

# **Clinical study on *Bifidobacterium lactis* BL-99 assisting to improve functional dyspepsia**

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## **Abstract**

Functional dyspepsia (FD) is a common chronic gastrointestinal disorder without known organic pathology changes. Recurrence symptoms and longer duration resulting in poor quality of life and high medical expenses for patients. Therefore, searching for a prolonged treatment of FD has considerable clinical value. There are two objectives in this research, one is to determine efficacy of BL-99 to improve FD symptoms and the underlying mechanism, and the other is to evaluate the impact of BL-99 on gastrointestinal microbiota after proton pump inhibitors (PPI) therapy. In this randomized controlled trial, corresponding to the research purpose 1, subjects will be randomized into four groups (mild placebo group, mild low dose group, mild high dose group, severe placebo group), and corresponding to the research purpose 2, subjects will be randomized into two groups (severe low dose group, and severe high dose group). Except the mild placebo group, other groups will receive BL-99 and/or PPI. The clinical trial registry is at [Chictr.org.cn](http://Chictr.org.cn) ID ChiCTR2000041430.

## **Introduction**

Functional dyspepsia (FD) is a common chronic gastrointestinal disorder without

known organic pathology changes.<sup>1</sup> FD is subdivided into Epigastric pain syndrome (EPS, including epigastric pain or epigastric burning symptoms) and Postprandial distress syndrome (PDS, including bloating or early satiety symptoms)]. Currently, there is a lack of efficient treatment for this refractory disease,<sup>2</sup> causing poor life quality and higher medical expenses for patients.<sup>3</sup> Therefore, searching for a prolonged treatment of FD has considerable clinical value.

Several anti-dyspepsia drugs (acid-suppressive therapy, prokinetics, neuro-modulators and herbal therapies) have been recommended to treat FD symptoms in clinical practice, with significant side effects and unknown long-term efficacy.<sup>4</sup> Among them, PPI are considered to be the most effective and first-line therapy but its long-term effect is limited, which may be related to the change of gut microbiota and the increased risk of intestinal infection.<sup>5</sup> Hence, it is an urgent need to develop an efficient, targeted and long-term therapy for FD.

Probiotics have been shown to have the potential to alleviate FD. Consuming probiotic products containing *Lactobacillus gasseri* OLL2716, *Lactobacillus paracasei* LC-37, et al., can significantly improve postprandial discomfort, epigastric pain, belching and other FD symptoms.<sup>6-8</sup> More importantly, Khoder G et al.<sup>9</sup> demonstrated that probiotics could regulate the release of serum pepsinogen. However, the efficacy of different strains varies, and the mechanism of probiotic intervention to alleviate FD needs to be further studied.

*Bifidobacterium animalis* subsp. *lactis*. BL-99 (BL-99) was isolated from the faeces of healthy infant. *In vitro* and *in vivo* experiments showed that BL-99 is a non-pathogenic strain and could be used in the production of functional food.<sup>10</sup> Then, it was confirmed that BL-99 could maintain intestinal health by reducing intestinal inflammation.<sup>11</sup> Moreover, recent studies suggested that BL-99 could utilize fructo-oligosaccharide (FOS) to regulate the composition and structure of gut microbiota in patients with constipation, thus promoting the production of short chain fatty acids (SCFAs).<sup>12</sup> Hence, a randomized parallel controlled trial will be performed to study the prolonged efficacy of BL-99 to improve FD symptoms and the

underlying mechanism, and evaluate the impact of BL-99 on gastrointestinal microbiota after PPI therapy.

### **Reagents and equipment**

NA

### **Procedure**

#### **Sample Size Calculation:**

Based on previous studies, the power for the primary outcome reached 80% (two-sided test,  $\alpha = 0.05$ ) with a sample size of 42 participants per group.<sup>13</sup> This study assumed that the overall dropout rate would be 10-12% during the entire study period. To account for probable follow-up loss, 50 study participants per group were recruited.

#### **Inclusion Criteria:**

- (1) Aged 18-60 years;
- (2) Meet one or more symptoms of Rome IV FD diagnostic criteria (epigastric pain, belching, early satiety, epigastric burning, acid regurgitation, bloating, nausea and vomiting), the course of the disease is more than 6 months, and symptoms have occurred in the past three months;
- (3) Willing to provide demographic information (age, weight, height, etc.);
- (4) Be willing to and complete daily and weekly questionnaires on general health, intestinal function and gastrointestinal symptoms.

#### **Exclusion Criteria:**

- (1) Indigestion caused by serious organic lesions (cardiovascular, liver, kidney, or hematopoietic) diseases and without *Helicobacter pylori* (*H. pylori*) infection (diagnosed by the C14-urea breath test);
- (2) Pregnancy;

- (3) Smokers and alcoholics;
- (4) Take any medication for constipation or diarrhea;
- (5) Currently taking any anti-inflammatory medication regularly;
- (6) Usually eat fermented foods or probiotics (for example, kimchi, sauerkraut, fermented bean curd, tempeh, cheese);
- (7) Received antibiotics in the past three months;
- (8) A history of clinically significant diarrhea or *C. diff* infection in the past 3 months.

### **Group and intervention:**

Group and intervention corresponding to the research purpose 1:

- (1) Mild placebo group: the placebo contained 2 g/day maltodextrin.
- (2) Mild low dose group: 2 g solid beverages containing  $1 \times 10^{10}$  CFU/day BL-99.
- (3) Mild high dose group: 2 g solid beverages containing  $5 \times 10^{10}$  CFU/day BL-99.
- (4) Severe placebo group: 10 mg/day proton pump inhibitors (PPI).

Group and intervention corresponding to the research purpose 2:

- (5) Severe low dose group: 2 g solid beverages containing  $1 \times 10^{10}$  CFU/day BL-99 and 10 mg/day PPI.
- (6) Severe high dose group: 2 g solid beverages containing  $5 \times 10^{10}$  CFU/day BL-99 and 10 mg/day PPI.

### **Time Taken**

After a 2-week run-in period, the participants underwent an 8-week intervention period; and an 8-week follow-up period.

### **Anticipated results**

The prolonged efficacy of BL-99 to improve FD symptoms and the underlying

mechanism will be explored. Moreover, the impact of BL-99 on gastrointestinal microbiota after PPI therapy will be evaluated.

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