***Indonesian Journal of Nursing Health Science*** **I**SSN (Print) : 2502-6127
Vol. 10, No.1, Maret 2025, p.56-68 I SSN (Online) : 2657-2257

# The Use of Probiotics in Nutritional Management of Critical Patients: A Literature Review

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*Submitted:* May 1, 2025, *Revised: June 27, 2025*, *Accepted: June 30, 2025*

***Abstract***

***Background****: Critical patients are individuals who face potentially life-threatening health issues. Probiotics are microorganisms that reside in the host's body in sufficient quantities to confer health benefits. For example, probiotic mechanisms can influence gut microbiota or enhance immune function. The use of probiotics in the ICU may involve food supplements administered enterally. Probiotics are employed in treating various gastrointestinal conditions, such as Clostridium difficile colitis (CDC), infectious diarrhea, inflammatory bowel disease (IBD), and irritable bowel syndrome (IBS).* ***Objective****: To review and discuss the findings related to the effectiveness of probiotics in ICU patients.* ***Method****: This literature review utilized electronic databases, including PubMed, Science Direct, and Google Scholar, to find relevant articles.* ***Results****: Using specific keywords, 57,862 articles were retrieved from the three databases; however, only two were selected based on the PRISMA flowchart from 2014 to 2023. An additional 384 articles were included after excluding 1,175 duplicates. Of these 384 articles, only 40 met the inclusion criteria, but ultimately, only 10 articles were reviewed because the remaining 30 focused on populations that did not match the criteria.*
**Keywords**: ICU patients, probiotics, nutrition

***Abstract***

**Latar belakang:** Pasien kritis merupakan pasien yang berpotensial mengancam jiwa untuk masalah kesehatan. Probiotik adalah mikroorganisme yang hidup dalam tubuh host dengan jumlah yang memadai yang akan memberikan manfaat kesehatan pada host. Mekanisme probiotik misalnya, memiliki dampak pada mikrobiota usus atau meningkatkan fungsi kekebalan tubuh. Penggunaan probiotik di ruang ICU dapat berupa suplemen makanan yang dapat diberikan melalui enteral. Probiotik digunakan dalam pengobatan berbagai penyakit gastrointestinal, seperti *clostridium difficile colitis* (CDC), diare infeksius, *inflammatory bowel disease* (IBD), dan *irritable bowel syndrome* (IBS). **Tujuan:** Untuk meninjau dan mendiskusikan hasil tentang efektivitas penggunaan probiotik pada pasien ICU. **Metode:** Literature review ini berdasarkan database elektronik seperti PubMed, Science Direct, dan Google Scholar digunakan untuk mendapatkan artikel yang relevan **Hasil:** Dengan kata kunci didapatkan 57.862 artikel dari ketiga database elektronik¸ tapi hanya menggunakan dua berdasarkan flowchart PRISMA dari tahun 2014 hingga 2023. Lalu, didapatkan 384 artikel setelah sebanyak 1.175 artikel dihapus karena artikel duplikat. Dari 384 artikel hanya 40 artikel yang memenuhi syarat, namun hanya 10 artikel terpilih untuk di review karena 30 artikel lainnya memiliki fokus populasi yang berbeda dari kriteria.
**Kata Kunci:** Pasien ICU, Probiotik, Nutrisi

## Introduction

The Intensive Care Unit (ICU) is a section of a hospital equipped with specialized staff and equipment designed for observing, treating, and managing patients with diseases, injuries, or other conditions that can be life-threatening or have the potential to become such but are expected to be reversible. Patients in the ICU typically have specific situations, such as experiencing failure of one or more organ systems (Amaliah et al., 2018). The critical care provided to each severely ill patient involves actions that require continuous medical documentation and monitoring to quickly detect physiological changes or declines in organ function (Amaliah et al., 2018).

The most common case in the ICU is ventilator-associated pneumonia (VAP). VAP is a bacterial infection of the respiratory tract that occurs after 48 hours of ventilator use. It is a common hospital-acquired infection found in the ICU (Widianingsih et al, 2022). The term probiotic was first introduced by Lilley and Stillwell in 1965, who defined probiotics as microbes that stimulate the growth of other microbes. According to the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), probiotics are microorganisms that live in the host's body in sufficient numbers to provide health benefits. The mechanisms of probiotics include effects on gut microbiota or enhancement of immune function. An effective probiotic must meet several criteria, including providing a beneficial impact on the host, being non-pathogenic and non-toxic, containing a large number of live cells, surviving and performing metabolic activities in the intestine, remaining viable during storage and use, having good sensory properties, and being isolated from the host.

Probiotic bacteria (Lactobacillus and Bifidobacterium) work anaerobically to produce lactic acid, which lowers the pH of the digestive tract and inhibits the growth of pathogenic bacteria. The group of bacteria classified as probiotics is a type of lactic acid bacteria that naturally resides in the human digestive tract, producing bacteriocins that can stimulate antibody formation and act as immunomodulators and antidiarrheals. Due to the promising potential of probiotics for critically ill patients, numerous randomized controlled trials (RCTs) have been conducted in recent years to evaluate their effectiveness in preventing VAP. A recent meta-analysis by Su et al. (2020) and Cheng et al. (2018) shows that probiotics are effective in reducing the incidence of VAP. Based on this background, the researcher aims to explore the effectiveness of probiotics in ICU patients through a literature review.

## Objective

This study aims to review and discuss the results on the effectiveness of probiotic use in ICU patients.

## Method

### Design

The design of this research is a *literature review*. With inclusion criteria: 1) in the form of research articles; 2) full text; 3) the language used in English; 4) Publication year 2014-2024.

### Database

The databases used are electronic databases such as PubMed, Science Direct, and Google Scholar, used to obtain relevant articles within the scope of this literature review article. The articles were initially selected based on inclusion criteria and then assessed using the

*Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) framework for each relevant article.

**Search Strategy**

The terms used to obtain relevant articles in this *literature review* include "Probiotics", "Administration of Probiotics in the ICU Room", "Administration of Probiotics in Critical Patients", "Administration of Probiotics in Adult Critical Patients", "Nutrition", "ICU Room", and "Critical Patients". The titles and abstracts obtained regarding the results of the effectiveness of probiotic use in critically ill patients were systematically reviewed and analysed to identify the most relevant articles.

| PICO | Mesh | Database |
|---|---|---|
| Populasi | "Critical Patients", "Adult Critical Patients" | PubMed Google Scholar |
| Intervention | "Administration of Probiotics in the ICU Room", "Administration of Probiotics in Critical Patients", "Administration of Probiotics in Adult Critical Patients" | |
| Comparison | - | |
| Outcome | Any result | |

**Research Eligibility Criteria**

Article eligibility is limited to those published between 2015 and 2023 to ensure that the article is current and relevant to the current situation. An article discussing the effectiveness of using probiotics in nutritional management for critical patients in the ICU. Study design types, including RCTs, pilot studies, quasi-experiments, Single-centre, double-blind, placebo-controlled, randomized trials.

**Synthesis Results**

All authors conduct a screening of relevant articles. The findings of this study are described narratively, including 1) Author, year, and country of origin; 2) Emergency training/first aid program strategy as an intervention; 3) Design; 4) Sample size or quantity; 5) The duration of the program; 6) Instruments used to measure research results; 7) Results of these programs.

## Results

**Search Results**

Using the initial keywords, we extracted 57,862 articles from three databases, but we only used two based on the PRISMA flowchart from 2014 to 2024. Of the 1,175 articles deleted due to duplication, 384 articles were ultimately entered. The researchers screened and selected relevant articles related to the use of probiotics in the nutritional management of

critically ill patients based on the titles and abstracts of the selected articles. Of these, 128 articles were removed due to improper criteria. To be precise, 88 studies were published in a review format, including concept analysis, literature review, systematic review, and meta-analysis. Another reason to exclude the 88 published studies is that they are not in full text. After filtering the relevant articles by research title, abstract, and full-text, the researchers extracted 40 eligible full-text research articles. Only 10 relevant articles meet the criteria. On the other hand, more than 30 articles were issued due to their focus on different populations: critical patients in children and patients with obesity.

Table 1. Source of Data

| Basis Data 2014-2024 | Amount |
|---|---|
| PubMed | 57.862 |
| Science Direct | 0 |
| Google Scholar | 612 |
| TOTAL | 58.474 |

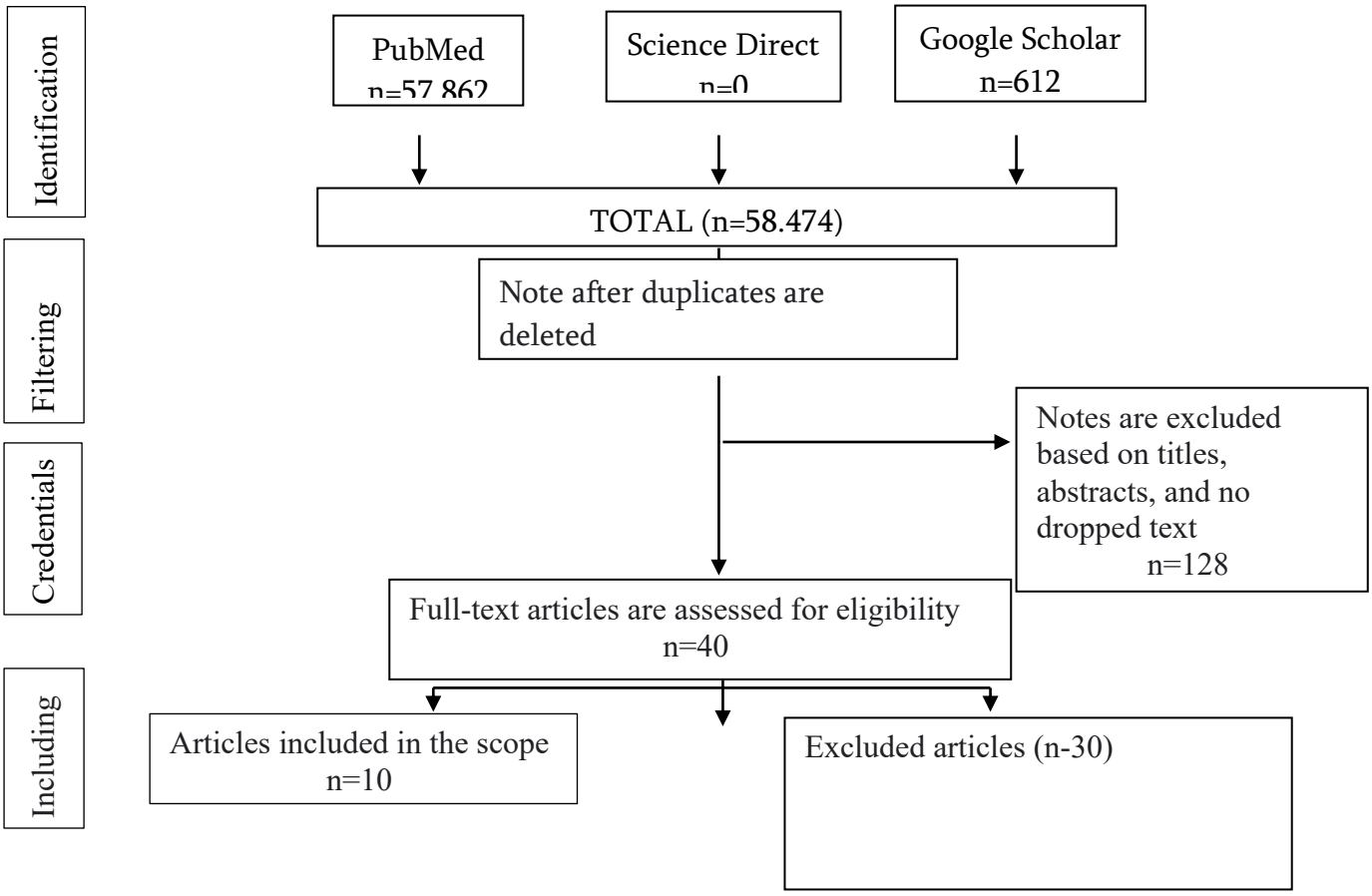


Diagram 1. PRISMA Flowchart

**Origin of Research**

This literature review draws on research from various countries. The countries that contributed to the preparation of this literature review were Canada, China, Iran, Italy, and Switzerland.

**Research Design**

This study was primarily a Placebo-Controlled Randomized Trial. Three articles (numbers 1, 2, 1,2,3) reported on Placebo-Controlled Randomized Trials; two articles (numbers 4, 5) described Pilot Studies; three articles (numbers 2, 3, 8, 2,3,8,9) were double-blinded studies; one article (number 2) was a Single-Center study; one article (number 6) was a Quasi-Experiment; one article (number 5) was an RCT; one article (number 5) was a Clinical Trial; and two articles (numbers 7, 10) were Prospectively Randomized.

**Instrument and Outcome**

The outcomes in article 1 (Jennie Johnstone et al., 2021, Canada) detailed the administration of probiotics to patients with VAP (Ventilator-Associated Pneumonia), with the final diagnosis of VAP determined by a centralized, duplicate, and blinded decision. Secondary outcomes included other ICU-acquired infections, such as Clostridioides difficile infection, diarrhea, antimicrobial use, length of stay in ICU and hospital, and mortality.

Outcomes in article 2 (Andreana De Mauri et al., 2022, Italy) explained the use of probiotics as a low-protein dietary supplement, showing effective results in reducing uremic toxins, microbiota derivatives, and traditional proatherogenic factors, especially when combined with low-protein diets (LDPs) and new probiotic formulations (Bifidobacterium longum and Lactobacillus reuteri).

Outcomes in article 3 (Hao Lai et al., 2023, China) describe the effects of dietary fiber or probiotics on symptoms of functional constipation and the role of gut microbiota, based on a double-blinded, randomized, placebo-controlled trial. Main results included changes in bowel movement frequency per week, with secondary outcomes such as BSS, DDS, fasting glucose, HDL, LDL, total cholesterol, triglycerides, and gut microbiome profiles over a 4-week intervention.

Outcomes in article 4 (Cathy Alberda et al., 2018, Canada) examined the use of Lactobacillus casei in the ICU to prevent antibiotic-related diarrhea and Clostridium difficile infections. The probiotic group experienced no severe side effects, compared to three in the control group. Antibiotic-associated diarrhea (AAD) occurred in 12.5% of the probiotic group versus 31.3% in the control group, and CDI developed in 1% of the probiotic group compared to three patients in the control group.

Outcomes in article 5 (Maria Ines Pinto-Sanchez et al., 2017, Switzerland) studied the use of Bifidobacterium longum as a probiotic to reduce depression scores and alter brain activity in patients with irritable bowel syndrome. The primary results showed a 2-point reduction in anxiety and/or depression scores over six weeks. Secondary outcomes included increased anxiety and depression scores (HAD, continuous data), as well as improvements in IBS symptoms, somatization, quality of life, brain activation patterns (fMRI), serum inflammatory markers, neurotransmitters, BDNF, and urinary and fecal microbiota profiles.

Outcomes in article 6 (Guohua Wan et al., 2019, China) described the combination of probiotics with early enteral nutrition in patients with severe TBI, using pseudo-experiments

and data collection tools like GCS, SOFA, APACHE II, serum levels, and ELISA. The main findings indicated that serum inflammatory factors gradually decreased over treatment time in both groups. The combination group showed more significant reductions in ET-1 on day 15, and IL-6, IL-10, TNF-α, and CRP on days 7 and 15. Hospitalization duration and lung infection rates were also significantly lower in the combined group. The GCS score on day 15 was notably lower in the combined treatment group compared to the enteral nutrition-only group.

Outcomes in article 7 (Najmeh Seifu et al., 2022, Iran) involved prospective randomized data collection on patients in the Edalatian Medical ICU, treated with synbiotic capsules containing Lactobacillus, Bifidobacterium, Streptococci, and fructooligosaccharides, or a placebo. The study focused on energy homeostasis, nitrogen balance, muscle mass, lipolysis, glucose regulation, inflammatory status, and serum endotoxin levels.

Outcomes in article 8 (Qun Yan et al., 2015, China) examined probiotics supplied by Bifico, a combination of Bifidobacterium longum, Lactobacillus acidophilus, and Enterococcus faecalis, using a double-blind, parallel-group trial. The primary outcome was an increased risk of developing diabetes after 24 months of probiotic use. Secondary outcomes included the prevalence and changes in blood glucose, lipid profile, insulin sensitivity, body weight, waist circumference, probiotic safety, gut bacterial abundance, blood LPS levels, and GLP-1 levels.

Outcomes in article 9 (Azimeh Hasanpour et al., 2023, Iran) explored the effect of probiotic capsules (one daily) combined with soy milk in patients with type 2 diabetes mellitus (T2 DM) through a double-blind randomized clinical trial, focusing on cardiovascular risk factors.

Outcomes in Article 10 (Rui Zhao et al., 2017, China) reported that combining fiber and probiotics for the treatment of diarrhea proved significantly effective in postoperative gastric cancer patients, based on controlled, randomized trials that utilized chi-square, Fisher's exact test, and fecal analysis.

## Discussion

Critical patients are those who have the potential to become life-threatening due to health problems. The more critical the condition, the more likely it is to become highly vulnerable, unstable, and complex, requiring intensive care and careful nursing (American Association of Critical-Care Nurses, 2016).

The Intensive Care Unit (ICU) is a part of a hospital equipped with specialized staff and equipment, designed for the observation, treatment, and therapy of patients suffering from diseases, injuries, or other conditions that can be life-threatening or have the potential to become so, but are expected to be reversible. Patients admitted to the ICU typically have specific circumstances, such as failure of one or more organ systems (Amaliah, et al. 2018). The intensive care provided to each critical patient involves actions that require continuous medical recording and monitoring to quickly detect physiological changes or declines in organ functions (Amaliah, et al. 2018).

According to the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), probiotics are microorganisms that live inside the host's body in adequate amounts, providing health benefits. Probiotics can affect gut microbiota or enhance immune function as part of their mechanisms. An effective probiotic must meet several criteria, such as providing beneficial effects, being non-pathogenic and non-toxic, containing a sufficient number of live cells, capable of surviving and metabolizing in the intestine, remaining

viable during storage and use, having good sensory properties, and being isolated from the host. Probiotic bacteria, such as Lactobacillus and Bifidobacterium, operate under anaerobic conditions, producing lactic acid that lowers the pH in the digestive tract and inhibits the growth of pathogenic bacteria. Probiotics are also used to treat various gastrointestinal diseases, including Clostridium difficile colitis (CDC), infectious diarrhea, inflammatory bowel disease (IBD), and irritable bowel syndrome (IBS).

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**Table 2. Research Articles**

| No | References | Interventiom /Program | Design | Population/ Sample | Program Duration | Instrument | Outcomes |
|---|---|---|---|---|---|---|---|
| 1. | Jennie Johnstone, et al (2021), Canada | Enteral l rhamnosus gg (1x10¹°) colony-forming units) (n=1321) or placebo (n=1332) twice daily in the ICU | Randomized placebo-controlled trial | 2.653 people | 60 days | Radiology | VAP |
| 2. | Andreana De Mauri, et al (2022), Italy | Probiotics- supplemented low-protein diet. | Single-center, double-blind, placebo-controlled, randomized trial | 87 subjects | 2 months | Tested through the total urine nitrogen (TUN) | The association between a low protein diet (LPD) and a new formulation of probiotics (Bifi-dobacterium Longum and Lactobacillus Reuteri) was effective at reducing traditional uremic, microbiota- derived,and proatherogenic toxins |
| 3. | Hao Lai a, et al (2023), China | A: polydextrose.<br>B: psyllium husk.<br>C: wheat bran + psyllium husk.<br>D: bifidobacterium animalis subsp. Lactis hn019 + lacticaseibacillus rhamnosus hn001; Placebo: maltodextrin. | Double-blind, randomized, placebo-controlled trial conducted | 250 adults with functional constipation | 4 weeks | Bowel movement frequency (BMF), bristol stool scale score (BSS), degree of defecation straining (DDS) | The primary outcome was the change of BMF recorded as the number of bowel movements per week.<br><br>The secondary outcomes include the changes in BSS, DDS, fasting glucose, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, triglycerides, and gut microbiome profiles over the 4-week intervention. |

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| 4. | Cathy Alberda et al (2018), Canada | Study patients received a probiotic yogurt drink, danactive (Danone, boucherville, QC, canada) containing 10 billion CFU of lactobacillus casei sp. paracasei CNCM I-1518 (formally DN-114 001) | Pilot study, randomized trials | 32 ICU patients | 30 days | APACHE II, data collection | Thirty-two patients participated in the trial. There were no serious adverse events in the probiotic group, compared to three in the control group. AAD was documented in 12.5% of the probiotic group and 31.3% in the control group. One patient in the probiotic group developed CDI compared to three in the control group. |
| 5. | Marialines Pinto-Sanchez, et al (2017), Switzerland | Giving Bifidobacterium Longum NCC3001 is a promising treatment for IBS Patients with concomitant depression.<br><br>The patients were then randomized to receive 42 sachets of<br>Either spray-dried BL (1.0eþ10 colony-forming units/1 g powder with maltodextrin) or placebo containing 1 g malto-dextrin.<br><br>Patients were instructed to dissolve the content of the sachet in 100 to 200 | Pilot study, RCT | 44 adults with irritable bowel syndrome | 10 weeks | HAD scale, state-trait anxiety inventory [STAI], functional magnetic resonance imaging (FMRI), diarrhea or a mixed-stool pattern, mild to moderate anxiety and/or depression, data collection | The primary outcome end point was a reduction in anxiety and/or depression scores of 2 points on had scale at 6 weeks.<br><br>The secondary included improvement in anxiety and depression scores (HAD, continuous data), anxiety (state-trait anxiety inventory [STAI]), IBS global adequate relief, IBS symptoms, somatization, quality of life, changes in brain activation patterns (FMRI), serum inflammatory markers, neurotransmitters and BDNF, and urine metabonomic and stool microbiota profiles. |

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|---|---|---|---|---|---|---|---|
| | | ml lactose-free milk, soy milk, or rice milk, pre-heated to 20c. | | | | | |
| 6. | Guohua Wan et al (2019), China | Probiotics combined with early enteral nutrition facilitated recovery in patients with severe TBI | Quasi Experiment | 76 adults with severe TBI | 15 days | Data collection, GCS, SOFA, acute physiology, APACHE II, serum levels, ELISA. | Serum levels of inflammatory factors gradually decreased with increasing treatment time in both groups. However, ET-1 at 15 days, and interleukin (IL)-6, IL-10, tumor necrosis factor (TNF)-a, and CRP at 7 and 15 days decreased significantly more in the combined treatment group.<br><br>Hospitalization duration and pulmonary infection rates were also significantly reduced in the combined compared with the enteral nutrition alone group. GCS scores at 15 days were significantly lower in the combined compared with the enteral nutrition group. |
| 7. | Najmeh Seifu, et al (2022), Iran | Receive the synbiotic capsule (containing a combination of lactobacillus, bifidobacterium, streptococcus, and | Prospectively randomized | A consecutive of 42 patients admitted to the | 14 days | Data collection, NUTRIC Score | Primary outcomes of this study were energy homeostasis, nitrogen balance, muscle wasting, lipolysis, glucose homeostasis, inflammatory status, and serum endotoxin level. |

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|---|---|---|---|---|---|---|---|
| | | fructooligosaccharides) or placebo. | | edalatian medical ICU | | | |
| 8. | Qun Yan, et al (2015), China | Eligible participants are randomly assigned in doubleblind to receive either probiotics or placebo which are blinded as tablet a and tablet b for 24 months. Probiotics are provided by bifico, an over-the-counter capsule consists of live combined bifidobacterium longum, lactobacillus acidophilus, and enterococcus faecalis. The study drug and the placebo are prepared in indistinguishable tablets. For both groups, the dose is 840 mg daily, 210 mg per one pill, two pills per time, two times daily. | Double-blinded, two-arm parallel group trial. | 200 middle-aged men and women aged 30-65 years-old with impaired glucose tolerance | 24 months | Screening and treatment | Primary outcomes the primary clinical outcome is the improvement of risk of developing diabetes after administration of probiotics for 24 months.<br><br>Secondary outcomes<br>(i) the cumulative prevalence of diabetes in the two groups, (ii) the changes of blood glucose, lipid profile and insulin sensitivity in the two groups, (iii) the changes of body weight and waist circumference, (iv) the safety assessment of probiotics, (v) the change of the abundance of gut bacteria, (vi) the change of blood lipopolysaccharides (LPS) and GLP-1 levels |
| 9. | Azimeh Hasanpour, et al (2023), Iran | The participants were asked to eat probiotics capsule (one capsule/day) half an hour before soymilk | Randomized double-blind, clinical trial | 100 diabetics | 6 weeks | Randomized double-blind clinical trial | The effects of soymilk plus probiotics co-administration on cardiovascular risk factors in T2DM patients. |

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| | | consumption. The patients were visited every two weeks and were evaluated for their adherence to the prescribed diet and soymilk or cow's milk intake. | | | | | |
| 10. | Rui Zhao, et al (2017), China | Adding combination of fiber and probiotics on treating diarrhea | Designed this prospective randomized-controlled trial. | Included 120 patients | 8 days | Chi-squared test, fisher exact test, king's stool chart | The combination of fiber and probiotics was significantly effective in treating diarrhea that is associated with en in postoperative patients with GC. |