing uptake in the cells, upsurges local availability of endocannabinoids and protects intestinal inflammation, making such drugs an important option for the treatment of Inflammatory Bowel Disease (IBD). [36] A similar study could be useful for describing potential beneficial therapy in IBS patients, yet no drugs so far.

Post-infectious IBS (PI-IBS), a sub-group of IBS has a prevalence of 4%–36% in patients with infectious gastroenteritis. According to a large case-control study in the United Kingdom, the incidence of IBS was 11.9 times higher in patients with the previous infection than uninfected controls. [37] The odds of having IBS are enhanced by six-fold after acute gastrointestinal disease uncovered by a meta-analysis. [38] PI-IBS patients are believed to have immune-mediated barrier defects in the gut [39] and different pathophysiological changes like an increased macrophage, T-lymphocytes, Interleukins, strongly points inflammatory role for PI-IBS development. [37] The dysbiosis of gut microbiota is also related to IBS. [40] A study in rodent gut mucosa, induction of CB2 expression in the intestine was done with lactobacillus acidophilus NCFM, causing recuperation of normal perception of visceral sensation. [41] Since many studies suggest activation of the endocannabinoid system during inflammation of the intestine could be for protection, further studies are needed to explore the possible role of the endocannabinoid system in the pathophysiology of PI-IBS and cannabinoid agents as the therapy.

3.4. How are IBS and IBD related?

We know IBS and IBD are different disease entity and at first look, it seems like they don't share anything except both affecting the bowel. In terms of prevalence, IBS is more prevalent throughout the world with more predilection in the female. Contrary to IBS, IBD is more common in the western population irrespective of gender. [42] In a study by Porter and Colleagues, incidence of IBD in IBS patients were 8.6 times greater than with non-IBS patients suggesting IBS as a risk factor for the development of IBD [43] Also another study in the UK highlighted that diagnosed IBD patients (most of them CD) had three times higher chances of prior diagnosis of IBS (usually in previous year). [44]

IBS and IBD both are related to some psychological and mood disorders. In response to the stress related to IBD, depression makes susceptible to increased inflammation as it increases inflammatory cytokines like IL-6, compared to normal controls. [45] Similarly, an increase in interleukins like IL-6 and 8, adrenocorticotrophic hormone and cortisols inducing a response in the enteric nervous system, causes symptoms like abdominal pain and diarrhea in IBS patients. [45]

Immune activation involving Tumor Necrosis Factor (Ligand)-Superfamily Member 15 (TNF-SF 15), causing inflammation, is proposed to be a common pathway for both IBS and IBD by several studies. In CD patients, TNF-SF15 is recognized to be associated nevertheless, increased risk of IBS is found to be in TNF-SF15 gene polymorphism. [46,47]

Both in IBS and post-infectious IBS patients dysbiosis has been remarked. Similarly, dysbiosis is also believed to set off the development of IBD. [45] In a study with Florescent in- situ hybridization, the rise of bacteria in the mucus layer of both IBD and IBS patients was observed. [48] Gut permeability is suggested to be increased in both IBS and IBD. In IBD, stress increasing gut mast cells attributes to increase in permeability of gut while in IBS patients, an increase in miRNA-29a causes downregulation of glutamine synthetase causing an increase in gut permeability. [49] This might be associated with transient receptor potential vallinoid receptor 1, protein zonulin 1, and a-catenin in both IBS and IBD presenting with IBS symptoms. [5] These all indicate there might be some common pathways in the pathophysiology of IBS and IBD.

3.5. Is Cannabis a potential therapy in IBS?

Many laboratory studies have shown the role of endocannabinoid systems in the inflammatory activity of IBD, decreasing inflammation with treatments of cannabinoids and ultimately decreasing the impact in the disease.[50] In a randomized controlled study to see potential therapy of cannabis in IBD patients by Naftali et al, Crohn's disease activity (CDAI) of > 100 was reduced in a greater percentage (90 %) in cannabis group compared to in the placebo group (40%) ($p = 0.0028$). But there was no change in C—RP (inflammatory biomarker) ([51]). In another study, cannabis user IBD patients were increasing relating to improved symptoms of IBD like pain, appetite, and diarrhea with the use of cannabis. [52] Mbachi et al.,[53] showed a decrease in complications of Crohn's disease in cannabis users patients compared to non-cannabis users. This is an interesting point that should be explored further in IBS patients as well.

Cannabis modulates different functions in our body including immunity, inflammations by activating receptors of endocannabinoid systems. [52] With the studies mentioned above, [5–9] we can say that IBS and IBD might share some common pathways during their evolution as a disease. Despite any strong, large scale study, we can see the potential sparkle of cannabis being likely therapy in IBD and hence IBS as well.

3.6. Cannabis as a therapy

Cannabis is itself an enigmatic term. It may be any of the following forms in which cannabinoids present [1] endocannabinoids like anandamide which are produced inside human body from arachidonic acid [2]; phytocannabinoids, which includes THC and cannabidiol and other many compounds from Cannabis Sativa plant; and [3] synthetic cannabinoids, developed by pharmaceutical company from other cannabinoids like THC and cannabidiol. [54] The primary cannabinoids in the cannabis plant are Δ9 -tetrahydrocannabinol (THC) and cannabidiol. THC causes euphoria and psychosis if taken in a large amount. In contrast to the effect of THC, cannabidiol is not psychoactive. Instead, cannabidiol has therapeutic benefits for anxiety and possibly psychosis. [55] Thus, for the potential use of cannabis as a therapy, the prime goal is to maintain the concentration of THC in the prospective drug. Also, in

the combined THC-cannabidiol, the ratio of THC to cannabidiol establishes the actual therapeutic effects of cannabis as cannabidiol overcomes the psychoactive effects of THC. Cannabidiol can even be used in higher doses (700 mg/day) or for the long term as it is not toxic compared to the psychotropic effect of THC. [56] Wong BS et al. [28] has proposed cannabidiol analogs for diarrheal disease including IBS and cannabinoids antagonists for relieving constipation. Endogenous cannabinoids inhibit the cholinergic mechanisms and cannabinoid receptor antagonist causes acceleration of colonic transit and increased intestinal secretion causing relieve of constipation.

The motive of medical use of cannabis is symptom relief however recreational users use to get high. [57,58] According to Van Os et al., [59] alteration of different neurotransmitter including dopamine within the brain causes an imbalance in endogenous cannabinoid system influencing negatively in cannabis users. And psychosis in cannabis users is considered to be due to vulnerability for this dysregulation in some individuals. However, a study by Henquet et al., [60] the synergy between gene and environment was accounted to trigger psychosis in certain cannabis users. Especially in peripuberty, itself being the vulnerable period of development, the use of cannabis adds more is more likely to cause a problem.

Dronabinol and nabilone are two cannabinoids available and prescribed in the United States which can be used as a therapy where cannabis itself is needed for the treatment. If further treatment is needed, it can be changed to Cannabis itself which has many cannabinoids and is pharmacologically active. Cannabidiol is not available in the United States but it shows influential effects in some conditions. Many synthetic pharmacologically active cannabinoids are being developed with its effect on various diseases. In the upcoming days, it is important to get into the market with new FDA indications. [61] Cannabis is categorized in Schedule I under the Controlled Substances Act according to the US government which is considered an illegal drug. It is supposed to have no accepted medical use rather inclined more toward the high risk of abuse. [62] Thus, the physician can only validate the use of Cannabis and cannot prescribe it. The issue of Cannabis has been left to the states by the US Department of Justice and has not been forced to the federal statute. But still, the federal stance on Cannabis has been a hesitation for many physicians to recommend Cannabis as medical therapy. [61]

The suboptimal therapeutic effects of drugs so far existed for the treatment of IBS like anticholinergics, opioids, and antidepressant, has led us to think out of the box and explore the cannabis-based agents as a potential therapy for IBS. Since ECS modulates different GI functions like propulsion, secretion, and inflammation, cannabinoids could be better therapy in IBS. [63]

The fact of quite suboptimal therapeutic effects with anticholinergic, opioids, and antidepressants has emerged the cannabis-based agents as a potential therapy for IBS. The rationale of cannabinoids for the treatment of IBS is the ECS modulating the functions of the gut like GI propulsion, secretion, and inflammation. [63] In a study of colonoscopy biopsies in 31 normal patients, the examination of circular muscle fibers supported ECS to have a vital role in modulation of gastrointestinal function during inflammatory or disease states.. .[64]. In another study in IBS patients, colonoscopic biopsy showed 3.5 –fold increase in TRPV1- immunoreactive nerve fibers compared with controls ($p < 0.0001$) credited to visceral hypersensitivity and pain in IBS patients. [65] This suggests the prime target is to uplift the levels of AEA or desensitize TRPV1 for the treatment of IBS. [66] Administration of FAAH in high doses also increases serum levels of AEA, [67] propounding its use for the treatment of IBS.

Cannabis shows an impressive effect against a broad spectrum of diseases recalcitrant to standard therapy. However, its use as a medical therapy has no scientific legitimacy proven by randomized controlled trials or any large-scale studies. [68] Therefore, to prove the medical worth of cannabis in IBS, randomized control trials and large-scale studies are highly needed in present evidence-based practicing medicine.

4. Limitations

Medical Use of cannabis has its limitations. There are different strains of cannabis, with claims of different uses and secondary side effects. The route of administration is not standardized. Though there have been few studies, the strength of the study is hard to determine. There is no large scale randomized study to claim the medicinal use of cannabis in IBS. Further studies should be done in patients with comorbidities to gauge safety such as in psychiatric patients with a history of substance abuse or substance-related psychosis. Effects of short term and long-term use as a medicine and its side effects should be established.

5. Conclusion

A substantial amount of studies demonstrates the ability of ECS to modulate the functions in the gastrointestinal tract by working at cellular levels. Yet, the knack to alter the system for various therapy is still insufficient. The alteration in the endocannabinoids family plays a key role in including IBS. The obscure pathophysiology of IBS has veiled the correct target to overcome the disease, nevertheless, some studies and evidence have uncovered the role of ECS in IBS. The worth of cannabinoid is supposed to be way beyond recreational use. It can be explored as a potential therapy in IBS modulating the different parts of the ECS family, like receptors, ligands, degrading enzymes. At the same time, cannabis is subtyped as Schedule I drug, restricting its research, trials, and studies for medicinal values. Unless it is removed from the Schedule I drug, hesitation for further study and hitherto unknown pharmacological potential in of IBS remains esoteric. The safety, efficacy, mode of intake, therapeutic index, toxic level all have to be established with studies in different subtypes of IBS patients but it is extremely important to have regular follow-ups in patients as it has high abuse potential. However, there is still much to know and explore the mechanism of IBS and cannabis as a potential therapy. It is only possible with further multiple studies, meta-analysis, randomized controlled trials all around the globe.

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