REVIEW / DERLEME

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Scoping Review of Lactic Acid Bacteria Use in Preventing Antibiotic-Associated Diarrhea: Mechanisms and Recent Clinical Trials

Antibiyotik İlişkili İshalin Önlenmesinde Laktik Asit Bakterilerinin Kullanımına İlişkin Kapsamlı Derleme: Mekanizmalar ve Güncel Klinik Çalışmalar

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Abstract

Dysbiosis of the gut microbiota is a potential adverse effect of antimicrobial therapy and can manifest as antibiotic-associated diarrhea (AAD). The use of lactic acid bacteria (LAB) as probiotics is one of the most extensively investigated interventions for the prevention and management of AAD. This review summarizes the existing literature on LAB use in AAD prevention and management, drawing on *in vivo* studies and clinical trials. A literature search was conducted in the PubMed and Scopus databases using the following keywords: ("lactic acid bacteria" OR "lactobacillus" OR "bifidobacterium" OR "probiotic") AND ("antibiotic-associated diarrhea"). Full-text articles reporting *in vivo* studies and randomized clinical trials published in English between 2000 and 2024 were considered. A total of 43 articles were included in the review. LAB may help prevent and manage AAD through several mechanisms, including modulation of tryptophan metabolism, increased short-chain fatty acid production, intestinal colonization, competition with pathogenic species, and bacteriocin production. However, clinical trials investigating LAB as probiotics for AAD prevention and management have yielded inconsistent results. Some trials have reported reductions in AAD incidence, severity, and duration, as well as improvements in other symptoms. Several factors complicate the assessment of the clinical benefits of LAB probiotics, including heterogeneity in the LAB strains and species used, whether administered individually or in combination; differences in probiotic dosages and formulations; variation in gut microbiota composition among populations; and a lack of outcome assessments examining changes in microbiota composition following probiotic administration, such as LAB colonization. The effectiveness of LAB in preventing AAD and reducing its incidence remains inconclusive. Further studies are needed to determine the optimal use of LAB probiotics for the prevention and management of AAD.

Keywords: Lactic acid bacteria, Lactobacillales, *Bifidobacterium*, antibiotic-associated diarrhea, probiotics

Öz

Bağırsak mikrobiyotasındaki disbiyoz, antimikrobiyal tedavinin olası bir yan etkisidir ve antibiyotik ilişkili ishal (Aİİ) olarak kendini gösterir. Probiyotik olarak laktik asit bakterilerinin (LAB) uygulanması, Aİİ'nin hem önlenmesinde hem de tedavisinde en çok araştırılan müdahalelerden biridir. Bu makale, Aİİ'nin önlenmesi ve yönetiminde LAB kullanımına dair mevcut literatürü, in vivo çalışmalar ve klinik araştırmalar ışığında gözden geçirmektedir. PubMed ve Scopus veri tabanlarında ("lactic acid bacteria" OR "lactobacillus" OR "bifidobacterium" OR "probiotic") VE ("antibiotic-associated diarrhea") anahtar kelimeleri kullanılarak bir literatür taraması yapılmıştır. 2000-2024 yılları arasında İngilizce dilinde yayımlanmış, in vivo çalışmaları ve randomize klinik araştırmaları içeren tam metin makaleler incelenmiştir. Derlemeye toplam 43 makale dahil edilmiştir. LAB; triptofan metabolizmasını düzenleyerek, kısa zincirli yağ asidi üretimini artırarak, bağırsak lümenine yerleşerek, patojen türlere karşı rekabetçi bir

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büyüme sergileyerek ve bakteriyosin üreterek Aİİ'nin önlenmesi ve tedavisinde etkili olmaktadır. Bununla birlikte, probiyotik olarak LAB kullanımına dair klinik çalışmalar farklı sonuçlar ortaya koymuştur. Bazı klinik çalışmalar, LAB kullanımının Aİİ insidansını, şiddetini ve süresini azalttığını, ayrıca diğer semptomları hafiflettiğini bildirmiştir. Probiyotik olarak LAB'lerin klinik faydalarının değerlendirilmesindeki zorluklar arasında; kullanılan LAB suş ve türlerinin (tek başlarına veya kombinasyon halinde) heterojenliği, probiyotik dozajı ve preparatlarındaki farklılıklar, popülasyonlar arasındaki bağırsak mikrobiyotası çeşitliliği ve probiyotik kullanımından sonra mikrobiyota kompozisyonundaki değişimlere (örneğin LAB kolonizasyonu) dair sonuçların yeterince değerlendirilmemiş olması yer almaktadır. LAB'lerin Aİİ'yi önlemedeki ve insidansını azaltmadaki faydaları henüz kesinlik kazanmamıştır. Aİİ'nin önlenmesi ve tedavisinde probiyotik olarak LAB kullanımından optimal klinik fayda sağlanabilmesi için daha fazla çalışmaya ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Laktik asit bakterileri, Lactobacillales, *Bifidobacterium*, antibiyotik ilişkili ishal, probiyotikler

Introduction

The human gut harbors a highly diverse microbial ecosystem (approximately 10^{11} bacteria per gram of intestinal content). This ecosystem, known as the gut microbiota, plays an important role in maintaining host health[1]. When antibiotics are used to eradicate pathogenic bacteria during bacterial infections, they may also affect part of the gut microbiota, disrupting its diversity and balance. This condition, known as dysbiosis, increases the risk of antibiotic-associated diarrhea (AAD). AAD is defined as diarrhea occurring within hours after the initiation of antibiotic therapy and up to 8 weeks after its discontinuation. The incidence of AAD ranges from 5% to 25%, depending on the antibiotics used. A previous meta-analysis found that approximately 27% of AAD cases among hospitalized patients were caused by *Klebsiella oxytoca*, followed by *Clostridioides difficile* (19.6%), *Clostridium perfringens* (14.9%), and *Staphylococcus aureus* (5.2%)[2]. However, the meta-analysis included only 56 English-language articles, most of which were from Asia (26 studies) and Europe (15 studies). AAD-attributable mortality among inpatients ranges from 12.03% to 18.7%, and 65.47% of patients with AAD require longer hospital stays[3,4].

The burden of AAD resulting from gut microbiota dysbiosis has prompted research into strategies to reduce antibiotic-induced dysbiosis. Probiotics have potential as preventive and therapeutic interventions for AAD. Lactic acid bacteria (LAB) are among the microorganisms most commonly used in probiotic preparations. They are also commonly used to ferment dairy, meat, and vegetable products[5]. Common LAB genera include *Lactobacillus* and *Bifidobacterium*. However, their effectiveness in treating gastrointestinal diseases remains unclear because findings from existing studies are inconsistent[6]. This review aims to summarize the mechanisms of action of LAB and their clinical use in the prevention and management of AAD.

Materials and Methods

This article used a scoping review design and was written according to the PRISMA Extension for Scoping Reviews (PRISMA-ScR) guidelines. Articles were screened through searches of the PubMed and Scopus databases using the keywords ("lactic acid bacteria" OR "lactobacillus" OR "bifidobacterium" OR "probiotic") AND ("antibiotic-associated diarrhea"). We included *Lactobacillus* and *Bifidobacterium* as keywords because 90% of probiotic formulations contain bacteria from these genera[7]. Although some studies do not classify *Bifidobacterium* as LAB[8,9], others do[10,11]. We included *Bifidobacterium* in this review because it is widely used as a probiotic agent alongside *Lactobacillus*.

The mechanisms of action of LAB against AAD were reviewed based on articles reporting *in vivo* studies, whereas updates on the use of LAB for AAD prevention and treatment were based on clinical trials. Research articles reporting *in vivo* studies and clinical trials published in English between 2000 and 2024 that investigated the use of LAB against AAD were screened for inclusion. The year 2000 was chosen as the starting year because research on probiotics was expanding rapidly. The definition of probiotics was also updated and introduced in 2001[12]. The final literature search was conducted on December 31, 2024. Articles involving interventions with non-LAB species or studies involving pregnant women, immunodeficient patients, patients with cancer, or patients with a history of gastrointestinal surgery were excluded. The initial search retrieved 575 articles. During screening, the following articles were excluded: duplicates (225), review articles (186), articles irrelevant to the review topic (75), articles without LAB interventions (31), articles without full-text access (5), articles that did not report AAD incidence (6), articles that did not report *in vivo* studies or randomized clinical trials (3), and articles that did not clarify probiotic content (1). A total of 43 articles were included in this review. All included clinical trial articles were assessed for risk of bias using the Cochrane Risk of Bias 2 Tool. The article screening process is presented in Figure 1.

Results

LAB Overview

LAB are a group of Gram-positive cocci or bacilli that are aerotolerant, non-spore-forming, nonmotile, acid-resistant, and catalase-negative[13]. LAB are widely distributed in nature and can be found in decomposing plant matter, human and

animal orifices (oral, genital, intestinal, and respiratory tracts), and other environments, such as water. LAB can also be found in vegetables, juice, dairy products, fermented meat and fish, mash, and sourdough[14]. LAB can survive across a wide temperature range (5°C–45°C), at an optimum pH of 4.0–4.5, in high-salinity environments, and in the presence of additive compounds[15].

Currently, LAB comprise six main families: *Aerococcaceae, Carnobacteriaceae, Enterococcaceae, Leuconostocaceae, Lactobacillaceae,* and *Streptococcaceae*[15]. A common application of LAB is in starter cultures. Starter cultures are preparations containing numerous microbial cells from one or more microbial species that are added to a product to utilize the microbes' enzymatic or metabolic activities[16]. The defining characteristic of LAB is the production of lactic acid as the main end product of carbohydrate fermentation. LAB lack functional cellular respiration systems and instead generate energy through substrate-level phosphorylation via two metabolic pathways for hexose fermentation: homofermentative and heterofermentative pathways[13]. The homofermentative pathway produces lactic acid as the main product without additional metabolites, such as gas and flavor compounds. In contrast, heterofermentative LAB produce lactic acid and other products, such as ethanol, acetic acid, and carbon dioxide[15].

The ability of LAB to synthesize various beneficial metabolites, including lactic acid, supports their use in biotechnological, food, and therapeutic products[13]. Common products made using LAB include dairy products such as yogurt, fermented

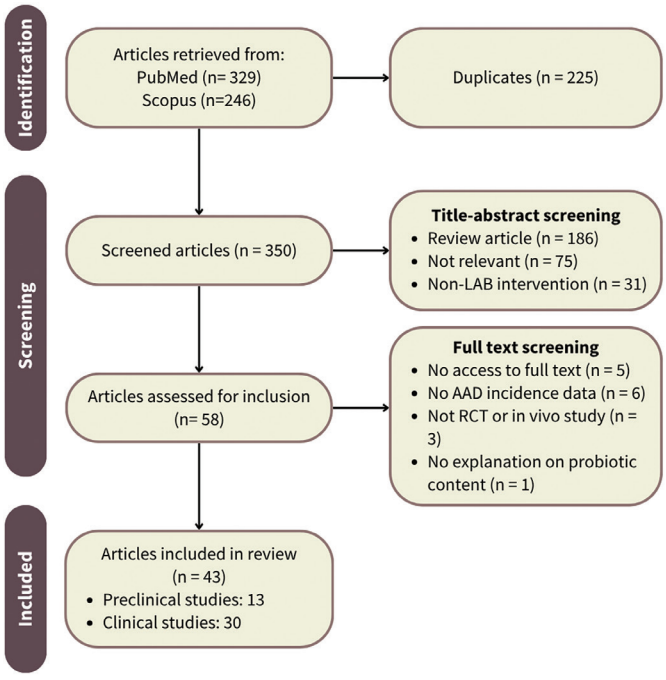


Figure 1. Article screening process.

milk, Yakult, tarhana, kefir, *acidophilus* milk, cheese, butter, and buttermilk (Figure 2)[17]. LAB play an important role in dairy fermentation by contributing to product preservation, flavor, and consistency. Some LAB species possess active proteolytic enzymes in milk and other food matrices, which increase the concentrations of bioactive peptides and polyamines. These peptides may exert antihypertensive, antithrombotic, immunomodulatory, and antioxidant effects. In addition, LAB may synthesize vitamins and help prevent intestinal infections[18].

LAB can also synthesize compounds with antimicrobial effects, particularly lactic acid and acetic acid. These compounds exhibit bioactive properties in their protonated forms at low pH. Other antimicrobial compounds are produced by LAB at concentrations below their minimum inhibitory concentrations, and they may act synergistically with lactic acid and acetic acid. Organic acids inhibit many pathogenic bacteria and other spoilage microorganisms through mechanisms associated with the creation of an acidic environment, which lowers the pH below the threshold required for microbial metabolism and growth. Additionally, lactic acid may inhibit cellular metabolism and proliferation by increasing the osmotic pressure of the medium. Organic acids may also alter the electrochemical balance and plasma membrane permeability, ultimately leading to microbial cell death[19].

LAB Mechanisms of Action Against AAD

Antibiotic administration directly affects the gut microbiota by decreasing the intestinal bacterial count, allowing pathogenic bacteria to grow and proliferate. Certain antibiotics also reduce gut bacterial diversity and abundance, leading to dysbiosis[20]. Short-term antibiotic use, such as a 7-day course of clindamycin, can cause a significant decrease in *Bacteroides* and enterococcal populations that persists for more than 2 years after treatment. This is also accompanied by an increase in antibiotic-resistant strains. In a small study (n = 10), a 10-day course of clindamycin decreased *Bifidobacterium* and *Lactobacillus* populations. The abundance of *Bifidobacterium* did not return to normal even 1 year after antibiotic therapy[21].

Some animal studies have shown that antibiotic therapy causes several pathological changes in the intestines, including crypt structural damage, submucosal edema, decreased villus number and density, mucosal thinning, and inflammatory cell infiltration. The severity of these changes depends on the antibiotic class and dosage. Antibiotic administration in animal models also caused changes in inflammatory markers. Pro-inflammatory mediators, such as interleukin (IL)-6, IL-1β, IL-17, and tumor necrosis factor-alpha (TNF-α), increased, whereas anti-inflammatory markers, such as IL-10, IL-4, transforming growth factor-beta (TGF-β), and interferon-gamma, decreased.

A summary of the pathological findings and changes in inflammatory markers after antibiotic administration in animal models is presented in Table 1.

Imbalances in pro-inflammatory and anti-inflammatory mediators may cause intestinal tissue damage. Pro-inflammatory mediators, such as IL-1β, IL-6, and TNF-α, play

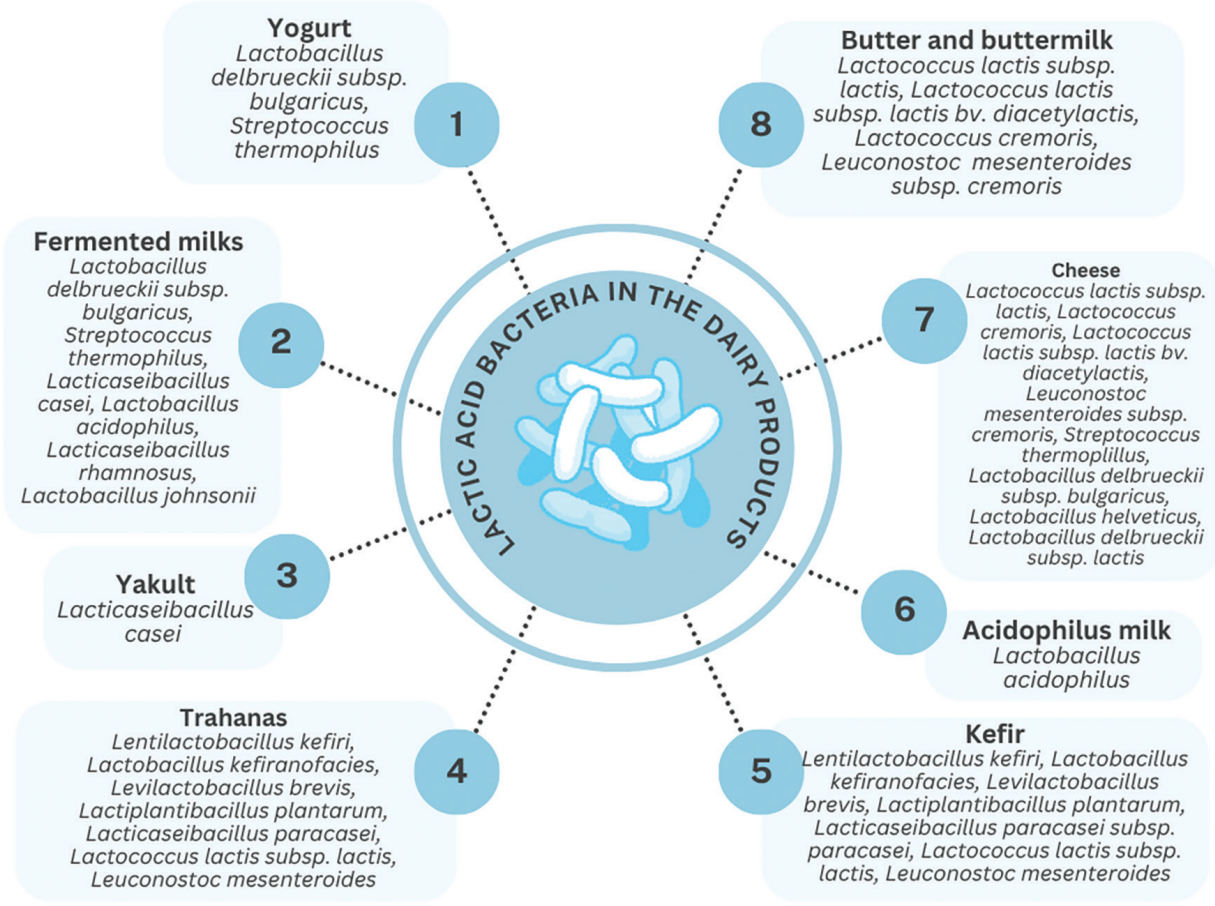


Figure 2. Use of LAB in various dairy products (data obtained from reference [17]).

Table 1. Summary of antibiotic-induced impacts on animal models.

Pathological findings	Inflammatory markers	Ref
• Crypt structure damage and inflammatory cell infiltration in colon tissue • ↓ Gut microbiota diversity • ↓ *Firmicutes* and *Desulfobacterota* populations • ↑ *Bacteroidetes* and *Verrucomicrobiota* populations	• ↑ IL-6 and IL-1β • ↓ IL-10 and TGF-β	[22]
• Severe damage of small intestinal mucosa and sparsely damaged villi • ↑ LPS and D-La titers • ↓ Total protein, serum albumin, and sIgA • ↓ ZO-1, occludin, claudin-1, and MUC2 expression • ↓ *Bacteroidetes* and *Proteobacteria* populations	• ↑ IL-6, TNF-α and IL-1β • ↓ IL-10	[23]
• Mild submucosal edema, accompanied by inflammatory cell infiltration and decreased gland cells • ↑ LPS titers • ↓ NHE3, occludin, and Mucin-2 expression • ↓ Acetic, propionic, isobutyric, and isovaleric acid titers • ↓ Gut microbiota diversity	• ↑ IL-6, IL-17, IL-1β, and TNF-α	[24]

Table 1. Continued

Pathological findings	Inflammatory markers	Ref
• Homogenous, integrated villi damage; most colon epithelial cells had severe swelling and some were ruptured • ↓ *Bacteroidetes/Prevotella, Clostridium* cluster XIVab and XI, *Faecalibacterium prausnitzii, Bifidobacterium* spp. populations • ↑ *Enterococcus* spp. and *Enterobacteriaceae* populations	• ↑ TNF-α • ↓ IL-10 and IFN-γ	[25]
• Shortening and loosening of intestinal villi, serous and muscular tissue thinning, and inflammatory cell infiltration • ↑ D-La, ET, and DAO titers • ↓ *Firmicutes* population • ↑ *Proteobacteria* population	• ↑ TNF-α • ↓ IL-10 and IFN-γ	[26]
• Mucosal epithelial shedding, loosely arranged intestinal glands, and slight edema accompanied by inflammatory cell infiltration • ↓ Acetic acid, propionic acid, butyric acid, and total SCFA titers • ↑ Regulation of TLR4/MyD88/NF-κB/IκBα signaling • ↑ Regulation of p-PI3K/p-AKT/NF-κB signaling • ↓ *Bacillota* population • ↑ *Bacteroidota* spp. and *Pseudomonadota* populations	• ↑ TNF-α • ↓ IL-10	[27]
• Cecum enlargement • ↓ Butyrate receptor GPR109A and butyrate transporter SLC5A8 expression • ↓ SLC16A3, AQP4, and NHE3 ion exchangers expression • ↓ ZO-1 and occluding expression	Not measured	[28]
• Thinning of colon mucosa and decreased goblet cell count • ↓ sIgA and IgG • ↑ LPS, D-La, and DAO • ↓ ZO-1, occludin, claudin-1, and MUC2 expression • ↑ p-Smad3 and ↓ Smad7 titers • ↑ *Bacteroidetes, Blautia, and Corpococcus* populations • ↓ *Firmicutes, Proteobacteria, Lactobacillus, Allobaculum,* and *Bifidobacterium* populations	• ↑ IL-4, IL-17A, TGF-β1	[29]
• ↑ *Firmicutes* population	• ↓ IL-4 and IL-10 • ↑ TNF-α and IFN-γ	[30]
• ↑ Cecum size and length • ↓ *Firmicutes* population • ↑ *Bacteroidetes* population	Not measured	[31]
• ↓ Acetic, propionic, and butyric acid titers • ↓ *Lactobacillaceae, Muribaculaceae, and Lachnospiraceae* populations	Not measured	[32]
• ↓ Cecum thickness • ↑ Surface gland degeneration and atrophy • ↑ *Bacteroides* population	• ↑ TNF-α • IL-6	[33]
• ↓ Ratio villous height to crypt depth • ↑ *Firmicutes* population • ↓ AQP1, AQP8, ZO-1, occluding, and Claudin-1 expression	Not measured	[34]

DAO, diamine oxidase; D-La, D-lactate; ET, endotoxin; IFN-γ, interferon-gamma; IL-1β, interleukin-1 beta; LPS, lipopolysaccharide; SCFA, short-chain fatty acid; sIgA, secretory immunoglobulin A; TGF-β, transforming growth factor-beta; TGF-β1, transforming growth factor-beta 1; TNF-α, tumor necrosis factor-alpha; ZO-1, zonula occludens-1; MUC2, mucin 2; NHE3, sodium-hydrogen exchanger 3; TLR4, toll-like receptor 4; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa B; IκBα, inhibitor of nuclear factor kappa B alpha; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; GPR109A, G protein-coupled receptor 109A; SLC5A8, solute carrier family 5 member 8; SLC16A3, solute carrier family 16 member 3; AQP1, aquaporin 1; AQP4, aquaporin 4; AQP8, aquaporin 8; Smad3, SMAD family member 3; Smad7, SMAD family member 7.

crucial roles in the inflammatory process. IL-6 is considered a major mediator involved in chronic inflammatory diseases, autoimmune disorders, cancer, and cytokine storms[35]. IL-1β can induce intestinal inflammation by disrupting tight junctions in the intestinal epithelium and increasing intestinal permeability[22].

In addition, IL-1β and TNF-α can activate transcription factors that induce IL-6 secretion. A combination of IL-6 and TGF-β is required to differentiate naïve CD4+ T cells into Th17 cells, whereas IL-6 inhibits Treg cell differentiation. An increased Th17/Treg ratio is considered important in disorders of immunological tolerance and the progression of inflammatory and autoimmune diseases[36]. TNF-α is secreted mainly by macrophages and monocytes, although other cells, including T-cell subsets, NK cells, dendritic cells, B cells, cardiomyocytes, fibroblasts, and astrocytes, may also secrete TNF-α. When TNF-α binds to its receptors (TNFR1 and TNFR2), several intracellular pathways are activated, mediating cell death and/or cell survival responses[37].

Probiotics can prevent AAD through several mechanisms. Some probiotic preparations containing *Bifidobacterium* and *Limosilactobacillus reuteri* can prevent colonic inflammation and alleviate inflammatory responses by increasing tryptophan concentrations and the production of indole-3-carboxaldehyde through the tryptophan metabolism pathway[22]. Tryptophan metabolites, including kynurenine and indole, are important for the binding and activation of the aryl hydrocarbon receptor (AhR) and for increasing the expression of the effector molecules CYP1A1 and CYP1B1, which are involved in intestinal immune regulation. A porcine study involving intraperitoneal lipopolysaccharide (LPS) injection showed that tryptophan administration increased the expression of AhR, CYP1A1, and CYP1B1 genes and decreased IL-1β, IL-6, IL-8, and TNF-α levels compared with those in controls that did not receive tryptophan[38]. Another study found that AhR activation inactivated actin-regulatory proteins, such as ezrin, resulting in decreased myosin II-induced actin contractility. This mechanism may also help maintain tight and adherens junctions, thereby reducing epithelial permeability[39]. Furthermore, indole derivatives, particularly indole propionic acid, bind to the pregnane X receptor, which may inhibit local inflammation and increase tight junction expression[40].

Probiotics may also exert beneficial effects by producing short-chain fatty acids (SCFAs) that help maintain intestinal barrier integrity. SCFAs are carboxylic acids with aliphatic tails containing fewer than six carbon atoms. Acetate (C2), propionate (C3), and butyrate (C4) are the main end products of fermentation by intestinal microbes. These molecules can be readily absorbed by the colon, where they provide energy for colonic cells and help repair epithelial injury. SCFAs are also involved in regulating glucose and lipid metabolism, thereby contributing to host energy homeostasis[41]. Each SCFA has distinct functions. Propionate may inhibit LPS-induced TNF-α and other cytokine production, as well as NF-κB activation. Butyrate may decrease IL-8 gene expression, improve intestinal permeability by activating peroxisome proliferator-activated receptors, inhibit NF-κB, upregulate MUC1–MUC4 expression, and promote the formation of regulatory T cells. Acetate may stimulate crypt cell proliferation, inhibit NF-κB activity, suppress IL-6 secretion, and serve as a precursor for butyrate formation[42].

Probiotics may also compete with pathogenic bacteria for nutrients. In addition, probiotics can secrete antimicrobial substances, such as bacteriocins and H_2O_2[43,44]. Bacteriocins are antimicrobial peptides produced by ribosomes and have various mechanisms of action. Some bacteriocins, such as nisin (secreted by *Lactococcus lactis*), plantaricin (*Lacticaseibacillus plantarum*), and lacticin B (*Lactobacillus acidophilus*), have demonstrated biological activity against foodborne enteropathogens, such as *Listeria*, *Clostridium*, *Staphylococcus aureus*, and vancomycin-resistant enterococci. Bacteriocins exert their biological effects by attaching to microbial cells and penetrating the phospholipid membrane, owing to their small size and varying hydrophobicity. They may then alter bacterial cytoplasmic membrane permeability, leading to the leakage of cellular contents. Bacteriocins may also inhibit RNA and DNA synthesis and/or cell wall synthesis[45]. Bacteriocins such as nisin have also shown inhibitory activity against *Clostridioides difficile* spores and vegetative growth[46,47].

Probiotics may also play a role in regulating electrolyte concentrations. SCFAs, particularly butyrate, have been shown to reduce cholera toxin-induced electrolyte and water secretion. Butyrate may bind to and activate GPR109A, thereby reducing intracellular cAMP levels. cAMP is a major signaling molecule in the gastrointestinal tract and is involved in regulating water and electrolyte absorption. Increased intracellular cAMP levels in the gastrointestinal tract can cause secretory diarrhea. In addition, butyrate may activate ion exchangers, such as SLC26A3, which triggers Na^+ absorption in the colon[28]. An *in vivo* study reported that mice infected with *Citrobacter rodentium* showed decreased expression of ion transporters, accompanied by reductions in serum chloride and sodium levels. The study also showed that *L. acidophilus* administration increased the expression and function of NHE3 (Na^+/H^+ exchanger 3) and DRA (Cl^-/HCO_3^- exchanger)[48]. An overview of the mechanisms through which probiotics containing LAB exert their effects against AAD is presented in Figure 3. A summary of *in vivo* studies, interventions, and the beneficial effects of probiotic administration in animal models is presented in Table 2.

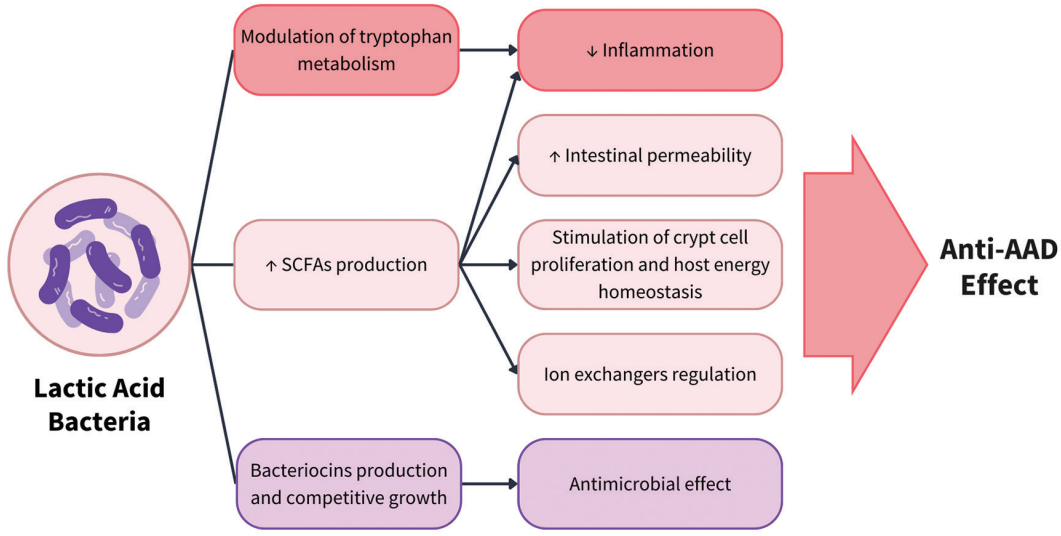


Figure 3. Overview of the main mechanisms of lactic acid bacteria action against AAD. SCFAs, short-chain fatty acids; AAD, antibiotic-associated diarrhea.

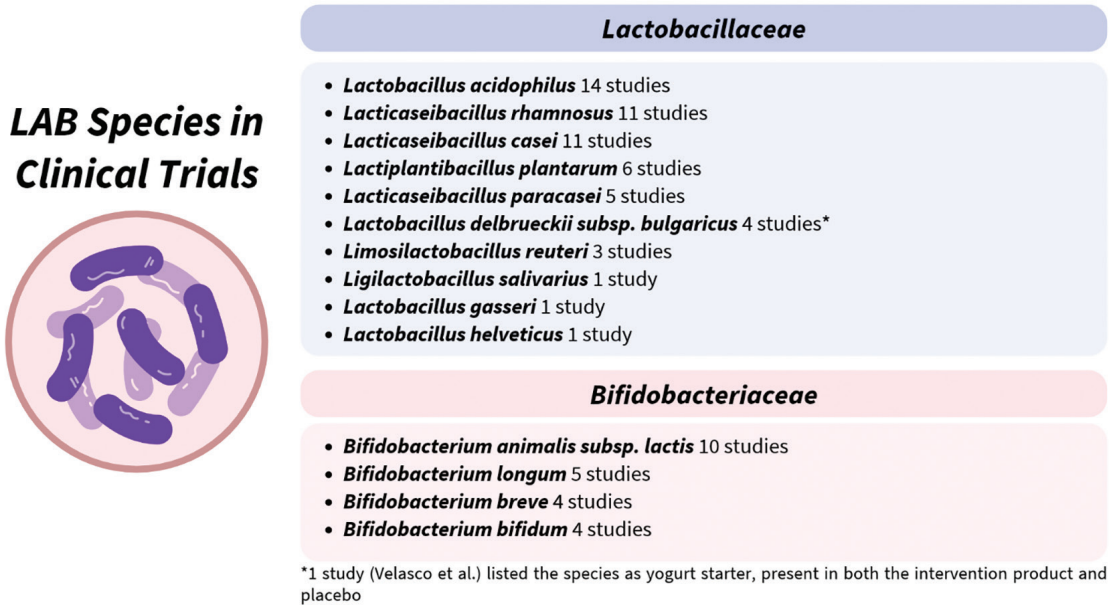


Figure 4. Lactic acid bacteria (LAB) species used in the clinical trials reviewed in this article.

Clinical Trials of LAB Use in AAD

Ten species of Lactobacillaceae and six species of Bifidobacteriaceae were used across the 30 clinical trials reviewed in this article (Figure 4). In addition, several studies included non-LAB species, such as *Streptococcus thermophilus* (six studies), *Bacillus coagulans* (one study), and *Saccharomyces boulardii* (one study), in their intervention products. Twenty-two studies used blends of multiple species and/or strains[49-62,66,68-73,78], whereas the remaining eight used single-strain interventions[63-65,67,74-77]. Details of the populations, interventions, and results of all reviewed studies are provided in Table 3.

Table 2. Preclinical testing of probiotic effects

No	Intervention	Probiotic benefits observed	Ref.
1.	• **Subject:** Mice • **Interventions:** AAD was induced by the administration of lincomycin hydrochloride G1: normal control (normal saline); G2: AAD + normal saline; G3: AAD + *Lacticaseibacillus plantarum* H-6; G4: AAD + *Weissella viridescens* J-1 • **Intervention duration:** 7 days	↓ diarrhea status score and significantly ↑ weight in G3 compared to G2 and G4 Repair of colon damage and ↓ inflammatory cell infiltration in G3 ↑ anti-inflammatory (IL-10 and TGF-β) and ↓ pro-inflammatory (IL-1β and IL-6) cytokines in G3 ↑ reduced riboflavin, threoninyl-methionine, L-tryptophan, and ↓ diethyl succinate levels in G3 ↑ abundance and diversity of colon microbiota in G3, approaching normal (G1)	[22]
2.	• **Subject:** BALB/c mice • **Interventions:** AAD was induced by administration AAD was induced by administration of ampicillin (2x/day, dose: 11,2 g/kg BW) G1: normal control (normal saline); G2: AAD mice + normal saline; G3: AAD mice + Bifico (contains *Bifidobacterium longum, Lactobacillus acidophilus,* and *Enterococcus faecalis);* 3 groups receiving complex probiotics with 3 doses: low (2.5×10^6 CFU, G4), medium (5×10^6 CFU, G5), and high (1×10^7 CFU, G6). • **Intervention duration:** 14 days	↓ fecal water content (most notably in G6) ↑ body weight (most notably in G6) ↓ lipopolysaccharide (LPS) and D-lactate (D-LA) levels (most notably in G3) ↑ total protein and albumin levels ↑ sIgA and IL-10 and ↓ IL-6 levels, (most notably in G6) ↑ ZO-1, occludin, claudin-1, and MUC2 mRNA expressions, (most notably in G6) ↑ abundance and diversity of gut microbiota in G6	[23]
3.	• **Subject:** Mice • **Interventions:** AAD was induced by the administration of lincomycin hydrochloride G1: normal control (phosphate buffer saline, PBS); G2: AAD mice + PBS; G3-G9: AAD mice + intervention regimens comprising various *Bifidobacterium* species, including *Bacteroides intestinalis* (Bi), *Bacteroides uniformis* (Bu), *Bacteroides adolescentis* (Ba), *Bacteroides bifidum* (Bb), and their combinations. • **Intervention duration:** 3 days	↓ diarrhea status score in groups receiving probiotic therapy, most notably in the group receiving Bu + Ba ↓ fecal water content, most notably in groups receiving Bi + Ba and Bu + Ba No significant pathological lesions from colon tissues retrieved from groups receiving Bu or Bu + Ba ↓ IL-6 levels in the Bu + Ba group ↓ LPS levels, most notably in the Bi + Ba group ↑ occludin and Mucin-2 expression, most notably in the Bu+Ba group ↑ NHE3 expression, most notably in groups receiving Bi, Bi +Ba, and Bu +Ba ↑ production of short-chain fatty acid/SCFA (acetic acid, propionic acid, isobutyric acid, and isovaleric acid) in groups receiving Bu + Ba and Bi + Bb ↑ abundance and diversity of gut microbiota in groups receiving probiotics	[24]
4.	• **Subject:** C57BL/6 mice • **Interventions:** AAD was induced by the administration of ceftriaxone 8 g/kg bw • G1: normal control (normal saline); G2: mice AAD; G3: AAD mice + sterile saline; G4: AAD mice + *Clostridium butyricum;* G5: AAD mice + *Bifidobacterium infantis;* G6: AAD mice + combination of probiotics *(Clostridium butyricum* + *Bifidobacterium infantis)*	Repair of edematous and ruptured colon tissue structures in G6 ↑ IL-10 and IFN-γ levels ↓ IL-1β and TNF-α levels Recovery of fecal microbiota diversity in the group receiving combination of probiotics	[25]
5.	• **Subject:** SPF Balb/c mice • **Interventions:** AAD was induced by the administration of lincomycin hydrochloride G1: normal control (normal saline); G2: AAD mice + normal saline; G3: AAD mice + suspension of *Streptococcus thermophilus* DMST-H2; G4: AAD mice + yogurt containing *Streptococcus thermophilus* DMST-H2 • **Intervention duration:** 6 days	Improves fecal consistency ↑ IL-10 and IFN-γ levels ↓ TNF-α levels ↓ infiltration of inflammatory cells ↓ cecum index ↑ *Firmicutes* and ↓ *Proteobacteria* populations	[26]

Table 2. Continued

No	Intervention	Probiotic benefits observed	Ref.
6.	• **Subject:** C57BL/6 mice • **Interventions:** AAD was induced by administration of amoxicillin 500 mg/kg + clindamycin 400 mg/kg + streptomycin 350 mg/kg G1: normal control (normal saline); G2: AAD mice; G3: AAD mice + *Lacticaseibacillus plantarum* 0.1 mL/10 g • **Intervention duration:** 14 days	↓ infiltration of inflammatory cells in colonic tissue, ↓ edema, and repair of intestinal gland tissue ↓ TNF-α and IL-1β levels ↑ SCFA production (acetic acid, butyric acid, total SCFA) Inhibition of TLR4/NF-κB signaling Inhibition of PI3K/AKT/NF-κB phosphorylation and activation ↑ abundance and diversity of gut microbiota	[27]
7.	• **Subject:** C57BL/6 mice • **Interventions:** AAD was induced by the administration of metronidazole + vancomycin + neomycin sulfate (in G2) Probiotics used: *Lacticaseibacillus rhamnosus* strain GG G1: mice without antibiotic therapy, divided into 4 interventional subgroups: G1a: control; G1b: probiotics; G1c: tributyrin; G1d: probiotics + tributyrin. G2: mice receiving antibiotic therapy divided into interventional subgroups similar to G1. • **Intervention duration:** 7 days	Prevents the decline of SLC5A8 butyrate transporter and GPR109A butyrate receptor expressions in the gut Prevents the decline of ion exchanger SLC26A3, NHE3, and water channel AQP4 expressions.	[28]
8.	• **Subject:** C57BL/6 mice • **Interventions:** AAD was induced by the administration of amoxicillin + clindamycin + streptomycin G1: normal control (normal saline); G2: AAD mice + normal saline; G3: AAD mice + *Lacticaseibacillus plantarum* ELF051; G4: AAD mice + *A.* polysaccharide; G5: AAD mice + *Lacticaseibacillus plantarum* + *A.* polysaccharide • **Intervention duration:** 14 days	↓ cecum index ↑ mucous membrane area and goblet cells in the colon ↑ sIgA and IgG levels ↓ IL-17A and IL-4 levels ↓ diamine oxidase, d-lactate, lipopolysaccharides, and TGF-β1 levels ↓ p-Smad3 and ↑ Smad7 proteins ↑ *Firmicutes, Lactobacillus, Bifidobacterium,* and Protebacteria populations, also ↓ *Bacteroides,* Coprococcus, and Blautia populations These effects are more pronounced in combination with Astragalus polysaccharide.	[29]
9.	• **Subject:** SPF KM mice • **Interventions:** AAD was induced by the administration of cefradine + gentamicin sulfate G1: normal control (normal saline); G2: AAD mice; G3: AAD mice + normal saline; G4: AAD mice + *Lacticasebacillus plantarum* ($1x10^7$ CFU/mL); G5: AAD mice + *Lacticasebacillus plantarum* ($1x10^8$ CFU/mL); G6: AAD mice + *Lacticaseibacillus plantarum* ($1x10^9$ CFU/mL)	Speeds up diarrhea resolution ↑ body weight and appetite ↑ IL-4 and IL-10 ↓ TNF-α and IFN-γ ↑ abundance and diversity of gut microbiota	[30]
10.	• **Subject:** Kunming mice • **Interventions:** AAD was induced by the administration of lincomycin + gentamicin sulfate G1: normal control (normal saline); G2: AAD mice; G3: AAD mice + tablet Lacidophilin *(Lactobacillus);* G4: AAD mice + ambrosial yogurt *(Streptococcus thermophilus);* G5: AAD mice + bifid triple capsule *(Bifidobacterium longum, Enterococcus faecalis, Lactobacillus acidophilus)* • **Intervention duration:** 10 days	↓ duration of diarrhea ↑ body weight and ↓ cecum enlargement (most notably in G4) ↑ abundance of microbial communities ↑ populations with *Firmicutes* and *Bacteroidetes*	[31]
11.	• **Subject:** C57BL/6 mice • **Interventions:** AAD was induced by the administration of amoxicillin G1: normal control (normal saline); G2: AAD mice + normal saline; G3: AAD mice + probiotic solution containing *Bifidobacterium lactis* BB-12; G4: AAD mice + yogurt without *Bifidobacterium lactis;* G5: AAD mice + yogurt with *Bifidobacterium lactis* BB-12 • **Intervention duration:** 10 days	↑ body weight in male mice ↑ *Streptococcaceae* and ↓ Erwiniaceae populations ↓ formate, glycine, and glutamate metabolite levels (approaching controls)	[32]

Table 2. Continued

No	Intervention	Probiotic benefits observed	Ref.
12.	• **Subject:** Wistar rats • **Interventions:** AAD induced by Lincomycin G1: Control (distilled water) G2: AAD rats + distilled water G3: AAD rats + distilled water G4: AAD rats + *Lactobacillus acidophilus* + *Lacticaseibacillus casei* + *Bifidobacterium bifidum* preparation with 3×10^9 CFU/g per strain density • **Intervention duration:** 5 days	↓ duration of diarrhea ↑ cecum thickness ↑ body weight ↓ TNF-α and IL-6 ↑ serum and tissue IgA ↑ population with *Firmicutes* and genera *Lactobacillus, Bacillus, and Romboutsia* ↓ *Bacteroides* population	[33]
13.	• **Subject:** ICR mice • **Interventions:** AAD induced by ceftriaxone sodium G1: Control (saline) G2: AAD mice + saline G3: AAD mice + unfermented apple juice G4: AAD mice + *Lacticaseibacillus plantarum* G5: AAD mice + fermented apple juice • **Intervention duration:** 7 days	↓ duration and severity of diarrhea Repair of intestinal damage (↑ villi count and height) *Effects were most significant in G5.	[34]

AAD, antibiotic-associated diarrhea; AQP4, aquaporin 4; BALB/c, Bagg albino/c mouse strain; CFU, colony-forming unit; G1–G9, groups 1–9; GPR109A, G protein-coupled receptor 109A; ICR, Institute of Cancer Research mouse strain; IFN-γ, interferon-gamma; IgA, immunoglobulin A; IgG, immunoglobulin G; IL-1β, interleukin-1 beta; KM, Kunming mice; LPS, lipopolysaccharide; MUC2, mucin 2; NF-κB, nuclear factor kappa B; NHE3, sodium-hydrogen exchanger 3; PBS, phosphate-buffered saline; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; SCFA, short-chain fatty acid; sIgA, secretory immunoglobulin A; SLC5A8, solute carrier family 5 member 8; SLC26A3, solute carrier family 26 member 3; SPF, specific pathogen-free; TGF-β, transforming growth factor-beta; TGF-β1, transforming growth factor-beta 1; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-alpha; ZO-1, zonula occludens-1.

Table 3. Summary of clinical trials of the benefits of probiotics in the treatment of AAD.

No.	Intervention	AAD definition in study	Probiotic effects	Risk of bias	Ref.
1.	• Participants: 350 pediatric patients aged 3 months–18 years receiving oral or intravenous broad-spectrum antibiotics • Probiotics used: Ecologic AAD 612, containing combination of 8 species: *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *Lactobacillus acidophilus* W37, *Lactobacillus acidophilus* W55, *Lacticaseibacillus paracasei* W20, *Lactiplantibacillus plantarum* W62, *Lacticaseibacillus rhamnosus* W71, and *Ligilactobacillus salivarius* W24 (formerly known as *Lactobacillus salivarius* W24) • Preparation form: Sachet • Dose: 5×10^9 CFU/sachet, 2 /days (10^{10} CFU/day) • Follow-up duration: 1 week after cessation of antibiotic therapy	"AAD defined as 3 or more loose or watery stools (a score of A on the AISS or 5–7 on the BSFS) per day in a 24-hour period, caused either by *Clostridioides difficile* or of otherwise unexplained etiology, after testing for common, predefined diarrheal pathogens." Testing for *Clostridioides difficile:* - Detection of glutamate dehydrogenase - Detection of toxins A and B via immunoassay	↓ all diarrhea cases regardless of etiology (20.9% vs. 32.3% [pro vs. pla], 95% CI: 0.44–0.94, *p:* 0.02) and AAD incidence (14.6% vs. 18.1% [pro vs. pla], 95% CI: 0.49–1.33) No significant difference in CDAD (0.6% vs. 1.9%, 95% CI: 0.05–2.26) ↓ number of patients requiring rehydration therapy	Low	[49]
2.	• Participants: 36 adult patients (≥18 years) receiving amoxicillin-clavulanic acid therapy for 7 days, divided into 2 groups: placebo and intervention groups • Probiotics used: *Lactobacillus acidophilus* NCFM, *Lacticaseibacillus rhamnosus* Lr-32, *Bifidobacterium breve* M-16V, *Bifidobacterium longum* BB536, *Bifidobacterium lactis* BI-04, and *Bifidobacterium bifidum* Bb-02 • Preparation form: Capsule • Dose: 10^9 CFU/capsule, 1×/day • Intervention duration: 30 days	"AAD was defined as at least 3 watery/fluid stools in a 24-h period."	Delay in diarrhea onset by 5.39 days ($p = 0.002$) compared to placebo No significant difference in defecation frequency per day	High	[50]

Table 3. Continued

No.	Intervention	AAD definition in study	Probiotic effects	Risk of bias	Ref.
3.	• Participants: 255 adult patients (50–70 years) receiving penicillin, cephalosporin, or clindamycin therapy, divided into 3 groups receiving 2 capsules of probiotics (G1); 1 probiotic + 1 placebo capsules (G2); or 2 placebo capsules (G3) per day • Probiotics used: *Lactobacillus acidophilus* CL1285 + *Lacticaseibacillus casei* LBC80R • Preparation form: Capsule • Dose: 5×10^9 CFU/capsule • Intervention duration: starting within 36 hours since antibiotic therapy initiation, up to 5 days after antibiotic cessation • Follow-up duration: Up to 21 days after the intervention stopped.	"Diagnosis of AAD was made when a patient produced three or more liquid stools in a 24-h period after antibiotic treatment with no other obvious reason for diarrhea." Testing for *Clostridioides difficile:* cytotoxin assay	↓ AAD (28.6% vs. 23% vs. 9.1%, [G3 vs. G2 vs. G1]) and CDAD incidence (19.1% vs. 9.5% vs. 0) Faster relief of symptoms, most notably in G1	Low	[51]
4.	• Participants: 89 adult inpatients receiving at least 3 days of systemic antibiotic therapy, divided into 2 groups receiving probiotics and placebo • Probiotics used: *Lacticaseibacillus casei* and *Lactobacillus acidophilus* • Preparation form: Fermented milk beverage • Dose: 50×10^9 CFU/container, 98 g/day (49 g/day for first 2 days) • Intervention duration: starting within 48 hours since antibiotic therapy initiation, up to antibiotic cessation • Follow-up duration: Up to 21 days after the intervention stopped.	"AAD was defined as three or more liquid stools in a 24-h period." Testing for *Clostridioides difficile:* cytotoxin assay	↓ AAD (15.9% vs. 35.6%, [pro vs. pla], 95% CI: 0.125–0.944, p = 0.05) and CDAD incidence (2.3% vs. 15.6%, 95% CI: 0.020–1.109, p = 0.06) No significant effect of probiotic use on the length of stay	Low	[52]
5.	• Participants: 450 adult inpatients receiving antibiotic therapy, divided into 3 groups receiving high-dose probiotics (G1), low-dose probiotics (G2), or placebo (G3) • Probiotics used: *Lactobacillus acidophilus, Lacticaseibacillus paracasei* Lpc-37, *Bifidobacterium lactis* Bi-07, *Bifidobacterium lactis* BI-04 • Preparation form: Capsule • Dose: 1.70×10^{10} CFU (high dose) or 4.17×10^9 CFU (low dose) • Intervention duration: starting at antibiotic therapy initiation, up to 7 days after antibiotic cessation • Follow-up duration: Up to 3 weeks after the intervention stopped	"AAD was defined as three or more liquid stools in a 24-h period. Testing for *Clostridioides difficile:* Cytotoxic and antigen detection assays	↓ AAD incidence (24.6% vs 19.6% vs. 12.5% [in G3 vs. G2 vs. G1], p = 0.005 in G1 vs. G3) ↓ CDAD incidence (4.8% vs 1.8% vs. 1.8%, [G3 vs. G2 vs G1], p = 0.04 in G1 vs. G3) ↓ defecation frequency High-dose probiotics shorten the AAD duration	Low	[53]
6.	• Participants: 437 adult inpatients receiving antibiotic therapy, divided into 2 groups receiving probiotics or placebo • Probiotics used: *Lacticaseibacillus casei* and *Lactobacillus acidophilus* • Preparation form: Fermented milk beverage • Dose: 50×10^9 CFU/container, 98 g/day (49 g/day for first 2 days) • Intervention duration: starting at antibiotic therapy initiation and administered for 4 weeks (28 days). • Follow-up duration: Up to 2 weeks after the intervention stopped.	"Diarrhea was defined as one or more episodes of unformed or liquid stool in a 24-h period." Testing for *Clostridioides difficile:* detection of toxin A or B	↓ AAD incidence (21.8% vs. 31.7% [pro vs. pla]; 95% CI: 0.405–0.971; p = 0.037) Shortens the AAD duration (in days, after adjusted analysis) No significant difference in CDAD incidence (6.2% vs. 13.3%, p = 0.645).	Some concerns	[54]

Table 3. Continued

No.	Intervention	AAD definition in study	Probiotic effects	Risk of bias	Ref.
7.*	• Participants: 555 adult outpatients receiving 1 or 2 antibiotics, divided into 2 groups receiving probiotics or placebo • Probiotics used: 7 species of *Lactobacillus* spp., 4 species of *Bifidobacterium* spp.; *Bacillus coagulans, Saccharomyces boulardii* • Preparation form: Enterosolvent capsule • Dose: Each capsule contains 7 species of *Lactobacillus* spp. (56×10^9 CFU), 4 species of *Bifidobacterium* spp. (38×10^9 CFU); *Bacillus coagulans* (1×10^9 CFU); *Saccharomyces boulardii* (5×10^9 CFU), given 1×/day (2 capsules per day for the duration of antibiotic therapy followed by 1 capsule/day for 14 days after antibiotics are stopped) • Intervention duration: starting at antibiotic therapy initiation and administered up to 14 days after antibiotic cessation • Follow-up duration: Up to 21 ± 2 days after cessation of antibiotics	"AAD was defined as ≥3 loose or liquid stools (types 5–7) according to the Bristol Stool Form Scale [BSFS] over a period of 24 hours."	↓ incidence (9.2% vs. 25.3%, [pro vs. pla], $p < 0.001$) and severity of AAD (1.1% vs. 8.4%, $p < 0.001$). Shortens the AAD duration Alleviation of gastrointestinal symptoms	Low	[55]
8.	• Participants: 113 adult inpatients receiving antibiotic therapy, divided into 2 groups receiving probiotics or no probiotics • Probiotics used: *Limosilactobacillus reuteri* LMG P-27481 + *Lacticaseibacillus* GG ATCC 53103 • Preparation form: Oral stick • Dose: 2×10^{10} CFU, 1/day • Intervention duration: starting within 24 hours from antibiotic therapy initiation, administered up to antibiotic cessation • Follow-up duration: Up to 4 weeks after discharge from the hospital (by phone)	"AAD was considered in cases of unexplained diarrhea, stool test negativity, or the presence of CDI toxin, occurring from the start of antibiotic therapy until 4 weeks after the end of antibiotic therapy." Testing for *Clostridioides difficile:* detection of toxins A and B	↓ AAD (11% vs. 28% [pro vs. pla], $p < 0.01$) and CDAD incidence (0 vs. 11% [pro vs. pla], $p < 0.01$) Alleviates gastrointestinal symptoms	High	[56]
9.	• Participants: 340 adult patients receiving antibiotic therapy, divided into 2 groups receiving probiotics or placebo • Probiotics used: *Lacticaseibacillus rhamnosus* GG + *Bifidobacterium longum* BB536 • Preparation form: Capsule • Dose: 1×10^{10} CFU/capsule, 2/day • Intervention duration: starting within 24 hours from antibiotic therapy initiation, administered up to antibiotic cessation.	Not available	↓ AAD incidence (18.23% vs. 31.17% [pro vs. pla]) Shortens the diarrhea duration No significant difference in diarrhea severity and length of stay	Low	[57]
10.	• Participants: 146 otherwise-healthy adults receiving amoxicillin-clavulanate therapy, divided into 2 groups receiving probiotics or placebo • Probiotic used: *Lactobacillus helveticus* and *Lacticaseibacillus rhamnosus* • Preparation form: capsule • Doses: *Lactobacillus helveticus* (2.0×10^8 CFU/mL) and *Lacticaseibacillus rhamnosus* (3.8×10^9 CFU/mL), twice daily • Intervention duration: 2 weeks • Follow-up duration: 10 weeks	"A diarrhea-like defecation, as defined, corresponded to a stool frequency ≥3/d and/or stool consistency ≥5 (on the BSS) for at least 2 consecutive days"	↓ diarrhea-like defecation duration (2.70 vs. 3.71 [pro vs. pla], $p = 0.037$)	Low	[58]

Table 3. Continued

No.	Intervention	AAD definition in study	Probiotic effects	Risk of bias	Ref.
11.	• Participants: 72 children receiving antibiotic therapy, divided into 2 groups receiving probiotics or placebo • Probiotic used: *Lacticaseibacillus rhamnosus, Bifidobacterium lactis,* and *Lactobacillus acidophilus* Placebo: pasteurized yogurt containing *S. thermophilus* (4.4×10^4 CFU/day) and *Lactobacillus bulgaricus* (1.2×10^8 CFU/day) • Preparation form: yogurt • Doses: *Lacticaseibacillus rhamnosus* (5.2×10^9 CFU/day), *Bifidobacterium lactis* (5.9×10^9 CFU/day), and *Lactobacillus acidophilus* (8.3×10^9 CFU/day), twice daily • Intervention duration: 1 week	Various definitions of diarrhea. These included: (A) stool consistency ≥5 and stool frequency ≥2/day for more than 2 days; (B) stool consistency ≥5 and stool frequency ≥3/day for more than 2 days; (C) stool consistency ≥6 and stool frequency ≥2/day for more than 2 days; and (D) stool consistency ≥6 and stool frequency ≥3/day for more than 2 days.	Less participants with defecation frequency ≥2×/day and fecal consistency score ≥5 in the probiotics group (significant in all definitions)	Low	[59]
12.	• Participants: 122 adult inpatients receiving systemic antibiotics, divided into 2 groups receiving probiotics or placebo • Probiotics used: *Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lacticaseibacillus plantarum, Lacticaseibacillus paracasei, L. delbrueckii* ssp. *Bulgaricus,* and *Streptococcus thermophilus* • Preparation form: powdered sachet • Doses: 4.5×10^{11} CFU/sachet, twice daily • Intervention duration: during the course of antibiotic therapy, resumed until 7 days after antibiotic cessation • Follow-up: 28 days after antibiotic cessation	"AAD was defined as more than two liquid stools (Bristol stool chart types 6 and 7) in excess of normal for each patient a day for two or more days."	↓ AAD incidence (0 vs. 11.4% [pro vs pla], p = 0.006)	Low	[60]
13.	• Participants: 63 adult patients receiving antibiotics for at least 7 days, divided into 2 groups receiving probiotics or placebo • Probiotic used: *Lacticaseibacillus rhamnosus, Lactobacillus acidophilus, and Bifidobacterium* • Preparation form: milk • Doses: *Lacticaseibacillus rhamnosus, Bifidobacterium* (10^8 CFU/mL), *Lactobacillus acidophilus* (10^7 CFU/mL), 250 mL/day • Intervention duration: 14 days	"Diarrhea defined as at least three fluid stools/day for at least 2 days during the test period" Testing for *Clostridioides difficile:* detection of toxin A via chromatographic assay, bacterial culture	↓ AAD incidence (5.9% vs. 27.6% [pro vs. pla], p = 0.035) No significant difference in CDAD incidence	High	[61]
14.	• Participants: 113 inpatients aged >50 years receiving antibiotic therapy, divided into 2 groups receiving probiotics or placebo • Probiotic used: *Lacticaseibacillus casei, Lactobacillus bulgaricus,* and *Streptococcus thermophilus* • Preparation form: Yogurt • Doses: *Lacticaseibacillus casei* and *Streptococcus thermophilus* (10^8 CFU/mL) and *Lactobacillus bulgaricus* (10^7 CFU/mL), twice daily • Intervention duration: 2 days after the start of antibiotic therapy up to 1 week after antibiotic cessation • Follow-up duration: 4 weeks following discharge	"Diarrhoea was defined as more than two liquid stools a day for three or more days in quantities in excess of normal for each patient." Testing for *Clostridioides difficile:* detection of toxins A and B via immunoassay	↓ AAD (12% vs. 34% [pro vs. pla], p = 0.007) and CDAD (0 vs. 17% [pro vs. pla], p = 0.001) incidence	Low	[62]

Table 3. Continued

No.	Intervention	AAD definition in study	Probiotic effects	Risk of bias	Ref.
15.	• Participants: 258 (study 1) and 60 (study 2) adult inpatients in the Internal Medicine wards • Probiotics used: Study 1: *Lacticaseibacillus casei* DN-114001 against placebo drink Study 2: *Lacticaseibacillus casei* DN-114001 (G1), *Lacticaseibacillus casei* Shirota (G2). • Preparation form: Probiotic drinks • Dose: 10^{10} CFU/container of drinks, 2×/day • Intervention duration: Study 1: 3 months Study 2: during the course of antibiotic therapy	"AAD was defined as at least 3 watery/fluid stools in a 24-h period."	Study 1: • ↓ AAD incidence (6.5% vs. 28.4% [pro vs. pla], $p < 0.001$) • ↓ AAD duration (1.7 vs. 3.1 days [pro vs. pla], $p = 0.015$) • No significant difference in length of hospital stay Study 2: • ↓ AAD incidence (6.7% vs. 33.3% [pro vs. pla], $p = 0.021$) • No significant difference in length of stay and AAD duration between the 2 groups	High	[63]
16.	• Participants: 23 adult inpatients receiving antibiotic therapy, divided into groups receiving probiotics or placebo • Probiotics used: *Limosilactobacillus reuteri* ATCC 55730 • Preparation form: Chewable tablet • Dose: 1×10^8 CFU/tablet, 2/day • Intervention duration: starting at antibiotic therapy initiation and administered for 4 weeks (28 days) • Follow-up duration: Up to 2 weeks after the intervention stopped.	"Diarrhea was defined as stool output meeting or exceeding 3 or more Type 6 (fluffy pieces with ragged edges and a mushy stool) or Type 7 (watery) bowel movements per day for 2 consecutive days."	↓ AAD incidence (8% vs. 50% [pro vs. pla], $p = 0.04$) ↓ defecation frequency No significant difference in gastrointestinal symptoms (nausea, abdominal pain/cramps, bloating, gas, vomiting, constipation, and reflux)	High	[64]
17.	• Participants: 158 adult patients with spinal cord injuries receiving antibiotics, divided into 2 groups receiving probiotics or placebo • Probiotic used: *Lacticaseibacillus casei* Shirota • Preparation form: beverages • Doses: 6.5×10^9 CFU/bottle, 1×/day • Intervention duration: 24 hours from the first antibiotic administration to 7 days after antibiotic cessation • Follow-up: 30 days after antibiotic cessation	"diarrhoea defined as more than two liquid stools (Bristol Stool Chart type 5, 6, or 7) a day for 3 or more days, in quantities in excess of normal." Testing for *Clostridioides difficile:* detection of glutamate dehydrogenase and toxin	↓ AAD incidence (17.1% vs. 54.9% [pro vs. pla], $p < 0.001$) No significant difference in CDAD incidence (0 vs. 1.2%)	Some concerns	[65]
18.	• Participants: 157 hospitalized infants (6–36 months) receiving antibiotic therapy, divided into groups receiving probiotic formula or placebo • Probiotics used: *Bifidobacterium lactis* and *Streptococcus thermophilus* • Preparation form: Formula milk • Dose: 10^7 viable cells of *Bifidobacterium lactis* and 10^6 viable cells of *Streptococcus thermophilus* • Intervention duration: starting at antibiotic therapy initiation and being administered for 15 days.	"Diarrhea was defined as a change in bowel habits with the passage of three or more liquid stools per day for at least 2 consecutive days."	↓ AAD incidence (16.3% vs 31.2% [pro vs. pla], $p = 0.044$) and dehydration (69.2% vs. 95.8%, $p = 0.039$) No significant difference in the duration or incubation period of AAD	High	[66]

Table 3. Continued

No.	Intervention	AAD definition in study	Probiotic effects	Risk of bias	Ref.
19.†	• Participants: 163 patients receiving antibiotic therapy, divided into groups receiving drinks with no probiotics or with probiotics • Probiotics used: *Lacticaseibacillus plantarum* • Preparation form: Beverage • Dose: 5×10^7 CFU/mL, 200 mL/day (total 10^{10} CFU/day) • Intervention duration: starting within 48 hours from antibiotic therapy initiation and administered up to 1 week after antibiotic cessation • Follow-up duration: up to 3 days after the intervention stopped	"Diarrhea was defined as at least 3 loose or watery stools per day for at least 2 consecutive days." Testing for *Clostridioides difficile:* detection of toxin via enzyme-linked immunosorbent assay	Probiotics did not affect diarrhea incidence (7.5% vs 6.0% [pro vs. pla], p = 0.86) ↓ risk of watery stool ↓ risk of nausea No significant difference in toxin-producing *Clostridioides difficile* between the groups	High	[67]
20.	• Participants: 88 adult patients with *Helicobacter pylori* infection receiving antibiotic therapy were divided into 3 groups receiving acidified milk without probiotics (G1), pasteurized fermented milk (G2), or fermented milk with probiotics (G3) • Probiotics used: *Lactobacillus acidophilus* LA-5, *B. animalis* subsp *Bifidobacterium lactis,* and *Streptococcus thermophilus* • Preparation form: Fermented milk beverage • Dose: 10^6 CFU/g, 2 × 125 g/day • Intervention duration: 5 weeks • Follow-up duration: up to 56 days after the initiation of the intervention.	"Diarrhoea was defined as three or more watery stools on two or more consecutive days."	No significant reduction in the incidence of diarrhea (4 vs. 2 vs. 3 [G3 vs. G2 vs. G1]) Shortens the diarrhea duration Alleviates abdominal pain (observed both in G2 and G3) Increased *Bifidobacterium* population in G1 and G3 Increased *Lactobacillus acidophilus* population in G3	Some concerns	[68]
21.	• Participants: 70 adult patients receiving antibiotic therapy, divided into 2 groups: placebo and probiotic groups • Probiotics used: *Lacticaseibacillus casei* and *Bifidobacterium breve* • Preparation form: Sachet • Dose: 2×10^7 to 10^9 cells of *Lactobacillus casei* and 5×10^7 to 10^9 cells of *Bifidobacterium breve,* 1×/day	"All of them contracted diarrhea during the use or in the next 7 days after the suspension of antimicrobial medication, which had been induced for at least 24h. This occurred with watery or semi-liquid stools on two or more occasions, in the last 24h."	No significant difference in diarrhea duration (4.87 vs. 4.52 days [pro vs. pla], p > 0.05) or recurrence (34.3% vs. 22.8% [pro vs. pla], p > 0.05) was found.	Some concerns	[69]
22.	• Participants: 314 adult patients receiving amoxicillin-clavulanate or levofloxacin antibiotic therapy, divided into 3 groups receiving no yogurt (G1), placebo yogurt with *Streptococcus thermophilus* + *L. delbrueckii* subsp. *Bulgaricus* as starters (G2), and probiotic yogurt (same as G2 with addition of probiotics) • Probiotics used: *Lactobacillus acidophilus* La-5, *B. animalis* subsp. *lactis* Bb-12, *Lacticaseibacillus casei* subsp. *casei* Lc-01 • Preparation form: Yogurt • Dose: *Lactobacillus acidophilus* La-5 (5×10^6 CFU/mL), *L. casei* Lc-01 (1×10^7 CFU/mL), and *Bifidobacterium lactis* Bb-12 (1×10^8 CFU/mL), given in 150–200 ml of yogurt per day • Intervention duration: starting within 48 hours of antibiotic therapy initiation up to 5 days after therapy cessation • Follow-up duration: up to 1 month after the cessation of antibiotic therapy (by phone)	"Definition of diarrhea was used: ≥3 loose or watery stools per day for ≥2 days."	Probiotics did not decrease the duration of AAD (3.2 vs. 3.7 days [pro vs. pla], p = 0.742), prevent AAD (28% vs. 22% [pro vs. pla], p = 0.30), or decrease the length of stay (2.4% vs. 0 [pro vs. pla], p = 0.243).	Low	[70]

Table 3. Continued

No.	Intervention	AAD definition in study	Probiotic effects	Risk of bias	Ref.
23.	• Participants: 172 adult patients with respiratory tract infections within 48 hours of receiving antibiotic therapy, divided into groups receiving probiotics and without probiotics • Probiotics used: *Lacticaseibacillus rhamnosus* R0011 + *Lactobacillus acidophilus* R0052 • Preparation form: Capsule • Dose: 2 × 10^9 CFU/capsule, 2/day • Intervention duration: 14 days • Follow-up duration: 14 days	Definition in the primary outcome "AAD-1 was defined as loose or watery stool more than 3 times per day for at least 2 days within 14 days of enrollment." Definition in the secondary outcome "AAD-2 was defined as loose or watery stool more than 2 times per day for at least 2 days within 14 days of enrollment."	No significant difference in AAD-1 (3.9% vs. 7.2% [pro vs. pla], p = 0.44) and AAD-2 (8.7% vs. 14.4% [pro vs. pla], p = 0.28) incidence	Low	[71]
24.	• Participants: 78 pediatric patients (5 months-16 years) receiving antibiotic therapy, divided into groups receiving probiotics and placebo • Probiotics used: *Lacticaseibacillus rhamnosus* KL53A + *Bifidobacterium longum* PL03 + *Lacticaseibacillus plantarum* PL02 • Preparation form: Food supplement • Dose: 10^8 CFU *[Bifidobacterium longum* PL03 (33%), *Lacticaseibacillus rhamnosus* KL53A (33%), and *Lacticaseibacillus plantarum* PL02 (34%)].	"Diarrhoea was defined as ≥ 3 loose or watery stools per day for a minimum of 48 h, occurring during and/or up to 2 weeks after the end of the antibiotic therapy."	Probiotic use did not decrease AAD incidence (2.5% vs. 5.2% [pro vs. pla], p > 0.05, 95%CI -0.8-15) Defecation frequency decreased with probiotic use.	Low	[72]
25.	• Participants: 2941 elderly patients (age ≥65 years) receiving antibiotics, divided into 2 groups receiving probiotics or placebo • Probiotic used: 2 strains of *Lactobacillus acidophilus* and 2 strains of *Bifidobacterium* • Preparation form: vegetarian capsule • Doses: 6 × 10^{10} live bacteria (proportion between strains/species not specified), once daily • Intervention duration: 21 days • Follow-up duration: 12 weeks	"Diarrhea as three or more loose stools (consistency 5–7 on the Bristol Stool Form Scale) in a 24 h period or as stools described as looser than normal." Testing for *Clostridioides difficile:* culture and detection of toxin via immunoassay	No significant difference was found in AAD (10.8% vs. 10.4% [pro vs. pla], p = 0.72, 95% CI: 0.83-1.32) and CDAD (0.8% vs. 1.2% [pro vs. pla], p = 0.35, 95% CI: 0.34-1.48) incidence Similar duration and severity of diarrhea between groups	Low	[73]
26.	• Participants: 32 adult ICU patients receiving one or more antibiotics during ICU care, divided into 2 groups with no probiotics and with probiotics • Probiotics used: *Lacticaseibacillus paracasei* • Preparation form: Commercial yogurt drink • Dose: 10^{10} CFU/container, 2 containers/day • Intervention duration: starting within 48 hours of antibiotic therapy initiation up to 7 days after therapy cessation • Follow-up duration: 1 month after the cessation of antibiotic therapy	"Diarrhoea was defined as three or more bowel movements per day or greater than 750 mL of liquid stool." Testing for *Clostridioides difficile:* detection of toxin A or B via immunoassay	There was no significant difference in AAD incidence (68.8% vs. 62.5% [pro vs. pla], p = 1.000), duration (2.13 vs. 3.69 days [pro vs. pla], p = 0.241), and CDAD in ICU (6.0% vs. 12.5%, p = 0.600).	High	[74]

Table 3. Continued

No.	Intervention	AAD definition in study	Probiotic effects	Risk of bias	Ref.
27.	• Participants: 438 pediatric outpatients receiving antibiotic therapy, divided into groups receiving probiotics and placebo • Probiotics used: *Lacticaseibacillus plantarum* DSM9843 • Preparation form: Capsule • Dose: 1×10^{10} CFU/capsule • Intervention duration: starting with antibiotic therapy initiation, up to 1 week after antibiotic cessation • Follow-up duration: Up to 1 week after the intervention was stopped (range: 15–28 days)	"Diarrhea was defined as ≥3 loose/watery stools/24 hours starting after initiation of antibiotic treatment."	No significant difference in AAD incidence (2.8% vs. 4.1% [pro vs. pla], p = 0.4), frequency of defecation, and other gastrointestinal symptoms.	Low	[75]
28.	• Participants: 267 adult inpatients receiving antibiotic therapy, divided into 2 groups receiving probiotics or placebo • Probiotics used: *Lactobacillus* GG • Preparation form: Capsule • Dose: 10×10^9 CFU/capsule, 2/day • Intervention duration: starting within the first 24 hours from antibiotic therapy initiation and being administered for 2 weeks • Follow-up duration: Up to 21 days after the intervention stopped	"Diarrhea was defined as watery or liquid stools (bowel movement consistency of 1, 2, or 3 on the Stool Consistency Continuum) for 2 or more consecutive days in a patient with normal stools (≤1 per day) at baseline or 3 or more bowel movements more than the patient's normal daily number of bowel movements." Testing for *Clostridioides difficile:* detection of toxin	No significant effect of probiotic use in preventing AAD incidence (29.3% vs. 29.9% [pro vs. pla], p = 0.93), reducing severity (3.1% vs. 7.1%, p = 0.47), and preventing CDAD (1.5% vs. 2.2%, p > 0.99).	Low	[76]
29.	• Participants: 359 adult patients with SC injuries receiving antibiotic therapy, divided into 2 groups receiving probiotics or placebo • Probiotic used: *Lacticaseibacillus casei* Shirota • Preparation form: beverage • Doses: 65×10^9 CFU/mL, once daily • Intervention duration: 7 days • Follow-up duration: up to 30 days after antibiotic cessation.	"Diarrhoea was defined as more than two liquid stools (Bristol stool scale type 5, 6, or 7) in any 24 h period." Testing for *Clostridioides difficile:* detection of glutamate dehydrogenase, toxin A and/or B via immunoassay, and polymerase chain reaction to detect toxin A and B	No significant difference in AAD (45% vs. 42.1% [pro vs. pla], p = 0.639) and CDAD (1.8% vs. 1.9%, p = 0.963) No difference in the duration and frequency of diarrheal episodes between groups Probiotic use only decreased AAD incidence in patients receiving routine PPI therapy (28% vs. 52.2%, p = 0.015).	Low	[77]
30.	• Participants: 854 patients aged >55 years receiving antibiotics 7 days before admission up to 72 hours since admission, divided into 2 groups receiving probiotics or placebo • Probiotic used: *Lacticaseibacillus casei, L. delbrueckii* ssp. *bulgaricus* and *Streptococcus thermophilus* • Preparation form: yoghurt • Doses: *Lacticaseibacillus casei* (10^8 CFU/mL), *L. delbrueckii, and Streptococcus thermophilus* (10^6 CFU/mL), 2×100 mL/day • Intervention duration: 7 days • Follow-up duration: 2 weeks	"Diarrhoea was initially defined in the protocol as more than two liquid stools a day for three or more days in quantities in excess of normal for each patient." Testing for *Clostridioides difficile:* detection of toxin via enzyme-linked immunosorbent assay	No significant difference in AAD (19.3% vs. 17.9% [pro vs. pla], 95% CI 0.82-1.49, p = 0.53) and CDAD incidence (0.2% vs. 0.45%)	Some concerns	[78]

* Studies using mix of LAB and non-LAB probiotics.

† Studies numbered 19-30 showed no significant effect of probiotics in AAD prevention.

AAD, antibiotic-associated diarrhea; AISS, Amsterdam Infant Stool Scale; BSFS, Bristol Stool Form Scale; BSS, Bristol Stool Scale; CDAD, *Clostridioides difficile-associated* diarrhea; CDI, *Clostridioides difficile* infection; CFU, colony-forming unit; CI, confidence interval; ICU, intensive care unit; LAB, lactic acid bacteria; PPI, proton pump inhibitor; SC, spinal cord; pro, probiotic; pla, placebo.

Most studies (18 of 30 trials) reported a decrease in AAD incidence following the administration of LAB as probiotics[49-66]. Wong et al.[77] reported a decrease in AAD incidence only among patients with spinal cord injury who received routine proton pump inhibitor (PPI) therapy. Among the 15 studies specifically assessing AAD incidence due to *Clostridioides difficile* infection (CDI)[49,51-54,56,61,62,65,67,73,74,76-78], only five reported a decrease in CDI incidence with LAB probiotic use[51-53,56,62]. Other outcomes assessed across clinical trials included diarrhea duration, length of hospital stay, occurrence of other gastrointestinal symptoms, and dehydration.

Several studies (6 of 30 trials) showed that LAB administration as probiotics reduced AAD duration[51,54,55,57,63,68]. Szymański et al.[72] reported that although probiotic use did not reduce AAD incidence, it notably decreased diarrhea frequency among pediatric patients receiving probiotics. Cimperman et al.[64] and Ouwehand et al.[53] also reported significant reductions in diarrhea frequency among adults receiving LAB-containing probiotics. Regarding the onset of diarrhea, García Trallero et al.[50] reported a 5.39-day delay in the onset of diarrhea in the group receiving probiotics. However, no difference in daily diarrhea frequency was observed between patients receiving probiotics and those receiving placebo[50]. Hodzhev et al.[55] found a mean reduction of 1.12 days in diarrhea duration in the group receiving multispecies probiotics, but no changes in diarrhea frequency were observed.

Some clinical trials involving inpatients also assessed length of hospital stay among patients receiving LAB as probiotics. Dietrich et al.[63] conducted two studies, one comparing probiotics with placebo and the other comparing two probiotic drinks containing different *Lacticaseibacillus casei* strains. Neither study found a significant difference in length of hospital stay between groups. A study involving adult ICU patients in Canada also found no significant difference in length of hospital stay following probiotic use[74].

Several studies compared the incidence of gastrointestinal symptoms accompanying AAD in patients receiving LAB probiotics with that in patients not receiving them. A study by de Vrese et al.[68] involving patients with *Helicobacter pylori* infection reported a decrease in abdominal pain among patients receiving fermented milk containing LAB probiotics. However, this decrease was also observed in the group receiving pasteurized fermented milk[68]. Gao et al.[51] reported reductions in several symptoms, including abdominal pain and distension, loose stools, and constipation, following LAB probiotic use. These reductions were more pronounced in the group receiving a higher probiotic dose[51]. Hodzhev et al.[55] also reported that multistrain probiotic use reduced nausea, abdominal pain and distension, and gas formation. In a study by Saviano et al.[56], LAB probiotic administration reduced nausea but did not significantly affect abdominal pain. Lönnermark et al. found a reduced risk of nausea and watery stool formation among patients receiving drinks containing *Lacticaseibacillus plantarum*[67]. However, Olek et al.[75] found no significant changes in gastrointestinal symptoms, including abdominal pain and distension, nausea, and flatulence, among pediatric patients receiving *Lacticaseibacillus plantarum*. In addition, two studies assessed the effects of LAB probiotic use on dehydration incidence in patients with AAD. A multicenter study in the Netherlands and Poland involving pediatric patients reported a reduction in the proportion of patients requiring rehydration therapy in the group receiving probiotics[49]. A Brazilian study involving infants also reported a decrease in dehydration incidence following the administration of formula milk containing LAB probiotics[66].

Discussion

Probiotics exert antibacterial effects by secreting antimicrobial peptides and competing with pathogens for nutrients. They also possess antibiofilm properties by binding pathogens into aggregates, thereby preventing pathogen colonization and biofilm formation. Probiotics prevent bacterial adhesion by competing for nutrients and binding sites (receptors) in the intestine. Antimicrobial substances, such as organic acids, oxidant catabolites (hydrogen peroxide), and antimicrobial peptides (bacteriocins), also prevent pathogen adhesion. A previous study reported that *Lacticaseibacillus plantarum* and *Lacticaseibacillus* rhamnosus inhibited the colonization of *Escherichia coli* and *Salmonella enterica serovar Typhimurium* by up to 30%–90%[79].

In vivo studies reviewed in this article showed that LAB exert beneficial effects by reducing diarrhea incidence, symptoms, and inflammation. However, clinical trials have yielded varying results, which may be attributable to several factors. First, phylogenetic and metagenomic analyses have revealed that, despite similarities in the genera present in the gut microbiota of mice and humans, their relative abundances differ substantially. The murine gut microbiota is characterized by the predominance of Lactobacillus and Turicibacter, whereas the human gut microbiota is dominated by Faecalibacterium. In addition, the mouse forestomach is lined with various Lactobacillus strains. This contrasts with the human stomach, which is colonized by Helicobacter *pylori*, *Prevotella* spp., and *Streptococcus* spp.[80]. These differences may affect the mechanisms by which probiotics act against AAD, including the modulation of SCFA production, secretion of antimicrobial peptides, and suppression of pro-inflammatory cytokines. Further studies are warranted to explore and confirm these effects.

Several challenges remain in generalizing findings across clinical studies. In the present review, probiotics showed beneficial effects in 15 of 25 studies involving adults and 3 of 5 studies involving pediatric patients. Thus, the benefits of probiotics in pediatric patients remain unclear. In one study, only three patients developed AAD (one in the probiotic group and two in the placebo group)[72]. Another study using a single-species probiotic found no significant preventive effect against AAD[75]. Numerous previous meta-analyses have examined the use of LAB as probiotics for AAD prevention. Most concluded that probiotics were effective in preventing AAD in adults[81-88]. However, their efficacy in pediatric and older adult populations remained controversial[83-85,89,90]. A meta-analysis by Guo et al.[91] reported that the benefits of probiotics in preventing AAD in pediatric patients were significant only when the probiotics were administered at doses of $\geq 5 \times 10^9$ colony-forming unit (CFU)/day. These studies also highlighted several limitations of existing clinical trials, including variations in AAD definitions, the use of single- and multistrain probiotics, differences in probiotic doses, and limited reporting of adverse events.

Variations in AAD definitions have been a challenge when applying clinical trial results in practice. Studies may use different definitions of AAD based on the number of bowel movements and stool consistency[84,86,92]. However, Jafarnejad et al.[84] concluded in a meta-analysis that AAD was most commonly defined in probiotic trials as the "abrupt onset of ≥3 loose or watery stools following antibiotic administration". This broader definition may help in interpreting trial results in clinical practice. In addition, the included clinical trials did not report the identification of causative pathogens of AAD (such as *Klebsiella oxytoca*, *Staphylococcus aureus*, or others) in all patients. Different causative agents of AAD may have affected the clinical outcomes of probiotic administration. Future studies should address this issue by identifying the causative agents of AAD to help establish a more specific relationship between AAD pathogens and the probiotic species used.

Current guidelines outline the use of probiotics for managing or preventing AAD or CDAD. The 2018 guidelines of the Infectious Diseases Society of America allow probiotic use in immunocompetent adults and pediatric patients (with weak evidence for adults and moderate evidence for pediatric patients),[93] but do not recommend probiotics to prevent AAD caused by *Clostridioides difficile*[94]. Meanwhile, the updated 2021 guidelines of the European Society of Clinical Microbiology and Infectious Diseases do not recommend probiotics for the prevention or management of AAD, particularly cases caused by *Clostridioides difficile*[95]. Nevertheless, a recent Cochrane meta-analysis by Esmaeilinezhad et al.[96] reported that CDAD incidence was 50% lower in groups receiving probiotics than in control groups (1.6% vs. 3.2%, respectively). In the present review, most studies on CDAD (10 of 15 studies) found that probiotics were not effective in preventing CDAD. However, methods for detecting *Clostridioides difficile* varied across studies, and most clinical trials did not distinguish between true infection and asymptomatic carriage. Globally, the prevalence of *Clostridioides difficile* colonization is estimated to be around 7.6%, while colonization occurs in 1.5% of healthy populations. This prevalence may be higher in vulnerable populations, such as patients with cancer or cystic fibrosis, older adults, inpatients, and ICU patients[97].

Currently available tests for CDI do not have sufficient sensitivity and specificity when used alone, so more than one testing method may be necessary. In addition, *Clostridioides difficile* may cause asymptomatic colonization, and available tests cannot clearly distinguish asymptomatic colonization from active infection[1]. Pattani et al.[87] also noted in a meta-analysis that cases of community-associated CDI may be excluded from trials because hospital-based trials often exclude outpatients who received antibiotics in the preceding weeks. Future trials should address these issues to provide better evidence on the use of probiotics for CDI prevention.

Most studies in this review involved hospitalized inpatients. This finding was similar among studies showing beneficial effects of probiotics for AAD (14 of 18 studies) and those showing no significant effects (9 of 12 studies). A meta-analysis by Blaabjerg et al.[92] found that probiotics were beneficial for AAD prevention in outpatients compared with placebo (8% vs. 17.7%; 95% CI, 0.36–0.66). Another meta-analysis found that probiotics reduced the pooled relative risk (RR) of AAD in both inpatient studies (RR, 0.67; 95% CI, 0.58–0.77) and outpatient studies (RR, 0.67; 95% CI, 0.49–0.92)[84]. Our findings suggest that probiotics may be used for AAD prevention in both inpatient and outpatient settings. However, the appropriate target population must be considered to ensure the safe and effective use of probiotics. Patients with certain conditions, such as immunocompromised status, a history of gastrointestinal surgery, or other relevant comorbidities, have been underrepresented in clinical trials because of medical risks. Therefore, careful consideration of the patient's clinical history and presentation is necessary before probiotic use.

Eight studies used only one LAB species as a probiotic, whereas 22 used combinations of two or more LAB species. One publication by Dietrich et al.[63] reported two studies: the first compared a single LAB species (*Lacticaseibacillus casei* DN-114001) with placebo, whereas the second compared two different strains of the same LAB species (*Lacticaseibacillus casei* DN-114001 and *Lacticaseibacillus casei* Shirota). In the present review, most studies showing beneficial effects of probiotics for AAD prevention or treatment (15 of 18 studies) used multispecies probiotics. The LAB species that showed the

most consistent beneficial effects was *Lactobacillus acidophilus* (10 of 18 studies), which was administered in combination with other Lactobacillaceae and *Bifidobacterium* spp. The use of multiple species and/or strains in probiotic preparations makes it difficult to independently associate each species and/or strain with a reduced risk of AAD. This limitation has also been noted in existing meta-analyses[81,83,84,87,92]. The selection of LAB species for probiotic combinations must consider possible inhibitory interactions between species. Chapman et al.[98] previously reported inhibitory interactions between LAB species in a multispecies probiotic. For instance, *Bifidobacterium breve* was shown to inhibit the growth of *Lacticaseibacillus casei*. Such interactions may reduce the effectiveness of a probiotic preparation. Therefore, although probiotics may provide overall benefits for AAD prevention, identifying the most effective agents through head-to-head comparisons remains an important area for future research.

All trials in the present review used Lactobacillaceae and *Bifidobacterium* spp. as probiotics, with only a few studies using multispecies probiotics that included other organisms, such as *Saccharomyces boulardii*, *Bacillus coagulans*, and *Streptococcus thermophilus*. No study in the present review used *Leuconostoc* spp. The beneficial effects of *Lactobacillus* spp. and *Bifidobacterium* spp. as probiotics vary by species and strain[99]. These differences may result from variations in bacteriocins, SCFAs, or other specific compounds secreted by LAB. For instance, plantaricin, a type of bacteriocin, contributes to the alleviation of colitis symptoms and a decrease in Mucispirillum abundance. Enterocin A, another bacteriocin secreted by *Enterococcus*, exerts its effects by eliminating some multidrug-resistant bacteria. In the context of AAD prevention, different bacteriocins may have distinct effects. In addition, bacteriocin production depends heavily on temperature and pH[100], so different probiotic formulations may result in different levels of bacteriocin secretion. This warrants further investigation into how different LAB species and genera interact and produce these metabolites, including Lactobacillaceae and *Bifidobacterium*. Future studies are needed to investigate the roles of specific compounds secreted by LAB as anti-AAD agents and to identify the optimal combinations of bacterial species for maximum benefit.

Currently, the assessment of strain specificity and benefits is hampered by variability in the strains or strain combinations used for the same disease or condition, changes in bacterial taxonomy (such as the reclassification of genera and species) and strain identification, and the lack of global consensus on strain designations. Strain designations are often not reported in early clinical trial publications[83]. This may require tracing the development of the probiotic product used in the trials to identify the bacterial strain. Additionally, different strains and species may vary in their ability to restore the host's normal microbiota[101]. Some trials may also use probiotic products containing proprietary strains. This may limit our understanding of the specific mechanisms of action of a given strain or explain why the strain was included in the product[102]. Misidentification and misclassification of strains, as well as the presence of unlabeled species in products, may present additional challenges[103].

The doses of probiotics used across trials have also varied considerably. The bacterial dose, measured in CFUs, may affect the desired outcome of probiotic therapy. In a previous meta-analysis, doses of 5×10^9 CFU/day or higher appeared to be more effective, but strain-specific dose studies are still needed[91]. In the present review, most studies showing beneficial effects of probiotics (13 of 18 studies) used doses of $\geq 5 \times 10^9$ CFU. Interestingly, most studies showing no beneficial effects of probiotics for AAD (8 of 12 studies) also used doses of $\geq 5 \times 10^9$ CFU. This suggests that, in addition to probiotic dosage, the benefits of probiotics for AAD may depend on the combination of species in the preparation. Previous meta-analyses have suggested a possible dose–response relationship between probiotic use and AAD incidence. However, these analyses included various probiotic species rather than specific strains[82,92]. More studies are needed to validate this dose–response effect, particularly for individual strains.

The trials reviewed in this article had varying follow-up periods, but most lasted less than eight weeks after antibiotic therapy was discontinued. Therefore, the follow-up periods may have been insufficient to assess AAD, and cases may have been missed or undocumented after follow-up ended[86,89]. Additionally, adverse event reporting varied across trials. This may be because adverse events are often not predefined before trial participants are enrolled[90]. More standardized adverse event reporting across trials would enable a more detailed assessment of the risk–benefit profile to ensure the optimal use of LAB for AAD prevention.

Five studies involving pediatric patients and 25 studies involving adults were reviewed in this article. Gut colonization by microorganisms begins soon after birth, and processes affecting the abundance and species diversity of the gut microbiota lead to substantial changes in its composition within weeks or even days during the first 2–3 years of life. After this period, the rate of change becomes more stable as the gut microbiota matures. The relatively stable adult gut microbiota may recover better from interventions, such as antibiotic use, or other disturbances. However, when the same interventions or disturbances affect an infant's or child's gut microbiota, the effects may persist longer[104]. Thomas et al.[76] also highlighted that differences in gut microbiota composition between children and adults may affect the

effects of probiotic use. Patients' individual conditions and the timing of probiotic initiation also need to be considered. In a study by de Souza and Jorge,[69] probiotic administration was started 7–10 days after the initiation of antibiotic therapy. This raises the possibility that dysbiosis had already occurred before probiotics were started[69]. Alberda et al.[74] also noted that ICU patients often receive antibiotics for other conditions before ICU admission. This may complicate the assessment of probiotics as primary preventive agents for AAD or CDI[74]. Previous meta-analyses have highlighted the need to identify patients at higher risk for AAD to ensure the optimal benefits of probiotic use[84,104]. Both host and drug factors need to be considered when identifying patients at high risk for AAD. Age, underlying conditions, and nasogastric tube use, which is common among ICU patients, are among the host factors associated with AAD risk[85]. Additionally, complications from probiotic use tend to occur in certain populations, such as immunocompromised patients. Therefore, alongside adverse event reporting, identifying patients at risk for AAD will help ensure the safe use of probiotics for AAD prevention.

Most clinical trials reviewed in this article were conducted in European and North American populations, with only a small number of studies from Asia, South America, and Oceania. These results may not be applicable to populations in Asia, Africa, or South America without local validation studies. Lactobacillus spp. belong to the phylum *Firmicutes*, which makes up approximately 90% of a healthy person's gut microbiota. Meanwhile, *Bifidobacterium* spp. are the most abundant members of the phylum Actinobacteria in the human gut microbiota. However, Actinobacteria have a relatively low abundance in the human gut[105]. The abundance of these two genera in the human gut microbiota may be affected by geographic distribution, ethnicity, and dietary habits. For example, a metagenomic study focusing on *Lactobacillus* spp. found that Lactobacillus types (LbTypes) were more evenly distributed and more numerous in Europe and North America, where Delbrueckii and *Casei* LbTypes were prevalent. Europe had the highest prevalence of these two LbTypes, which may be attributed to yogurt consumption and the use of probiotic products. In contrast, these two LbTypes tend to be absent in Asia and nonindustrialized nations[106]. *Bifidobacterium* spp. are more commonly identified in the gut microbiota of Asian and European populations. The abundance of *Bifidobacterium* in Asian countries, such as Japan, China, and India, may be associated with the consumption of high-starch foods in these populations[107].

In addition to geographic factors, ethnicity may also affect the composition of the human gut microbiota. These differences remained observable after controlling for other relevant variables, including demographics and diet[108]. Dietary habits may also contribute to variations in gut microbiota diversity across populations. For example, gluten-free and Western diets were shown to decrease the abundance of Lactobacillus in the gut microbiota, whereas Mediterranean diets increased the abundance of both *Lactobacillus* and *Bifidobacterium*. In addition, dietary effects on the gut microbiota were observed across age groups in one study population[105]. In the present review, three trials explicitly instructed participants not to consume other probiotic or prebiotic products or fermented foods, apart from the intervention product, during the trials[55,67,68]. However, detailed information on participants' dietary habits was not recorded. This lack of dietary data may have confounded the results[102]. Consideration of participants' microbiomes and the factors influencing them (geography, ethnicity, and diet) is necessary because probiotics interact with the microbiota. However, baseline microbiome data are more widely available from Europe, North America, and China. In contrast, major gaps in microbiome data remain in other parts of the world, especially in low- and middle-income countries of the Global South[109]. Future clinical trials need to consider ethnogeographic and dietary variations between populations, as these factors influence gut microbiota dynamics and may affect the ability of LAB to prevent AAD. In addition, considering substantial microbiome variations within regions and among individuals in a trial may create opportunities to tailor probiotics by strain or species combination to achieve the greatest benefit in each population[109].

The forms of probiotic preparations used in trials also need to be considered, as they may help maintain LAB viability or provide additional effects. *Lactobacillus* spp. may be more suitable for non-gastroprotective probiotic preparations because of their ability to survive gastric pH. *Bifidobacterium* spp. are mostly found in the colon, where they play a role in the fermentation and digestion of complex carbohydrates from the host's diet. Therefore, the desired effects may be achieved if *Bifidobacterium* spp. in the probiotic preparation can reach and successfully colonize the colon[99]. Most trials reviewed in this article administered probiotics using conventional preparations, such as capsules, chewable tablets, and oral sticks or sachets. Conventional preparations are better characterized than nonconventional preparations, such as foods and drinks, for probiotic administration. Meanwhile, nonconventional probiotic preparations, such as cheese, yogurt, cream, and other food products, are easier to obtain and consume. However, both conventional and nonconventional products may differ in their effects because of the formulation process, bacterial viability, the varying ability of bacterial species to survive different host physiological processes, and their ability to adhere to the intestinal lumen[99].

Some trials used dairy-based food and beverage products, such as formula milk, fermented milk, and yogurt, as probiotic preparations. Dairy-based products are known to provide suitable media for probiotic growth. Probiotic bacteria obtain carbon and essential amino acids from lactose-hydrolyzing enzymes and a proteolytic system that digests casein[108,109]. The flavor, preservation, and presentation of dairy-based probiotic products are affected by compounds resulting from the metabolism of these nutrients[110]. Milk also has buffering capacity and fat content, which may help probiotic bacteria tolerate and survive conditions in the gastrointestinal tract[111]. Fermented dairy products require starter cultures to initiate fermentation. However, antagonistic interactions between the starter culture and added probiotic bacteria may occur because of the production of acidic compounds, peroxides, bacteriocins, and other metabolites. Therefore, when using dairy-based products and their fermented forms for probiotic preparations, compatibility between starter cultures and added probiotic bacteria also needs to be considered[110,111]. The addition of other ingredients, such as fruits, the introduction of oxygen during product preparation, and the fermentation process itself may further affect probiotic bacterial viability in dairy-based preparations[110].

Some trials used commercially available probiotic products as interventions. In addition to processing and preparation form, storage also plays a crucial role in maintaining LAB viability in probiotic products. Important factors to consider during storage include temperature, water activity or moisture, oxygen content, preparation composition, storage time, and pH. In general, probiotic products need to be stored at 4°C because of the temperature sensitivity of the bacteria. Storing products at room temperature may reduce their shelf life. In addition, LAB are anaerobic bacteria, so low-oxygen conditions and probiotic preparations made from low-water-activity matrices may improve their viability and maintain their physiological functions[112].

Another possible problem associated with probiotic use is the possibility that probiotic bacteria may serve as reservoirs of antimicrobial resistance genes. For example, resistance traits in *Lactobacillus* have two possible implications. Intrinsic resistance may be a desirable trait in probiotic bacteria, as it would allow them to survive antibiotic exposure. However, acquired resistance in probiotic bacteria may pose a risk of resistance spreading through mobile genetic elements, such as plasmids or integrated mobile genetic elements. The spread of resistance genes may affect nonpathogenic and facultative-pathogenic bacteria in both the gastrointestinal microbiota and the environment[111,112]. Studies have assessed the possibility of resistance spreading through mobile genetic elements in probiotic bacteria. Both phenotypic antibiotic resistance and antimicrobial resistance genes, such as the ESBL gene blaTEM and the tetracycline resistance gene tetK, have been found in isolates from commercially available products[113,114]. A bioinformatics study of LAB genomes from the orders Bifidobacteriales and Lactobacillales, obtained from food and probiotic supplements, also identified several antimicrobial resistance genes on mobile genetic elements[115]. Daniali et al. stated that horizontal transfer of resistance genes between probiotics and the microbiota may occur under dysbiotic conditions and may be influenced by target size, probiotic strain, and the ability to link to plasmids[116]. However, in addition to horizontal gene transfer, other mechanisms by which probiotics may confer resistance have been proposed, such as promoting the abundance of resistant bacteria or increasing resistome expansion in the lower gastrointestinal tract mucosa[117–119].

Several case reports have described bacteremia caused by bacteria found in probiotics. Some reported LAB, such as *Lacticaseibacillus* rhamnosus[120–122], and non-LAB bacteria, such as *Bacillus clausii*, as causative agents[123]. Bacteremia caused by *Lactobacillus* from probiotics has been reported in patients with immunosuppression, prolonged hospital stays, and a history of surgery[124]. These infections may occur when a damaged intestinal barrier allows bacteria such as *Lactobacillus* to enter the bloodstream. Therefore, probiotics are not recommended for patients with certain conditions, such as immunosuppression, and future studies should explore alternative strategies to prevent AAD in these vulnerable populations.

Several strategies may help address resistance modulation or transfer from probiotics. Strains intended for probiotic use may be selected or deliberately made resistant to multiple antibiotics to allow concurrent administration with antibiotic therapy and reduce gastrointestinal side effects. However, although selecting resistant traits may help ensure the effective colonization of probiotic bacteria in the gut mucosa, probiotic strains must be carefully selected to avoid those carrying resistance genes located on mobile genetic elements. This would help prevent the spread of resistance genes and further serious health consequences[112,115]. Another option in probiotic product development is to select strains carrying resistance genes that are not clinically significant and do not affect human antimicrobial therapy, or strains that carry no antimicrobial resistance genes[125].

Limitations and Future Directions

Several limitations remain in the present review. First, we included only articles published in English from two databases (PubMed and Scopus). As a result, the included articles were mostly from studies conducted in Europe and North America, with a small number of studies from Asia, South America, and

Oceania. This may limit the generalizability of our findings, as local studies published in other languages might have provided more data on other populations and a broader perspective on the use of LAB as probiotics for AAD. This review focused on Lactobacillaceae and *Bifidobacterium* because fewer studies have investigated LAB species outside these two groups (such as *Enterococcus* spp. or *Leuconostoc* spp.) as probiotics. Therefore, more studies are needed to provide a more complete picture of the benefits of LAB for AAD. We also noted that most of the included clinical trials (23 of 30 studies) were funded by probiotic manufacturers or pharmaceutical companies. Although we assessed the overall quality of all included clinical trials, sponsorship bias could not be ruled out.

Based on the findings of the present review, we recommend the following for future clinical studies.

1. The use of multispecies probiotic mixtures at a minimum dose of 5×10^9 CFU may be more beneficial. Additionally, although the use of *Lactobacillus acidophilus* consistently showed beneficial effects, the selection of species combinations in multispecies LAB preparations must consider interactions between species, such as possible inhibitory or synergistic effects, to ensure optimal benefits.

2. Preparation forms should be optimized in future studies to ensure effective probiotic delivery to the target site of action.

3. To reduce the possibility of missing AAD cases, the follow-up period should ideally extend to 8 weeks after antibiotics are discontinued, in accordance with the WHO definition of AAD.

4. Only a few trials further investigated whether AAD was caused by specific pathogens or by gut dysbiosis following antibiotic use. Future studies may need to identify the specific effects of probiotics on AAD caused by certain organisms. Additionally, studies on gut dysbiosis have mostly been limited to animal models. Further investigation is needed to determine how probiotics affect or alleviate dysbiosis in the human gut in relation to AAD.

5. To ensure probiotic safety and anticipate the risk of resistance gene transfer, future studies should ensure that the LAB used in trials are free of antimicrobial resistance genes.

Conclusion

The potential use of LAB as probiotics for AAD prevention and management may be explained by several mechanisms, including the prevention and alleviation of inflammatory responses, regulation of intestinal barrier integrity through SCFA production, competition with pathogenic species, and secretion of antimicrobial peptides, such as bacteriocins. However, these proposed mechanisms are based on *in vivo* studies and may not be directly extrapolated to humans because of biological differences in gut microbiota composition. Further studies are therefore needed.

Most clinical trials suggest that LAB have potential as probiotics for AAD prevention and management in adults. However, their clinical applicability remains challenging because of the heterogeneity of participating patients, LAB species and strains, use of single strains or combinations, doses and preparations, and follow-up durations. In addition, most trials have yet to consider other factors that may affect patients' gut microbiota, such as ethnogeographic background and dietary habits.

Further studies are needed to optimize LAB doses and preparation forms to maximize their benefits in AAD prevention and management. Factors that may influence baseline gut microbiota diversity in study populations, such as geographical distribution, ethnicity, and dietary habits, should also be considered. In addition, safety concerns, particularly the potential for adverse effects and probiotic-induced modulation of the gut resistome, warrant careful consideration in both clinical research and future probiotic product development.

Footnotes

Authorship Contributions

Concept: K.M., R.B., Design: K.M., R.B., Analysis or Interpretation: R.A.N., Literature Search: K.M., R.A.N., R.B., Writing: K.M., R.A.N., R.B.

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