IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Role Of Cannabinoids In Grahani (Ibs) And Their Therapeutic Application

Dr Geetha B Markande[1], Dr Premsagar M P [2], Dr Prashanth Jain[3]

Professor, 1st Year PG scholar, HOD and Professor

[1]Professor, Department of Roga Nidana Evum Vikriti Vigyana, Alva's Ayurveda Medical College, Moodbidri, Dakshina Kannada, Karnataka

[2]Final year PG Scholar, Department of Roga Nidana Evum Vikriti Vigyana, Alva's Ayurveda Medical College, Moodbidri, Dakshina Kannada, Karnataka

[3]HOD and Professor, Department of Roga Nidana Evum Vikriti Vigyana, Alva's Ayurveda Medical College, Moodbidri, Dakshina Kannada, Karnataka

ABSTRACT:

The endocannabinoid system is a complex cell-signalling system that plays a role in regulating internal activities such as sleep, emotions, pain, reproduction, immunity, appetite, GI function, and metabolism. Endocannabinoids (Anandamide, 2AG) bind to CB1 and CB2 receptors in the gut and regulate motility and inflammation. Endocannabinoid deficiency or dysregulation of the ECS might lead to chronic GI disorders. Grahani roga is one such ailment described in our classics in which the digestive system is altered. Vijaya (*Cannabis sativa*) is one such therapeutic herb that includes phytocannabinoids (CBD, THC) that operate similarly to endocannabinoids. The processed Vijaya is used as a single ingredient and as a component in various ayurvedic formulations in the treatment of Grahani roga. As a result, the current paper is an attempt to appreciate the role of *Vijaya* and its therapeutic applications in Grahani.

Keywords: IBS, endocannabinoid system, cannabinoids, Vijaya, Grahani roga.

INTRODUCTION

Irritable bowel syndrome is a functional gastrointestinal disorder with symptoms including abdominal pain associated with altered bowel habits without structural abnormalities[1]. The IBS Global Impact Report states that the prevalence of IBS globally is 11%[2]. It has a significant effect on health, cost, and quality of life. IBS has many etiological factors and no clear pathophysiology, with a different range of symptoms. Major etiologies are altered GI motility, an increase in visceral sensitivity, which is abnormally processed by the central nervous system, psychological changes, an alteration in mucosal immune activation, changed intestinal permeability, and neurohormonal mechanisms. The heterogeneous symptoms of IBS could be due to the interactions among these different etiologies. Environmental contributors to IBS include early life stressors, food intolerance, antibiotics, enteric infections, etc.[3]. Depending on the predominant pattern of altered bowel habits, the Rome IV criteria divided IBS into 4 different entities: IBS with constipation

(IBS-C), IBS with diarrhea (IBS-D), IBS with a mixed pattern of constipation and diarrhea (IBS-M), and unclassified IBS.[4]

Disease *Grahani Roga*, explained in Ayurveda, has similar presentations as IBS. *Grahani Roga* is a disease caused by derangements in dosha (body humours) and various systems (*srotas*). The systems involved are *Annavaha* (gastrointestinal), *Purishavaha* (excretory), *Manoavaha* (psychological), *Vatavaha* (neurological), *Ahara* (dietary), *Vihara* (behavioural), *Agni* (major metabolic factor), and *Kostha* (gut health). These components play a complex, interconnected, reciprocal role, and this warrants a systems approach. Manifestations include derangements in the bowel like constipation or loose stools, a change in frequency associated with pain or burning, foul-smelling, etc. Other symptoms include bloating, loss of appetite, debility, etc.[5]

The endocannabinoid system (ECS) is a widespread neuromodulatory system that plays important roles in central nervous system (CNS) development, synaptic plasticity, and the response to endogenous and environmental insults.[6] ECS plays a role in regulating internal activities such as sleep, emotions, pain, reproduction, immunity, appetite, GI function, and metabolism. The ECS is comprised of endogenous cannabinoids (endocannabinoids), cannabinoid receptors (CB1 and CB2), and the proteins that transport, synthesize, and degrade endocannabinoids. Evidence suggests that dysregulation of the endocannabinoid system might play a role in intestinal disorders, including inflammatory bowel disease, irritable bowel syndrome, and obesity.[7]

Although ECS has gained attention in modern science as a potential new therapeutic target for treating IBS, it has already been practiced under the Ayurveda System of Medicine in the management of *Grahani* (IBS).

FUNCTIONAL FINDINGS IN IBS

- **Altered GI secretions:** Secretions play a role in chemical digestion and involve the secretion of enzymes throughout the digestive tract. The secretions vary in composition but usually contain water, acids, salts, and various enzymes. Gastric juice makes food particles soluble, initiates digestion, and converts the contents to a semiliquid mass called chyme. In the duodenum, digestive secretions from the liver, pancreas, and gallbladder play an important role in digesting chyme. Motilin is a digestive hormone produced by enteroendocrine cells in the proximal small intestine that stimulates gall bladder emptying and pancreatic and gastric enzyme secretion.[8] IBS patients do exhibit changes in intestinal hormone secretion both in the fasting state and postprandially, as well as increased intestinal secretion in response to perfused bile acids in the ileum. There is enhanced reactivity of the secretory component of the migrating motor complex (MMC) in the small intestine in diarrhea-predominant IBS and, to some extent, also in constipation-predominant IBS.[9]

- **Altered GI motility:** IBS has, for a long time, been considered a disorder of disturbed gastrointestinal motility. Most studies of motility in IBS have focused on the large and small bowel, although there are also reports of disturbed motility in the esophagus and the stomach.[10]
  Esophageal and gastric motility: Esophageal motility includes rhythmic muscle contractions, which help with deglutition. Gastric emptying or postprandial motility acts to provide a reservoir for food by mixing and grinding the food and ensuring a controlled flow of food to the intestines. Patients with IBS demonstrate, for instance, lower pressure in the lower esophageal sphincter and more esophageal contraction abnormalities. Delayed gastric emptying was found in IBS patients with concurrent dyspeptic symptoms. Altered esophageal and gastric motor function is more related to the presence of upper GI symptoms in IBS, like bloating, early satiety, nausea, vomiting, epigastric discomfort, or pain.[11]

Small intestine motility: The small intestine produces a number of different contractions that promote efficient digestion and absorption. The primary type of motility in the small intestine is peristalsis, responsible for mixing intraluminal nutrients with digestive enzymes, propulsion of the contents at a rate that is neither too fast nor too slow, and allowing time for proper digestion and absorption of nutrients. Findings of accelerated motility through the small bowel in diarrhea-predominant IBS and delayed motility in constipation-predominant IBS.[12]

Colonic motility: The colonic motility function has a major impact on the frequency and timing of defecation as well as on the consistency and shape of stools.[13] Patients with IBS experience an altered gastrocolonic motor response, which includes a powerful contraction and a shortened colon transit time.[14]

- **Dysregulation of the Gut-brain axis:** The gut-brain axis (GBA) is a bidirectional pathway linking emotional and cognitive centres in the brain with visceral afferent sensation and intestinal function. GBA regulates digestion, secretion, absorption, blood flow, appetite, energy balance, and metabolism. The gut secretes peptides or hormones in response to nutrients, which can act directly on the brain or indirectly on local vagal and spinal afferent neurons. Central nervous system communication with the gut is mediated through the parasympathetic and sympathetic pathways of the autonomic nervous system (ANS) by modulation of the enteric nervous system. IBS patients exhibit increased sympathetic and decreased parasympathetic activity.[15]
- Another important system in the communication between the brain and the gut is the hypothalamic-pituitary-adrenal (HPA) axis, which has important effects on GI motility, sensation, and immune function.[16] Activation of this system takes place in response to both physical and psychological stressors. Since patients with IBS often report stress-related symptoms.[17]
- **Visceral Hypersensitivity:** Visceral sensations are transmitted from the gut via afferent nerves travelling through the spinal cord to the brain. Visceral hypersensitivity has been recognized as a characteristic of patients with irritable bowel syndrome (IBS). It may be involved in the pathogenesis of abdominal pain or discomfort and seems to result from the sensitization of visceral sensory endings and the sensitization of central nervous system neurons. Visceral hypersensitivity can be caused by altered gastrointestinal motility, gut dysbiosis, stress, and other psychological factors, etc.[18]

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 endocannabinoid system, along with its intercellular signalling, was identified as a result of the study of the mechanism of action of cannabinoids. The receptors and ligands are the main constituents of this ECS system. The two primary endocannabinoids are N-arachidonoylethanolamine, or anandamide, and 2-arachidonoylglycerol (2-AG). These ligands are synthesized from cellular membrane phospholipids and bind to presynaptic receptors, namely the G protein-coupled receptors cannabinoid type 1 and type 2 receptors (CB1 and CB2). Then, the activation of the receptors and signal induction yield 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 activate 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.[19]

ENDOCANNABINOID SYSTEM IN THE GI TRACT

The endocannabinoid system (ECS) plays a significant role in regulating various gastrointestinal (GI) functions and is crucial in maintaining GI homeostasis. The functions of the CB1 and CB2 receptors are ascertained by their locations in the organ systems. In the gut, CB1 receptors are found in the myenteric plexus (responsible for motor control of the GI tract) and submucosal plexus (responsible for secretomotor and vasomotor actions of the gut). CB2 receptors are present in immune cells, such as plasma cells and macrophages, in the *lamina propria* of the GI tract and are also thought to be present in peripheral nerve terminals. Regional variation in receptor distribution influences regulations of gastrointestinal functions like sensation, motility, secretion, and inflammation.[20]

- **Appetite and Food Intake:** Endocannabinoids influence appetite by acting on the central nervous system and peripheral tissues. CB1 receptors, particularly in the hypothalamus, are involved in stimulating appetite and promoting food intake. The activation of CB1 receptors also helps control nausea and vomiting by reducing excitatory neurotransmitters such as glutamate in the dorsal vagal complex (a specialized vomiting centre in the brainstem)[21].
- **Secretion and Absorption:** Endocannabinoids also affect gastrointestinal secretions and nutrient absorption. For instance, endocannabinoids can influence the secretion of gastric acid and digestive enzymes, impacting digestion and nutrient absorption processes that are likely to be mediated via CB1.[22]
- **Regulation of Gastrointestinal Motility:** Activation of CB1 receptors can slow down gastrointestinal motility by inhibiting the excitatory neurotransmitter acetylcholine in the GIT, which may be beneficial in conditions like diarrhea. Conversely, inhibition of CB1 receptors can enhance motility, which is useful in conditions like constipation.[23]
- **Pain and Sensory Modulation:** CB1 and CB2 receptors play a role in modulating pain and discomfort in the GI tract. They can influence the perception of pain and discomfort by altering pain signalling pathways. This is particularly relevant in conditions like irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD).[24]
- **Gut-Brain Axis:** The ECS is integral to the gut-brain axis. Bidirectional interaction affects both emotional and cognitive functions related to GI health and can influence conditions like anxiety and depression, which often accompany chronic GI disorders.[25]
- **Inflammation and Immune Response:** CB2 receptors are predominantly involved in modulating the immune response and inflammation. Activation of CB2 receptors in the GI tract can help reduce inflammation and protect against conditions like IBD by decreasing the production of pro-inflammatory cytokines and other mediators.[26]

Endocannabinoids in the intestine activate CB1 receptors in both physiological and pathological states, CB2 receptors in only pathological states, and TRPV1 receptors in some inflammatory conditions.[27] Clinical Endocannabinoid Deficiency (ECD) is a theory that advocates that the deficient tone of endocannabinoid production causes different pathophysiological syndromes, including IBS, IBD, migraine, post-traumatic stress disorder (PTSD), etc. Thus, CB1 and CB2 receptors give signals and change the function of the body, as they are the pharmacologic targets of cannabinoids in chronic GI disorders.[28]

CANNABINOIDS: These are the group of chemicals which activates the CB receptors.

Table:1 Different types of cannabinoids[29]:

Endocannabinoids (within the human body)	Phytocannabinoids (plant-based cannabinoids)	Synthetic cannabinoids
Anandamide (derived from Sanskrit term-'*Ananda*') 2-arachidonoylglycerol (2-AG)	Δ-9-tetrahydrocannabinol (THC) Cannabidiol (CBD) Cannabigerol Cannabichromene	Naphthylindoles Phenylacetylindoles Benzoylindoles

PHYTOCANNABINOIDS

Phytocannabinoids are naturally occurring compounds found in the cannabis plant (*Cannabis sativa, family Cannabinaceae).* Among the phytocannabinoids, delta-9-tetrahydrocannabinol (THC) is considered the most pharmacologically active, having a variety of central and peripheral effects. It is also thought to be the most active psychotropic agent. Other phytocannabinoids include cannabidiol, cannabigerol, and cannabichromene, all of which are mostly devoid of central effects. Phytocannabinoids (CBD, THC) act on CB receptors similarly as endocannabinoids (Anandamide, 2-AG) and modify various functions in the body. In diarrhea-predominant IBS, phytocannabinoids bind to the CB1 receptor and slow down the GI motility.[30]

CANNABIS PLANT (*VIJAYA*) IN AYURVEDIC PHARMACOPOEIAS

The plant *Cannabis sativa (Vijaya)* has been used in the Ayurveda system of medicine for thousands of years. Many classical Ayurveda textbooks systematically recorded the parts used, pharmacological properties, *Shodana* (processing) procedures, indications and contraindications of the medicinal plant. Its utilization as an ingredient of compound formulations was recorded in various *Sangraha Granthas* like *Baishajya Ratnavali, Rasa Ratna samuchhaya, Bharata Bhaishajya Ratnakara Yogaratnakara, Rasa-Jala-Nidhi, Rasendra sara sangraha,* and other *Nigantus.*[31]

The herb *Vijay* (commonly *Bhang*) is categorised under the *Upavisha Varga* with 34 *Paryayas* (*Ananda, Bhang, Jaya, Madini, Mohini, Ganja, Shivamoli, Siddhi, Manonmana etc.).* It has *Tikta Rasa, Laghu, Tikshna Guna*, possess *Ushna Virya* and *Katu Vipaka.* And it does *Karma* like *Deepana, Pachana, Grahi, Vyavayi, Medhya, Madakari*. It brings effect on *Doshas i.e. Kapha-Vata Hara, Pitta Kara*. Processed drug (*Vijaya*) is used as a single or ingredient of 191 formulations, which are effective in more than 29 diseases including *Grahani roga, Atisara, Anidra etc.*[32]

Table: 2 Ayurveda formulations containing *Vijaya* in *Grahani* (IBS) *Chikitsa*[33,34]:

Formulations	References
Vajrakapata Rasa	*Basavarajiyam*
Grahani Kapata Rasa	*Bharata Bhaishajya Ratnakara, Rasayogasagara*
Grahani Gajendra Vatika	*Brihat Rasarajasundara, Rasayoga Sagara*
Jathiphaladi Churna	*Brihat Yogatarangini*
Grahanyari Rasa	*Brihat Rasarajasundara, Rasayoga Sagara, Bharata Bhaishajya Ratnakara*
Grahani Gaja Kesari Rasa	*Rasa-Jala-Nidhi*
Grahanisetu Rasa	*Rasayogasagara*
Grahani Vajrakapata Rasa	*Rasakamadhenu, Vaidhyachintamani, Rasachintamani*
Sreekameshwara Modaka	*Sharangadhara Samhita- Madhyama Khanda*

Madhya Ganagadhara Churna	*Sharangadhara Samhita Madhyama Khanda*
Kanakasundara Rasa	*Rasayogasagara, Rasendra Chintamani, Bharat Bhaishajya Ratnakara, Rasamanjiri*
Grahanikaparda Pottali Rasa	*Rasa-Jala-Nidhi*
Grahani Shardoola Churna	*Rasa-Jala-Nidhi*

LIMITATIONS

The medical use of cannabis has its limitations. The route of administration is not standardized in modern science.[35] There are different strains of cannabis, with claims of different uses and side effects such as dizziness, dry mouth, altered mental state, and impaired motor coordination. Long-term use might also have implications for mental health, such as anxiety or paranoia in some individuals.[36] There is a risk of misuse or overuse, especially if the medication is not used under the supervision of a healthcare professional. *Vijaya* should be administered internally after specific *Shodana* (processing) and in the appropriate *Matra* (dose), as recommended in the classical texts of Ayurveda.[37]

CONCLUSION

Irritable bowel syndrome (IBS) is a common digestive disorder that can cause abdominal discomfort and irregular bowel movements. IBS is considered a lifelong condition that has a significant impact on health, cost, and quality of life. In the GI tract, the ECS regulates gastrointestinal functions such as sensation, motility, secretion, and inflammation. Clinical Endocannabinoid Deficiency is a theory that suggests that low levels of endocannabinoids (anandamide, 2-AG) and their production cause a variety of disorders, including IBS. Studies have shown that modulating the ECS has a therapeutic effect on chronic GI disorders. Studies also evidenced valuable changes in diarrhea predominant IBS at the cellular level. The medicinal plant cannabis contains phytocannabinoids (THC, CBD), which act on CB receptors similarly to endocannabinoids. In Ayurveda, *Vijaya (Cannabis sativa)* was used to treat many gastrointestinal diseases, which includes *Grahani Roga* (IBS). Several classical Ayurvedic texts describes the *Shodana* (processing) procedure, dosage, and potential therapeutic properties. Some of the compound formulations which are mentioned under *Grahani Chikitsa* (IBS), contains *Vijaya* as an active ingredient and has been successfully practicing since long time under the supervision. As the name says, *Vijaya*, we can succeed in managing of *Grahani Roga*.

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