

Phytotherapy for managing irritable bowel syndrome

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Abstract

An irritable bowel syndrome is a chronic gastrointestinal disorder causing pain in the stomach, diarrhoea, bloating, constipation etc. The exact cause of irritable bowel syndrome is unknown. However, the diagnosis is often made based on symptoms. Because of long time of syndrome, inadequacy of current treatment, financial burden and pharmacologic burden most of the patient turned to the use of complementary and alternative medicines (CAM) like hypnosis, acupuncture, cognitive behaviour therapy, herbal medicines and nutraceuticals. Many patients use nutraceuticals, in case if the treatment is limited. Nutraceuticals is medicinal therapy that uses herbal plants in the prevention and cure of clinical conditions. The main aim of this study is to assess the potency of nutraceuticals in the control or cure of IBS. Nutraceuticals are an important part of health care system in most of the developing countries.

Keywords: irritable bowel syndrome, nutraceutical, aloe, mentha, turmeric, psyllium.

1. Introduction: Irritable Bowel Syndromes

Irritable bowel syndrome (IBS) is a functional disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel habit. Irritable bowel syndrome (IBS) is a chronic and debilitating functional gastrointestinal disorder that affects 9%-23% of the population across the world. The percentage of patients seeking health care related to IBS approaches 12% in primary care practices and is by far the largest subgroup seen in gastroenterology clinics [4]. The understanding of IBS has undergone a rapid evolution with scientific advancement, but historically it was recognized over 150 years ago. IBS is a common functional bowel disorder that generates a significant health care burden and can severely impair quality of life and is the most commonly diagnosed gastrointestinal condition [5]. Understanding the pathogenesis of IBS is important because today's newer pharmacotherapy agents are beginning to target the known pathophysiologic mechanisms of IBS. Altered gastrointestinal motility, visceral hypersensitivity, post infectious reactivity, brain-gut interactions, alteration in faecal micro flora, bacterial overgrowth, food sensitivity, carbohydrate mal-absorption, and intestinal inflammation all have been implicated in the pathogenesis of IBS [6]. However, the perceived symptoms from these mechanisms consist of abdominal pain or discomfort, bloating, diarrhoea, and constipation. Not all symptoms are gastrointestinal, for instance, fatigue is very common. Historically, medical management has focused on symptomatic treatment of these individual complaints [5].

Neutraceuticals

Neutraceuticals can be defined as any substance that may be considered as a food or a part of food or a nutrient and provides medical or health benefits including the prevention and treatment of disease. The term "neutraceutical" combines two words – "nutrient" (a nourishing food

component) and "pharmaceutical" (a medical drug). The term "neutraceutical" was coined in 1989 by Stephen DeFelice, founder and chairman of the Foundation for Innovation in Medicine, an American organization located in Cranford, New Jersey. In short, nutraceuticals are a group of products that are more than food but less than pharmaceuticals [8]. They possess important physiological functions and valuable biological activities. Products as diverse as isolated nutrients, dietary supplements and diets to genetically engineered "designer" foods, herbal products, and processed foods (cereals, soups, beverages) may be included under nutraceuticals. In India, nutraceuticals have been defined under Clause 22 of the Food Safety and Standards Act (FSSA), 2006 [9]. They can be classified on the basis of their natural sources, pharmacological conditions, as well as chemical constitution of the products. Most often they are grouped in the following categories: dietary supplements, functional food, medicinal food, pharmaceuticals [8].

Pathophysiology

- Traditionally, IBS has been conceptualized as a condition of visceral hypersensitivity (leading to abdominal discomfort or pain) and gastrointestinal motor disturbances (leading to diarrhoea or constipation).
- The gastrointestinal motor disturbances identified, including changes in intestinal transit, do not easily explain mixed or alternating IBS [6].
- Some have suggested that these abnormalities are secondary to psychological disturbances rather than being of primary relevance.
- However, not all patients with IBS have significant psychological overlay and referral bias may partly account for the psychological associations.
- Visceral hypersensitivity and gastrointestinal motor disturbances are emerging [7].

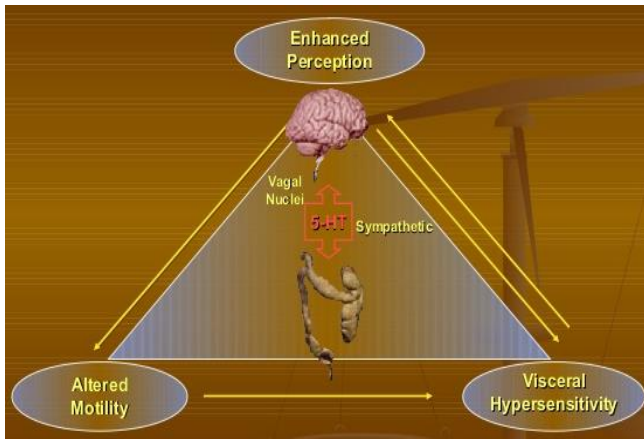


Fig 1

Causes

Irritable bowel syndrome may be related to other intestinal assaults such as food poisoning or gastroenteritis. We will discuss some common causes.

The fury of food poisoning

An infection of intestinal tract known as gastroenteritis can cause IBS. Salmonella, a pathogenic bacteria specie, is often the culprit. Infections are mainly cause by the improperly preparing and cooking of eggs, chicken, meat etc. although this food poisoning is usually mild but in rare cases it is fatal. Bacteria assaults are not the only cause for IBS.

Painful problems with parasites

Parasites and virus can cause IBS. They live off a host and can cause a lot of damage to your GIT. Parasites can cause gastroenteritis with diarrhoea and intestinal damage that persists for months, even after you have been treated. IBS that develops after parasitic gastroenteritis usually only lasts for a few weeks. However, it can last for months (or) even years after a severe bout of parasitic gastroenteritis.

Lactose intolerance

Lactose intolerance is an inability to properly digest milk and milk products. During digestion lactose, (or) milk sugar, is normally broken down into simple sugars called monosaccharaides, glucose and galactose. Due to this effectively, your body needs the enzyme lactase. If you don't have enough lactase in the body, lactose remain in your GIT causing diarrhoea, bloating, gas and abdominal cramps.

Antibiotic attack on gut

Use of antibiotic over an extended period of time leads to irritable bowel syndrome (or) usage of powerful antibiotics even for a short period of can trigger irritable bowel syndrome in some individuals. In addition, over use of antibiotic can lead to bacterial overgrowth in the small intestine (bacteria normally thrive in your healthy colon) i.e., these bacteria ferment carbohydrates and starches and produce excess gas, bloating and abdominal pain.

Candida Calamities

In colon along with bacteria yeast (or) candida is present. It is quite normal and harmless because its growth is held in check by the good bacteria that live there. When the delicate

balance is lost, yeast may grow out of control, these overgrowth releases its own set of dangerous toxins (or) poisons, creating even more symptoms of IBS. It also causes fatigue, allergies, depression, chemical sensitivities and problems with immune function.

Leaky Gut Syndrome

When the villi that line the small intestine have been damaged, tiny particles of undigested food, bacterial toxins and yeast toxins can pass freely into your bloodstream where they wreak all kinds of havoc. The breakdown of this barrier is a condition known as increased intestinal permeability (or) leaky gut syndrome. Increased intestinal permeability commonly produces all of the symptoms of IBS, especially diarrhoea after eating, bloating, gas and abdominal pain^[3].

Signs and Symptoms

Abdominal pain

Abdominal pain is the main symptom. It usually feels like a cramping pain, but it may be sharp (or) dull. It's more commonly located in the left lower quadrant of the abdomen.

Irregular bowel function

You may experience irregular bowel function, alternating with normal function. In other words, you may have either bouts of constipation (or) diarrhoea, (or) both.

An urgency to have a bowel movement

It is one that seemingly can strike at any time is another symptom. This urgency can be very unpredictable and very embarrassing. It usually occurs at meal times (or) shortly thereafter

Abdominal swelling

This is another very common symptom along with bloating, which generally occurs after eating. Pain and swelling usually go away as you sleep.

Mucus in the stools

It is very common if you have IBS. Mucus is secreted by the lining of the colon and rectum, and it functions as a lubricant to ease the passage of the stools. If you have IBS, your body may produce extra mucus, but it is not dangerous and it is not a serious sign of disease.

Incomplete emptying of rectum

Another common symptom is a feeling of incomplete emptying of the rectum after a bowel movement. People suffering from IBS feel they have only had a partial bowel movement, and thus they strain more in an attempt to pass more stool. This is very hard on the anus and can lead to the development of haemorrhoids and eventually rectal prolapse^[3].

2. Nutraceuticals for irritable bowel syndrome

Aloes

Synonym: aloes^[2].

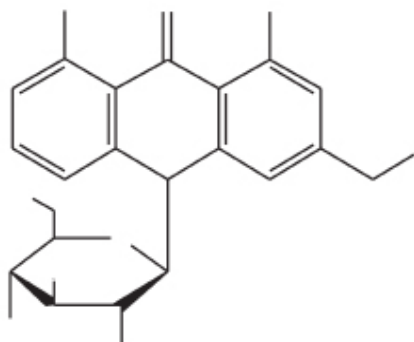
Biological source

Aloe is an unorganised drug prepared as a dried juice (or) the solid residue obtained by evaporating the liquid juice which flows from the transversely cut fleshy leaves of various species of aloe^[2].

Family: Liliaceae ^[2].

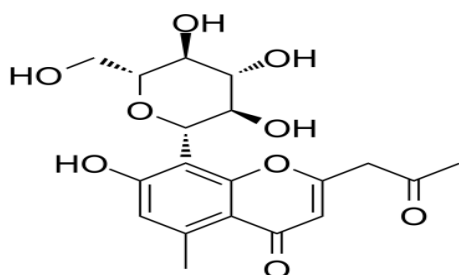
Chemical constituents

- Commercially aloes contain C-glycoside and resin as major constituents.
- C-glycoside content in aloes is to the extent of about 30 percent in the form of mixture of three isomers namely, barbaloin, β -barbaloin, and Iso-barbaloin.



Barbaloin

- These anthrone derivatives as a whole are termed as 'aloin', which is present in almost all types of commercial aloes. C-glycosides are 10- β -D-glucopyranosyl derivative of aloes-emodin anthrone.
- Cape aloes also contain O-glycoside of barbaloin known as aloinoside A and B in which rhamnose sugar as glycosylated at the OH group of hydroxymethyl function.
- Aloes also shows the presence of resins Aloenin A and Aloenin B.
- Aloesin B, a C-glycosyl chromone derivative and Aloesin A, which is p-coumaric acid ester of Aloesin B on glycosyl OH group.



Aloesin

- Chromone glycosides have been detected in *A. ferox* ^[2].

Uses

Irritable Bowel Syndrome

Aloe (*Aloe spicata* and *Aloe Vera*) is commonly considered safe for internal ingestion and is used commonly with IBS. *Aloe Vera* is classified by the U.S. Food and Drug Administration (FDA) as a class 1 harsh stimulant laxative because anthraquinones in aloe significantly increase colonic peristalsis. Aloe should be regarded as being in the same class as other anthranoid laxatives, such as cascara (*Cascara sagrada*) and senna (*Cassia senna*). The juice (not

the gel) stimulates colonic motility, augmenting propulsion and accelerating colonic transit, which reduces fluid absorption from the faecal mass and increases the water content in the large intestine. The laxative effects are due to the glycosides aloin A and B (formerly known as barbaloin). These are hydrolyzed in the colon by intestinal bacteria and then reduced to active metabolites, which act as stimulants and irritants to the GI tract. The laxative effect of aloe is generally not observed before 6 hours after oral administration, and sometimes not until 24 hours or longer after administration (WHO, 1999). Results from the studies showed that aloe vera significantly improved symptoms of IBS when compared to a placebo. No adverse effects were reported, though more research is needed using a larger study size ^[1].

Other uses

- Aloe Vera* is used to heal burns due to its soothing, moisturizing and cooling properties.
- It helps to soothe and cure stomach ailment and it inhibits the growth of *H. pylori* bacteria.
- Aloe vera* toothpaste and mouthwash are natural options for improving oral hygiene and reducing plaque.
- Using fresh aloe on your face may help clear up acne. You can also purchase aloe products designed for acne, including cleansers, toners, and creams ^[11].
- If you have anal fissures, applying an aloe vera cream to the affected area several times may help promote healing.
- Aloe vera* has antioxidant and antibacterial property.
- Aloe vera* gel not only accelerated the healing of mouth ulcers, it also reduced the pain associated with them ^[10].
- Aloe vera* reduced erythema (redness of the skin), but was also found to dehydrate skin cells.
- It is said to enhance insulin sensitivity and help improve blood sugar management ^[12].
- Evidence shows that applying an aloe extract 0.5% cream three times daily increases healing rates in men with genital herpes.
- Applying aloe vera gel powder twice daily to the rectal area for 4 weeks can reduce rectal symptoms caused by radiation to the pelvic area ^[13].
- It can also be used in aphthous stomatitis ^[14].

Mentha

Synonym: Peppermint ^[2].

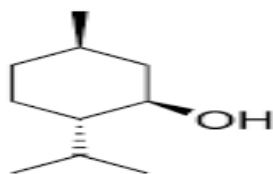
Biological Source

A peppermint leaf consists of dried leaves of *Mentha piperata* L. *Mentha x piperata* L is a hybrid of *M. aquatica* L. (watermint) and *M. spicata*, L. (spearmint), the later itself being a hybrid of *M. longifolia* L. and *M. suaveolens* Ehrhart ^[2].

Family: Labiatae ^[2].

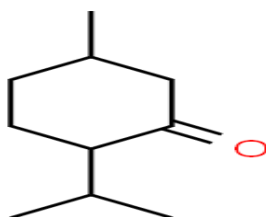
Chemical constituents

- Peppermint contains about 1-3 percent volatile oil, of which the major component is usually (-) menthol up to 35-55 per cent and occasionally up to 60 per cent.



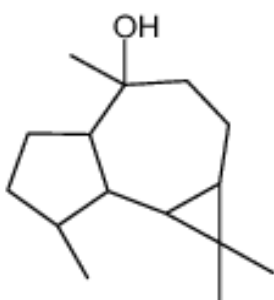
(-) – Menthol

- Along with menthol it contains the stereoisomers of menthol such as (+) neo-menthol and (+) iso-menthol.
- Other mono-terpenoid components of peppermint oil include menthone (10-40 per cent) menthylacetate (1-10 per cent), menthofuran (1-10 per cent), cineol (2-13 per cent) and limonene (0.2-6 per cent).



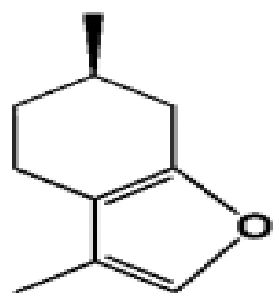
(-) – Menthone

- A small amount of sesquiterpene alcohol viridoflorol is present in the oil.



Viridoflorol

- Among the other non-volatile components of the mentha leaf flavonoids like luteolin, hesperidin, rutin, mentho side and isorhoifolin are found.



Menthofuran

- Phenolic acids such as chlorogenic acid and rosmarinic acids, triterpenoids like α -amyrin, ursolic acid and carotenoids, choline and betaine have been reported from the leaves.
- Menthol is usually prepared from peppermint oil by refrigeration at -22°C , during which the menthol crystallises.

- Menthol occurs as colourless, hexagonal crystals or as a crystalline powder with pleasant [2].

Uses

Irritable Bowel Syndrome

Mentha Piperita is a naturally-occurring carminative herb containing monoterpene compounds that target the pathophysiology of IBS. IBS is a clinical entity that includes a group of functional bowel disorders with chronic, intermittent, or continuous abdominal complaints or abnormal bowel habits, which are specifically defined by, most currently, the Rome II Diagnostic Criteria [16]. Patients with IBS usually can be described as having one of three IBS sub-groups: constipation-predominant, diarrhoea-predominant, or alternating IBS [17].

Mechanism

The use of peppermint oil in IBS stems from several proposed mechanisms of action. Peppermint oil has been shown to reduce gastric motility by directly acting on gut calcium channels to relax gastrointestinal smooth muscle, similar to the actions of dihydropyridine calcium antagonists [18]. A recent review of peppermint oil supports in vitro research showing that peppermint oil relaxes animal and human gastrointestinal smooth muscle, and that menthol has two distinct calcium-antagonistic activities [15]. Peppermint oil also is known to relax the lower oesophageal sphincter, which can lead to symptoms of heartburn after oral administration. For this reason, several manufacturers have developed enteric-coated preparations, delivering the peppermint oil to the small bowel, allowing its effects to focus on the area of the gastrointestinal tract most relevant in cases of IBS.

Other uses

- Mint plants contain an antioxidant and anti-inflammatory agent called rosmarinic acid. The mint plant family provides a range of plant compounds that have anti-allergenic effects.
- Spasmolytic activity is derived from the menthol, which is a calcium antagonist.
- The volatile oil of peppermint inhibits hunger pains in the stomach, but peristalsis resumes shortly with increased intensity, in essence stimulating appetite [15].
- Mint leaves are a tender herb with gentle stems. It is best to add them raw or at the end of the cooking process and help they maintain their delicate flavour and texture.
- The volatile oils works directly on smooth muscle, resulting in decreased tone of the lower oesophageal sphincter, and facilitate belching [9].

Turmeric

Synonym: Curcuma, Turmeric, Rhizoma, Curcuma [2].

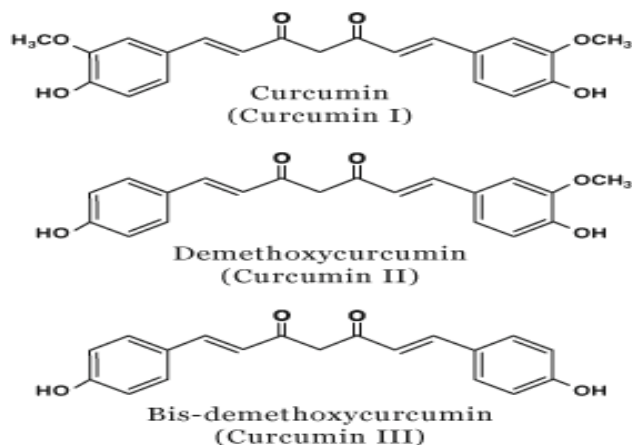
Biological Source: Turmeric consist of dried (or) prepared rhizomes of *Curcuma longa* [2].

Family: Zingiberace [2].

Chemical constituents

- Turmeric rhizome contain about 5 per cent curcuminoids consisting of a mixture of compounds known as curcumins and its derivatives.
- These compounds are diary] heptanoid compounds of dark yellow colour.

- The standardized extracts of curcumin generally consist of curcumin, desmethoxycurcumin and bisdesmethoxycurcumin.
- It also contains dicaffeoylmethane and caffeoylferuloylmethane.
- The essential oil is present to the extent of 5 per cent and constitutes about 25 per cent of zingiberine as a major constituent along with sesquiterpene ketone, turmerone sesquiterpenes and monoterpenoids.



- Monosaccharides such as glucose (28 percent), fructose (12 percent) and arabinose are other compounds present in the rhizome.
- It consists of abundant starch grains [2].

Uses

Irritable Bowel Syndrome

Turmeric has been used to treat conditions, including colds, digestive problems, and infections. Its potential healing properties come from curcumin, which is an anti-inflammatory compound it contains. Turmeric has recently attracted attention for its potential to reduce IBS symptoms. IBS is a common disorder of the digestive system that causes symptoms, such as stomach cramps, diarrhoea, and constipation. The cause of IBS is unknown, and there are currently no available cures. Symptoms of IBS are typically managed using medicine and lifestyle changes that tend to involve changes in diet. Including turmeric as part of a healthful diet-based approach to managing IBS symptoms is an easy step to take [19].

Other uses

- Taking curcumin, a chemical found in turmeric, seems to reduce hayfever symptoms such as sneezing, itching, runny nose, and congestion [20].
- Most available research shows that taking curcumin, a chemical found in turmeric, reduces depression symptoms in people already using an antidepressant [23].
- Turmeric seems to lower levels of blood fats called triglycerides. The effects of turmeric on cholesterol levels are conflicting but it is not known which ones work best [22].
- Research shows that taking turmeric extract reduces markers of liver injury in people who have a liver disease not caused by alcohol. It also seems to help prevent the build-up of more fat in the liver in people with this condition [24].
- Some research shows that taking turmeric extracts, alone or in combination with other herbal ingredients,

can reduce pain and improve function in people with knee osteoarthritis. In some research, turmeric worked about as well as ibuprofen for reducing osteoarthritis pain. But it does not seem to work as well as diclofenac for improving pain and function in people with osteoarthritis.

- Taking turmeric by mouth three times daily for 8 weeks reduces itching in people with long-term kidney disease. Also, some research suggests that taking curcumin plus black pepper or long pepper daily for 4 weeks reduces itching severity and improves quality of life in people with chronic itching caused by mustard gas [21].

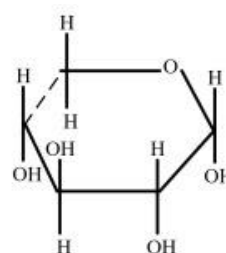
Psyllium

Synonym Psyllium, Flea seeds [2].

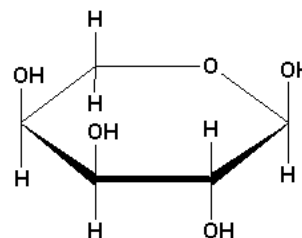
Biological Source: Psyllium consists of seeds of *Plantago psyllium* Linn. (Or) *P. afra* and also from other species such as *P. indica* (or) *P. arenaria* [2].

Chemical Constituents

- Psyllium also contains mucilage in the epidermal layer of testa like ispaghula seeds.
- Mucilage after hydrolysis affords xylose, arabinose, galactose and galacturonic acid.



Xylose



Arabinose

- It also contains fixed oil, sugars, proteins, sterols and a glycoside known as aucubin [2].

Uses

Irritable Bowel Syndrome

Psyllium is mainly used as a viscous, soluble dietary fibre that is not absorbed by the small intestine. The purely mechanical action of psyllium mucilage is to absorb excess water while stimulating normal bowel elimination. Although its main use has been as a laxative, it is more accurately regarded as a dietary fibre and as such can help reduce the symptoms of both constipation and mild diarrhoea. The laxative properties of psyllium are attributed to the fibre: it absorbs water and subsequently softens the stool. It does increase flatulence (gas) to some degree [25].

Other uses

- Psyllium as a soluble fibre would reduce the risk of

heart disease by lowering blood cholesterol [26].

- Psyllium husk may reduce the risk of type-2 diabetes, although the FDA has concluded that there is very little scientific evidence for this claim [27].
- Psyllium has been used as a thickener in ice cream and other frozen desserts. A 1.5% weight/volume ratio of psyllium mucilage exhibits binding properties that are superior to a 10% weight/volume ratio of starch mucilage.

3. Discussion

Aloe

The transparent gel of aloe has a curative action. In IBS, the aloe vera is used as laxative in treatment of constipation. In a study, when men and women were given capsule having celandine - aloe vera - psyllium, or placebo for 28 days and it is reported that abdominal pain was not reduced but this preparation is effective as laxative. In another study by aloe Vera has no effect in IBS but according to Iranian clinical study, 33 patients with constipation was given aloe vera 30ml twice daily for 8 weeks. It is reported that, pain and flatulence decreases, and stool consistence, urgency and frequency of defecation does not changed. However, aloe vera has beneficial effect in controlling IBS symptoms.

Mentha

It is used in Persian traditional medicine for thousands of years. According to the available evidence, mentha is used in gastrointestinal diseases than other neutraceuticals. Enteric coated peppermint oil is effective in treating IBS. IBS patients on treatment with peppermint oil (two enteric coated capsules twice per day for 4 weeks) is effective in controlling IBS symptoms especially abdominal pain. Peppermint oil in IBS has following effects like reducing gastric motility, antispasmodic effect on smooth muscle, anti-inflammatory and anti-microbial activities in small intestine.

Turmeric

Turmeric is used in Iranian and Chinese traditional medicine for digestion, abdominal pain, bloating and distension. When two doses of turmeric extract was given to IBS patients for 8 weeks, it has reported that the symptoms are improved in those patients. Curcumin is an anti-inflammatory and antioxidant agent. The efficacy of curcuma may be due to anti-bacterial, anti-inflammatory and spasmolytic activities.

Psyllium

Psyllium is a dietary fibre used in the management of constipation, a symptom of IBS. In a study a soluble fibre (psyllium) and an insoluble fibre (bran) in 275 IBS patients were evaluated. They convey that those who had three months after treatment, symptom severity in the psyllium group had reduced by 90 points, compared with 58 points in the bran group. They offered that Psyllium benefits patients with IBS in primary care whereas in other articles, it reveals that fiber reducing IBS symptoms, particularly patients with constipation, but were not effective in abdominal pain. Similar results in six studies were observed, but when the treatment effect was considered in the meta-analysis of these studies, there was no statistical significance.

4. Conclusion

As we have observed above that the irritable bowel syndrome has many complicated components and causes. Nowadays, most of the IBS patients are widely using neutraceuticals. Various neutraceutical preparations and their mechanism of action have been illustrated above in the treatment of irritable bowel syndrome viz. aloe vera and curcuma shows pro-secretory activity, anti-inflammatory activity and induces gastrointestinal motility whereas mentha aids in controlling abdominal pain and psyllium eases relieve from constipation. As per the various parameters that influence the pathophysiology of IBS, it is believed that neutraceuticals are more beneficial than other products.

5. Acknowledgement

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6. References

1. Herbal Medicinals-A Clinician's Guide by Lucinda G, Miller, Wallance J, Murray, 84-87.
2. Pharmacognosy & Phytochemistry by Vinod D Rangari, 3rd edition, volume-1, pg.no.-237 to 241, 337 to 340, 422 to 424.S
3. The Bible Cure for Irritable Bowel Syndrome by Don Colbert MD, 2-12.
4. Drossman DA, Corraziari E, Delvaux M, Spiller R, Talley NJ, Thompson WG, *et al.* Rome III: The Functional Gastrointestinal Disorders. McLean, VA: Degnon Associates, 2006. [Google Scholar].
5. Occhipinti K, Smith JW. Irritable bowel syndrome: a review and update. *Clin Colon Rectal Surg.* 2012; 25:46-52. [PMC free article] [PubMed] [Google Scholar].
6. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology.* 2002; 123:2108-2131. [PubMed] [Google Scholar].
7. Talley NJ, Spiller R. Irritable bowel syndrome: a little understood organic bowel disease? *Lancet.* 2002; 360:555-564. [PubMed] [Google Scholar].
8. István G Télessy, in the Role of Functional Food Security in Global Health, 2019.
9. Dudeja P, Gupta RK, in Food Safety in the 21st Century, 2017.
10. Syed TA, Afzal M, Ashfaq AS. Management of genital herpes in men with 0.5% Aloe vera extract in a hydrophilic cream. A placebo-controlled double-blind study. *J Derm Treatment.* 1997; 8(2):99-102.
11. Syed TA, Cheema KM, Ashfaq A, Holt AH. Aloe vera extract 0.5% in a hydrophilic cream versus Aloe vera gel for the management of genital herpes in males. A placebo-controlled, double-blind, comparative study. [Letter.]. *J Eur Acad Dermatol Venereol.* 1996; 7:294-295.

12. Syed TA, Cheema KM, Ahmad SA. Aloe vera extract 0.5% in hydrophilic cream versus aloe vera gel for the measurement of genital herpes in males. A placebo-controlled, double-blind, comparative study. *Journal of the European Academy of Dermatology & Venerology* 1996;7(3):294-295.
13. Vazquez B, Avila G, Segura D, Escalante B. Antiinflammatory activity of extracts from Aloe vera gel. *J Ethnopharmacol.* 1996; 55(1):69-75.
14. Garnick JJ, Singh B, Winkley G. Effectiveness of a medicament containing silicon dioxide, aloe, and allantoin on aphthous stomatitis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1998; 86:550-6. [PubMed] [Google Scholar].
15. Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: A critical review and meta-analysis. *Am J Gastroenterol.*1998; 93:1131-1135.
16. Thompson WG. Functional bowel disorders and functional abdominal pain. *Gut.* 1999; 45(2):1143-1147.
17. Kiefer D, Ali-Akbarian L. A brief evidence-based review of two gastrointestinal illnesses: Irritable bowel and leaky gut syndromes. *Altern Ther Health Med* .2004; 10:22-30.
18. Hills JM, Aaronson PI. The mechanism of action of peppermint on gastrointestinal smooth muscle: An analysis using patch clamp electrophysiology and isolated tissue pharmacology in rabbit and guinea pig. *Gastroenterology.* 1991; 101:55-65.
19. Irritable bowel syndrome (IBS), 2017. <https://www.nhs.uk/conditions/irritable-bowel-syndrome-ibs/diet-lifestyle-and-medicines/>
20. Wessler S, Muenzner P, Meyer TF, Naumann M. The anti-inflammatory compound curcumin inhibits *Neisseria gonorrhoeae*-induced NF-kappaB signaling, release of pro-inflammatory cytokines/chemokines and attenuates adhesion in late infection. *Biol.Chem.* 2005; 386(5):481-490. View abstract.
21. Vareed SK, Kakarala M, Ruffin MT, Crowell JA, Normolle DP, Djuric Z, *et al.* Pharmacokinetics of curcumin conjugate metabolites in healthy human subjects. *Cancer Epidemiol. Biomarkers Prev.* 2008; 17(6):1411-1417. View abstract.
22. Wongcharoen W, Jai-Aue S, Phrommintikul A, Nawarawong W, Woragidpoonpol S, Tepsuwan T, *et al.* Effects of curcuminoids on frequency of acute myocardial infarction after coronary artery bypass grafting. *Am J Cardiol.* 2012; 110(1):40-44. View abstract.
23. Xu Y, Ku BS, Yao HY, Lin YH, Ma X, Zhang YH, *et al.* The effects of curcumin on depressive-like behaviors in mice. *Eur.J Pharmacol.* 2005; 518(1):40-46. View abstract.
24. Yiu WF, Kwan PL, Wong CY, Kam TS, Chiu SM, Chan SW, *et al.* Attenuation of fatty liver and prevention of hypercholesterolemia by extract of *Curcuma longa* through regulating the expression of CYP7A1, LDL-receptor, HO-1, and HMG-CoA reductase. *J Food Sci.* 2011; 76(3):H80-H89. View abstract.
25. Christodoulides S, Dimidi E, Fragkos KC, Farmer AD, Whelan K, Scott SM. "Systematic review with meta-analysis: effect of fibre supplementation on chronic idiopathic constipation in adults". *Alimentary Pharmacology & Therapeutics.* 2016; 44(2):103-116. doi:10.1111/apt.13662. ISSN 1365-2036. PMID 27170558.
26. Sec. 101.81 Health claims: Soluble fiber from certain foods and risk of coronary heart disease (CHD) U.S. Food and Drug Administration, Code of Federal Regulations Title 21.
27. Qualified Health Claim for Diabetes US Food and Drug Administration, 2014.