DR SHANTI ESWARAN (Orcid ID : 0000-0002-4660-3670)

Received Date : 19-Jan-2017
Revised Date : 31-Jan-2017
Accepted Date : 31-Jan-2017
Article type : Mini-review

**Title:**

Low FODMAP in 2017: Lessons learned from clinical trials and mechanistic studies.

**Author:**
Shanti Eswaran, MD, RFF
Clinical Assistant Professor
Division of Gastroenterology
University of Michigan Health System
3912 Taubman Center, SPC 5362
Ann Arbor, MI 48109-5362
Phone: 734-936-4785
E-mail: seswaran@med.umich.edu

**Competing Interests:** The author has no competing interests
**Funding: Not applicable**
**Authorship: SE wrote the entire manuscipt**

**Abstract**

Given the prevalence of irritable bowel syndrome (IBS) and the suboptimal response to most therapeutic approaches, there has been increasing interest in and adoption of dietary treatment strategies, such as the low FODMAP diet. FODMAPs are a diverse group of carbohydrates that exert effects in the GI tract not only via fermentation but likely via alterations in the microbiota, metabolome, permeability, and intestinal immunity as well. Clinical evidence for efficacy of this diet is mounting, but there are significant questions regarding short- and long-term safety and effects on the microbiota and nutrition that remain unanswered. This review article interprets the recent findings reported in this issue of *Neurogastroenterology and Motility* and summarizes the mechanistic and clinical efficacy data of the low FODMAP diet in IBS patients to date.

Irritable bowel syndrome (IBS) is a prevalent condition that leads to considerable morbidity and disability.[1] Despite this, health care expenditures for the treatment of organic diseases consume a disproportionate portion of the health care pie and leave little for so-called "quality of life" disorders like IBS. In addition, the heterogeneity inherent to the phenotype and pathogenesis of IBS has created significant challenges in drug therapy development for this chronic disease, and the absolute therapeutic gain from traditional therapies has been marginal, typically ranging from 7-15%.[2] As a consequence, providers and IBS patients are increasingly being forced to find solutions for their symptoms that do not involve prescription medications. When one considers that two thirds of IBS patients associate their symptoms with eating a meal,[3,4] the importance of finding effective, evidence-based dietary solutions becomes obvious. Furthermore, IBS patients are demanding more "natural," accessible, cost-effective, and safe options to treat their disease. Unfortunately, traditional dietary advice for IBS patients, such as regulating fiber intake or fat content, is not evidence-based and often has proven ineffective.[5-8] Thus, the low FODMAP (Fermentable Oligo-, Di-, & Mono-Saccharides and Polyols) diet has been gaining popularity for the treatment of this condition. This review article interprets the recent findings of Hustoft et al[9] reported in this issue of *Neurogastroenterology and Motility* and summarizes the mechanistic and clinical efficacy data of the low FODMAP diet in IBS patients to date.

***Mechanistic Insights***

FODMAPs are a diverse group of poorly absorbed carbohydrates thought to contribute to GI symptoms, likely via multiple pathways [**Figure 1]**. Conventional thinking has focused on the cumulative effects of consuming excessive amounts of all FODMAPs. Undigested, non-absorbed FODMAPs create an osmotic load and are then fermented by small intestinal and colonic bacteria. This leads to the production of short chain fatty acids and gases (hydrogen, methane, carbon dioxide), which can trigger symptoms particularly in patients who have underlying abnormalities in gut motility and visceral sensation.[10,11] Collectively, these effects can exert primary and secondary effects on motility, visceral sensation, and the gut microbiota that may result in symptoms of cramping, bloating, distention, and flatulence in a subset of IBS patients.[12-14] However, recent work suggests that different FODMAPs exert different effects in different parts of the GI tract. Using fMRI, investigators from the UK showed differential effects of fructose and fructans in the small intestine and colon in healthy volunteers and IBS patients.[15,16] After fructose and inulin (a fructan) challenges, healthy controls had significantly lower symptom scores after either fructose or inulin consumption than patients with IBS, despite similar fMRI parameters and breath hydrogen responses.[16] Fructose led to increased small-bowel water content in both IBS patients and controls (potentially accelerating small bowel transit and peristalsis as well) whereas inulin increased colonic volume and gas via fermentation by resident bacteria. This indicates that colonic hypersensitivity, rather than greater gas production or distension, drives FODMAP-related symptoms in some IBS patients.

Aside from fermentation effects, FODMAPs may also generate symptoms via immune activation. Given that wheat products contain high FODMAP content, predominantly fructans and galacto-oligosaccharides (GOS), studies focusing on non-celiac wheat sensitivity (NCWS) may be potentially extrapolated to IBS patients.[17,18] Possible mechanisms for NCWS (and thus a response to a low FODMAP diet) include increased intestinal permeability of tight junctions or stimulation of lamina propria macrophages leading to pro-inflammatory cytokines.[19,20] Histamine, a signaling molecule known to underlie IBS symptoms, may also be affected by the low FODMAP diet. McIntosh et al[21] compared urinary metabolomic profiles of 40 IBS patients after 21 days of a low- or high-FODMAP diet. Following dietary intervention there was a significant separation in urinary metabolomic profiles of patients with IBS in the two diet groups. In the low

FODMAP diet group, urinary histamine level decreased significantly after the intervention ($p<0.05$) compared to the high-FODMAP group. The authors postulate that degranulation of mast cells may occur due to direct signaling from short chain fatty acids (SCFAs) or from intestinal distension via fermentation, thereby modulating IBS symptoms.

***Evidence of Clinical Benefit***

There is a growing body of evidence to support the efficacy of the low FODMAP diet in patients with IBS symptoms.[22-26] The first study demonstrating a link between dietary FODMAPs and symptoms comes from Shepherd and Gibson's 2008 Australian work during which IBS patients were more likely to experience gastrointestinal symptoms after blinded consumption of escalating doses of fructose or fructans than after glucose.[23] This approach was novel because until this time, dietary strategies focused on the elimination of a single carbohydrate type (ie, lactose, sorbitol, fructose) rather than entire groups of carbohydrates. Subsequent retrospective and randomized studies of dietary FODMAP restriction have reported symptomatic improvement in 52%-76% of IBS patients.[27-31] Many studies involving diet for IBS suffer from placebo effect, limited duration, lack of rigorous endpoints, lack of randomization/blinding, and limited dietary assessment to confirm adherence.

The results of RCTs in IBS patients have not been uniformly positive, especially when compared with active interventions in a more "real world" setting where food was not supplied to subjects.[32,33] Bohn et al[33] compared the low FODMAP diet to standard dietary advice and found that about half of each group improved with the intervention, with no significant difference between the two groups after 4 weeks. Each group received dietitian counselling, and all IBS subtypes were included. Similar improvements in each group were noted for most individual symptoms as well (bloating, abdominal pain). Our group recently completed the first US comparative effectiveness trialcomparing the low FODMAP diet versus usual dietary recommendations in IBS patients with diarrhea (IBS-D) using a similar study design in 92 patients.[32] There was no significant difference between the interventions for the primary endpoint of adequate relief (52% with a low FODMAP diet versus 41% with usual dietary recommendations. However, a significantly greater proportion in low FODMAP diet group than the usual

dietary recommendation group experienced improvement in abdominal pain and bloating, two of the most bothersome complaints associated with IBS. In addition, significant improvements were seen in stool consistency, stool frequency, and urgency compared to usual dietary recommendations for IBS. Significant improvements in quality of life measures, as well as anxiety were seen in the low FODMAP diet compared to usual dietary recommendations for IBS.[34] The primary endpoints were negative in both trials that utilized an active comparator and dietitian-directed dietary interventions, pointing to the some of the limitations of the low FODMAP diet in the clinical setting (see below). However, the secondary endpoints differed, likely explained by intrinsic differences in genetics, microbiome, diet, and cultural issues between the study populations, in addition to variation in dietary advice and IBS subtype.

***Diet Limitations***

Though the popularity of this dietary approach has progressively increased worldwide, the low FODMAP diet has a number of important shortcomings. This approach, while clinically effective, is highly restrictive and may be confusing to administer, leading to potential problems with adherence. Another issue is that the full elimination phase is *not* intended to be continued indefinitely; if a patient improves during the full elimination phase, providing tailored dietary counseling to re-introduce FODMAP containing food groups to arrive at each individual's version of the low FODMAP diet is recommended. The duration of the full low FODMAP diet has potential long term implications considering that fermentable carbohydrates such as FODMAPs provide substrates for "healthy" GI bacteria. Indeed, several studies comparing the effects of a low FODMAP diet to a habitual diet demonstrated a reduction of the proportion and concentration of *Bifidobacteria.*[9,24] Another study did not demonstrate a decrease in *Bifidobacteria*, but did show a decrease in total bacteria abundance,[35] the consequences of which have not been well characterized. In addition to changing the microbiota, fermentation creates by-products such as SCFAs, including butyrate, providing nutrients and other benefits for the colonic mucosa and playing a critical role to the luminal microenvironment [**Figure 1**].[36] Thus, while the low FODMAP diet may improve GI symptoms, long term avoidance of FODMAPs may have potentially harmful effects on colon health. Studies investigating the effects of the low FODMAP diet on the colon metabolome are conflicting. Halmos et al found no change in SFCA concentration between the low FODMAP diet and a

habitual Australian diet,[35] while others have observed a decrease in SCFA compared to a habitual diet.[9]

In this issue, Hustoft et al[9] report the results of a crossover study designed to investigate the importance of fructo-oligosaccharides (FOS) in symptom generation in IBS patients. After 3 weeks of a low FODMAP diet, 20 patients with non-constipated IBS received either 10 days of FOS or placebo supplements, followed by a washout period of three weeks, followed by another 10-day crossover period. The authors analyzed inflammatory cytokines throughout the study, and SCFAs and gut microbiota composition were analyzed as well. Most patients had severe IBS symptoms as measured by IBS-SSS. Interestingly, all patients improved with the low FODMAP diet (defined as reduction in at least 50 points IBS-SSS) and all patients completed the trial. When the FOS supplement was introduced, significantly fewer subjects reported control of IBS symptoms compared to placebo, with no order effect observed (80% v 30%). There was a large intersubject variability in the responses to FODMAP provocation (FOS vs placebo) as compared to FODMAP reduction. Levels of IL-6 and IL-8 both decreased significantly after 3 weeks of LFD, with a median reduction of 0.065 pg/mL and of 2.95 pg/mL, respectively. There were no changes seen in levels of TNF-α. Cytokine levels did not change in response to FOS supplementation, however. *F. prausnitzii*, *Actinobacteria*, and *Bifidobacterium* abundance were significantly altered in both dietary interventions (decreased in low FODMAP diet, increased again with FOS supplementation). Levels of total SCFAs and n-butyric acid both decreased significantly following a low FODMAP diet as compared to baseline, but SCFA levels were otherwise not significantly altered when comparing values from samples obtained at baseline, following a low FODMAP diet, and after FOS supplementation.

This manuscript from Norway addresses several unanswered questions about the low FODMAP diet. Because of its crossover design and lack of worsening symptoms with the maltodextrin placebo, it is clear that a placebo response is not entirely responsible for the effect of the diet. Also, although IBS symptoms significantly worsened in response to FOS, the severity was not comparable to the symptom level observed at baseline. This lends weight to the belief that while individual FODMAP restriction may be partially beneficial, collective FODMAP restriction (at least in this patient population) may

be required to achieve maximum symptom response. There was however a larger inter-subject variability in response to the 2 supplements, supporting the view that each patient's threshold/FODMAP sensitivity is specific and may be individualized.

Based on this and other studies,[21,24,35] it seems clear that the low FODMAP diet has effects on the microbiota and metabolome, decreasing SCFAs and bacteria thought to promote GI health. The fact that the abundance of several bacteria (*F. prausnitzii*, Actinobacteria, and Bifidobacterium) rebounded after 10 days of FOS supplementation is reassuring, that the effect of dietary change is temporary. However after FOS supplementation, both cytokine levels and SCFA levels were unchanged. Reasons for this are not clear--perhaps 10 days of FOS supplementation is not of sufficient duration, or that alternate FODMAPs are driving those changes.

***Unanswered questions***

The efficacy of a low FODMAP diet for IBS is becoming increasingly obvious but several areas remain to be clarified: (1) the mechanism(s) by which FODMAP restriction improves symptoms, (2) long term effects/safety in terms of gut microbiota and potential nutritional deficiencies, (3) standardization of a reintroduction protocol, (4) whether or not complete exclusion of all FODMAPs is necessary for full clinical benefit, and (5) improving patient selection to enrich symptom response. These questions are linked, and as we determine the mechanism(s) by which FODMAP exclusion alleviates IBS symptoms, the answers to the remaining questions will become more apparent.

If an IBS patient improves with the full elimination of dietary FODMAPs, a reintroduction phase begins to determine an individual patient's FODMAP intolerances. Given both the concerns about long term effects of the low FODMAP diet on the microbiota and overall nutrition, as well as the restrictive nature of the diet, the full low FODMAP diet is not meant to serve as a long term solution for patients with IBS. The current means by which FODMAP reintroduction is conducted varies dramatically from center to center and is driven by the biases and clinical experiences of providers rather than evidence. It is a poorly defined trial-and-error process which is clearly suboptimal and may expose patients to prolonged or even unnecessary suffering as they try to identify their personal

FODMAP triggers. There are currently little scientifically rigorous data to allow an evidence-based approach to FODMAP reintroduction and consequently, there is no widely accepted protocol for this process. This leaves providers to develop their own non-evidence based protocols to address the complexities surrounding (1) specific foods used to challenge patients, (2) FODMAP dose, and (3) duration of exposure. Generating a structured reintroduction protocol for clinical practice would serve as a construct for clinicians worldwide to guide dietitians and patients during this process. Additionally, further investigative efforts should be made to determine if the observed changes in the microbiota mitigated by the low FODMAP diet remain once certain FODMAPs are re-introduced to tolerance.

One could image a future where it may then be possible to construct a less restrictive version of the low FODMAP diet which offers similar clinical benefits to most IBS patients. Determining a less restrictive version of the low FODMAP diet could improve adherence, create wider appeal, and ease the financial and logistic burden for this dietary approach. Facebook, Netflix, and Google currently curate user content based on our demographics, past purchases, and search history. There is no reason then that we as clinicians cannot grasp the tools to do the same for our patients: to curate their care based on their preferences, symptoms, and biomarker data including stool and metabolomic profiles.

**References**


1. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *Jama.* Mar 03 2015;313(9):949-958.
2. Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med.* Jul 18 2000;133(2):136-147.
3. Simrén M, Månsson A, Langkilde AM, et al. Food-related gastrointestinal symptoms in the irritable bowel syndrome. *Digestion.* 2001;63(2):108-115.

4. Chey WD. The role of food in the functional gastrointestinal disorders: introduction to a manuscript series. *Am J Gastroenterol.* May 2013;108(5):694-697.
5. Bohn L, Storsrud S, Simren M. Nutrient intake in patients with irritable bowel syndrome compared with the general population. *Neurogastroenterol Motil.* Jan 2013;25(1):23-30 e21.
6. Heizer WD, Southern S, McGovern S. The role of diet in symptoms of irritable bowel syndrome in adults: a narrative review. *J Am Diet Assoc.* Jul 2009;109(7):1204-1214.
7. Eswaran S, Muir J, Chey WD. Fiber and functional gastrointestinal disorders. *Am J Gastroenterol.* May 2013;108(5):718-727.
8. Ford AC, Talley NJ, Spiegel BM, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. *BMJ.* 2008;337:a2313.
9. Hustoft TN, Hausken T, Ystad SO, et al. Effects of varying dietary content of fermentable short-chain carbohydrates on symptoms, fecal microenvironment, and cytokine profiles in patients with irritable bowel syndrome. *Neurogastroenterol Motil.* Oct 16 2016.
10. Ong DK, Mitchell SB, Barrett JS, et al. Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. *J Gastroenterol Hepatol.* Aug 2010;25(8):1366-1373.
11. Shepherd SJ, Lomer MC, Gibson PR. Short-chain carbohydrates and functional gastrointestinal disorders. *Am J Gastroenterol.* May 2013;108(5):707-717.
12. Gibson PR, Newnham E, Barrett JS, Shepherd SJ, Muir JG. Review article: fructose malabsorption and the bigger picture. *Aliment Pharmacol Ther.* Feb 15 2007;25(4):349-363.
13. Brighenti F, Casiraghi MC, Pellegrini N, Riso P, Simonetti P, Testolin G. Comparison of lactulose and inulin as reference standard for the study of resistant starch fermentation using hydrogen breath test. *Ital J Gastroenterol.* Apr 1995;27(3):122-128.

14. Tazoe H, Otomo Y, Kaji I, Tanaka R, Karaki SI, Kuwahara A. Roles of short-chain fatty acids receptors, GPR41 and GPR43 on colonic functions. *J Physiol Pharmacol.* Aug 2008;59 Suppl 2:251-262.
15. Murray K, Wilkinson-Smith V, Hoad C, et al. Differential effects of FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols) on small and large intestinal contents in healthy subjects shown by MRI. *Am J Gastroenterol.* Jan 2014;109(1):110-119.
16. Major G, Pritchard S, Murray K, et al. Colon Hypersensitivity to Distension, Rather Than Excessive Gas Production, Produces Carbohydrate-Related Symptoms in Individuals With Irritable Bowel Syndrome. *Gastroenterology.* Jan 2017;152(1):124-133 e122.
17. Biesiekierski JR, Peters SL, Newnham ED, Rosella O, Muir JG, Gibson PR. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. *Gastroenterology.* Aug 2013;145(2):320-328 e321-323.
18. Biesiekierski JR, Iven J. Non-coeliac gluten sensitivity: piecing the puzzle together. *United European gastroenterology journal.* Apr 2015;3(2):160-165.
19. Verdu EF, Armstrong D, Murray JA. Between celiac disease and irritable bowel syndrome: the "no man's land" of gluten sensitivity. *Am J Gastroenterol.* Jun 2009;104(6):1587-1594.
20. Vazquez-Roque MI, Camilleri M, Smyrk T, et al. A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function. *Gastroenterology.* May 2013;144(5):903-911.
21. McIntosh K, Reed DE, Schneider T, et al. FODMAPs alter symptoms and the metabolome of patients with IBS: a randomised controlled trial. *Gut.* Mar 14 2016.
22. Eswaran S, Tack J, Chey WD. Food: the forgotten factor in the irritable bowel syndrome. *Gastroenterol Clin North Am.* Mar 2011;40(1):141-162.
23. Shepherd SJ, Parker FC, Muir JG, Gibson PR. Dietary Triggers of Abdominal Symptoms in Patients With Irritable Bowel Syndrome: Randomized Placebo-

Controlled Evidence. *Clinical Gastroenterology and Hepatology.* 2008;6(7):765-771.

24. Staudacher HM, Lomer MC, Anderson JL, et al. Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. *J Nutr.* Aug 2012;142(8):1510-1518.

25. Staudacher HM, Whelan K, Irving PM, Lomer MC. Comparison of symptom response following advice for a diet low in fermentable carbohydrates (FODMAPs) versus standard dietary advice in patients with irritable bowel syndrome. *J Hum Nutr Diet.* May 25 2011.

26. Halmos EP, Power VA, Shepherd SJ, Gibson PR, Muir JG. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology.* Jan 2014;146(1):67-75.

27. Shepherd SJ, Gibson PR. Fructose malabsorption and symptoms of irritable bowel syndrome: guidelines for effective dietary management. *J Am Diet Assoc.* Oct 2006;106(10):1631-1639.

28. Staudacher HM, Whelan K, Irving PM, Lomer MC. Comparison of symptom response following advice for a diet low in fermentable carbohydrates (FODMAPs) versus standard dietary advice in patients with irritable bowel syndrome. *J Hum Nutr Diet.* Oct 2011;24(5):487-495.

29. Staudacher HM, Lomer MC, Anderson JL, et al. Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. *J Nutr.* Aug 2012;142(8):1510-1518.

30. de Roest RH, Dobbs BR, Chapman BA, et al. The low FODMAP diet improves gastrointestinal symptoms in patients with irritable bowel syndrome: a prospective study. *Int J Clin Pract.* Sep 2013;67(9):895-903.

31. Shepherd SJ, Lomer MC, Gibson PR. Short-chain carbohydrates and functional gastrointestinal disorders. *Am J Gastroenterol.* May 2013;108(5):707-717.

32. Eswaran SL, Chey WD, Han-Markey T, Ball S, Jackson K. A Randomized Controlled Trial Comparing the Low FODMAP Diet vs. Modified NICE Guidelines in US Adults with IBS-D. *Am J Gastroenterol.* Dec 2016;111(12):1824-1832.

33. Bohn L, Storsrud S, Liljebo T, et al. Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: a randomized controlled trial. *Gastroenterology.* Nov 2015;149(6):1399-1407 e1392.
34. Eswaran S, Chey W, Jackson K, Pillai S, Chey S, Han-Markey T. A Low FODMAP Diet Improves Quality of Life, Reduces Activity Impairment, and Improves Sleep Quality in Patients With Irritable Bowel Syndrome and Diarrhea: Results From a U.S. Randomized, Controlled Trial. *Gastroenterology.* 2016;150(4):S172.
35. Halmos EP, Christophersen CT, Bird AR, Shepherd SJ, Gibson PR, Muir JG. Diets that differ in their FODMAP content alter the colonic luminal microenvironment. *Gut.* Jul 12 2014.
36. Hamer HM, Jonkers D, Venema K, Vanhoutvin S, Troost FJ, Brummer RJ. Review article: the role of butyrate on colonic function. *Aliment Pharmacol Ther.* Jan 15 2008;27(2):104-119.

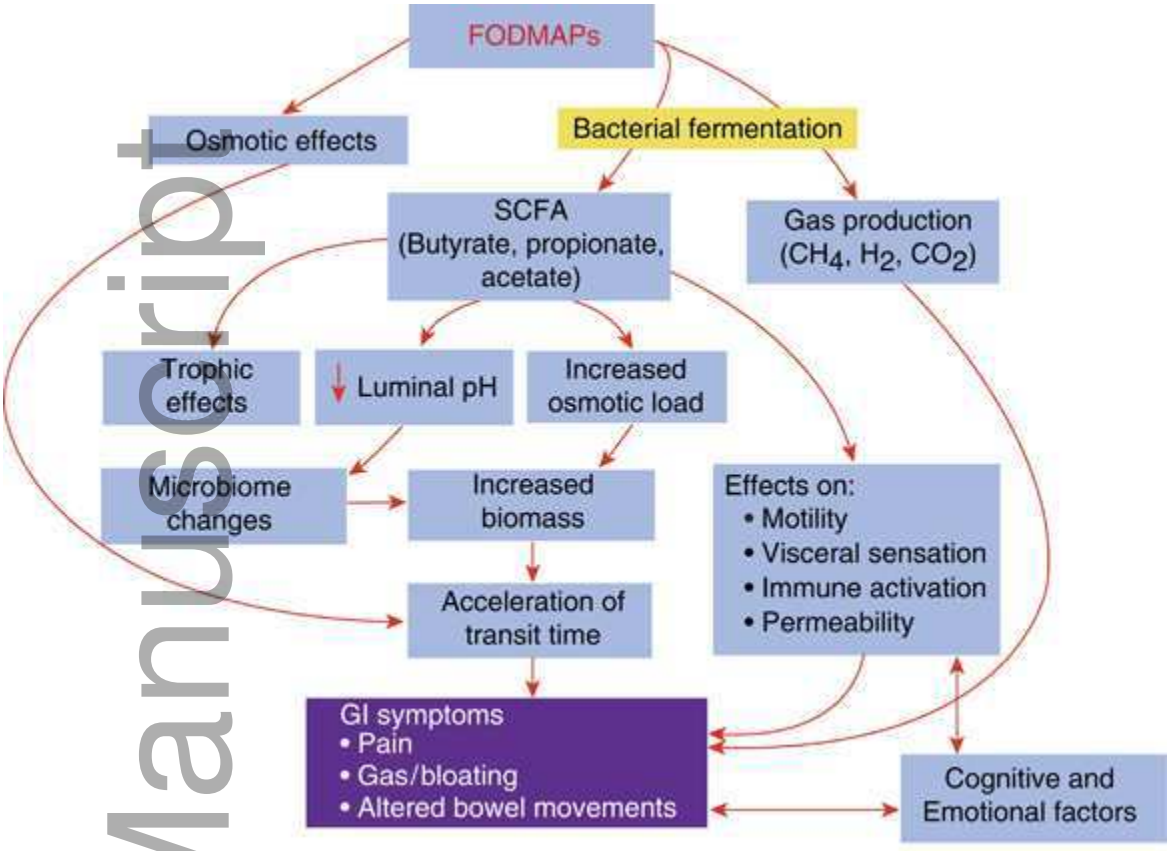


Figure 1. Mechanisms by which FODMAPs may cause GI symptoms. Adapted from Spencer M, et al. Current treatment Options in Gastroenterology. 2014; 12:424-440.