The Potential of Probiotics to Eradicate Gut Carriage of Pathogenic or Antimicrobial-Resistant Enterobacterales

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Abstract: Probiotic supplements have been used to decrease the gut carriage of antimicrobial-resistant Enterobacterales through changes in the microbiota and metabolomes, nutrition competition, and the secretion of antimicrobial proteins. Many probiotics have shown Enterobacterales-inhibiting effects ex vivo and in vivo. In livestock, probiotics have been widely used to eradicate colon or environmental antimicrobial-resistant Enterobacterales colonization with promising efficacy for many years by oral supplementation, in ovo use, or as environmental disinfectants. In humans, probiotics have been used as oral supplements for infants to decrease potential gut pathogenic Enterobacterales, and probiotic mixtures, especially, have exhibited positive results. In contrast to the beneficial effects in infants, for adults, probiotic supplements might decrease potentially pathogenic Enterobacterales, but they fail to completely eradicate them in the gut. However, there are several ways to improve the effects of probiotics, including the discovery of probiotics with gut-protection ability and antimicrobial effects, the modification of delivery methods, and the discovery of engineered probiotics. The search for multifunctional probiotics and synbiotics could render the eradication of “bad” Enterobacterales in the human gut via probiotic administration achievable in the future.

Keywords: probiotics; synbiotics; antimicrobial-resistant; Enterobacterales; gastrointestinal tract; livestock

1. Introduction

Trillions of bacteria colonize in various anatomical locations in the human body, including the mouth, the upper airways, the skin, the vagina, the genitourinary system, and the intestinal tract. These colonized locations represent a highly integrated ecosystem collectively called “microbiota” [1,2]. Thus, humans are considered to be metaorganisms (also termed superorganisms or holobionts) [1,2]. The overlap of the phylogenetic trees of bacterial microbiota and primates suggests the coevolution, especially the genetic co-evolution, between host and microbiota [2–4]. The microbial colonization of the human body starts immediately following birth, and the community composition is shaped by
various environmental factors [5]. The infant gut microbiota is mostly predominated by the members of Actinobacteria, Proteobacteria, Firmicutes, and Bacteroidetes [3]. Factors influencing microbiome composition and diversity include the mode of delivery, the feeding type, maternal antibiotic and probiotic use, dietary intake, pre-pregnancy body mass index, gestational weight gain, diabetes mellitus, mood, and others [6]. For example, vaginally delivered (SVD) and breast-fed (BF) infants had a higher abundance of gut microbiota than caesarean-section-delivered, milk-powder-fed, and mixed-fed infants [7]. The genera Enterobacterales and Bifidobacterium were highly abundant in the SVD and BF groups [7]. Prior antibiotic therapy was independently associated with the carriage of extended-spectrum β-lactamase (ESBL)-producing Enterobacterales in an infant cohort upon admission to a tertiary teaching hospital in France [8]. Moreover, neonatal enteral tube feeding has been noted to serve as loci for colonization by the members of Enterobacterales [9]. Although established during infancy, the complex gut microbial community will be shaped by further medical interventions and societal preferences, such as caesarean section, formula feeding, and antibiotic use [10].

The microbiota in the gut of patients with diseases or who are aging, compared to the relative healthy population, is characterized by a decrease in diversity, greater interindividual variability, fewer beneficial microbes, such as the Firmicutes, Bifidobacterium, and Clostridium species and Faecalibacterium prausnitzii, and more pathogenic Enterobacterales [11]. The carriage of Enterobacterales in the gut is associated with lower phylogenetic diversity, dysbiotic microbiota, and the depletion of anaerobic commensals in the gut microbiota [12,13]. Moreover, among persons with gut colonization by carbapenem-resistant Enterobacterales (CRE), compositional and functional changes in the microbiota are linked to an increased risk in subsequent systemic infection and bacteremia [12].

The prevalence rate of antimicrobial-resistant organisms (AMROs), including ESBL-producing Escherichia coli and CRE, has increased in recent years [14]. Fortunately, these AMROs have been suppressed by the supernatant of some probiotics, such as Clostridium butyricum, Enterococcus faecium, and Lactobacillus plantarum, in a dose-dependent manner ex vivo [15]. Thus, it has been suggested that oral probiotic supplements can be used to eradicate Enterobacterales colonization in the gut.

Oral antibiotics, probiotics, and fecal microbiota transplantation have recently been analyzed for their potential use in decolonizing ESBL-producing Enterobacterales or CRE in the gut over the past 10 years [16]. However, in a review in 2019, Gaud Catho et al. suggest that there is not enough available evidence to recommend these decolonization strategies for the intestinal carriage of antimicrobial-resistant Enterobacterales in routine clinical practice [16]. Although the results of the routine clinical practice of probiotics in eradicating the gut carriage of antimicrobial-resistant Enterobacterales were inconclusive before 2019, many subsequent ex vivo, in vivo, and animal studies are now ongoing [17–23].

1.1. Rationale for Probiotic Supplements to Eradicate Enterobacterales Carriage in the Gut

Probiotics, by definition, are live microorganisms, and should remain viable when they reach the intended site of action, which is typically the cecum and/or the colon [24]. Most probiotics originate from fermenting food, an ancient form of preservation ingrained in human societies around the world [25]. The microbiome of all fermented foods shows increasing amounts of Lactobacillales during the fermentation process, which replaces the initial dominant composition of Enterobacterales in these foods [25]. The incorporation of probiotics into food results in higher counts of lactic acid-producing bacteria and lower counts of Enterobacterales [26]. To date, probiotics have been widely used as food additives.

The eradication of pathogenic Enterobacterales by supplementation with probiotics has been confirmed in several animal models [17–20,23]. Mice pretreated with B. bifidum ATCC 29521 exhibited a significant increase in the diversity of the gut microbiome, and a decrease in the abundance of the genus Escherichia-Shigella, belonging to the family Enterobacterales [17]. These changes in microbiota after B. bifidum ATCC 29521 pretreatment were associated with a decrease in the severity of inflammatory bowel disease [17]. More-
over, *L. rhamnosus* GG could reduce the mortality rate of septic mice by modulating gut microbiota composition, especially reducing the lipopolysaccharide producers, such as *Enterobacterales* [18]. *Bacillus coagulans* SANK 70258 suppressed *Enterobacterales* and enhanced butyrogenesis in microbiota models [19]. *L. plantarum*, isolated and identified from yak yogurt, increased the content of beneficial bacteria, including *Bacteroides*, *Bifidobacterium*, and *Lactobacillus*, and reduced the content of harmful bacteria, including *Firmicutes*, *Actinobacteria*, *Proteobacteria*, and *Enterobacterales*, and, thus, could protect against alcoholic liver injury [20]. The oral administration of *L. rhamnosus* GG can improve the survival rate of mice with sepsis by reducing lipopolysaccharide-producing *Enterobacterales*, decreasing epithelial apoptosis, and increasing the proliferation of colonic epithelium and the expression of tight junction proteins [23]. A mixture of probiotics showed more efficient eradication of pathogenic *Enterobacterales* in vivo. In mice, the mixture of *L. fermentum* GOS47 and *L. fermentum* GOS1 significantly decreased the viable count of *Enterobacterales* with potential anti-inflammatory activity and short-chain fatty acid production [27]. Thus, the favorable effect of probiotic supplements on at least the partial elimination of pathogenic *Enterobacterales*, ex vivo and in vivo, has promoted their application in clinical diseases.

Supplementation with probiotics has been investigated for the alleviation of the disease severity of systemic or gastrointestinal inflammatory diseases, such as sepsis, inflammatory bowel disease, and chemotherapy- or radiation-induced gastrointestinal mucositis [17–19,28,29]. For example, patients receiving cytotoxic and radiation therapy showed striking alterations in intestinal microbiota with, most frequently, a decrease in *Bifidobacterium*, *Clostridium* cluster XIVa and *F. prausnitzii*, and an increase in *Enterobacterales* and *Bacteroides* [28]. These pathogenic alterations resulted in the development of mucositis and bacteremia [28,29]. The prevention of cytotoxic chemotherapy-induced mucositis by probiotics has been investigated in randomized clinical trials with some promising results. Moreover, in a meta-analysis of randomized controlled trials with patients undergoing a colorectal resection, the perioperative administration of probiotics or synbiotics was associated with increased numbers of *Lactobacillus* and decreased counts of *Enterobacterales* [30]. These changes in gut microbiota were associated with less diarrhea, less symptomatic intestinal obstruction, and a lower incidence of total postoperative infections [30]. Accordingly, the use of probiotics in modulating gut microbiota and decreasing pathogenic *Enterobacterales* has become popular for application in many bowel or extra-bowel diseases, and more extensive probiotic usage can be expected in the future.

1.2. Probiotic Supplements to Decrease Gut Carriage of Enterobacterales in Livestock or Domesticated Animals

The use of probiotics in preventing gut *Enterobacterales* colonization has been applied in livestock breeding [31–36]. *Lactobacillus* supplementation, in directly fed microbes or used as phytophobic feed additives, reduced the prevalence of ESBL-producing *Enterobacterales* in broilers [31]. In young broilers, the neonatal colonization of *Enterobacterales* strains led to immune dysregulation and chronic inflammation, but early life exposure to a mixture of probiotics containing lactic-acid-producing bacteria could modulate the immune functions through the activation and trafficking of immune cells [32]. In weaned piglets, *B. subtilis* DSM25841 treatment reduced enterotoxigenic *E. coli* (ETEC) F4 infection and decreased the risk of diarrhea [34]. *L. reuteri* KUB-AC5 possessed antimicrobial activity in reducing *Salmonella* contamination in live poultry [35]. The above data further support the use of probiotics as feed additives in livestock breeding.

Other than oral intake, the in ovo administration of probiotics for eradicating gut *Enterobacterales* colonization has been used in chickens [37,38]. Via the in ovo route during hatching, a Bacillus-based probiotic (BPP) can reduce the severity of the virulent *E. coli* horizontal transmission among broiler chickens, which might be achieved by alterations in the microbiota composition, including a decrease in *Enterobacterales* and an increase in *Lachnospiraceae* [37]. In another chicken study, the in ovo administration of lactic-acid-producing bacteria resulted in an increased abundance in the *Lactobacillaceae* family and *Lactobacillus* genus, and a decrease in *Enterobacterales* and *Enterococcaceae* [38]. For
bird species, the early in ovo administration of probiotics seems to be more efficient in eradicating gut Enterobacterales colonization before hatching.

A mixture of probiotics may work better to eradicate gut Enterobacterales in livestock breeding [33,39–41]. The administration of multistrain probiotics containing L. acidophilus LAP5, L. fermentum P2, Pediococcus acidilactici LS, and L. casei L21 could modulate intestinal microbiota (increase Lactobacillaceae abundance and reduce Enterobacteriales abundance), increase the gene expression of tight junction proteins (ZO-1 and Mucin 2) and the immunomodulatory activity (downregulation of mRNA levels of interferon-γ [IFN-γ] and lipopolysaccharide-induced tumor necrosis factor-α [TNF-α], and upregulation of IL-10) in broiler chickens [33]. Commercially available synbiotics, either BioPlus 2B® or Cylactin® LBC, had a more significant impact on the concentration of lactic acid, short-chain fatty acids (SCFAs), and branched-chain fatty acids (BCFAs), than a single probiotic in sows [39]. Mixed probiotics composed of three thermophilic lactic-acid-producing bacteria (LAB) strains, L. helveticus BGRA43 (strong proteolytic activity, antimicrobial activity, and adhesion to gut cell activity), L. fermentum BGH14 (immunomodulatory effect), and Streptococcus thermophiles BGVJ1–44 (strong proteolytic activity and immunomodulatory effect), influenced the colonization of piglet guts with beneficial bacteria, and reduced the number of Enterobacteriales in some treated sows [41]. Thus, the commercially available mixed regimens of probiotics may be more efficient in eliminating Enterobacteriales carriage in the guts of livestock.

Furthermore, probiotics in combination with prebiotics (foods that promote the growth of beneficial microbes), or phytobiotics (plant-derived products), have been utilized in livestock breeding for the eradication of gut colonization by Enterobacteriales [40,42]. Lactobacillus strains (L. agilis and L. salivarius), combined with phytobiotics, have been used to reduce the survival of potentially problematic bacteria, such as ESBL-producing E. coli in broilers [42]. The symbiotics (L. rhamnosus HN001 and P. acidilactici) combined with the phytobiotics (Agave tequilana fructans) induced morphological modifications in the duodenal mucosa of broilers that, in turn, promoted resistance to infections caused by S. typhimurium and C. perfringens [40].

In addition, a probiotic-based cleaning strategy to decontaminate Enterobacteriales in livestock environments has been reported [43]. The cleaning product, containing B. subtilis, B. pumilus, and B. megaterium spores, was used to clean fresh and reused broiler litters [43]. These Bacillus spores were able to successfully colonize reused poultry litters to decrease the mean counts of total aerobic bacteria, Enterobacteriales, and coagulase-positive Staphylococcus [43]. A decrease in Enterobacteriales, mainly the genus Escherichia, was also observed in the ceca of broilers reared on reused litters treated with the cleaning product [43]. The efficacy and safety issues of this probiotic-based cleaning product are still ongoing for livestock environments, but have not been tested for human environments.

Among domesticated animals, such as weaning rabbits, L. buchneri could decrease Enterobacteriales counts in the gut and upregulate anti-inflammatory interleukin (IL)-4 and the expression of intestinal barrier-related genes, such as zonula occludens-1 (ZO-1), and, thus, may prevent diarrhea [36]. In a randomized controlled trial of healthy cats, Enterobacteriales declined after the administration of symbiotics, a combination of probiotics (Proviable-DC® containing E. faecium, B. bifidum, E. thermophilus, L. acidophilus, L. bulgaricus, L. casei, and L. plantarum) [21]. Among dogs fed Queso Blanco cheese with B. longum KACC 91563 for eight weeks, a reduction in harmful bacteria, such as the Enterobacteriales and Clostridium species, was noted [22]. The successful decrease in Enterobacteriales after probiotic supplementation in pet animals arouses hope for the eradication of gut Enterobacteriales carriage via the use of probiotics in humans.

1.3. The Selection of Probiotics to Decrease Gut Colonization of Enterobacteriales in Humans

The common, safe, and well-studied probiotics used to eradicate the gut carriage of Enterobacteriales in humans include the Lactobacillus [44–47] and Bifidobacterium [17,47,48] species. In extremely low-birth-weight infants, L. reuteri supplementation for one week
resulted in a lower abundance of Enterobacterales and Staphylococcaceae [44]. Among infants fed B. infantis EVC001, a high abundance of Bifidobacteriaceae developed rapidly with a reduced abundance of antibiotic-resistant genes among Enterobacterales and/or Staphylococcaceae [48].

As noted in livestock, probiotic mixtures might provide better protection against gut Enterobacterales colonization than a single probiotic regimen in humans [45,49–51]. A probiotic mixture (Bactiol duo®) containing Saccharomyces boulardii, L. acidophilus NCFM, L. paracasei Lpc-37, B. lactis BI-04, and B. lactis Bi-07, provides better eradication of AmpC-producing Enterobacterales carriage than S. boulardii CNCM I-745® [45]. Oral daily supplementation with a combination of a prebiotic (Emportal®: lactitol) and probiotics (Infloran®: B. bifidum and L. acidophilus) for three weeks decreased the intestinal load of OXA-48-producing Enterobacterales among eight patients with long-term intestinal carriage [49]. Moreover, the ingestion of combined probiotics containing L. plantarum LK006, B. longum LK014, and B. bifidum LK012 could significantly reduce the abundance of Enterobacterales and increase the abundance of Lactobacillaceae in preterm infants [50]. These changes in microbiota were correlated with a decreased serum inflammatory cytokine level of IL-6 and improved the survival rate of these infants. A mixture of B. breve M-16V, B. longum subsp. infantis (B. infantis) M-63, and B. longum subsp. longum BB536, achieved significantly higher levels of Bifidobacterium-predominant microbiota and lower detection rates for Clostridium and Enterobacterales than a single B. breve strain [51]. For human safety, the most common probiotics for combination are the Lactobacillus and Bifidobacterium species.

1.4. Probiotic Supplementation to Decrease Potential Gut Pathogenic Enterobacterales from Infants to Children

Probiotics have been used as supplements for infants to decrease potential gut pathogenic Enterobacterales [44,48,50,52–57] (Table 1). Among hospitalized infants, early administration of L. reuteri DSM 17938 was associated with less colonization by diarrheagenic E. coli [55]. In a randomized placebo-controlled study that administered B. infantis to 24 infants with gastroschisis, the microbial communities were not significantly influenced [52]. In a double-blind, placebo-controlled randomized clinical study conducted on 69 preterm infants, B. lactis BB-12 supplementation resulted in lower viable counts of Enterobacterales [57]. Moreover, in a randomized trial of 300 healthy newborns, the receipt of B. longum BB536 was associated with a higher Bifidobacterium/Enterobacterales ratio (B/E), an increased number of IFN-γ-secreting cells, and a higher ratio of IFN-γ/IL-4-secreting cells, which is indicative of the increased Th1 response [54]. Among 21 neonates that underwent surgery for congenital heart disease >7 days after birth, the enteral B. breve strain Yakult (BBG-01) supply led to significantly fewer Enterobacterales in the gut [56]. Since infants, especially preterm infants, are susceptible to intestinal infection, many probiotic studies have been conducted on these susceptible hosts that have provided promising results against pathogenic Enterobacterales colonization in the gut.

However, not all studies have shown the presence of the beneficial effects of the addition of probiotics for infants. In a double-blind randomized control trial, 21 bottle-fed preterm infants receiving L. rhamnosus GG did not show a decrease in the numbers of Enterococcus and Enterobacterales in the gut, increased weight gain, or a decreased hospital stay compared to 26 control infants [58]. In an early review of randomized controlled trials including preterm infants, the B. animalis subsp. lactis supplement could increase fecal Bifidobacterium counts and reduce Enterobacterales and Clostridium counts, but it did not influence the risk of necrotizing enterocolitis or sepsis [59]. The diverse inhibitory potential of Enterobacterales, and the microbiota-modulating effect of probiotics, are likely due to the intrinsic diversity of the gut microbiota of infants and children inhabiting different areas [60].
Table 1. Probiotic supplements for infants and children to decrease potential pathogenic *Enterobacterales* in the gut.

| First Author | Country   | Publish Year | Patient Population/Number | Probiotics | Main Findings after Probiotic Supplementation | References |
|--------------|-----------|--------------|----------------------------|------------|-----------------------------------------------|------------|
| Mohan R      | Germany   | 2006         | Preterm infants/69         | *Bifidobacterium lactis* Bb12 | Lower viable counts of *Enterobacterales* | [57]       |
| Chrzanowska-Liszewska D | Poland | 2012         | Bottle fed preterm/60      | *Lactobacillus rhamnosus* GG (LGG) | Increase number of *Enterobacterales* in gut | [58]       |
| Umenai T     | Japan     | 2014         | Neonates undergoing cardiac surgery/21 | *B. breve* strain Yakult (BBG-01) | Significantly fewer *Enterobacterales* in gut | [56]       |
| Savino F     | Italy     | 2015         | Hospitalized infant/60     | *L. reuteri* DSM 17938 | Less colonization by diarrheagenic *E. coli* | [55]       |
| Wang C       | Japan     | 2015         | In preschool and school-age children/23 | *L. casei* strain Shirota | Increased population levels of *Bifidobacterium* and total *Lactobacillus*, decreased *Enterobacterales*, *Staphylococcus* and *Clostridium perfringens* | [53]       |
| Wu BB        | China     | 2016         | Healthy newborns/300       | *B. longum* BB536 | Higher *Bifidobacterium/Enterobacterales* ratio and increased the ratio of IFN-γ/IL-4 secretion cells | [54]       |
| Powell WT    | USA       | 2016         | Infants/24                 | *B. longum* subsp. *infantis* | Overall, microbial communities were not significantly influenced, with trends only toward lower *Enterobacterales* | [52]       |
| Li YF        | China     | 2019         | Low birth weight infants/36 | *L. plantarum* LK006, *B. longum* LK014, and *B. bifidum* LK012 | Increase in *Streptococcaceae* and *Lactobacillaceae* and decrease in *Enterobacterales* | [50]       |
| Nguyen M     | USA       | 2021         | Infants/77                 | *B. infantis* | Reduced abundance of antibiotic resistance genes among *Enterobacterales* and *Staphylococcaceae* | [48]       |
| Marti M      | Sweden    | 2021         | First month/132            | *L. reuteri* | Lower abundance of *Enterobacterales* and *Staphylococcaceae* | [44]       |

1.5. Probiotic Supplementation to Decrease Gut Pathogenic or Antimicrobial-Resistant *Enterobacterales* Colonization in Adults

Among adults, probiotic supplements have been shown to decrease, but have failed to totally eradicate, potential antimicrobial-resistant or pathogenic *Enterobacterales* in the gut [45,47,61–66] (Table 2). To eradicate potential antimicrobial-resistant *Enterobacterales*, a clinical trial of a probiotic mixture (Bactiol duo®: *S. boulardii*, *L. acidophilus* NCFM, *L. paracasei* Lpc-37, *B. lactis* Bl-04, and *B. lactis* Bi-07) showed that colonization with AmpC-producing *Enterobacterales* transiently increased after amoxicillin-clavulanate therapy and declined after probiotic intervention [45]. To eradicate potential pathogenic *Enterobacterales* in human-immunodeficiency-virus-infected individuals, *L. rhamnosus* GG supplementation was used and resulted in a decrease in intestinal inflammation, along with a reduction in *Enterobacterales* in the gut [62]. The consecutive intake of fermented soymilk (containing isoflavone) and *L. casei* Shirota among 60 healthy premenopausal Japanese women was able to decrease the fecal levels of *Enterobacterales* and to increase isoflavone bioavailability [63]. In contrast to the promising results of the probiotic trials on the eradication of potential antimicrobial-resistant *Enterobacterales* mentioned above, a randomized single-blind, placebo-controlled trial in southern Sweden used a probiotic mixture of eight living bacterial strains, Vivomixx®, but the successful eradication of fecal ESBL-producing *Enterobacterales* carriage was rarely observed [47]. Among 31 Danish adults who traveled to India for 10–28 days, the ingestion of *L. rhamnosus* GG had no effect on the risk of ESBL-producing *Enterobacterales* colonization [61]. Of note, in 75 patients who underwent elective colon surgery, the oral intake of *L. plantarum* 299v for one week resulted in increased *Enterobac-
terales and Gram-negative anaerobes in the colon, but no change in the incidence of bacterial translocation or postoperative complications [66]. The diverse effect of probiotic supplements on gut Enterobacterales carriage is likely due to the different baseline gut microbiota and the decolonization efficacy of a variety of probiotic components. To date, probiotic supplementation is not routinely recommended to replace routine antibiotic decontamination in the preoperative preparation of the digestive tract [67]. However, probiotics or synbiotics might be used in combination with a conventional bowel preparation to reduce the fecal carriage of Enterobacterales [68]. However, the majority of larger-scale clinical trials show no evident clinical benefits, such as lower inflammatory responses, fewer infectious complications, or higher survival rates, among adults who consume probiotic supplements.

Table 2. Probiotic supplements for adults to decrease potential pathogenic Enterobacterales in gut.

| First Author | Country     | Publish Year | Patient Number | Probiotics                                      | Main Findings after Probiotic Supplementation                                                                 | References |
|--------------|-------------|--------------|----------------|------------------------------------------------|-------------------------------------------------------------------------------------------------------------|------------|
| Mangell P    | Sweden      | 2012         | 75             | Lactobacillus plantarum 299v                   | Increased Enterobacterales and Gram-negative anaerobes in the colon 1 week after probiotics without change in the incidence of bacterial translocation and postoperative complications | [66]       |
| Larsen N     | Denmark     | 2013         | 50             | L. salivarius Ls-33                           | No significant influence on Clostridium cluster I, Clostridium cluster IV, Faecalibacterium prausnitzii, Enterobacterales, Enterococcus, the Lactobacillus group, and Bifidobacterium | [65]       |
| Bajaj JS     | USA         | 2014         | 30             | L. rhamnosus GG                               | Among cirrhotic patients with minimal hepatic encephalopathy, reduced Enterobacterales and increased Clostridiales Family XIV Incertae Sedis and Lachnospiraceae relative abundance, but no change in cognition | [64]       |
| Nagino T     | Japan       | 2018         | 60             | L. casei Shirota                              | Consecutive intake of fermented soymilk (containing isolavone), and L. casei Shirota decreased the levels of Enterobacterales | [63]       |
| Arnbjerg CJ  | Denmark     | 2018         | 45             | L. rhamnosus GG                               | Decrease in intestinal inflammation, along with a reduction of Enterobacterales in the gut microbiome among human-immunodeficiency-virus-infected individuals | [62]       |
| Dall LB      | Denmark     | 2019         | 31             | L. rhamnosus GG                               | No effect on the risk of colonization with extended spectrum β-lactamase (ESBL)-Enterobacterales                | [61]       |
| Ljungquist O | Sweden      | 2020         | 80             | Vivomixx® ¹                                   | No support of Vivomixx® as being superior to the placebo for intestinal decolonization in adult patients with chronic colonization of ESBL-producing Enterobacterales | [47]       |
| Ramos-Ramos JC| Spain       | 2020         | 8              | B. bifidum and L. acidophilus (Infloran®)     | Three weeks of a combination of prebiotics and probiotics decreased the intestinal load of OXA-48-producing Enterobacterales | [49]       |
| Wieërs G     | Belgium     | 2021         | 120            | Bactiol duo® ²                                | Colonization with AmpC-producing Enterobacterales declined after the probiotic intervention                      | [45]       |

1 contains 4 Lactobacillus strains (L. paracasei 24733, L. acidophilus 24735, L. delbrueckii subspecies bulgaricus 24734, and L. plantarum 24730), 3 Bifidobacterium strains (B. breve 24732, B. longum 24736, and B. infantis 24737), and S. thermophilus 24731; ² contains S. boulardii, L. acidophilus NCFM, L. paracasei Lpc-37, B. lactis Bi-04, and B. lactis Bi-07.

1.6. Possible Mechanisms by Which Probiotic Supplementation Decreases Gut Enterobacterales Carriage

The decrease in gut Enterobacterales carriage after probiotic supplementation might be related to the increase in beneficial bacteria, such as Bacteroides, Bifidobacterium, and Lactobacillus [20,48,50], and SCFA-producing bacteria (such as Lachnospiraceae and Ruminococcaceae) [69], as well as to the changes in the metabolome in the gut (Figure 1) [39,70]. The continuous intake of a combination of probiotic cheese enriched with L. reuteri CCM 8617RIF and crushed flaxseed resulted in an alleviation of the infection course induced by...
pathogenic *E. coli* O149:F4NAL, favored n-3 polyunsaturated fatty acid metabolism, and inhibited n-6 PUFA metabolism in the gut [70]. Moreover, a probiotic mixture resulted in a greater increase in lactic acid, SCFAs, and branched-chain fatty acids (BCFAs), than a single probiotic in sows [39]. Conclusively, the gut metabolome changes after probiotic supplementation builds up an environment that is not friendly to *Enterobacterales*.

Figure 1. In humans, some clinical settings or interventions might promote intestinal carriage of *Enterobacterales*. Probiotics might be beneficial in eradicating gut carriage of pathogenic or antimicrobial-resistant *Enterobacterales*. In addition, a microbe is regarded as a beneficial probiotic if it can secrete antimicrobial proteins targeting pathogenic *Enterobacterales*. For example, a probiotic strain, *E. coli* Nissle 1917, secretes small proteins called microcins that possess antimicrobial activity against pathogenic *Enterobacterales* during intestinal inflammation [71]. Therefore, probiotics capable of producing antimicrobial proteins might provide better *Enterobacterales* eradication efficacy. The *Enterobacterales* eradication capacity of probiotics can also result from the nutrition competition between probiotics and *Enterobacterales*. Commensal microbiota contributes to colonization resistance by competing with *Salmonella enteritidis* for oxygen, a resource critical for pathogen expansion [72]. An analysis of the complex nutrition competition in the microbiota of the gut provides an alternative method for selecting appropriate probiotics against *Enterobacterales*.

1.7. Improve the Effect of Probiotics in Eradicating *Enterobacterales*

Changes in the delivery method of probiotics might provide alternative ways of eradicate *Enterobacterales* in the gut [73]. Among patients with mild left-sided ulcerative colitis, the oral intake of *L. casei* DG failed to affect colonic flora, but the rectal administration of the same probiotics increased *Lactobacillus* spp. and reduced *Enterobacterales*, significantly decreased Toll-like receptor (TLR)-4 and IL-1β mRNA levels, and increased mucosal IL-10 [73]. For probiotics vulnerable to gastric acid or intestinal enzymes, rectal administration might provide better efficacy for eradicating *Enterobacterales* in the gut.

Other than naturally found probiotics, engineered probiotics specifically targeting *Enterobacterales* have been investigated to improve gut colonization eradication. The introduction of genes with beneficial effects into probiotics provides additional effects, such as...
acid resistance, immune modulation, and gut barrier protection effects. A genetically engineered plasmid was delivered to E. coli that gained the capacity to produce tetrathionate which can inhibit the growth of Salmonella [74].

To facilitate the buildup of healthy gut microbiota, the ex vivo selection of appropriate probiotics is mandatory. Bacteriocin-producing bacteria capable of inhibiting bovine and wastewater E. coli isolates have been tested for their activity against Shiga toxin-producing E. coli, antimicrobial-resistant E. coli, and related enteric pathogens [75]. The selected bacteriocin-producing bacteria show potential as next-generation control strategies in livestock and humans. Another selected probiotic is B. infantis, a unique gut bacterium with a prodigious capacity to digest human milk oligosaccharides, that was specifically selected for the focused manipulation of infant intestinal microbiota [76].

1.8. Clinical Trials of Probiotics or Synbiotics to Improve Gut Health

There are three ongoing randomized clinical trials on dietary supplementation with probiotics aimed at gut Enterobacterales eradication registered at ClinicalTrials.gov, posted from July 2008 to July 2021 (Table 3) [77]. Commercial probiotic mixtures, synbiotics, are being applied in these three trials, and the commonly used probiotic strains include the Lactobacillus, Bifidobacterium, and Streptococcus species. Of note, one interesting trial is comparing the effects of gut Enterobacterales eradication between synbiotics and fecal microbiota transplantation.

### Table 3. Three clinical trials of dietary supplementation with probiotics for the eradication of gut Enterobacterales carriage registered at ClinicalTrials.gov, as posted from July 2008 to July 2021.

| ClinicalTrials.gov Identifier | Official Title | First Posted | Study Design/Case Number | Probiotic Strain | Location | Outcome Measures | Status |
|-------------------------------|---------------|--------------|--------------------------|-----------------|----------|-----------------|--------|
| NCT 00722410                  | Safety and efficacy study of eradication of carbapenem-resistant Klebsiella pneumoniae from the gastrointestinal tract by probiotics | 25 July 2008 | Open-label, randomized/60 | VSL#3® | Jerusalem, Israel | Negative stool culture for carbapenem-resistant Klebsiella pneumoniae | Not yet recruiting |
| NCT 03967301                  | Prevention and decolonization of multidrug-resistant bacteria with probiotics | 30 May 2019 | Double-blinded, randomized/228 | Bioflora® | Buenos Aires, Argentina | Risk of colonization and/or infection by carbapenem-resistant Enterobacterales | Not yet recruiting |
| NCT 04431934                  | Open-label, randomized study to assess the efficacy of a probiotic or fecal microbiota transplantation (FMT) on the eradication of rectal multidrug-resistant Gram-negative bacilli (MDR-GNB) carriage (PROFTMDECOL) | 16 June 2020 | Open-label, randomized/437 | Vivomixx® | Barcelona, Spain | Eradication of rectal multidrug-resistant Gram-negative bacilli carriage | Recruiting |

1.9. Clinical Safety Issue of Probiotics

Although the efficacy of probiotics in decreasing the gut carriage of Enterobacterales has been recognized, there are still concerns regarding their clinical safety, including potential infections or the inflammatory/fatal effects derived from toxins produced either by the probiotic strains or bacterial contaminants [78]. Lactobacillus infections after taking probiotic products containing the Lactobacillus species have been reported in immunocompromised patients [79–81]. Lactobacillus endocarditis has been reported in an otherwise healthy patient taking a probiotic formulation containing Lactobacillus [82]. Moreover, there are substantial concerns about the transfer of resistance genes among probiotics, pathogens, and gut microbiota through horizontal gene transfer and the adverse potential of probiotics as the source of antimicrobial resistance genes [83,84]. Thus, the clinical application of probiotics for decreasing Enterobacterales gut carriage among patients with an immunocom-
promised status should consider the possibility of opportunistic infections caused by these probiotic strains.

2. Conclusions

The rationale for using probiotic supplements to eradicate gut Enterobacterales carriage includes changes in the microbiota and metabolomes, nutrition competition, and the secretion of antimicrobial proteins to establish a gut environment that is not friendly to Enterobacterales. Many probiotics indeed do show Enterobacterales-inhibiting effects ex vivo and in vivo. In livestock, probiotics have been widely used to eradicate colonic or environmental Enterobacterales colonization for years, either administered by oral supplementation, in ovo use, or used as environmental disinfectants. For humans, probiotics have been used as dietary supplements for infants to decrease potentially pathogenic Enterobacterales in the gut, and probiotics mixtures have shown promising results. This encouraging effect of probiotics on decreasing the gut carriage of Enterobacterales is likely related to the simple gut microbiota in infants, and less interference from underlying chronic diseases and prior antimicrobial exposure.

In contrast to the beneficial effects in infants, for adults, probiotic supplements might decrease potentially pathogenic Enterobacterales in the gut, but they fail to eradicate them. More efforts to confront dysbiosis resulting from comorbidities or antimicrobial therapy, and to select multifunctional probiotics or synbiotics to improve gut health in elderly patients with complex health problems, are currently required.

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