Clinical Nutrition ESPEN 42 (2021) 15–21

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Narrative Review

Bifidobacterium longum W11: Uniqueness and individual or combined clinical use in association with rifaximin

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ARTICLE INFO

Article history:
Received 16 September 2020
Accepted 4 December 2020

Keywords:
Bifidobacterium longum W11 (LMG P-21586)
Rifaximin
IBS
IBD
Antibiotic resistance
Minimal hepatic encephalopathy

SUMMARY

Backgrounds & aims: Strains belonging to bifidobacteria have been documented as being helpful in adults with intestinal dysbiosis conditions, like those related to irritable bowel syndrome (IBS). This review aims to present the most relevant evidence regarding the efficacy of *Bifidobacterium longum* W11, a *Bifidobacterium* used in clinical settings for conditions such as IBS and inflammatory bowel disease.
Methods: The following electronic databases were systematically searched up to August 2020: MEDLINE (via PubMed), EMBASE, Cochrane Central Database of Controlled Trials (via CENTRAL), Google Scholar, and Clinicaltrials.gov.
Results: Data arising from pooled analysis, 7 *in vitro*/pharmacological studies, 7 clinical trials including 1 randomized, double-blind and placebo-controlled, showed that the probiotic strain *B. longum* W11 has been extensively studied for its efficacy in subjects with IBS with constipation, leading to a significant reduction in symptoms. In particular, its role in alleviating constipation was also confirmed in subjects for whom a low-calorie weight-loss diet led to the slowing down of gut motility. The probiotic characteristics of *B. longum* W11 were further demonstrated in the treatment of minimal hepatic encephalopathy and hepatic disease. The most remarkable trait of *B. longum* W11 is its non-transmissible antibiotic resistance, due to a nucleotide polymorphism mutation in the *rpoB* gene, making it resistant to antibiotics of the rifampicin group, including rifaximin. The co-administration of *B. longum* W11 and rifaximin in patients with symptomatic uncomplicated diverticular disease brought about a further significant improvement in the clinical condition compared to patients treated with rifaximin alone. *B. longum* W11 is a probiotic which could synergize with rifaximin as an adjuvant to antibiotic treatment.
Conclusions: Taken altogether these findings demonstrate the clinical role of the strain W11 both in some functional and in some inflammatory bowel diseases.

1. Introduction

It has been widely recognized that the bacterial component of the human intestine plays an extraordinarily important role for the gut in terms of immunity, inflammation and metabolism [1]. The complexity of bacterial species inhabiting the intestine, also known as the intestinal microbiota, is also a possible source of new and once unthinkable therapeutic microorganisms, such as *Akkermansia muciniphila* or *Prevotella copri* [2]. Among bacteria with a potential therapeutic effect, bifidobacteria have certainly played a key role for several decades. A Gram-positive, anaerobic, lactic acid-producing, non-spore-forming and non-motile bacterial genus, it was isolated for the first time in 1899 from the stool of a breastfed infant [3]. Today, *Bifidobacterium longum* subsp. *infantis*, *Bifidobacterium bifidum* and *Bifidobacterium breve* species are considered fundamental for newborn well-being [4] and possibly characterize neonatal bifidotypes [5]. Although the role of bifidobacteria in neonatal well-being is given close attention today, the therapeutic potential with respect to well-being of other age groups does not appear “less” important. The administration of *Bifidobacterium* strains may be a powerful tool to help solve problems that are specific and widespread and still largely unresolved, such as irritable bowel syndrome (IBS) [6]. Among bifidobacteria, *B. longum*

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https://doi.org/10.1016/j.clnesp.2020.12.025

W11 is one of the most investigated strains for its potential use in this clinical setting.

2. Methodology and search strategy for identification of studies

The following electronic databases were systematically searched up to August 2020 for relevant studies: MEDLINE (via PubMed), EMBASE, Cochrane Central Database of Controlled Trials, Google Scholar, and the web site www.clinicaltrials.gov. The last literature search was conducted on 16 August 2020. The text word terms used were: *B. longum* W11 and LMG P-21586). In addition, we hand-searched the bibliographies of papers of interest to provide additional references. Relevant meeting abstracts via EMBASE and the International Probiotic Conference were also hand-searched. When needed, we contacted the authors for additional data and clarification of study methods. Finally, the company Probiotical (Novara, Italy), which manufactures the strain object of our research was contacted to identify possible unpublished studies. No limit was imposed regarding the language of publication, and both studies published as full text or as abstracts at conferences/proceedings of scientific meetings were included in the review.

3. *B. longum* W11: probiotic features and colonization

B. longum W11 (LMG P-21586), isolated from a healthy human donor and fully sequenced with its genome deposited at DDBJ/EMBL/GenBank (access number: MRBG00000000), has been thoroughly characterized [7]. Under acidic conditions, which simulate the gastric environment (pH = 2), strain W11 survives very well (approximately 80%) while maintaining a certain growth capacity (approximately 55%), thus demonstrating a much stronger resistance than the strain *B. longum* BB536, which is often considered to be a reference. When placed in an environment with 3% bile, it retains a significant growth capacity (approximately 57%), which is also higher than that for strain BB536. Under experimental intestinal conditions, far from an actual colonization, strain W11 shows twice as much adhesiveness as the BB536 strain [8]. Under real conditions, however, strain W11 produces a considerable quantity of exopolysaccharides (Fig. 1) [9] which increase its adhesion to the intestinal epithelium, thus making its adhesiveness similar to that found with *Bifidobacterium animalis* subsp. *lactis* BB12 [10], long considered the reference standard in the intestinal adhesion test. Moreover, contact between W11 and peripheral blood mononuclear cells (PBMCs) from a healthy donor induces a Th1-type response, immunologically aimed at enhancing the intracellular pathogen killing capacity within the host. This reaction is encouraged by an increase in IFN-γ and IL-2 and a concomitant reduction in IL-10 [11]. This modulation in the production and release of lymphokines in the host can take place in the absence of non-specific inflammatory consequences, as demonstrated by the absence of TNF-α induction [11] (Table 1). Considering actual colonization patterns, *B. longum* W11 was assessed in a study of 13 elderly subjects, aged over 70, in a permanent vegetative state and with total enteral nutrition. After 12 days of treatment, the levels of total intestinal bifidobacteria showed a 2–3 log increase, depending on the patient. This increase, concomitant with a reduction in the Clostridiales populations, was still noticeable even after a short washout period [12] suggesting long-term colonization of the strain.

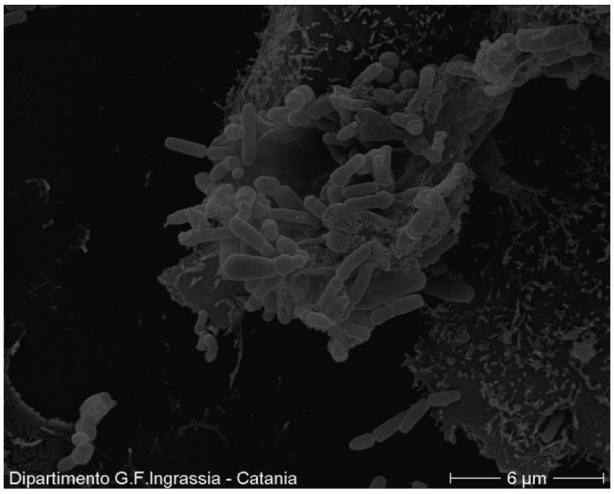


Fig. 1. Formation of exopolysaccharide by *B. longum* W11 while adhering to intestinal epithelium.
Legend: EPS (exopolysaccharide) formation by *Bifidobacterium longum* W11 attached to HT29 cells after 60 min of incubation (magnification 5000×). Figure taken from Inturri et al., 2014.

4. Clinical role of *B. longum* W11 in constipation and IBS-C

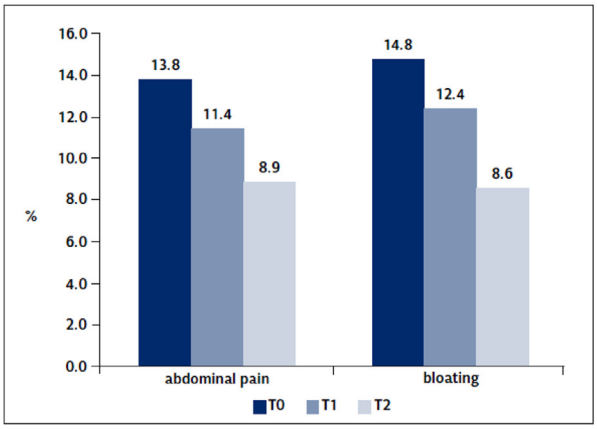
A proven consequence of W11 strain colonization is a reduction in signs and symptoms of constipation, especially when related to a diagnosis of IBS. A trial study with 636 subjects diagnosed with IBS with constipation as a primary feature (IBS–C) showed that, when administered at 5 billion live bacterial units per dose, W11 increased intestinal motility by approximately 25%. Furthermore, following the administration, the average number of evacuations per week increased from 2.9 to 4.1 with 80% of participants reporting their condition as being “improved” at the end of the study and 60% of participants reporting maintained improvement after treatment discontinuation in the follow-up period [13]. Based on patient responses to visual scale items, frequency increased significantly after treatment in the "no symptom" class from 3% to 26.7% for bloating and from 8.4% to 44.1% for abdominal pain. In the more severe symptoms classes (moderate-severe), symptom frequency dropped significantly from 62.9% to 9.6% and from 38.8% to 4.1% for bloating and abdominal pain, respectively. Overlapping results, with a significant increase in the number of weekly evacuations, from approximately 14 to 17, and a reduction of approximately 40% in signs and symptoms of intestinal discomfort, namely abdominal pain and bloating (Fig. 2A), were later obtained by other authors with 129 enrolled subjects diagnosed with IBS-C. Based on patient responses to visual scale items at the beginning of the study and at the end of the treatment, a significant efficacy with respect to moderate-to-severe abdominal pain was observed (Fig. 2B) [14]. Furthermore, *B. longum* W11 affected constipation not related to IBS diagnosis, such as in subjects with hypocaloric diet-induced constipation [15]. In approximately 300 female patients with constipation induced by reduced dietary intake, adherence to *B. longum* W11 treatment brought about a statistically significant improvement in the number of evacuations for approximately 30% of the enrolled subjects.

Table 1
Release of lymphokines (pg/mL) from mononucleated cells obtained from peripheral blood in the presence of strain W11.

Test	IFN-γ	TNF-α	IL-2
RPMI	9.5 ± 1.0	not detected	57.7 ± 2.6
LPS	11.9 ± 0.5	27.8 ± 3.1	398.0 ± 7.1
B. longum W11	131.0 ± 13.7	not detected	19.56 ± 12.6

Taken from: Medina et al., 2007.

(A)



(B)

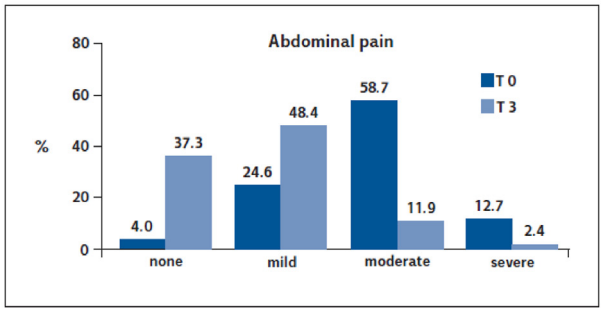


Fig. 2. (A): Clinical effect on intestinal discomfort in subjects diagnosed with IBS-C; (B): clinical effect on abdominal pain in subjects diagnosed with IBS-C, classified according to symptom severity.
Legend (2A): Effect on the severity of abdominal pain and bloating. The reduction rate is evaluated by the Visual Analogic Scale (VAS) measurement recorded at each visit. T0: enrolment; T1: 1 month of treatment; T2: 2 months of treatment. T2 versus T0: $p < 0.0001$. Figure taken from: Dughera et al., 2007.
Legend (2B): Comparison between abdominal pain at the beginning and at the end of the study. T0: enrolment; T3: 3 months of treatment. T3 versus T0: $p < 0.0001$. Figure taken from: Dughera et al., 2007.

5. Uniqueness of *B. longum* W11: rifaximin resistance

Rifaximin is a broad-spectrum, non-absorbed antibiotic, considered to be a "eubiotic" and is thus used in the treatment of many functional gastroenterological disorders, including IBS [16], even if this use is off-label. In a study, rifaximin was administered to 70 enrolled IBS patients, followed by probiotic treatment with strain W11. According to the results, increased colonization by *B. longum* W11, after the cyclic administration of rifaximin, may reduce symptoms, especially those related to bowel habits and stool frequency, in patients with IBS. Patients who received rifaximin followed by probiotic treatment reported a greater improvement of symptoms compared to patients receiving rifaximin alone. The use of strain W11 doubled the positive effects observed in the control group treated with rifaximin alone, showing a significant additive effect [17].

Among the targeted applications of rifaximin, albeit off-label, the treatment of diverticular disease is certainly the most widespread [18]. However, the clinical approach to this disease suggests the use of rifaximin should be followed by the use of probiotics [19]. A caveat to this type of "sequential" approach is that it could determine a poor therapeutic adherence profile. This phenomenon may be caused by the perception of the patient of good clinical results upon completion of the rifaximin cycle. This perception could reduce subsequent adherence to the prescribed probiotic treatment, which, conversely, aims to recover potentially probiotic taxa or functions inadvertently lost during the administration of antibiotics. In this case, the ideal probiotic should therefore display its rifaximin–resistance properties so that it can be administered concomitantly with antibiotic medication. Antibiotic-resistant probiotics do not generally exist, at least among those that can be medically used [20]. The only exceptions are some intrinsically vancomycin-resistant *Lactobacillus casei* and/or *L. paracasei* [21] and *B. longum* W11, which is the subject of this review.

Nevertheless of its antibiotic–sensitivity profile (Table 2), as clearly shown in Fig. 3 strain W11 is resistant to the entire rifampicin group, including rifaximin, due to a mutation in the *rpoB* (DNA-mediated RNA polymerase β subunit) gene [22]. The mutations related to this gene and their biological effects are well-described [23]. The analysis performed on the strain W11-gene showed a mutation at the DNA level which causes a change in an amino acid (P564L) of the protein that is compatible with the resistance to the rifamycin. Figure 4 shows the protein sequence alignments of the *rpoB* genes for *Escherichia coli* (used as reference for the mutation positions), the reference *B. longum* present in the Ensembl database, indicated in the Figure as "ref", and the *B. longum* strain W11, indicated in the Figure as "pro". Highlighted in red is the Cluster II of the protein sequence, where rifamycin resistance mutations were originally described [23], while in blue are marked the positions of the mutations on the *B. longum* W11. This gene mutation occurs in a tract of the genome that is entirely devoid of mobile genetic elements, as verified by the software TransposonPSI. Thus, this antibiotic-resistance trait harbored by *B. longum* W11 can be considered intrinsic and not transferable to other bacteria, and in compliance with EFSA guidelines [24]. This specific resistance allows for the *B. longum* W11 strain to be recommended to patients for all those diseases where the use of rifaximin is required. Recently, a clinical trial aiming to demonstrate the adjuvant effect of co-administration of rifaximin and strain W11 in patients with symptomatic uncomplicated diverticular disease (SUDD) reported a 20% further improvement compared to patients treated with rifaximin alone. By evaluating symptoms like abdominal pain and tenderness, diarreha, constipation, bowel habits change and bloating, the improvement started to be significant after the second month of treatment. A further improvement in feces consistency as measured by the Bristol Stool Scale, and a 30% increase in compliance during the treatment, was also shown [25]. It has been reported [26] that short antibiotic treatment could bring changes to the gut microbiota that are observable by three different parameters: first, a reduced richness and α-biodiversity with the loss of some low-expressed taxa; second, a probable increase in the absolute number of bacteria; and third, an increase in the global gut Gram-negative bacteria. The Authors of the study speculated that the W11 strain administered along with rifaximin somewhat improved the clinical outcome as it limited these factors, thereby preventing damage to the gut bacterial consortium [25].

6. Use of *B. longum* W11 in minimal hepatic encephalopathy and liver disease

The clinical applications of rifaximin include the treatment of acute and chronic Gram-positive and/or Gram-negative gut infections, diarrheal syndromes, summer diarrhea, traveler's diarrhea, bacterial enterocolitis (caused by *Shigella*, *Salmonella*, *Yersinia*, *Campylobacter*, *V. cholerae*, *E. coli*), pre- and post-bowel surgery prophylaxis and hyperammonemia. With respect to the latter application, or rather, within the context of the milder variant of

Table 2
Antibiotic-sensitivity profile of strain W11.

Antibiotic groups	MIC μg/mL	*B. longum* W11 LMG P-21586	EFSA Limit 2018
Aminoglycosides	Gentamicin	24	64
	Streptomycin	32	128
Quinolones	Ciprofloxacin	8	–
Glycopeptides	Vancomycin	0.38	2
Lincosamides	Clindamycin	0.023	1
Macrolides	Azithromycin	0.25	–
	Clarithromycin	0.023	–
	Erythromycin	0.023	1
Oxazolidinones	Linezolid	0.125	4
Streptogramins	Quinupristin/dalfopristin	0.047	1
Tetracyclines	Chloramphenicol	0.50	4
	Tetracycline	0.25	8
β-Lactams	Amoxicillin	0.25	–
	Ampicillin	0.19	2
	Cefoxitin	4	–
	Cefuroxime	1	–
	Imipenem	0.38	–

EFSA reference MICs for *Bifidobacterium*. Taken from: Graziano T. et al., 2016.

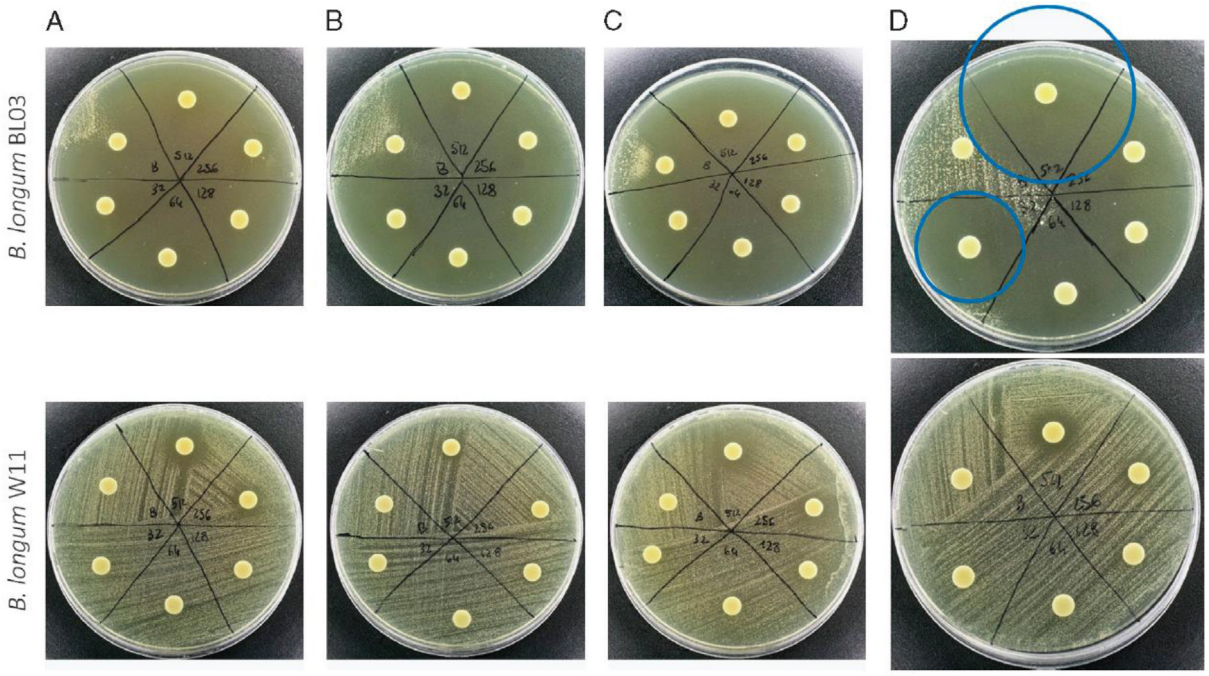


Fig. 3. Occurrence of circular areas of growth inhibition of two strains of *Bifidobacteria*, strains BL03 (top) and W11 (bottom), caused by the presence of rifampicin (A), rifapentine (B), rifabutin (C) and rifaximin (D).
Legend: Strain W11 appears to be resistant to all tested dosages: 32, 64, 128, 256 and 512 mg/L. The first "slice" on the left within each plate, marked by the handwritten letter B, corresponds to the antibiotic-free disc. Figure taken from Graziano T. et al., 2016.

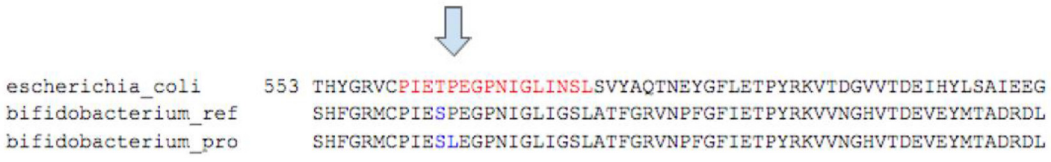


Fig. 4. Amino acid sequence of the rpoB protein in a rifaximin-sensitive *Escherichia coli* strain, in a rifaximin-sensitive *Bifidobacterium* reference (ref) and in strain W11 (pro).
Legend: The gene mutation in strain W11 replaces an L-proline instead of an L-leucine. Figure taken from Graziano et al., 2016.

hepatic encephalopathy known as minimal hepatic encephalopathy (MHE), where increased ammonia levels have been implicated in the pathogenesis of the disease, strain W11 displayed significant clinical activity in a double-blind, placebo-controlled trial without the use of rifaximin, resulting in a 54% reduction in plasma ammonia levels after 90 days of administration [27]. This effect, as

reported by the same authors, could be due to one or more of the properties that characterize strain W11, possibly leading to a decrease in the urease activity of the gut microbiota; a reduction in the intestinal absorption of ammonia due to lower intestinal pH; reduced intestinal permeability; an improvement in trophic conditions for the intestinal epithelium; a decrease in liver inflammation resulting in improved liver clearance of ammonia; an improvement in immunity to urease-producing strains and/or a reduction in mercaptan production by the patient microbiota. A further important clinical role for strain W11 in the treatment of liver disease is demonstrated by additional evidence, such as the use of the strain in patients with non-alcoholic steatohepatitis (NASH), where treatment with strain W11 appeared to significantly reduce parameters such as TNF-α, CRP, AST, HOMA-IR, serum endotoxin, steatosis and the NASH activity index [28], as assessed by liver biopsy. Considering the interaction and probable causal relationship between the gut microbiota and NASH [29], we may explain clinical observations by reconsidering the eubiotic role of *B. longum* W11.

7. Conclusions and prospective use of *B. longum* W11

B. longum W11 is a widely investigated, including within a clinical setting (Table 3), strain within the *B. longum* species. Its genome, which has been completely described, demonstrates a total absence of virulence factors. This strain also shows some functional properties such as resistance to gastric acidity and bile that are considered of paramount importance for probiotics. After

Table 3
Summary of clinical evidence with respect to strain W11.

Published articles	Focus on the treatment	Dosage of *Bifidobacterium longum* W11/Country	Treatment period	Study population	Results
Amenta et al. [15], 2006	Chronic constipation	5×10^9 (cells) Italy	20 days	297 patients	Reduced constipation in 27% of patients after at least 17 days of treatment and in 11% of patients after fewer than 17 days of treatment
Colecchia et al. [13], 2006	Irritable bowel syndrome (IBS)	5×10^9 (cells) Italy	At least 36 days	636 patients	Based on patient responses to visual scale items, frequency increased significantly after treatment in the "no symptom" class from 3% to 26.7% for bloating and from 8.4% to 44.1% for abdominal pain. In the more severe symptoms classes (moderate-severe), symptom frequency dropped significantly from 62.9% to 9.6% and from 38.8% to 4.1% for bloating and abdominal pain, respectively. Stool frequency significantly increased from 2.9 ± 1.6 times/week to 4.1 ± 1.6 times/week. After 36 days of therapy 26.6% of patients did not feel any discomfort and 44.1% did not experience flatulence. 83.8% of respondents felt better after their therapy. Clinical evaluation 1 month after the end of therapy showed that the improvement effect was maintained in 63.2% of subjects
Fanigliulo et al. [17], 2006	Irritable bowel syndrome (IBS)	5×10^9 (cells) Italy	2 months	70 patients	2 groups of patients; group A: rifaximin therapy for 10 days a month, followed by *Bifidobacterium longum* W11 treatment for 10 days and group B: therapy with rifaximin only without the probiotic. Reduction of discomfort in both groups on the VAS after 2 months of treatment. Significantly greater reduction in complaints among patients in group A compared to group B
Malaguarnera et al. [27], 2007	Minimal hepatic encephalopathy (MHE)	5×10^9 (CFU) Italy	90 days	60 patients	Significant reduction in parameters such as TNF-α, PCR, AST, HOMA-IR, serum endotoxin, steatosis and the NASH activity index
Dughera et al. [14], 2007	Irritable bowel syndrome (IBS)	5×10^9 (CFU) Italy	3 months	129 patients	Significant reduction in pain and bloating, including reduction after a month of therapy. Significant impact and increased frequency of bowel movements and improvement of peristalsis
Del Piano et al. [12], 2004	Intestinal colonization by Clostridiales	5×10^9 (CFU) Italy	15 days	13 patients	After 12 days of treatment, the levels of total intestinal *Bifidobacteria* showed a 2–3 log increase. This increase was accompanied by a decrease in the Clostridiales populations and was still noticeable even after a short washout period, suggesting a long-term colonization of the strain
Di Pierro et al. [25], 2019	Diverticular disease	10×10^9 (AFU) Italy	7 days	45 patients	Co-administration of rifaximin and strain W11 in patients with symptomatic uncomplicated diverticular disease (SUDD) resulted in a 20% further improvement compared to patients treated with *Bifidobacterium longum* W11 after rifaximin cycle. A further improvement in feces consistency as measured by the Bristol Stool Scale, and a 30% increase in compliance during the treatment, was also observed

producing an important exopolysaccharide, based on galactopyranose and galactofuranose [10], it adheres to the gut epithelium and shows good persistence characteristics. Biologically, it establishes a Th1-type host response, which allows the host to develop a solid defense against intracellular pathogens, without stimulating the pro-inflammatory component (TNF-α) of the system. In terms of functionality, it shows efficacy in relieving functional constipation, which characterizes IBS-C, and constipation that can sometimes arise in individuals consuming a low-calorie diet[15]. Furthermore, *B. longum* W11 improves NASH conditions, as well as MHE conditions. However, its most remarkable feature is certainly the single nucleotide polymorphism mutation affecting the *rpoB* gene. This mutation renders the W11 strain highly resistant to rifaximin, which offers an important new range of clinical uses that have a common determinant in both on-label and off-label use of rifaximin, be it for hyperammonemia, diverticular disease, infectious enterocolitis or IBS. However, rifaximin and strain W11 could be beneficially used for other purposes. For example, recent data show how the strongly dysbiotic microbiota can be related to, or even be the cause of, diseases that are not necessarily intestinal in nature, such as atherosclerosis, hypertension, fibromyalgia and so on [30–32]. The known non-absorption and broad-spectrum characteristics of rifaximin would then make it the ideal antibiotic to counteract the bacterial species whose presence characterizes such dysbiosis. The decompensation of the dysbiotic microbiota by administration of an antibiotic (rifaximin), associated with strain W11, could become a new therapeutic approach in the future to mitigate the adverse effects that the antibiotic treatment would also have on the "healthy" component of the microbiota. This would be useful both to improve the good clinical outcomes resulting from the use of rifaximin and to counteract cardiovascular, neurological or osteoarticular diseases, at least those associated with evident dysbiosis.

Contributions section

All authors equally contributed in writing the manuscript. All authors read and approved the final version of the manuscript.

Declaration of competing interest

Francesco di Pierro is employed by Velleja Research. Marco Pane is employed by Probiotical Research Srl (Novara, Italy).

Acknowledgments

Nina Vinot contributed to the proofreading of the manuscript. Ruth Dilleen carried out English language revision of the manuscript.

List of abbreviations

IBS-C	Irritable Bowel Syndrome Type constipation)
IBD	Inflammatory Bowell Disease
MHE	Minimal Hepatic Encephalopathy
DDBJ	DNA Data Bank of Japan
EMBL	European Molecular Biology Laboratory
PBMCs	Peripheral Blood Mononuclear Cells
Th1	T helper 1
TNF	Tumor Necrosis Factor
IL	Interleukin
rpoB	DNA-mediated RNA polymerase β subunit
NASH	Non-Alcoholic Steato Hepatitis
CRP	C Reactive Protein
AST	Aspartate Amino Transferase
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance

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