ASSESSMENT OF LOW FERMENTABLE OLIGOSACCHARIDES, DISACCHARIDES, MONOSACCHARIDES AND POLYOLS (FODMAP) ON CLINICAL, PSYCHOLOGY AND QUALITY OF LIFE OUTCOMES ASSESSED IN PATIENT WITH IRRITABLE BOWEL SYNDROME (IBS) IN HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM), KELANTAN

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LIST OF ABBREVIATIONS

BMI	Body mass index
DNA	Double Nucleic Acid
FODMAP	Fermentable Oligosaccharide, Disaccharide, Monosaccharide, and Polyols
IMO	Iso-malto-oligo-saccharide/s
GOS	Galacto-oligo-saccharide/s
GI	Gastro-intestinal
IBS	Irritable Bowel Syndrome
IBS-C	Irritable Bowel Syndrome – Constipation
IBS-D	Irritable Bowel Syndrome – Diarrhea
IBS-M	Irritable Bowel Syndrome – Mixed
IBS-SSS	Irritable Bowel Syndrome – Symptoms Severity Score
i.e.	id est (Latin) – in other words
MLT	Medical Lab Technician
PI	Principal Investigator
SEM	Standard error of the mean
SIBO	Small Intestine Bacterial Overgrowth
SN	Staff nurse/s
S.W.T	"subhanallahu'wata'alla"
XOS	Xylo-oligo-saccharide/s

LIST OF SYMBOLS

<	Less than
>	More than
=	Equal to
≤	Less than and equal to
≥	More than and equal to
%	Percentage
km	kilometre/s
kg	kilogram/s

ABSTRAK

Pemakanan yang mempunyai kandungan rendah karbohidrat rantai pendek yang boleh ditapai (oligo-, di-, monosakarida dan poliol, FODMAPs) telah dilaporkan mempunyai keberkesanan dalam rawatan pesakit dengan sindrom iritasi usus (IBS). Oleh itu, kajian ini bertujuan untuk membandingkan kesan diet-rendah FODMAP ke atas simptom IBS dalam kalangan pesakit luar yang mempunyai IBS. Pesakit IBS dewasa dalam populasi di Malaysia menawarkan peluang yang unik bagi kajian interaksi antara mikrobiata usus, pemakanan, dan gejala usus. Kami telah menjalankan kajian ke atas 18 orang pesakit yang memenuhi kriteria Rome III bagi IBS, yang berdaftar di klinik pesakit luar gastroentrologi di Kubang Kerian. Subjek-subjek telah diklasifikasikan kepada kumpulan yang mengambil pemakanan tertentu selama 4 minggu; diet yang mempunyai rendah kandungan FODMAP (n=18), dengan penekanan utama terhadap cara dan waktu makan berbanding makanan apa yang perlu diambil. Tahap keseriusan simptom telah diuji melalui IBS-SSS, HADS, EQ-5D dan soalan-soalan kekembungan perut, dan pesakit menyiapkan buku diari makanan untuk tiga hari semasa intervensi. Sebanyak enam subjek terkawal yang sihat telah dimasukkan dalam kajian (n=6). Kajian dibuat berdasarkan tujuan rawatan. Pesakit IBS (n=18) merangkumi mereka yang mengalami simptom awal dan simptom selepas intervensi selama 4 minggu. Tiada perbezaan signifikan pada skor median bagi skor pra dan pasca IBS-SSS (p=0.054) dalam kalangan pesakit IBS. Dari segi kekembungan perut pesakit, terdapat perbezaan signifikan pada skor median untuk skor pra dan pasca SevGen (keseriusan kembung perut umum), Sev24 (keseriusan kembung perut 24 jam) dan kualiti hidup untuk kembung perut dalam kalangan pesakit IBS (p=0.043, p=0.007, p=0.010 masing-masing). Kesimpulan telah dibuat bahawa diet-rendah FODMAP tidak menunjukkan keberkesanan terhadap simptom pesakit IBS. Namun begitu, kualiti hidup dan kembung perut umum juga mempunyai perbezaan signifikan. Diet-rendah FODMAP boleh menjadi alternatif untuk mengurangkan kembung perut dan memperbaiki kualiti hidup dalam kalangan IBS. Kajian lanjut yang berskala lebih besar diperlukan untuk mewakili populasi IBS setempat.

ABSTRACT

A diet with low content of fermentable short-chain carbohydrates (fermentable oligo-, di-, monosaccharides and polyols, FODMAPs) has been reported to be effective in the treatment of patients with irritable bowel syndrome (IBS). Therefore, the study aimed to compare the effect of a low FODMAP diet on IBS symptom in outpatients with IBS. The IBS adults of Malaysian population offers a unique opportunity to study the interaction between gut microbiota, diet, and functional GI symptoms. We performed a study of 18 patients who met the Rome III criteria for IBS, enrolled at gastroenterology outpatient clinics in Kubang Kerian. Subjects were assigned to groups that eat specific diets for 4 weeks: a diet low in FODMAPs (n=18), with greater emphasis on how and when to eat rather than on what food to ingest. Symptom severity was assessed using the IBS-SSS, HADS, EQ-5D and bloat questionnaires, and the patients completed a 3-day food diary during the intervention. A number of six healthy controlled subjects were enrolled (n=6). The analysis was based on the intention to treat. The IBS patients (n=18) were assessed based on the baseline symptoms and symptoms after 4 weeks of interventions. There were no significant differences in median score for pre- and post-IBS-SSS score (p=0.054) in IBS patients. For patient's bloat, there were significant differences in the median score for pre- and post-score of SevGen (generalized bloat severity), Sev24 (24 hours bloat severity) and quality of life for bloat in IBS patients (p=0.043, p=0.007, p=0.010 respectively). We concluded that a low FODMAP diet did not show effectiveness in IBS patients' symptoms. Nevertheless, there was a significant difference between Malay and Chinese ethnicity alone in IBS symptoms. Besides, quality of life and generalized bloat had significant differences. Low FODMAP diet can be an alternative to reduce bloat and improve quality of life in IBS. Further larger studies are required to represent the IBS population locally.

CHAPTER 1: INTRODUCTION

IBS is a chronic dysfunctional gastrointestinal disorder (GI). In the world population, it is estimated about 11 percent (%) people were affected (Choung & Saito, 2014) by a group of symptoms that include abdominal pain and altered bowel habit. Predominantly, it included either diarrhea (IBS-D), constipation (IBS-C), or both (IBS-M). Earliest data related to IBS were from the 19th and 20th century (Chaudhary & Truelove, 1962). IBS remained "common misdiagnosed and less understood" in those years. Local data reported the incidence ranging from around 6.8% to 15.8% (Tan *et al.*, 2003; Rajendra & Alahuddin, 2004), and in Malay ethnicity, the IBS symptom was demonstrated around 10.9% (Lee *et al.*, 2012). This appears to be a global phenomenon.

The widespread presence of IBS has become more significant with infectious pathogens (Klem *et al.*, 2017), decreasing age and increasing psychological pressure, and was associated with female sex and current smoking (Nam *et al.*, 2010). However, the incidence of IBS in Asia-specific studies has no significant genre difference (Gwee, Lu & Ghoshal, 2009; Gwee *et al.*, 2010; Kim & Park, 2011; Lee *et al.*, 2012). New evidence supports the collaborations of gut microbiotas in IBS symptoms as well as the onset (Saulnier *et al.*, 2011; Simrén *et al.*, 2013; De Palma *et al.*, 2017; Tap *et al.*, 2017).

Recently, the management of irritable bowel syndrome (IBS) concerning the restriction of Fermentable Oligosaccharide, Disaccharide, Monosaccharide, and

Polyols in the diet (low FODMAP diet) has emerged. The majority of patients with IBS on a low FODMAP diet has shown the benefits gained. The core for the success of FODMAP is the dietary compliance by the patient and intervention led by a trained dietician in FODMAP.

Up to 86% of IBS patients find the upswing in overall gastrointestinal symptoms along with individual symptoms like abdominal pain, bloating, constipation, diarrhea, flatulence and abdominal distension after the diet (Nanayakkara *et al.*, 2016).

FODMAP diet restriction lessens the osmotic load and gas production in distal small bowel, and proximal colon giving symptomatic relief in patients with IBS. The long-term effect of low FODMAP diet is unknown. Potential adverse effects from altered gut microbiota and the risk of inadequate nutrient intake in strict low FODMAP diet are less recommended.

There is an interest in using dietary change to influence clinical outcomes in patients with (IBS). Low FODMAP diet is gaining popularity in many Western countries. The strategy of the diet is to avoid food high in FODMAPs and replace them with food low in FODMAPs. This approach dramatically depends on the detailed knowledge of the FODMAP composition of food commonly consumed in Malaysia. Thus, this dietary approach holds potential and a significant reason for treating IBS patients in Malaysia. The objective of this research was to focus on the low FODMAP outcomes assessed among IBS patients in Malaysia and locally in Kelantan. This study

again offers a unique opportunity to study the interaction between gut microbiota, diet, and functional GI symptoms.

CHAPTER 2: LITERATURE REVIEW

2.1 Intestinal microbiota, fermentable substrate and their interactions

Intestinal microbiota in human plays an important role in the human lifecycle by providing nutrients, immunological protection and energy. In an infant the composition of intestinal microbiota is simple and becomes complicated with increasing in age, up to a high level of complexity in adults. Food is one of the major determinants for the existence of a given bacterium in the GI tract. It provides nutrient not only to the human but also for the bacteria therein. Some nondigestible food component delivers as a source of energy and carbon for the gut bacteria. Food has an indirect effect on the GI function of the human and thereby on their health. Bowel microbiota has a vast catalytic benefit, which may lead to the arrangement of metabolites with beneficial or adverse health effects.

The vast number of fermentable substrates available to microbiota in the GI tract is the main reason for the complexity of the bacterial community in the gut. The intermediates formed during the bacterial breakdown of indigestible dietary components leading to large variety of substrates. The major substrates available in the colon are dietary carbohydrates that have escaped digestion in the small intestine. These include resistant dietary fibre, starches, unabsorbed sugars and sugar alcohol. Other potential substrate is produced by the host mucus and sloughed epithelial cells.

The interactions established between host and microbiota have important implications in determining human health and diseases (Blaut & Clavel, 2007; Frémont *et al.*, 2013). Various factors such as diet, environment, mode of delivery and

antibiotherapy affect the population and colonization of gut microbiota. Distinct variations in the composition and functional capacity of human microbiota in geographically distant populations point towards a crucial role of the diet in these populations (De Filippo *et al.*, 2010; Yatsunenko *et al.*, 2012; Lin *et al.*, 2013; Iacovou *et al.*, 2015). Microbiota in Western populations has shown to be enriched in *Bacteroides spp* due to the consumption of a high animal protein, sugar, starch, and fat as compared to the microbiota of non-Western populations enriched in *Prevotella spp* as a result of the consumption of a diet high in plant-derived carbohydrates (Salonen & de Vos, 2014).

2.2 The functional gastrointestinal disorder

IBS is a functional GI disorder that affects up to one in five people over their lifetime. It may cause abdominal pain or discomfort, constipation, diarrhea and other related symptoms. IBS is common, with prevalence reaching more than 20% in some countries, including Southeast Asian countries (Lovell & Ford, 2012; Canavan, West & Card, 2014; Iacovou *et al.*, 2015). Rajilić-Stojanović et al. concluded in their recent review that interactions between intestinal microbial communities and distinct dietary patterns may in part be responsible for the fact that IBS has not yet shown to be defined by specific microbiota profiles (Rajilić-Stojanović *et al.*, 2015). In another recent study, it was reported that higher Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols (FODMAP) content of Australian diet compared to that of the low FODMAP (regular diets) is linked to the growth stimulation of specific bacterial groups with putative health benefits such as butyrate-producers and mucus-associated *Akkermansia muciniphila* (Halmos *et al.*, 2015).

2.3 The FODMAP foods

FODMAPs are found naturally in the vast majority of foods. They are a group of short-chain, fermentable carbohydrates that are either slowly absorbed in the small bowel, or indigestible in the gut. They consist of: non-digestible “oligosaccharides” that contain fructo-oligosaccharides (fructans) found in garlic, onion, wheat, barley and rye; and galacto-oligosaccharides (GOS) found in legumes, nuts, soybeans, and soy goods; “lactose” (a di-saccharide that is non-absorbable if undigested by lactase) found in milk and yoghurt; “fructose” (a monosaccharide) when in excess glucose, found in apple, pear, mango, watermelon, tamarillo, and honey; and “polyols” (or sugar alcohols) that include sorbitol found in apricots, avocado and lychee, and mannitol found in mushrooms, snow peas, and cauliflower.

Other short-chain carbohydrates might act as FODMAPs. Isomalto-oligosaccharides (IMO) are partly hydrolyzed (Kohmoto *et al.*, 1992; Chen *et al.*, 2001) and found in honey. According to Japanese studies, it is found some food such as soy sauce, miso and sake (White Jr & Hoban, 1959; Chen *et al.*, 2001) but the actual accumulation is undetermined. Some food added IMO as a prebiotic/fibre. Another class of oligosaccharides, the xylo-oligosaccharides (XOS), does not seem to be naturally present in food. However, they can still be derived from arabinoxylans and are being explored as prebiotics to add to food.

2.4 Management of IBS subject

Management of IBS is a multi-modal approach. It consists of pharmacological, dietary psychological, neuromodulatory and other behavioural strategies. In the

western countries (Australia, North America, New Zealand, Western Europe) there has been an interest in modifying diet as the primary approach modality rather than a pharmacotherapy. Many diets were described and applied in the study. Nevertheless, the evidence-based for the majority of the diets is not well understood.

There has been an increasing number of studies that consistently describe the efficacy of diet that reduces the intake of foods containing indigestible and slowly-absorbed short-chain carbohydrate (fermentable oligo-, di-, monosaccharides, and polyols – FODMAPs) in about 70% of an unselected population of patient with IBS. Following the studies, the low FODMAP diet is emerging as the primary treatment for IBS patients. (Table 2.1).

The low FODMAP diet varies distinctly across geographical regions. The latest database of food content, specifically describing FODMAPs is majority from Australia and, to a lesser degree, North America, United Kingdom, and Scandinavian. The introduction of Western food consumption pattern and culture into Asian countries are likely to change in their traditional dietary pattern (Nam, Jo & Lee, 2010; Canavan, West & Card, 2014).

The administration of low FODMAP diet is essential in IBS patient. The principles are to avoid all foods with high FODMAP content. All food high in FODMAP content diet in a standard serving potion is replaced with a low FODMAP diet. The ‘exchange’ is essential as FODMAPs are found in a variety of food groups and it ensures patients are taking food from all of five core food groups: meat and their alternatives, dairy, vegetables, fruits, grains and cereals.

Australian Guide to Healthy Eating guidelines recommend a low FODMAP standard serving size in making sure that patient's optimal nutrition is not compromised once a diagnosis of IBS has been made by experts, such as a gastroenterologist. A trained dietitian with expertise in the area of GI tract dysfunction typically recommends the low FODMAP diet in IBS patient. The consultation between dietician and patient is usually conducted through face-to-face meeting, but a group consultation may also be effective and more cost-effective (Whigham *et al.*, 2015).

A prescription of a strict low FODMAP diet by a dietitian for 2-6 weeks after which a steady re-introduction phase follows, and closely monitored until a balance between tolerated doses and symptom control is achieved. Dietitians in this area have the expertise to not only educate patients on which foods to consume and those to avoid but also how to add flavour to their foods and interpret food labels/ingredients lists. They are also able to provide recipe ideas. A key to the diet's successful implementation is the knowledge of FODMAP content of the usual serving sizes of food.

These lists of low FODMAP diet can be easily found on the internet but might be outdated and inaccurate. Monash University had developed a Low FODMAP diet App (Figure 2.1) (DoG, 2019) and Low FODMAP diet booklet (DoG, 2015). These two resources were built in the attempt to circumvent these inaccuracies, since they are based entirely on measured food content and are regularly revised. It helps to support their management of diet, with the help of a trained dietician. Both resources

contain a comprehensive list of diet: including foods, beverages, and condiments that can become as a reference while on a low FODMAP diet, including how to read labels, a dietary fibre counter and a menu guide with recipes.

There is no first-line protocol when applying re-introduction techniques of higher FODMAP containing foods. The re-introduction is individualised to a patient's symptoms, food preference, or what they are missing the most. Alternatively, a dietitian may first introduce less disturbing FODMAPs to a patient's diet such as polyol-containing foods, followed by lactose or fructose-containing food (in excess of glucose) and fructans and/or GOS containing foods. This will differ from one subject to another. Regardless of any approach, one food item is generally re-introduced at a time, every couple of days, until an achievable stable dose is identified. At the same time, symptoms are manageable and under control.

It is essential between the collaboration of patients and a dietitian to help identify "optimum levels" while ensuring that their daily intake is balanced, contains optimum dietary fibre, is adequate and not entirely restricted. While FODMAP tolerances differ between individuals, it may mean that IBS patients take high FODMAP foods less often or in a smaller amount to maintain a balance between the diet and their IBS symptoms.

The low FODMAP dietary efficacy to treat IBS has attracted worldwide attention since the publication of high-quality research to support its benefit in $>70\%$ of patients. Their experience of the diet is expanding in many centres (Halmos *et al.*, 2014; Tuck *et al.*, 2014; Whigham *et al.*, 2015). Details of the studies and their precise

results are shown in Table 2.1. Such studies, as well as those published in abstract form, were subjected to the latest meta-analysis and systematic review, with the conclusion that the diet is beneficial in patients with IBS (Marsh, Eslick & Eslick, 2016). The outcomes also prompted the escalation of the need to translate the diet for practical use by other countries (Whigham *et al.*, 2015).

2.5 Symptom improvement

The most significant improvement in overall GI symptoms appears to happen within seven days of compliance to a low FODMAP diet, after which symptoms are relatively constant (Biesiekierski *et al.*, 2013; Chumpitazi *et al.*, 2015; Halmos *et al.*, 2015). This swift improvement is likely due to the result of osmotic and motility changes in the bowel (Ong *et al.*, 2010). The durability of such benefits has been suggested in a prospective observational study (De Roest *et al.*, 2013), but further study of long-term effects is warranted. However, the adverse effects of low FODMAP diet in the short-term have not been discovered yet.

2.6 Current IBS consensus

The latest IBS consensus recommends the use of patient food diary to identify the triggered foods. However, no specific diet has been recommended for patients in Asia-Pacific for IBS. Moreover, there is no precise recommendation to call for dietitians in the management of IBS in this region. The focus recommendations at present include the avoidance of excessive chilies, dairy products, curries, excess fructose/fructo-oligosaccharide, and dietary fibre intake if they happen to be the cause of symptoms, with a priority on maintaining a nutritionally healthy diet. The IBS

consensus also admits that food is commonly cited by subjects as a provoke to their symptomatology (Halpert *et al.*, 2007; Heizer, Southern & McGovern, 2009), and that dietary restriction of certain "provoke" foods appears to improve symptoms.

The Asia-Pacific Consensus statements for IBS concluded that the current aims of treatment are relief of symptoms and improvement in the quality of life (Johannesson *et al.*, 2011; Gwee *et al.*, 2019). Treatments in Asian-Pacific region is much similiar to those in the Western countries with the focus on a multi-disciplinary modality: including quality doctor-patient relationship, pharmacotherapy, psychiatrists, dietary modification and the use of cognitive behavioral therapy (Li *et al.*, 2014) and hypnotherapy. Various pharmacotherapy combinations are recommended, including, antispasmodic, laxative, prokinetic, antidiarrheal, anxiolytic/antidepressant, fibre, along with antibiotic and probiotic agents (Gwee *et al.*, 2010).

Therefore, the study aimed to compare the effect on IBS symptoms of a low FODMAP diet in outpatients with IBS. A setting in a multi-ethnic population and their effect on gut microbiota can be further explored.

Table 2.1 Methods and Results for Studies of Low FODMAP Diet in Patients with Irritable Bowel Syndrome (Iacovou *et al.*, 2015).

Reference	Design	Intervention	Sample size	How delivered	Duration of intervention or study	Effect of low FODMAP on symptoms
Randomized controlled trials						
(Ong *et al.*, 2010)	Cross-over	Low vs high FODMAP diet	IBS (n = 15) Healthy (n = 15)	All food provided	3 days	Gastrointestinal symptoms and lethargy significantly induced by the high FODMAP diet in IBS patients. Only increased flatus production reported by healthy controls.
(Halmos *et al.*, 2014)	Cross-over	Low FODMAP diet vs typical Australian diet (vs habitual diet)	IBS (n = 30) Healthy (n = 8)	All food provided	3 weeks	Lower overall gastrointestinal symptom scores on VAS (22.8 [16.7-28.8] mm) compared to Australian diet (44.9 [36.6-53.1]; $p < 0.001$) and habitual diet. Significant improvement of bloating, pain, passage of wind and satisfaction with stool consistency. Improvement in overall symptoms in 70%. Symptoms were minimal and unaltered by diets in controls
(Chumpitazi *et al.*, 2015)	Cross-over	Low FODMAP diet vs typical American childhood diet (TACD)	Paediatric IBS (n = 33)	All food provided	3 days	Abdominal pain reduced vs TACD (1.1 + 0.2 [SEM] episodes/day vs 1.7 + 0.4, $p < 0.05$). Compared to baseline, fewer daily abdominal pain episodes (1.4 + 0.2; $p < 0.01$) but more episodes during the TACD ($p < 0.01$).
(Pedersen, Andersen, *et al.*, 2014)	Parallel groups	Low FODMAP diet vs probiotic (LGG) vs habitual diet	Low FODMAP diet (n = 34) Probiotic (n = 37) Control (n =37)	e-health	6 weeks	For IBS-SSS: there was a significant reduction (mean ± SD) in all patients from baseline to week 6, (77 ± 104, $p < 0.01$), as well as in each treatment group (LFD, $p < 0.001$; LGG, $p < 0.01$; and ND, $p = 0.03$). Adjusted changes of IBS-SSS for baseline covariates showed statistically significant reduction in LFD group compared to ND (75; 95% CI: 24-126, $p < 0.01$), but not in LGG compared to ND (32; 95%CI: 18-80, $p = 0.200$).
Non-randomized comparative						
(Staudacher *et al.*, 2011)	Parallel group	Low FODMAP diet vs standard dietary advice based on NICE guidelines	Low FODMAP diet (n = 43) NICE (n = 39)	Dietitian	9 months	Greater satisfaction with symptom response (76%) compared to the standard group (54%, $p = 0.038$); improved overall symptom response (86% vs 49%, $p < 0.001$), bloating (82% vs 49%, $p = 0.002$), abdominal pain (85% vs 61%, $p = 0.023$) and flatulence (87% vs 50%,$p = 0.001$).
(Whigham *et al.*, 2015)	Non-randomized comparative	Low FODMAP diet group education vs one-to one education	group (n = 142), one-to-one (n = 61)	Dietitian	6 weeks	Significant patient symptom satisfaction following dietary advice in group and one-to-one education and decrease in symptom severity from baseline to follow-up ($p < 0.001$ for all groups). No differences between group and one-to-one education.
Prospective observational						
(De Roest *et al.*, 2013)	Consecutive	Low FODMAP diet	IBS (n = 90)		Mean follow-up 15.7 months	Abdominal pain, bloating, flatulence and diarrhea improved ($p < 0.001$ for all); 72% of patients were satisfied with their symptoms.
(Pedersen, Vegh, *et al.*, 2014)	Consecutive	Habitual diet followed by low FODMAP diet	IBS (n = 19)	e-health	6 weeks for each diet	Reduction in IBS-SSS in all patients from median 320 (range: 260-406) to 278 (122-377) ($p = 0.020$).

LFD, low fermentable oligo-, di-, monosaccharides, and polyols (FODMAP) diet; TACD, typical American childhood diet; LGG, *Lactobacillus rhamnosus* GG; VAS, visual analogue scale; IBS-SSS, irritable bowel syndrome-severity scoring system; NICE, National Institute of Health and Clinical Excellence; SEM, standard error of the mean.

Figure 2.1 Monash University FODMAPS diet application.

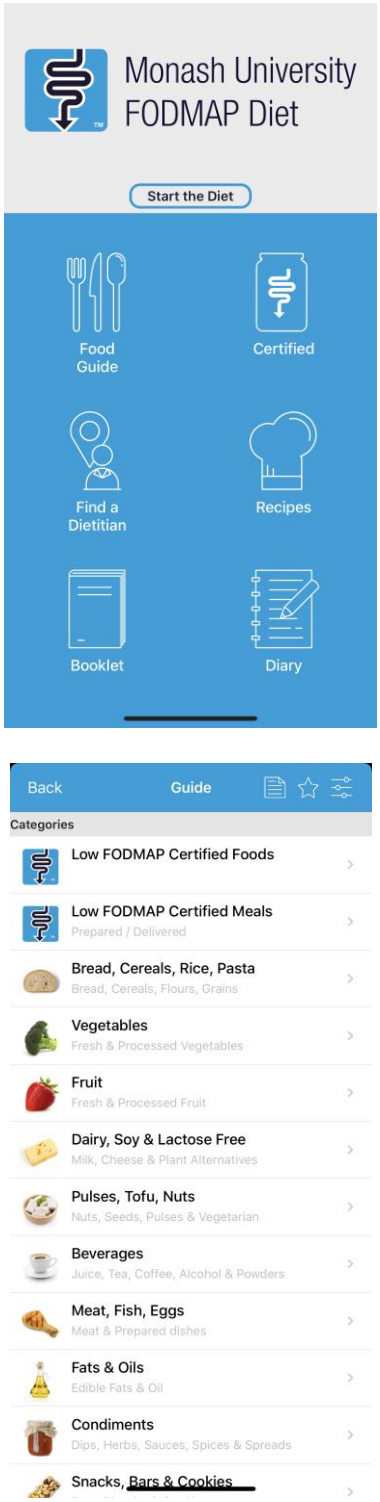

Figure 2.1 Monash University FODMAPS diet application.

CHAPTER 3: OBJECTIVE

3.1 General objectives

To determine the low FODMAP diet on all main study outcomes among adults with irritable bowel syndrome (IBS).

3.2 Specific objectives

3.2.1 To investigate the effect of low FODMAP diet on the symptoms among adult patients with IBS:

a) To compare the effect of low FODMAP diet on IBS patient's IBS - Symptoms Severity Score (IBS-SSS).
b) To compare the effect of low FODMAP diet on IBS patient’s bloating (Bloating Severity Questionnaires – BSQL).
c) To compare the effect of low FODMAP diet on IBS patient's quality of life (EuroQol – EQ-5D-5L).
d) To compare the effect of low FODMAP diet on IBS patient's Hospital Anxiety and Depression Scale (HADS).

3.3 Research questions

1. What is the effect of a low FODMAP diet on symptoms in adults with IBS?

3.4 Research hypothesis

1. IBS patients on a low FODMAP diet have a better symptom response to dietary intervention.

CHAPTER 4: METHODOLOGY

4.1 Study design

This was a cross-sectional interventional study. All IBS patients underwent medical, nutritional therapy of all FODMAP diet, and all outcomes were assessed in IBS patients after 4 weeks.

The study was carried out concurrently with two centres [Universiti Malaya MREC ID No.:20163-2320 (Appendix J) and Universiti Kebangsaan Malaysia] with a total of 60 subjects (45 IBS and 15 healthy controls).

A total of 18 IBS adult were the subjects in this study. They were subjected to a low FODMAP diet over a period of 4 weeks, guided by an experienced dietitian. The diet record (with 2 weekdays and 1-day in the weekend) collected after the intervention.

The aim was to assess all the outcomes. The data were collected in all subjects, including:

a) Fecal sample collection for microbiome analysis before (week 0) and after (week 4) low FODMAP diet.

b) IBS symptom severity score before (week 0) and after (week 4) low FODMAP diet.

c) EQ-5D (Euroqol) data before (week 0) and after (week 4) low FODMAP diet.

d) Hospital anxiety and depression scale (HADS) data before (week 0) and after (week 4) low FODMAP diet.

e) Severity of abdominal bloating and quality of life data (Sev24 and SevGen) before (week 0) and after (week 4) of low FODMAP diet.

4.2 Study duration

This study data were collected from Dec 2018 to Dec 2019

4.3 Study location

Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan.

4.4 Reference population

Adult patients with a clinical diagnosis of IBS. The IBS categories using Rome III criteria are presented in Table 4.1 (Drossman, 2006; Longstreth *et al.*, 2006).

Recurrent abdominal pain or discomfort (defined as uncomfortable sensation not described as pain) for at least 3 days/month in the last 3 months, associated with two or more of the following:
1. Improvement with defecation 2. Onset associated with a change in the frequency of stool 3. Onset associated with a change in the form (appearance) of stool
*****These criteria should be fulfilled for the last 3 months with symptom onset of at least 6 months prior to diagnosis

Table 4.1 Rome III Diagnostic criteria for Irritable Bowel Syndrome

4.5 Source population

Patients were recruited from outpatient gastroenterology clinics of this institution, who fulfilled the inclusion and did not meet the exclusion criteria.

4.6 Study population

Patients of age between 18 – 65 years old with a clinical diagnosis of IBS and healthy controls are members of staff in USM institution.

4.7 Inclusion criteria

1. Patients fulfilling ROME III criteria for the diagnosis of IBS.
2. Age > 18 and < 75 years old.
3. No evidence of small intestine bacterial overgrowth (SIBO) evidenced by a negative Hydrogen breath test
4. No evidence of organic diseases such as inflammatory bowel disease, thyroid disease.
5. Patients are not on laxatives or anti-diarrheal agents.
6. IBS patients that are not on dietary management or treatment for IBS.

4.8 Exclusion criteria

1. Patients recently treated with antibiotics < 6 weeks.
2. Previous abdominal surgery.
3. Medical condition like diabetes mellitus.
4. Pregnant women.
5. Patients taking probiotics for the past 1 month.

4.9 Withdrawal criteria

1. Participation in the study is voluntary and they are allowed to withdraw at any point without any explanation.
2. Participation is a health risk for the subject based on physician discretion.
3. Subject is not able to tolerate low FODMAPs diet during the course of study.
4. In case of subjects who fail to return for follow-up (lost to follow-up).
5. Not compliant to protocol.

The decision to withdraw a subject from the study should be made by Principal Investigator (PI). For any subject who discontinues participation before the completion of the study protocol, the investigator must complete and sign the Case Report Form. Whenever feasible, all scheduled procedures of final visit should be completed as soon as possible and completed diaries and non-used study products should be collected.

For those subjects who discontinue due to the occurrence of adverse event potentially related to the study, follow-up will be carried out until the adverse event has ended, or until a stable situation is reached, with findings being recorded in the Case Report Form.

Healthy controls can be recruited from members of staff in this institution from another department (Not subordinate). Subjects recruited are not under direct of the PI. However, potential subject can be referred to PI.

4.10 Medical screening

Following the approval from the Human Research Ethics Committee pf Universiti Sains Malaysia (USM/JEPeM/18070296 - Appendix I), IBS follow-up patients were approached and briefed regarding the study objectives and procedures. An informed consent form was signed by each the recruits. Then, they were screened by a medical doctor from HUSM for their eligibility. A urea breath test for glucose was performed to exclude SIBO.

4.11 Sample size calculation

Participants recruited were among IBS patients who attended the Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan (HUSM) out-patient clinic review. The sample size was calculated by using G*Power software version 3.1.9.6 for macOS.

Based on a clinically significant improvement in the IBS-SSS mean score using an effect size of 0.4, the power was kept at 80% with a confidence interval of 95%, and the calculated sample size was 30 (Halmos et al., 2014). Estimation dropout rate was at 20%. Thus, 53 participants were required.

(80% x $\boldsymbol{x}$ = 42 participants, thus $\boldsymbol{x}$ = 52.5 participants).

Variable IBS-SSS

t tests - Means: Wilcoxon signed-rank test (one sample case)		
Analysis: A priori: Compute required sample size		
Input	Tail(s)	One
	Effect size d	0.4
	α err prob	0.05
	Power (1-β err prob)	0.8
Output	Non-centrality parameter δ	2.5332049
	Critical t	1.6847629
	Df	39.1070457
	Total sample size	**42**
	Actual power	0.8007016

In a multi-centre study, the sample size is already fixed with a total of 60 subjects (45 IBS and 15 healthy controls). The requirement for HUSM is 18 subjects (15 IBS and 3 healthy controls). Having said that, a total of 24 subjects (18 IBS and 6 healthy controls) recruited and this study only analysed the data from this centre.

4.12 Sampling method

A convenience sampling method was used. All patients who fulfilled the inclusion and did not meet the exclusion criteria fulfilled ROME III criteria for IBS from the period of Dec 2018 to Dec 2019, were included in the study.

4.13 Data collection

Mode of data collection

1. First screening from USM IBS database (Gastro-enterology and U-Sains clinic visit).
2. Potential subjects were called to meet the requirement criteria for the study.
3. Patients who met the study protocol (fulfill inclusion criteria and do not meet exclusion criteria) were enrolled in the study.
4. Clinical information was recorded as per study proforma.

Data extracted including:

1. Demographic data
    a) Age
    b) Gender
    c) Ethnicity
    d) Sex (Male and female)
    e) Use of probiotic and antibiotic

2. Baseline symptom at week 0
    a) IBS – SSS
    b) EuroQol (EQ-5D)
    c) Hospital Anxiety and Depression Scale (HADS)
    d) "Soal Selidik Tahap Kembung Perut Umum (SevGen)".