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Review Article

A Systematic Mapping Review of *In-vitro* and *In-vivo* Evidences Exploring the Role of Strain-Specific Probiotic *Bifidobacterium longum W11*

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ABSTRACT

The gut microbiome has a significant role in overall well-being. Various probiotics are currently used for the improvement of the gut microbiome; the current scoping review aimed to critically examine the effectiveness of *Bifidobacterium longum W11* in healthy and disease states. A thorough search of the literature was done in three scientific databases (PubMed, ScienceDirect, and Google Scholar) to identify 21 articles that evaluated the effect of *B. longum W11* probiotic. Data suggest that *B. longum W11* can withstand the harsh GI environment and colonize the intestinal epithelial cells. Due to the presence of a specific *EPS* cluster gene, *B. longum W11* is capable of producing unique exopolysaccharides that might be responsible for the adhesion and functional capabilities. Additionally, the specific mutation in the *rpoB* gene confers the *B. longum W11* resistance to all rifamycin derivatives (including rifaximin). B. longum W11 has been clinically evaluated in various GI disease conditions including constipation, irritable bowel syndrome, minimal hepatic encephalopathy, active celiac disease, and uncomplicated diverticular disease conditions. All this evidence suggests that *B. longum W11* is a promising probiotic with potential applications in various functional and inflammatory GI-related complications.

Introduction

The human gut microbiome is composed of several microbial niches that play an important role in the overall maintenance and healthy well-being of the gastrointestinal tract (GIT).[1] Dysbiosis, defined as the imbalance between microbial communities leading to an increase in pathogenic microbial count, is known to have a central role in various acute and chronic GIT disease conditions.[2] Probiotics are living microorganisms with a variety of health advantages, and prebiotics are defined as the agents that promote the growth of probiotics and are the most widely studied and clinically accepted therapeutic options for the treatment of dysbiosis.[3]

Currently, the probiotics family includes members from the *Bacillus, Saccharomyces, Lactobacillus, Leuconostoc, Bifidobacterium, Enterococcus, Streptococcus, Pediococcus, and Escherichia* genera.[4] The *Bifidobacterium* family is one of the first microorganisms to colonize human GIT and is considered fundamental for newborn well-being.[5,6] The use of various *Bifidobacterium* species is well-documented in numerous disease conditions (including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), diarrhea, and constipation).[7,8] Among them, the use of *Bifidobacterium longum W11* is one of the emerging probiotic strains.[5]

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The current systematic scoping review was aimed at evaluating the scientific data regarding the effect of *B. longum W11* on overall health promotion and disease conditions. A complete literature search was conducted using the PubMed, ScienceDirect, and Google Scholar databases, and articles were selected for the review based on a pre-designed eligibility criterion. The eligibility criteria were research papers reporting *in-vitro*, pre-clinical, and clinical study evidence; available as full-text articles; available in English or any other language that can be converted to English language using online language conversion tools; articles published between the years 2000 to May 2023. Two independent reviewers (DK and VS) conducted the search process, while two other review authors (SD and VD) validated the search result. After duplicate removal, all articles were primarily screened using the abstract and title of the study. Full-text articles of deemed eligible studies were screened for eligibility. The two reviewers (DK and VD) retrieved data separately from the eligible studies, while three independent reviewers (VS, SD, and JK) validated the extracted data. Any discrepancies were solved between the reviewers using the full-text articles. The complete process of study identification, selection, and inclusion in the study was according to the guidelines stated by Peters *et al*. (2015).[9]

B. longum W11: Current Literature Available

A literature search using the online databases revealed 663 articles and after the initial screening process and duplicate removal, 211 articles were screened for their eligibility. From 211 articles, 21 articles were considered in the complete review process. The complete process of study selection is depicted in Fig. 1.

B. longum W11: Pre-clinical Evidences

B. longum W11 (accession strain number LMG P-21586) was first isolated from the human. The complete genome was sequenced and characterised thoroughly (deposited in DDBJ/EMBL/GenBank with access number: MRBG00000000).[10]

The GI survivability of *B. longum W11* was validated using stimulated GI conditions.[11] *B. longum W11* showed 84% survivability in an acidic environment (pH 2) with around 55% growth capacity, while the growth rate was around 55% in stimulated-bile conditions (3% bile). These data suggest that *B. longum W11* can survive the GI transit, can tolerate the low gastric pH, and can resist the harsh bile environment.[11] The mucin adherence ability of *B. longum W11* was also evaluated using the porcine stomach mucin layer, which showed that *B. longum W11* was capable to adhere the stomach mucin layer.[11] Another study evaluated the adhesion capacity of *B. longum W11* in the cell line (HT-29 cell line).[12] Scanning electron microscopy (SEM) revealed that *B. longum W11* can adhere to the intestinal epithelium within 30 minutes of incubation, and the rate of adhesion increased with time. The cellular adhesion was evident even after 120 minutes of incubation. The SEM analysis revealed the production of a special biopolymer (exopolysaccharide) layer by the *B. longum W11*, which was extracted, purified, and analyzed for its molecular identification. The exopolysaccharide was found to be composed of different types of sugars along with other non-carbohydrate constituents.[12]

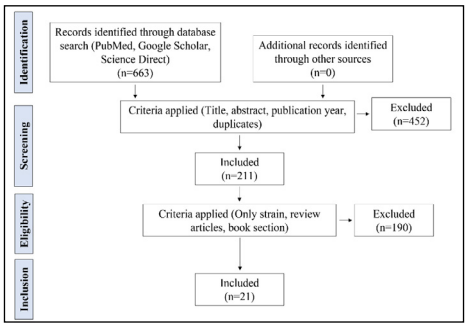


Fig. 1: Preferred reporting items for systematic reviews and meta-analyses (prisma) flowchart of study inclusion

Various studies have demonstrated that the production of exopolysaccharides by microbes increases their mucous adherence ability and also acts as microbial-associated molecular patterns (MAMP) and further interacts with the host's pattern recognition receptors (PRR) causing the stimulation of both innate and adaptive immunity.[13–16] The exopolysaccharides-producing ability of *B. longum W11* was due to the strain-specific gene cluster (*EPS* cluster; 24,689 bp) identified to be present in the W11 genome.[17] The *B. longum W11* strain is the only one that possesses the *EPS* cluster containing the genetic components, which is distinct due to its structural arrangement. This indicates that the production of W11 exopolysaccharides is strain-specific, and the W11 exopolysaccharides-mediated actions are also strain-specific and might not be observed in other *B. longum* strains. An investigation was carried out to try and characterize the exopolysaccharides that *B. longum W11* produces on a molecular level.[17] The exopolysaccharides contain significant levels of D-glucose and D-galactose together with trace amounts of galacturonic acid and rhamnose. These sugars were found to form repeating structural units, which were identified as the main structural unit of the exopolysaccharides (identified using the ^{1}H-NMR method). Additionally, the evaluation of GI-survivability in the study revealed that W11 can survive the GI transit. Also, the W11 adhesion capacity was evaluated using HT-29 colonocytes, which revealed an equivalent adhesion capacity of W11 compared to the *B. longum* BB-12 strain, which might be due to the production of exopolysaccharides by W11.[17] Additionally, the W11-specific exopolysaccharides were found to be non-cytotoxic, provided an antioxidant effect, and improved cellular antioxidant system activity *in-vitro*.[17] Additionally, the immunomodulatory ability of *B. longum W11* was evaluated in a study using peripheral

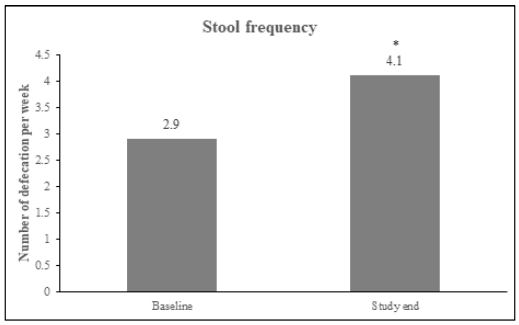
blood mononuclear cells (PBMCs) isolated from human volunteers.[18] The stimulation of PBMCs with W11 significantly increased Th-1 activity and altered cytokines production, which confirms the immunomodulatory efficacy of *B. longum W11.*[18,19]

Another group of researchers conducted an *in-vitro* study to evaluate the antibiotic susceptibility of *B. longum W11.*[20] The vulnerability of *B. longum W11* was assessed with all rifamycin derivatives (namely rifaximin, rifampicin, rifapentine, and rifabutin) using the disc diffusion method and using *B. longum* BL03 strain as control. While all antibiotics inhibited BL03 at the lowest assessed concentration (32 µg/mL), W11 was not inhibited by rifampicin, rifabutin, and rifaximin at the resistant concentration range from 32 to 256 µg/mL. The genomic DNA analysis of *B. longum W11* was conducted to understand the genomic pattern for the observed antibiotic resistance. The analysis identified a specific genomic mutation of the *rpoB* gene (the beta subunit of DNA-mediated RNA polymerase) which was responsible for the antibiotic resistance of *B. longum W11*. This particular genetic mutation was confirmed to be strain-specific and is not transposable or flanked using mobile genetic elements.[20]

B. longum W11: Clinical Evidences

Constipation and irritable bowel syndrome

A clinical trial evaluated the effect of *B. longum W11* supplementation for 60 days on 297 subjects with chronic constipation.[21] While there was significant improvement in all subjects after *B. longum W11* supplementation, the effect was more significant in subjects who had good adherence to the therapy. Also, there was a notable rise in the number of subjects who did not use laxatives for overall improvement. Additionally, after *B. longum W11* supplementation there was an improvement in physical activity level, while the difference did not achieve significance. The study concluded that *B. longum W11* supplementation improved overall bowel movements and improved overall physical activity levels.[21] In a similar open-label study involving IBS patients with pre-dominant constipation (IBS-C) were treated with a combination of *B. longum W11* with FOS for 36 days.[22] Data from 636 subjects revealed that *B. longum W11* supplementation significantly improved symptoms of abdominal pain and bloating. The mean stool frequency was also significantly increased by the end of therapy (Fig. 2).[22] Similar open-label trials with 129 IBS-C individuals showed that treating *B. longum W11* and FOS significantly improved the frequency of stools and decreased the intensity of symptoms related to bloating and stomach pain (Fig. 3). These data suggest that the use of *B. longum W11* is effective in improving bowel movements and reducing symptoms in subjects with IBS-C and chronic constipation.[23] Subjects with constipation and IBS from a mean duration

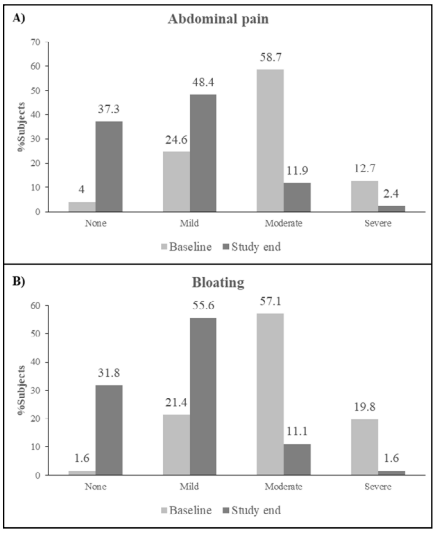


Source -Data adopted from Colecchia A *et al.*[22]

Fig. 2: Change in stool frequency after *B. longum W11* supplementation. *p < 0.001 vs baseline

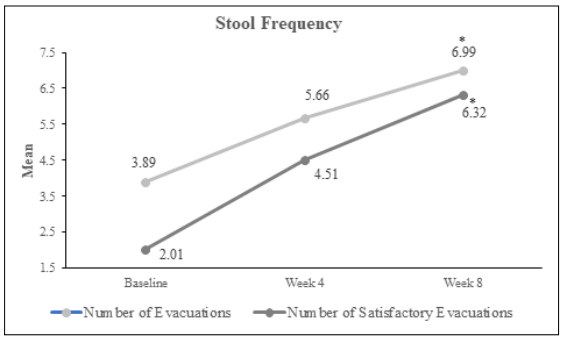
of 2.3 years were included in an open-label study.[24] The supplementation of *B. longum W11* for 8 weeks resulted in significant rise in number of evacuations and number of satisfactory evacuations compared to baseline (Fig. 4). The change in bristol stool score significantly improved from baseline (1.9 to 4.0; p < 0.001) indicating improvement in stool consistency, while there was significant reduction in severity of various symptoms like abdominal distension, meteorism, abdominal pain/discomfort, and global abdominal discomfort compared to baseline values (p < 0.0001 for all symptoms). No treatment-related side effects hindered the overall effectiveness of *B. longum W11* therapy.[24]

Rifaximin is widely used to treat various GI-related conditions including IBS.[25–27] A randomized open-label study involving 70 IBS subjects was conducted.[28] Subjects were randomized to either receive 400 mg of rifaximin for 10 days every month or rifaximin therapy followed by *B. longum W11* supplementation for the following 6 days on alternative weeks for two months. While rifaximin



Source - Data adopted from Dughera L *et al.*[23]

Fig. 3: Change in severity of (A) Abdominal pain and (B) Bloating in subjects with IBS-C.



Source - Data adopted from Valdovinos-Díaz M *et al.*[24]

Fig. 4: Improvement in number of evacuations and number of satisfactory evacuations after *B. longum W11* supplementation. *p < 0.05 vs respective baseline values

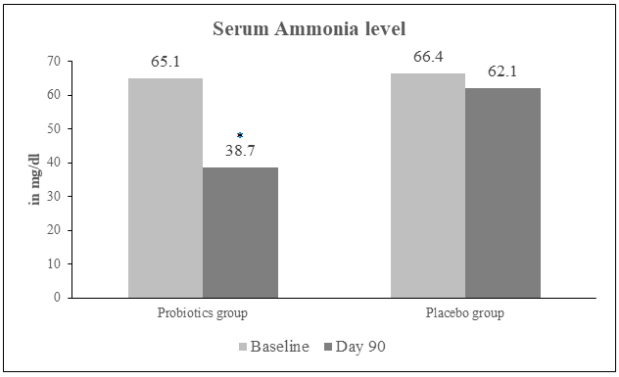
supplementation significantly improved the overall health status of subjects (assessed using a visual analog scale by gastroenterologists and subjects) and provided significant remission from symptoms of IBS at study end duration, the subjects treated with *B. longum W11* showed significantly better improvement in all parameters compared to rifaximin alone group. The results of this study confirm the rifaximin resistance capability of *B. longum W11* and suggest the use of *B. longum W11* along with rifaximin to provide synergistically better patient outcomes.[28] The use of partially hydrolyzed guar gum is a water-soluble, non-gel-forming, galactomannan fiber that is found to be effective in subjects with chronic constipation.[29] In a randomized controlled trial with IBS-C patients, it was found that the supplementation of *B. longum W11* provides a synergistic effect to partially hydrolyzed guar gum therapy in reducing symptoms of bloating. These data suggest the use of *B. longum W11* along with dietary fiber therapy for improvement in IBS-C subjects.[30]

Total enteral nutrition

In a study involving 13 elderly subjects affected by permanent vegetative status, subjects with a lower baseline level of fecal *Bifidobacterium* count (less than 10 million bacterial counts) were treated with *B. longum W11* (5 billion CFU) and FOS (2.5 g) for 12 days. Treatment with *B. longum W11* resulted in a 1-log increase in the fecal *Bifidobacterium* count. While this increase in Bifidobacterial colonization subsequently resulted in a reduction in *Clostridium* level, there was no observable change in the clinical response. These results are preliminary and need more stringent clinical studies with a higher number of subjects to determine the effects of intestinal *Bifidobacterium* level on overall clinical response.[31]

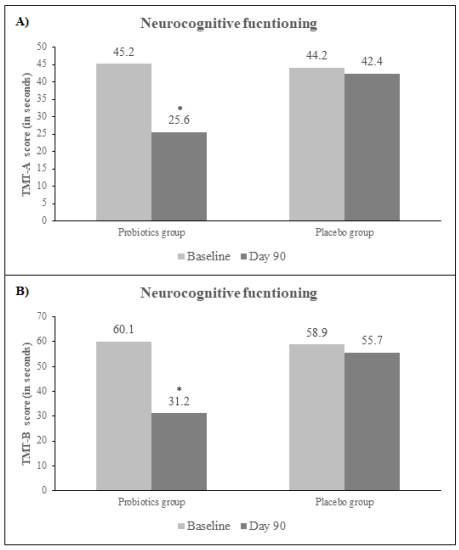
Minimal hepatic encephalopathy

Minimal hepatic encephalopathy (MHE) is the initial form of hepatic encephalopathy that has been shown to affect up to 80% of subjects who are suffering from liver cirrhosis.[32] MHE is identified by the increased level of circulating ammonia levels, which leads to neurocognitive impairment in vigilance, attention, and integrative function. Various data suggest that gut dysbiosis plays a key role in increasing ammonia levels in the body of cirrhotic subjects, and modulation of gut-derived ammonia production is a potentially useful therapy for the management of MHE.[32,33] A randomized double-blinded placebo-controlled trial that involved 60 cirrhotic subjects with MHE were randomized to either receive symbiotic preparation of *B. longum W11* (5 billion CFU) and FOS (2.5 g) or a combination of B-vitamins (vitamin B1, 1.4 mg; vitamin B6, 2.0 mg; vitamin B2, 1.6 mg; vitamin B12, 1.0 mg) as a placebo for 90 days of duration.[34] At study end, subjects treated with *B. longum W11* had a significantly reduced level of venous ammonia level compared to the placebo group (Fig. 5). The neurocognitive performance was evaluated using the trail-making test. The trail-making test (TMT) is divided into two parts (TMT-A and TMT-B) which evaluates various neurocognitive functioning ability, and a decrease in the time in the TMT test indicates improvement in neuropsychological functioning.[34] After 90 days of supplementation, the subjects treated with *B. longum W11* showed significant improvement in all neuropsychological parameters compared to baseline and placebo-treated subjects (as indicated by a decrease in the TMT-A and TMT-B sore; Fig. 6). Similarly, the block design test (BDT) and mini-mental state examination (MMSE) was used to assess the intellectual cognitive ability and mental health respectively. An increase in BDT score indicates improved cognitive functioning while an increase in MMSE score indicates improved overall mental health.[34] Similar results were obtained, in which significant improvement was observed in *B. longum W11* treated subjects compared to placebo-treated subjects for both BDT and MMSE scores (Fig. 7). No treatment-related side effects were observed in any subjects treated with *B. longum W11* or placebo. These data suggest that *B. longum*



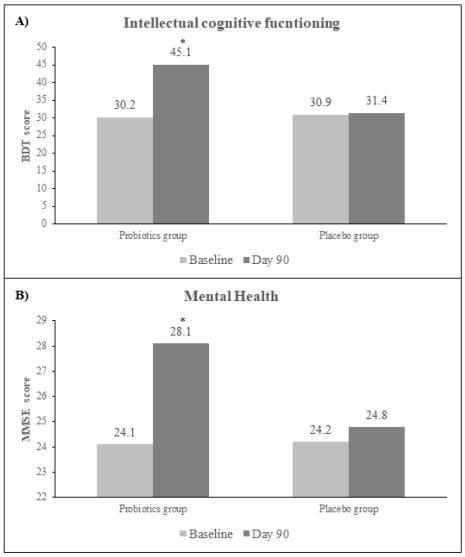
Source - Data adopted from Malaguarnera M *et al.*[34]

Fig. 5: Venous ammonia level in MHE subjects at baseline and after 90 days supplementation of *B. longum W11* or placebo. *p < 0.05 vs baseline and placebo group



Source - Data adopted from Malaguarnera M *et al*.[34]

Fig. 6: Improvement in neurocognitive functioning assessed using (A) TMT-A and (B) TMT-B in MHE subjects after 90 days supplementation of *B. longum W11* or placebo. *p < 0.05 vs baseline and placebo group.



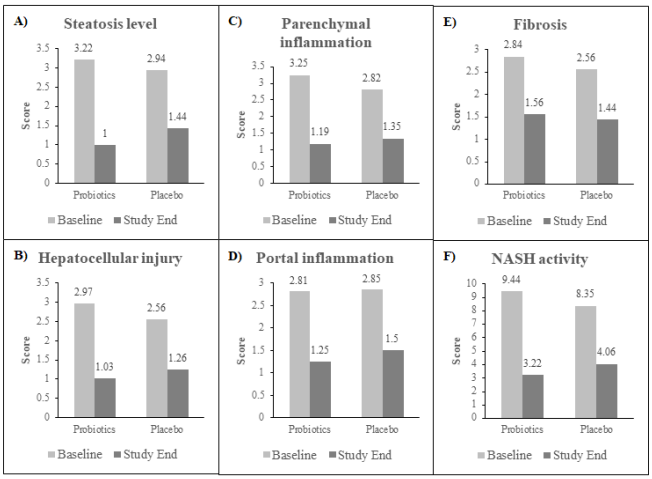
Source - Data adopted from Malaguarnera M *et al*.[34]

Fig. 7: Improvement in (A) Intellectual cognitive ability using BDT score and (B) Overall mental health using MMSE score in MHE subjects after 90 days supplementation of *B. longum W11* or placebo. *p < 0.05 vs baseline and placebo group

W11 is an effective and safe therapy for modulating the gut microbiome in MHE subjects and resulting in an overall reduction of serum ammonia levels along with improving neuropsychological functioning, intellectual cognitive ability, and overall mental health.[34]

Non-alcoholic steatohepatitis

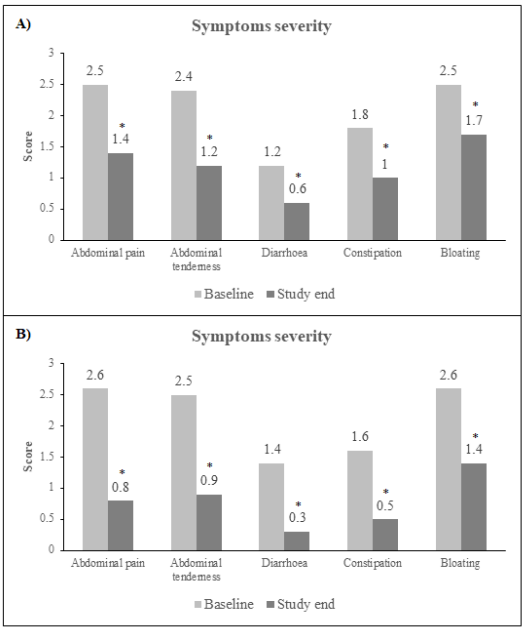
Non-alcoholic steatohepatitis (NASH) is a liver fat-infiltration disease that is characterized by hepatic inflammation, necrosis, and fibrosis, which in turn can lead to hepatocellular carcinoma.[35] While various risk factors are associated with NASH, the change in the microbiome is considered one of the risk factors that can progress liver damage.[36] Currently, various therapeutic options are used for the management of NASH including lifestyle modifications (diet and exercise), pharmacological therapies (medications like antidiabetics, anti-obesity agents, antioxidants, antibiotics, and anti-fibrotic agents), nutraceutical and herbal supplements (like vitamin D, vitamin E, vitamin C, carnitine, omega-3 fatty acids, silymarin, and resveratrol), and gut microbiome modulatory supplements (mainly prebiotics and probiotics).[37,38]



Source - Data adopted from Malaguarnera M *et al*.[39]

Fig. 8: Change in liver parameters after 24 weeks of *B. longum W11* supplementation along with lifestyle modifications compared to lifestyle modifications alone

In a randomized, double-blind, placebo-controlled study design involving 66 subjects with NASH, the effectiveness of *B. longum W11* with FOS along with lifestyle modifications was evaluated and compared with the effect of placebo supplementation with lifestyle modifications.[39] Subjects were randomly assigned either to receive the symbiotic preparation or the placebo (vitamin B1, 1.4 mg; vitamin B6, 2.0 mg; vitamin B2, 1.6 mg; and vitamin B12, 1.0 mg) for 24 weeks along with lifestyle modifications. After 24 weeks of supplementation, while both groups showed significant improvement in all anthropometric, biochemical, lipid, and liver parameters compared to respective baseline values, the improvement was greater in *B. longum W11* supplemented groups compared to the placebo group. The reduction in liver enzyme level was greater in the *B. longum W11* group (AST: -63.85%; ALT: -53.37%; bilirubin: -2.88%) compared to the placebo group (AST: -42.86%; ALT: -39.54%; bilirubin: 0.99%). The improvement in lipid parameters was also more in the *B. longum W11* group compared to the placebo group for total cholesterol (-11.03 *vs* -3.92%), HDL (12.38 *vs* 1.85%), LDL (-21.48 *vs* -4.72%), and triglycerides (-25 *vs* -11.44%) levels, respectively.



Source - Data adopted from Pierro F *et al.*[43]

Fig. 9: Improvement in gastrointestinal symptoms of abdominal pain, tenderness, diarrhoea, constipation, and bloating in (A) Group A and (B) Group B. *p<0.05 vs respective baseline value

Similarly, greater reduction in inflammatory markers (CRP: -41.43 *vs* -10.45% and TNF: -35.16 *vs* -9.68%) and insulin resistance (insulin level: -21.58 *vs* -5.80% and HOMA-IR score: -29.97 *vs* -16.35%) was observed in *B. longum W11* group compared to the placebo group.[39]
In the same study, supplementation of *B. longum W11* was associated with greater a reduction in serum endotoxin levels compared to the placebo group (-45.38 *vs* -10.79%). This reduction in serum endotoxin level was associated with greater improvement in liver histological parameters (including steatosis, parenchymal inflammation, hepatocellular injury, portal inflammation, fibrosis, and NASH activity) in subjects treated with *B. longum W11* compared to placebo-supplemented subjects. The overall change in liver parameters in both groups is depicted in Fig. 8. None of the subjects had any side effects and the *B. longum W11* treatment was very well-tolerated.[39]
These data suggest that *B. longum W11* supplementation is associated with improvement in gut microbial niche which results in improved lipid and inflammatory parameters in subjects with NASH. These improved lipid and inflammatory parameters further result in greater improvement in liver histological parameters. Hence, *B. longum W11* supplementation can be used to improve the overall effectiveness of lifestyle modifications in NASH subjects.[39]

Active celiac disease

Celiac disease (CD) is a genetic-autoimmune disease characterized by a unique serological and histological profile due to the consumption of gluten (alcohol-soluble proteins found in grains like wheat).[40] In a randomized clinical trial, 25 subjects with active celiac disease and consuming a gluten-free diet were randomly treated with either *B. longum W11* and FOS therapy or placebo for 6 weeks. After the study duration, subjects treated with *B. longum W11* therapy had significant improvement in the gastrointestinal symptom rating scale for symptoms of indigestion, diarrhea, dyspepsia, and abdominal pain compared to the placebo group. Additionally, *B. longum W11* supplementation positively altered the immune status and resulted in improved inflammatory status.[41]

Symptomatic Uncomplicated Diverticular Disease

Symptomatic uncomplicated diverticular disease (SUDD) is a clinical condition characterized by the simultaneous existence of diverticula and symptoms of stomach pain and bloating, bowel habit alterations such as diarrhea and constipation, or a mixed bowel habit.[42] A retrospective study evaluated the efficacy of *B. longum W11* supplementation for 7 days after the treatment period of rifaximin (400 mg every 12 hours for 7 days; Group A) and rifaximin and *B. longum W11* simultaneous supplementation for 7 days (Group B) for 3 months.[43] At the study end, both treatment groups showed a significant reduction in symptoms of abdominal pain, abdominal tenderness, diarrhea, constipation, and bloating compared to respective baseline values (Fig. 9). Between-group analysis revealed significantly greater symptomatic improvement in group B compared to group A (-62.5 *vs* -43.9%; p <0.05), while adherence to therapy was also significantly better in group B compared to group A (95 *vs* 65%; p <0.01).[43] These data suggest that *B. longum W11* co-supplementation with rifaximin provides clinical benefits in subjects with SUDD.

Strength, Limitation, and Future Perspectives

This scoping review revealed that up to date there is no systematic review approach used to evaluate the efficacy of *B. longum W11* in disease or healthy conditions. The shreds of evidence described in the current study confirm that *B. longum W11* is effective in various disease conditions, and the action observed by W11 consumption might be strain-specific due to the natural and unique exopolysaccharides produced by this strain. Additionally, the genetic mutation of W11 in the *rpoB* gene was found to provide the strain with significant antibiotic resistance, which was non-transposable or non-transferable to other micro-organisms using mobile genetic elements. Data suggest that *B. longum W11* is stable and able to survive the harsh GI conditions, adhere to intestinal epithelium, colonize, and produce immunomodulatory action. Thus, we can speculate that the consumption of *B. longum W11* is safe and effective in various disease conditions, and it can be consumed along with rifamycin derivatives. Although the current scoping review tried to include all available

evidence regarding *B. longum W11* (since the year 2000), the current study does not meet the criteria of a systematic review. Hence, the data from the current study can be used for the design of further systematic reviews. The inability of the current study to conduct heterogeneity and bias analysis needs to be addressed by conducting further studies.

CONCLUSION

The modulation of gut microbiota using probiotics is a widely researched area. *Bi. longum W11* is a probiotic with a proven ability to survive and colonize the gut. The possible mechanism of action of *B. longum W11* involves immunomodulation, SCFA production, and supporting a healthy gut barrier. With clinical efficacy in various digestive disorders, including irritable bowel syndrome, constipation, minimal hepatic encephalopathy, non-alcoholic steatohepatitis, and celiac disease, *B. longum W11* holds the potential for promoting gut health and managing gastrointestinal conditions. Further research and clinical trials are warranted to fully understand their potential and optimize their use in clinical practice.

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REFERENCES

1. Thursby E, Juge N. Introduction to the human gut microbiota. Biochem J.2017;474(11):1823–36.
2. DeGruttola AK, Low D, Mizoguchi A, Mizoguchi E. Current Understanding of Dysbiosis in Disease in Human and Animal Models. Inflamm Bowel Dis. 2016;22(5):1137–50.
3. Appanna V. Dysbiosis, Probiotics, and Prebiotics: In Diseases and Health. In: Appanna V, editor. Human Microbes - The Power Within. Singapore: Springer Nature Singapore Pte Ltd.; 2018. p. 81–122.
4. Fijan S. Microorganisms with claimed probiotic properties: an overview of recent literature. Int J Environ Res Public Health. 2014;11(5):4745–67.
5. Pierro F Di, Pane M. *Bifidobacterium longum* W11: Uniqueness and individual or combined clinical use in association with rifaximin. Clin Nutr ESPEN. 2021;42:15–21.
6. O'Callaghan A, Sinderen D van. *Bifidobacteria* and Their Role as Members of the Human Gut Microbiota. Front Microbiol. 2016;7:925.
7. Tojo R, Suárez A, Clemente MG, Reyes-Gavilán CG de los, Margolles A, Gueimonde M, *et al*. Intestinal microbiota in health and disease: role of bifidobacteria in gut homeostasis. World J Gastroenterol. 2014;20(41):15163–76.
8. Martínez-Martínez MI, Calabuig-Tolsá R, Cauli O. The effect of probiotics as a treatment for constipation in elderly people: A systematic review. Arch Gerontol Geriatr. 2017;71:142–9.
9. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc. 2015;13(3):141–6.
10. Inturri R, Ventura M, Ruas-Madiedo P, Lugli GA, Blandino G. Complete Genome Sequence of *Bifidobacterium longum* W11 (LMG P-21586), Used as a Probiotic Strain. Genome Announc. 2017;5(10):e01659-16.
11. Izquierdo E, Medina M, Ennahar S, Marchioni E, Sanz Y. Resistance to simulated gastrointestinal conditions and adhesion to mucus as probiotic criteria for *Bifidobacterium longum* strains. Curr Microbiol. 2008;56(6):613–8.
12. Inturri R, Stivala A, Sinatra F, Morrone R, Blandino G. Scanning Electron Microscopy Observation of Adhesion Properties of *Bifidobacterium longum* W11 and Chromatographic Analysis of Its Exopolysaccaride. Food Nutr Sci. 2014;5(18):1787–92.
13. Lu Y, Han S, Zhang S, Wang K, Lv L, McClements DJ, *et al*. The role of probiotic exopolysaccharides in adhesion to mucin in different gastrointestinal conditions. Curr Res Food Sci. 2022;5:581–9.
14. Oerlemans MM, Akkerman R, Ferrari M, Walvoort MT, Vos P de. Benefits of bacteria-derived exopolysaccharides on gastrointestinal microbiota, immunity and health. J Funct Foods. 2021;76:104289.
15. Caselli M, Vaira G, Calo G, Papini F, Holton J, Vaira D. Structural bacterial molecules as potential candidates for an evolution of the classical concept of probiotics. Adv Nutr. 2011;2(5):372–6.
16. Hidalgo-Cantabrana C, Sánchez B, Milani C, Ventura M, Margolles A, Ruas-Madiedo P. Genomic overview and biological functions of exopolysaccharide biosynthesis in Bifidobacterium spp. Appl Environ Microbiol. 2014;80(1):9–18.
17. Inturri R, Molinaro A, Lorenzo F Di, Blandino G, Barbara Tomasello, Hidalgo-Cantabrana C, *et al*. Chemical and biological properties of the novel exopolysaccharide produced by a probiotic of *Bifidobacterium longum*. Carbohydr Polym. 2017;174:1172–80.
18. Medina M, Izquierdo E, Ennahar S, Sanz Y. Differential immunomodulatory properties of Bifidobacterium logum strains: relevance to probiotic selection and clinical applications. Clin Exp Immunol. 2007;150(3):531–8.
19. Inturri R, Mangano K, Santagati M, Intrieri M, Marco R Di, Blandino G. Immunomodulatory Effects of *Bifidobacterium longum* W11 Produced Exopolysaccharide on Cytokine Production. Curr Pharm Biotechnol. 2017;18(11):883–9.
20. Graziano T, Amoruso A, Nicola S, Deidda F, Allesina S, Pane M, *et al*. The Possible Innovative Use of *Bifidobacterium longum* W11 in Association With Rifaximin: A New Horizon for Combined Approach? J Clin Gastroenterol. 2016;50(Suppl 2):S153–6.
21. Amenta M, Cascio MT, Fiore P Di, Venturini I. Diet and chronic constipation. Benefits of oral supplementation with symbiotic zir fos (*Bifidobacterium longum* W11+ FOS Actilight). Vol. 77, Acta Bio-medica. 2006. p. 157–62.
22. Colecchia A, Vestito A, Rocca A La, Pasqui F, Nikiforaki A, Festi D, *et al*. Effect of a symbiotic preparation on the clinical manifestations of irritable bowel syndrome, constipation-variant. Results of an open, uncontrolled multicenter study. Minerva Gastroenterol Dietol. 2006;52(4):349–58.
23. Dughera L, Elia C, Navino M, Cisarò F, Group AS. Effects of symbiotic preparations on constipated irritable bowel syndrome symptoms. Acta Bio-medica. 2007;78(2):111–6.
24. Valdovinos-Díaz M, Abreu AA y, Frati-Munari A. Clinical experience with a synbiotic (*Bifidobacterium longum* AW11-Fos cc. Actilight) in the relieve of constipation and other digestive symptoms. Med interna México. 2017;33(4):476–86.
25. Saadi M, McCallum RW. Rifaximin in irritable bowel syndrome: rationale, evidence and clinical use. Ther Adv Chronic Dis. 2013;4(2):71–5.
26. Pimentel M, Lembo A, Chey WD, Zakko S, Ringel Y, Yu J, *et al*. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med. 2011;364(1):22–32.
27. Li J, Zhu W, Liu W, Wu Y, Wu B. Rifaximin for Irritable Bowel Syndrome: A Meta-Analysis of Randomized Placebo-Controlled Trials. Medicine (Baltimore). 2016;95(4):e2534.
28. Fanigliulo L, Comparato G, Aragona G, Cavallaro L, Veronica Iori, Maino M, *et al*. Role of gut microflora and probiotic effects in the irritable bowel syndrome. Acta Bio-medica. 2006;77(2):85–9.
29. Polymeros D, Beintaris I, Gaglia A, Karamanolis G, Papanikolaou IS, Dimitriadis G, *et al*. Partially hydrolyzed guar gum accelerates colonic transit time and improves symptoms in adults with chronic constipation. Dig Dis Sci. 2014;59(9):2207–14.

30. Sarnelli G, Russo L, Giorgi F De, Efficie E, Esposito I, Atteo E, *et al*. Effects of oral supplementation with the symbiotic (*Bifidobacterium longum* w11+ fos actilight) on IBS with constipation: a randomized, dose finding trial, versus fibers. Dig Liver Dis. 2008;40:S141.
31. Piano M Del, Ballarè M, Montino F, Marco Orsello, Garello E, Ferrari P, *et al*. Clinical experience with probiotics in the elderly on total enteral nutrition. J Clin Gastroenterol. 2004;38(6 Suppl):S111-114.
32. Stinton LM, Jayakumar S. Minimal hepatic encephalopathy. Can J Gastroenterol. 2013;27(10):572–4.
33. Zhang Z, Zhai H, Geng J, Yu R, Ren H, Fan H, *et al*. Large-scale survey of gut microbiota associated with MHE Via 16S rRNA-based pyrosequencing. Am J Gastroenterol. 2013;108(10):1601–11.
34. Malaguarnera M, Greco F, Barone G, Gargante MP, Malaguarnera M, Toscano MA. *Bifidobacterium longum* with fructo-oligosaccharide (FOS) treatment in minimal hepatic encephalopathy: a randomized, double-blind, placebo-controlled study. Dig Dis Sci. 2007;52(11):3259–65.
35. Wang J, He W, Tsai P-J, Chen P-H, Ye M, Guo J, *et al*. Mutual interaction between endoplasmic reticulum and mitochondria in nonalcoholic fatty liver disease. Lipids Health Dis. 2020;19(1):72.
36. Fang J, Yu C-H, Li X-J, Yao J-M, Fang Z-Y, Yoon S-H, *et al*. Gut dysbiosis in nonalcoholic fatty liver disease: pathogenesis, diagnosis, and therapeutic implications. Front Cell Infect Microbiol. 2022;12:997018.
37. Ben M Del, Polimeni L, Baratta F, Pastori D, Angelico F. The role of nutraceuticals for the treatment of non-alcoholic fatty liver disease. Br J Clin Pharmacol. 2017;83(1):88–95.
38. Zhang C, Yang M. Current Options and Future Directions for NAFLD and NASH Treatment. Int J Mol Sci. 2021;22(14):7571.
39. Malaguarnera M, Vacante M, Antic T, Giordano M, Chisari G, Acquaviva R, *et al*. *Bifidobacterium longum* with fructo-oligosaccharides in patients with non alcoholic steatohepatitis. Dig Dis Sci. 2012;57(2):545–53.
40. Caio G, Volta U, Sapone A, Leffler DA, Giorgio R De, Catassi C, *et al*. Celiac disease: a comprehensive current review. BMC Med. 2019;17(1):142.
41. Copaci I, Chiriac G, Micu L. The effects of a prebiotic/probiotic combination in active celiac disease. In: Celiac Disease and Other Small Bowel Disorders. Amsterdam (The Netherlands): Falk Symposium 193; 2014. p. 20.
42. Maconi G. Diagnosis of symptomatic uncomplicated diverticular disease and the role of Rifaximin in management. Acta Bio-medica. 2017;88(1):25–32.
43. Pierro F Di, Bertuccioli A, Pane M, Ivaldi L. Effects of rifaximin-resistant *Bifidobacterium longum* W11 in subjects with symptomatic uncomplicated diverticular disease treated with rifaximin. Minerva Gastroenterol Dietol. 2019;65(4):259–64.

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