

EVALUATION OF THE EFFICACY OF PROBIOTICS (MCP® BCMC® STRAINS) TREATING CONSTIPATION IN ELDERLY PATIENTS WITH MULTIPLE CHRONIC CO-MORBIDITIES: A RANDOMIZED CONTROL TRIAL

M.Y.A. GHAFAR¹, H. YAAKUP^{1,2}, R.A.R. ALI^{1,3}, S.A. SHAH⁴

1. Department of Internal Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; 2. Palliative Care Unit, Department of Internal Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; 3. Gastroenterology Unit, Department of Internal Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; 4. Department of Community Health, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia. Corresponding author: Dr. Hayati Yaakup, Palliative Care Unit, Department of Internal Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia, Tel: +60391456074, Fax: +60391456692, Email: rati98@hotmail.com

Abstract: *Objectives:* To evaluate the impact of a microbial cell preparation (MCP®) (Hexbio®; comprising MCP® BCMC® strains) on stool frequency, consistency, and constipation-related symptoms in elderly patients with multiple chronic medical conditions. *Design:* Randomised control trial. *Setting:* Medical outpatient and medical/surgical in-patient unit in single tertiary center. *Participant:* Patients aged ≥ 60 years who experience constipation and have multiple chronic medical conditions. *Methods:* Participants with constipation were blindly randomized into either a treatment (MCP® BCMC® strains) or a placebo group. The treatment was administered twice daily. *Measurement:* Gastrointestinal symptoms and stool habits were assessed over a week during the intervention via the use of a questionnaire and stool diary. *Results:* Stool frequency was seen to be higher and the improvement in stool consistency was more significant in the treatment group than in the placebo group ($p = <0.001$). A significant improvement in symptoms was demonstrated in patients who received MCP® BCMC® strains, specifically with respect to straining ($p = < 0.001$) and a sensation of incomplete evacuation ($p = < 0.001$). reduction in anorectal blockage symptoms and the need for manual stool evacuation was also demonstrated, but this finding was not statistically significant. Significant adverse events were not observed. *Conclusions:* An improvement in stool frequency and consistency was reported in elderly patients with chronic medical conditions following the administration of MCP® BCMC® strains.

Key words: MCP® BCMC® strains, Hexbio®, probiotics, elderly, chronic medical conditions, constipation.

Introduction

In general, healthcare providers define constipation as reduced bowel movement (≥ 3 the frequent passing of hard stools, having to strain in order to defecate, and/or the inability to pass stools normally. In 2013, the American Gastroenterological Association classified constipation "as a syndrome that is defined by bowel symptoms (difficult or infrequent passage of stools, hardness of stools, or a feeling of incomplete evacuation) that may occur either in isolation or secondary to another underlying disorder" (1). The American Gastroenterological Association and the Rome IV criteria place emphasis on bowel-related symptoms, such as straining or lumpy/hard stools in their definition of constipation (1-3). However, the terms "functional constipation" or "idiopathic constipation" remain controversial because it is thought that constipation relates to neurological abnormality at the cellular level.

Worldwide, the prevalence of constipation increases with age, especially in those aged ≥ 65 years (4). Previously, it has been shown that certain medical conditions are associated with constipation, including diabetes mellitus, hypothyroidism, and chronic kidney disease (1). Elderly patients, especially those with advanced medical conditions, commonly complain of difficulty emptying their bowels, and this is usually associated with hard faeces, straining, feeling of incomplete evacuation,

and non-productive urges. The management of constipation in this group is always challenging for healthcare providers owing to multifactorial causes, such as loss of mobility, underlying illnesses, the use of medication, an impaired anorectal sensation, and irritable bowel syndrome.

It has been reported that the prevalence of constipation is higher in elderly patients living in nursing homes (74%), compared to those living in a community (50%) (5-7). Nursing home residents are known to have multiple co-morbid illnesses and may use several medications, which contributes to defecation-related difficulties. The condition worsens with a diagnosis of coexisting advanced cancer, in conjunction with the use of opioid prescriptions. Regardless of the underlying aetiology and need to manage underlying illness, healthcare providers commonly treat constipation by disimpacting the hard faeces in the colon or rectum. Thereafter, the aim is to achieve soft stools via the co-administration of softer based laxatives and a high-fiber diet. However, this does not necessarily result in a satisfactory improvement in constipation and associated symptoms in many patients (8).

Probiotics have been investigated for their positive effects in the management of idiopathic constipation. The proposed mechanism of probiotics on constipation is based on the concept that they modify and stabilize the intestinal microflora, which are subject to alteration in people with chronic constipation (9, 10). Probiotics have been shown to

regulate bowel sensations and motility (11). Several studies have been conducted to determine the efficacy of probiotics in reducing functional constipation in adults, and they have shown promising results. Dimidi et al. conducted a systematic review of 14 studies on the use of probiotics to treat functional constipation. They concluded that probiotics improved whole gut transit time, stool frequency, and stool consistency (12). Probiotic have known to improve gut microbiota haemostasis and immune defence in elderly with additional certain probiotic strains has shown to improve the frequency of bowel movement (13).

The current study objective was to investigate the impact of probiotics (a microbial cell preparation [MCP® BCMC® strains], Hexbio®) on the management of constipation in an elderly group of patients with multiple medical illnesses. It is known that medical co-morbidities are associated with constipation, but they are not thought to cause constipation directly.

Study design and setting

A randomized, and placebo-controlled with 1: 1 allocation ratio clinical trial was performed. The study was approved by the Local Ethics Committee (Project code: FF-2016-417) and registered with The National Medical Research of Malaysia. It was conducted in accordance to the guidelines of good clinical practice (GCP). This was a single centre trial conducted at the Universiti Kebangsaan Malaysia (UKM) Medical Centre. The subjects were recruited from the outpatient medical clinics those who were admitted to either the medical or surgical wards between August and December of 2017.

Inclusion and exclusion criteria

The inclusion criterion was patients diagnosed with constipation who fulfilled the criteria for the Rome IV for functional constipation (2, 3, 14, 15). The constipation is defined as the following:

1. "Must include 2 of the following:
 - a. Straining during more than one-fourth (25%) of defecations
 - b. Lumpy or hard stools according to The Bristol Stool Form Scale (BSFS) 1&2 more than one-fourth (25%) of defecations
 - c. Sensation of incomplete evacuation more than one-fourth (25%) of defecations
 - d. Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations
 - e. Manual maneuvers to facilitate more than one fourth (25%) of defecations (e.g., digital evacuation, support of the pelvic floor)
 - f. Fewer than 3 spontaneous bowel movements per week"

The symptoms must be presence at least 3 months prior to recruitment. Screening colonoscopy for patient aged 60 years old and above is not mandatory unless patients have other symptoms the warrant an endoscopic investigation and the

patient will be automatically excluded from the study. This is due to limited financial support for this study. Participants will be excluded if they found to have irritable bowel syndrome, constipation secondary to Parkinson's disease, spinal cord lesions, and post radiation strictures, calcium supplements of greater than 1,500mg per day, any form of neoplasm, immune-deficient or critical illness.

Intervention

The subjects received either the probiotics or a placebo. The treatment sample is an orange-flavoured, granulated microbial cell preparation (Hexbio®, MCP® BCMC® strains), containing 30 billion colony forming units (c.f.u) of Lactobacilli and Bifidobacteria strains (5 billion CFU or 107mg of each strains): Lactobacillus acidophilus BCMC® 12130, Lactobacillus casei BCMC® 12313, Lactobacillus lactis BCMC® 12451, Bifidobacterium bifidum BCMC® 02290, Bifidobacterium infantis BCMC®02129, Bifidobacterium longum BCMC® 02120. The placebo sample was similar in appearance and taste, but contained no microbial cells. Both preparations were consumed twice daily for a duration of 7 days.

Consent was obtained from the patients to participate in the study. The patients' medical details and constipation-related signs and symptoms were recorded during their first visit. All patients were asked to not consumed any probiotic related products as supplement or medications during the study period. All dietary and medications consumption and changes were to be recorded in the daily dairy provided. Patient compliance was ensured through timely bedside visits by the researcher and via telephonic follow-up with outpatients. The study participants were also asked to retain the empty sample sachets and to be collected on completion of the intervention.

Outcomes evaluation

Primary outcomes were changes in stool output frequency and stool consistency according to the BSFS (16, 17). Secondary outcomes were the patients' perceptions of an improvement in their constipation-related symptoms, i.e., the extent to which they needed to strain, the presence of lumpy or hard stools, a sensation of incomplete evacuation, a sensation of anorectal obstruction/blockage, and the need to use manual manoeuvres to aid defecation during the seven-day intervention

The Garrigues questionnaire is an old but validated screening tool chosen for this study as it was consistent with the depth of the research (15). The participants were required to complete the Garrigues Questionnaire detailing the nature of the constipation and the related symptoms (18). Each participant was also taught on the usage of a stool diary as the main tool outcomes measurement. Participants were required to self-assess their stool habit and marking it on the daily frequency chart and in the BSFS chart. BSFS is a diagnostic tool designed to classify the consistency of human faeces into seven categories (19). Types 1 and 2 indicate constipation, with 3, 4 and 5 being the ideal stools and 6 or 7 indicate diarrhoea). The

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Table 1
The baseline characteristics of the treatment versus the placebo groups

Patient parameters	Treatment	Placebo	p-value	Test
Number of patients (n)	36	36	N/A	N/A
Age, median (range) (years)	70.4 (61–83)	73 (61–88)	0.152	Mann-Whitney
Gender, n (%)				
Men	19 (52.8)	21 (58.3)	0.813	Chi-square
Women	17 (47.2)	15 (41.7)		
Ethnicity, n (%)				
Malay	18 (50.0)	17 (47.2)	0.792	Chi-square
Chinese	14 (38.9)	13 (36.1)		
Indian	4 (11.1)	6 (16.7)		
Months of constipation, n (median)	10 (6–21)	12 (4–24)	0.817	Mann-Whitney

BSFS is used worldwide but has not been validated vigorously. All of the data and information were collected at the end of 7 days' intervention and analysed accordingly. Any changes in daily dietary intake or additional or stopping medication that been recorded will be review in detail. Participants who have significant changes in either their daily diet or medications will be excluded from the main data collections.

Sample size

The sample size was estimated using PS: Power and Sample Size Calculation® version 3.1.2, based on a prior study conducted by Jayasimhan et al (20). The study indicated that the probability of exposure among the controls was 0.67, and that the true probability of exposure among the cases was 0.3. The study was powered at 80 percent with alpha at 5 percent (0.05). A total sample size of 54 (27 in each group) was required with a 1:1 allocation was calculated to be sufficient to reject the null hypothesis that the exposure rates for the cases and controls were equal.

Randomization and blinding

A randomization process was performed using a block design via computer generated allocation done by independent personnel. Both investigators and patients were unaware of the assignment and were blinded to the labelling process performed by the sample supplier. The patients were randomly allocated to one of two groups; those who received sample labelled A or B. Emergency code break were kept at the manufacturing factory and no code break was needed throughout the trial duration. Both MCP® BCMC® strains, and placebo were manufactured and supplied by B-Crobes Laboratory Sdn. Bhd. as powder in identical sachets and labelled as A and B. Investigators have no contact with the manufacturing staffs at any point during the trial process. Following data analysis, unblinding was performed to complete the study process.

Statistical analysis

The collected data was analysed using IBM SPSS Statistics for Windows version 21.0 software (IBM Corp., Armonk, NY, USA) and Microsoft Office Excel 2010 software (Microsoft, Redmond, WA, USA). Statistical significance was set at $p = <0.050$. All of the data was assessed for normality via the usual processes.

The baseline characteristic differences between the two groups were evaluated using the Mann-Whitney U and chi-squared tests. The median results of the improvement in stool frequencies and stool consistency between the treatment and placebo group were compared using the Mann-Whitney U test. The constipation-related symptom improvements were analysed using the chi-squared test.

Intention to treat analysis was used in this trial, where only the final results within the group which they were randomized, receiving the treatment and completed the treatment assignment were analysed. Participants who deviates from the protocol as being non-compliance or withdrew consent were not included into the analysis.

Results

Baseline characteristics

One hundred patients aged ≥ 60 years with at least two previously identified chronic medical conditions (Figure 1 and Table 1) who fulfilled the inclusion criteria were recruited. Ten patients were excluded owing to constipation secondary to Parkinson's disease, spinal cord lesions, post-radiation urethral stricture, the use of calcium supplements of $\geq 1,500$ mg per day, being immunocompromised, or critical illness. Wide variation in dietary or significant changes in oral medications and addition use of aperients were excluded from data analysis. Ninety patients were randomized into the two groups. However, of these, 18 were excluded from the overall data analysis for various reasons. The median age was 70.4 years old

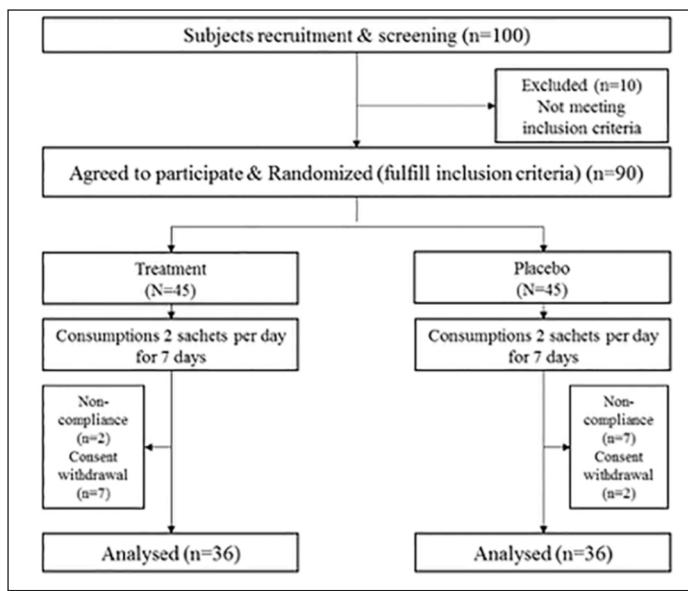
Table 2
An overview of the medical conditions of the patients

Medical conditions	Treatment group, n (%)	Placebo group, n (%)	p-value
Diabetes mellitus	26 (72.2)	26 (72.2)	1.000
Hypertension	36 (100.0)	32 (88.9)	0.115
Hyperlipidemia	23 (63.9)	21 (58.3)	0.809
Chronic kidney disease	11 (30.6)	11 (30.6)	1.000
Bronchial asthma	0 (0.0)	5 (13.9)	0.054
Congestive cardiac failure	11 (30.6)	14 (38.9)	0.621
Other	18 (50.0)	11 (30.6)	0.149

*: The p-value was calculated using the chi-square test.

(interquartile range [IQR] of 61–83 years) for the treatment group and 73 years old (IQR of 61–88 years) for the placebo group. There were more male (55.6%) than female patients (44.4%), but any differences in age, gender, and ethnicity between the patients in the two groups were without statistical significance. The median constipation duration was 10 months (IQR of 6–21 months) and 12 months (IQR of 4–24 months) in the treatment and placebo groups, respectively.

Figure 1
A flow chart of the patient selection process



Most of the patients had diabetes mellitus, hypertension, and hyperlipidemia (Table 2). Other medical illnesses included chronic kidney disease, bronchial asthma, congestive heart failure, chronic lung disease, and chronic liver disease. The randomization procedure was performed effectively and bias was not identified with regard to patient selection during the recruitment process.

Stool frequency

The median defecation frequency for the placebo and treatment groups was similar (twice a week; IQR of 1–3) prior to the intervention. During the treatment period, the placebo group reported no difference in stool frequency, but the median defecation frequency increased to 5 (IQR of 2–8) in the treatment group, and this was statistically significant ($p = <0.050$) (Table 3). Stool frequency increased to ≥ 3 times a week for 70.0% of patients in the treatment group, compared to only 14.8% of patients in the placebo group (Table 4). Absolute risk reduction was 55.2%, and the calculated number needed to treat was 1.8.

Stool consistency

Prior to the intervention, median stool consistency for the patients in both groups was Bristol Stool Scale type 2. The placebo group observed no difference in stool consistency after the intervention, whereas a significant improvement in median stool consistency (i.e., Bristol Stool Scale type 4) was demonstrated in the treatment group following the treatment, and this was statistically significant ($p = <0.050$) (Table 3).

Constipation-related symptoms

The most common constipation-related symptoms experienced by the study patients are listed in Table 4. The treatment group reported a significant improvement in most of their symptoms on completion of the study. Treatment group patients reported less straining (76%), an improvement in stool consistency (72.2%), a reduction in the sensation of incomplete evacuation (77.3%), and less need to perform a manual manoeuvre to aid defecation (90.0%). In addition, the treated patients reported a greater reduction in the sensation of anorectal obstruction/blockage compared to the placebo group; however, this was without statistical significance.

Adverse events

Post the intervention, of the 90 patients, only 1 (1.4%) of them reported type 7 BSFS consistency (i.e., approaching diarrhoea). However, the patient was well clinically, and the

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Table 3

A median comparison of the end-point measures (stool frequency and consistency) between the treatment and placebo groups

Parameters	Patient group	Pre-intervention	Post intervention (day 7)	p-value*
Stool frequency	A	2 (IQR of 1-3)	5 (IQR of 2-8)	< 0.050
	B	2 (IQR of 1-3)	2 (IQR of 1-4)	
Stool consistency ^a	A	2 (IQR of 1-3)	4 (IQR of 1-6)	< 0.050
	B	2 (IQR of 1-3)	2 (IQR of 1-4)	

IQR: interquartile range; *: The p-value was calculated using the Mann-Whitney test; a: Stool consistency was determined using the Bristol Stool Scale (ranging from 1-7)

Table 4

An evaluation of an improvement in constipation-related symptoms in the treatment and placebo groups

Improvement in constipation-related symptoms	Treatment (%)	Placebo (%)	p-value
Straining	76.0	17.2	<0.001
Lumpy or hard stools	72.2	16.7	<0.001
Sensation of incomplete evacuation	77.3	20.0	0.001
Sensation of anorectal obstruction/blockage	77.8	22.2	0.570
Manual maneuvers to aid defecation	90.0	28.6	0.035
Defecation \leq 3 times per week	70.0	14.8	<0.001

*: The p-value was calculated using the chi-square test.

symptoms resolved without medical intervention after the study. Other adverse events were not observed during the trial.

Discussion

The estimated prevalence of constipation in the elderly is 24–74%, especially in those aged \geq 60 years and being institutional (4, 6, 7, 13, 21-23). There are multifactorial aetiologies, and the pathophysiology of constipation remains poorly elucidated. It is especially challenging managing constipated elderly patients with multiple medical conditions. Over the last few decades, a growing body of evidence has demonstrated that probiotics are beneficial in the treatment of chronic idiopathic constipation. Bifidobacterium and Lactobacillus strains are often evaluated in probiotics trials (24). Dimidi et al observed a significant improvement in stool frequency and consistency, as well as other constipation-related symptoms following the administration of Lactobacillus and Bifidobacterium strains to the study participant (12). In this trial, MCP® BCMC® strains, was given to an interventional arm of elderly patients with constipation with at least two medical conditions, and the effects were compared with those of a placebo. To the best of our knowledge, similar studies have not been conducted on elderly constipated patients with medical conditions that have a direct association with constipation. Consistent with the outcomes of previous constipation trials using MCP® BCMC® strains, it was hypothesized in the current study that MCP® BCMC® strains, a mixture of six

microbial strains of Lactobacillus and Bifidobacterium, would reduce constipation in the patient cohort (12, 20). Overall, the findings of this randomized, placebo-controlled trial were that MCP® BCMC® strains, was efficacious in treating constipation in elderly patients with chronic medical conditions. The improvement in stool frequency during the one-week intervention was significantly greater group (MCP® BCMC® strains) compared to the placebo group ($p = <0.001$). This finding is consistent with that of a previous study that was conducted by Jayasimhan et al. in which MCP® BCMC® strains were used in a younger and healthier cohort (20).

Multiple studies have revealed quantitative differences between the intestinal microbiota of constipated patients and those of healthy controls (13). It has been demonstrated that Lactobacillus and Bifidobacterium concentrations are low in patients with chronic constipation compared to those who are not constipated (13). Therefore, the addition of a probiotic to a patient's diet might restore the microbiota composition and reduce constipation and related symptoms. However, this could be regarded as a simplistic view because the exact role of the intestinal microbiota in gut motility remains poorly understood. Current evidence supports the claim that the addition of MCP® BCMC® strains that contains Lactobacilli and Bifidobacterium has a beneficial effect on constipation. It was shown to improve the bowel movements of the elderly cohort of constipated patients with chronic medical illnesses in the current research.

The addition of MCP® BCMC® strains to the normal diet of a patient was observed to improve stool consistency in the present

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study. A similar rapid effect was reported by Jayasimhan et al. who evaluated the efficacy of MCP® BCMC® strains in the treatment of constipation in healthy individuals over a brief intervention period (20). A significant increase in stool frequency and stool softness in constipation-predominant irritable bowel syndrome patients was also reported in a double-blinded controlled trial carried out by Koebnick et al., in which the effects of the consumption of Lactobacillus casei strain Shirota on constipation were evaluated (16). It has been speculated that the probiotics fermentation process produces short-chain fatty acids that later promote the excretion of water and electrolytes to soften the stools (25, 26). Some researchers have proposed that an increase in the production of short-chain fatty acids and lactate, along with a reduction in luminal pH, as a consequence of probiotics usage, enhances peristalsis and shortens gut transit time (12, 18, 27).

An improvement in the constipation-related symptoms of patients taking MCP® BCMC® strains were evident through enhanced symptom control; specifically, with respect to straining and sensations of incomplete evacuation and anorectal obstruction/blockage. A reduction in bloating, flatulence, and pain during defecation has also been reported in other studies following the consumption of probiotics (12). However, the incidence of bloating, flatulence, and pain during defecation among the patients in the current study was minimal at the start of the trial, and this may account for the lack of a significant improvement in the outcomes overall.

The positive effects on MCP® BCMC® strains on constipation-related symptoms indicate that it is a promising intervention for use in elderly patients with multiple medical conditions. In the present trial, adverse events were not reported with the use of MCP® BCMC® strains. It is well tolerated generally; with minimal adverse events being reported in previous clinical trials. A lack of sufficient data from high-quality controlled trials may hinder recommendations for the use of probiotics in elderly patients with chronic medical illnesses. Nevertheless, this randomized, controlled study should create opportunities for further probiotics trials beyond the size of the current patient cohort.

The current trial was conducted on a select group of patients at a single centre concentration on hospital population, and this may have constituted selection bias. Thus, the results obtained for the current sample may not be representative of the intended population. It is likely that the use of larger sample sizes and multi-centre studies would produce better outcomes. Another limitation was that the research relied on self-reported outcomes rather than an objective measurement thereof, and this might have influenced the reliability of the data. A rigorous research protocol with post-interventional follows-up would have helped to determine whether or not the beneficial effects were long-lasting and to detect any late adverse events.

Conclusions

The consumption of MCP® BCMC® strains that contained Lactobacillus and Bifidobacterium in the current study was seen to confer positive effects to elderly patients with two or more chronic medical illnesses not normally not related directly to constipation. Specifically, an increase in stool frequency and an improvement in stool consistency were observed. The MCP® BCMC® strains used in this study was observed to be safe in general, and it is known not to cause any significant side-effects.

Trial registrations: NCT 04035616. The National Medical Registry of Malaysia (NMRR-19-1761-49477).

Acknowledgements: MCP® BCMC® strains and placebo were provided by B-Crobes Laboratory Sdn. Bhd. This company had no direct involvement in the actual study. This study was registered with The National Medical Registry of Malaysia (NMRR-19-1761-49477) where the full trial protocol can be accessed.

Grant and Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution statements: Y.A.G, H.Y, R.A.R.A and S.A.H. contributed to the design and implementation of the research, to the analysis of the results. Y.A.G and H.Y involved in the preparation of the manuscript. The final version of the manuscript was approved by all authors.

Conflict of interest: The authors declare that they have no conflicts of interest with regard to this clinical trial.

Ethical Standards: The study was approved by Institutional Review Board, Universiti Kebangsaan Malaysia Medical Research Ethics Committee (Project code: FF-2016-417). All patients provided written informed consent to participate in the clinical trial.

References

1. Bharucha AE, Pemberton JH, Locke GR 3rd. American Gastroenterological Association technical review on constipation. *Gastroenterology* 2013; 144(1):218–238.
2. Simren M, Palsson OS, Whitehead WE. Update on Rome IV Criteria for Colorectal Disorders: Implications for Clinical Practice. *Curr Gastroenterol Rep.* 2017. doi:10.1007/s11894-017-0554-0
3. Lacy B, Patel N. Rome Criteria and a Diagnostic Approach to Irritable Bowel Syndrome. *J Clin Med.* 2017;6(11):99
4. Rao SS. Constipation: Evaluation and treatment of colonic and anorectal motility disorders. *Gastroenterol Clin North Am.* 2007; 36(3):687–711, x.
5. Rao SS, Go JT. Update on the management of constipation in the elderly: new treatment options. *Clin Interv Aging* 2010; 5: 163–171.
6. Flach J, Koks M, van der Waal MB, Claassen E, Larsen OFA. Economic potential of probiotic supplementation in institutionalized elderly with chronic constipation. *PharmaNutrition.* 2018. doi:10.1016/j.phanu.2018.10.001
7. O.F.A. Larsen, M. Van den Nieuwboer, M. Koks, J. Flach, E. Claassen, Probiotics for healthy ageing: innovation barriers and opportunities for bowel habit improvement in nursing homes, *Agro. FOOD Ind. Hi Tech* 28 (5) (2017) 12–15
8. Bongers ME, Benninga MA, Maurice-Stam H, Grootenhuis MA. Health-related quality of life in young adults with symptoms of constipation continuing from childhood into adulthood. *Health Qual Life Outcomes.* 2009; 7:20.
9. Khalif IL, Quigley EM, Konovitch EA, Maximova ID. Alterations in the colonic flora and intestinal permeability and evidence of immune activation in chronic constipation. *Dig Liver Dis* 2005; 37:838–849.
10. Zoppi G, Cinquetti M, Luciano A, Benini A, Muner A, Bertazzoni Minelli E. The intestinal ecosystem in chronic functional constipation. *Acta Paediatr* 1998; 87(8):836–841.
11. Quigley EM. Bacteria: a new player in gastrointestinal motility disorders— infections, bacterial overgrowth, and probiotics. *Gastroenterol Clin North Am* 2007; 36(3):735–748.
12. Dimidi E, Christodoulides S, Fragkos KC, Scott SM, Whelan K. The effect of probiotics on functional constipation in adults: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2014; 100(4):1075–1084. doi: 10.3945/ajcn.114.089151.

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13. Lakshminarayanan, B., Stanton, C., O'Toole, P. W., & Ross, R. P. (2014). Compositional dynamics of the human intestinal microbiota with aging: Implications for health. *The Journal of Nutrition, Health & Aging*. doi:10.1007/s12603-014-0513-5
14. Talley NJ, O'Keefe EA, Zinsmeister AR, Melton LJ 3rd. Prevalence of gastrointestinal symptoms in the elderly: a population-based study. *Gastroenterology* 1992; 102(3):895–901.
15. Garrigues V, Gálvez C, Ortiz V, Ponce M, Nos P, Ponce J. Prevalence of constipation: agreement among several criteria and evaluation of the diagnostic accuracy of qualifying symptoms and self-reported definition in a population-based survey in Spain. *Am J Epidemiol* 2004; 159(5): 520–526.
16. Koebnick C, Wagner I, Leitzmann P, Stern U, Zunft HJ. Probiotics beverage containing *Lactobacillus casei* Shirota improves gastrointestinal symptoms in patients with chronic constipation. *Can J Gastroenterol* 2003; 17(11):655–659.
17. Koh H, Lee MJ, Kim MJ, Shin JI, Chung KS. Simple diagnostic approach to childhood fecal retention using the Leech score and Bristol stool form scale in medical practice. *J Gastroenterol Hepatol* 2010; 25 (2): 334–338.
18. Waller PA, Gopal PK, Leyer GJ, Ouwehand AC, Reifer C, Stewart ME, Miller LE. Dose-response effect of *Bifidobacterium lactis* HN019 on whole gut transit time and functional gastrointestinal symptoms in adults. *Scand J Gastroenterol* 2011; 46(9):1057–1064.
19. O'Donnell L, Virjee J, heaton KW. Detection of pseudodiarrhoea by simple clinical assessment of intestinal transit rate. *BMJ* 1990; 300: 439–40.
20. Jayasimhan S, Yap NY, Roest Y, Rajandram R, Chin KF. Efficacy of microbial cell preparation in improving chronic constipation: a randomized, double-blind, placebo-controlled trial. *Clin Nutr* 2013; 32(6): 928–933.
21. Talley NJ, Fleming KC, Evans JM, O'Keefe EA, Weaver AL, Zinsmeister AR, Melton LJ 3rd. Constipation in an elderly community: a study of prevalence and potential risk factors. *Am J Gastroenterol* 1996; 91(1):19–25.
22. Everhart JE, Go VL, Johannes RS, Fitzsimmons SC, Roth HP, White LR. A longitudinal survey of self-reported bowel habits in the United States. *Dig Dis Sci* 1989; 34(8):1153–1162.
23. Whitehead WE, Drinkwater D, Cheskin LJ, Heller BR, Schuster MM. Constipation in the elderly living at home. Definition, prevalence, and relationship to lifestyle and health status. *J Am Geriatr Soc* 1989; 37(5):423–429.
24. Yang YX, He M, Hu G, Wei J, Pages P, Yang XH, Bourdu-Naturel S. Effect of a fermented milk containing *Bifidobacterium lactis* DN-173010 on Chinese constipated women. *World J Gastroenterol*. 2008; 14(40):6237–6243.
25. Zhao Y, Yu YB. Intestinal microbiota and chronic constipation. *Springerplus* 2016; 5(1): 1130.
26. Canani RB, Costanzo MD, Leone L, Pedata M, Meli R, Calignano A. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. *World J Gastroenterol* 2011; 17(12):1519–1528.
27. Salminen S, Salminen E. Lactulose, lactic acid bacteria, intestinal microecology and mucosal protection. *Scand J Gastroenterol Suppl* 1997; 222:45–48.