Biomedical Letters
2017 | Volume 3 | Issue 2|Pages 51-59

A META ANALYSIS OPEN ACCESS

Efficacy of Probiotics in the Treatment of IBD

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Abstract
Inflammatory bowel disease (IBD) is caused by deregulated immune responses to host intestinal bacterial flora and are characterized by the chronic inflammation at various sites of the gastrointestinal tract (GIT). Certain probiotic bacteria have shown that they can produce chemicals (e.g. neurotransmitters and neuromodulators) that can have an effect on gastrointestinal functions like sensation or motility. These mechanisms suggest potential roles for probiotics in the management of irritable bowel syndrome (IBS) and IBD. The main purpose of this meta-analysis is to assess the evidence for the role and clinical efficacy of probiotics in IBD. The meta-analysis was performed following the Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines (PRISMA guidelines) recommended by the Cochrane Collaboration. 13 papers including 960 patients with IBD were selected for the meta-analysis, which fulfilled the inclusion, and exclusion criteria set for the meta-analysis. Our results showed that probiotics group have better improvement in overall disease symptoms response (abdominal pain p <0.1, MD 0.12; bloating p=0.03, MD 0.16; quality of life p=0.35, MD 0.19; diarrhea p=0.56, RR=1.07; constipation p=0.36, RR=0.86 with CI 95%). The probiotic treatment had an overall positive efficacy than the placebo group in the treatment of IBD's symptoms and that single strains of probiotic bacteria with lower doses and shorter treatment time appear to be more effective in improving the quality of life and the overall disease symptom response. The use of probiotics is safe.
Keywords: Intestinal bacterial flora, inflammatory bowel disease (IBD), gastrointestinal tract, probiotics.

Received February 04, 2017; **Revised** March 19, 2017; **Accepted** March 26, 2017
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***To cite this manuscript*:** KC B, Giri RK, Maharjan M, Thapa N, Gang YH. Efficacy of Probiotics in the Treatment of IBD. Biomed Lett 2017; 1(1):51-59.

1. Introduction

Inflammatory Bowel Disease (IBD) is a syndrome with obstructive microbiology, physiology, genetics and immunology [1]. The disease includes two other conditions namely ulcerative colitis (UC) and Crohn's disease (CD) with unique characteristics for both the conditions. The CD is characterized by inflammation in the intestinal wall linings whereas UC causes inflammation and long lasting scoring in the rectum or colon [2]. IBD is termed as an idiopathic condition which occurs due to deregulation of immune responses to the host bacteria and hence causes long-lasting chronic inflammation at different sites of the Gastrointestinal (GI) tract [3]. Intestinal microbiota plays a crucial role in the digestive system and hence is associated with IBD. To be more specific, IBD is characterized by inflammation at different sites of the GI tract as a result of cell-mediated GI mucosa response, which in turn results in symptoms such as abdominal pain, rectal bleeding, and severe diarrhea. According to Thia *et al*.[4] IBD occurs in almost all age groups and its usual incidence is recorded before the age of 30. However, the peak incidence is found to be around 14 to 24 years of age [4]. Previous studies suggested the potential role of probiotics in the management of Irritable bowel syndrome (IBS) and IBD. In this context, the present study investigated the overall role and clinical efficacy of probiotics in the treatment of inflammatory bowel disease, which is achieved through a meta-analysis.

1.1 Gastrointestinal health

A report by Kaplan [5] states that more than 2.5 million Europeans and 1 million Americans are estimated to suffer from IBD and hence substantial costs are incurred for healthcare. The exact causes of IBD and associated conditions such as ulcerative colitis (UC) and Crohn's disease (CD) are not known; however, oral contraceptives, breastfeeding, and dietary habits contribute to IBD [3].

1.2 The role of gut Microbiota on IBD

One of the most accepted IBD pathogenesis till date is the abnormal immune response against microbiota in the gut, which is regulated by environmental factors. According to Sartor [6], the main factors which are associated with IBD are genetic

susceptibility, immune responses, environmental factor wherein all these factors act against the gut microbiota. Gut microbiota plays a major role in the pathophysiology of IBD, which is highlighted by several studies. Sechrist [7] discerns that more than 100 trillion bacteria reside in the gut of human beings and 99 percent of the DNA in the human body is made up of bacteria. Several evidences suggest that gut microbiota plays an important role in intestinal inflammation. In rat models of IBD such as the $CD45Rb^{high}$ transfer model and the IL-10-deficient mice, transferred naïve helper T cells enabled microbiota-dependent inflammation in the intestine in $Rag2^{-/-}$ mice which are immune-deficient recipients; however, animals which are germ-free never develop colitis. Fecal stream diversion improves intestinal inflammation in cases of CD [8].

1.2.1 Dysbiosis

Dysbiosis is defined as the alterations in the balance between beneficial and aggressive microbes in the gut which leads to inflammatory conditions in the gut. Dysbiosis commonly contributes to long-lasting inflammation in the intestine. Several studies examined the pathogenesis of IBD and intestinal inflammation wherein organisms such as Enterococcus, Klebsiella, Eschericia coli (*E. coli*) species and Bacteroides are revealed to be the commensal organisms [9]. Lactobacillus and Bifidobacterium species are the beneficial microbes residing in the intestine and are traditionally used as probiotic therapy in patients with IBD and intestinal inflammation. According to Sartor [10], probiotics can have a positive influence on the residing of Bifidobacterium and Lactobacillus species enhancing their growth and help in the production of short chain fatty acids (SCFA's), especially butyrate which can help with the mucosal barrier functions [10].

1.3 Probiotics

Lactobacillus and Bifidobacterium species are widely used probiotic bacteria and are often considered as topics of great interest by researchers in the field of probiotics [11]. The re-administration of probiotic bacteria to human beings should be passed to the gastrointestinal tract and should be capable of withstanding the low pH values during digestion and the stomach acids. Furthermore, these bacteria should be of human origin. The different health effects of probiotic bacteria include serum cholesterol level reduction, immunomodulatory effects, and protection against inflammation in the intestine. Other effects include protection against colon cancer, lactose digestion improvements and so on [12]. Probiotics are capable of affecting the functions of the intestinal barrier positively and exert effects of anti-inflammation [12]. Several clinical trials conducted with probiotics revealed successful results in terms of their effectiveness in treatment and reduction of IBD symptoms [13]. Systematic reviews and meta-analysis on the efficacy of probiotics also discerned similar results [14–17].

With the efficacy of probiotics in the management of IBD examined by several researchers, no meta-analysis has been published on the role and clinical efficacy of probiotics in the treatment of inflammatory bowel disease, which lead us to develop a meta-analysis on this subject.

2. Materials and Methods

2.1 Selection of studies

The data search for Meta-analysis was performed electronically by the use of keywords and Medical Subject Headings (MeSH) in the search string. Following are the keywords used for the electronic search- *probiotics, IBD, Ulcerative Colitis, Crohn's disease, inflammation, food allergy and chronic diarrhoea*. Medical databases such as PubMed, EMBASE, SpringerLink, Wiley online library, NIH US clinical trials and Cochrane Library databases were used to search for studies. Keywords and MeSH headings were used either separately or in combination to search for relevant literature pertaining to our meta-analysis. Clinical Trials conducted in the last 20 years were considered for this meta-analysis. Randomized and non-randomized controlled trials were included in this meta-analysis and research articles published in English were considered for inclusion.

2.2 Inclusion and Exclusion criteria

Inclusion criteria	Exclusion criteria
Clinical trial studies (Human trial)	Studies which considered patients with chronic medical conditions such as colorectal cancer and other gastrointestinal diseases but not IBD.
Studies involving the comparison of probiotic and placebo groups	Studies which only had an abstract
Studies involving Probiotic treatment for more than one week	Studies involving combined efficacy of Probiotics with other drugs
Studies with patients fulfilling the Rome III criteria as test subjects	Studies lacking data

2.3 Assessment of studies

A quality check on the studies to be included in a meta-analysis is essential which ensures that more

methodologically sound papers have been chosen [18]. This study undertakes a quality assessment of the chosen RCTs using the Downs and Black's quality assessment checklist [19]. This is a quality check used for both randomized and nonrandomized studies and provides an overall score of the quality of the study with a scoring system taking into consideration the study's quality of reporting, internal validity (confounders and bias factors), external validity and finally power. The checklist was further refined to score based on 5 categories which were (reporting, external validity, bias, confounders, and power). A study would be deemed low quality if it scores < 10 points in the quality index score and all studies scored above 20 in this quality index scoring except [20] being the only exception as it only scored 19.

2.4 Statistical analysis

The Risk Ratio (RR) is used to express the summary statistics of dichotomous variables. Mean Difference (MD) summarizes the statistics of continuous data wherein pooled estimates are presented with a 95% Confidence Interval (CI) and a 'p-value <0.05' will be considered statistically significant. Statistical heterogeneity among the studies is detected using I^2 value. An I2 > 50 percent is considered positive for heterogeneity and a Random- effect model is selected for analysis of such data. If I^2 is < 50 percent, it means no heterogeneity and hence a Fixed-effect model will be taken. The relative risk reduction (RRR) is calculated using the formula (1-Relative Risk) x 100. The statistical analysis for the outcome measures, flow chart of the search of literature strategy, the risk of bias summary and graph are performed using the Review Manager Software version 5.3 (RevMan 5.3) developed by the Cochrane Collaboration. Table for study characteristic is created using Microsoft Excel 12.

3. Results

Out of 1937 citations identified during the electronic search, only 13 RCTs are eligible and are included in the study. The filtering of studies is as follows: (1) 1937 citations were identified relating to IBD, IBS and probiotics intervention; (2) 1844 citations were rejected after the review of the title and the abstract; animal studies and review studies were also rejected; (3) From the 93 citations, 80 citations were further rejected based on the inclusion and exclusion criteria set, and (4) 13 citations were hence used to conduct a systematic review and meta-analysis.

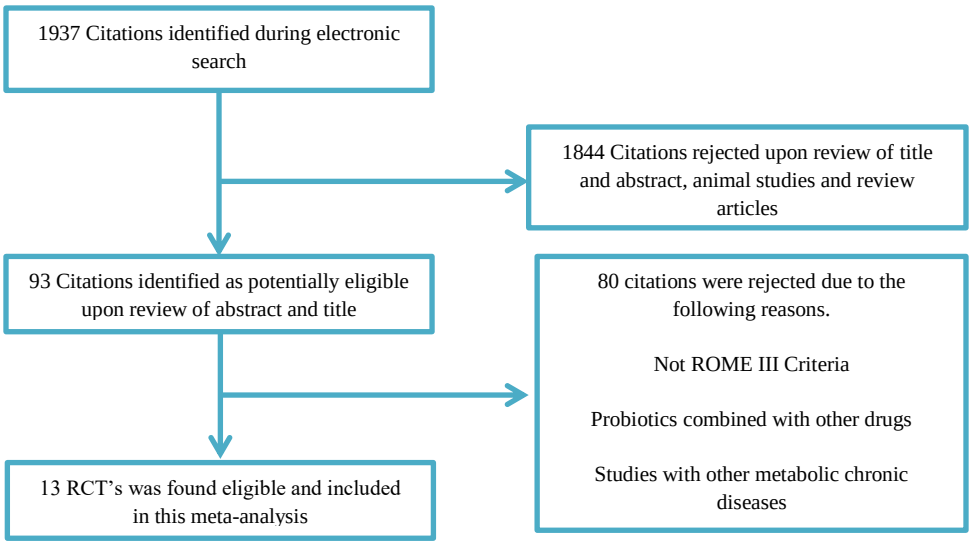

Figure 1: Selection of studies for Meta-analysis- PRISMA flow diagram.

The regions of the included studies were the USA (n=1), Netherlands (n=1), Iran (n=1), Korea (n=3), Italy (n=1), France (n=1), Denmark (n=1), Pakistan (n=1), UK (n=1), Singapore (n=1) and Germany (n=1). A total of 969 participants were involved which is the sum of all the samples involved in the selected studies. Supplementary data **Table 1** shows the characteristics of studies included in Meta-analysis and significance are expressed through its *p-value* where $p \leq 0.001$ taken as statistically significance value while $p \geq 0.001$ is considered as insignificant value.

From the collective data in all the studies in this meta-analysis, a total of 960 patients have participated with 522 patients with IBS have been allocated to the probiotics group and a total of 438 patients had been studied under the placebo group. In the probiotic subtype group, 5 of these studies used a low dose (<1x10^{10} colony forming units (CFU)), while 8 studies used a high dose of probiotic bacteria (>1x10^{10}CFU). In the studies included in this meta-analysis, 6 studies used a single probiotic strain of bacteria for the intervention in patients with IBS while 7 studies used a combination of different probiotic bacteria. When considering the duration of the studies, 8 studies used a short-term treatment intervention (< 8 weeks) and 5 studies conducted the treatment intervention for a relatively longer period (≥ 8 weeks).

3.1 Meta- analysis

The results of the meta-analyses are made to compare the IBS symptoms such as diarrhea, constipation, Effects on Quality of life (QoL), effects on abdominal pain and effects n bloating among patients in probiotics group and placebo group which is analyzed, reported and interpreted. The present report includes funnel plots, which show the individual and pooled mean difference and effect size, heterogeneity values and the significant values (P). The findings of the meta- analysis are thus presented in the effects of the symptoms beginning with effects of the abdominal pain.

3.1.1 Effects of Abdominal Pain in IBS patients

A total of 685 individuals were included in the present meta-analysis for estimating the effects of abdominal pain among Probiotics in comparison to Placebo groups. Among the total meta-analysis population, 388 were Probiotics and 297 was identified as controls.

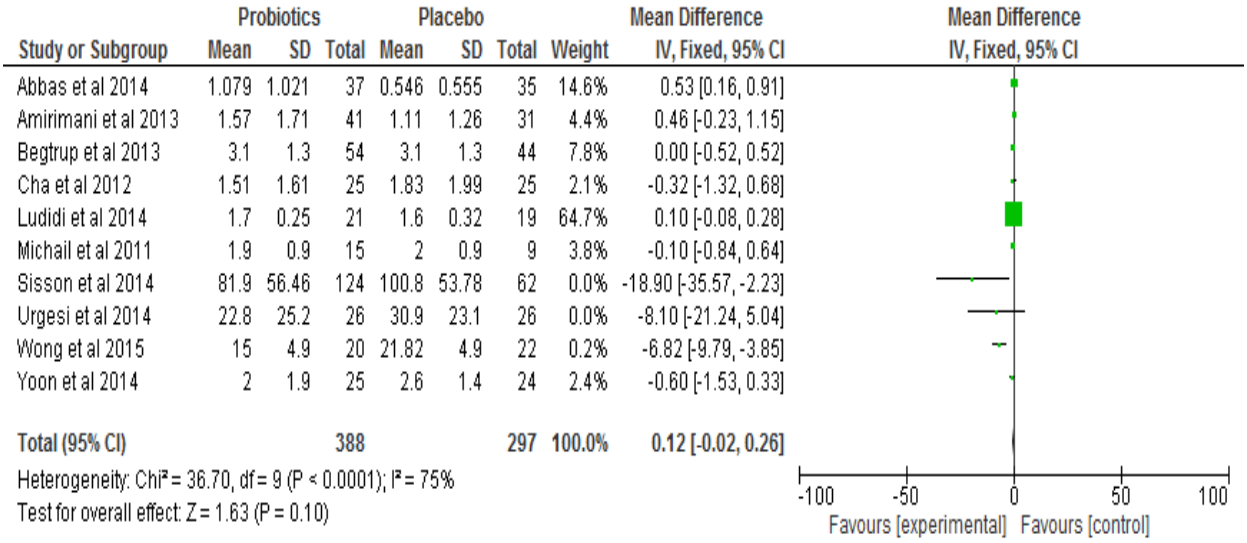

Figure 2: Forest plot of the ten included studies that quantitatively assessed the mean effects of abdominal pain between Probiotics and Placebo group.

Figure 2 summarizes the effect estimates of the selected ten studies (Authors) based on the study design of 10 RCT studies. Heterogeneity tests show that there was a high and statistically significant heterogeneity between the studies included in the meta-analysis (I^2 =75%, Chi-square(X^2) =36.70, degree of freedom (df) = 9, P<0.001) which implies that there is a huge variation that exists between the studies included in this meta-analysis. A summary of mean difference was found to be 0.12 (95% CI -0.02, 0.26), which are higher in Probiotics compared to Placebo groups. The overall test effect for the comparison was Z= 1.63 which is lower and not statistically significant (meta-regression, p=0.10).

Although the findings indicated that there is no statistically significant difference in the effects of abdominal pain among probiotics and placebo groups, this should be interpreted with the caution as the I^2 showed higher heterogeneity (75%) which indicates that there is a higher variation between the studies included in this meta-analysis.

Figure 3 shows that two studies were outside the funnel as indicated by the dotted lines. Therefore, it is concluded that the studies did have publication bias

as shown in the Figure. This variation in study design might have an effect on the findings. The smaller sample size with larger variation is towards the bottom of the funnel while larger studies with less variation are at the top. The overall test effect for the comparison was Z= 1.63 and was not statistically significant (meta-regression, p=0.10).

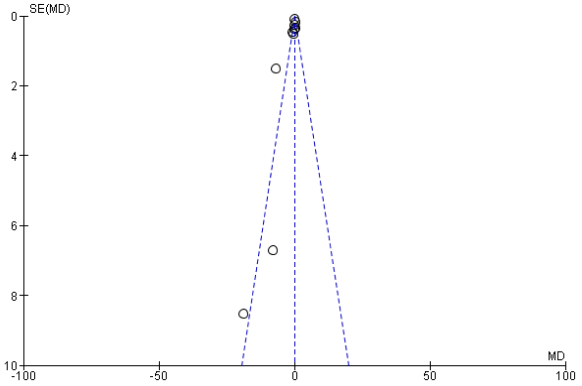

Figure 3: Funnel plot of the ten included studies that quantitatively assessed the mean effects of abdominal pain between Probiotics and Placebo group.

3.1.2 Effects of bloating in IBS patients

Figure 4 presents effect size and the findings revealed that the overall effect size was positive and the confidence interval for four studies was negative while other five studies did show positive. The overall MD was 0.16 (95% CI 0.02, 0.30) A summary effect size was 2.71 which suggests that the effect size is small and significant (P=0.03<0.05).

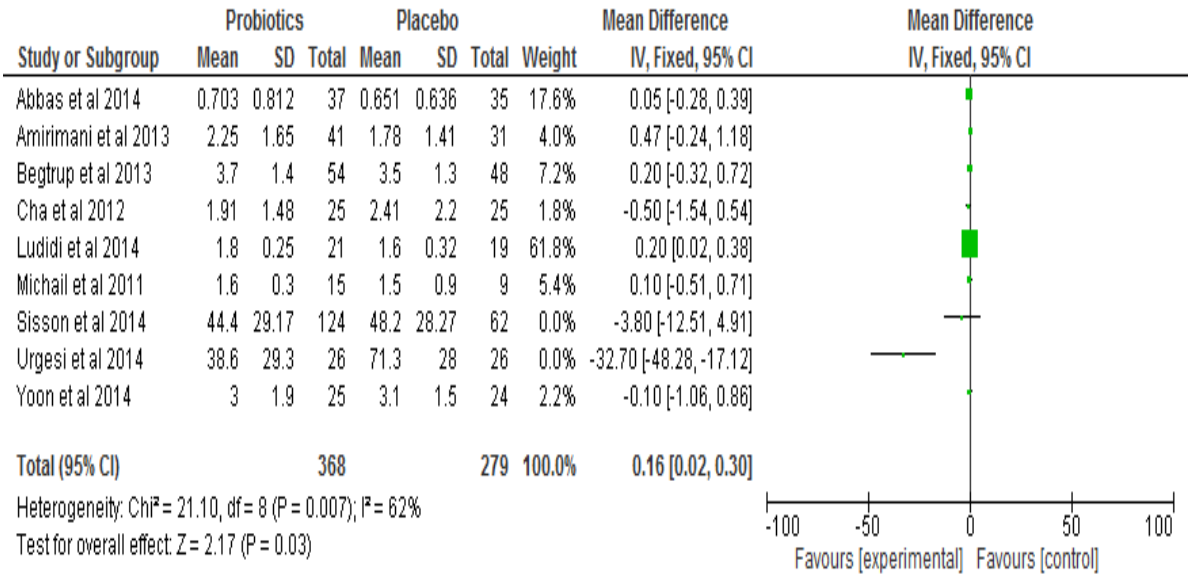

Figure 4: Forest plot of the nine included studies that quantitatively assessed the mean effects of bloating between Probiotics and Placebo group.

Figure 5 shows that one study was outside the funnel as indicated by the dotted lines. Therefore, it is concluded that the studies did have publication bias as shown in the Figure. This variation in study design might have an effect on the findings. The smaller sample size with larger variation is towards the bottom of the funnel while larger studies with less variation are at the top. The overall test effect for the comparison was Z= 2.71 and was statistically significant (meta-regression, p=0.03<0.05).

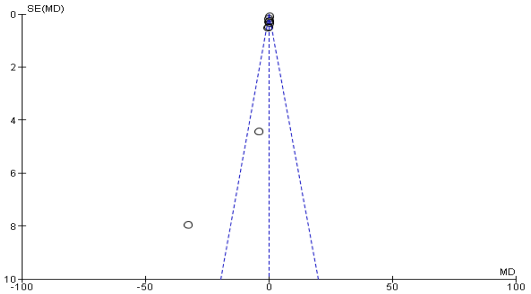

Figure 5: Funnel plot of the nine included studies that quantitatively assessed the mean effects of bloating between Probiotics and Placebo group.

3.1.3 Effect of QOL in IBS patients

Figure 6 represents effect size and the findings revealed that the overall effect size was positive and the confidence interval for two studies was negative while other four studies did show positive. The overall MD was 0.19 (95% CI -0.21, 0.59) A summary effect size was 0.94 which suggests that the effect size is small and insignificant (P=0.35>0.05).

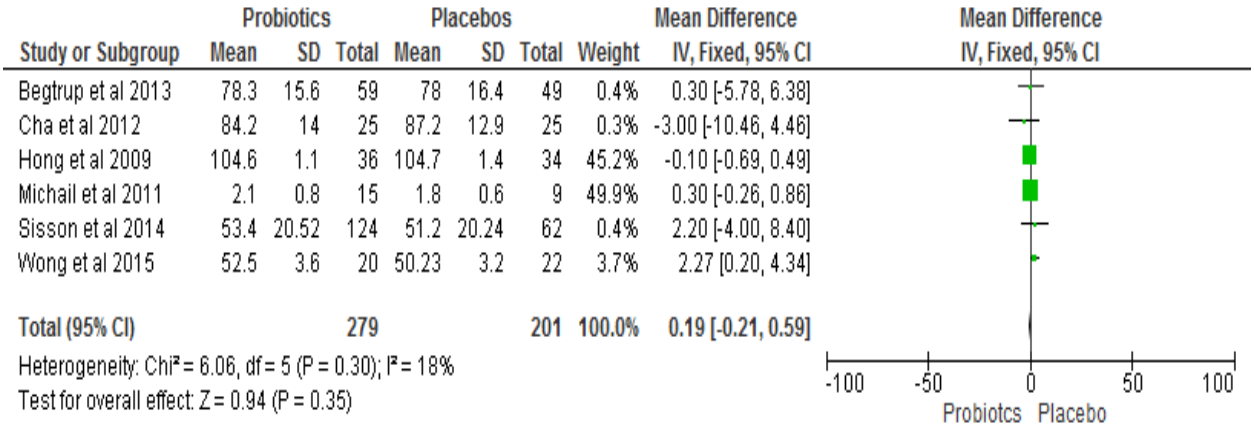

Figure 6: Forest plot of the six included studies that quantitatively assessed the mean effects of QOL between Probiotics and Placebo group

Figure 7 shows that all six studies are inside the funnel as indicated by the dotted lines. Therefore, it is concluded that the studies did have publication bias as shown in the Figure. This variation in study design might have an effect on the findings. The smaller sample size with larger variation is towards the bottom of the funnel while larger studies with less variation are at the top. The overall test effect for the comparison was Z= 0.94 and was statistically insignificant (meta-regression, p=0.35>0.05).

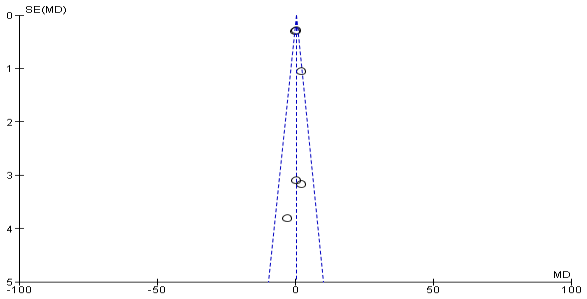

Figure 7: Funnel plot of the six included studies that quantitatively assessed the mean effects of QOL between Probiotics and Placebo group.

3.1.4 Diarrhoea among patients in Probiotics and Placebo group

Figure 8 represents the effect size and the findings revealed that the overall effect size was positive. The overall RR was 1.07 (95% CI 0.86, 1.33) A summary effect size was 0.58 which suggests that the effect size is small and insignificant (P=0.56 >0.05).

Figure 9 shows that all seven studies were inside the funnel as indicated by the dotted lines. Therefore, it is concluded that the studies did have publication bias as shown in the Figure. This variation in study design might have an effect on the findings. The smaller sample size with larger variation is towards the bottom of the funnel while larger studies with less variation are at the top. The overall test effect for the comparison was Z= 0.58 and was statistically insignificant (meta-regression, p=0.56>0.05).

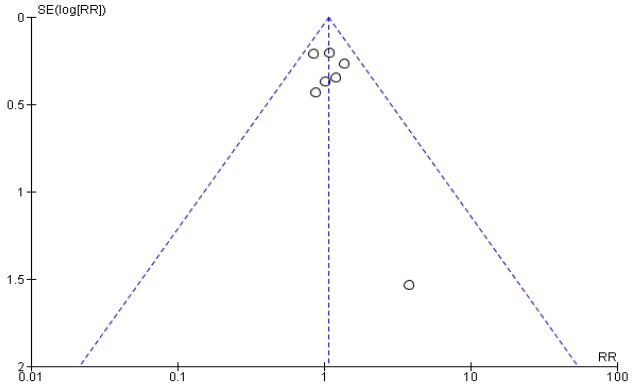

Figure 9: Funnel plot of the seven included studies that quantitatively assessed the Diarrhoea response of IBS patients between Probiotics and Placebo group

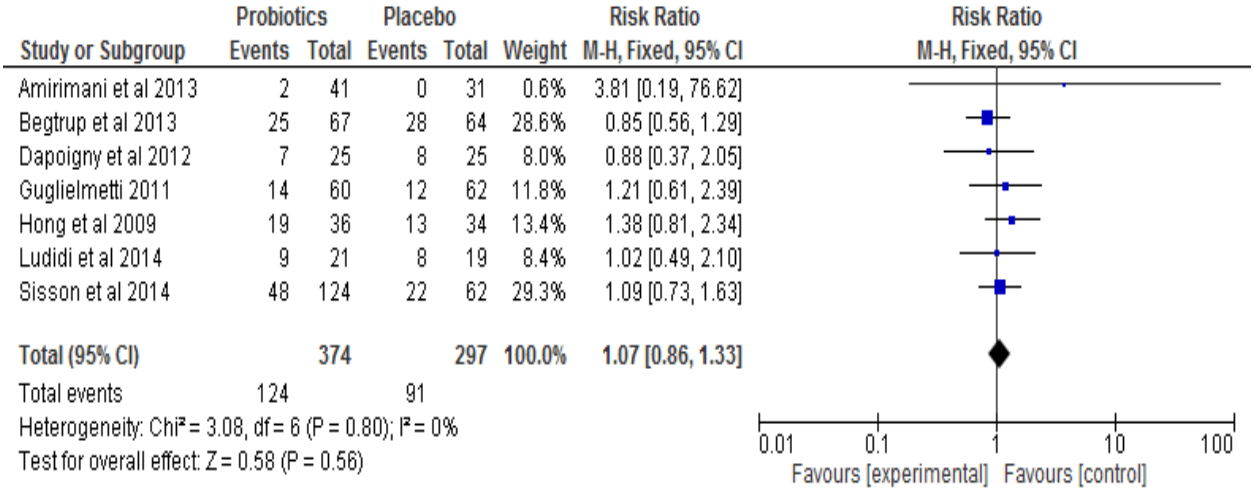

Figure 8: Represents the effect size and the findings revealed that the overall effect size was positive. The overall RR was 1.07 (95% CI 0.86, 1.33) A summary effect size was 0.58 which suggests that the effect size is small and insignificant (P=0.56 >0.05).

3.1.5 Constipation among patients in Probiotics and Placebo group

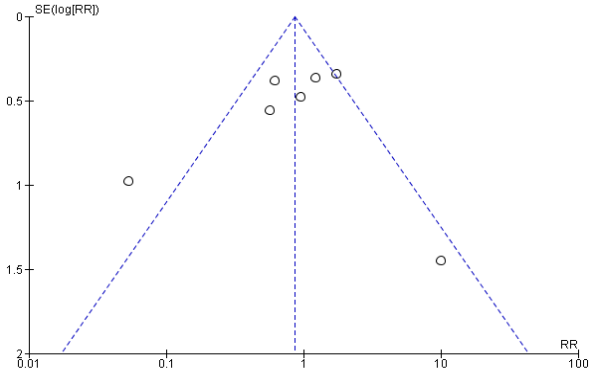

Figure 11: Funnel plot of the seven included studies that quantitatively assessed the Constipation response of IBS patients between Probiotics and Placebo group.

Figure 10 presents effect size and the findings revealed that the overall effect size was positive. The overall RR was 0.86 (95% CI 0.63, 1.18) A summary effect size was 0.92 which suggests that the effect size is small and insignificant (P=0.36>0.05).

Figure 11 shows that one study was outside the funnel as indicated by the dotted lines. Therefore, it is concluded that the studies did have publication bias as shown in the Figure. This variation in study design might have an effect on the findings. The smaller sample size with larger variation is towards the bottom of the funnel while larger studies with less variation are at the top. The overall test effect for the comparison was Z= 0.92 and was statistically insignificant (meta-regression, p=0.36>0.05).

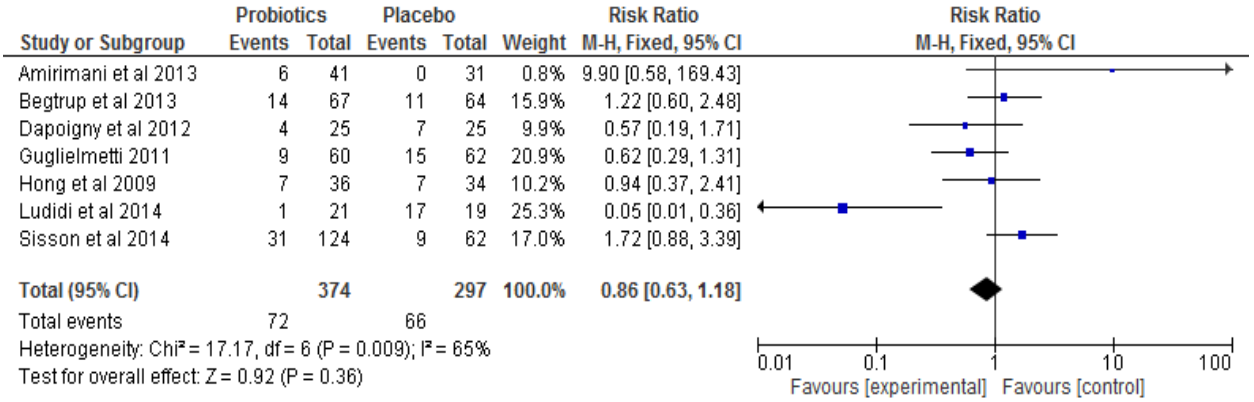

Figure 10: Presents effect size and the findings revealed that the overall effect size was positive. The overall RR was 0.86 (95% CI 0.63, 1.18) A summary effect size was 0.92 which suggests that the effect size is small and insignificant (P=0.36>0.05).

4. Discussion

The results of this systematic review and meta-analysis revealed that probiotics group showed better improvement in the overall disease symptom response and also displayed significant improvements in the bloating effects in-patient with IBS symptoms when compared to the placebo group. This is similar to the previous systematic reviews and meta-analysis [13,14,17]. Though this is the case, when the individual IBS symptoms are compared between probiotics and placebo groups, no significant differences were found between the probiotics and the placebo group in terms of symptoms relief. Such a result is inconsistent based on the examination of the previous meta-analysis results [14] which is associated with probiotic bacterial strains, a combination of various probiotic or individual strains and the treatment duration of IBS. In almost all studies, the treatment using probiotics is short-termed which is mainly due to lack of participation of the subjects with most test subjects adhering to the study protocols. In addition, previous studies recommend that different strains of probiotic bacteria prove to be effective in the treatment of IBS symptoms [14,17]. This further explains the insignificance in the difference in relief of individual IBS symptoms such as bloating and abdominal pain since most studies in this meta-analysis examined the efficacy of a single strain of lactobacilli or Bifidobacteria. The results of the present study reveal that individual probiotic bacterial strains are more effects in relieving the IBS symptoms; however, the overall quality of life is least affected. Studies by Begtrup *et al*.[28] Ki Cha *et al*. [27] and Ludidi *et al*. [21] revealed insignificant results in the symptoms of IBS which is associated with factors such as studies' duration, strains of probiotic bacteria and the adherence to the studies' protocol. Therefore, the benefits of using individual or multiple strains of probiotic bacteria are not discerned.

The study by Yoon *et al.* [24] interpreted the combined effect of the different probiotic strains which are beneficial for the treatment of IBD wherein each species has the potential to deliver unique action on the GI tract. However, other researchers contrasted to the idea and reported that combined effects may also lead to negative or no effects. However, in the present study, it was revealed that short-term probiotic treatment is more effects towards relieving the symptoms of IBS. In addition, the effects of individual strains of probiotic bacteria on the treatment of IBD are low which requires further clarification of evidences whether individual or multiple probiotic species of bacteria is effective.

The comparison of the levels of dosages revealed that five studies used low doses ($<1x10^{10}$ CFU) whereas 8 studies used high probiotic bacteria doses ($>1x10^{10}$ CFU). The studies considered in the present meta-analysis claim that both low and high bacterial doses are effective and are associated with the overall improvement of the symptom responses and the quality of life. However, similar results were not observed in the relief of individual symptoms. A study by [33] compared the effects of low and high doses of probiotics which revealed that the combination of the probiotic bacterial species proved effective in the treatment of IBS and IBD which is more evident after 6 weeks when both low and high doses of bacteria proved effective. However, the current meta-analysis warrants further evidence.

To confirm what dose is ideal for delivering positive effect on the symptoms of IBD since this also depends on the species of the probiotic bacteria. However, the examination of the duration of studies considered in the meta-analysis and its association with treatment intervention revealed that short-term probiotic treatment is more effective than long-term treatment.

5. Conclusion

As a whole, the current meta-analysis concludes that the overall positive efficacy of the probiotic treatment is higher in the treatment group involving the use of probiotics. The study also reveals that single probiotic bacterial strains with low doses and short treatment time tend to be more effect in improving the quality of life and disease symptom response. However, there is heterogeneity in the data, which is analyzed, in the clinical trials. To avoid the comparison of such heterogeneous data, the study further recommends future researchers to focus on the following factors- probiotic species, treatment time, dose, strain and their efficacy in relieving the symptoms of IBD. This further helps identification of the outcome pattern based on which conclusions could be drawn.

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