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Review

Potential Health Benefits of Probiotic Strains of *Clostridium butyricum*

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Abstract

Clostridium butyricum is a well-known Gram-positive, spore-forming, obligate anaerobic, and butyrate-producing bacterium with a few species of next-generation probiotic strains. By far, the most well-known strain is *Clostridium butyricum* CBM588 (also known as MIYAIRI 588). This strain has gained significant attention for its therapeutic potential across a variety of human health conditions. Preclinical studies have shown its ability to stabilize gut microbiota, enhance short-chain fatty acid (SCFA) production, and modulate immune responses, which contribute to its therapeutic effects in conditions such as ulcerative colitis, allergies, and cancer. We examined 28 interventional clinical trials and 7 observational studies investigating the effect of *Clostridium butyricum* strains. These studies have supported the findings of preclinical trials and demonstrated symptom improvement and immune modulation in diverse conditions. *Clostridium butyricum* CBM588 has shown efficacy in managing gastrointestinal diseases, such as acute gastroenteritis and inflammatory bowel disease, and has also proven beneficial in immune modulation, as evidenced by its positive effects in allergic rhinitis and cancer immunotherapy. Additionally, CBM588 has been reported to have a favorable safety and tolerability profile in various patient populations, including children, adults, and critically ill patients. Despite these promising results, clinical studies face limitations such as small sample sizes, varied protocols, and short study durations. Future well-designed, large-scale trials are necessary to further validate the long-term safety and efficacy of *Clostridium butyricum* in clinical practice.

Keywords: *Clostridium butyricum*; spore-forming bacteria; probiotics; health benefits

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1. Introduction

Probiotics are defined as 'live microorganisms that, when administered in adequate amounts, confer a beneficial effect on the host' [1]. There are many well-known probiotic strains supported by well-designed human clinical trials [2,3]. Using novel nomenclature [4–6], these probiotic strains include: *Bifidobacterium animalis* subsp. *lactis* BB12 [7,8], *Lactiplantibacillus plantarum* 299v (previously *Lactiplantibacillus plantarum* 299v) [9], *Limosilactobacillus reuteri* DSM 17938 [8,10], *Lacticaseibacillus paracasei* Shirota (previously *Lactobacillus casei* Shirota) [11], *Lacticaseibacillus rhamnosus* GG (previously *Lactobacillus rhamnosus* GG) [12], *Lactobacillus acidophilus* LA-5 [13], *Heyndrickxia coagulans* Unique IS-2 (previously known as *Bacillus coagulans* Unique IS2) [14], *Escherichia coli Nissle* 1917 [15], *Saccharomyces cerevisiae* var. *boulardii* [13,16] and many others as confirmed by systematic reviews and meta-analyses of clinical trials.

The most important evidence-based health benefits of probiotics include alleviation of gastrointestinal symptoms [17], modulating the immune system [18], prevention and

treatment of diarrhoea [19,20], inducing remission in inflammatory bowel disease [21] and ulcerative colitis [22], reduction of developing postoperative infectious complications [23] and other postoperative complications [24] and even mental health [25]. It is obvious that the health benefits of probiotics are not limited to one species of microorganisms and several health traits are strain-specific [1,26]. In addition to probiotics, combinations of probiotics and specific substrates have also been developed to enhance beneficial microbial activity in the gut. These combinations are referred to as synbiotics and are defined as mixtures comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confer a health benefit on the host [27].

Next-generation probiotics (NGPs) are organisms with potential health benefits, although many of these are still at the very early stage of mechanistic investigation [28,29]. NGPs are often intended to become drugs rather than dietary supplements or functional foods [30]. They are treated as non-conventional and are mainly recently discovered residents of the gut microbiota through comparative microbiota analysis using molecular methods. They include strains of *Akkermansia muciniphila*, *Bacteroides acidifaciens*, *Bacteroides fragilis*, *Bacteroides xylanisolvens*, *Christensenella minuta*, *Eubacterium hallii*, *Clostridium butyricum*, *Faecalibacterium prausnitzii*, *Prevotella copri*, *Parabacteroides goldsteinii*, and others. Sometimes they are referred to as live biotherapeutic products and can include live biotherapeutics engineered with synthetic biology tools to enhance their therapeutic functions for the treatment of human disease [29,31–34]. For example, *Faecalibacterium prausnitzii* is one of the most abundant species found in the large intestine and is reported to be depleted in individuals with inflammatory bowel disease [29]. *Akkermansia muciniphila,* also very abundant in the human intestinal microbiota, is inversely associated with obesity, diabetes, cardiometabolic diseases, and low-grade inflammation [35]. *Bacteroides fragilis* ZY-312, isolated from the feces of a healthy breastfed infant, and other strains of the *Bacteroides* genus have potential health-promoting phenotypes [29,36]. Among these next-generation probiotics, *Clostridium butyricum* represents one of the earliest and most extensively studied candidate species.

Clostridium butyricum, is a Gram-positive, obligate anaerobic, spore-forming, butyrate-producing, rod-shaped bacterium [37,38] belonging to the phylum Bacillota (previously Firmicutes) [39]. It is found in soil [40] and in sour milk and cheeses [41]. Butyric acid is an important short-chain fatty acid; its salt or ester, butyrate, is rapidly absorbed into the gut, where it acts as a signalling molecule in the gut immune cells and epithelial cells for the restoration of impaired colonic barrier function and gut homeostasis [42]. It is the main energy source for colonocytes, maintains mucosal barrier integrity, reduces pro-inflammatory cytokines and induces apoptosis [43]. Although there are some reports of pathogenicity [40,44], *Clostridium butyricum* is mainly a human commensal with beneficial effects including butyrate production, increasing levels of beneficial bacteria, and inhibition of pathogenic bacteria [14,37]. The most studied probiotic strain is *Clostridium butyricum* MIYAIRI 588 (CBM 588) [45–49]. This strain was isolated from the feces of healthy individuals in Japan in 1933 by Dr. Miyairi and has been studied for over 50 years, mainly in Asia and is used as a probiotic in clinical and veterinary medicine [29,37]. Other investigated next-generation probiotic or potential probiotic strains include *Clostridium butyricum* CCFM1299 [50], *Clostridium butyricum* M-55 [51,52], *Clostridium butyricum* FZM 240 [53], and *Clostridium butyricum* GKB7 [52]. *Clostridium butyricum* S-45-5 [54]. To better understand the therapeutic potential of these strains, it is important to consider the available preclinical evidence demonstrating strain-specific benefits in various in vitro and animal studies. In vitro studies have assessed various characteristics of *Clostridium butyricum* MIYAIRI 588 [49,55,56]. *Clostridium butyricum* FZM 240, a mutant strain engineered for enhanced therapeutic functions, has shown improved enzyme production

and tolerance [31,53]. Furthermore, *Clostridium butyricum* CCFM1299 and other strains reduced obesity in mice [50,57]. *Clostridium butyricum* S-45-5 exhibited immune modulatory effects, providing prophylactic protection against fatal doses of influenza A subtypes (H1N1, H3N2, and H9N2) [54]. *Clostridium butyricum* MIYAIRI 588 CBM588 has shown numerous benefits, including improved intestinal homeostasis and overcoming resistance to PD-1 blockade [58], modifying bacterial composition [59], protecting intestinal barrier function [60], and exhibiting anti-inflammatory effects [61] in antibiotic-induced dysbiosis in mice. Despite its long history of use and promising results from various preclinical studies demonstrating strain-specific benefits, the health effects of individual *Clostridium butyricum* strains have not yet been comprehensively and critically reviewed.

The aim of this review is to critically evaluate the established and emerging health effects of *Clostridium butyricum* strains, with a particular focus on strain-specific evidence from preclinical and clinical studies.

2. Search Strategy

Search dates: The literature search was conducted from 3 January to 5 January 2026. Search strings: In PubMed, the following search strategy was used: ("Clostridium butyricum" [Title/Abstract]) AND ("probiotic" OR "probiotics") AND ("health benefit" OR "clinical effect" OR "treatment"). In ScienceDirect, an equivalent search string adapted to the database interface was applied: ("Clostridium butyricum") AND ("probiotic" OR "probiotics") AND ("health benefit" OR "clinical effect" OR "treatment"). To provide a comprehensive overview of clinical evidence, all studies investigating the effects of *Clostridium butyricum* in humans were considered. Although this is a narrative review, both clinical trials and observational studies were included to capture a broader spectrum of evidence. Animal and in vitro studies were excluded due to their limited direct clinical relevance. Only English-language articles with full-text availability were included to ensure accurate data extraction and interpretation. Possible bias and level of evidence were assessed for each study [62,63]. The level of evidence for each study was determined according to the Oxford Centre for Evidence-Based Medicine [64]. Differences in study design and level of evidence were considered during the interpretation and discussion of the results.

3. Results

A total of 35 clinical studies were identified, including 28 interventional clinical trials and 7 observational studies investigating the health benefits of the probiotic strains of *Clostridium butyricum*, as of the 5 January 2026. For clarity and ease of comparison, the 28 clinical trials are grouped according to disease category and presented in Table 1 in descending chronological order and, within each year, alphabetically by the first author. Table 2 summarizes key characteristics of the 7 observational studies grouped according to disease category.

Table 1. Main findings of the 28 clinical trials found on *Clostridium butyricum* strains, listed by disease category.

Reference	Study Type	Investigated Aim	Population	Intervention/Dosage	Main Findings	Possible Bias	Level of Evidence
Category 1: Gastrointestinal diseases and microbiota-related conditions							
Li et al., 2020 [65], China	Open-label RCT	To develop and apply a mathematical model to simulate gut microbiota dynamics and optimize CBM588 treatment for managing irritable bowel syndrome (IBS)-associated microbiota.	61 IBS patients, 3 groups: group 1 (n = 21), group 2 (n = 22), group 3 (n = 18)	Group 1 (LP): Laxative + colonoscopy, immediately followed by 2 tablets CBM588 three times daily for 2 weeks. Group 2 (L2P): Laxative + colonoscopy, 2 tablets CBM588 three times daily 2 weeks later for 2 weeks. Group 3 (P): No laxative/colonoscopy, 2 tablets CBM588 three times daily immediately for 2 weeks.	The LP regimen (laxative followed immediately by optimized CBM588 treatment) most effectively relieved IBS symptoms and shifted gut microbiota toward a healthy profile.	Some concerns (open-label design, relatively small groups)	2
Sun et al. [66], 2018	Double-blind RCT	To assess the efficacy and safety of *C. butyricum* in the treatment of diarrhea-predominant IBS and to analyze changes in fecal microbiota after treatment.	200 patients with diarrhea-predominant IBS; 2 groups, group 1 (n = 105), group 2 (n = 95)	Group 1: *C. butyricum* * capsules (420 mg per capsule, 1.5×10^7 CFU/g), 3 capsules three times daily for 4 weeks. Group 2: Patients received matching placebo capsules with identical shape, taste, and packaging, 3 capsules three times daily for 4 weeks.	Compared with placebo, *C. butyricum* significantly improved overall IBS symptoms, quality of life, and stool frequency. *C. butyricum* treatment was associated with favorable changes in fecal microbiota. The intervention was considered safe and effective for clinical use in IBS patients.	Low risk (double-blind, placebo-controlled RCT, large sample)	2

Table 1. *Cont.*

Reference	Study Type	Investigated Aim	Population	Intervention/Dosage	Main Findings	Possible Bias	Level of Evidence
Chen et al. 2018 [67], China	Open-label RCT	To investigate the effects of CBM588 on gut microbiota and gastrointestinal symptoms in patients undergoing *Helicobacter pylori* eradication therapy.	105 adults, 3 groups. Group 1: (n = 35). Group 2: (n = 35). Group 3: (n = 35)	Group 1: *H. pylori*-positive patients received BQT supplemented with CBM588, 40 mg three times daily) for 14 days. Group 2: *H. pylori*-positive patients received 14-day bismuth-containing quadruple therapy (BQT). Group 3: *H. pylori*-negative patients, no eradication therapy.	Probiotic supplementation with CBM588 was associated with improved gastrointestinal symptoms and favorable alterations in gut microbiota composition, including an increased Bacteroidota vs. Bacillota ratio (previously Bacteroidetes vs. Firmicutes ratio) ** ratio, compared with eradication therapy alone.	Some concerns (open-label design)	2
Yasueda 2016, [68], Japan	RCT	To evaluate the safety and efficacy of CBM588 for the prevention of pouchitis in ulcerative colitis (UC) patients.	17 patients with UC undergoing total proctocolectomy with ileal pouch anal anastomosis (IPAA); 2 groups: group 1 (n = 9), group 2 (n = 8)	Group 1: 9 tablets of MIYA-BM® (20 mg of CBM588 per tablet) orally once daily, administered after surgery or ileostomy closure depending on surgical stage. Group 2: 9 matching placebo tablets containing lactose, orally once daily, administered in the same schedule as the CBM588 group.	Probiotic therapy with CBM588 achieved favorable results in preventing pouchitis. Therapy was well tolerated with no side effects, might be a useful complementary therapy for the prevention of pouchitis inpatients with UC who have undergone IPAA.	Some concerns (very small sample)	2

Table 1. *Cont.*

Reference	Study Type	Investigated Aim	Population	Intervention/Dosage	Main Findings	Possible Bias	Level of Evidence
Investigating group, 2012 [69], China ##	RCT	To evaluate the efficacy and safety of the live *C. butyricum* and *Bifidobacterium* to prevent antibiotic-associated diarrhea (AAD) in hospitalized children with pneumonia.	380 hospitalized children with pneumonia aged from 3 months to 3 years, 2 groups: group 1 (n = 193), group 2 (n = 179).	Group 1: 5×10^9 CFU of *C. butyricum* * and *Bifidobacterium* combined powder daily for 7 days alongside antibiotics. Group 2: Antibiotic therapy. No probiotics.	Daily administration of *C. butyricum* and *Bifidobacterium* powder during antibiotic therapy significantly reduces the risk of antibiotic-associated diarrhea in young, hospitalized children, without any observed adverse effects.	Some concerns (no placebo)	2
Sato et al., 2012 [70], Japan	Prospective, non-randomized interventional cohort study	To investigate the effects of CBM588 in patients with ulcerative colitis (UC).	27 UC patients, 2 groups: group 1 (n = 15), group 2 (n = 12).	Group 1 (distal UC): patients with distal UC, initially treated with mesalazine or salazosulfapyridine (5-ASA) and subsequently received CBM588 (3.0 g/day) in addition to 5-ASA for 4 weeks. Group 2 (pancolitis UC): patients with pancolitis, initially treated with mesalazine or salazosulfapyridine (5-ASA) and subsequently received CBM588 (3.0 g/day) in addition to 5-ASA for 4 weeks.	After 4 weeks, the patients with pancolitis UC showed significantly higher % chenodeoxycholic acid (CDCA) and lower % deoxycholic acid (DCA) compared to healthy controls, while no significant changes were observed in the distal UC group. Probiotic therapy restored intestinal microbiota involved in 7α-dehydroxylation in the distal UC group, but not in the pancolitis UC group.	High risk (non-randomized, small sample)	3

Table 1. *Cont.*

Reference	Study Type	Investigated Aim	Population	Intervention/Dosage	Main Findings	Possible Bias	Level of Evidence
Imase et al. 2008, [71], Japan	RCT	To evaluate the preventive effect of CBM588 on antibiotic-associated diarrhea and intestinal microbiota alterations during *H. pylori* eradication therapy.	19 *H. pylori*-positive patients with peptic ulcer disease, 3 groups: group 1 (n = 7), group 2 (n = 5), group 3 (n = 7)	Group 1: *H. pylori* eradication therapy plus CBM588 (MIYA-BM tablets; ~10^7 CFU/tablet). Group 2: *H. pylori* eradication therapy plus CBM588 (MIYA-BM tablets; ~10^7 CFU/tablet) at a double dose. Group 3: *H. pylori* eradication therapy. No probiotics.	Diarrhea incidence decreased dose-dependently with CBM588 (43% no probiotic, 14% regular dose, 0% double dose). Double-dose CBM588 preserved obligate anaerobes with *C. difficile* toxin A not detected in this group.	High risk (very small sample size, unequal groups)	2
Fujii et al., 2006 [72], Japan ##	Prospective, multi-group interventional study	To investigate the effect of CBM588, when combined with vancomycin in the treatment of *Clostridium difficile*-associated diarrhea (CDAD).	71 patients suffering from CDAD, 3 groups, group sizes not reported	Group 1: Vancomycin with CBM588 (~10^7 CFU/tablet). Group 2: Vancomycin with *Streptococcus faecalis* Group 3: Vancomycin alone. No probiotics.	Co-administration of vancomycin with CBM 588 significantly reduced daily stool frequency compared to vancomycin alone ($p < 0.05$) and shortened the duration of vancomycin treatment, indicating a beneficial effect in CDAD. No significant effect was observed with vancomycin plus *Streptococcus faecalis.*	High risk (non-randomized, group sizes not reported)	3
Shimbo et al., 2005 [73], Japan	RCT	To assess the effect of CBM588 on intestinal microbiota changes during *H. pylori* eradication therapy.	35 *H. pylori*-positive patients with gastric or duodenal ulcers, 2 groups: group 1 (n = 18), group 2 (n = 17).	Group 1: CBM588 (120 mg three times daily) administered 7 days prior to and during triple therapy, plus eradication therapy as in group 2. Group 2: Triple therapy for 7 days (amoxicillin 1500 mg, clarithromycin 400 mg, lansoprazole 60 mg, all two times daily). No probiotics.	Obligate anaerobes decreased significantly in the control group but remained stable in the CBM588 group.	Some concerns (no placebo, small groups)	2

Table 1. *Cont.*

Reference	Study Type	Investigated Aim	Population	Intervention/Dosage	Main Findings	Possible Bias	Level of Evidence
Guo et al., 2004, [74], China ##	RCT	To assess the efficacy and safety of CBM588 for the eradication of *H. pylori* and for the prevention of antibiotic-associated diarrhea during the therapy.	88 adults with symptomatic *Helicobacter pylori* infection, 2 groups: group 1 (n = 44), group 2 (n = 44).	Group 1: CBM588 (1×10^7 cfu/day with eradication therapy, tablet, for one week. Group 2: Eradication therapy. No probiotics.	The probiotic group showed a numerically higher eradication rate than the control group (94% vs. 88%), with reported prevention of antibiotic-associated diarrhea.	Some concerns (no placebo)	2
Seki et al., 2003 [75], Japan	Prospective, multi-group interventional study	To examine the effect of CBM588 on antibiotic-associated diarrhea in children.	110 children (1 month–15 years) with upper respiratory tract infection or gastroenteritis, 3 groups: group 1 (n = 38), group 2 (n = 45), group 3 (n = 27)	Group 1: Antibiotics + CBM588 (10^7 CFU/g; 1–4 g/day) introduced at the midpoint of therapy. Group 2: Antibiotics + CBM588 (10^7 CFU/g; 1–4 g/day) administered concomitantly from the start of therapy. Group 3: Antibiotic therapy only.	Incidence of diarrhea was 59% in the antibiotics-only group, compared to 5% and 9% in the CBM588 midpoint and concomitant groups, respectively. Antibiotic therapy markedly reduced total fecal anaerobes, especially *Bifidobacterium*, whereas CBM588 administration increased anaerobes and prevented the decrease in *Bifidobacterium*.	Some concerns (non-randomized, no blinding, unequal groups)	3
Category 2: Gastrointestinal surgery and perioperative applications							
Radice et al., 2025 [76], Italy	Pilot RCT	To investigate immune and inflammatory modulation by probiotics in colorectal surgery	15 patients undergoing colorectal surgery, 3 groups, 5 per group.	Group 1: CBM 588 ($\geq 4.5 \times 10^5$ CFU per tablet, two tablets daily). Group 2: *Bifidobacterium longum* ES1 (1×10^9 CFU/day). Group 3: No probiotics.	Reduction in overall infectious complications and inflammation after colorectal surgery for groups 1 and 2.	High risk (small sample, pilot study, no blinding)	2

Table 1. *Cont.*

Reference	Study Type	Investigated Aim	Population	Intervention/Dosage	Main Findings	Possible Bias	Level of Evidence
Yang et al., 2025 [77], China	Open-label RCT	To update and expand evidence-based evidence on probiotics in postoperative colorectal cancer management.	400 patients, 2 groups, 200 per group	Group 1: CBM588 (40 mg CBM588 orally three times daily from 5 days before surgery to 7 days after surgery, except on the day of surgery). Group 2: No probiotics.	CBM588 promoted recovery of intestinal function following radical colorectal surgery, reduced postoperative infectious complications, and enhanced systemic immune responses.	Some concerns (open-label, no placebo)	2
Cao et al. 2022 [78], China	Double-blind RCT	To investigate the effect of oral *C. butyricum* CGMCC0313.1 on early postoperative recovery, inflammation, gut microbiota composition, and short-chain fatty acid (SCFA) levels in patients following gastrectomy.	100 patients following gastrectomy, 2 groups, 50 patients per group	Group 1: *C. butyricum* CGMCC0313.1, 6 capsules/day (2× daily) for 21 days post-gastrectomy. Group 2: Placebo capsules, identical in appearance and taste, 6 capsules/day (2× daily) for 21 days post-gastrectomy.	Oral administration of *C. butyricum* CGMCC0313.1 after gastrectomy can reduce early postoperative inflammation, enhance immune ability, restore intestinal microbiota eubiosis, increase intestinal SCFAs, reduce the occurrence of postoperative complications, and ultimately promote the early recovery of the patient.	Low risk (double-blind, placebo-controlled RCT)	2
Iida et al., 2020 [79], Japan	Non-randomized controlled study	To clarify the influence of preoperative symbiotic therapy containing CBM588 on surgical-site infections after hepatic resection.	284 patients who underwent hepatic resection without biliary tract reconstruction and resection of other organs, 2 groups, group 1 (n = 115), group 2 (n = 169)	Group 1: CBM588 in dose of 6.0 g/day plus partially hydrolyzed guar gum for 2 weeks preoperatively. Group 2: Standard preoperative care for hepatic resection, which did not include synbiotics.	Preoperative synbiotic treatment using CBM588 combined with partially hydrolyzed guar gum did not significantly reduce the incidence of surgical-site infections after hepatic resection when compared with conventional treatment.	Some concerns (non-randomized, potential selection bias)	3

Table 1. *Cont.*

Reference	Study Type	Investigated Aim	Population	Intervention/Dosage	Main Findings	Possible Bias	Level of Evidence
Chen et al., 2016 [80], China	RCT	To determine if administration of probiotics improves symptomatic gastrointestinal (GI) episodes after gastric bypass surgery.	60 patients who underwent gastric bypass for severe obesity and experienced postoperative symptomatic GI episodes, 3 groups, 20 per group	Group 1: 1 g CBM588 (5×10^9 CFU) orally twice daily for 2 weeks. Group 2: 300 mg *Bifidobacterium longum* BB536 (8×10^9 CFU) orally twice daily for 2 weeks. Group 3 (Digestive enzymes): Aczym (100 mg takadiastase N, 20 mg cellulase AP, 50 mg lipase MY, 100 mg pancreatin) orally twice daily for 2 weeks.	Both probiotics improved postoperative GI symptoms and quality of life, as measured by the modified Gastrointestinal Quality of Life Index (mGIQLI), compared with digestive enzymes.	Some concerns (small sample, active comparator instead of placebo)	2
Category 3: Oncology and immunotherapy							
Wang et al., 2025 [81], Taiwan	Randomized, single-blind, 2-year crossover trial	To evaluate the efficacy of probiotics in preventing colorectal adenoma recurrence.	398 patients with a history of adenomatous polyps, 2 groups, 199 per group	Group 1: CBM588 (40 mg CBM588/g; 1 g per packet, orally twice daily) in year 1, followed by 3-month washout, no treatment in year 2. Group 2: No treatment) in year 1, CBM588 (same dose) in year 2.	CBM588 demonstrated potential to reduce colorectal adenoma recurrence in high-risk patients, supporting its role as a feasible, non-invasive preventive strategy.	Some concerns (single-blind, crossover design)	2

Table 1. *Cont.*

Reference	Study Type	Investigated Aim	Population	Intervention/Dosage	Main Findings	Possible Bias	Level of Evidence
Ebrahimi et al., 2024 [82], USA	Open-label RCT	To evaluate the effect *of* CBM588 in combination with cabozantinib plus nivolumab on gut microbiome modulation in patients with metastatic renal cell carcinoma (mRCC).	30 patients with locally advanced or metastatic renal cell carcinoma, 2 groups: group 1 (n = 20), group 2 (n = 10)	Group 1: Cabozantinib (40 mg orally once daily) + nivolumab (480 mg IV every 4 weeks) + CBM588 (80 mg orally twice daily). Group 2: No probiotics, Cabozantinib (40 mg orally once daily) + nivolumab (480 mg IV every 4 weeks).	Although the addition of CBM588 to cabozantinib and nivolumab did not significantly alter *Bifidobacterium* levels or overall gut microbiome diversity, it showed a preliminary signal of improved clinical outcomes in treatment-naive patients with metastatic renal cell carcinoma without increasing toxicity.	High risk (small sample, open-label, unequal groups)	2
Dizman et al., 2022 [83], USA	Open-label RCT	To evaluate the effects of CBM588 inpatients with mRCC receiving nivolumab and ipilimumab.	29 treatment-naive patients with mRCC (clear cell and/or sarcomatoid histology, 2 groups: group 1 (n = 19), group 2 (n = 10)	Group 1: Nivolumab 3 mg/kg IV every 3 weeks + Ipilimumab 1 mg/kg IV every 3 weeks for 12 weeks. Followed by Nivolumab 480 mg IV monthly + CBM588: 80 mg orally twice daily (2 × 40 mg sachets; ~4 × 10^8 CFU CBM588 daily). Group 2: No probiotics, same nivolumab + ipilimumab schedule.	The addition of CBM588 to standard first-line immunotherapy with nivolumab and ipilimumab was well tolerated and did not increase toxicity. Although CBM588 did not significantly modulate gut microbiota, patients receiving the probiotic showed a notable improvement in clinical outcomes, including longer disease control and higher response rates compared with those receiving immunotherapy alone.	High risk (small sample, open-label, unequal groups)	2

Table 1. *Cont.*

Reference	Study Type	Investigated Aim	Population	Intervention/Dosage	Main Findings	Possible Bias	Level of Evidence
Sandhu et al., 2021 [84], USA	Open-label RCT **	To determine the safety, feasibility, biologic activities, and preliminary efficacy of CBM588 in Hematopoietic Cell Transplantation (HCT) recipients.	36 patients undergoing HCT, 2 groups: group 1 (n = 21), group 2 (n = 15)	Group 1: CBM588, 160 mg orally twice daily, administered from day −8 or hospital admission until day +28 or discharge, in addition to standard peri-transplant supportive care. Group 2: Received standard care. No probiotics.	Administration of CBM588 during the peri-transplant period was feasible and safe, with no serious adverse events attributed to the probiotic. CBM588 demonstrated a favourable biological impact on the gut microbiome and suggested potential early clinical benefit in older patients receiving reduced-intensity conditioning hematopoietic cell transplantation.	Some concerns (open-label design, small sample)	2
Category 4: Immune-mediated and allergic diseases							
Xu et al., 2016 [85], China	RCT	To evaluate whether co-administration of *C. butyricum* enhances the efficacy of allergen-specific immunotherapy (SIT) in patients with allergic rhinitis (AR).	158 patients with AR for more than two years, sensitized only to house dust mite, without asthma or chronic rhinosinusitis, and naïve to allergen-specific immunotherapy. 4 groups: group 1 (n = 44), group 2 (n = 48), group 3 (n = 20), group 4 (n = 46)	Group 1: SIT injections + *Clostridium butyricum* # capsules (420 mg/capsule), twice daily. Group 2: Placebo injections + *Clostridium butyricum* capsules (420 mg/capsule), twice daily. Group 3: Placebo injections + placebo capsules, twice daily. Group 4: Patients received SIT injections + placebo capsules, twice daily.	Co-administration of *C. butyricum* enhanced the efficacy of SIT, improving nasal symptom scores, medication scores, serum specific IgE levels, Th2 cytokines, and skin prick test index. Regulatory B cell frequency increased, and the beneficial effect persisted throughout the 12-month observation period.	Some concerns (multiple groups, unclear blinding)	2

Table 1. *Cont.*

Reference	Study Type	Investigated Aim	Population	Intervention/Dosage	Main Findings	Possible Bias	Level of Evidence
Liao et al., 2016 [86], China	RCT	To modulate antigen-specific B cell function and improve the efficacy of allergen-specific immunotherapy (SIT) in asthma patients by co-administration of *C. butyricum*.	56 asthma patients with mild to moderate symptoms, solely sensitized to house dust mite. 4 groups: group 1 (n = 14), group 2 (n = 13), group 3 (n = 14), group 4 (n = 15)	Group 1: Allergen immunotherapy injections + *C. butyricum* # capsules (420 mg/capsule) twice daily. Group 2: Placebo injections + *C. butyricum* capsules (420 mg/capsule) twice daily. Group 3: Saline injections + placebo capsules. Group 4: Allergen immunotherapy injections + placebo capsules.	The combination of allergen-specific immunotherapy and *C. butyricum* improved clinical asthma symptoms, reduced serum levels of allergen-specific IgE, and enhanced regulatory B cell function.	Some concerns (small sample, unclear blinding)	2
Category 5: Metabolic and systemic diseases							
Lu et al., 2023 [87], China	Single-blind RCT	To investigate the effects of synbiotics on gut microbiota and function, and to assess whether symbiotic supplementation provides benefits for patients with cirrhosis.	Adults with histologically confirmed stable cirrhosis and BMI < 25 kg/m^2, 4 groups: group 1 (n = 29), group 2 (n = 21), group 3 (n = 57), group 4 (n = 30)	Group 1: Synbiotic-treated group (10 g packet of lactulose oral solution and three capsules of probiotics (each containing >4.2 × 10^6 CFU *C. butyricum* ** and > 4.2 × 10^5 CFU *Bifidobacterium longum infantis*) three times daily. Group 2: Placebo (10 g packet of glucose oral solution and three capsules of starch) three times daily. Group 3: Non–intervention group. Group 4: Healthy controls.	The synbiotic intervention showed limited effects on clinical parameters in early-stage cirrhotic patients but improved intestinal dysbiosis and metabolic alterations.	Some concerns (single-blind, multiple groups, variable sizes)	2

Table 1. *Cont.*

Reference	Study Type	Investigated Aim	Population	Intervention/Dosage	Main Findings	Possible Bias	Level of Evidence
Perraudeau et al. [88], 2020, USA	Double-blind RCT	To evaluate whether a multi-strain probiotic containing butyrate-producing and gut barrier–supporting bacteria can safely improve glycemic control and systemic inflammation in adults with type 2 diabetes.	76 adults with type 2 diabetes (T2D), 3 groups: group 1 (three-strain probiotic, *n* = 27), group 2 (*n* = 23), group 3 (*n* = 26)	Group 1: Probiotic formulation containing inulin, *Clostridium beijerinckii*, *C. butyricum* * and *Bifidobacterium infantis*. Group 2: Probiotic formulation including inulin, *Akkermansia muciniphila*, *Clostridium beijerinckii*, *C. butyricum*, *Bifidobacterium infantis*, and *Anaerobutyricum hallii*. Group 3: Capsule with no live microorganisms. Three capsules twice daily with meals for 12 weeks.	Probiotic formulation WBF-011 is safe, well-tolerated, and more effective than WBF-010 in improving postprandial glucose control in adults with type 2 diabetes, particularly those on metformin monotherapy.	Low risk (double-blind, placebo-controlled RCT)	2
Category 6: Neurological and psychiatric conditions							
Miyaoka et al., 2018 [89], Japan	Open-label RCT	To evaluate the efficacy and safety of CBM588 in combination with antidepressants in adults with treatment-resistant major depressive disorder (TRD).	40 adult inpatients with TRD; 2 groups, 20 patients per group.	Group 1: CBM588, 60 mg/day (20 mg orally twice daily in week 1, then 20 mg three times daily for weeks 2–8). All patients were also on their antidepressant medications. Group 2: Antidepressant therapy without CBM588 supplementation.	CBM588 in combination with antidepressants improved depressive symptoms and was effective and well-tolerated in the treatment of TRD, with no serious adverse events reported.	Some concerns (open-label design, small sample)	2

Table 1. *Cont.*

Reference	Study Type	Investigated Aim	Population	Intervention/Dosage	Main Findings	Possible Bias	Level of Evidence
Category 7: Critical care and special populations							
Matsuoka et al., 2022 [90], Japan	RCT *	Primary aim: To determine the effects of enteral nutrition (EN) on the intestinal environment in patients in a persistent vegetative state. Secondary aim: To evaluate whether supplementation with CBM588 can prevent dysbiosis in these patients.	10 patients in a persistent vegetative state, 3 groups: group 1 (n = 5), group 2 (n = 5), group 3 (n = 10)	Group 1: EN + CBM588 (1×10^7 cfu/g, dose: 3 g/day). Group 2: EN alone. Group 3: Healthy controls	EN causes dysbiosis of the intestinal microbiota and an imbalance in some intestinal metabolites in patients in a persistent vegetative state. CBM588 improved the imbalance of some intestinal metabolites after EN, it did not prevent dysbiosis of the intestinal microbiota.	Some concerns (very small sample size, unequal groups, unclear blinding)	2
Liu et al., 2022 [91], China	Single-blind RCT	To evaluate the effects of CBM588 supplementation on gut microbiota, metabolism, nutrition, and immunity in elderly people in long-term care with malnutrition.	19 elderly individuals in long-term care (aged 83.2 $\pm$ 5.3 year) with malnutrition (MNA-SF score $\leq$ 7), 2 groups: group 1 (n = 11), group 2 (n = 8)	Group 1: CBM588 (3.5×10^5–3.5×10^8 CFU after each meal for 12 weeks). Group 2: No probiotics.	CBM588 supplementation promoted the growth of beneficial gut microbes (e.g., *Akkermansia muciniphila*), enhanced microbial functional pathways related to vitamin/cofactor production and carbohydrate metabolism, increased plasma metabolites including short-chain fatty acids (SCFAs) and amino acids, and improved immunity and nutritional biomarkers.	Some concerns (small sample size, single-blind design, unequal groups)	2

Table 1. *Cont.*

Reference	Study Type	Investigated Aim	Population	Intervention/Dosage	Main Findings	Possible Bias	Level of Evidence
Wang et al., 2021 [92], China	Single-blind RCT	To investigate whether oral CBM588 could improve the intestinal barrier function via attenuating inflammation and immunomodulation to improve the clinical outcomes in critically ill patients.	61 critically ill patients in a respiratory intensive care unit; 2 groups, group 1 (n = 28), group 2 (n = 33)	Group 1: CBM588 (MIYA-BM® tablets, 10^6 CFU per tablet), administered orally or via nasogastric/orogastric tube, three times daily. Group 2: Placebo tablet, three times daily.	Probiotic administration with CB588 in critically ill patients did not improve primary clinical outcomes such as mortality or hospital stay and had a limited impact on gut microbiota composition. However, it reduced the duration of fever, incidence of constipation, and the burden of Gram-negative bacteria in the gut.	Some concerns (single-blind design)	2

* No strain information reported in the study; ** updated bacterial phyla nomenclature [88]; # no strain information provided; ## article published in Chinese or Japanese; however, the English abstract contained sufficient information for data extraction. Abbreviations: *C. butyricum*—*Clostridium butyricum*; CBM588—*Clostridium butyricum* MIYAIRI 588; mRCC—metastatic renal cell carcinoma; RCT—randomized controlled trial; EN—enteral nutrition; SCFAs—short-chain fatty acids; HCT—hematopoietic cell transplantation; T2D—type 2 diabetes; IBS—irritable bowel syndrome; TRD—treatment-resistant major depressive disorder; BQT—bismuth-containing quadruple therapy; IPAA—ileal pouch–anal anastomosis; AR—allergic rhinitis; GI—gastrointestinal; mGIQLI—modified Gastrointestinal Quality of Life Index; AAD—antibiotic-associated diarrhea; CDCA—chenodeoxycholic acid; DCA—deoxycholic acid; CDAD—*Clostridioides difficile*-associated diarrhea. Risk of Bias was assessed for each study using a simplified, uniform approach considering study design, randomization, blinding, sample size, and control group [63]. Ratings: Low risk = well-designed RCTs with adequate blinding and controls; Some concerns = open-label, small sample, or partial blinding; High risk = non-randomized, retrospective, or very small sample size. Levels of evidence were assigned according to the Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 classification [64]: Level 1—systematic reviews or high-quality randomized controlled trials; Level 2—lower-quality randomized trials or prospective cohort studies; Level 3—retrospective cohort or case–control studies; Level 4—case series or uncontrolled observational studies; Level 5—expert opinion or mechanism-based evidence.

Table 2. Main findings of the 7 retrospective observational studies (ROSs) found on *Clostridium butyricum* strains, listed by disease category.

Reference	Investigated Aim	Population	Intervention/Dosage	Main Findings	Possible Bias	Level of Evidence
Category 1: Gastrointestinal diseases and microbiota-related conditions						
Urgesi et al., 2025 [93], Italy	To compare the clinical outcomes of patients with symptomatic uncomplicated diverticular disease treated with either CBM588 or cyclic rifaximin over a 12-month period.	70 patients with confirmed symptomatic uncomplicated diverticular disease, 2 groups: group 1 (n = 35), group 2 (n = 35).	Group 1: CBM588, 3 × 30 mg tablets/day ($\geq 4.5 \times 10^5$ CFU/tablet), continuously for 1 month, then 14 days/month for 11 months. Group 2: Rifaximin 400 mg twice daily for 7–10 days/month for 12 months.	CBM588 was safe and showed similar efficacy to rifaximin in preventing diverticulitis, with potential benefits in reducing symptom frequency and severity in patients with symptomatic uncomplicated diverticular disease.	Selection bias, small sample	3b
Lee et al. 2022 [94], Republic of Korea	To evaluate the clinical efficacy of probiotic therapy for IBS-like symptoms in ulcerative colitis (UC) patients in endoscopic remission	43 patients with UC and persistent IBS-like symptoms.	Biotop capsule® *Lactobacillus acidophilus* 75 mg, *C. butyricum* TO-A 25 mg, *Bacillus mesentericus* TO-A 25 mg, *Streptococcus faecalis* T-110 5 mg; administered three times daily for 4 weeks	Probiotic therapy improved bowel-related symptoms and quality of life in UC patients with IBS-like symptoms during endoscopic remission, including stool frequency and stool form.	Selection bias, small sample	4
Category 2: Gastrointestinal surgery and perioperative applications						
Fukushima et al., 2024 [95], Japan	To evaluate the effect of CBM588 on intestinal microbiota composition in the early post-haematopoietic stem-cell transplantation (HSCT) period.	37 patients undergoing allogeneic HSCT, 2 groups: group 1 (n = 11), group 2 (n = 26).	Group 1: CBM588 60 mg daily in addition to standard postoperative antimicrobials. Group 2: Standard postoperative antimicrobials	CBM588 maintained α-diversity and gut microbiota structure post-transplant. 1-year survival: 81.8% in CBM588 group vs. 69.2% in control group.	Small sample	3b

Table 2. *Cont.*

Reference	Investigated Aim	Population	Intervention/Dosage	Main Findings	Possible Bias	Level of Evidence
Category 3: Oncology and immunotherapy						
Tomita et al., 2023 [96], Japan	To evaluate the effect of CBM588 on overall survival and efficacy of chemoimmunotherapy combinations in patients with advanced non-small-cell lung cancer (NSCLC).	100 patients with stage IV or recurrent metastatic NSCLC, 2 groups: group 1 (n = 45), group 2 (n = 55).	Group 1: CBM588 (MIYA-BM®) administered orally within 3 weeks before or concurrently with chemoimmunotherapy until cessation. Group 2: Chemoimmunotherapy. No probiotics.	CBM588 significantly improved overall survival in NSCLC patients receiving chemoimmunotherapy. CBM588 may enhance the efficacy of chemoimmunotherapy via modulation of commensal gut microbiota.	Selection bias, small sample, confounding, information bias.	3b
Tomita et al., 2022 [97], Japan	To investigate the effect of CBM588 on the efficacy of immune checkpoint blockade (ICB) therapy and gut microbiota in advanced non-small-cell lung cancer (NSCLC) patients, especially those receiving proton pump inhibitors (PPIs).	118 patients with advanced or recurrent NSCLC, 2 groups: group 1 (n = 72), group 2 (n = 46).	Group 1: ICB therapy in addition to PPI use. Group 2: ICB therapy without PPI use. Additional therapy analyzed: CBM588 (MIYA-BM®) prescribed within six months before or concurrently with ICB therapy. Dose not specified.	CBM588 restored the diminished efficacy of ICB therapy in NSCLC patients receiving PPIs, improving overall survival. PPI use was associated with a higher abundance of harmful oral-related bacteria, whereas CBM588 reduced these bacteria and improved the gut microbiota.	Selection bias, small sample, information bias (unclear dosage), confounding bias	3b
Tomita et al., 2020 [98], Japan	To evaluate the effect of CBM588 on progression-free survival and overall survival in patients with advanced non-small-cell lung cancer (NSCLC) treated with ICB.	118 patients with advanced NSCLC treated with ICB (nivolumab, pembrolizumab, or atezolizumab), 2 groups: group 1 (n = 39), group 2 (n = 79).	Group 1: CBM588, administered within 6 months before or concurrently with ICB therapy. Dose not specified. Group 2: ICB therapy. No probiotics.	CBM588 enhanced progression-free survival and overall survival in NSCLC patients receiving ICB therapy.	Selection bias, small sample, information bias (unclear dosage), confounding bias	3b

Table 2. *Cont.*

Reference	Investigated Aim	Population	Intervention/Dosage	Main Findings	Possible Bias	Level of Evidence
Category 4: Critical care and special populations						
Sato et al., 2022 [99], Japan	To assess whether prophylactic administration of CBM588 reduces the incidence of *Clostridioides difficile* infection (CDI) in critically ill ICU patients.	Adult ICU patients, 2 groups: group 1 (n = 1047), group 2 (n = 755).	Group 1: CBM588 (MIYABM®), 1 g three times daily, administered prophylactically before or at the start of enteral nutrition until ICU discharge. Group 2: No probiotics.	Prophylactic CBM588 significantly reduced CDI incidence and recurrent CDI compared with control. ICU stay was slightly shorter in patients receiving CBM588.	Selection bias, information bias	3b

Abbreviations: *Clostridium butyricum*: *C. butyricum*; CBM588: *Clostridium butyricum* MIYAIRI 588; HSCT: post-haematopoietic stem-cell transplantation; NSCLC: non-small-cell lung cancer; ICB: immune checkpoint blockade; PPI: proton pump inhibitors; CDI: *Clostridioides difficile* infection; IBS: Irritable Bowel Syndrome. Risk of bias was assessed for retrospective observational study design using a simplified, uniform approach [62]. Ratings: Selection bias—non-random assignment or unequal group allocation; Information bias/measurement error—unclear or missing data, recall bias, or incomplete reporting of dose/outcome; Confounding—uncontrolled variables that may influence results. Small sample size—limited statistical power to detect effects. Levels of evidence were assigned based on the Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 classification: Level 1: Evidence from systematic reviews or high-quality randomized controlled trials (RCTs); Level 2: Evidence from well-designed prospective cohort studies or lower-quality RCTs; Level 3: Evidence from retrospective cohort studies or case–control studies; Level 3b: Individual retrospective cohort study or case–control study; Level 4: Evidence from case series or observational studies without a control group; Level 5: Evidence from expert opinion, mechanism-based reasoning, or laboratory research.

4. Discussion

Clostridium butyricum is an important butyrate-producing commensal intestinal bacterium and several strains have been used as probiotics in a wide range of human diseases [100]. Butyrate-producing bacteria ferment undigested carbohydrates in the intestinal lumen to produce butyric acid and butyrate, which mediate the intestinal barrier, have salutary effects on intestinal epithelial cells and mitigating effects on gut inflammatory diseases [37,101–103]. The majority of clinical trials and observational studies included in our review investigated the strain *Clostridium butyricum* MIYAIRI 588 (CBM588) [65–68,70–77,79–81,83,84,89–93,95–99]. However, several in vitro and in vivo studies have explored other strains as well [31,53,78,94]. These studies have demonstrated that, apart from CBM588, other *Clostridium butyricum* strains also offer promising benefits in various preclinical models. For instance, *Clostridium butyricum* MIYAIRI 588 (CBM588) has shown significant effects in stabilizing the gut microbiota in piglets [45], reducing *Clostridioides difficile*-induced diarrhoea in rats [104], was safe and well-tolerated in broilers, piglets, and turkeys [46] and improved the number of $CD4^+$T cells in dairy cows [105]. Both *Clostridium butyricum* CBM588 and CGMCC0313.1 suppressed experimental acute pancreatitis in mice [106], while *Clostridium butyricum* combined with germinated barley was effective against ulcerative colitis in rats [107,108]. In contrast, *Clostridium tyrobutyricum*, but not *Clostridium butyricum*, protected prenatal neonates from necrotizing enterocolitis (NEC) in a mouse study. It restored intestinal barrier integrity, alleviated inflammation, and increased *Akkermansia muciniphila* levels [109]. However, the *Clostridium butyricum* strain used (ATCC 19398) originated from a pig intestine, which might not be compatible with mice, potentially explaining conflicting results. This highlights the importance of strain-specific probiotic properties [3].

Additional strains, such as *Clostridium butyricum* DKU_butyricum 4-1, isolated from infants, has been fully sequenced [38]. Rapid species identification and partial strain differentiation of *Clostridium butyricum* by PCR has been developed [110]. Overall, these preclinical studies emphasize the strain-specific beneficial effects of *Clostridium butyricum* on gut microbiota composition, intestinal barrier function, metabolic regulation, and immune modulation across various animal models. However, when addressing gut microbiota composition, it remains challenging to draw firm conclusions on a "healthy" human microbiome as it is not universally defined. Recently, the International Scientific Association for Probiotics and Prebiotics published a new consensus document stating that gut health is defined as "a state of normal gastrointestinal function without active gastrointestinal disease and gut-related symptoms that affect quality of life" [111–115].

Based on these preclinical findings, a growing number of clinical studies have investigated the therapeutic potential of *Clostridium butyricum* across diverse human conditions, including gastrointestinal disorders, postoperative recovery, metabolic and immune modulation, and cancer immunotherapy. Clinical research included both randomized controlled trials (RCTs), in which participants are randomly assigned to intervention or control groups to evaluate the efficacy of a treatment, and retrospective observational studies (ROSs), with the latter reviewing existing patient data to analyze outcomes and complement the evidence from interventional trials [116,117].

4.1. Application of Clostridium butyricum Strains in Gastrointestinal Diseases and Microbiota-Related Conditions

CBM588 has shown promise in chronic gastrointestinal disorders. In symptomatic uncomplicated diverticular disease, long-term administration demonstrated comparable efficacy to rifaximin in preventing diverticulitis while reducing symptom burden, as shown by Urgesi et al. 2025 [93]. In irritable bowel syndrome, optimized regimens combining

bowel preparation with CBM588 produced the most pronounced symptom relief and favorable microbiota shifts in the study by Li et al., 2020 [65], while earlier work in diarrhea-predominant IBS by Sun et al. 2018 [66] confirmed improvements in stool frequency, quality of life, and microbial composition. In ulcerative colitis, the evidence base remains modest but suggests potential benefits in specific clinical scenarios. CBM588 has been associated with the prevention of pouchitis after ileal pouch–anal anastomosis in the study by Yasueda et al. 2016 [68] and with modulation of bile acid metabolism in distal ulcerative colitis, as demonstrated by Sato et al. 2012 [70], supporting a mechanistic link between *C. butyricum*, bile acid homeostasis, and mucosal health. Patients with ulcerative colitis in endoscopic remission but persistent IBS-like symptoms also experienced symptomatic improvement when receiving probiotic formulations containing *C. butyricum*, as reported by Lee et al. 2022 [94]. In a recent review, conducted on the effects of probiotics, available in Japan, on acute gastroenteritis in children, it was found that certain strains of *Clostridium butyricum* as well as strains of *Bifidobacterium* spp., *Lactobacillus acidophilus*, *Enterococcus faecium*, and *Bacillus subtilis* may improve diarrhea approximately one day earlier [118]. Several studies in our review addressed the effect of probiotic supplementation as an adjuvant in *Helicobacter pylori* eradication therapy [67,71,73,74]. The use of probiotics to supplement standard therapy in patients infected with *H. pylori* increased the eradication rate of the organism and decreased the overall rate of adverse events, independent of patient age, genera or dosage of probiotics, time of standard therapy or assessment, and therapy regimen [74,119,120]. Supplementation with *Bacillus mesentericus*, *Clostridium butyricum* and *Streptococcus faecalis* was most beneficial for *Helicobacter pylori* eradication rates in pediatric patients [121]. In the clinical trials included in our review, CBM588 reduced antibiotic-associated diarrhea, stabilized obligate anaerobes during eradication therapy, and in some cases, modestly improved eradication rates, with dose-dependent preservation of gut microbiota observed in both adult and pediatric populations [67,71,73,74]. Similar protective effects have been reported in *Clostridioides difficile*-associated diarrhea, where co-administration of CBM588 with vancomycin reduced stool frequency and shortened treatment duration in the study by Fujii et al. 2006 [72]. In pediatric populations, CBM588 combined with *Bifidobacterium* significantly reduced antibiotic-associated diarrhea in children with pneumonia, as shown by Zheng et al. 2012 [69]. An earlier study by Seki et al. 2003 [75] demonstrated substantial reductions in diarrhea incidence and preservation of beneficial anaerobes in children receiving antibiotics for respiratory or gastrointestinal infections. The most consistent and clinically relevant results is observed in antibiotic-associated diarrhea and adjunctive therapy during *Helicobacter pylori* infection eradication, where multiple studies reported protective effects on gut microbiota and reduced gastrointestinal side effects. These findings suggest that *Clostridium butyricum* strains have promising potential in selected gastrointestinal indications, particularly where microbiota disruption played a central role in disease pathophysiology, but the overall evidence base remains inconsistent due to heterogeneous study designs, co-interventions, and probiotic formulations.

4.2. Application of Clostridium butyricum Strains in Gastrointestinal Surgery and Perioperative Applications

In colorectal surgery, randomized trials by Radice et al. 2025 [76] and Yang et al. 2025 [77] demonstrated that perioperative supplementation with CBM588 can reduce infectious complications, improve inflammatory profiles, and accelerate the return of bowel function. These findings were observed both in a small pilot setting and in a large multicenter cohort, suggesting that CBM588 may enhance postoperative recovery pathways in colorectal cancer surgery [76,77]. Beyond colorectal procedures, postoperative recovery after gastrectomy also appears to benefit from *C. butyricum* supplementation. In this context, Cao et al. 2022 [78] showed that administration of the CGMCC0313.1

strain reduced postoperative inflammation, improved immune function, restored microbial balance, and increased short-chain fatty acid production, ultimately supporting faster clinical recovery. Similarly, Seki et al. 2003 [75] reported that probiotic supplementation improved gastrointestinal symptoms and quality of life following gastric bypass surgery, highlighting a broader role for CBM588 in postoperative symptom management. An observational study by Fukushima et al. 2024 [95] demonstrated that CBM588 helped preserve gut microbial diversity in the early post-transplant period and was associated with improved survival outcomes, suggesting potential benefits in maintaining microbiome stability during intensive perioperative care.

However, not all gastrointestinal surgical settings show equally strong effects. In hepatic resection, preoperative synbiotic therapy containing CBM588 did not significantly reduce surgical-site infections, as reported by Iida et al. 2020 [79], highlighting that benefits may vary depending on the underlying pathology and surgical context. The most consistent clinical benefits of *Clostridium butyricum* strains in gastrointestinal surgery is observed in colorectal surgery and gastrectomy, where supplementation reduces postoperative infections, modulates inflammation, and supports microbiota recovery. Evidence from other surgical contexts, such as hepatic resection, remained limited or inconclusive due to small samples, open-label designs, or lack of placebo control in some studies.

4.3. Application of Clostridium butyricum Strains in Oncology and Immunotherapy

CBM588 has also gained attention in oncology, particularly as an adjunct to immunotherapy. In metastatic renal cell carcinoma, early clinical trials by Ebrahimi et al. 2024 [82] and Dizman et al. 2022 [83] combining CBM588 with nivolumab, ipilimumab, or cabozantinib suggest potential improvements in clinical outcomes without added toxicity, although effects on microbiota composition were modest. Additional evidence from hematopoietic cell transplantation indicates that CBM588 is safe and feasible, with favorable microbiota modulation and signals of early clinical benefit, particularly in patients undergoing intensive immunosuppressive therapy, as reported by Sandhu et al. 2021 [84]. A randomized crossover trial by Wang et al. 2025 [81] demonstrated that CBM588 may reduce colorectal adenoma recurrence in high-risk patients, supporting its role as a non-invasive strategy for colorectal cancer prevention.

The most compelling oncological evidence comes from advanced non-small-cell lung cancer, where multiple retrospective analyses by Tomita et al. 2020, 2022, and 2023 [96–98] show that CBM588 enhances both progression-free and overall survival in patients receiving immune checkpoint inhibitors or chemoimmunotherapy. Notably, CBM588 appears to counteract the negative impact of proton pump inhibitors on immunotherapy efficacy. These findings support the hypothesis that CBM588 may enhance antitumor immunity through microbiota-mediated mechanisms. Overall, CBM588 shows the clearest clinical signal as an adjunct to immunotherapy in advanced non-small-cell lung cancer, with retrospective analyses indicating improvements in progression-free and overall survival. Early-phase studies in metastatic renal cell carcinoma and hematopoietic cell transplantation suggest safety, feasibility, and modest clinical or microbiota benefits. Evidence for colorectal adenoma prevention is limited to a single randomized crossover trial. Across oncology indications, the strength of evidence is restricted by small sample sizes, retrospective study designs, and concomitant therapies, precluding definitive conclusions on efficacy.

4.4. Application of Clostridium butyricum Strains in Immune-Mediated and Allergic Diseases

The immunomodulatory properties of *C. butyricum* extend beyond gastrointestinal and critical-care contexts. In allergic rhinitis, co-administration of CBM588 with allergen-specific immunotherapy enhanced clinical efficacy, reduced medication use, and increased

regulatory B cell frequency in the study by Xu et al. 2016 [85]. Similar benefits were observed in asthma, where CBM588 improved clinical symptoms and modulated allergen-specific immune responses, as demonstrated by Liao et al. 2016 [86]. These findings align with broader evidence that *C. butyricum* can modulate inflammatory pathways, enhance mucosal immunity, and support systemic immune homeostasis [85,86,91]. *Clostridium butyricum* strains show promising immunomodulatory effects in allergic rhinitis and asthma, with studies suggesting improvements in clinical symptoms, reduced medication use, and modulation of allergen-specific immune responses. However, evidence is limited to a small number of trials with heterogeneous designs (e.g., differences in sample size, randomization, blinding, and follow-up duration) and co-interventions (e.g., concomitant allergen immunotherapy or other medications), which constrain the ability to draw firm conclusions regarding its efficacy across immune-mediated and allergic diseases.

4.5. Application of Clostridium butyricum Strains in Metabolic and Systemic Diseases

In metabolic and chronic systemic conditions, the evidence is more limited but suggests potential benefits. In early-stage cirrhosis, synbiotic supplementation including CBM588 improved dysbiosis and metabolic alterations, although clinical outcomes remained largely unchanged, as reported by Lu et al. 2023 [87]. In type 2 diabetes, multi-strain probiotic formulations containing *C. butyricum* improved postprandial glucose control and reduced systemic inflammation in the study by Perraudeau et al. 2020 [88]. *Clostridium butyricum* strains show potential benefits in metabolic and systemic diseases, particularly in modulating gut microbiota, metabolic parameters, and systemic inflammation. Evidence is strongest for type 2 diabetes, while effects in early-stage cirrhosis are more modest.

4.6. Application of Clostridium butyricum Strains in Neurological and Psychiatric Conditions

In neurological and psychiatric conditions, evidence for CBM588 is extremely limited. In a small open-label RCT in treatment-resistant major depressive disorder, adjunctive CBM588 improved depressive symptoms and was well tolerated [89]. However, the small sample size and open-label design restrict confidence in these findings, highlighting the need for larger, controlled studies to establish efficacy in this context.

4.7. Application of Clostridium butyricum Strains in Critical Care and Special Populations

In critically ill and specific populations, CBM588 has demonstrated protective effects in settings characterized by profound dysbiosis. In respiratory intensive care units, supplementation reduced fever duration, constipation, and the burden of Gram-negative bacteria, although it did not significantly affect mortality or length of stay, as reported by Wang et al. 2021 [92]. Among elderly individuals with malnutrition in long-term care, CBM588 increased beneficial microbial taxa such as *Akkermansia muciniphila*, enhanced metabolic pathways related to vitamin and carbohydrate metabolism, and improved nutritional and immune biomarkers, as shown by Liu et al. 2022 [91]. Patients in a persistent vegetative state receiving enteral nutrition experienced improvements in intestinal metabolite profiles, although dysbiosis was not fully prevented, as shown by Matsuoka et al. 2022 [90]. Importantly, prophylactic administration of CBM588 in intensive care unit patients significantly reduced the incidence and recurrence of *Clostridioides difficile* infection and was associated with a modest reduction in ICU stay, as demonstrated by Sato et al. 2022 [99]. These findings suggest that CBM588 may help stabilize gut microbiota in settings of severe physiological stress. CBM588 shows potential for stabilizing gut microbiota in critically ill and special populations, with consistent benefits in reducing Clostridioides difficile infection and improving microbial composition and metabolic profiles. Evidence for broader clinical outcomes, such as mortality or ICU stay, remains limited, and heterogeneous study designs (e.g., single- vs. double-blind, observational vs. RCT) and

co-interventions (e.g., enteral nutrition, multi-strain formulations) constrain definitive conclusions regarding efficacy.

4.8. Clostridium butyricum Strains—Tolerability and Safety

Clostridium butyricum has generally demonstrated a favorable safety and tolerability profile across various populations. In children, it has been well tolerated in studies on gastrointestinal issues, such as gastroenteritis [118]. In adults, CBM588 has demonstrated safety in conditions like ulcerative colitis [22,68,99] and allergic rhinitis [85], with significant symptom improvement and no major side effects. In critically ill patients, CBM588 has been safely used to reduce the incidence of *Clostridioides difficile* infection and slightly shorten ICU stays [99]. Moreover, studies on cancer patients have demonstrated that CBM588 is well tolerated when used in combination with cancer therapies [76,77,82].

However, there are considerations regarding the pathogenic potential of certain *Clostridium* strains. While non-toxigenic strains, such as the ones used in clinical practice, have been validated for their probiotic properties, other strains have been linked to pathological conditions like botulism in infants or necrotizing enterocolitis (NEC) in preterm neonates [40,122]. This emphasizes the complex relationship between different strains of *Clostridium butyricum*, as some may have beneficial effects while others may cause harm. As both toxigenic and non-toxigenic Clostridia are part of the normal gut microbiota, understanding the triggers for their beneficial or virulent behavior remains challenging. Accurate identification of bacterial strains is crucial to ensure their safety, as different strains within the same species can have antagonistic effects on human health. Bacterial culture remains the only method for strain-level identification, which is essential for discovering emerging enteropathogenic strains [40]. Additionally, there have been isolated reports of adverse events, such as a case study where two patients after major hepatectomy developed sepsis following CBM588 supplementation, one of whom unfortunately died while the other recovered [123].

More cases of bacteremia have been reported, with several patients having pre-existing gastrointestinal conditions that may predispose them to bacterial translocation across the intestinal mucosal barrier. For instance, a 62-year-old woman with a history of restrictive food intake disorder developed bacteremia after receiving oral *Clostridium butyricum* 588 supplementation for severe diarrhea. A 73-year-old woman with diabetes mellitus and intracranial hemorrhage, and a 76-year-old man with a history of hemodialysis due to diabetes, both developed bacteremia after receiving CBM588 treatment—one for severe diarrhea and the other following coronary artery bypass graft surgery. These cases suggest that pre-existing gastrointestinal conditions, combined with other comorbidities, may increase the risk of bacterial translocation, leading to bacteremia and subsequent complications. However, all patients improved and stabilized after receiving appropriate antimicrobial treatment [124].

4.9. Limitations and Future Perspectives of Clinical Trials Assessing the Effect of Clostridium butyricum Strains

Clostridium butyricum strains show the most consistent and clinically reliable benefits in antibiotic-associated diarrhea, *Helicobacter pylori* eradication, colorectal surgery, gastrectomy, and prevention of *Clostridioides difficile* infection. Evidence in other gastrointestinal, oncological, immune-mediated, metabolic, and critical-care contexts is promising but limited by small sample sizes, heterogeneous study designs, and concomitant interventions, and should be interpreted cautiously. While clinical research on the probiotic properties of *Clostridium butyricum* strains has demonstrated these promising results, several limitations must be considered.

One key limitation is the relatively small sample sizes used in the majority of included studies, which could limit the generalizability of the findings. Small cohorts may not adequately represent the broader patient population. Furthermore, there is a wide variation in study protocols, including differences in dosage, strain selection, treatment duration, and administration schedules, which makes it difficult to draw definitive conclusions about the optimal conditions for CBM588 use. Additionally, the duration of many studies is relatively short, often limited to a few months. This short timeframe may not fully capture the long-term effects or potential side effects of CBM588 supplementation. Longer-term studies are needed to assess both the durability of the observed benefits and any potential delayed adverse effects. These factors emphasize the need for larger, well-designed randomized controlled trials with standardized protocols to provide more robust and reliable evidence regarding the safety and efficacy of *Clostridium butyricum* across different clinical applications.

5. Conclusions, Cautions, and Perspectives

Various probiotic *Clostridium butyricum* strains, particularly CBM588, have demonstrated promising therapeutic potential across a range of clinical conditions, including gastrointestinal disorders, immune modulation, and oncology-related settings. Whilst preclinical studies consistently support their role in stabilizing gut microbiota, enhancing short-chain fatty acid (SCFA) production, and modulating immune responses, the available clinical evidence remains heterogeneous in terms of study design, patient populations, probiotic formulations (including multi-strain and synbiotic interventions), and clinical outcomes. On one hand, beneficial effects have been reported in conditions such as antibiotic-associated diarrhea, *Helicobacter pylori* eradication support, and selected perioperative settings; on the other hand, evidence in other indications—including irritable bowel syndrome, ulcerative colitis, allergic and respiratory diseases, and oncology—remains limited, context-dependent, or based on small and exploratory studies.

The observed effects are strain-specific and should not be generalized across the species level. In particular, most clinical evidence relates to CBM588, whereas data for other strains remain scarce. *Clostridium butyricum* strains, especially CBM588, show a favorable safety profile in the studied populations. However, safety considerations should be interpreted within specific clinical contexts, particularly in vulnerable or critically ill patients, where rare adverse events have been reported. Further well-designed, large-scale randomized controlled trials with standardized protocols are required to confirm efficacy, clarify strain-specific effects, and establish their role in clinical practice.

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