



## **Probiotics as a Therapeutic Approach in Treatment of Inflammatory Bowel Disease**

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### **Authors' contributions**

*This work was carried out in collaboration between both authors. Both authors contributed in data collection, data compilation and drafting of the paper. Both authors read and approved the final manuscript.*

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### **ABSTRACT**

Inflammatory bowel disease is an immune mediated chronic inflammatory disorder, wherein including Ulcerative colitis, Crohn disease these are two major phenotypes of Inflammatory Bowel Disease. Even though the mechanism of Inflammatory disease is still unclear, probiotic strains have found to have a potential effect in management of the disease. Until now, remarkable advancement has been elucidated in the treatment, however, numerous alternative choices are persistently hunted that might prevent remission of disease. Probiotics are described as living organisms that act as a driving force, wherein exerting health benefits beyond primary nourishment. In view of clinical perspective the efficacy of probiotics seems to be absolutely robust in terms of experimental analysis. Moreover, there is a substantial rise in evidence that probiotics may likely modify the disease manifestations including animal models and in those suffering from Inflammatory Bowel Disease. Considerably, the effect might occur due to divergence in concentration of micro organism used and the vulnerability of the progression of disease is managed. In striking contrast, due to ambiguous research in sequencing technology has conditionally led to the recognition of gut microbiota framework of IBD. Numerous clinical trials depicted the use of probiotics, dysbiosis, microbiota as promising therapies in Inflammatory Bowel Disease. This review elucidates about the role of probiotics, its beneficial effects, summary of literature review in treatment of Inflammatory bowel disease.

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## 1. INTRODUCTION

Digestive health plays a significant impact on quality of life wherein health care burden is increased due to such diseases, namely Inflammatory bowel disease is one of those chronic disorders caused by intestinal inflammation wherein constitutes either as ulcerative colitis (UC) or Crohn's disease [1,2]. The frequent manifestations associated with both Ulcerative colitis and Crohn disease constitutes abdominal pain, cramping, loose stools, diarrhoea, bloody stools, bleeding from rectum, fatigue, anorexia [3]. Furthermore, they can be distinctly identified by presence of mucosal involvement specifically affecting colon in Ulcerative colitis whereas in Crohn disease particularly effectuate any part of digestive tract leading to transmural inflammation thereby correlated with various hallmark complications such as abscesses, fistulas and strictures [4]. Henceforth it has been imposing a significant global problem, thus unprecedentedly leading to increased prevalence worldwide however Inflammatory bowel disease can occur at any particular age irrespective of any significant criteria, comparatively Crohn disease most probably affects adolescents such as youth [5].

Even though the exact aetiology of Inflammatory Bowel Disease is not fully understood various attributable pathogenic factors are thought to be linked with pathogenesis of IBD some of them are genetic susceptibility, environment factors, intestinal microbial flora and immune responses [6-8]. Recent studies conducted by animal models demonstrated that the inflammatory mechanism is most probably arising as a consequence of likewise amplified effect on T-cell function, ultimately leading to excess production of proinflammatory cytokines, such as tumour necrosis factor alpha (TNF- $\alpha$ ) and interleukin-12 (IL-12) [9,10].

In addition, the main goal is to provide symptomatic standard care management in order to attain and counteract disease flare and to manage the disease remission by sustainable use of pharmacologic therapies, whilst in those with pronounced disease which is thought to be refractory, surgery is only therapeutic option [11,12].

## 2. PHYSIOLOGICAL EFFECTS OF GUT MICROBIOTA

The microbiota leads an inevitable significant role in maintaining the well-being and robustness of the host. In turn, it is effective in stimulating the immune system and controlling various pathogenic mechanisms including the proliferation of pathogenic Bacteria, modulating absorption of sufficient amount of nutrients, regulating the metabolism and Physiology, interceding the manufacturing of vitamins and enzymes [13-15].

Not long ago, genome wide clinical studies have encompassed more than 200 Inflammatory Bowel Disease interlinked -susceptible genes, most importantly, these have also been suspected in mediating presumable host response to microbiota of gut whilst also induced to be involved in path mechanism of Inflammatory bowel disease [16-18]. On the other hand, this process alteration of design in gut microbiota is exemplified as dysbiosis, wherein compiling about four considerable phyla. Furthermore, Firmicutes (49–76%) and Bacteroidetes (16–23%) phyla control, in contrary to a much lesser magnitude by the Proteobacteria and Actinobacteria phyla [19-20]. Indeed, the microbiota is useful in regulating the inflammatory process in those manikins who seemed to be genetically predisposed previously or substantially lost endurance to synergistic bacteria [21]. Similarly, notable alterations in the microbiome were established by the use of a metagenomic approach that disclosed sporadic Bacteroidetes and Firmicutes, bacteria that are investigated to maintain a predominant butyrate-generating and anti-inflammatory pursuit [22-24].

## 3. CLINICAL PHARMACOLOGY OF PROBIOTICS

Probiotics are the foremost living species that notably confers favourable impact on the host by modifying the intestinal microbiota [25]. In the year 1953 probiotic term was firstly coined by Werner Kollath [26]. Meanwhile, Various probiotic strains of bacteria such as Lactobacillus, Bifidobacterium and Streptococcus have been predominantly used to be associated with therapeutic effects in inflammation of digestive tract [27-29]. In addition, the mechanisms through which probiotics mediate

are by competitively interacting with gut microbiota, involved in modulation of immune response, yielding of antimicrobial metabolites [30,31]. Surprisingly, probiotics are also capable of antagonizing various form of pathogenic bacteria by causing a reduction in luminal pH wherein apparently leading to impediment of bacterial adherence and translocation.

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apparently leading to impediment of bacterial adherence and translocation [32,33].

In addition ,numerous clinical studies were investigated to demonstrate the efficacy of probiotics in management of IBD, one of the trials was conducted by using VSL#3, a probiotic mixed with 4 Lactobacilli (L.) (L. casei, L. acidophilus, L. delbrueckii subsp., Bulgaricus), 3 Bifidobacterium(B.)and a Streptococcus have generated the most accessible affirmation in managing those with IBD [34].

**Table 1. Summary of various clinical studies conducted in IBD [49]**

Study Author	Type/Subjects/Duration	Probiotic Intervention	Results
Tamaki et al., 2016[40]	Those suffering from UC 56 Subjects Time period;8 weeks	<i>B. longum</i> 536	Application of probiotics resulted in improvement of clinical manifestations in the subjects with mild to moderately active Ulcerative colitis.
Yoshimatsu et al.,2015[41]	Subjects with UC in Remission stage (60 Participants) 12 months	<i>S. faecalis</i> , <i>C. butyricum</i> and <i>B. sentericus</i>	Probiotic might be efficacious in managing clinical remission in Ulcerative colitis
Krag et al., 2013[42]	Mild-to-moderate UC 76subjects 8 weeks	<i>L. plantarum</i> 299v	It has been found that supplementation of probiotics was safe, easily acceptable wherein causing a reduction in disease index scores.
Petersen et al., 2014[43]	100In patients with UC 7 Weeks	<i>E. coli</i> Nissle 1917	Addition of E coli Nissle showed no advantage as an add onconventional therapy in Ulcerative colitis.
Hevia et al., 2014[44]	In those with healthy volunteers, constitutes 37 CD and 15 UC patients	<i>L. casei</i> subsp. rhamnosus GG	Levels of IgA antibodies progress edacross the cell-wall hydrolase from L. casei subsp. rhamnosus GG were remarkably greater in the IBD.
Bourreille et al., 2013	165 patients with CD	<i>S. boulardii</i>	In this study probiotics were easily accepted but did not show any benefit, Infact twenty-one AEs prevailed in course of treatment,Affecting 17, 9 subjects in the <i>S. boulardii</i> and 8 in placebo category.
Asto et.al 2019 [45]	Probiotics Versus Placebo Subjects with Active Ulcerative colitis Conducted in 18 studies. 1419 Patients.	Bifidobacteria	Conclusively, Bifido Bacteria use led to encouraging results for active Ulcerative colitis. However no significant difference was found for mesalamine and controlled trials.
Peng et.al 2017 [46]	Subjects with Active UC Study carried out in 27 Studies in 1942 Patients	Probiotics with 5-ASA vs 5-ASA vs Sulfasalazine	Probiotics when incorporated with 5-ASA proliferates the remission rate in Inactive Ulcerative colitis.
Chen et.al 2019 [47]	Those with Active UC 60 Studies 4954 Patients	Bifid valid triple Probiotic	Addition of BTV to mesalamine led to significant improvement in remission rate and caused a reduction rate in UC
Jia et al 2018 [48]	In IBD subjects 10 studies 1049 Patients	<i>E. coli</i> Nissle 1917 And VSL #3	In conclusion, no significant difference was found between probiotic and placebo group. However <i>E. coli</i> and VSL #3 can be used as alternative Treatment for IBD.

#### 4. EVIDENCE IN SUPPORT OF ROLE OF PROBIOTICS

Various clinical studies have been carried out to determine the potential efficacy of probiotics use in two major sub types of Inflammatory bowel disease that includes ulcerative colitis and crohn disease. Moreover, when probiotics are administered orally as VSL#3 consisting of three Bifidobacterium species, four Lactobacillus species, and Streptococcus thermophilus, was found to regulate beneficial effect on intestinal dendritic cells (DCs), ultimately causing a significant induction of the response of T lymphocytes [35]. Recently, numerous studies have been conducted in Crohn Disease to demonstrate the efficacy in order to ameliorate remission. Another study was examined in adults whilst, by addition of mesalamine to the probiotic yeast *S. boulardii*, conclusively, a notable diminution of rate of relapse was observed, thereby determining its effectiveness in crohn disease [36]. Unfortunately, recently a systematic review validated the dearth of confirmation of use of *S. boulardii* in IBD [37]. Similarly, Various clinical trials were conducted in Ulcerative colitis, However, further randomized studies were evaluated and concluded the effectiveness of UC. *Lactobacillus* GG in comparison with standard treatment for nurturing remission in those subjects with ulcerative colitis. Conclusively, diverse systematic reviews and Cochrane review displayed the role of probiotics in Ulcerative colitis, wherein, pronounced that probiotics are no longer efficacious in in prompt remission of the UC [38,39].

#### 5. FUTURE RESEARCH ON PROBIOTICS: A WAY FORWARD

In the modern-day pharmacotherapy, recent advancements in the technology and robust progress in development of various tailored therapies including probiotics, symbiotic, newer antibiotics, intestinal gut microbiota plays a significant contribution in minimizing the disease burden of IBD which apparently causes a significant global impact on the world wide. Moreover, Probiotics along with gut microbiota acts a crucial role in the maintenance of intestinal homeostasis and causing alteration in intestinal microbiota. Similarly, several studies on literature have reported the evidence about the favourable effects of probiotics in various animal models in ulcerative colitis. Numerous studies have been conducted in adults with Ulcerative colitis,

Crohndisease, pouchitis Additionally, Probiotic species such as lactobacillus were considerably found to be ineffective in maintaining the remission in those patients with adults and children in crohn disease. However, some trials concluded no significant beneficial effects of probiotics in minimizing remission under crohn disease. Henceforth, newer trials are underway in order to determine the therapeutic paradigm of use of effective therapies and antibiotics to achieve the paradoxical need of the patient. Surprisingly, the emerging evidence from randomised clinical trials suggested the use of probiotics such as VSL#3 in ulcerative colitis as an alternative to adjunct therapy.

#### 6. CONCLUSION

Robust experimental evidences from various randomizedtrials indicated the potential benefit of probiotics in the treatment of inflammatory bowel disease. Furthermore, more trials are underway to determine its effectiveness if use, duration of treatment recommended, dosage, mechanism of action and its sub types all parameters should be addressed which eventually might leads to therapeutic and economic outcomes in patients with Inflammatory bowel disease.

#### CONSENT

It is not applicable.

#### ETHICAL APPROVAL

It is not applicable.

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#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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