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Antimicrobial Effects of Probiotics and Novel Probiotic-Based Approaches for Infectious Diseases

Ping Li and Qing Gu

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Abstract

Probiotics are live microorganisms, which confer health benefits on host when administered in adequate amounts. Probiotics exert their beneficial effects by maintenance flora healthy, enhancement of mucosal barrier integrity and modulation of immune responses. Antimicrobial substances including bacteriocins, hydrogen peroxide, organic acids, and short-chain fatty acids (SCFAs) produced by probiotics allow them to inhibit mucosal and epithelial adherence of pathogens and compete for limiting resources, thus suppress the growth of bacterial and fungal pathogens. Probiotics effect the colonization of fungal pathogen *Candida* to host surfaces, suppress *Candida* growth and biofilm development *in vitro*. Clinical results have shown that some probiotics can reduce oral, vaginal, and enteric colonization of *Candida*, alleviate clinical signs and symptoms, and potentially reduce the incidence of invasive fungal infection. Therefore, probiotics may be potential antifungals for prevention and treatment of candidiasis.

Keywords: probiotics, mechanism of action, antimicrobial activity, candidiasis, safety

1. Introduction

Probiotics are "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host," which was defined by the Food and Drug Organization of the United Nations (FAO) and World Health Organization (WHO) [1–3]. Probiotics should have some fundamental characteristics, such as human origin, nonpathogenic in nature, resistance to destruction by technical processing, acid and bile tolerances, adequate adherence and colonization on epithelial surfaces, antagonistic activity against pathogens, regulation of immune response, and influence human metabolic activities [4–7].

Bacteria belonging to the genera *Lactobacillus* and *Bifidobacterium* are the most frequently used probiotics. Besides, *Enterococcus*, *Streptococcus*, *Saccharomyces*, and *Bacillus* are also commonly used probiotics (representative species are listed in **Table 1**). The administration of probiotics has been confirmed as an alternative biological approach to combat bacterial and fungal pathogens in the oral cavity, GI tract, and urogenital system [4, 5, 7–14]. It has been reported that probiotics could reduce *Candida*, which cause fungal infections in different organ systems of the human body and prevent bacterial infectious diseases [9, 10, 15]. Probiotics were capable of preventing cancers [16], modulating blood pressure [17, 18], and repressing cholesterol levels [19]. Recently, species of *Akkermansia muciniphila*, *Eubacterium hallii*, and *Faecalibacterium prausnitzii* are identified as new potential probiotics because of their great benefits to the microbial metabolic networks and human health, especially the effects on correcting the imbalance of gut microbiota composition [7, 20–22]. A combination of probiotics with traditional treatment has been thought to be a potential approach for treatment of certain diseases.

It is noteworthy that health benefits of probiotic bacteria are strain specific, which cannot be generalized to other strains, not even the same species, although some properties may be common for different strains because of the similarities in the metabolism of ecological functionality [5, 6]. Thus, the selection of certain probiotics for therapeutic purposes should be targeted for specific pathogens. Probiotics effects are dose specific [5, 6]. It has been suggested that a daily intake of 10^6–10^9 colony-forming units (CFUs) of probiotic microorganisms is the minimum effective dose for therapeutic purposes [5, 6, 8].

A number of probiotics are currently commercially available, and they have been categorized into single-strain or multi-strain/multispecies products [7, 23, 24]. Multi-strain/multispecies probiotics exhibited better effects than single-strain probiotics. The multispecies probiotic consortium VSL#3 (*Streptococcus thermophilus*, *Eubacterium faecium*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Lactobacillus*

Genera	Species
Lactobacillus	*Lactobacillus rhamnosus, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus acidophilus, Lactobacillus reuteri, Lactobacillus paracasei, Lactobacillus sporogenes, Lactobacillus lactis, Lactobacillus helveticus*, and *Lactobacillus fermentium*
Lactococcus	*Lactococcus lactis, Lactococcus lactis* subsp. lactis, *Lactococcus lactis* subsp. diacetylactis, and *Lactococcus Lactis* subsp. cremoris
Bifidobacterium	*Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium bifidus*, and *Bifidobacterium lactis*
Enterococcus	*Enterococcus faecalis* and *Enterococcus faecium*
Saccharomyces	*Saccharomyces cerevisiae* and *Saccharomyces boulardii*
Streptococcus	*Streptococcus thermophiles*
Bacillus	*Bacillus coagulans* and *Bacillus subtilis*
Others	*Akkermansia muciniphila, Eubacterium hallii*, and *Faecalibacterium prausnitzii*

Table 1. Representative microbe commonly considered as probiotics.

plantarum, *Lactobacillus casei*, and *Lactobacillus delbrueckii* subsp. bulgaricus) was proven more effective than single-strain probiotics for the treatment of ulcerative colitis [23]. The multispecies probiotic consortium, Ecologic AAD (*Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W18, *Bifidobacterium longum* W51, *Enterococcus faecium* W54, *Lactobacillus acidophilus* W37 and W55, *Lactobacillus paracasei* W72, *Lactobacillus plantarum* W62, *Lactobacillus rhamnosus* W71, and *Lactobacillus salivarius* W24), combined with amoxicillin, could reduce diarrhea-like bowel movements, while the single strain could not [25]. Thus, the combination-specific probiotic effects from diverse strains can lead to synergistic effects.

Among the most frequently used probiotics, the genera *Lactobacillus*, *Bifidobacterium*, *Lactococcus*, and *Saccharomyces* have been included in the category of "generally regarded as safe" (GRAS) [4, 6]; however, other probiotic organisms such as *Enterococcus*, *Bacillus*, and *Streptococcus* are not generally regarded as safe. Since probiotics have been applied in food production, disease treatment, and others, it is important to undergo safety evaluation of probiotics before human consumption.

In this chapter, we briefly review the mechanisms of action of probiotics, the safety concern of probiotics, and their potentials for prevention and treatment of diseases. Here, we discuss the application of probiotics in the fungal *Candida*-infected and invasion candidiasis.

2. Probiotics mechanism of action

Probiotics mechanism of action is with important differences among different species and strain, examples are listed in **Table 2**.

2.1. Maintenance flora healthy by reduction the growth and colonization of pathogens

The ability of probiotics to establish in the gastrointestinal (GI) tract, maintain flora healthy, and reduce the growth of pathogens and colonization is enhanced by their ability to eliminate competitors. Probiotic strains release different antimicrobial molecules such as organic acids, hydrogen peroxide (H_2O_2), and antimicrobial peptide bacteriocins into the intestinal environment to limit the growth of bacterial and fungal pathogens [6, 39–43].

Lactic acid and acetic acid are the main metabolites formed by lactic acid bacteria (LAB). Both lactic acid and acetic acid could result in acidity environment and thus inhibit the growth of various microorganisms. Acetic acid has a broader spectrum of antimicrobial activity when compared to lactic acid. Moreover, it is known that a synergistic effect exists between the two acids: mixtures of acetic and lactic acids suppress the growth of the pathogenic enteric bacterium *Salmonella typhimurium* [44].

LAB can also produce H_2O_2, the antimicrobial activity of which is linked to the strong oxidizing effect. Hydrogen peroxide showed a bactericidal effect on most pathogens when in

Mechanism of action	Probiotics	Study outcomes	References
Maintenance flora healthy by reduction the growth and colonization of pathogens	*L. rhamnosus* GG, *L. casei* Shirota, *L. reuteri* SD2112 and *L. brevis* CD2	*L. rhamnosus* GG showed the strongest inhibitory activity in fructose and glucose medium against *C. albicans*, followed by *L. casei* Shirota, *L. reuteri* SD2112 and *L. brevis* CD2	[26]
	L. plantarum, commercial preparation LactoLevure®	Increased survival of mice infected by multidrug resistant *P. aeruginosa* and *E. coli*	[27]
	B. breve, *L. casei* (randomized controlled trial, RCT)	Levels of beneficial organic acids significantly increased in the gut, and the incidences of infectious (pneumonia and bacteremia) complications were significantly lower in the probiotic group	[32]
	Synbiotic (*Lactobacillus*, *Bifidobacterium*, and galactooligosaccharides) for 8 weeks (RCT)	Acetic acid concentration significantly increased (100 times), pH value decreased, Gram-negative rod (1/10) in the gut decreased, and *P. aeruginosa* decreased in the probiotic group	[33]
	Multi-strain synbiotic for 7 days (RCT)	Synbiotic group had lower pathogenic bacteria (43% versus 75%) and multiple organisms (39% versus 75%) in nasogastric aspirates than controls	[34]
	B. lactis Bb12 for 7–21 days (RCT)	Probiotic group had great higher counts of *Bifidobacterium* ($P = 0.001$) and lower counts of *Enterobacteriaceae* ($P = 0.015$) and *Clostridium* spp. ($P = 0.014$) than in placebo group	[35]
	L. casei subsp. *rhamnosus* for 6 weeks (RCT)	Colonization of *Candida* in gut was reduced in probiotic group ($P = 0.01$)	[28]
Enhancement of mucosal barrier integrity	*L. plantarum* 299v for 8 days (RCT)	Bacterial translocation in mesenteric lymph nodes and liver was reduced to 0 and 12%, respectively	[29]
	Microencapsulated *Bifidobacteria*	Bacterial translocation to mesenteric lymph nodes was reduced by encapsulated *Bifidobacteria* ($P < 0.05$)	[30]
	VSL#3 (RCT)	Decreased incidence of bacterial translocation in VSL#3 group than in water group (8% versus 50%; $P = 0.03$)	[31]
Immune modulation	VSL#3 (*Lactobacillus*, *Bifidobacterium*, and *S. thermophilus*) for 7 days (RCT)	Reduced acute physiology and chronic health evaluation II score; reduced sequential organ failure assessment, IL-6, procalcitonin, and protein	[36]
	L. plantarum 299v (RCT)	Late attenuating effect (after 15 days), serum IL-6 levels reduced	[37]

Table 2. Mechanism of action of probiotics.

combination with lactoperoxidase-thiocyanate milk system [45]. *L. johnsonii* NCC933 and *L. gasseri* KS120.1 killed enteric uropathogenic and vaginosis-associated pathogens due to the production of lactic acid and hydrogen peroxide [46].

Bacteriocins are ribosomally synthesized antimicrobial peptides, which have broad spectrum of inhibitory effect against Gram-positive and Gram-negative bacteria, viruses, and fungi [47–50]. *L. plantarum* 2.9, a bacteriocinogenic strain, inhibited a set of foodborne pathogens including *B. cereus*, *E. coli* O157:H7, and *S. enterica* [51]. Bacteriocin-producing strains identified in our lab, e.g., *L. plantarum* ZJ316, *L. plantarum* LZ95, *L. plantarum* ZJ008, and *L. plantarum* ZJ005, showed antimicrobial activity against various pathogens *in vitro* such as *S. aureus*, *E. coli*, *S. enterica*, *L. monocytogenes*, and *C. albicans* [42, 52–54].

2.2. Enhancement of mucosal barrier integrity

Probiotics have been shown to improve barrier function and the mechanisms of barrier function including alteration of tight junction protein expression and/or localization, induction of mucus secretion, increased production of cytoprotective molecules such as heat-shock proteins, inhibition of apoptosis of epithelial cells, and promoting cell survival [29, 55, 56]. They compete with pathogens and prevent their invasion through the epithelium by the ability of adherence to the intestinal epithelium and mucus. *L. plantarum* has been shown to enhance mucosal barrier by adhering to the mucosal membrane and reducing Gram-negative bacteria [29]. Probiotics also compete for limiting resources, thus suppressing the growth of bacterial and fungal pathogens. The probiotic *E. coli* Nissle 1917 is able to effectively take up multiple limited environmental irons and simultaneously competitively inhibit the growth of other intestinal microbes and pathogens [57].

Furthermore, butyrate, a short-chain fatty acid (SCFA), could reduce bacterial translocation, improve the organization of tight junctions, modulate intestinal motility in addition to being an energy source for colonocytes, and maintain the integrity of the intestinal epithelium [29–31, 58–60]. *E. hallii* is an important anaerobic butyrate producer resident in our gut, which influences the intestinal metabolic balance and enhances the host-gut microbiota homeostasis [61]. Thus, the administration of probiotics with butyrate-producing bacteria, in particular, could be an effective way to achieve health benefits.

2.3. Immune modulation

Probiotics are reported to enhance phagocytic activity of granulocytes and cytokine excretion in lymphocytes, increase immunoglobulin-secreting cells, and attenuate inflammasome activation. They are able to affect cells involved in immune responses, including epithelial cells, dendritic cells (DCs), T cells, regulatory T (Treg) cells, monocytes/macrophages, immunoglobulin A (IgA)-producing B cells, and natural killer cells [62, 63].

Probiotic bacteria have an effect on intestinal DCs, which have the ability to recognize and respond to different bacteria by linking the innate immune system to the adaptive immune response and to develop T- and B-cell responses. Badia et al. found that the immunomodulatory role of *S. boulardii* in the DCs prior to infection was related to the upregulation of tumor necrosis factor alpha (TNFα) and C—C chemokine receptor type 7 mRNAs, which might make the DCs more effective in antagonizing bacteria [64, 65]. Smith et al. reported that *S. boulardii* stimulated the production of cytokines TNFα, IL-1, IL-12, IL-6, and IL-10 in DCs and also

induced high levels of costimulatory molecules CD80 and CD86, thus modulated the immune system and led to an efficient clearing of enteropathogenic bacteria from the blood stream coupled with a faster cytokine response [65, 66].

Probiotics also influence intestinal epithelial cells through interaction with Toll-like receptors (TLRs) and downregulate the expression of NF-κB and proinflammatory cytokines [67, 68]. This effect is supported by the following studies: the supernatant of probiotic *Faecalibacterium prausnitzii* inhibited the NF-κB pathway *in vitro* and *in vivo* and showed protective effects in different models such as dinitrobenzene sulfate (DNBS)-induced colitis model and dextran sodium sulfate (DSS)-induced colitis [69]; the probiotic strain *L. rhamnosus* GG prevented cytokine-induced apoptosis in intestinal epithelial cells [70]; and *L. rhamnosus* GR-1 reduced the adhesion of *E. coli* by promoting TLR2 and NOD1 synergism and attenuating ASC-independent NLRP3 inflammasome activation [71].

3. Probiotic as antifungals for prevention and treatment of candidiasis

Candida is an opportunistic pathogen, causing mucosal infections including infections in the oral cavity, oropharynx, esophagus, and vagina, and potentially life-threatening systemic candidiasis. *Candida albicans* is the most common fungal pathogen in humans responsible for causing superficial as well as deep invasive candidiasis, which are essentially caused by *Candida* biofilms attached to body surfaces. Other *Candida* species such as *Candida tropicalis*, *Candida guilliermondii*, *Candida krusei*, and *Candida glabrata* are less frequently isolated in healthy and diseased humans [72–74]. Probiotics are known to reduce *Candida* infection in different organs and are generally considered to be beneficial for overall health. They appear to assist the host combat the pathogen by suppressing filamentation formation and reducing biofilm development, the mechanism of which may be related to expression of genes associated with biofilm formation and filamentation in *Candida* species. *In vitro* and *in vivo* studies have demonstrated the role of probiotics in the prevention of *Candida* colonization and invasive candidiasis [38, 75–86].

3.1. *In vitro* evidences: probiotics in prevention/treatment of *Candida* infections

Several *in vitro* studies have addressed the antifungal effects of probiotics against *Candida* isolated from the human oral cavity, GI tract, and genitourinary tract [77–81, 86, 87]. The probiotics that have been investigated against *Candida* species include *Lactobacillus* (e.g., *L. rhamnosus*, *L. plantarum*, *L. fermentum*, *L. acidophilus*, *L. paracasei*, *L. johnsonii*, and *L. salivarius*), *Bifidobacterium* (e.g., *B. bifidum* and *B. infantis*), *Saccharomyces* (e.g., *S. boulardii*), and *Streptococcus* (e.g., *S. thermophilus*). **Table 3** shows candidacidal activity of probiotic strains in different studies. *C. albicans* appears to be more susceptible to the antifungal effect of *Lactobacillus* than *C. pseudotropicalis* [81], and the probiotics exhibited growth inhibitory activities against *C. glabrata*, *C. krusei*, and *C. parapsilosis* [79, 87].

Probiotics	Target pathogen	Study outcome	References
14 strains: *L. fermentum*, *L. rhamnosus*, *L. plantarum*, and *L. acidophilus*	*C. albicans* and *C. pseudotropicalis*	All probiotics inhibited the growth of *C. albicans* by H_2O_2 production and alternative mechanism	[81]
S. boulardii	*C. albicans* SC5314	*S. boulardii* inhibited the affecting hyphae formation, *Candida* adhesion, and biofilm formation by capric acid production	[87]
L. paracasei IMC 502	*C. glabrata*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis*	High activity toward *Candida* strains except *C. glabrata* and *C. tropicalis*	[79]
L. plantarum ATCC 8014 and *L. johnsonii* enriched or not with SeNPs	*C. albicans* ATCC 14053	Strong inhibition of *C. albicans* by supernatant of selenium-enriched *Lactobacillus* spp.	[86]
L. acidophilus, *L. rhamnosus*, *L. salivarius*, *B. bifidum*, *S. thermophiles*, and *B. infantis*	*C. albicans* 10341	Significant inhibitory effect on biofilm formation and reduce viability of *Candida*	[80]
L. rhamnosus GR-1 *and L. reuteri* RC-14	*C. albicans* SC5314	Visible inhibition zones of fungal *C. albicans* by probiotic treatment; low pH environment caused by lactic acid and the H_2O_2 production may be anti-*Candida* factors	[77]
L. acidophilus ATCC 4356	*C. albicans* ATCC 18804	Reduce growth of *C. albicans* cells by 45.1%	[78]
L. casei subsp. *rhamnosus*	*Candida* spp.	80 preterm neonates with a very low birth weight: probiotic reduced incidence and intensity of enteric colonization by *Candida* spp. (RCT)	[28]
L. rhamnosus GG, *L. rhamnosus* LC705, *P. freudenreichii* subsp. *shermanii* JS	*Candida* spp.	276 elderly people: probiotic intervention reduced the risk of high yeast counts by 75% and the prevalence of hyposalivation (RCT)	[76]
L. rhamnosus GR-1 *and L. reuteri* RC-14	*Candida* spp.	55 women: probiotics significant reduced vaginal discharge, itching, and/or burning vaginal feeling, dyspareunia, and/or dysuria, and reduced the presence of *Candida* spp. (RCT)	[82]
L. acidophilus, *L. rhamnosus*, *B. longum*, *B. bifidum*, *S. boulardii*, and *S. thermophilus*	*Candida* spp.	150 children (aged 3 month to 12 year) on broad-spectrum antibiotics for at least 48 h: probiotic therapy avoided a significant increase in the number of patients colonized by *Candida* spp., significantly reduced the presence of *Candida* in the urine (RCT)	[83]
L. bulgaricus, *B. longum*, and *S. thermophilus*	*Candida* spp.	65 patients with *Candida*-associated stomatitis: detection rate of *Candida* spp. was reduced in the probiotic group; significant relief of clinical signs and symptoms after probiotic administration (RCT)	[84]

Probiotics	Target pathogen	Study outcome	References
L. acidophilus, *B. lactis*, *B. longum, and B. bifidum*	*Candida* spp.	112 preterm neonates (gestational age < 37 wk and birth weight < 2500 g): probiotics may reduce enteral fungal colonization and invasive fungal sepsis in low-birth-weight neonates (RCT)	[75]
L. reuteri DSM 17938 and *L. reuteri* ATCC PTA 5289	*Candida* spp.	215 elderly people (aged 60–102 y): significant reduction of *Candida* cells in saliva and plaque (RCT)	[85]

Table 3. Probiotics in prevention/treatment of **Candida** infections.

However, the mechanisms involved in antifungal activity of probiotics against *Candida* remain unclarified. Strus et al. found that *Lactobacillus* strains could inhibit the growth of *C. albicans* to a certain degree and their anticandidal activity related to H_2O_2 production [81]. Murzyn et al. reported that *S. boulardii* was able to secrete active compounds, mainly capric acid, reduced the expression of *hwp1*, *ino1*, and *csh1* genes that encode virulence factors in *C. albicans* SC5314 cells, and inhibited filamentation of *C. albicans* and its mycelial development [87]. Therefore, it is likely that the antimicrobial molecules, organic acids, and H_2O_2 produced by probiotic are major factors to limit growth of fungal pathogen *Candida*. This idea was supported by the research of Köhler et al. They demonstrated that low pH environment caused by lactic acid and the H_2O_2 production of *L. rhamnosus* GR-1 and *L. reuteri* RC-14 strains played important role in their inhibition activity to *C. albicans* SC5314. Moreover, *L. rhamnosus* GR-1 and *L. reuteri* RC-14 inhibited genes associated with *C. albicans* biofilm formation [87]. This result, together with the findings in Murzyn et al. study, shed light on a novel approach for uncovering the molecular mechanisms of the probiotic effect by using gene expression and related technology.

3.2. *In vivo* evidences: probiotics in prevention/treatment of *Candida* infections

In vivo studies, especially RCTs, have also been performed to substantiate the antifungal activity of probiotics in humans. These studies mostly focus on the sites of oral cavity, GI tract, and urogenital tract, which are susceptible to *Candida* infections (**Table 3**).

The elderly are a group particularly susceptible to oral candidiasis, because of frequent usage of dentures, hyposalivation, and their weakened immune status. Researches by Hatakka et al. and Kraft-Bodi et al. have shown that the daily consumption of food with *L. reuteri* DSM17938, *L. reuteri* ATCC PTA 5289, and *L. rhamnosus* GG ATCC 53103 significantly reduced the high yeast counts in saliva and biofilms in the elderly [76, 85]. The removal of biofilms by the use of probiotics that reduce the oral burden of *Candida* could play a major role in preventing oral candidiasis in denture wearers.

For the urogenital tract, chronic vulvovaginal candidiasis (VVC) is the most common candidiasis disease and impacts the life quality of thousands of women around the world. Researches on the effect of probiotics in the treatment and prophylaxis of VVC have been performed [82]. Martinez et al., in an RCT involving 55 women, demonstrated that the administration of *L. rhamnosus*

GR-1 and *L. reuteri* RC-14 significantly reduced the presence of *Candida* and therefore reduced the vaginal discharge, itching, and/or burning vaginal feeling, dyspareunia, and/or dysuria [82].

For the GI tract, *Candida* species are common inhabitants of GI tract. Dysbiosis of GI tract may lead to candidal overgrowth and possible invasive infections, especially in infants. Hence, immunocompromised children, especially preterm neonates with low birth weight, have been the target population of a large number of studies to evaluate the prevention or/and treatment potentials of probiotics to *Candida* infections [28, 75, 83]. Manzoni et al., in an RCT involving 80 very low birth weight (VLBW) neonates, demonstrated that orally administered *L. casei* subsp. rhamnosus significantly reduced incidence and intensity of enteric colonization by *Candida* [28]. Another RCT, by Roy et al., found *L. acidophilus*, *B. lactis*, *B. longum*, and *B. bifidum* reduced enteral fungal colonization and invasive fungal sepsis in 112 preterm neonates (gestational age < 37 wk and birth weight < 2500 g) [75].

Together, both the laboratory studies and clinical studies showed that probiotics could prevent *Candida* colonization by inhibiting adhesion, filamentation, and biofilm formation, and therefore supplementation of probiotics could be a potential approach for reducing *Candida* colonization and invasive candidiasis.

4. Safety of probiotics

Although most commercially available probiotic strains are generally regarded as safe and none of the clinical studies mentioned above were reported to have adverse effects directly related to probiotics, there are some concerns regarding the safety of probiotics, including potential of bacteremia and/or endocarditis occurrence, toxicity to the gastrointestinal tract, and transfer of antibiotic resistance [4].

4.1. Potential of bacteremia and/or endocarditis occurrence

Lactic acid bacteria, including *Bifidobacterium*, have been reported to cause bacteremia as well as endocarditis [88–92]. Cannon et al. described that *L. rhamnosus* caused liver abscess, lactobacillemia, and infective endocarditis in a few case studies, and also the occurrence of *Lactobacillus* sepsis was directly linked with the ingestion of probiotic supplements, especially among immunocompromised patients and those with endocarditis [89]. Kunz et al. found two premature infants with short gut syndrome developed Lactobacillus bacteremia while taking *Lactobacillus* GG supplements. However, the risk of infection due to Lactobacilli is extremely rare. Statistic data from surveillance in Finland suggest that there was no increase in *Lactobacillus* bacteremia during 1990–2000, and Lactobacilli were isolated in 0.02% of all blood cultures [93].

4.2. Toxicity to the gastrointestinal tract

The role of probiotics on gastrointestinal physiology suggests a theoretical possibility that the production of metabolites might be undesirable and also might lead to malabsorption due to deconjugation of bile salts. These might increase the risk of colon cancer; however, there is no epidemiologic or clinical evidence to support this hypothesis [94, 95].

4.3. Transfer of antibiotic resistance

Another major safety concern of theoretical importance is genetic transfer of antibiotic resistance from probiotic strains to pathogenic cells in the gastrointestinal tract [96, 97]. Plasmids with antibiotic-resistance genes, including genes encoding resistance to tetracycline, erythromycin, chloramphenicol, and macrolide-lincosamide-streptogramin, have been found in *L. plantarum*, *L. fermentum*, *L. acidophilus*, and *L. reuteri* strains. *L. plantarum* 5057 exhibited tetracycline resistance, and *L. lactis* was with streptomycin, tetracycline, and chloramphenicol resistances [98–100]. Although the transfer of native *Lactobacillus* plasmids is quite rare, there are some cases, e.g., the antibiotic-resistance plasmids from *Lactococcus* species could transfer to *Leuconostoc* species and *Pediococcus* species.

With respect to the potential risks of probiotics, it is important to conduct population-based surveillance for safety concern.

5. Conclusions

Probiotics have the ability to restore the imbalance of intestinal microbiota and could act as both prophylactic and adjunctive therapy against candidiasis. Antifungal effect of probiotics is likely due to their interference with *Candida* biofilm development and hyphal differentiation. Safety may be of concern in application, as probiotic strains may, although quite rarely, cause bacteremia, fungemia, and sepsis. Well-designed RCTs are required to address these issues before the routine use of probiotics is recommended.

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