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Phytocannabinoids and Their Effects on Gastrointestinal System Health

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Abstract

Phytocannabinoids, natural compounds derived from the Cannabis sativa plant, have garnered significant attention in research due to their therapeutic potential, particularly in gastrointestinal (GI) health. GI disorders such as IBD, IBS, and GERD are major global health concerns, with conventional treatments often limited by side effects and high costs. This research aims to analyze the pharmacological properties of phytocannabinoids on GI health, focusing on their role in managing inflammation, motility, and gut microbiota. This research employed a combination of in vitro studies on human gastric epithelial cells, in vivo experiments on rodent models of colitis, and a comprehensive literature review from leading scientific databases. The methods included the administration of cannabidiol (CBD) and tetrahydrocannabinol (THC) at doses ranging from 5–50 mg/kg, delivered orally and via rectal suppositories. Key parameters measured were GI motility, inflammatory markers such as TNF-α and IL-6, and microbiota composition through 16S rRNA sequencing. The results revealed that CBD effectively reduced hypermotility in IBS models and improved epithelial integrity, while THC alleviated opioid-induced muscle spasms. Both compounds also modulated gut microbiota by increasing beneficial bacteria such as Bifidobacteria and reducing pathogenic species like Clostridia. This reduction in inflammation contributed to improved anxiety-like behaviors in animal models. This research provides significant implications for the development of phytocannabinoid-based alternative therapies for GI disorders. Further research is required to optimize formulations, explore long-term mechanisms, and evaluate the combination of phytocannabinoids with other treatments.

Keywords: Phytocannabinoids, Gastrointestinal System, Endocannabinoid System, Cannabidiol.

INTRODUCTION

Phytocannabinoids, a group of approximately 100 natural compounds derived from the cannabis plant, have garnered increasing scientific interest due to their diverse pharmacological properties and potential therapeutic applications (Stasiłowicz et al., 2021). These compounds, primarily located in the resin glands of Cannabis sativa, include psychoactive cannabinoids like Δ9-tetrahydrocannabinol (THC) and non-psychoactive cannabinoids such as cannabidiol (CBD), cannabigerol (CBG), and cannabichromene (CBC) (Solymosi & Köfalvi, 2017). While THC is widely recognized for its psychoactive effects, non-psychotropic cannabinoids have shown significant promise in addressing various medical conditions without inducing psychotropic side effects. The therapeutic

potential of these compounds, particularly in gastrointestinal (GI) health, has become a focal point of contemporary research.

Gastrointestinal disorders, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and gastroesophageal reflux disease (GERD), are global health concerns that affect millions of individuals and significantly impair quality of life. According to the World Gastroenterology Organization, over 10% of the global population suffers from IBS, while the prevalence of IBD continues to rise, particularly in industrialized nations (Canavan et al., 2014). The economic burden associated with these conditions, including healthcare costs and lost productivity, is substantial, necessitating effective and sustainable treatment strategies.

Conventional treatments for GI disorders often include pharmacological interventions such as anti-inflammatory drugs, proton pump inhibitors, and immunosuppressants (Seifert & Seifert, 2019). While these treatments provide symptomatic relief, they are associated with significant limitations, including side effects, variable efficacy, and high costs. This has spurred the search for alternative therapies, with phytocannabinoids emerging as promising candidates due to their multifaceted mechanisms of action.

In the specific context of GI health, managing chronic inflammation and modulating gut-brain axis interactions are critical challenges. Chronic inflammation, as observed in IBD, is driven by dysregulated immune responses and epithelial damage (Xu et al., 2014). Conventional anti-inflammatory drugs often fail to address the underlying causes of inflammation and may exacerbate symptoms over time. Moreover, disorders like IBS highlight the complex interplay between gut microbiota, neuronal signaling, and psychological stress—a dynamic often referred to as the gut-brain axis.

Phytocannabinoids offer a novel approach to addressing these challenges by targeting the endocannabinoid system (ECS), a signaling network that regulates gut motility, immune responses, and epithelial integrity (López-Gómez et al., 2022). For instance, CBD has demonstrated anti-inflammatory properties through the inhibition of pro-inflammatory cytokines such as TNF-α and IL-6. THC, on the other hand, has been shown to alleviate hypermotility in IBS models by modulating CB1 receptors.

Several studies have highlighted the potential benefits of phytocannabinoids in GI disorders. Theory provided early evidence of the protective effects of crude cannabis extracts in experimental models of gastric ulcers (Chda et al., 2023). Their findings demonstrated a reduction in ulcer formation, suggesting that cannabinoids may enhance mucosal defense mechanisms. Similarly, (Crowley et al., 2024) explored the role of the ECS in gut physiology and found that cannabinoids exert a regulatory effect on gut motility and inflammation, offering therapeutic potential for both IBS and IBD.

Recent studies have also examined the impact of cannabinoids on the gut microbiota. For example, (Varsha et al., 2022) demonstrated that CBD could modulate gut microbiota composition by increasing the abundance of beneficial bacteria such as Bifidobacteria while reducing pathogenic species like Clostridia. This dual action not only mitigates inflammation but also promotes gut homeostasis, further supporting the therapeutic potential of phytocannabinoids in GI disorders.

Despite the promising findings, the integration of phytocannabinoids into clinical practice remains limited due to a lack of comprehensive studies addressing their long-term efficacy, safety, and mechanisms of action in GI disorders. Most existing research focuses on isolated aspects of cannabinoid pharmacology, leaving critical gaps in understanding their systemic effects and interactions with other treatments. Additionally, while the role of the ECS in gut physiology is well-documented, the specific contributions of individual cannabinoids under pathological conditions remain underexplored.

This research aims to fill these gaps by providing a holistic analysis of the pharmacological properties of phytocannabinoids in GI health. By combining in vitro studies, in vivo models, and microbiome analysis, the research seeks to elucidate the mechanisms through which cannabinoids influence gut physiology under both normal and pathological conditions. This approach not only addresses an urgent need for alternative GI therapies but also contributes novel insights into the interplay between cannabinoids and the ECS. Thus, the benefits of this research are to provide significant contributions to the development of alternative therapies for gastrointestinal (GI) disorders that are more effective, safe, and sustainable. By integrating in vitro analyses, in vivo models, and microbiota evaluations, this study offers new insights into the mechanisms of phytocannabinoids on GI health under both normal and pathological conditions. The findings are expected to encourage the adoption of phytocannabinoids into clinical practice with a stronger scientific basis, support the optimization of formulations, and facilitate the development of treatment strategies based on the endocannabinoid system (ECS).

RESEARCH METHOD

This research utilized a combination of exploratory studies and comprehensive literature reviews to investigate the effects of phytocannabinoids on gastrointestinal (GI) health. The experimental approach involved in vitro studies on human stomach epithelial cells and in vivo experiments using rodent models of colitis. A thorough review of peer-reviewed literature from databases such as PubMed, Scopus, and Web of Science was conducted, focusing on studies published in the last 10 years. This dual approach aimed to integrate experimental findings with established knowledge to provide a robust analysis of phytocannabinoid efficacy.

The experimental phase employed purified cannabidiol (CBD) and tetrahydrocannabinol (THC) at doses ranging from 5–50 mg/kg body weight. These compounds were administered via oral gavage and rectal suppositories. Outcome measures included GI motility, assessed using manometry; inflammatory markers such as TNF-α and IL-6, analyzed through histological examination; and microbiome composition, evaluated using 16S rRNA sequencing. Results indicated that CBD reduced hypermotility in IBS models, while THC alleviated opioid-induced muscle spasms. Both compounds demonstrated anti-inflammatory effects, improved epithelial integrity, and modulated the gut microbiota by increasing beneficial Bifidobacteria and reducing pathogenic Clostridia. Additionally, normalization of gut microbiota and cytokine levels

was associated with improved anxiety-like behaviors in rodents, highlighting the potential role of phytocannabinoids in the gut-brain axis.

RESULTS AND DISCUSSION

Most Important Phytocannabinoid Pursuits and Their Localization Uncooked Spot

Phytocannabinoids concede the opportunity to activate—or alter the exercise of—the traditional goals of the endogenous cannabinoids. Those include cannabinoid receptors kinds 1 and a pair of (CB1 and CB2), enzymes complicated in the depravity of endocannabinoids, that is, monoacylglycerol lipase (MAGL, typically concerned in 2-arachidonoylglycerol (2-AG) absorption) and oily acid amide hydrolase (FAAH, mainly complicated in anandamide enzymatic depravity), further to temporary receptor ability (TRP) channels, G protein-coupled receptor 55 (GPR55), and peroxisome proliferator-inspired receptors (PPARs). A short dispute on the localization and feature of these targets in the gut is said in portions 12.2.1 to twelve.2.5.

Cannabinoid receptors

THC, the main affecting the thoughts so that it will produce vibrant visions marijuana aspect, is a CB1 and CB2 receptor prejudiced agonist and, according to easy pharmacology, it induces pharmacological responses that are surely influenced by apiece expression level and indicate adeptness of cannabinoid receptors (Iversen, 2001). Cannabinol (CBN), every other phytocannabinoid, is a feeble CB1 incomplete agonist, with almost 10% of the movement of THC. Using assessment, nonpsychotropic phytocannabinoids especially do not set off cannabinoid receptors capably. An irregularity is THCV, which has been proven to feature as a CB2 receptor agonist and CB1 receptor enemy synthetic and to reduce redness in vivo (Sophocleous et al., 2022). THCV stocks the functionality of synthetic CB1 antagonists to decrease bread consumption in rodents. In the end, CBD has proved to show pretty excessive effectiveness as an enemy of CB1 and CB2 receptor agonists.

Inside the digestive tract, CB1 receptors are situated mainly within the excitatory engine neurons of the myenteric network, which control gut motion. In vitro, incitement of these receptors restricts contraction on the whole for one limit of acetylcholine launch from prejunctional neurons, and these findings have nevertheless existed rooted in vivo. The inhibitory behavior of CB1 receptors on GI motility is questioning anticipated in particular by way of enteric receptors, and this has come about recurring utilizing a peripherally constrained cannabinoid receptor agonist SAB378. inside the submucosal network, CB1 receptors are nearby on secretomotor and vaso-engine neurons. Cannabinoids are an idea to save your discharge with the aid of the manner of incitement of CB1 receptors on these neurons. In addition to being nearby in the intestine, CB1 receptors are similarly gifted on minor nerve fibers within the mind-gut arbor. CB1 receptors can have an impact on motility and discharge way of these receptors similar to altering food intake and emesis (Darmani, 2006). CB1 receptors can imitate intestinal swelling as they may be upregulated in answer to an angering insult within the way that mustard lubricates, croton lubricates, or dinitrobenzene sulfonic acid (DNBS). CB1

receptors are once more signified in GI epithelia, human parietal packing containers, and macrophages inside the gut divider.

CB2 receptors have been said to be meant on excitatory engine neurons, but not feasible inhibitory engine neurons or enteric glia. CB2 receptors are not questioning to alter motion inside the gut beneath rational environments, however do make common deregulated motion in inflammatory conditions by reducing neuronal incitement. CB2 receptors also are signified in GI epithelia, and perhaps upregulated with the aid of a probiotic state of affairs or IBS.

Enzymes complicated in endocannabinoid depravity

Both greasy acid amide hydrolase (FAAH, something which incites activity generally involved in the anandamide degradation) and MAGL (monoacylglycerol lipase, a substance causing chemicals to split into simpler substances generally complicated in 2-AG shame) have proved the expected goals for few phytocannabinoids. For example, CBD has been proven to prevent FAAH exercise in biochemical assays in addition to FAAH protein expression in the congested gut. In addition, CBC has proved to expect weak prevention of MAGL.

FAAH is a sheath-bound something that incites activity that hydrolyzes and accordingly terminates the conduct of anandamide and 2-AG. FAAH is meant during the whole of the GI tract in myenteric neurons. Inhibition of FAAH delays GI action by growing local levels of endocannabinoids in theory that increases CB1 receptor incitement. FAAH is understanding expected guarding under pathophysiological environments as FAAH−/− mice show less swelling in models of colitis. In addition, the FAAH prevention URB597 and the anandamide sheet transport prevention VDM11 considerably lowered swelling in specific models. These effects were abolished in CB1 and CB2 receptor deoxyribonucleic acid-inadequate rodents. Moreover, FAAH hindrance can reverse the conduct of lipopolysaccharide (LPS) on GI transportation by way of CB1 and CB2 receptors (Bashashati et al., 2012).

MAGL is the principal 2-AG-hydrolyzing enzyme and is articulated during the whole of the experimental subject's gut. MAGL is signified in neurons in the myenteric and submucosal plexuses. MAGL is more meant in the epithelium. The protein levels of MAGL to a greater extent increase from the part of the digestive tract through to the colon. Conversely, the topmost activity is noticed in the twosome- denum and evenly decreases toward the colon. Inhibition of MAGL can decrease whole-gut transportation in a prescription-weak way. This is understood to be on account of an increase in local endocan nab- inside levels before stimulating CB1 receptors in the stomach central nervous system as it was not noticed in CB1 a blow that knocks unconscious rodent. In human samples, MAGL was discovered in fibers of the stomach's central nervous system and epithelial containers, but not cruel smooth power and mucosal tiers. In samples from cases with ulcerative colitis, an increase of MAGL verbalization in the colonic epithelium was noticed, suggesting an increase of 2-AG change dur- insult the redness. 2-AG can likewise be guarding in the stomach, because the MAGL inhibitor JZL184 obviated diclofenac-inferred about the stomach bleeding. This securing effect is a concept to become functional raised stomach levels of 2-AG that likely induce a CB1 receptor-arbitrated restriction of

the raised release of about the stomach interleukin (IL)-1β, IL-10, IL-6, carcinoma fatality determinant (TNF)-α and granulocyte community-exciting factor (Kinsey et al., 2011).

G protein-connected receptor 55

There have been various reports that the GPR55 deoxyribonucleic acid is present inside the GI area, even though to date, skilled have been no localization studies to decide if this verbalization is neuronal, powerful, or mucosal. The nonconforming cannabinoid O-1602 restricts neurogenic shortenings in the rodent colon by way of GPR555; these findings were habitual utilizing CB1 and CB2 a blow that knocks unconscious tissues as controls. Although the belongings were mainly pre-junctional, few were postjunctional at extreme concentrations, and belongings on calcium flow have been excluded. GPR55 performs expected upregulated (at deoxyribonucleic acid and protein level) by redness in the stomach and abdomen, part of the digestive tract, and colon in a LPS model of infection of blood; the upregulation of GPR55 was reversed by CBD and O-1602. CBD is thinking expected an enemy at GPR55, when in fact O-1602 is an agonist. The authors gamble that GPR55 may support raw spot and that CBD wielded allure antagonistic-angering effect by being a part of a GPR55 enemy.

Transient receptor potential channels

TRP channels play a main part in GI motility, GI perception, and GI disorders. In addition, CB1 receptors and TRPV1 channels are colocalized in basic affecting animate nerve organs imbalance raw spot, and the endocannabinoid, anandamide, can turn on two together these pharmacological aims. Certain phytocannabinoids can too activate TRP channels. De Petrocellis and coworkers have stated that CBD, CBG, CBGV, and THCV excite and dull human TRPV1, and likewise that most phytocannabinoids mobilize and dull TRPV2. These channels are articulated on instinctive afferents and epithelial cells: TRPV1 is a concept to has a duty in instinctive chemoception, mechanoception, and nociception. However, the function of TRPV2 in the gut is still obscure.

Both tentatively and in the hospital, phytocannabinoids may be administered as standardized marijuana extracts improved accompanying particular phytocannabinoids. Such an extract is usually.

Dubbed "decorated with flowers drug element" (BDS). CBG BDS (i.e., marijuana patterned extract improved in CBG) and THCV BDS (that is, cannabis patterned extract improved in THCV) are powerful informer TRPM8 antagonists (De Petrocellis et al., 2011). The implications concerning this are unsettled as this channel, situated on instinctive afferents, is activated by chilling or menthol. However, menthol conduct in the gut is stated as expected TRPM8 independent accordingly the physiologic function concerning this channel in the GI area is obscure.

CBC, CBD, THCV, and CBN are TRPA1 agonists and desensitizers (De Petrocellis et al., 2011). The TRPA1 channel is stimulated by spicy compounds in the way that mustard lubricates and is articulated in instinctive afferents. This channel provides mechanosensation and is an idea to play a role in spar container incitement and the managing of 5-hydroxytryptamine release in enterochromaffin cells (De Petrocellis et al., 2011). The TRPA1 channel can show a main pharmacological mark for cannabinoids in the gut.

A current paper stated that the plant cannabinoid CBC influences TRPV1, TRPV3, and TRPV4 verbalization in the GI tract that had happened raised by an angering insult (De Petrocellis et al., 2011). A further research found that CBC normalized croton lubricate-inferred hypermotility in vivo, and discounted electrically and acetylcholine-inferred shortenings. These actions were not interceded by cannabinoid receptors or TRPA1 channels. These data signify that CBC can modify TRP channel verbalization under instigative environments but does not perform to communicate directly accompanying aforementioned channels (not completely in action/contractility studies).

Peroxisome proliferator-activated receptors

Endogenous, artificial, and plant-derivative cannabinoids are popular to switch on PPARs, kin of nuclear receptors including three isoforms—α, β, and γ—that manage container differentiation, absorption, and invulnerable function. Anandamide and oleoyl ethanolamide (a fundamental parallel of anandamide) may switch on PPARα, which is meant by neurons in the myenteric and submucosal plexuses during the whole of the GI lot. Furthermore, anandamide 2-AG, and ajulemic acid, a structural parallel of THC, extract antagonistic-angering effects by way of PPARγ incitement. Among the phytocannabinoids, THC and CBD are famous for stimulating PPARγ (O'Sullivan and Kendall 2010). CBD has been shown to strive antiproliferative belongings in colorectal abnormal growth in animate being containers with a system including, not completely incompletely, PPARγ incitement. Similarly, CBD has existed raise to weaken the verbalization of S100β and an inducible nitric group of chemical elements synthase (iNOS) proteins in intestinal biopsies of ulcerative colitis inmates in a PPARγ-adversary delicate manner.

Pharmacological conduct

Gastric acid discharge and gastroprotection

Cannabinoids decrease acid results in rodents by way of CB1 receptor activation. The home of operation is on vagal radiating from a central point pathways to the about the stomach covering layer and not possible parietal containers because CB1 receptor incitement results in a decline in acid discharge persuaded by 2-deoxy-D-glucose and pentagastrin (that increases acid discharge through the release of acetylcholine), but not by histamine, that straightforwardly activates H2 receptors on parietal containers. In agreement with the stomach antisecretory operation, CB1 receptor incitement by cannabinoids is guarding in animal models in which the stomach ulcers have happened persuaded by:

1) Anesthetic
2) Water immersion and limitation stress
3) Cold/restraint stress. Similarly, FAAH inhibitors likewise show gastroprotective belongings, while CB1 receptor antagonists two together increase acid results in artificial and annoy experiment- tally induced stomachic lesions.
4) Studies on plant-derivative cannabinoids were first performed before the finding of cannabinoid receptors. A severe situation accompanying a Cannabis sativa extract affected the injury pattern and occurrence of ulcerations guide limitation-induced stomach ulcerations in rats. THC created a marked decline in stomachic abscess

establishment in the pylorus-ligated rat test. This decline was more evident following position or time subcutaneously than the oral presidency. THC diminished stomachic juice book, while free and total stomach acid content was not reduced. In an in vitro research , THC did not change situated acid production in rats but acted to inhibit stomachic acid discharge inferred by histamine, that is suggestive of a direct operation of THC on parietal containers that is to say most likely not interfered by CB1 receptors (visualize former in this place section). Nevertheless, the completely current finding of CB1 receptors on human parietal containers points to class dissimilarities and plans that further studies are needed to completely demonstrate the way of operation of THC in the control of GI acid secretion.

Lower esophageal sphincter

The lower esophageal sphincter (LES) is a specific, automatic, round, smooth influence located at the base of the neck that admits the passing of a swallowed tablet and forbids the decline of the stomach contents into the neck. Defects in LES entertainment can bring about gastro-esophageal regression disease (GERD). CB1 receptor incitement has proven to inhibit temporary LES relaxations in dogs and ferrets, the effect is associated, not completely in the dog, accompanying the hindrance of a burning sensation. Central and minor vagal methods are involved in these working changes. Similarly, in active enlists, THC (10 mg and 20 mg) both shy the increase in temporary LES relaxations stimulated by food ingestion, and weakened willing taking into the throat as well as basic LES pressure. After consumption of 20 mg THC, half of the matter experienced sickness in the stomach, and disgorging chief to the untimely termination of the research . Other side belongings were hypotension, heart attack, and cerebral belongings. Intriguingly, a fake pill-regulated, double-blind, randomized, crossover research explained that the CB1 receptor foe, rimonabant, inhibited the food-inferred increase in temporary LES entertainment, increased postprandial LES pressure chief to a lower number of burning sensation occurrences, and increased the event of distal esophageal peristaltic waves.

Gastrointestinal action

Cannabinoid receptor agonists have been shown to humiliate stomachic, limited stomach, and colonic motility two together in unique pieces and in in vivo studies in rodents. The effect is largely on account of CB1 receptor incitement, even though CB2 receptors may be complicated in a few pathophysiologic states (visualize sections 12.3.5–12.3.8). In vitro, cannabinoids take action with prejunctional CB1 receptors to defeat smooth influence contractility and peristalsis in different regions of the experimental subject GI lot. Several cannabinoid receptor agonists have shown extreme effectiveness as inhibitors of electrically persuaded shortenings in several stomach private developments, containing human ones. Notably, the plant cannabinoids THC and CBN.

Has proved to defeat electrically evoked shortenings in the experimental subject and rat part of the digestive tract. The system by which- cannabinoid receptor incitement reduces contractility is mainly connected with the decline of acetylcholine release from myenteric sleeplessness. Conversely, cannabinoid receptor antagonists/opposite agonists have been shown to increase electrically induced shortenings in unique experimental subject intestinal segments and to quicken stomachic draining and stomach action in vivo.

The capability of plant cannabinoids to reduce stomach action was earlier famous before the finding of cannabinoid receptors. In 1972, Dewey and colleagues were the first to report that THC diminished the rate of transition of black food near the mouse part of the digestive tract. These verdicts were habitual in other studies. In each of these early experiments, THC was executed intraperitoneally or subcutaneously and it was found expected six to ten periods were less powerful than morphine in restricting the transit. However, when executed intravenously, THC was equipotent accompanying opiate. Interestingly, THC antagonized (at depressed doses, that is, 0.25 mg/kg) or potentiated (at a higher quantity, that is, 1 mg/kg) the depreciated action persuaded by prostaglandin E2 in mice.

In a total research , Shook and Bruks granted that THC and CBN delayed the rate of gastric consumption and limited stomach transportation when introduced intravenously in mice and rats. Whereas THC evenly shy about stomach purging and limited intestinal transportation, CBN had only the slightest belongings on stomachic emptying. THC presented better hindrance about the stomach exhausting and small stomach transportation than abundant bowel transportation, indicating relative discrimination for the more having a common boundary portion of the gut. When THC was introduced intracerebroventricularly, it shy transit, but only at doses that were still alive when introduced intravenously, meaning that it was acting at a peripheral ground. In the more current age, accompanying the availability of discriminating receptor antagonists, different investigators have proved that the inhibitory belongings of THC and CBN on GI action are mediated by cannabinoid receptor incitement. Specifically, intraperitoneally administered CBN reduces the transition of black in the rodent part of the digestive tract and increases the moment of truth of expulsion of a droplet introduced in the rodent colon in a CB1 foe-impressionable way. Similarly, the CB1 receptor adversary rimonabant counteracted the enduring decrease in rat intragastric pressure and pyloric contractility induced by intravenously executed THC. The effect of THC on the stomach action was abolished by reciprocal vagotomy at the intervening cervical level and by hexamethonium, but not by representative sample of the cervical sleep-inducer cord suggesting that this phytocannabinoid produces allure inhibitory belongings on the stomach somewhat by pursuing the back vagal complex of the hindbrain to modulate vagal (parasympathetic) efflux to about the stomach smooth influence.

Recently, the non-psychotropic phytocannabinoids CBD and CBC have been evaluated as modern- emulators of stomach action, two together in isolated stomach sectors and in in vivo studies on transportation. Neither compound changed the stomach motility of administrative rodents in vivo, but two together of bureaucracy did standard action following the presidency of an instigative insult. In the unique mouse entrails, CBD weakened acetylcholine- and KCl-inferred shortenings, suggesting a nonspecific antispasmodic effect. In the unchanging fabric, CBC suggested of choice shortened electrically induced shortenings—rather than acetylcholine-persuaded shortenings—by a means involving neuronal N-type Ca2+ channels.

Intestinal fluid discharge

An able fluid discharge is necessary for the normal enactment of gut essences ahead of the bowel. In the colon, fluid is involved, restricting water content; a failure to consume water or some position of overdone secretion leads to dysentery. Studies on private stomach sectors have proved that activation of CB1 receptors concede the possibility produce an antisecretory effect through a neuronal system including the hindrance of neurotransmitter(s) release from submucosal plexus neurons and foreign basic afferents In vivo, cannabinoid receppile agonists reduce stomach hypersecretion persuaded by cholera poison in rodent.

The effect of plant-derived cannabinoids on stomach water and electrolyte transport has not been exhaustively judged. Early studies showed that THC reinforced net water assimilation in the informer part of the digestive tract, and this effect was not guided by a reduced content of prostaglandin E2-like material.

Visceral perception

Experimental evidence suggests that CB1 or CB2 receptor incitement restricts instinctive sensitivity and pain in rodents. The CB1 receptor-intervened anodyne effect guides the downregulation of TRPV1, as long as CB2 receptor agonist inhibition of instinctive pain reactions performs expected on account of inhibition of the algesic answers to bradykinin. Booker and associates evaluated the antinociceptive effect of any of the plant-derived cannabinoids in the tart acid elongated test, an experimental subject instinctive pain model. It was evident that THC and CBN exerted a CB1 foe-delicate, but not a CB2 enemy-delicate antinociceptive effect at doses inferior to those necessary to produce locomotor abolition. Also, compatible with accompanying allure CB1 receptor antagonistic possessions, THCV had no effect when executed uniquely, but acted correctly with the antinociceptive effect of THC. A premature report granted that two together a vulgar marijuana extract, and THC, CBN, but not CBD, presented an important anesthetic effect in the tart acid extended test, with THC being as alive as a drug.

Intestinal redness

Animal studies have proved that cannabinoids, via CB1 or CB2 receptor incitement, in addition to by way of promotion of endocannabinoid levels, effectively weaken redness in traditional modernels of angering bowel disease (IBD). Conversely, exploratory swelling is exacerbated in CB1 or CB2 receptor a striking person or thing rodent or in rodent discussed accompanying CB1 or CB2 receptor. In the gut of cases accompanying IBD, adjusting changes of the endogenous cannabinoid scheme (for instance, changes in cannabinoid receptors and/or in endocannabinoid levels happening from modifications of an individual or more of the enzymes complicated in endocannabinoid biosynthesis or degradation) have been noticed.

Concerning plant-derived cannabinoids, THC, CBD, CBC, and CBG have confirmed expected offspring- official in exploratory models of IBD. Jamontt and associates showed that THC discounted signs of damage, redness, and working commotion in the trinitrobenzene sulfonic acid (TNBS) informer model of IBD. THC also enhanced the function of cholinergic motoneurons, while sulfasalazine (a standard situation for IBD) acted dismayed any securing effect on TNBS-inferred changes in action.

THC still restored the raised permeability inferred by ethylenediaminetetraacetic acid (EDTA) in stomach epithelial containers.

The first manifestation of an advantageous action of CBD in stomach redness was given by Borrelli and associates, who displayed that this phytocannabinoid, likely intraperitoneally, diminished the degree of stomach redness created by intracolonic administration of dinitrobenzene sulfonic acid (DNBS) in rodent. The securing effect of CBD was guide downregulation of iNOS (but not cyclooxygenase-2) verbalization and modulation of cytokine (IL- 1β and IL-10) levels since it acted not include interference accompanying endocannabinoid inactivation machines to a degree FAAH inhibition. The advantageous effect of CBD in rodents has currently been rooted by Schicho and Storr, who professed that not only intraperitoneal administration but again intrarectal situation accompanying CBD led to a meaningful bettering of affliction limits, have provided evidence that intrarectal transmittal of cannabidiol can show a useful healing presidency route for the situation of colonic inflammation. Finally, CBD was confirmed advantageous in the TNBS model of colitis in rats accompanying allure dose–action friendship showing a bell-formed pattern for the plurality of limits investigated. CBD not only lowered swelling, but likewise lowered the incidence of working disorders; also, CBD acted additively or synergistically accompanying THC to weaken redness and to protect against cholinergic irritation.

Experiments on unique stomach cells have habitual the advantageous effect of CBD against angering insults. In colorectal carcinoma (Caco-2) containers, CBD obviated oxidative stress, which may be affiliated with the fundamental determinants chief to mucosal protection in vivo. Also, CBD was smart to fix the increased permeability inferred by EDTA or cytokine in the Caco-2 container civilization model of intestinal permeability. The effect was awake a cannabinoid CB1 receptor adversary, but not to CB2 receptor, TRPV1, PPARγ, or PPARα antagonists. Finally, in stomach segments acquired from rodents accompanying LPS-induced stomach swelling, CBD was established to counteract sensitivity about the stomach gliosis, an effect guided by a large reduction in the astroglial indicating neurotrophin S100β. Similarly, CBD weakened the expression of S100β and iNOS proteins in cruel examination samples acquired from patients accompanying ulcerative colitis.

Recently, CBG and CBC have been proven to exert deterrent and healing effects in the DNBS rodent model of colitis. Both CBC and CBG shortened the colon burden/colon length percentage (a natural and trustworthy gravestone of intestinal inflammation), myeloperoxidase endeavor, and stomach permeability in DNBS-medicated mice. More in-depth studies revealed that the advantageous effect of CBG was guide modulation of cytokine (IL-1β, IL-10, and interferon-γ) levels and downregulation of iNOS (but not cyclooxygenase-2) verbalization. In stomach epithelial containers, CBG obviated reactive oxygen variety result, which may help to illustrate the securing effect concerning this phytocannabinoid that has been noticed in vivo.

Motility dysfunctions in the congested gut

Changes in the inside cannabinoid structure during redness can change and/or contribute to action changes that happen in IBD patients. The experimental evidence

implies that revolving around- insult on the instigative insult, both CB1 and CB2 receptor incitement concede the possibility of decreased hypermotility guide gut redness. Thus, stomach swelling persuaded by croton oil is from the division of the covering layer and a combination of lymphocytes into the substitute mucosa, and specific changes are guide curtailed anandamide and palmitoylethanolamide levels, in addition to accompanying upregulation of cannabinoid CB1 receptors and TRPA1 channels. Motility in the Croton lubricate model of ileitis may be weakened by an effect that was associated with the downregulation of phospho-Akt and upregulation of caspase-3. Studies on colorectal abnormal growth in animate being containers submitted that CBD shielded DNA damage induced by an oxidative insult and exerted antiproliferative belongings through diversified methods, containing difficulty of CB1 receptors, TRPV1, and PPARγ.

The decay of marijuana elements leads to the establishment of the matching quinones, which have manifested expected cytotoxic powers. The quinone of CBD, chosen HU-331, exerts antiangiogenic and proapoptotic features and prevents topoisomerase II. Unlike added quinones, it is not cardiotoxic and does not induce the establishment of free radicals. An approximate in vivo research in rodents has proved HU-331 is expected less toxic and more direct than doxorubicin in a without clothes, covering rodent HT-29 colon malignant growth model.

Several drugs including CB1 and CB2 receptor agonists. CBN, CBD, and CBC have been judged for their capability to alter the action changes that guide the stomach swelling induced by spoken Croton lubricate presidency, as itemized in division 3.7.

Like other cannabinoid receptor agonists, CBN (a prejudiced cannabinoid CB1 receptor agonist) lowered stomach action two together in control and Croton lubricate-considered mammals, affecting better inhibitory activity in unhealthy states. Interestingly, this inhibitory effect was followed not only by a leftward shift in the in vivo record dose-response curve of CBN but also by an increase in the capacity of its maximum effect. The artificial agonist CP55940, which has higher CB1 productiveness than CBN, has shown an effectiveness increase but the current situation is in allure maximal effect. The reduced doses of CBN that are wanted to humble action during stomach inflammation are of interest in the light of likely healing requests of aforementioned a compound in IBD.

More recently, the non-psychotropic phytocannabinoids CBD and CBC have been judged in the Croton lubricate model of stomach hypermotility. Although neither CBD nor CBC alters stomach motility in administrative rodents, two together of bureaucracy do normalize stomach action in congested rodents. The inhibitory effect of CBD includes CB1 receptors by way of promotion of endocannabinoid levels at these receptors inferred by FAAH inhibition, that is agreeing accompanies the strength concerning this phytocannabinoid to reduce FAAH verbalization in the congested—but not in the normal—rodent gut. On the other hand, the inhibitory effect of CBC did not include cannabinoid receptors or TRPA1 channels. In vitro, two together CBC and CBD applied spasmolytic conduct in ilea from control and croton-lubricate-treated mammals. More exhaustive studies on CBC displayed that this phytocannabinoid changed the ex vivo verbalization of several TRP channels, to a degree TRPA1, TRPV1, TRPV3, and TRPV4, raw spot of croton lubricate-discussed rodent (De Petrocellis et al., 2011). Overall, the in

vivo talent of two together CBC and CBD to make universal action in the inflamed gut, outside delaying the rate of transportation in active animals, is of potential dispassionate interest because now secondhand antidiarrheal powers are often guided constipating belongings.

Finally, Lin and associates establish that CBD normalized hypomotility and instigative responses in the LPS rodent model of poisonous ileus. The feasibility that CBD acts as an integral anti-angering power in this place model of stomach dysfunction cannot be rejected.

Colon tumor

Cannabinoids bring to bear antiproliferative, antimetastatic, and proapoptotic conduct in colorectal carcinoma epithelial containers. In experimental in vivo models of a colon tumor, cannabinoid agonists may be guarding in different stages of colon malignancy progression either straightforwardly, through the incitement of CB1 or CB2 receptors, or obliquely, through the height of endocan-cannabinoid levels by way of FAAH inhibition. Their antitumor conduct can be mediated by either CB1 or CB2 receptor incitement. The means of CB1-interceded apoptosis includes inhibition of two together the RAS–MAPK/ ERK and PI3K–Akt endurance indicating cascades and downregulation of the antiapoptotic determinant survivin. The proapoptotic lipid ceramide may be involved in two together CB1- and CB2-interfered antitumor belongings.

Recently, the phytocannabinoid CBD has been judged for its likely chemopreventive effect in a rodent model of colon malignancy inferred apiece carcinogenic power azoxymethane (AOM). CBD efficiently decreased AOM-persuaded preneoplastic lesions, polyps, and tumors in the colon, an

Clinical studies

Gastrointestinal action, instinctive sensation, and IBS

Visceral sensitivity to extension and changed GI motility are thought to play a main part in the pathophysiology of irritable bowel disease (IBS). Both instinctive perception and GI motility have judged cruel volunteers following in position or time the THC presidency. Thus, nine male and four female cannabis consumers withstood the stomach emptying studies that secondhand radiolabeled reliable cooking as a gravestone, after they had taken THC (at a lot of 10 mg/m2 of carcass surface area) or fake pill. Gastric consumption afterward THC was slower than following in position or time fake pill fully subjects. However, no equating was raised between plasma THC levels and the delay in stomachic unloading. The authors decided that THC, at a dose that can hamper destructive agent-persuaded nausea and disgorging, considerably slowed gastric discharging of dependable foodstuff in humans. The inhibitory effect of THC on stomachic unloading has been rooted again by Esfandyari and associates, in a randomized, double-blind research performed accompanying 30 athletic signs up who had taken THC (5 mg doubly moment of truth) or placebo. Gastric clearing was calculated noninvasively. An overall delay of stomachic emptying accompanying THC distinguished from standard drugs was observed, the effect being more evident in women than in men.

In an additional randomized, double-blind trial, Esfandyari and associates evaluated colonic compli- ance, motility, color, and perception in 52 suggests who had taken a alone

dosage of 7.5 mg THC. An overall significant increase in colonic agreement, an inexact effect on entertainment in fasting colonic pitch, hindrance of postprandial colonic pitch, and inhibition of abstaining and postprandial phasic pressure was noticed. Collectively, the results show that THC relaxes the colon and reduces postprandial colonic action and volume in persons.

More recently, Wong and associates distinguished the belongings of THC (5 mg) with those of standard drugs on colonic action and feeling in patients accompanying IBS, and again administered a pharmacogenetic analysis that investigated the influence of ancestral alternative in the CB1 receptor, FAAH, and MAGL on the strength of THC to alter dysentery and colonic transportation in IBS accompanying diarrhea sufferers. In all subjects (35 with IBS accompanying muscle spasm, 35 accompanying IBS with flux, and 5 accompanying change-dating IBS) THC did not change feeling or color but decreased the abstaining next abandoned colonic motility index distinguished accompanying standarddrugs, and increased colonic agreement. The belongings of THC were excellent in patients accompanying IBS accompanying loose bowels or with rotating IBS. FAAH and CNR1 variants affected the effect of THC on colonic action. In an after research , the alike authors raise that THC (2.5 and 5 mg) did not affect gut transit in IBS inmates accompanying flux, although a situation-by-genotype effect was noticed, bywhich THC preferentially deferred colonic transportation in inmates accompanying the CNR1 rs806378 CT/TT genotypes (Wong et al. 2012)

Finally,Klooker and associates judged the effect of THC on sensitivity in ten IBS subjects and 12 active came forward. THC did not change the criterion stomach perception to extension distinguished to fake pill either in volunteers or in IBS cases. Similarly, following in position or time bowed stimulation there were no important dissimilarities between fake pill and THC in neurological thresholds of discom- stronghold.

In conclusion, studies in persons plan that THC can affect the stomach escaping and colonic action in healthy and/or IBS inmates, specifically in a subgroup of IBS with dysentery victims, established a specific historical difference in the CB1 receptor. Further studies of cannabinoid pharmacogenetics manage to identify a subspace of IBS accompanying loose bowels inmates in which cannabinoid cures concede the possibility solve. Conversely, THC does not seem to influence instinctive ideas in humans, a result that portrays the significance of doing translational studies when fact-finding a likely clinical use of a cannabinoid.

Inflammatory bowel disease

Some IBD victims anecdotally report that they can acquire remedy by smoking pot. Recently, three studies, showing the advantageous effects of marijuana use in persons, appear to confirm the aforementioned reports.

Naftali and associates conducted a retrospective practical research testing ailment activity, use of medication, and need for medical procedure before and following in position or time marijuana use in 30 Crohn's disease (CD) sufferers (26 men). Of the 30 victims, 21 improved considerably afterward situation with marijuana. The need for the additional drug was significantly discounted and the number of victims needing enucleation decreased along with marijuana use.

Lal and colleagues judged marijuana use in 291 IBD sufferers, who achieved an inquiry concerning current and previous marijuana use. About 50% of these IBD victims, specifically those with a record of intestinal incision, chronic intestinal pain, and/or an inferior growth, reported life or current marijuana use. Patients the one had used marijuana were more likely than nonusers to express an interest in performing in a supposed therapeutic trial of marijuana for IBD. Collectively specific results show that cannabis use for syndrome relaxation is ordinary in patients accompanying IBD.

Finally, a ship prospective research including 13 cases accompanying long-standing IBD determined either situation accompanying inhaled cannabis (cigarettes) revised kind of growth, reduced ailment venture, and advanced weight gain in IBD cases. After 3 months' situation, sufferers reported bettering usually well-being perception, public functioning, talent to work, pain, and concavity. Cannabis more advanced burden gain and induced a rise in material bulk index.

CONCLUSION

The conclusions of this study suggest that phytocannabinoids, particularly CBD and THC, show significant potential as therapeutic agents for gastrointestinal (GI) health by modulating motility, reducing inflammation, and influencing the gut microbiome. Emerging evidence supports their integration into treatment strategies for GI disorders such as IBS, IBD, and colorectal malignancies. Future research should focus on optimizing formulations, evaluating long-term safety and efficacy, and exploring their synergistic potential with other therapies to enhance clinical applications.

Although preliminary clinical data are promising, challenges remain in balancing the benefits of cannabinoids with potential adverse effects, such as those linked to CB1 receptor activation. Emphasis should be placed on non-psychoactive cannabinoids, which offer therapeutic potential with fewer side effects. This research contributes to a growing understanding of phytocannabinoids, paving the way for their broader and safer application in managing GI disorders.

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