IBS and Probiotics

By Shady Shamy

What is IBS?

Irritable Bowel Syndrome: Gastrointestinal (GI) disorder causing bloating, abdominal, pain and/or cramps affecting around 11% of the population globally

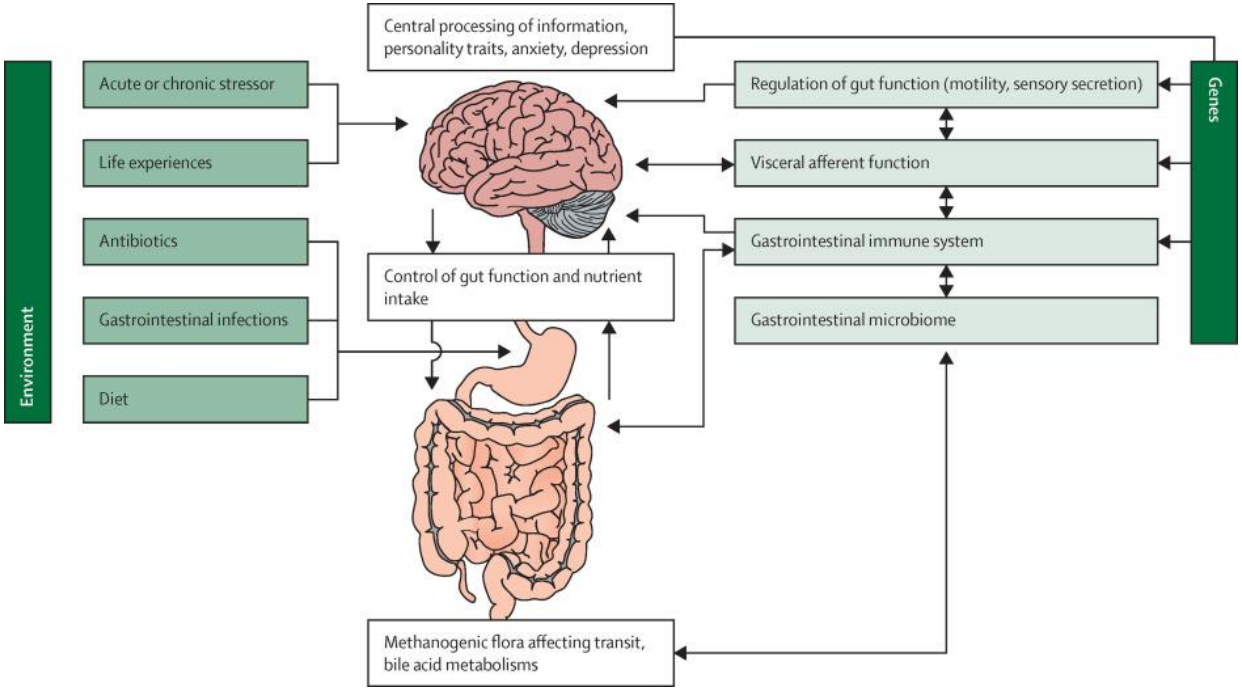
- IBS-D: Diarrhea predominant
- IBS-C: Constipation predominant
- IBS-M: Mixed diarrhea and constipation symptoms

Rome 4 Diagnostic Criteria:

- Recurrent abdominal pain on average at least one day/week in the last 3 mo associated with two or more of the following:
  - Related to defecation
  - Associated with a change in frequency of stool
  - Associated with a change in form (consistency) of stool

https://journals.physiology.org/doi/full/10.1152/ajpgi.00338.2016
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3921083/

Pathophysiology of IBS



https://www.thelancet.com/journals/langas/article/PIIS2468-1253%2816%2930023-1/fulltext

Diet

- Specific food intolerances
- Poorly absorbed carbohydrates and fiber
- low FODMAPs intake induces favorable changes in the intestinal microbiota
- A Western diet can potentially increase the bad bacteria in the gut while decreasing the amount of good bacteria
- A diet higher in plant based foods can increase the amounts of good bacteria while decreasing the bad bacteria

https://www.mdpi.com/2072-6643/13/8/2795

Genetics and Gut Microbiota

- Monozygotic twins that ate similarly had significantly higher similarity in their gut microbiota when compared to unrelated individuals
- Married individuals who have similar eating habits had low similarity in their gut microbiota when compared to unrelated individuals
- In a Swedish study, there was higher risk of having IBS in first, second and third-degree relatives compared to unrelated individuals
- More than 60 gene candidates have been proposed to play a role in the genetic predisposition to IBS such as including genes involved in serotonin synthesis and reuptake, mucosal immune activation and inflammation, neuropeptide signaling, and intestinal secretion

https://www.tandfonline.com/doi/abs/10.1080/089106001750462669

Genetics of irritable bowel syndrome

Visceral Hypersensitivity

- Reduced pain threshold to a painful stimuli
- Common in IBS patients
- Can potentially be affected by genetics and the gut microbiome

https://journals.physiology.org/doi/full/10.1152/ajpgi.00338.2016

Immune Function

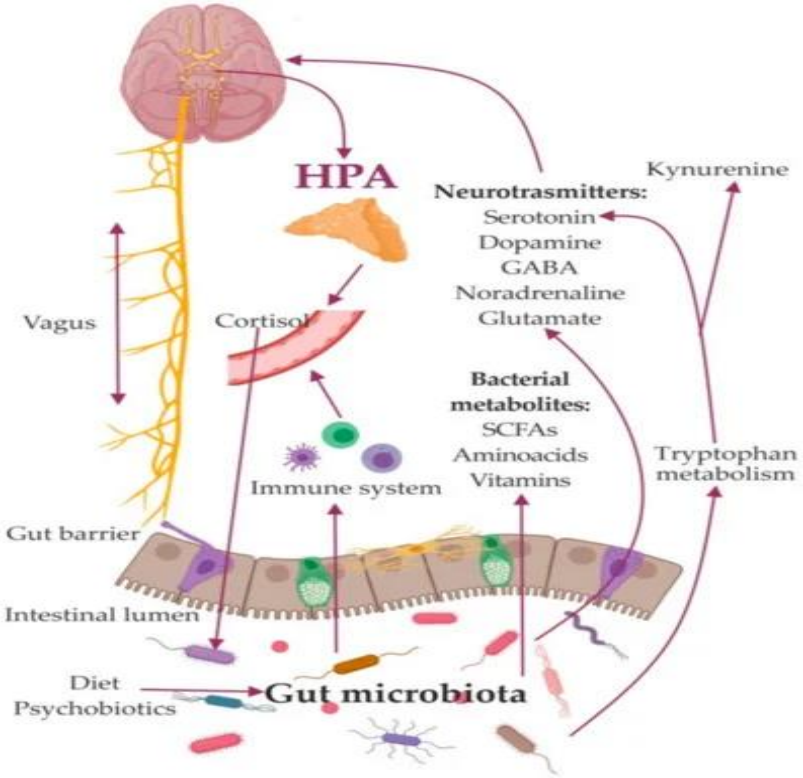
Mast cells in the gut regulate immunity

- Bacterial metabolites can can bind to mast cells and release inflammatory mediators
- These inflammatory mediators can increase the excitability of enteric neurons and may contribute to visceral hypersensitivity (pain)

https://journals.physiology.org/doi/full/10.1152/ajpgi.00338.2016

Role of the Gut Brain Axis

- Anxiety and depression 20-60% of cases of IBS
- Depression and stress have been associated with alterations in gut microbiota
- Brain also influences gastric motility and visceral hypersensitivity
- The gastrointestinal microbiota plays a role in gastrointestinal motility, gut immune defense, digestion and metabolism, and inflammation
- Gut dysbiosis can affect some of these pathways



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6492884/

https://www.mdpi.com/1422-0067/21/23/9234

How does an IBS gut microbiota differ from a healthy microbiota?

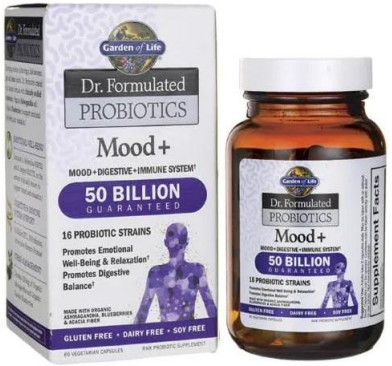
- No consistent evidence possibly due to different studies having different methods
- Most consistent finding is **decreased microbiota diversity** in individuals with IBS
- Some studies suggest those with IBS have
  - an increase in Firmicutes to Bacteroidetes ratio
  - increase in Streptococci and Ruminococcus species
  - decrease in Lactobacilli and Bifidobacteria population

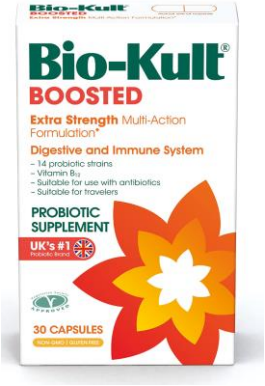
IBS-D	*Lactobacillus* spp.	Decreased	Malinen et al., 2005
	Clostridium symbiosum-like	Decreased	Rajilić-Stojanović, 2007
	Proteobacteria	Increased	Krogius-Kurikka et al., 2009
	Firmicutes (*Lachnospiraceae*)	Increased	
	Actinobacteria	Decreased	
	Bacteroidetes	Decreased	
	B. catenulatum	Decreased	Kerckhoffs et al., 2009
	C. thermosuccinogenes	85% phylotype increased	Lyra et al., 2009
	R. torques	94% phylotype increased	
	Collinsella aerofaciens	Decreased	
	B. intestinalis-like phylotype	Decreased	
	Lactobacillus spp.	Increased	Carroll et al., 2010
	Enterobacteriaceae	Increased	Carroll et al., 2012
	Fecalibacterium (Faecalibacterium prausnitzii)	Decreased	
	Bifidobacteria	Decreased	Parkes et al., 2012
	Ruminococcaceae, unknown Clostridiales, Erysipelotrichaceae, Methanobacteriaceae	Decreased	Pozuelo et al., 2015

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6579922/

Probiotics

- A mixture of live bacteria and/or yeast
- Can either be in a single strain or with multiple strains
- Measured in colony forming units (CFU)





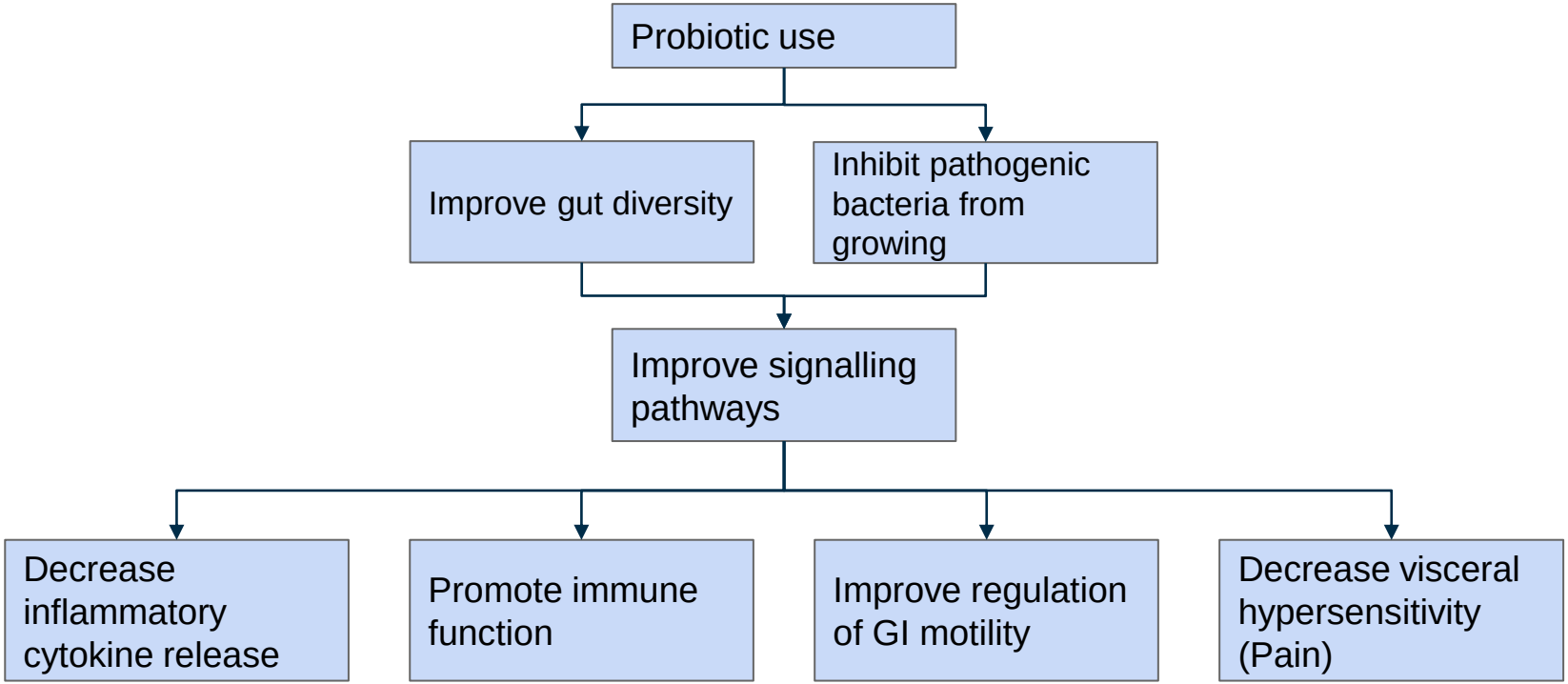
Probiotics

- In a healthy body, pathogenic and good microbiota coexist without problems, but a disturbance to this balance can cause GI symptoms
- Common strains in probiotics include:
  - Lactobacillus
  - Bifidobacterium
  - Saccharomyces
  - Streptococcus
- Good bacteria maintain a low PH to inhibit growth of pathogenic bacteria and compete for resources with pathogenic bacteria

USA Probiotic Guide

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4053917/

Mechanism of Action



A randomized placebo-controlled clinical trial of a multi-strain probiotic formulation (Bio-Kult®) in the management of diarrhea predominant irritable bowel syndrome

Published by BMC gastroenterology in 2018

Methods

Participants:

- Male and female patients in Bangladesh
- 18 to 55 years old
- Moderate to severe IBS-D diagnosed according to Rome III criteria
- Excluded if used probiotics in the last 3 months, had severe illnesses, previous GI surgery, or were treated with antibiotics in the past 2 months

Methods

- Bio-Kult contained 7 Lactobacilli strains, 4 Bifidobacteria, 1 Bacillus, 1 Lactococcus, and 1 Streptococcus strain
- 8 billion CFU total per day
- Participants instructed to remain on their normal diets

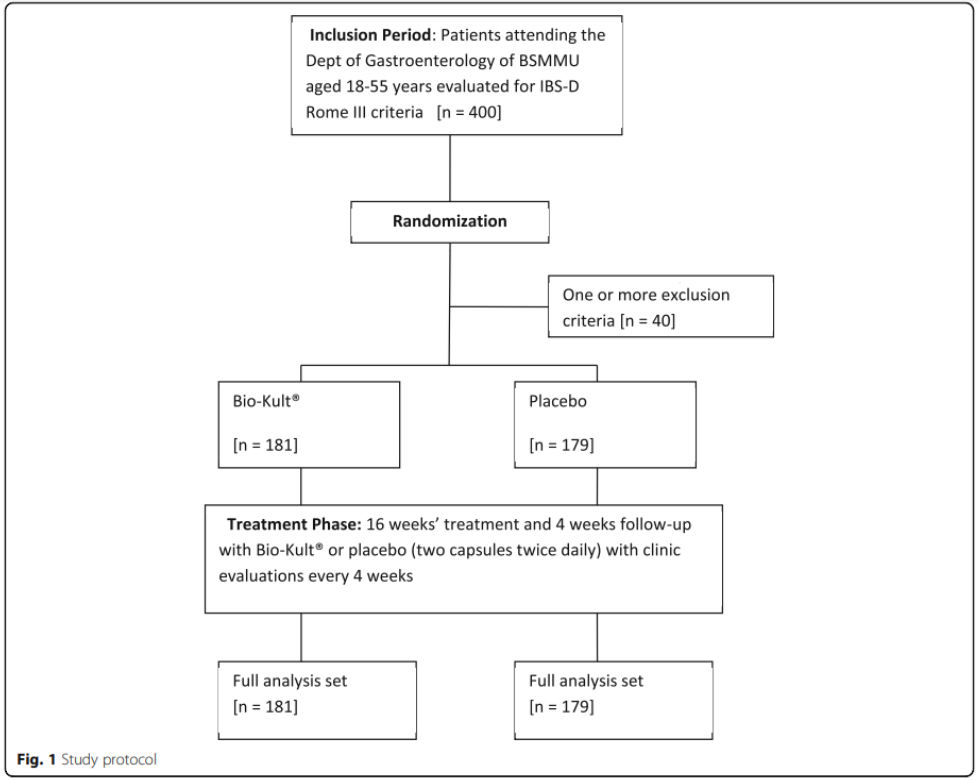


Fig. 1 Study protocol

Methods

Dependent Variables measured every month:

IBS symptoms:

- IBS-QoL questionnaire: 34-item questionnaire asking about quality of life measures such as health related worries, social interactions, and interference with activities
- IBS-Severity Scoring System (IBS-SSS): measure severity of abdominal pain, frequency of abdominal pain, severity of abdominal distension, dissatisfaction with bowel habits, and interference with quality of life, each on a 100-point scale

Table 1

Demographics were mostly the same between groups

Table 1 Patient demographics

Variable	Probiotic ($n = 181$)	Placebo ($n = 179$)	*P*-value
Age (years) [mean ± SD]	32.2 ± 10.1	31.7 ± 9.7	0.642
Gender (males/ females)	136/45	145/34	0.179
IBS-D (Rome III criteria)	181 (100)	179 (100)	NS
Moderate	39 (21.5)	52 (29.1)	0.101
Severe	142 (78.5)	127 (70.9)	
Occupation:			
Service industry	59	50	0.043
Student	51	38	
Business person	19	23	
Housewife	22	25	
Worker (painter, tailor, driver, farmer)	30	43	

Table 2 IBS symptom scores at baseline, during 16 weeks' treatment and after one month's follow-up

	Probiotic (Bio-Kult®) (n = 181)	Placebo (n = 179)	*P*-value
Overall IBS-SSS scores			
Before treatment	333.0 ± 40.4	332.9 ± 42.0	0.992
Month 1	187.9 ± 61.3	215.4 ± 75.0	< 0.001
Month 2	146.5 ± 76.4	188.0 ± 92.0	< 0.001
Month 3	122.0 ± 78.3	199.5 ± 104.1	< 0.001
Month 4	115.2 ± 75.0	179.7 ± 100.2	< 0.001
Month 5	110.0 ± 71.8	176.0 ± 100.0	< 0.001
IBS-SSS: Severity score of abdominal pain			
Before treatment	58.5 ± 11.1	57.2 ± 10.6	0.264
Month 1	30.3 ± 14.8	35.3 ± 15.9	0.002
Month 2	23.8 ± 16.2	31.1 ± 18.8	< 0.001
Month 3	20.3 ± 15.8	33.1 ± 19.7	< 0.001
Month 4	18.5 ± 16.2	30.4 ± 20.3	< 0.001
Month 5	18.1 ± 15.2	30.2 ± 19.9	< 0.001
IBS-SSS: Number of days in the last 10 days with pain			
Before treatment	7.7 ± 2.3	8.1 ± 2.3	0.056
Month 1	3.6 ± 2.1	4.4 ± 2.5	0.001
Month 2	2.9 ± 2.3	3.8 ± 2.7	0.001
Month 3	2.5 ± 2.2	4.2 ± 2.8	< 0.001
Month 4	2.4 ± 2.1	4.1 ± 3.2	< 0.001
Month 5	2.2 ± 1.9	3.9 ± 3.0	< 0.001
IBS-SSS: Severity score of abdominal distension			
Before treatment	58.5 ± 11.5	58.9 ± 12.0	0.695
Month 1	34.2 ± 16.2	38.4 ± 19.3	0.028
Month 2	25.7 ± 16.9	35.6 ± 20.2	< 0.001
Month 3	21.1 ± 16.4	37.5 ± 22.3	< 0.001
Month 4	20.1 ± 16.6	36.3 ± 23.3	< 0.001
Month 5	19.6 ± 15.8	35.9 ± 23.5	< 0.001

Table 3 Severity of symptoms at baseline, during 16 weeks' treatment and after one month's follow-up)

Severity of IBS-D	Probiotic (Bio-Kult®) (n = 181)	Placebo (n = 179)	*P*-value
Baseline			
Moderate	39 (21.5)	52 (29.1)	0.101
Severe	142 (78.5)	127 (70.9)	
Month 1			
Symptoms free period	2 (1.1)	2 (1.1)	0.086
Mild	78 (43.1)	58 (32.4)	
Moderate	91 (50.3)	99 (55.3)	
Severe	10 (5.5)	20 (11.2)	
Month 2			
Symptoms free period	16 (8.8)	18 (10.1)	< 0.001
Mild	112 (61.9)	61 (34.1)	
Moderate	42 (23.2)	82 (45.8)	
Severe	11 (6.1)	18 (10.1)	
Month 3			
Symptoms free period	54 (29.8)	20 (11.2)	< 0.001
Mild	98 (54.1)	62 (34.6)	
Moderate	23 (12.7)	57 (31.8)	
Severe	6 (3.3)	40 (22.3)	
Month 4			
Symptoms free period	56 (30.4)	22 (11.2)	< 0.001
Mild	99 (54.7)	68 (38.0)	
Moderate	21 (11.6)	66 (36.9)	
Severe	6 (3.3)	23 (12.8)	
Follow-up: Month 5			
Symptoms free period	61 (33.7)	23 (12.8)	< 0.001
Mild	95 (52.5)	70 (39.1)	
Moderate	21 (11.6)	65 (36.3)	
Severe	4 (2.2)	21 (11.7)	

The unpaired Chi-square test was used to determine the level of statistical significance

Table 4:

Table 4 IBS-QoL scores at baseline, during 16 weeks' treatment and after one month's follow-up)

	Probiotic (Bio-Kult®) (n = 181)	Placebo (n = 179)	*P*-value
Before treatment	22.6 ± 10.5	27.5 ± 13.0	< 0.001
At 1st month	46.5 ± 13.6	44.8 ± 15.8	0.270
At 2nd month	59.0 ± 18.9	48.7 ± 20.3	< 0.001
At 3rd month	66.4 ± 21.6	47.6 ± 22.9	< 0.001
At 4th month	68.3 ± 21.8	48.4 ± 24.5	< 0.001
At 5th month	72.0 ± 16.5	58.5 ± 16.8	< 0.001

The unpaired t-test was used to determine the level of statistical significance
Note: In this scoring system, higher scores indicate better QoL

Conclusion from this study

- After just 1 month of this particular probiotic, a large amount of participants saw significant improvements in IBS symptoms such as abdominal pain, bowel motions, and overall quality of life compared to a placebo
- Improvements continued after every month for 4 months and remained after a 1 month follow up with no treatment
- However, it is important to note that the placebo group also saw lots of improved symptoms

Probiotics therapy for adults with diarrhea-predominant irritable bowel syndrome: a systematic review and meta-analysis of 10 RCTs

Journal of Colorectal Disease 2022

Methods

Inclusion Criteria:

- RCT
- Used a placebo as a control
- IBS-D

Exclusion

- Did not differentiate between IBS subtypes

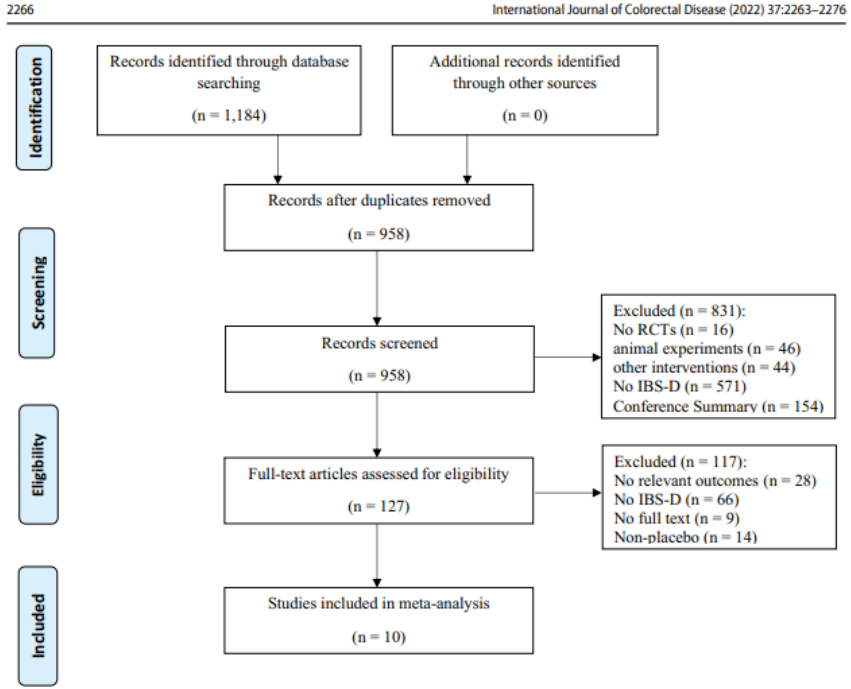


Fig. 1 Flow diagram of the literature screening process and results

Table 1 The main characteristics of included studies

Study	Country	Simple (I/C)	Gender (M/F)	Age	Diagnostic criteria	Probiotics	Probiotic dosage	Duration of treatment	Outcomes
Ishaque et al. [49]	Bangladesh	181/179	I: 136/45 C: 145/34	I: 32.2 ± 10.1 C: 31.7 ± 9.7	Rome III	*Bacillus subtilis PXN 21*, *Bifidobacterium* spp., and *Lactobacillus* spp.	8×10^8 CFU	16 weeks	↓IBS-D symptoms ↑QoL
Choi et al. [52]	Korea	34/33	I: 18/17 C: 19/20	I: 43.0 ± 12.5 C: 40.6 ± 12.9	Rome II	*Saccharomyces boulardii*	Twice daily in capsules	4 weeks	↓IBS-D symptoms ↑QoL
Sun et al. [31]	China	105/95	I: 63/42 C: 53/42	I: 43.0 ± 12.5 C: 44.9 ± 13.0	Rome III	*Clostridium butyricum*	Thrice daily in capsules	4 weeks	↓IBS-D symptoms ↑QoL stool frequency
Kim et al. [48]	USA	12/13	I: 2/10 C: 5/8	I: 48 ± 19.75 C: 38 ± 12.26	Rome II	*VSL#3*	450 billion lyophilized bacteria/day	8 weeks	↓IBS-D symptoms ↓Abdominal bloating
Zeng et al. [30]	China	14/15	I: 10/4 C: 9/6	I: 44.6 ± 12.4 C:45.8 ± 9.2	Rome II	*Probiotic fermented milk* (*Streptococcus thermophilus*, *Lactobacillus bulgaricus*, *Lactobacillus acidophilus*, and *Bifidobacterium longum*)	Probiotic fermented milk 200 g or placebo drink 200 mL twice daily	4 weeks	↓IBS-D symptoms ↓Abdominal pain and flatulence
Abbas et al. [18]	Pakistan	37/35	I: 27/10 C: 26/9	I: 37 0.7 ± 11.6 C: 33.0 ± 12.0	Rome III	*Saccharomyces boulardii*	3×10^9 CFU	6 weeks	IBS-D symptoms ↑QoL
Michail et al. [51]	USA	15/9	I: 5/10 C: 3/6	21.8 ± 17	Rome III	*VSL#3*	9×10^{11} CFU	8 weeks	↓IBS-D symptoms ↓Abdominal pains QoL
Cha et al. [25]	Korea	25/25	I: 12/13 C: 14/11	I: 37.9 ± 12.4 C:40.3 ± 11.2	Rome III	*Multispecies probiotic mixture* (*Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Bifidobacterium breve*, *Bifidobacterium lactis*, *Bifidobacterium longum*, *Streptococcus thermophilus*)	1×10^9 CFU	8 weeks	↓IBS-D symptoms ↓Abdominal pains

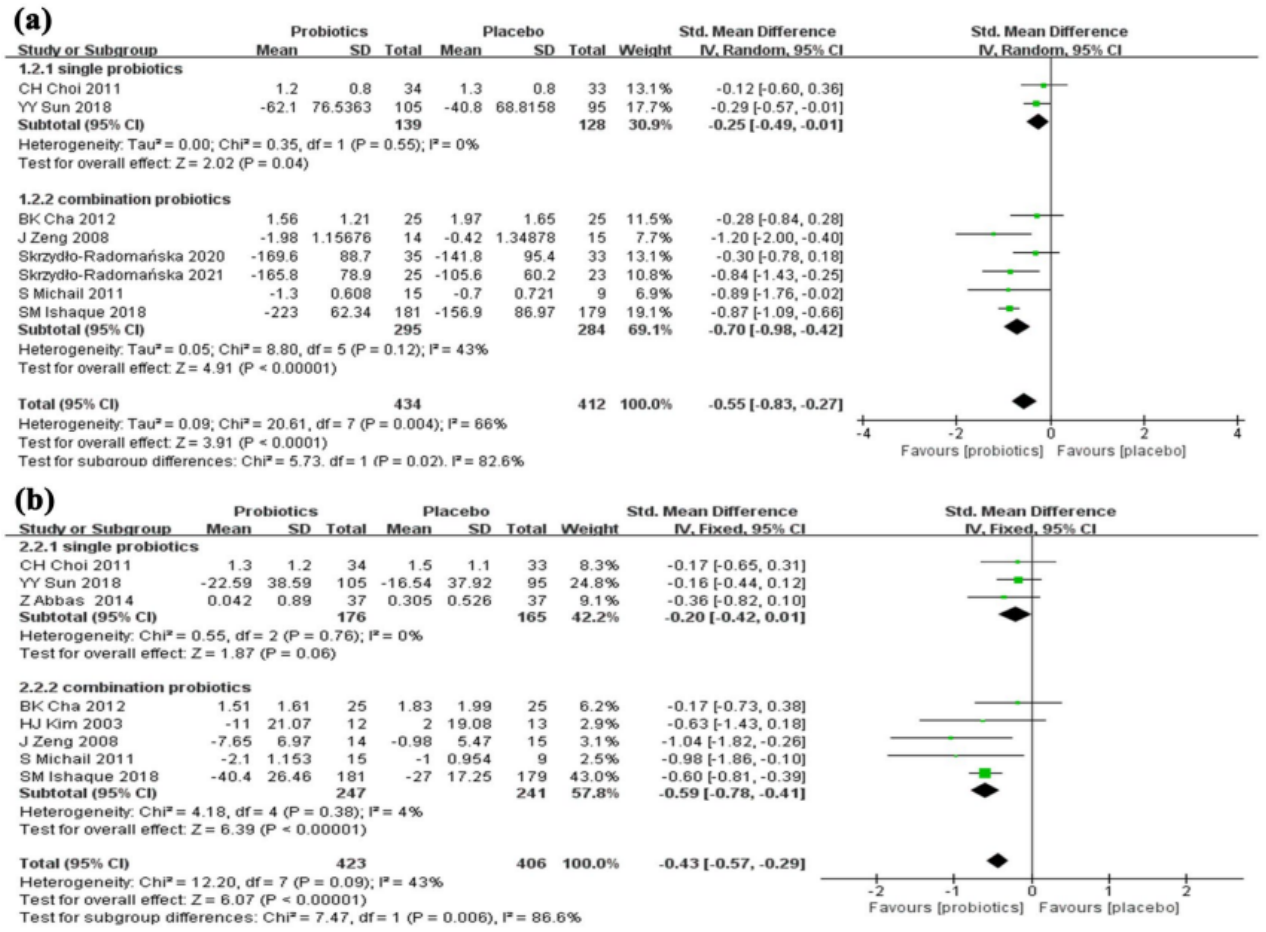


Fig. 3 Effect on IBS-D symptom (**a**) and abdominal pain (**b**) of IBS-D patients to probiotics: probiotic subgroups

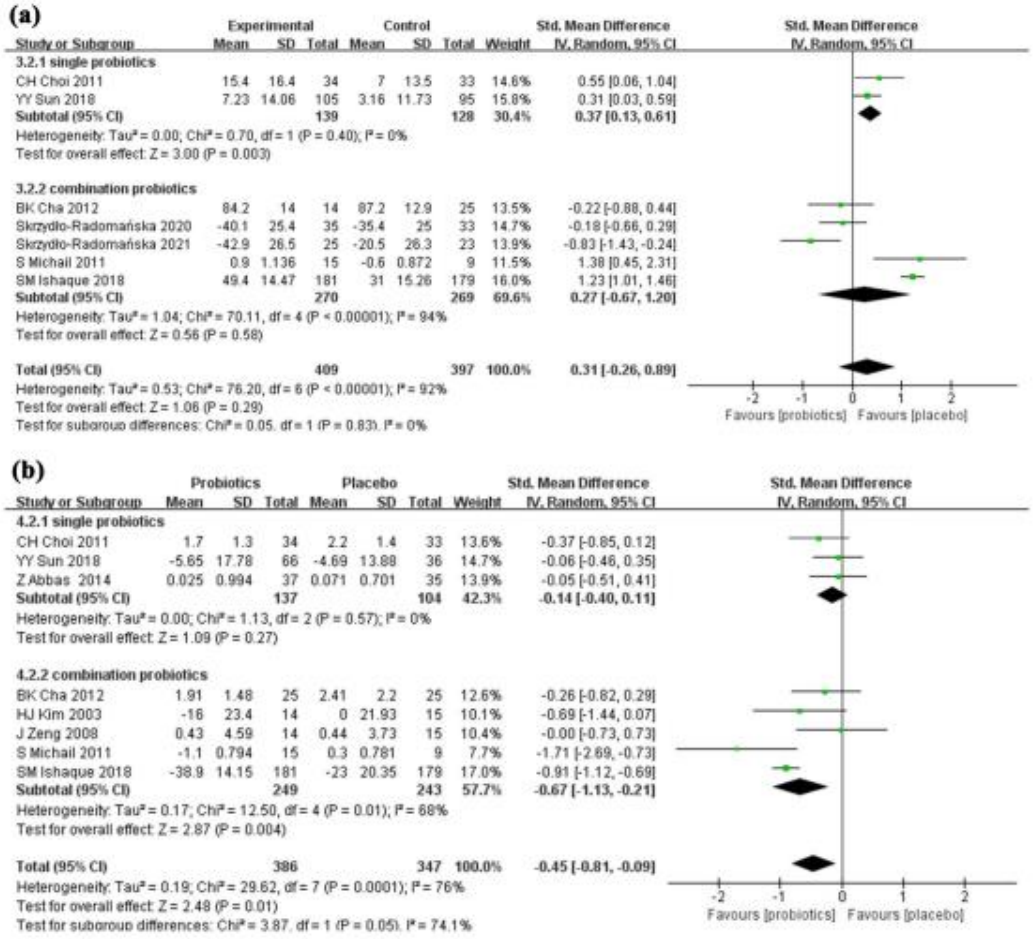


Fig. 4 Effect on the quality of life (**a**) and abdominal distension (**b**) of IBS-D patients to probiotics: probiotic subgroups

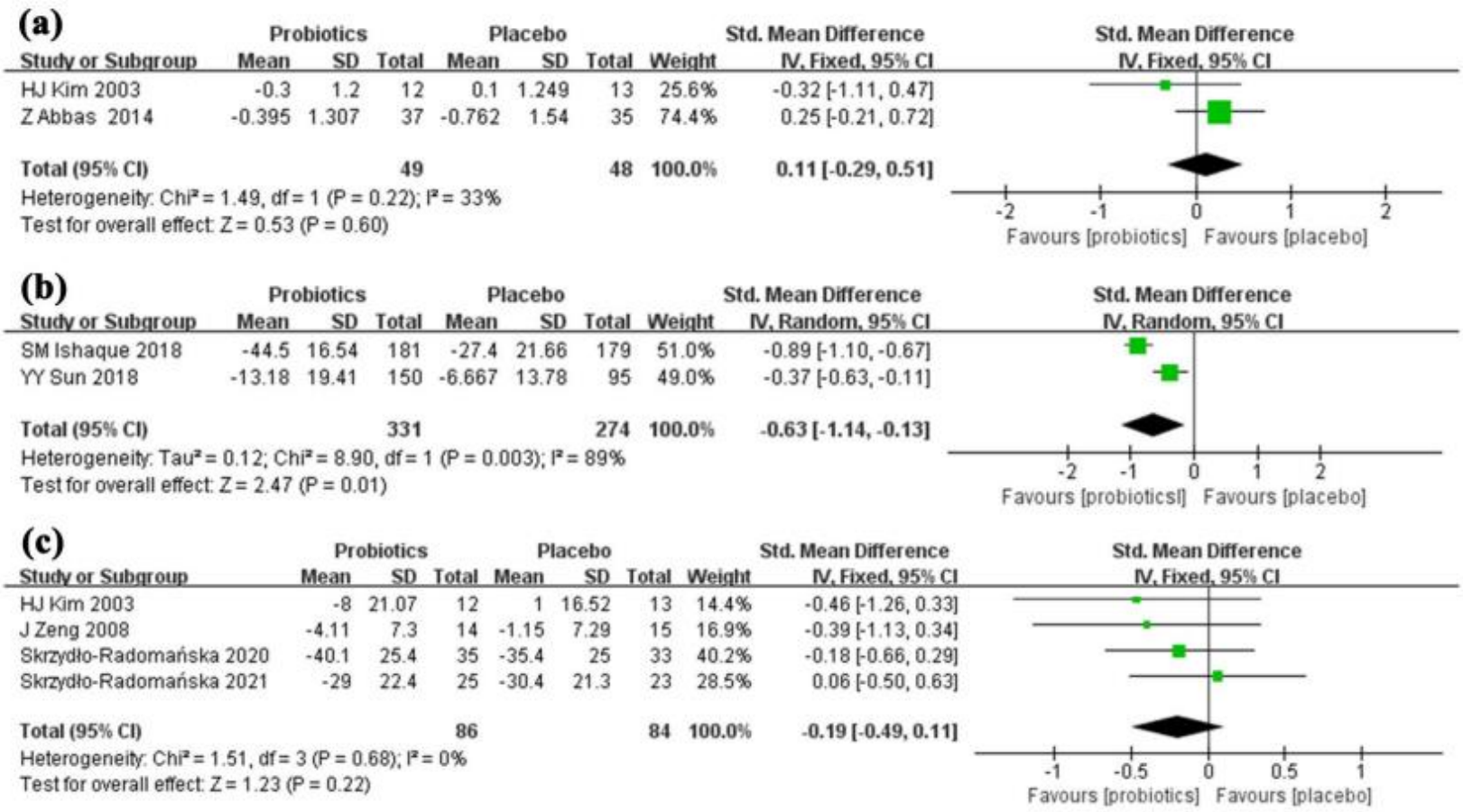


Fig. 5 Effect on stool frequency (**a**), satisfaction with bowel habits (**b**), and flatulence (**c**) of IBS-D patients to probiotics

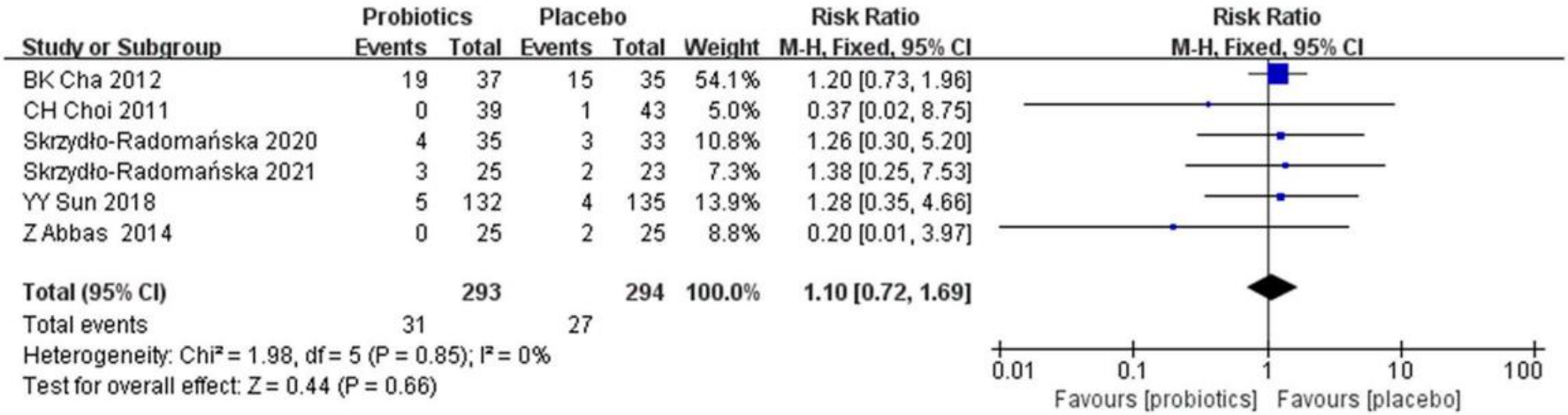


Fig. 6 Comparison between probiotics and placebo in terms of adverse events for IBS-D

Table 2:

- High heterogeneity
- High risk of bias in studies
- Wide confidence intervals

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with probiotics			
IBS-D symptoms	-	SMD 0.55 SD lower (0.83 lower to 0.27 lower)	-	846 (8 RCTs)	⨁◯◯◯[a] Very low
Abdominal pain	-	SMD 0.43 SD lower (0.57 lower to 0.29 lower)	-	829 (8 RCTs)	⨁◯◯◯[b] Very low
Quality of life	-	SMD 0.31 SD higher (0.26 lower to 0.89 higher)	-	806 (7 RCTs)	⨁◯◯◯[c] Very low
Abdominal distension	-	SMD 0.29 SD lower (1.43 lower to 0.84 higher)	-	733 (8 RCTs)	⨁◯◯◯[d] Very low
Stool frequency	-	SMD 0.06 SD higher (0.47 lower to 0.59 higher)	-	97 (2 RCTs)	⨁⨁◯◯[e] Low
Satisfaction with bowel habits	-	SMD 0.63 SD lower (1.14 lower to 0.13 lower)	-	605 (2 RCTs)	⨁◯◯◯[f] Very low
Flatulence	-	SMD 0.19 SD lower (0.49 lower to 0.11 higher)	-	170 (4 RCTs)	⨁◯◯◯[g] Very low
Adverse events	-	-	RR 1.10 (0.72 to 1.69)	587 (6 RCTs)	⨁◯◯◯[h] Very low

Current Gaps in the Literature

- No long-term studies done on probiotic supplements for IBS treatment
- What happens when someone stops taking probiotics?
- Which probiotic strains are the most effective?
- How many CFUs are needed?

Conclusions

- Most studies point towards improvements in IBS symptoms from probiotics
- Differences in study designs such as different strains, amount of bacteria, length of treatments and confounding variables such as diet indicate poor strength of evidence to support probiotics use
- Placebo effect is possible because of the gut brain access
- Adverse events are uncommon
- Probiotics may help improve IBS symptoms in some people but there is not enough evidence to support probiotic use as a first line of treatment

Monash University Recommendations

“While many of these studies have shown that probiotic supplementation is both safe and effective in some individuals with IBS, firm recommendations about which dose or strain to recommend in practice still cannot be made.”

- Benefits observed in one patient profile may not translate to another
- Try 1 probiotic product at a time for a minimum of 4 weeks and monitor symptoms. If you notice no improvement after 12 weeks, discontinue use
- Probiotic supplements should be taken regularly – benefits are not permanent and lost within days if you stop taking a probiotic

https://www.monashfodmap.com/blog/probiotics-ibs-update/

References

1) Bhattarai, Y., Muniz Pedrogo, D. A., & Kashyap, P. C. (2017). Irritable bowel syndrome: a gut microbiota-related disorder?. *American journal of physiology. Gastrointestinal and liver physiology*, *312*(1), 52–62. https://doi.org/10.1152/ajpgi.00338.2016
2) Canavan, C., West, J., & Card, T. (2014). The epidemiology of irritable bowel syndrome. *Clinical epidemiology*, 6, 71–80. https://doi.org/10.2147/CLEP.S40245
3) Smith, J., Petrovic, P., Rose, M., De Souz, C., Muller, L., Nowak, B., & Martinez, J. (2016). Pathophysiology of irritable bowel syndrome. *Lancet Journal of Gastroenterology and Hepatology 1*(2), 133-146. https://doi.org/10.1016/S2468-1253(16)30023-1
4) Beam, A., Clinger, E., & Hao, L. (2021). Effect of Diet and Dietary Components on the Composition of the Gut Microbiota. *Nutrients*, *13*(8), 2795. https://doi.org/10.3390/nu13082795
5) Beam, A., Clinger, E., & Hao, L. (2021). Effect of Diet and Dietary Components on the Composition of the Gut Microbiota. *Nutrients, 13*(8), 2795. https://doi.org/10.3390/nu13082795
6) Henström, M., & D'Amato, M. (2016). Genetics of irritable bowel syndrome. *Molecular and cellular pediatrics, 3*(1), 7. https://doi.org/10.1186/s40348-016-0038-6
7) Moloney, R. D., Johnson, A. C., O'Mahony, S. M., Dinan, T. G., Greenwood-Van Meerveld, B., & Cryan, J. F. (2016). Stress and the Microbiota-Gut-Brain Axis in Visceral Pain: Relevance to Irritable Bowel Syndrome. *CNS neuroscience & therapeutics, 22*(2), 102–117. https://doi.org/10.1111/cns.12490
8) Averina, O. V., Zorkina, Y. A., Yunes, R. A., Kovtun, A. S., Ushakova, V. M., Morozova, A. Y., Kostyuk, G. P., Danilenko, V. N., & Chekhonin, V. P. (2020). Bacterial Metabolites of Human Gut Microbiota Correlating with Depression. I*nternational journal of molecular sciences, 21*(23), 9234. https://doi.org/10.3390/ijms21239234
9) Chong, P. P., Chin, V. K., Looi, C. Y., Wong, W. F., Madhavan, P., & Yong, V. C. (2019). The Microbiome and Irritable Bowel Syndrome - A Review on the Pathophysiology, Current Research and Future Therapy. *Frontiers in microbiology, 10*, 1136. https://doi.org/10.3389/fmicb.2019.01136
10) Zhang, Y. J., Li, S., Gan, R. Y., Zhou, T., Xu, D. P., & Li, H. B. (2015). Impacts of gut bacteria on human health and diseases. *International journal of molecular sciences, 16*(4), 7493–7519. https://doi.org/10.3390/ijms16047493
11) Ishaque, S. M., Khosruzzaman, S. M., Ahmed, D. S., & Sah, M. P. (2018). A randomized placebo-controlled clinical trial of a multi-strain probiotic formulation (Bio-Kult®) in the management of diarrhea-predominant irritable bowel syndrome. *BMC gastroenterology, 18(*1), 71. https://doi.org/10.1186/s12876-018-0788-9
12) Wang, Y., Chen, N., Niu, F., Li, Y., Guo, K., Shang, X., E, F., Yang, C., Yang, K., & Li, X. (2022). Probiotics therapy for adults with diarrhea-predominant irritable bowel syndrome: a systematic review and meta-analysis of 10 RCTs. *International journal of colorectal disease, 37*(11), 2263–2276. https://doi.org/10.1007/s00384-022-04261-0
13) Varney J., Yao C., & Collins L. (2021). *Probiotics for IBS*. Retrieved March 2, 2023 from, https://www.monashfodmap.com/blog/probiotics-ibs-update/

Case Study

- John is a 38 year old male who has been diagnosed with IBS-D and is seeking dietary counseling help from a dietitian to help improve his symptoms. He states that he has struggled with bloating and diarrhea most of his life and is finally seeking treatment help. He also has not been on any antibiotic treatments recently. He has read online that probiotics can help his symptoms and wants to know which is the best probiotic to take to help improve his symptoms.

- You inform John that a lot of people see improvements in IBS symptoms after identifying which foods are causing the bloating and diarrhea. You recommend that the patient tries out a low FODMAP diet until his symptoms have improved (if at all). Once they have improved, he can reintroduce foods back into his diet to try to identify which foods are causing him troubles. If John is still not satisfied with the results from the low FODMAP intervention, you can try recommending probiotic foods or a supplement. If the patient is okay with buying and taking probiotics for the long-term, then you can inform him that a multi strain probiotic supplement is currently the best option for treating symptoms, however which exact strains are the best is currently unknown. If he does not want to be on a supplement the rest of his life, you can inform him that fruits and vegetables that he can tolerate are a good option to introduce healthy bacteria in the gut, as well as any fermented foods or yogurts only if he can tolerate them.