Review Article **Open Access**

Angry Gut: Irritable Bowel Syndrome

Izrum Shafi Rajput, Syed Ijaz Hussain Zaidi, Sajid Abbas Jaffri, Syed Wajahat Hasib, Kashif Razaq

ABSTRACT

Irritable bowel syndrome (IBS) is a functional disorder of the intestine characterized by abdominal pain and altered bowel habits. At present, no biological marker has been identified. Hence, the disease is clinically assessed on the basis of the symptoms according to ROME IV criteria. Epidemiological data revealed that the prevalence of IBS varies widely around the world, and more thorough research is needed to pinpoint any discrepancies that may exist between countries, as well as possible reasons. Both pharmacological and non-pharmacological therapy is being used in order to treat IBS. There is no specific treatment for irritable bowel disease that has come across the patients and only possible measures have been taken to treat the severity of symptoms. Symptomatic treatment with spasmolytic agent like mebeverine has been considered a standard therapy to relieve pain but to deal with constipation and diarrhea different treatment modalities have been adopted by the physician.

KEY WORDS: Constipation, Diarrhea, Irritable bowel syndrome, ROME IV criteria.

How to cite this Article:
Rajput IS, Zaidi SIH, Jaffri SA, Hasib SW, Razaq K. Angry Gut: Irritable Bowel Syndrome J Bahria Uni Med Dental Coll. 2022; 12(2):105-111 DOI: https://doi.org/10.51985/JBUMDC2021112

INTRODUCTION

Irritable bowel syndrome is a functional disorder of intestine associated with persistent pain, irregular bowel habits, and abdominal cramps. In order to diagnose IBS clinically, the Rome IV criteria is been widely used. In order to implement this criteria, persistent pain in the abdominal region is occurred in the previous 3 months for at least 1 day per week; with two or more of the following associations :1) defecation-associated, 2) associated with alteration in frequency of stool, 3) correlated with a modification in stool form.[1]

Izrum Shafi Rajput
MPhil Candidate Department of Pharmacology
Bahria University of Health Science, Karachi
Email: izrumnafees@gmail.com

Syed Ijaz Hussain Zaidi
Senior Professor, Department of Pharmacology
Bahria University of Health Science, Karachi
Email: Col_zaidi@yahoo.com

Muhammad Sajid Abbas Jaffri
Senior Professor, Head Department of Medicine
Bahria University of Health Science, Karachi
Email: Drsajid.jaffry@live.com

Syed Wajahat Hasib
MPhil Candidate, Department of Anatomy
Bahria University of Health Science, Karachi
Email: s.wajahat.hasib@outlook.com

Kashif Razaq
Associate Professor, Department of Gastroenterology,
Pakistan Navy Ship Shifa Hospital, Karachi
Email: izrumnafees@gmail.com

Received: 30-Nov-2021
Accepted: 09-Mar-2022

Worldwide, the prevalence of disease is varied, but in Pakistan the prevalence of this disease is 45%. Epidemiological information uncover that the pervasiveness of IBS fluctuates generally all throughout the planet, and more intensive exploration is expected to pinpoint any errors that might exist between nations, that could be the expected reasons. In relation with scientific evidences and several changes have been made in diagnostic criteria and sub classification of IBS to date. IBS is not a solely condition but an array of symptoms with clinical differences in its sub types. It is prevalent in all age groups that have a chiefly influence on healthcare systems and unpleasantly affecting eminence of life.[2] On the premise of stool pattern, the syndrome has been sorted out into four categories: irritable bowel syndrome accompanied by diarrhea (IBS-D), irritable bowel syndrome associated with constipation (IBS-C), a mix of diarrhea and constipation associated irritable bowel syndrome (IBS-M), or undefined predominant stool form of irritable bowel syndrome (IBS-U).[3]

METHODOLOGY:

Following search engines such as Google scholar, Pub med and Cochrane library were used to retrieve data. Almost about 70 articles were being reviewed from year 2016 to 2021. From these, 10 were of pediatric, 5 were animal study, 3 were abstract only and 2 were non-English version therefore they were excluded. A total number of 51 articles well assessed in order to write this article. The key words were irritable bowel syndrome, constipation, ROME IV criteria, infections, functional disorder, gut-brain axis, anti-spasmodic, laxatives, pathophysiology. The main focus in this article is on pathophysiology and treatment modalities regarding the management of this disease.

PATHOPHYSIOLOGY

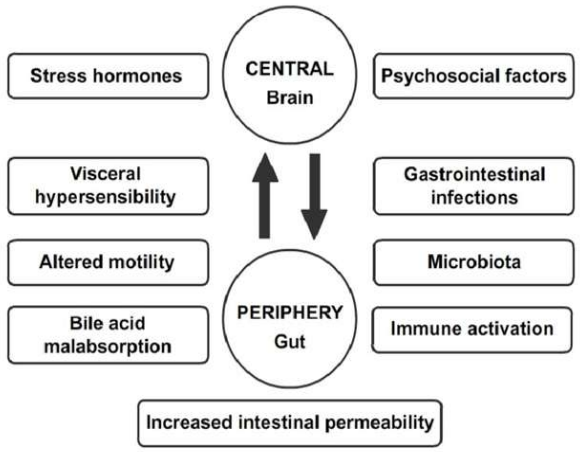
Exact pathophysiology is still idiopathic but multiple factors are considered as aggravating or triggering. It's thought to be a condition caused by a complex combination of circumstances. Although genetic/social learning variables, food, microflora, gastrointestinal moderate inflammation, and aberrant gastrointestinal endocrine cells have all been proven to play a vital role. Literature review spotlighting the contradictory data on the occurrence of circumstances in association with the disease.[4] Generally, the focus is mainly on alterations in gastrointestinal motility and visceral hypersensitivity. Despite the fact that irritable bowel syndrome (IBS) symptoms are mainly concerned to both small intestinal and colonic motility, no familiar correlation of motor activity has been appeared as a diagnosti0c marker for IBS.[5]

GASTROINTESTINAL MOTILITY:

Motor activity of the bowel maybe one of the markers for IBS. Even though more attention has been given to small intestinal and colonic motility as the manifestation of IBS, no major pattern of this activity has emerged.[6] However, motor anomalies of the gastrointestinal tract (GIT) are spotted in few patients with IBS. Some anomalies observed comprise of heightened motor response to cholecystokinin and food ingestion in IBS (diarrhea-predominant), and greater frequency and irregularity of contractions of the lumen, extended transit time in IBS (constipation-predominant). Stimulation of gut motility in IBS patients pharmacologically, has resulted fruitful results in improving symptoms and decreasing gas retention, implying that disturbance in motility is the underlying complaint in some patients.[7]

VISCERAL HYPERSENSITIVITY

Irritable bowel syndrome (IBS) patients commonly experience extreme visceral sensitivity due to irritation. The stimulation of different receptors in the gut wall promotes sensibility in the intestinal (GI) tract. The above receptors send nerve impulses via afferent neural circuits to the posterior horn of the spinal cord.[8] A major contributing factor to the symptoms in IBS is visceral hypersensitivity (VH) which is a complex mechanism arising either in the central nervous system or the peripheral nervous system. Visceral hypersensitivity plays a vital role in pathophysiology and intensity of this disease. As a result, controlling VH can significantly reduce IBS symptoms.[9]



GENETIC INFLUENCE

According to the analysis of genetic polymorphisms (CRH-related), IBS-linked cognitive problems and tolerance to stressful events were affected by the CRH-BP SNP rs10474485[10.] Researchers identified COL6A1 rs13051496, a one-of-a-kind risk variant for IBS-D.[11] When IBS patients (584) and asymptomatic controls (1380) were tested after sequencing the SCN5A gene, 2.2 percent of the IBS cases showed physiologically detrimental mutations while the asymptomatic controls showed none[12].

ALTERATION IN GUT MICROBIOTA

In the etiology of IBS, dysbiosis of the gut microbiota is thought to be a new element. The gut microflora plays an essential part in the advancement of inborn immunity, normal GI physiology, and the fermentation of ingested carbohydrates. A variety of GI syndromes (including IBS) have been a result of changes in structure and balance of the gut microflora[13]. According to the pathophysiological theory of a rise in Bacteroidetes and a decrease in Firmicutes, dysbiosis with bacterial imbalance was identified as an important component of this disease.[14]

LOW GRADE MUCOSAL INFLAMMATION AND IMMUNE ACTIVATION

Some IBS symptoms (e.g., flatulence, dissatisfaction, and increased intestinal transit time) were related to particular gut microbial composition and elevations in proinflammatory mediators in individuals with IBS.[15]

DIETARY INFLUENCE

The digestive system engages a number of complicated systems when a meal is consumed, allowing it to execute the complicated task of digestion and nutrient absorption, as well as waste ejection. In ordinary conditions, gut has specialized response with a properly controlled set of neuro-immune interconnections that is expected to sustain optimal gut activity and homeostasis. Nutritional variables, on the other hand, could be hazardous in some cases, causing intolerant, allergic, or hypersensitive through a variety of processes.[16]

ALTERATION IN GUT-BRAIN AXIS

The gut and its activities (metabolic, immunological, and neuroendocrine) are connected to the neurological system and psyche via the gut-brain-microbiota axis. The gut microbiota influences the growth of the hypothalamic-pituitary-adrenal axis (HPA-axis). [17] Along with an effect on social cognition, incentive, and emotional response pathways, suggests that endurance and cognitive adaptability

to stressors are significant. Stress, on the other hand, can reduce the diversity and makeup of the intestinal flora.[18]

BILE ACIDS ABSORPTION

Bile acids are lipophilic and hydrophilic amphiphatic compounds. They are released into the small intestine by the liver in response to food ingestion to facilitate lipid and fat-soluble vitamin absorption.[19] Despite the fact that IBS has a wide range of symptoms, in comparison to controls, patients with IBS demonstrated substantial differences in network connections between food and fecal microbiomes, as well as differences in fecal metabolomes. Patients with IBS who have BAM can be distinguished by fecal metabolome profiling. These findings could lead to the development of microbe-based therapies for these illnesses.[20]

TREATMENT OF IBS

PROBIOTICS:

Probiotics are microbes that, when given in sufficient proportions, boost the host's health and may be a therapeutic strategy for disorders defined by dysbiosis, such as IBS. In IBS patients, probiotics give a therapeutic benefit above placebo in terms of overall symptoms while also showing a good safety profile.[21] Probiotics are essential for maintaining a healthy microflora in the small intestine (eubiosis) and preventing the formation of harmful microbiota.[22] A handful of studies investigating the impact of probiotics on IBS patients have been conducted, with many of them reporting positive results. Several studies, on the other hand, found no improvement when compared with the control. The disparity could be attributable to study subject variability, probiotic composition, and usage, as well as procedural discrepancies between trials.[23] Many RCT with probiotic Streptococcus thermophilus UASt-09 showed great potentials in reprocessing gastric mucosa and gastrointestinal wellbeing colonic epithelial cells by analysing gene expression of mucus biosynthesis and intestinal immune response markers.[24] Some clinical trials reported the usage of Saccharomyces cerevisiae CNCM I-3856 in IBS improved stomach pain and stool consistency in people with IBS due to its analgesic and anti-inflammatory effect.[25] When compared to some live strains, using effective, non-viable bacterial strain preparations has several significant advantageous.[26]

VITAMIN D:

Vitamin D having previously been reported to have an important role in metabolism of calcium and phosphorus. Several recent research have revealed new information on vitamin D's role in the body, including its immunomodulatory and anti-inflammatory properties. Vitamin D insufficiency is predicted to affect 30–50 percent of the world's population, which seems to be a prevalent percentage in GI disorders.[27] In comparison to the control subjects, patients undergoing vitamin D therapy experienced a considerably larger reduction in IBS symptoms such as abdominal discomfort and abdominal distension, gas, rumbling, and overall gastrointestinal (GI) symptoms.[28] Low vitamin D level is widespread in IBS patients, according to the research, and should be assessed in order to improve the health state. It's been hypothesized that there's an inverse relationship between plasma vitamin D and the intensity of IBS symptoms, and vitamin D supplements can help to improve symptoms. The present RCTs, however, do not provide robust, generalizable data; bigger, appropriately powered interventions are needed to make a case for vitamin D therapy in IBS [29]

ALO VERA:

Aloe vera (AV) is a medicinal herb being used traditional medicine to treat a variety of ailments. Immunomodulatory characteristics of aloe vera as glucomannans, acemannan, and mannose are present, aloe vera may likewise have a prebiotic potential with expansions in bifidobacterial. Studies have looked into whether aloe vera could help with IBS symptoms because of these physiological properties. Hepatoprotective, anti-inflammatory, and anti-ulcerative properties have been demonstrated. The aloe reduced the severity of stress-induced IBS at all doses tested, but not in a dose-dependent manner, by reducing intestinal MPO activity and improving oxidative stress status.[30] Aleo vera is frequently used as a laxative and to increase gastrointestinal peristalsis. In people with constipation, aloe vera can help relieve gastrointestinal pain and discomfort, as well as flatulence. While it can't help with urgency or frequency, it can help with pain in these patients, as well as the consistency of their stools. [31]

PEPPERMINT OIL:

Peppermint oil is thought to have a variety of digestive effects, including antispasmodic, carminative, and antiemetic properties, as well as other digestive effects.[32] Irritable bowel syndrome patients have been reported to benefit from peppermint oil, which has been shown to alleviate abdominal pain. It is evident that peppermint oil relaxes intestinal smooth muscle and desensitizes nociceptive nerve afferents.[33] The blocking of calcium channels that influence smooth muscle is assumed to be the mechanism of action for these antispasmodic effects.[34]

COGNITIVE BEHAVIOUR THERAPY IN IBS:

Visceral hypersensitivity, central processing impairments, and visceral anxiousness are among the psychological and central processing factors that contribute to brain–gut disruption, according to research. These cerebral processes have a role in the onset and progression of the condition, and psychological treatments that tackle these cognitive processes can have a direct impact on the brain–gut axis, resulting in symptom relief. While Cognitive conduct treatment for IBS is very compelling, the restricted accessibility of skilled advisors and absence of admittance to treatment stay tricky.[35]

DIETARY FIBERS:

Different forms of dietary fibers have distinct physical and chemical structures, and the health advantages of each fiber type are unique.[36] Dietary fiber's laxative effects are one of the mechanisms of action in IBS. By mechanically stimulating/irritating the colonic mucosa and boosting secretions and peristalsis, insoluble dietary fiber increases fecal bulk and speeds intestinal transit. Dietary fiber's interaction with the microbiota and the immune system.[37] Dietary fiber appears to work as a prebiotic, influencing the composition of the gut microbiota, according to a growing body of research.[38] Dietary fiber appears to improve all symptoms of IBS, including abdominal discomfort, bloating, digestion, and changes in bowel habits, possibly by affecting the gut nervous system, PH changes, and lumen pressure in the intestine, as well as stimulating the release of serotonin hormone, which is important for visceral sensitivity. Short-chain fatty acids, which are formed by dietary fiber, have an effect on a number of intestinal hormones, including neuropeptide YY (PYY) and glucagon-like peptide. Prostaglandin E2 and vasoactive polypeptide, in addition to PYY, reduce intestinal stimulation, which could explain the effects of dietary fiber on the gastrointestinal tract and its secretions.[39]

LAXATIVE:

In people with IBS, laxatives are commonly used to treat constipation. Bulking agents, osmotic laxatives, stimulant laxatives, and surfactant laxatives are the four types of laxatives accessible. Bulking agents (such as wheat straw, corn fibers, calcium polycarbophil, and ispaghula/psyllium husk) are commonly used to speed intestinal transit in IBS patients.[40]

In IBS, psyllium is the most effective. The fiber's water retention capacity is the first consideration. Water is absorbed and retained by soluble fiber. As a result, the water-holding capability of soluble fiber aids in constipation relief. The fiber's viscous/gel-forming capacity is the second quality. This property makes the fiber viscous, allowing it to pass through the gastrointestinal tract easily. If the bowel movement is too slow (constipation), the viscous fiber speeds it up; if the bowel movement is too quick (diarrhea), the viscosity slows it down and lengthens the transit time. The level of fiber fermentation in the gut is the third quality. A fiber that ferments well would be neither water-resistant nor viscous. Bloating and aggravation of IBS symptoms are caused by gas produced as a result of excessive fermentation.[41]

Patients with neat, soft stools that are difficult to pass should use a stimulant laxative. Because they have the potential to cause addiction, they are only indicated for short-term, infrequent usage. Tachyphylaxis and dependence are linked to stimulant laxatives.[42]

Lubiprostone is a type 2 chloride channel agonist. Lubiprostone enhances chloride-rich fluid secretion and lumbrication of the gut mucosa. These secretions softer the faeces, enhance motility, and encourage the bowels to move on their own. Lubiprostone is a medication that is both safe and effective in the treatment of IBC-C.[43]

Linaclotide is a peptide guanylate cyclase-C agonist that increases fluid secretion into the intestinal lumen. It is a minimally absorbed peptide guanylate cyclase-C agonist. Fluid secretion boosted transit, most likely by stimulating stretch and distention sensitive local receptors. Linaclotide improves bowel function and decreases IBS-C symptom severity by reducing stomach discomfort, bloating, and overall symptom severity.[44]

Osmotic laxatives are administered if the stools remain firm. Osmotic laxatives are poorly absorbed by the gut and cause water to be secreted into the intestinal lumen, softening and easing stool transit. Osmotic treatments for chronic constipation, such as polyethylene glycol (PEG), lactulose, sorbitol, and magnesium hydroxide, are affordable and have been validated in RCTs.[45]

ANTISPASMODICS:

Patients suffering from discomfort or abdominal pain should use antispasmodics (anticholinergic drugs). They act by inducing smooth muscle in the bowel to relax. They treat a subset of IBS patients who have aberrant gastrointestinal smooth muscle contractility and altered gastrointestinal transit, both of which contribute to discomfort and stool irregularities.[46]

Because otilonium bromide is mostly made up of quaternary ammonium, it is only poorly absorbed from the gastrointestinal system. Otilonium bromide inhibits muscarinic receptors as well as L-type and T-type calcium channels. It promotes spasmolysis while lowering peripheral sensory afferent input to the central nervous system, resulting in increased efficacy. These findings show that otilonium bromide may be useful in lowering spasms and stomach pain, which are two of the most common symptoms of IBS.[47]

Pinaverium bromide is a quaternary ammonium derivative that functions as an antispasmodic drug in the gut smooth muscle cells by inhibiting both muscarinic receptors and calcium channels. In vitro studies have shown that PB binds to the -1 subunit21 of l-type (long-lasting) voltage-operated channels on the outside of intestinal smooth muscle cells, inhibiting calcium channels. The principal mechanism for triggering contractile activity is calcium entry into these channels; consequently, inhibiting them produces an antispasmodic action. One of the most distinguishing characteristics of PB is its low systemic absorption and focus on the gastrointestinal tract rather than the cardiovascular system, resulting in a high safety profile.[48]

Mebeverine, a beta-phenylethylamine obtained from reserpine, acts on smooth muscle cells in a rather particular manner without exhibiting atropine-like effects in humans.

It decreases the accumulation of intracellular calcium by blocking sodium channels directly, and it was three times more effective than papaverine at decreasing the ileal peristaltic reflex.[49] It is an antispasmodic agent that directly affect smooth muscle of intestine hence alleviating spasm without acting on motility of gut. Antispasmodic have excellent safety profile, but the inflicting action of mebeverine is still unknown yet its numerous actions like reduced ion permeability, reuptake of nor-adrenaline was blocked, acting as a local anesthetic, anti-muscarinic and phosphodiesterase inhibitory out-turn might put-up to the local effects of mebeverine.[50] The drug produced regulatory effects on bowel function no indication of adverse effects have been seen with the drug in previous studies like nausea, vomiting, heart burn, constipation, headache, indigestion, dizziness.[51]

CONCLUSION:

Despite of evidences in literature, various IBS therapies have questionable efficacy. Irritable bowel syndrome (IBS) is a commonly encountered bowel problem that practitioners face on a regular basis. Though IBS is not life threatening, but its chronic nature has a negative impact on patients' quality of life. In addition to that, it may have a great financial burden on the healthcare system. The identification of specific symptoms and the elimination of other organic disorders are used to diagnose IBS. Treatment for irritable bowel syndrome (IBS) is complicated due to the intricacy and variety of symptoms. There are few trials that provide solid evidence of effectiveness in treating the IBS symptom complexity. IBS has no clear cure, however it can be managed by avoiding exacerbating variables such as specific medicines, stressful situations, and dietary changes. IBS has traditionally been treated symptomatically. A personalized, comprehensive approach to IBS management that includes dietary adjustment, lifestyle amendment, pharmacological, and behavioral therapies are most effective. We did a systematic evaluation of the existing literature on pharmacologic therapy of irritable bowel syndrome to provide evidence-based guidance for clinicians.

Authors Contribution:
Izrum Shafi Rajput: Selection of topic, introduction, literature review, conclusion
Syed Ijaz Hussain Zaidi: Abstract writing, methodology
Sajid Abbas Jaffri: Clinical diagnosis, pathophysiology
Syed Wajahat Hasib: Visceral hypersensitivity and gastrointestinal motility
Kashif Razaq: Laxatives and current clinical guidelines

REFERENCE:

1. Ng QX, Soh AY, Loke W, Lim DY, Yeo WS. The role of inflammation in irritable bowel syndrome (IBS). Journal of inflammation research. 2018;11:345. doi: 10.2147/JIR.S174982
2. Ford AC. Commentary: estimating the prevalence of IBS globally—past, present and future. Alimentary pharmacology & therapeutics. 2020;51(1):198-9.https://doi.org/10.1111/apt.15508
3. Vork L, Weerts ZZ, Mujagic Z, Kruimel JW, Hesselink MA, Muris JW, Keszthelyi D, Jonkers DM, Masclee AA. Rome III vs Rome IV criteria for irritable bowel syndrome: A comparison of clinical characteristics in a large cohort study. Neurogastroenterology & Motility. 2018;30(2):e13189.https://doi.org/10.1111/nmo.13189
4. Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. The lancet Gastroenterology & hepatology. 2016;1(2):133-46. https://doi.org/10.1016/S2468-1253(16)30023-1
5. El-Salhy M, Hausken T, Gilja OH, Hatlebakk JG. The possible role of gastrointestinal endocrine cells in the pathophysiology of irritable bowel syndrome. Expert review of gastroenterology & hepatology. 2017;11(2):139-48. https://doi.org/10.1080/17474124.2017.1269601
6. Masuy I, Van Oudenhove L, Tack J, Biesiekierski JR. Effect of intragastric FODMAP infusion on upper gastrointestinal motility, gastrointestinal, and psychological symptoms in irritable bowel syndrome vs healthy controls. Neurogastroenterology & Motility. 2018;30(1):e13167. https://doi.org/10.1111/nmo.13167
7. Barros LL, Farias AQ, Rezaie A. Gastrointestinal motility and absorptive disorders in patients with inflammatory bowel diseases: Prevalence, diagnosis and treatment. World journal of gastroenterology. 2019;25(31):4414. doi: 10.3748/wjg.v25.i31. 4414
8. Fuentes IM, Christianson JA. Ion channels, ion channel receptors, and visceral hypersensitivity in irritable bowel syndrome. Neurogastroenterology & Motility. 2016;28(11):1613-8. https://doi.org/10.1111/nmo.12979
9. Farzaei MH, Bahramsoltani R, Abdollahi M, Rahimi R. The role of visceral hypersensitivity in irritable bowel syndrome: pharmacological targets and novel treatments. Journal of Neurogastroenterology and Motility. 2016;22(4):558. doi: 10.5056/ jnm16001
10. Sasaki A, Sato N, Suzuki N, Kano M, Tanaka Y, Kanazawa M, Aoki M, Fukudo S. Associations between single-nucleotide polymorphisms in corticotropin-releasing hormone-related genes and irritable bowel syndrome. PloS one. 2016 Feb 16;11(2):e0149322. https://doi.org/ 10.1371/journal.pone.0149322
11. Zhu S, He M, Liu Z, Qin Z, Wang Z, Duan L. Shared genetic susceptibilities for irritable bowel syndrome and depressive disorder in Chinese patients uncovered by pooled whole-exome sequencing. Journal of advanced research. 2020;23:113-21. https://doi.org/10.1016/j. jare.2020.01.016
12. Henström M, D'Amato M. Genetics of irritable bowel syndrome. Molecular and cellular pediatrics. 2016;3(1):1-5. https://doi.org/10.1186/s40348-016-0038-6
13. Bhattarai Y, Muniz Pedrogo DA, Kashyap PC. Irritable bowel syndrome: a gut microbiota-related disorder?. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2017; 312(1):G52-62. https://doi.org/10.1152/ajpgi.00338.2016
14. Harris LA, Baffy N. Modulation of the gut microbiota: a focus on treatments for irritable bowel syndrome. Postgraduate medicine. 2017;129(8):872-88. https://doi.org/10.1 080/00325481.2017.1383819

15. Wang Z, Xu CM, Liu YX, Wang XQ, Zhang L, Li M, Zhu SW, Xie ZJ, Wang PH, Duan LP, Zhu HQ. Characteristic dysbiosis of gut microbiota of Chinese patients with diarrhea-predominant irritable bowel syndrome by an insight into the pan-microbiome. Chinese medical journal. 2019;132(8):889. https://doi.org/10.1097/CM9.0000000000000192
16. Volta U, Pinto-Sanchez MI, Boschetti E, Caio G, De Giorgio R, Verdu EF. Dietary triggers in irritable bowel syndrome: is there a role for gluten?. Journal of Neurogastroenterology and Motility. 2016;22(4):547.doi: 10.5056/jnm16069
17. Moser G, Fournier C, Peter J. Intestinal microbiome-gut-brain axis and irritable bowel syndrome. Wiener Medizinische Wochenschrift. 2018;168(3):62-6. https://doi.org/10.1007/s10354-017-0592-0
18. Pellissier S, Bonaz B. The place of stress and emotions in the irritable bowel syndrome. Vitamins and hormones. 2017; 103:327-54. https://doi.org/10.1016/bs.vh.2016.09.005
19. Peleman C, Camilleri M, Busciglio I, Burton D, Donato L, Zinsmeister AR. Colonic transit and bile acid synthesis or excretion in patients with irritable bowel syndrome–diarrhea without bile acid malabsorption. Clinical Gastroenterology and Hepatology. 2017;15(5):720-7. https://doi.org/10.1016/j.cgh.2016.11.012
2 0. Jeffery IB, Das A, O'Herlihy E, Coughlan S, Cisek K, Moore M, Bradley F, Carty T, Pradhan M, Dwibedi C, Shanahan F. Differences in fecal microbiomes and metabolomes of people with vs without irritable bowel syndrome and bile acid malabsorption. Gastroenterology. 2020;158(4):1016-28. https://doi.org/10.1053/j.gastro.2019.11.301
21. Barbara G, Cremon C, Azpiroz F. Probiotics in irritable bowel syndrome: Where are we?. Neurogastroenterology & Motility. 2018;30(12):e13513. https://doi.org/10.1111/nmo.13513
22. Principi N, Cozzali R, Farinelli E, Brusaferro A, Esposito S. Gut dysbiosis and irritable bowel syndrome: The potential role of probiotics. Journal of Infection. 2018;76(2):111-20. https://doi.org/10.1016/j.jinf.2017.12.013
23. Oh JH, Jang YS, Kang D, Chang DK, Min YW. Efficacy and safety of new Lactobacilli probiotics for unconstipated irritable bowel syndrome: A randomized, double-blind, placebo-controlled trial. Nutrients. 2019;11(12):2887. https://doi.org/10.3390/nu11122887
24. Shastri MD, Chong WC, Vemuri R, Martoni CJ, Adhikari S, Bhullar H, Kunde D, Tristram SG, Eri RD. Streptococcus thermophilus UASt-09 upregulates goblet cell activity in colonic epithelial cells to a greater degree than other probiotic strains. Microorganisms. 2020;8(11):1758. https://doi.org/10.3390 /microorganisms8111758
25. Gayathri R, Aruna T, Malar S, Shilpa B, Dhanasekar KR. Efficacy of Saccharomyces cerevisiae CNCM I-3856 as an add-on therapy for irritable bowel syndrome. International journal of colorectal disease. 2020;35(1):139-45. https://doi.org/10.1007/s00384-019-03462-4
26. Harper A, Naghibi MM, Garcha D. The role of bacteria, probiotics and diet in irritable bowel syndrome. Foods. 2018 ;7(2):13. https://doi.org/10.3390/foods7020013
27. Barbalho SM, Goulart RD, Araújo AC, Guiguer ÉL, Bechara MD. Irritable bowel syndrome: a review of the general aspects and the potential role of vitamin D. Expert review of gastroenterology & hepatology. 2019;13(4):345-59. https://doi.org/ 10.1080/17474124.2019.1570137
28. Nwosu BU, Maranda L, Candela N. Vitamin D status in pediatric irritable bowel syndrome. PLoS One. 2017;12(2):e0172183. https://doi.org/10.1371/ journal.pone.0172183
29. Jalili M, Vahedi H, Poustchi H, Hekmatdoost A. Effects of vitamin D supplementation in patients with irritable bowel syndrome: a randomized, double-blind, placebo-controlled clinical trial. International journal of preventive medicine. 2019;10. doi: 10.4103/ijpvm.IJPVM_512_17
30. Hong SW, Chun J, Park S, Lee HJ, Im JP, Kim JS. Aloe vera is effective and safe in short-term treatment of irritable bowel syndrome: a systematic review and meta-analysis. Journal of neurogastroenterology and motility. 2018;24(4):528. doi: 10.5056/jnm18077
31. Dimidi E, Whelan K. Food supplements and diet as treatment options in irritable bowel syndrome. Neurogastroenterology & Motility. 2020; 32(8):e13951. https://doi.org/10. 1111/nmo.13951
32. Weerts ZZ, Masclee AA, Witteman BJ, Clemens CH, Winkens B, Brouwers JR, Frijlink HW, Muris JW, De Wit NJ, Essers BA, Tack J. Efficacy and safety of peppermint oil in a randomized, double-blind trial of patients with irritable bowel syndrome. Gastroenterology. 2020;158(1):123-36. https://doi.org/10.1053/j.gastro.2019.08.026
33. Weerts ZZ, Keszthelyi D, Vork L, Aendekerk NC, Frijlink HW, Brouwers JR, Neef C, Jonkers DM, Masclee AA. A novel ileocolonic release peppermint oil capsule for treatment of irritable bowel syndrome: A phase I study in healthy volunteers. Advances in therapy. 2018;35(11):1965-78.https://doi.org/10.1007/s12325-018-0802-1
34. Cash BD, Epstein MS, Shah SM. A novel delivery system of peppermint oil is an effective therapy for irritable bowel syndrome symptoms. Digestive diseases and sciences. 2016;61(2):560-71.https://doi.org/10.1007/s10620-015-3858-7
35. Kinsinger SW. Cognitive-behavioral therapy for patients with irritable bowel syndrome: current insights. Psychology research and behavior management. 2017;10:231.doi: 10.2147/ PRBM.S120817
36. El-Salhy M, Ystad SO, Mazzawi T, Gundersen D. Dietary fiber in irritable bowel syndrome. International journal of molecular medicine. 2017;40(3):607-13. https://doi.org/10.3892/ijmm.2017.3072
37. Zhuang Z, Chen M, Niu J, Qu N, Ji B, Duan X, Liu Z, Liu X, Wang Y, Zhao B. The manufacturing process of kiwifruit fruit powder with high dietary fiber and its laxative effect. Molecules. 2019;24(21):3813. https://doi. org/10.3390 /molecules 24213813
38. Taylor AM, Holscher HD. A review of dietary and microbial connections to depression, anxiety, and stress. Nutritional neuroscience. 2020;23(3):237-50. https://doi.org/10.1080/1028415X.2018.1493808
39. Oskouie FH, Vahedi H, Shahrbaf MA, Sadeghi A, Rashidkhani B, Hekmatdoost A. Dietary fiber and risk of irritable bowel syndrome: a case-control study. Gastroenterology and hepatology from bed to bench. 2018;11(Suppl 1):S20. doi: 10.1097/MD.0000000000027541
40. Casado-Bedmar M, Keita ÅV. Potential neuro-immune therapeutic targets in irritable bowel syndrome. Therapeutic advances in gastroenterology. 2020;13:1756284820910630. https://doi.org/10.1177/1756284820910630

41. Garg P. Inflammation in Irritable Bowel Syndrome (IBS): Role of Psyllium Fiber Supplementation in Decreasing Inflammation and Physiological Management of IBS. Turk J Gastroenterol. 2021;32(1):108-10. DOI: 10.5152/ tjg.2020. 20229

42. Radovanovic-Dinic B, Tesic-Rajkovic S, Grgov S, Petrovic G, Zivkovic V. Irritable bowel syndrome-from etiopathogenesis to therapy. Biomedical Papers of the Medical Faculty of Palacky University in Olomouc. 2018;162(1). https://doi. org/ 10.5507/bp.2017.057

43. Chen L, Ilham SJ, Feng B. Pharmacological approach for managing pain in irritable bowel syndrome: a review article. Anesthesiology and pain medicine. 2017;7(2).doi: 10.5812/aapm.42747

44. Yang Y, Fang J, Guo X, Dai N, Shen X, Yang Y, Sun J, Bhandari BR, Reasner DS, Cronin JA, Currie MG. Linaclotide in irritable bowel syndrome with constipation: a phase 3 randomized trial in China and other regions. Journal of gastroenterology and hepatology. 2018;33(5):980-9. https://doi.org/10.1111/jgh.14086

45. Song KH, Jung HK, Kim HJ, Koo HS, Kwon YH, Shin HD, Lim HC, Shin JE, Kim SE, Cho DH, Kim JH. Clinical practice guidelines for irritable bowel syndrome in Korea. Journal of neurogastroenterology and motility. 2018;24(2):197. doi: 10.5056/jnm17145

46. Barney VA, Hernández AF. The role of antispasmodics in managing irritable bowel syndrome. Rev Colomb Gastroenterol. 2019;34(3):267-73. https://doi.org/10.22516 /25007440.309

47. Evangelista S, Traini C, Vannucchi MG. Otilonium Bromide: a drug with a complex mechanism of action. Current pharmaceutical design. 2018;24(16):1772-9. https://doi.org/ 10.2174/ 1381612824666180507122935

48. Schmulson MJ, Chiu-Ugalde J, Sáez-Ríos A, López-Colombo A, Mateos-Pérez GJ, Remes-Troche JM, Sobrino-Cossio S, Soto-Pérez JC, de la Cuesta JL, Teramoto-Matsubara OT, López-Alvarenga JC. Efficacy of the combination of pinaverium bromide 100 mg plus simethicone 300 mg in abdominal pain and bloating in irritable bowel syndrome: a randomized, placebo-controlled trial. Journal of Clinical Gastroenterology. 2020;54(4):e30. https://doi.org/10.1097 /MCG.0000000000001242

49. Heghes SC, Vostinaru O, Rus LM, Mogosan C, Iuga CA, Filip L. Antispasmodic effect of essential oils and their constituents: A review. Molecules. 2019;24(9):1675. https://doi.org/10.3390/molecules24091675

50. Hatami K, Kazemi Motlagh A, Ajdarkosh H, Zargaran A, Karimi M, SHAMSHIRI A, GHADIR M. Comparing the Efficacy of Cumin Sofouf With Mebeverine on Irritable Bowel Syndrome Severity and Quality of Life: A Double-blind Randomized Clinical Trial. Crescent Journal of Medical and Biological Sciences. 2020;7(2):186-94. eISSN 2148-9696

51. Chakraborty DS, Hazra A, Sil A, Pain S. Will controlled release mebeverine be able to surpass placebo in treatment of diarrhoea predominant irritable bowel syndrome?. Journal of family medicine and primary care. 2019;8(10):3173. doi: 10.4103/jfmpc.jfmpc_522_19