The Potential of Probiotics

Subjects: Cell Biology | Infectious Diseases
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Keywords: probiotics ; synbiotics ; antimicrobial-resistant ; Enterobacterales ; gastrointestinal tract ; livestock

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 [1]. Most probiotics originate from fermenting food, an ancient form of preservation ingrained in human societies around the world [2]. 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 [2]. The incorporation of probiotics into food results in higher counts of lactic acid-producing bacteria and lower counts of *Enterobacterales* [3]. 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 [4][5][6][7][8]. 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* [4]. These changes in microbiota after *B. bifidum* ATCC 29521 pretreatment were associated with a decrease in the severity of inflammatory bowel disease [4]. Moreover, *L. rhamnosus* GG could reduce the mortality rate of septic mice by modulating gut microbiota composition, especially reducing the lipopolysaccharide producers, such as *Enterobacterales* [5]. *Bacillus coagulans* SANK 70258 suppressed *Enterobacterales* and enhanced butyrogenesis in microbiota models [6]. *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 [7]. 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 [8]. 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 [9]. 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 [4][5][6][10][11]. 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* [10]. These pathogenic alterations resulted in the development of mucositis and bacteremia [10][11]. 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* [12]. These changes in gut microbiota were associated with less diarrhea, less symptomatic intestinal obstruction, and a lower incidence of total postoperative infections [12]. 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.

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 [13][14][15][16][17][18]. *Lactobacillus* supplementation, in directly fed microbes or used as phytobiotic feed additives, reduced the prevalence of ESBL-producing *Enterobacterales* in broilers [13]. 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 [14]. In weaned piglets, *B. subtilis* DSM25841 treatment reduced enterotoxigenic *E. coli* (ETEC) F4 infection and decreased the risk of diarrhea [16]. *L. reuteri* KUB-AC5 possessed antimicrobial activity in reducing *Salmonella* contamination in live poultry [17]. 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 [19][20]. 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* [19]. 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* [20]. 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 [15][21][22][23]. 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 *Enterobacterales* 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 [15]. 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 [21]. 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* BGHI14 (immunomodulatory effect), and *Streptococcus thermophiles* BGVLJ1–44 (strong proteolytic activity and immunomodulatory effect), influenced the colonization of piglet guts with beneficial bacteria, and reduced the number of *Enterobacterales* in some treated sows [23]. Thus, the commercially available mixed regimens of probiotics may be more efficient in eliminating *Enterobacterales* 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 *Enterobacterales* [22][24]. *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 [24]. The synbiotics (*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* [22].

In addition, a probiotic-based cleaning strategy to decontaminate *Enterobacterales* in livestock environments has been reported [25]. The cleaning product, containing *B. subtilis, B. pumilus*, and *B. megaterium* spores, was used to clean fresh and reused broiler litters [25]. These *Bacillus* spores were able to successfully colonize reused poultry litters to decrease the mean counts of total aerobic bacteria, *Enterobacterales*, and coagulase-positive *Staphylococcus* [25]. A decrease in *Enterobacterales*, mainly the genus *Escherichia*, was also observed in the ceca of broilers reared on reused litters treated with the cleaning product [25]. 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 *Enterobacterales* 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 [18]. In a randomized controlled trial of healthy cats, *Enterobacterales* declined after the administration of synbiotics, a combination of probiotics (Proviable-DC® containing *E. faecium, B. bifidum, E. thermophilus, L. acidophilus, L. bulgaricus, L. casei,* and *L. plantarum*) [26]. Among dogs fed Queso Blanco

cheese with *B. longum* KACC 91563 for eight weeks, a reduction in harmful bacteria, such as the *Enterobacterales* and *Clostridium* species, was noted [27]. The successful decrease in *Enterobacterales* after probiotic supplementation in pet animals arouses hope for the eradication of gut *Enterobacterales* carriage via the use of probiotics in humans.

3. The Selection of Probiotics to Decrease Gut Colonization of Enterobacterales in Humans

The common, safe, and well-studied probiotics used to eradicate the gut carriage of *Enterobacterales* in humans include the *Lactobacillus* [28][29][30][31] and *Bifidobacterium* [4][31][32] species. In extremely low-birth-weight infants, *L. reuteri* supplementation for one week resulted in a lower abundance of *Enterobacterales* and *Staphylococcaceae* [28]. 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* [32].

As noted in livestock, probiotic mixtures might provide better protection against gut *Enterobacterales* colonization than a single probiotic regimen in humans [29][33][34][35]. A probiotic mixture (Bactiol duo®) containing *Saccharomyces boulardii*, *L. acidophilus* NCFM, *L. paracasei* Lpc-37, *B. lactis* Bl-04, and *B. lactis* Bi-07, provides better eradication of AmpC-producing *Enterobacterales* carriage than *S. boulardii* CNCM I-745® [29]. 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 [33]. 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 [34]. 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 [35]. For human safety, the most common probiotics for combination are the *Lactobacillus* and *Bifidobacterium* species.

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

Probiotics have been used as supplements for infants to decease potential gut pathogenic *Enterobacterales* [28][32][34][36][37][38][39][40][41] (**Table 1**). Among hospitalized infants, early administration of *L. reuteri* DSM 17938 was associated with less colonization by diarrheagenic *E. coli* [39]. In a randomized placebo-controlled study that administered *B. infantis* to 24 infants with gastroschisis, the microbial communities were not significantly influenced [36]. 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* [41]. 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 [38]. 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 [40]. 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.

Table 1. Probiotic supplements for infants and children to decease 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*	[41]
Chrzanowska-Liszewska D	Poland	2012	Bottle fed preterm/60	*Lactobacillus rhamnosus* GG (LGG)	Increase number of *Enterobacterales* in gut	[42]
Umenai T	Japan	2014	Neonates undergoing cardiac surgery/21	*B. breve* strain Yakult (BBG-01)	Significantly fewer *Enterobacterales* in gut	[40]
Savino F	Italy	2015	Hospitalized infant/60	*L. reuteri* DSM 17938	Less colonization by diarrheagenic *E. coli*.	[39]

First Author	Country	Publish Year	Patient Population/Number	Probiotics	Main Findings after Probiotic Supplementation	References
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*	[37]
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	[38]
Powell WT	USA	2016	Infants/24	*B. longum* subsp. *infantis*	Overall, microbial communities were not significantly influenced, with trends only toward lower *Enterobacterales*	[36]
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*	[34]
Nguyen M	USA	2021	Infants/77	*B. infantis*	Reduced abundance of antibiotic resistance genes among *Enterobacterales* and *Staphylococcaceae*	[32]
Martí M	Sweden	2021	First month/132	*L. reuteri*	Lower abundance of *Enterobacterales* and *Staphylococcaceae*	[28]

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 [42]. 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 [43]. 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 [44].

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 [29][31][45][46][47][48][49][50] (**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 [29]. 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 [46]. 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 [47].

Table 2. Probiotic supplements for adults to decease 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	[50]

First Author	Country	Publish Year	Patient Number	Probiotics	Main Findings after Probiotic Supplementation	References
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*	[49]
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	[48]
Nagino T	Japan	2018	60	*L. casei* Shirota	Consecutive intake of fermented soymilk (containing isoflavone), and *L. casei* Shirota decreased the levels of *Enterobacterales*	[47]
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	[46]
Dall LB	Denmark	2019	31	*L. rhamnosus GG*	No effect on the risk of colonization with extended spectrum β-lactamase (ESBL)-*Enterobacterales*	[45]
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*	[31]
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*	[33]
Wieërs G	Belgium	2021	120	Bactiol duo® [2]	Colonization with AmpC-producing *Enterobacterales* declined after the probiotic intervention	[29]

[1] contains 4 Lactobacillus strains (L. paracasei 24733, L. acidophilus 24735, L. delbrueckii subspecies bulgaricus 24734, and L. plantarum 24730), 3 Bifidobacterium strains (B. brief 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 Bl-04, and B. lactis Bi-07.

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 [31]. 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 [45]. Of note, in 75 patients who underwent elective colon surgery, the oral intake of *L. plantarum* 299v for one week resulted in increased *Enterobacterales* and Gram-negative anaerobes in the colon, but no change in the incidence of bacterial translocation or postoperative complications [50]. 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 [51]. However, probiotics or synbiotics might be used in combination with a conventional bowel preparation to reduce the fecal carriage of *Enterobacterales* [52]. 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.

References

1. Berreta, A.; Kopper, J.J.; Alexander, T.L.; Kogan, C.J.; Burbick, C.R. Effect of an In Vitro Proximal Gastrointestinal Tract on Viability of Commercially Available Equine Probiotics. J. Equine Vet. Sci. 2021, 104, 103671.

2. Raghuvanshi, R.; Grayson, A.G.; Schena, I.; Amanze, O.; Suwintono, K.; Quinn, R.A. Microbial Transformations of Organically Fermented Foods. Metabolites 2019, 9, 165.
3. Cavalheiro, C.P.; Ruiz-Capillas, C.; Herrero, A.M.; Jimenez-Colmenero, F.; Pintado, T.; de Menezes, C.R.; Fries, L.L.M. Effect of different strategies of Lactobacillus plantarum incorporation in chorizo sausages. J. Sci. Food Agric. 2019, 99, 6706–6712.
4. Weng, Y.J.; Jiang, D.X.; Liang, J.; Ye, S.C.; Tan, W.K.; Yu, C.Y.; Zhou, Y. Effects of Pretreatment with Bifidobacterium bifidum Using 16S Ribosomal RNA Gene Sequencing in a Mouse Model of Acute Colitis Induced by Dextran Sulfate Sodium. Med. Sci. Monit. 2021, 27, e928478.
5. Chen, L.; Li, H.; Chen, Y.; Yang, Y. Probiotic Lactobacillus rhamnosus GG reduces mortality of septic mice by modulating gut microbiota composition and metabolic profiles. Nutrition 2020, 78, 110863.
6. Sasaki, K.; Sasaki, D.; Inoue, J.; Hoshi, N.; Maeda, T.; Yamada, R.; Kondo, A. Bacillus coagulans SANK 70258 suppresses Enterobacteriaceae in the microbiota of ulcerative colitis in vitro and enhances butyrogenesis in healthy microbiota. Appl. Microbiol. Biotechnol. 2020, 104, 3859–3867.
7. Yi, R.; Tan, F.; Liao, W.; Wang, Q.; Mu, J.; Zhou, X.; Yang, Z.; Zhao, X. Isolation and Identification of Lactobacillus plantarum HFY05 from Natural Fermented Yak Yogurt and Its Effect on Alcoholic Liver Injury in Mice. Microorganisms 2019, 7, 530.
8. Chen, L.; Li, H.; Li, J.; Chen, Y.; Yang, Y. Lactobacillus rhamnosus GG treatment improves intestinal permeability and modulates microbiota dysbiosis in an experimental model of sepsis. Int. J. Mol. Med. 2019, 43, 1139–1148.
9. Linninge, C.; Xu, J.; Bahl, M.I.; Ahrne, S.; Molin, G. Lactobacillus fermentum and Lactobacillus plantarum increased gut microbiota diversity and functionality, and mitigated Enterobacteriaceae, in a mouse model. Benef. Microbes 2019, 10, 413–424.
10. Touchefeu, Y.; Montassier, E.; Nieman, K.; Gastinne, T.; Potel, G.; Bruley des Varannes, S.; Le Vacon, F.; de La Cochetiere, M.F. Systematic review: The role of the gut microbiota in chemotherapy- or radiation-induced gastrointestinal mucositis—Current evidence and potential clinical applications. Aliment. Pharmacol. Ther. 2014, 40, 409–421.
11. Yamashiro, Y.; Nagata, S. Beneficial microbes for premature infants, and children with malignancy undergoing chemotherapy. Benef. Microbes 2010, 1, 357–365.
12. He, D.; Wang, H.Y.; Feng, J.Y.; Zhang, M.M.; Zhou, Y.; Wu, X.T. Use of pro-/synbiotics as prophylaxis in patients undergoing colorectal resection for cancer: A meta-analysis of randomized controlled trials. Clin. Res. Hepatol. Gastroenterol. 2013, 37, 406–415.
13. Saliu, E.M.; Ren, H.; Boroojeni, F.G.; Zentek, J.; Vahjen, W. The Impact of Direct-Fed Microbials and Phytogenic Feed Additives on Prevalence and Transfer of Extended-Spectrum Beta-Lactamase Genes in Broiler Chicken. Microorganisms 2020, 8, 322.
14. Rodrigues, D.R.; Wilson, K.M.; Trombetta, M.; Briggs, W.N.; Duff, A.F.; Chasser, K.M.; Bottje, W.G.; Bielke, L. A Proteomic View of the Cross-Talk Between Early Intestinal Microbiota and Poultry Immune System. Front. Physiol. 2020, 11, 20.
15. Chang, C.H.; Teng, P.Y.; Lee, T.T.; Yu, B. Effects of multi-strain probiotic supplementation on intestinal microbiota, tight junctions, and inflammation in young broiler chickens challenged with Salmonella enterica subsp. enterica. Asian-Australas. J. Anim. Sci. 2020, 33, 1797–1808.
16. Luise, D.; Bertocchi, M.; Motta, V.; Salvarani, C.; Bosi, P.; Luppi, A.; Fanelli, F.; Mazzoni, M.; Archetti, I.; Maiorano, G.; et al. Bacillus sp. probiotic supplementation diminish the Escherichia coli F4ac infection in susceptible weaned pigs by influencing the intestinal immune response, intestinal microbiota and blood metabolomics. J. Anim. Sci. Biotechnol. 2019, 10, 74.
17. Nakphaichit, M.; Sobanbua, S.; Siemuang, S.; Vongsangnak, W.; Nakayama, J.; Nitisinprasert, S. Protective effect of Lactobacillus reuteri KUB-AC5 against Salmonella Enteritidis challenge in chickens. Benef. Microbes 2019, 10, 43–54.
18. Zhou, Y.; Ni, X.; Wen, B.; Duan, L.; Sun, H.; Yang, M.; Zou, F.; Lin, Y.; Liu, Q.; Zeng, Y.; et al. Appropriate dose of Lactobacillus buchneri supplement improves intestinal microbiota and prevents diarrhoea in weaning Rex rabbits. Benef. Microbes 2018, 9, 401–416.
19. Arreguin-Nava, M.A.; Graham, B.D.; Adhikari, B.; Agnello, M.; Selby, C.M.; Hernandez-Velasco, X.; Vuong, C.N.; Solis-Cruz, B.; Hernandez-Patlan, D.; Latorre, J.D.; et al. Evaluation of in ovo Bacillus spp. based probiotic administration on horizontal transmission of virulent Escherichia coli in neonatal broiler chickens. Poult. Sci. 2019, 98, 6483–6491.
20. Wilson, K.M.; Rodrigues, D.R.; Briggs, W.N.; Duff, A.F.; Chasser, K.M.; Bielke, L.R. Evaluation of the impact of in ovo administered bacteria on microbiome of chicks through 10 days of age. Poult. Sci. 2019, 98, 5949–5960.

21. Slizewska, K.; Chlebicz, A. Synbiotics impact on dominant faecal microbiota and short-chain fatty acids production in sows. FEMS Microbiol. Lett. 2019, 366, i133–i146.

22. Villagran-de la Mora, Z.; Nuno, K.; Vazquez-Paulino, O.; Avalos, H.; Castro-Rosas, J.; Gomez-Aldapa, C.; Angulo, C.; Ascencio, F.; Villarruel-Lopez, A. Effect of a Synbiotic Mix on Intestinal Structural Changes, and Salmonella Typhimurium and Clostridium Perfringens Colonization in Broiler Chickens. Animals 2019, 9, 777.

23. Veljovic, K.; Dinic, M.; Lukic, J.; Mihajlovic, S.; Tolinacki, M.; Zivkovic, M.; Begovic, J.; Mrvaljevic, I.; Golic, N.; Terzic-Vidojevic, A. Promotion of Early Gut Colonization by Probiotic Intervention on Microbiota Diversity in Pregnant Sows. Front. Microbiol. 2017, 8, 2028.

24. Ren, H.; Vahjen, W.; Dadi, T.; Saliu, E.M.; Boroojeni, F.G.; Zentek, J. Synergistic Effects of Probiotics and Phytobiotics on the Intestinal Microbiota in Young Broiler Chicken. Microorganisms 2019, 7, 684.

25. De Cesare, A.; Caselli, E.; Lucchi, A.; Sala, C.; Parisi, A.; Manfreda, G.; Mazzacane, S. Impact of a probiotic-based cleaning product on the microbiological profile of broiler litters and chicken caeca microbiota. Poult. Sci. 2019, 98, 3602–3610.

26. Whittemore, J.C.; Stokes, J.E.; Price, J.M.; Suchodolski, J.S. Effects of a synbiotic on the fecal microbiome and metabolomic profiles of healthy research cats administered clindamycin: A randomized, controlled trial. Gut Microbes 2019, 10, 521–539.

27. Park, H.E.; Kim, Y.J.; Do, K.H.; Kim, J.K.; Ham, J.S.; Lee, W.K. Effects of Queso Blanco Cheese Containing Bifidobacterium longum KACC 91563 on the Intestinal Microbiota and Short Chain Fatty Acid in Healthy Companion Dogs. Korean J. Food Sci. Anim. Resour. 2018, 38, 1261–1272.

28. Marti, M.; Spreckels, J.E.; Ranasinghe, P.D.; Wejryd, E.; Marchini, G.; Sverremark-Ekstrom, E.; Jenmalm, M.C.; Abrahamsson, T. Effects of Lactobacillus reuteri supplementation on the gut microbiota in extremely preterm infants in a randomized placebo-controlled trial. Cell Rep. Med. 2021, 2, 100206.

29. Wieers, G.; Verbelen, V.; Van Den Driessche, M.; Melnik, E.; Vanheule, G.; Marot, J.C.; Cani, P.D. Do Probiotics During In-Hospital Antibiotic Treatment Prevent Colonization of Gut Microbiota With Multi-Drug-Resistant Bacteria? A Randomized Placebo-Controlled Trial Comparing Saccharomyces to a Mixture of Lactobacillus, Bifidobacterium, and Saccharomyces. Front. Public Health 2020, 8, 578089.

30. Zhou, Y.; Ni, X.; Duan, L.; Niu, L.; Liu, Q.; Zeng, Y.; Wang, Q.; Wang, J.; Khalique, A.; Pan, K.; et al. Lactobacillus plantarum BSGP201683 Improves the Intestinal Barrier of Giant Panda Microbiota-Associated Mouse Infected by Enterotoxigenic Escherichia coli K88. Probiotics Antimicrob. Proteins 2021, 13, 664–676.

31. Ljungquist, O.; Kampmann, C.; Resman, F.; Riesbeck, K.; Tham, J. Probiotics for intestinal decolonization of ESBL-producing Enterobacteriaceae: A randomized, placebo-controlled clinical trial. Clin. Microbiol. Infect. 2020, 26, 456–462.

32. Nguyen, M.; Holdbrooks, H.; Mishra, P.; Abrantes, M.A.; Eskew, S.; Garma, M.; Oca, C.G.; McGuckin, C.; Hein, C.B.; Mitchell, R.D.; et al. Impact of Probiotic B. infantis EVC001 Feeding in Premature Infants on the Gut Microbiome, Nosocomially Acquired Antibiotic Resistance, and Enteric Inflammation. Front. Pediatr. 2021, 9, 618009.

33. Ramos-Ramos, J.C.; Lazaro-Perona, F.; Arribas, J.R.; Garcia-Rodriguez, J.; Mingorance, J.; Ruiz-Carrascoso, G.; Borobia, A.M.; Pano-Pardo, J.R.; Herruzo, R.; Arnalich, F. Proof-of-concept trial of the combination of lactitol with Bifidobacterium bifidum and Lactobacillus acidophilus for the eradication of intestinal OXA-48-producing Enterobacteriaceae. Gut Pathog. 2020, 12, 15.

34. Li, Y.F.; Zhu, C.R.; Gong, X.L.; Li, H.L.; Xiong, L.K.; Wang, K.J.; Liu, G.S. Beneficial Effects of Probiotic Treatment on Gut Microbiota in Very Low Birth Weight Infants. Gastroenterol. Res. Pract. 2019, 2019, 3682836.

35. Ishizeki, S.; Sugita, M.; Takata, M.; Yaeshima, T. Effect of administration of bifidobacteria on intestinal microbiota in low-birth-weight infants and transition of administered bifidobacteria: A comparison between one-species and three-species administration. Anaerobe 2013, 23, 38–44.

36. Powell, W.T.; Borghese, R.A.; Kalanetra, K.M.; Mirmiran, M.; Mills, D.A.; Underwood, M.A. Probiotic Administration in Infants With Gastroschisis: A Pilot Randomized Placebo-Controlled Trial. J. Pediatr. Gastroenterol. Nutr. 2016, 62, 852–857.

37. Wang, C.; Nagata, S.; Asahara, T.; Yuki, N.; Matsuda, K.; Tsuji, H.; Takahashi, T.; Nomoto, K.; Yamashiro, Y. Intestinal Microbiota Profiles of Healthy Pre-School and School-Age Children and Effects of Probiotic Supplementation. Ann. Nutr. Metab. 2015, 67, 257–266.

38. Wu, B.B.; Yang, Y.; Xu, X.; Wang, W.P. Effects of Bifidobacterium supplementation on intestinal microbiota composition and the immune response in healthy infants. World J. Pediatr. 2016, 12, 177–182.

39. Savino, F.; Fornasero, S.; Ceratto, S.; De Marco, A.; Mandras, N.; Roana, J.; Tullio, V.; Amisano, G. Probiotics and gut health in infants: A preliminary case-control observational study about early treatment with Lactobacillus reuteri DSM 17938. Clin. Chim. Acta 2015, 451, 82–87.
40. Umenai, T.; Shime, N.; Asahara, T.; Nomoto, K.; Itoi, T. A pilot study of Bifidobacterium breve in neonates undergoing surgery for congenital heart disease. J. Intensive Care 2014, 2, 36.
41. Mohan, R.; Koebnick, C.; Schildt, J.; Schmidt, S.; Mueller, M.; Possner, M.; Radke, M.; Blaut, M. Effects of Bifidobacterium lactis Bb12 supplementation on intestinal microbiota of preterm infants: A double-blind, placebo-controlled, randomized study. J. Clin. Microbiol. 2006, 44, 4025–4031.
42. Chrzanowska-Liszewska, D.; Seliga-Siwecka, J.; Kornacka, M.K. The effect of Lactobacillus rhamnosus GG supplemented enteral feeding on the microbiotic flora of preterm infants-double blinded randomized control trial. Early Hum. Dev. 2012, 88, 57–60.
43. Szajewska, H.; Guandalini, S.; Morelli, L.; Van Goudoever, J.B.; Walker, A. Effect of Bifidobacterium animalis subsp lactis supplementation in preterm infants: A systematic review of randomized controlled trials. J. Pediatr. Gastroenterol. Nutr. 2010, 51, 203–209.
44. La-Ongkham, O.; Nakphaichit, M.; Leelavatcharamas, V.; Keawsompong, S.; Nitisinprasert, S. Distinct gut microbiota of healthy children from two different geographic regions of Thailand. Arch. Microbiol. 2015, 197, 561–573.
45. Dall, L.B.; Lausch, K.R.; Gedebjerg, A.; Fuursted, K.; Storgaard, M.; Larsen, C.S. Do probiotics prevent colonization with multi-resistant Enterobacteriaceae during travel? A randomized controlled trial. Travel Med. Infect. Dis. 2019, 27, 81–86.
46. Arnbjerg, C.J.; Vestad, B.; Hov, J.R.; Pedersen, K.K.; Jespersen, S.; Johannesen, H.H.; Holm, K.; Halvorsen, B.; Fallentin, E.; Hansen, A.E.; et al. Effect of Lactobacillus rhamnosus GG Supplementation on Intestinal Inflammation Assessed by PET/MRI Scans and Gut Microbiota Composition in HIV-Infected Individuals. J. Acquir. Immune Defic. Syndr. 2018, 78, 450–457.
47. Nagino, T.; Kaga, C.; Kano, M.; Masuoka, N.; Anbe, M.; Moriyama, K.; Maruyama, K.; Nakamura, S.; Shida, K.; Miyazaki, K. Effects of fermented soymilk with Lactobacillus casei Shirota on skin condition and the gut microbiota: A randomised clinical pilot trial. Benef. Microbes 2018, 9, 209–218.
48. Bajaj, J.S.; Heuman, D.M.; Hylemon, P.B.; Sanyal, A.J.; Puri, P.; Sterling, R.K.; Luketic, V.; Stravitz, R.T.; Siddiqui, M.S.; Fuchs, M.; et al. Randomised clinical trial: Lactobacillus GG modulates gut microbiome, metabolome and endotoxemia in patients with cirrhosis. Aliment. Pharmacol. Ther. 2014, 39, 1113–1125.
49. Larsen, N.; Vogensen, F.K.; Gobel, R.J.; Michaelsen, K.F.; Forssten, S.D.; Lahtinen, S.J.; Jakobsen, M. Effect of Lactobacillus salivarius Ls-33 on fecal microbiota in obese adolescents. Clin. Nutr. 2013, 32, 935–940.
50. Mangell, P.; Thorlacius, H.; Syk, I.; Ahrne, S.; Molin, G.; Olsson, C.; Jeppsson, B. Lactobacillus plantarum 299v does not reduce enteric bacteria or bacterial translocation in patients undergoing colon resection. Dig. Dis. Sci. 2012, 57, 1915–1924.
51. Oudhuis, G.J.; Bergmans, D.C.; Dormans, T.; Zwaveling, J.H.; Kessels, A.; Prins, M.H.; Stobberingh, E.E.; Verbon, A. Probiotics versus antibiotic decontamination of the digestive tract: Infection and mortality. Intensive Care Med. 2011, 37, 110–117.
52. Reddy, B.S.; Macfie, J.; Gatt, M.; Larsen, C.N.; Jensen, S.S.; Leser, T.D. Randomized clinical trial of effect of synbiotics, neomycin and mechanical bowel preparation on intestinal barrier function in patients undergoing colectomy. Br. J. Surg. 2007, 94, 546–554.