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Review Article

Exploring the dark side of probiotics to pursue light: Intrinsic and extrinsic risks to be opportunistic pathogens

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ABSTRACT

Probiotics, live microorganisms with multiple health benefits, have gained popularity for their roles in maintaining daily health and treating a variety of diseases. However, they have the potential to be opportunistic pathogens in some conditions. This review delves into the intrinsic and extrinsic risks associated with probiotics. Intrinsic risks involve the production of harmful substances, such as toxins and invasive factors, biofilm formation, bacteria emboli, antibiotic resistance with relevant genetic materials, genetic plasticity, and metabolic issues, while extrinsic risks include problems in regulatory oversight and public awareness, host health status and appropriately administration. It emphasizes the need for a balanced view of their therapeutic benefits and potential hazards, advocating for further research to understand the complex interactions between probiotics and the human microbiome, to optimize the safety and efficacy of probiotics.

1. Introduction

Probiotic, a living microorganism, renowned for their myriad health benefits when administered in adequate amounts (Gilliam et al., 2023; Hill et al., 2014), have found widespread application not only in treating gastrointestinal disorders (Tabatabaeizadeh and Tafazoli, 2023), but progressively in addressing diseases of other bodily systems (Liu et al., 2023). Their extensive benefits, both physical and mental (Radford-Smith and Anthony, 2023), underscore their status as a pivotal cornerstone of human health. While the intricate mechanisms of probiotics remain only partially understood, their primary functions include enhancing intestinal barrier functions (Ait Abdellah et al., 2023), modulating the immune system, synthesizing crucial substances for their host, and inhibiting the growth of pathogenic bacteria through competitive exclusion and production of antimicrobial substances (Dimidi et al., 2017; Hossain et al., 2017).

The burgeoning interest in probiotics, driven by their significant health benefits, has led to a substantial increase in both research and consumer adoption. However, this enthusiasm must be tempered by an awareness of the potential risks associated with probiotics. These risks, as evidenced by case studies and research, include the potential pathogenicity of probiotics. Intrinsic risks encompass a range of virulence factors, invasive capabilities, metabolic complications, biofilm formation, and platelet aggregation (Haranahalli Nataraj et al., 2023). A particularly concerning issue is the possibility that probiotics could exacerbate problems related to harmful and antibiotic-resistant genes, due to mutations and horizontal gene transfers between normal and pathogenic bacteria (Merenstein et al., 2023).

In addition to these intrinsic risks, extrinsic factors such as the host's health status, regulatory frameworks, and public awareness also play crucial roles in determining the safety and efficacy of probiotic use. The health condition of the host is particularly pivotal in assessing whether probiotics will be beneficial or harmful. Given the complexity of the human microbiome and the intricate interactions between probiotics and host health, further research and more stringent regulatory oversight are imperative. Healthcare providers must adopt comprehensive administration strategies, while consumers should be well-informed about the potential risks and benefits of probiotics.

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This review illuminates the intrinsic and extrinsic risks associated with probiotics and the challenges in their administration. By doing so, it fosters balanced and informed dialogue on probiotics, enhancing public understanding. It offers data and theoretical support for the proper production, utilization, and consumption of probiotics, paving the way for safer and more effective use of these potent agents in promoting human health and wellness and aiding in the development of future probiotics.

2. Beneficial contributions of probiotics to human health

Probiotics, live microorganisms that confer health benefits when administered in adequate amounts (Gilliam et al., 2023; Hill et al., 2014), have been recognized for their positive impact on human health for centuries (Ozen and Dinleyici, 2015). The concept of probiotics gained prominence in the early 1900s, when Nobel Laureate Elie Metchnikoff suggested that lactic acid bacteria could enhance health, a belief he attributed to his extended lifespan through regular probiotic consumption (Boyle et al., 2006). Over time, it has become evident that the human body hosts trillions of microorganisms, collectively known as the normal microbiota, which inhabit various areas including the skin, oral cavity, gastrointestinal tract, respiratory system, and urogenital tract. These microorganisms play crucial roles in maintaining health and homeostasis.

Probiotics, commonly used as food supplements and drugs, are predominantly used to support intestinal health (Zucko et al., 2020). Well-known bacterial strains include *Lactobacillus, Enterococcus, Escherichia, Bacillus, Bifidobacterium, Propionibacterium,* and *Clostridium butyricum*, as well as fungi like *Saccharomyces cerevisiae* and *Saccharomyces boulardii* (Sanders et al., 2010). These exclude known pathogenic strains, like *Enterococcus faecalis* Aus0004 and Aus0085 (Vc et al., 2018).

They exert their beneficial effects through a variety of mechanisms, particularly within the gastrointestinal tract. Primarily, they enhance the integrity of the intestinal barrier, which helps prevent the translocation of harmful pathogens and toxins. Probiotics also compete with pathogenic bacteria for nutrients and adhesion sites on the gut lining, effectively inhibiting the growth and colonization of these harmful microbes. Additionally, they produce antimicrobial substances, such as bacteriocins and organic acids, which directly target and neutralize pathogens (Zucko et al., 2020). Probiotics modulate the immune system by interacting with gut-associated lymphoid tissue, thereby enhancing the body's immune response and promoting tolerance to dietary antigens. Furthermore, they play a role in synthesizing essential nutrients, such as vitamins and short-chain fatty acids, which contribute to gut health and overall well-being. Through these multifaceted mechanisms, probiotics help maintain a balanced microbiome, support digestive health, and bolster immune function, making them a crucial component in the maintenance of human health (Puntillo et al., 2022).

While probiotics contribute broadly to health maintenance, engineered bacteria are tailored for specific therapeutic interventions, representing an advanced frontier in microbiome-based therapies. Building from the foundational benefits of traditional strains, functional probiotics with specific health effects, are often achieved through a selection of strains or probiotic engineering. Engineered probiotics are designed to deliver therapeutic molecules or perform specific functions within the host, with mechanisms tailored to achieve desired health outcomes. These could include targeted drug delivery, the production of therapeutic compounds, or the degradation of harmful substances. Engineered bacteria could be designed to respond to environmental or disease-specific triggers, offering precision in treatment. This advancement in personalized medicine within holistic health allows for designed probiotic therapies based on individual health needs and genetic profiles (Hill et al., 2014).

3. Potentially intrinsic risk factors of probiotics

3.1. Certain substances produced by probiotics could cause disease

Probiotics are often hailed for their health benefits, promoting gut health and boosting the immune system. However, recent studies suggest that certain substances, such as toxins and invasive factors, produced by these microorganisms might have adverse effects. These substances, under specific conditions, could potentially contribute to the development of diseases.

Evaluating the potential toxigenic and invasive risks associated with probiotics requires both genotypic and phenotypic strategies (Merenstein et al., 2023), as gene expression is also influenced by environmental conditions. Genetic analysis provides only a maximum potential risk assessment. It is crucial to determine if, and to what extent, corresponding genes are expressed, and any differences in expression levels need investigation. However, traditional safety assessments, aimed at evaluating probiotic toxicity or pathogenicity, fall short because animal models or cell tests cannot replicate complex interactions present in genetically susceptible human populations. The intricate human microbiome and dynamic host-probiotic interactions demand extensive research to understand how probiotics use these substances and their safety standard. For instance, while effective adhesion and colonization enhance probiotic functions (Colautti et al., 2022), excessive colonization may cause long-term persistence leading to issues such as infections (Apostolou et al., 2001). Therefore, balancing these factors for individual patients can optimize probiotics' benefits (see Fig. 1).

3.1.1. Probiotics may have toxigenicity

While most probiotic strains exhibit non-haemolytic activity, some studies have identified specific strains that are hemolytic positive, potentially due to the bacteria's need for iron (Toprak et al., 2022). Grace Adzo Motey and her team assessed the probiotic properties of lactic acid bacteria isolated from traditionally fermented milk in Ghana, finding that none of these strains exhibited β-hemolysis, though 38 % displayed α-hemolysis (Motey et al., 2021). Other study shows that certain *Lactococcus lactis* strains could produce an exotoxin with β-hemolytic effects (Wu et al., 2023). Among *Enterococci*, several strains show α-hemolytic and β-hemolytic activity on blood agar, while a few species display partial or γ-hemolytic activity, likely due to the production of hydrogen peroxide or surfactants (Haranahalli Nataraj et al., 2023).

Cytolysin is a peptide bacteriocin of *Enterococci*, which could kill many kinds of gram-positive bacteria by forming pores in the cytoplasmic membrane, possesses β-hemolysin function, killing human red blood cells, and damage the liver (Lang et al., 2020; X. Wang et al., 2020). Eight important genes in *Cyl* operon, which is located on self-transmissible plasmids that respond to pheromones. The genes $cylL_L$ and $cylL_S$ are responsible for producing small peptide precursors. These precursors undergo post-translational modifications by the enzyme Cyl_M, are transported outside the cell through Cyl_B, and are activated by Cyl_A, resulting in the formation of components known as $CylL_L$ and $CylL_S$. These compact molecules play a crucial role in the hemolytic and bactericidal functions (Coburn and Gilmore, 2003). The active version of $CylL_S$ triggers the activation of cytolysin genes via a distinctive quorum-sensing process. In addition, *Cyl* gene could cooperate with *Agg* gene, increasing the risks of infections, especially endocarditis (Ben Braïek and Smaoui, 2019; X. Wang et al., 2020).

Colibactin is known to kill other bacteria by breaking down their DNA, and it could also damage the DNA of human cells, leading to abnormal mitosis and an increased frequency of gene mutations, thus acting as an oncogenic factor in colorectal cancer (Nougayrède et al., 2021). Nougayrède et al. report that *Escherichia. coli* Nissilä et al., 2017, a widely used probiotic strain, possesses colibactin synthesis genes (Nougayrède et al., 2021). Additionally, Haranahalli Nataraj et al.

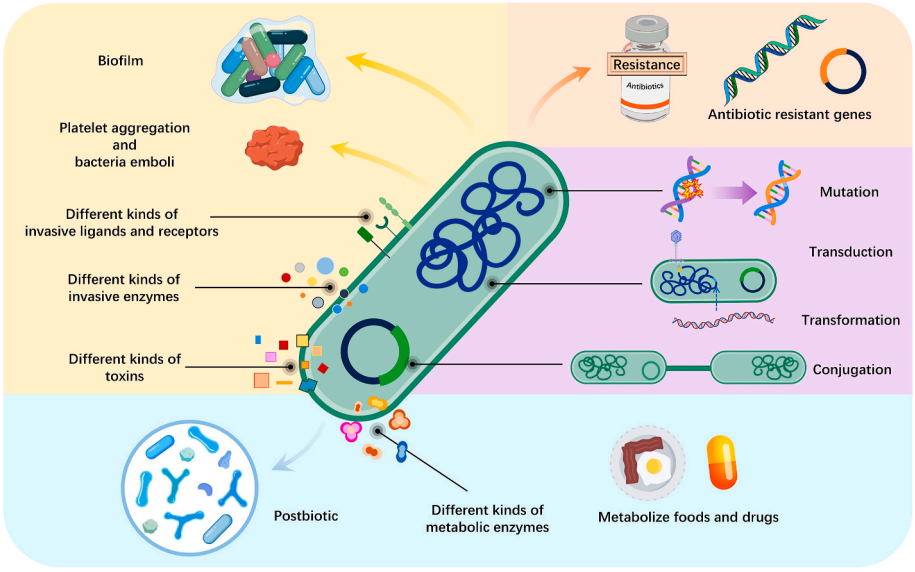

Fig. 1. A summary of potentially intrinsic risk factors of probiotics. It includes the production of harmful substances (toxins, invasive factors, biofilm formation, and emboli), antibiotic resistance and associated genetic material, genetic plasticity (mutation and horizontal gene transfer), and metabolic complications (e.g., toxic metabolites, and drug interactions).

described that while some lactic acid bacteria strains exhibit extracellular DNase activity, *Enterococcus lactis* JDM1 possesses DNase genes but does not express them (Haranahalli Nataraj et al., 2023).

3.1.2. *Invasive factors and adhesion ability of probiotics may lead to disease*

The successful colonization of probiotics is important for their normal functions. Therefore, after entering the body, probiotics will release adhesion-related enzymes and proteins (Haranahalli Nataraj et al., 2023). However, the efficacy of probiotics does not absolutely depend on their term of colonization (Merenstein et al., 2023), and sometimes these factors may lead to further deeper invasion. The following discussion is organized by mechanism categories, including multiple invasive enzymes, adhesion-associated proteins, and other risk

Table 1
Probiotics and clinical isolated strains' invasive factors and adhesion ability with their mechanisms, clinical implications, associated strains, and relevant case reports or research.

Factor	Mechanism	Potentially associated side effects or disease	Certain probiotic or clinically isolated strains	References
Biofilm	A polymer matrix secreted by microorganism for reproduce and protect	Over proliferation Infection, especially catheter-related infections Antibiotic resistance	Certain L. *rhamnosus* GG strains Certain L. *paracasei* strains Certain *Enterococcus*, like *E. faecalis* (clinical isolates)	(Ben Braïek and Smaoui, 2019; Chiang et al., 2021; Deng et al., 2021; Im et al., 2023; Kim et al., 2023; Rossi et al., 2019; Tang et al., 2021)
Platelet Aggregation	Aggregate platelet to form emboli and valvular vegetations Evading phagocytosis	Widely infection Endocarditis, even with systemic emboli	Certain *Lactobacillus* strains, like *L. salivarius* CCUG_47,825, *L. johnsonii* (isolated from calf feces); certain *L. casei*, *L. rhamnosus*, and *L. plantarum* (isolated from *Lactobacillus* endocarditis cases)	(Ajam et al., 2019; Antikainen et al., 2007; Campagne et al., 2020, 2020, 2020; Cannon et al., 2005; Colautti et al., 2022; DeMarco et al., 2023; Kirjavainen et al., 1999; Nissilä et al., 2017; Rahman et al., 2023, 2023, 2023)
Hyaluronidase	Breaks down hyaluronic acid	Deep tissue or organ infection	*E. faecalis* (clinical strains) food-derived strains: *E. mundtii*, *E. durans*, *E. casseliflavus*; *L. mucosae*, *L. plantarum*, *L. delbrueckii* subsp. *bulgaricus*, and *L. curvatus* (They have *hyl* gene.).	(Ben Braïek and Smaoui, 2019; Vankerckhoven et al., 2004).
Multiple adhesion-associated proteins and pili	Mediates binding to host extracellular matrix (e.g., collagen, fibronectin).	Deep infection Vegetations formation Endocarditis	Certain *Bifidobacteria*, like *B. breve* UCC2003 Certain probiotic *E. faecium* and *E. faecalis*	(Ben Braïek and Smaoui, 2019; Colautti et al., 2022; Deng et al., 2021; Nissilä et al., 2017; Westermann et al., 2016)
Gelatinase	Degrade type IV collagen, haemoglobin, casein, *β*-insulin, other bioactive peptides Assist in forming biofilm	Break normal tissue Infection, e.g., endocarditis, bacteremia and septicemia Affect metabolism	Some Enterococci (clinically isolated strains, usually nosocomial pathogens)	(Vankerckhoven et al., 2004; Haranahalli Nataraj et al., 2023; Krawczyk et al., 2021; Ben Braïek and Smaoui, 2019; J. Wang et al., 2020)
Urease	Hydrolyse urea to ammonia and carbon dioxide	Over proliferation, even dysbacteriosis	*B. longum* subsp. *Infantis*	Esaiassen et al. (2017)
Mucinase	Degrades the mucins in the gut	Break gut barrier integrity	Certain *Bifidobacterium* strains (Traditional probiotics usually have associated tests to ensure they cannot degrade mucin.) *Akkermansia muciniphila* (could renew mucus layer, offering benefits)	(Esaiassen et al., 2017; Haranahalli Nataraj et al., 2023; Merenstein et al., 2023; Q. Zhao et al., 2023)

factors. These factors, listed in Table 1, are ranked by clinical severity, with biofilm listed first.

Mucins are crucial for maintaining gut barrier integrity and facilitating nutrient absorption, so the ability to break down mucins or mucolysis is essential in pathogenesis (Haranahalli Nataraj et al., 2023; Merenstein et al., 2023). Although many studies suggest that probiotics limit mucin-degrading ability, there are still several research studies that exhibit that certain *Bifidobacterium* strains could degrade mucins (Esaiassen et al., 2017). However, the pathogenicity of mucinase is not absolute. For instance, the next generation of probiotics, *Akkermansia muciniphila*, degrades mucins to acquire carbon and nitrogen sources for itself and is vitally involved in the renewal of the mucus layer, which offers benefits to humans (Q. Zhao et al., 2023).

Gelatinase, a Zn^{2+}-dependence metalloprotease, hydrolase multiple matrix and proteins. It facilitates bacterial invasion by breaking down the physical barriers of host tissues, allowing the bacteria to penetrate and establish infections. Additionally, gelatinase could degrade bioactive peptides, which may contribute to immune evasion and the persistence of bacterial colonies within-host environments (Ben Braïek and Smaoui, 2019). Despite its rarity among probiotics, some lactic acid bacteria isolated from the intestine have been found to possess gelatinase activity (Haranahalli Nataraj et al., 2023). In *E. faecalis*, most strains carry the gelatinase gene (*GelE*). However, the expression of this enzyme is not universal among *Enterococcus*, indicating that additional regulatory mechanisms govern its production (Vankerckhoven et al., 2004). Thus, it is important to have a safety properties screening before confirming this *E. faecalis* strain could be used as probiotics, like Symbioflor® (J. Wang et al., 2020).

Hyaluronidase could assist in invading human connective tissues, facilitating microorganisms' spread within the host. The presence of hyaluronidase is a characteristic of pathogen species, like *Staphylococcus* and *Streptococcus*. The *hyl* gene, responsible for hyaluronidase production, has been identified in some clinical strains of *Enterococcus* and *Lactobacillus* (listed in Table 1). Despite the absence of documented evidence that these *Lactobacilli* produce hyaluronidase, they do have *hyl* gene (Ben Braïek and Smaoui, 2019; Vankerckhoven et al., 2004).

Urease, increasing pH to fit bacteria survival, might aid in protecting *Bifidobacterium longum* subsp. *infantis* against gastric acidity during transit through the stomach, enhancing its ability to colonize the intestines. *UreA* and *ureB* genes are detected in this strain, which is responsible for urease A and urease B respectively. Meanwhile, this pH-modulating mechanism may also support the bacterium's role in outcompeting other microbial species in the gut, increasing their number and invasion capabilities (Esaiassen et al., 2017).

To enhance the adhesion of bacteria, some proteins mediate binding to fibronectin, collagen, and laminin (Colautti et al., 2022). Genes encoding type IVb tight adherence (*Tad*) pili are detected in *Bifidobacteria breve* UCC2003, and moonlighting proteins, a group of proteins involved in adhesion, assist bacteria adhering to host cells, also detected in *Bifidobacteria* (Westermann et al., 2016). Probiotic *E. faecium* and *E. faecalis* have detected adhesion-associated genes, including endocarditis and biofilm associated pili (*Ebp*), which are important for endovascular infection, *Enterococcus* collagen-binding adhesin (*EcbA*), Promotion aggregation complex (*PrgB*), Cell wall anchored collagen membrane adhesin (*Acm*), Adhesin to collagen (*Ace*) (Deng et al., 2021; Nissilä et al., 2017). The *Ace* gene and *Acm* gene mediate binding to collagen I and IV respectively (Ben Braïek and Smaoui, 2019). *Enterococcus* surface protein, aggregation substances (*Agg* and *asa1*), mediate bacterial conjugation, and specific binding to epithelial cells. For now, *Agg* determinant only appeared in *E. faecalis* strains (Ben Braïek and Smaoui, 2019).

Biofilm is formed through the accumulation of microorganisms and their secretions, which play a significant role in bacterial colonization and confer resistance to antibiotics. When bacteria adhere to various artificial medical materials implanted in the human body, like artificial heart valves, they easily form biofilms. *Quorum sensing* genes, the *bopD* gene, and the *Srt* gene (which encodes sortase) are responsible for biofilm formation and are commonly found in *Enterococcus* species (Ben Braïek and Smaoui, 2019; Deng et al., 2021). Notably, *E. faecalis* isolates from endocarditis cases (not all these strains originate from probiotics; some *E. faecalis* are common nosocomial pathogens), exhibit a much greater capacity for biofilm formation compared to non-endocarditis *Enterococcus* strains (Im et al., 2023). In addition to *Enterococcus*, certain *Lactobacillus* strains, particularly *L. paracasei*, have demonstrated a strong ability to form biofilms (Rossi et al., 2019). This ability was confirmed through a comparison between *L. paracasei* strains isolated from the blood of patients with *Lactobacillus* endocarditis and the original probiotic strain, as demonstrated by Tang et al. (2021) and Chiang et al. (2021). It may also facilitate colonization in the gallbladder, potentially leading to acute cholecystitis and increased resistance to antibiotics (Kim et al., 2023). Furthermore, the study by Chiang et al. suggests that biofilm formation in *L. rhamnosus* GG is influenced by environmental conditions (Chiang et al., 2021). For example, in media with limited fermentable carbon sources, biofilm formation is promoted. Specific factors such as glucose (the primary carbon source for *L. rhamnosus*) and Tween 20 enhance biofilm formation, while the presence of 0.05 % bile significantly impairs it. The study also indicates that catheter-associated bloodstream infections in preterm infants caused by *L. rhamnosus* may be primarily due to the translocation of them into the bloodstream, where parenteral nutrition glucose promotes biofilm formation around peripherally inserted central catheters (PICC) (Chiang et al., 2021).

The continuous platelet aggregation may make emboli or vegetation, forming infected masses. *Lactobacillus* could synthesize fibrin to induce platelet aggregation (Nissilä et al., 2017), and also lyse fibrin clots (Pasala et al., 2020), which is proved by the *in vitro* test of Kirjavainen et al. (1999). The *Lactobacillus salivarius* CCUG_47,825, which is isolated from a septicemia case, has a specific protein, compared with *Staphylococcus aureus*, exhibits an equivalent ability to bind fibrinogen and then induce platelet aggregation (Colautti et al., 2022). Emboli could hide the bacteria inside for anti-phagocytosis. Alpha enolases, coded by *eno* genes in *L. curvatus* isolated from chicken and *Lactobacillus johnsonii* isolated from calf feces, bind plasminogen, causing lysis of fibrins, releasing bacteria where they want (Antikainen et al., 2007). These are like the invasive ways of *Streptococcus pyogenes*, *Streptococcus pneumoniae,* and *Staphylococcus aureus.* Emboli also create a matrix for bacteria to proliferate (Colautti et al., 2022), since several endocarditis cases report patients have valvular vegetation (Ajam et al., 2019; Campagne et al., 2020; DeMarco et al., 2023; Rahman et al., 2023). Cannon et al. suggest that systemic emboli happened in 26 % of *Lactobacillus* endocarditis cases (Cannon et al., 2005).

3.2. Potential probiotic antibiotic resistance and associated genes, and their transmission

The growing concern over antibiotic resistance has extended into the realm of probiotics (Murray et al., 2022). A study disposed data from 1901 to 2022, revealing that frequently used probiotic bacteria could carry a variety of antibiotic resistance genes (ARGs) (Tóth et al., 2023). For example, *Lactobacillus* isolates from bacteremia patients exhibit high resistance rates to vancomycin (89.5 %) and imipenem (26.7 %) (Lee et al., 2015). Even an immunocompetent case with *Lactobacillus* endocarditis presented meropenem resistance (DeMarco et al., 2023). Meanwhile, the multidrug-resistant strain, including those resistant to vancomycin, meropenem, ceftriaxone, and cefuroxime, have been reported in immunosuppressed individuals (Land et al., 2005; Rahman et al., 2023; Wu et al., 2023). Notably, *L. casei* strains, which caused bacterium and septic shock, showing meropenem resistance may match with the ARGs of commercially certain *Lactobacillus* probiotics (Guzek et al., 2023). These studies highlight the presence of ARGs and super resistance potential in probiotics.

Antibiotic resistance in probiotics could occur through various

mechanisms, like those found in pathogenic bacteria. These include the modification of antibiotic targets, enzymatic degradation or modification of antibiotics, reduced permeability to antibiotics, and active efflux of antibiotics (Li et al., 2020).

Intrinsic ARGs are present in many strains of probiotics, as highlighted by various studies (Li et al., 2020). For instance, Wu et al. describe an isolated strain of *L. lactis* exhibiting multidrug resistance (Wu et al., 2023), which is attributed to a heterodimeric transporter protein in the membrane called LmrCD, a member of the ATP-binding cassette (ABC) family. Within this family, LmrA, the LmrA protein is particularly notable for its ability to resist over 20 distinct antibiotics by expelling various cytotoxic drugs. Similarly, LmrP, another ABC transporter, confers resistance to multiple antibiotics, including lincosamides, macrolides, streptogramins, and tetracyclines. Importantly, all strains of *L. lactis* harbor genes encoding both LmrA and LmrP (Wu et al., 2023). Tang et al. isolate *L. paracasei* LP10266 from an infective endocarditis case, showing the 2 spaCBA pilus clusters and one new exopolysaccharides cluster, making it resistant to cefuroxime, cefazolin, cefotaxime, meropenem, and vancomycin, which is proved by comparing this strain with original *L. paracasei* (Tang et al., 2021). In addition to these examples, glycopeptide resistance in *Enterococcus* is governed by six key genes: *vanA, vanB, vanC, vanD, vanE*, and *vanG* (Ben Braïek and Smaoui, 2019). The *vanA* operon, identified primarily in strains exhibiting strong resistance to both vancomycin and teicoplanin, predominantly exists in *E. faecium* (Im et al., 2023). The *vanB* operon is known to resist vancomycin without affecting teicoplanin resistance. The genes *vanA* and *vanB* are unique in their capability to be transferred both vertically and horizontally, offering high resistance levels. The *vanC* gene leads to a minimal increase in vancomycin resistance while maintaining a natural sensitivity towards teicoplanin. It's noteworthy that the genes *vanA*, *vanB*, *vanD*, *vanE*, and *vanG* are considered acquired characteristics, whereas the *vanC* gene is an inherent feature of motile *Enterococci* (Ben Braïek and Smaoui, 2019).

Acquired ARGs could be taken by mutation or horizontal gene transfer (Shahali et al., 2023). Yelin et al. discovered that a unique mutation (H487D) in the *rpoB* RNA polymerase gene was identified in a blood isolate from patient R1 (Yelin et al., 2019). This patient had been taking *L. rhamnosus* GG and rifaximin, a rifampin derivative, together for three months before developing bacteremia. The mutation alters a particular amino acid in the cleft of the *rpoB* DNA-binding site and is recognized for conferring resistance to rifampin (Yelin et al., 2019). Therefore, after probiotics enter the human body, under the complex interaction with the human body, the birth of new drug resistance is not impossible. The horizontal gene transfer of ARGs is to transfer between different bacteria. Crits-Christoph et al. describe that many certain ARGs transmission events, such as a plasmid encoding transfer an efflux pump from the commensal *Blautia hansenii* to *Klebsiella*, and a multidrug efflux pump plasmid transfer from *E. coli* to the commensal *Bacteroides* A1C1 (Crits-Christoph et al., 2022). Furthermore, the widespread use of probiotics in food and agriculture amplifies the opportunities for antibiotic resistance to disseminate through the environment and food chain (Im et al., 2023). Therefore, probiotics could potentially serve as reservoirs of resistance genes, promoting the development and dissemination of antimicrobial resistance (Tóth et al., 2023). If these genes are transferred to pathogenic bacteria, could exacerbate the already critical issue of antibiotic resistance (Li et al., 2020; Shahali et al., 2023).

These discussed ARGs are listed in Table 2. If left unchecked, the human microbiome may accumulate harmful ARGs from all over the food chain, which may be promoted by probiotic use (Cannon et al., 2005; Kullar et al., 2023). At the same time, negative genetic shaping due to abuse of probiotics and exogenous contamination could also contribute to the formation of invasion and virulence factors reservoir (Deng et al., 2021).

Table 2
A summary of part probiotic antibiotic resistance and associated genes with their transmission.

Antibiotic resistance genes		Transmission pathways	Relevant probiotic strains	Reference
Intrinsic ARGs	*Lmr* gene	vertical gene transfer	An isolated L. *lactis* strain	Wu et al. (2023)
	vanA, vanB, vanC, vanD, vanE, vanG genes	vertical and horizontal gene transfer	Most *Enterococcus*	Ben Braïek and Smaoui (2019).
Acquired ARGs	Efflux pump gene	horizontal gene transfer, special plasmid	Isolated *Blautia hansenii, Klebsiella, E. coli,* and *Bacteroides* sp. A1C1	Crits-Christoph et al. (2022)
	A H487D mutation in *rpoB* (DNA-binding site) of RNA polymerase gene	vertical gene transfer	Isolated L. *rhamnosus* GG strain from ICU patient	Yelin et al. (2019)
	A D220G mutation in ABC transporter CcmA	vertical gene transfer	Isolated L. *rhamnosus* GG strain from ICU patient	Yelin et al. (2019)

3.3. Potential probiotic genetic plasticity

Horizontal gene transfer (HGT) and mutations contribute to genetic plasticity. HGT is a process by which genetic material is exchanged between different microorganisms. Their genetic substances with various invasive and virulent factors could transfer between various bacteria. This exchange is mediated by mobile genetic elements such as plasmids, transposons, and bacteriophages, and naked DNA from dead cells could also be transformed or transduction via phage (Crits-Christoph et al., 2022; Merenstein et al., 2023). For instance, *Enterococcus* genome plasticity is widely acknowledged due to its capability to incorporate and utilize various mobile genetic elements, including plasmids, transposons, prophages, and insertion sequences, which facilitates the efficient exchange of acquired genetic traits among strains within the same species, as well as between species of the same genus and even with other pathogenic and non-pathogenic bacteria (Krawczyk et al., 2021). Virulence characteristics and antibiotic resistance in *Enterococcus* could be attributed to mechanisms of horizontal or vertical gene transfer, some linked to certain highly transmissible plasmids, as well as *Enterococcus*'s capacity to acquire genetic material (Ben Braïek and Smaoui, 2019; Krawczyk et al., 2021). A study by Ben Braïek and Smaoui revealed that *Enterococcus* could exchange virulent and ARGs by bacterial conjugation (Ben Braïek and Smaoui, 2019). The widespread biofilm function in *Enterococus* also suggests that biofilm-associated genes transfer between *Enterococcus* species (Deng et al., 2021).

Mutations represent another genetic mechanism that could alter the characteristics of these microorganisms. While mutations could sometimes lead to beneficial traits, they could also result in the loss of beneficial properties and the emergence of harmful traits. Tang et al. isolate *L. paracasei* LP10266 from an infective endocarditis case, showing higher biofilm-forming capacity and adhesion to human vascular endothelial cells than the original *L. paracasei* (Tang et al., 2021). *E. faecalis* isolated from endocarditis cases have a much stronger capacity to make biofilms than non-endocarditis *Enterococcus* (Im et al., 2023). A study shows emerging single nucleotide variation (SNV) in an

isolate from the probiotic product (Rossi et al., 2022). The study of Yelin et al. based on whole-genome phylogeny revealed that *Lactobacilli* from treated patients' blood were genetically similar to those from a probiotic product, with small differences reflecting the product's heterogeneity of probiotics themselves. Some blood isolates had new mutations, indicating that probiotic strains could evolve adaptively in ICU patients (Yelin et al., 2019). Hence spontaneous mutations occurring within the genomes of probiotic strains could, over time, lead to short-term adaptive evolution, which diminished health benefits or increased pathogenic potential.

3.4. Potential metabolic consequences associated with probiotics

3.4.1. Metabolic enzymes of probiotics may produce toxic metabolites or affect drug effectiveness

Some special metabolic enzymes could make toxic metabolites. For instance, lactic acid, a common metabolite in humans, exists in two enantiomeric forms: L-lactic acid and D-lactic acid. While L-lactic acid could participate in various metabolic pathways, D-lactic acid cannot (Pohanka, 2020). Accumulation of D-lactic acid could lead to D-lactic acidosis, a condition particularly common in infants with intestinal structural alterations, such as short bowel syndrome or impaired metabolic capacity (Pohanka, 2020). A study on the use of probiotics in pancreatitis suggests that one factor contributing to the high mortality rate in the probiotic-treated group may be the elevated levels of lactic acid, especially D-lactic acid, produced through the fermentation of carbohydrates by probiotics, in conjunction with the activity of proteolytic pancreatic enzymes (Bongaerts and Severijnen, 2016). Certain probiotic strains, such as *Lactobacillus reuteri* DSM-17938, possess D-lactate dehydrogenase, an enzyme capable of producing D-lactic acid. Consequently, evaluating the amount of D-lactate production and associated enzymes is essential when screening probiotic strains (Ruiz-Moyano et al., 2009).

Another crucial point is that some probiotics may affect drug effectiveness. The gut microbiome is involved in a wide range of drugs' metabolism, thereby affecting their bioavailability, activity, and toxicity. This biotransformation could occur through various mechanisms, including reduction, hydrolysis, and deconjugation processes that could activate, inactivate, or alter the pharmacokinetics of drugs. Specific probiotic strains have been shown to possess enzymatic activities capable of metabolizing drugs directly, thereby potentially altering their therapeutic profiles (Žuntar et al., 2020). Matuskova et al. suggested that *E. coli* Nissilä et al., 2017 changes the absorption of amiodarone in rats. *E. coli* Nissilä et al., 2017 *could* also increase desethylamiodarone levels in the plasma of rats (Matuskova et al., 2014). Some members of the gut flora could activate prodrugs into their active forms, or assist their absorption, both enhancing therapeutic effects (Noh et al., 2017). Conversely, microbial metabolism could also inactivate drugs or convert them into toxic metabolites, potentially leading to reduced efficacy or increased toxicity (Noh et al., 2017).

3.4.2. Probiotic metabolites and postbiotics may hurt the body

In the process of probiotics interacting with the body, many substances are released, some of which may harm the body. For instance, biogenic amines play various physiological roles, excessive production could lead to toxicity and adverse effects, including hypertension, allergic reactions, and other symptoms related to amine intolerance. Twelve kinds of biogenic amines made by *Streptococcus thermophilus,* which are isolated in homemade natural yogurt, are detected (Gezginc et al., 2013). For another example, *E. faecalis*, through the production of extracellular superoxide, has the potential to activate factors that cause chromosome damage (Krawczyk et al., 2021). When tested on immortal human and non-transformed mouse colon epithelial cells, *E. faecalis* was observed to create clusters of aneuploid, tetraploid, and gamma-H2AX. Additionally, directly exposing these cells to *E. faecalis* resulted in a G2 phase arrest of the cell cycle, which might play a role in the process of cellular transformation and the development of tumors (X. Wang et al., 2008). Thus, commercial probiotic *E. faecalis* strains need to be screened to ensure that they do not express such factors.

Postbiotic is a general term for the probiotic metabolite components after probiotics have been processed, including bacteria and metabolites. For instance, short-chain fatty acids, exert anti-inflammatory, immunomodulatory, and protective effects on the gut barrier (Zhong et al., 2022). The deficiencies of postbiotics are mainly manifested in their weak efficacy, susceptibility to inactivation technology, and unpredictable side effects that may be caused by the rapid and large-scale release of related substances (Ma et al., 2023).

4. Potentially extrinsic risks of probiotics

4.1. Certain problems in regulatory strength and public awareness associated with probiotics

The regulatory landscape and legislative framework for probiotics vary significantly across countries, reflecting differing approaches to defining and overseeing these products (Spacova et al., 2023). In the European Union, probiotics are typically classified as food supplements. They must adhere to safety and labeling standards but could be marketed without pre-market approval if no health claims suggest they treat or prevent diseases. In the United States, probiotics fall under the Dietary Supplement Health and Education Act of 1994, allowing them to be marketed without FDA approval, provided they do not claim to diagnose, treat, cure, or prevent diseases. Health claims must be substantiated and not misleading (Zucko et al., 2020). In Canada, probiotics are regarded as natural health products (NHPs), requiring pre-market approval and evidence of safety and efficacy for health claims. Japan's Foods for Specified Health Uses (FOSHU) system allows probiotics to be marketed with health claims if approved by the Ministry of Health, Labour, and Welfare, based on scientific evidence. In China, probiotics are regulated as health foods or food additives by the National Health Commission and the State Administration for Market Regulation, depending on their use. Australia categorizes probiotics as either foods or therapeutic goods, with the latter requiring rigorous regulatory approval.

However, the lack of uniform and clear regulatory mechanisms could lead to exogenous contamination. The contamination of probiotics by other miscellaneous bacteria cannot be ignored (Vermeulen et al., 2020). Gundogdu et al. analysis suggests a great difference between sequencing results and product information when they test probiotic products. The existence of additional microorganisms, which do not appear on the label, commonly appears in test results (Gundogdu et al., 2023). Probiotics may be transferred the antimicrobial resistance and other genes by pathogenic microbes, when they are contaminated by pathogens, increasing potential risks as well (Rannikko et al., 2021). In a review of the safety perspective of probiotic and non-probiotic yogurts, the presence of yeasts and molds in industrial yogurt is a sign of contamination in manufacturing and packaging. Additionally, aflatoxins, a toxic and carcinogenic metabolite of fungi, are found in milk and dairy products. The most frequent mycotoxin in contaminated yogurt is Aflatoxin B1, which has a strong correlation with consumer's associated illness (Homayouni et al., 2019).

Chaotic management could also mislead consumers by positive promotion of excessive probiotics, potentially contributing to the occurrence of adverse events. In popular opinion, probiotics are often seen as a good thing without any defection, so there are several cases with adverse effects after self-purchase and consumption of probiotics to improve their health, even though relevant cases with adverse effects due to probiotics are few compared to their widespread use. In 1999, Mackay et al. presented what they consider to be the initial instance of endocarditis caused by *L. rhamnosus* resulting from self-administration of a freeze-dried probiotic product, in an individual who was previously healthy (Mackay et al., 1999). On behalf of the Yokohama

Cooperative Study Group for Hematology (YACHT) reported that a 54-year-old man with acute promyelocytic leukemia underwent intensive chemotherapy and autologous peripheral blood stem cell transplantation. He chose probiotic yogurt to help with severe diarrhea but ended up with septic shock a week later, caused by the same strain of *L. rhamnosus* GG found in yogurt he consumed (On behalf of the Yokohama Cooperative Study Group for Hematology (YACHT) et al., 2019). These consumers purchase probiotics for health, but the results are not always what they want.

The global patchwork of regulatory frameworks reflects the balance between ensuring consumer safety and allowing the availability of probiotic products, with ongoing debates about the best ways to classify and regulate these products that are seen as occupying a space between food and medicine. Therefore, regulatory frameworks need to further clarify the distinction between dietary supplement probiotics and medical probiotics, strengthening monitoring of the potential pathogenesis, and exogenous contamination (Spacova et al., 2023). The diversity in regulation is further complicated by the rapid advancement in probiotic research, which often outpaces legislation, leading to calls for international regulatory harmonization to ensure consumer safety and support the global probiotics market. Simultaneously, public awareness of the safe use of probiotics is essential. Consumers need to realize that probiotics are not harmless at all. They should be informed about the benefits and potential risks of probiotics, encouraging responsible use and consultation with healthcare professionals (see Fig. 2).

4.2. *Immunodeficiency or immunocompromised status of the host or the change of probiotic inhabiting sites may lead probiotics to opportunistic pathogens*

If normal flora or probiotics change their inhabiting sites, or our bodies do not have enough power to eliminate them, they may become opportunistic pathogens (Fig. 3). Compared with the huge scale of probiotic use, the global probiotics market size is projected to exceed US $ 10.5 billion by 2025 (Global Probiotics Ingredients Market Size Analysis - Market Share, Forecast Trends and Outlook Report (2025–2034), n. d.), this kind of situation is rare. For instance, in a retrospective analysis of hospitalized patients, *S. boulardii* was used to prevent *Clostridioides difficile* infection. The *S. boulardii* fungemia occurred in 18 of the 16,404 patients (0.11 %) in four years (Wombwell et al., 2021). However, if these happen, it usually means the patient's status needs to improve. The first thing healthcare facilities need to do, when considering probiotic administration, is to take full account of the acceptor's status. Immunodeficiency, or immunocompromised status, and impaired or incomplete intestinal barrier are the main risk factors. Heart valve abnormalities, structural heart, and dental conditions could increase the risk of endocarditis. The nosocomial infection includes medical invasion, frequent broad-spectrum antibiotic treatment, and immunosuppressive drug use. Meanwhile, probiotic administration also should avoid disease-active periods and possible exposure and invasion periods, and minimize the introduction of probiotics into the bloodstream during invasive medical procedures (On behalf of the Yokohama Cooperative Study Group for Hematology (YACHT) et al., 2019).

4.2.1. *Probiotics may enter the blood through the gut*

In the gut, translocation is the process by which bacteria or microbial products could cross the intestinal barrier and invade normal sterile tissues and organs, due to increased intestinal permeability, disrupted mucosal barriers, or weakened immune defenses. Multiple microorganisms could utilize this weakness to enter deeper places (Twardowska et al., 2022), including probiotics, whose main action site is the gastrointestinal system. Therefore, structural or functional abnormalities of the gut cause impaired or incomplete intestinal barrier, increasing the permeability of intestine barriers and unable to resist invasion (Dani et al., 2016; Naqvi et al., 2018). A study by Rannikko et al. suggested that 59 % of *Saccharomyces* fungemia patients have gastrointestinal diseases (Rannikko et al., 2021). In addition, probiotics could also enter the lymphatic system through the lymphatic vessels

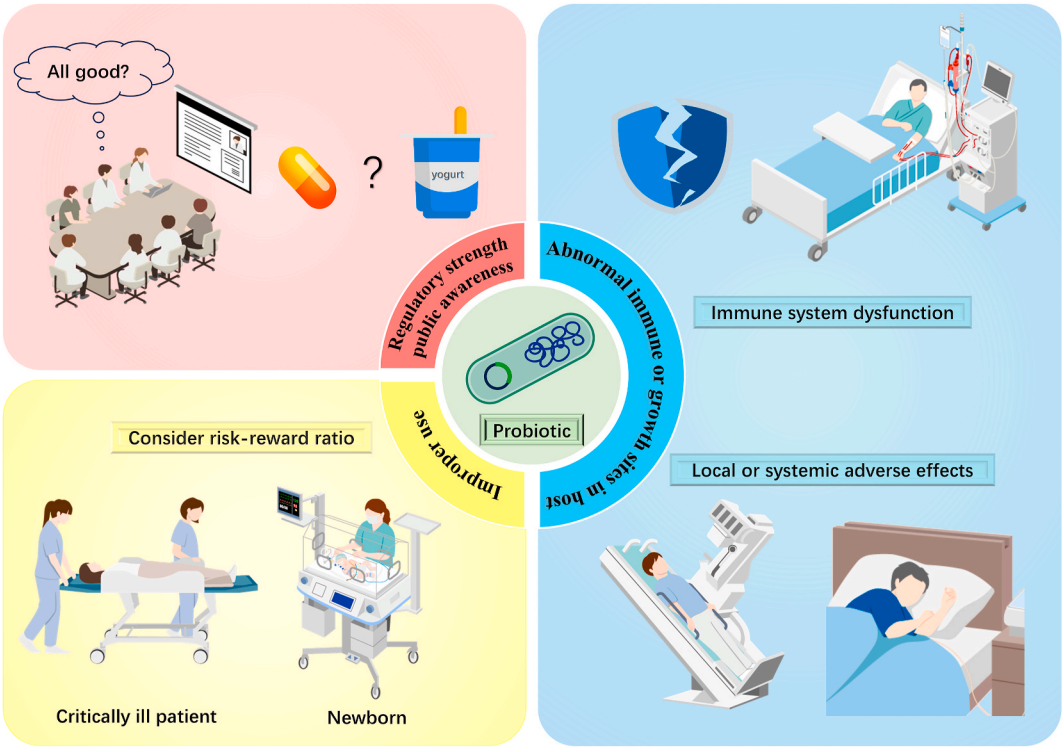

Fig. 2. A summary of potentially extrinsic risk factors of probiotics. It includes problems in regulatory oversight and public awareness, host health status, and appropriate administration. The regulator needs to define which kind of probiotics is drug or food regulatory. The public need to know probiotics are not totally beneficial. The inappropriate use probiotics in people with abnormal immune, critically ill patients and newborns may lead to local or systemic adverse effects.

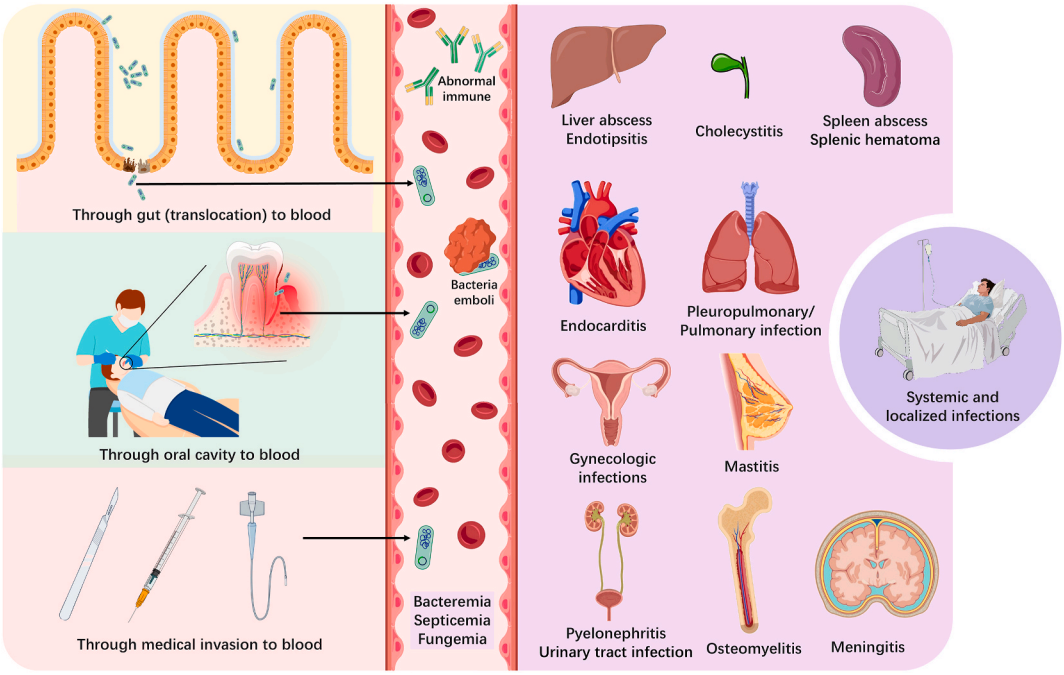

Fig. 3. Some probiotics could invade blood through the gut, oral cavity, and medical wounds. In most cases, the immune system could eliminate them. However, in immunodeficiency or immunocompromised patients, and rare cases with normal immune, these probiotics could be opportunistic pathogens, causing multiple local or systemic infections, even death.

present in the intestinal wall. From the lymphatic system, they could then enter the bloodstream as well (Guzek et al., 2023).

Structural abnormalities usually lead by diseases such as short gut syndrome (De Groote et al., 2005; Kunz et al., 2004), gastrointestinal bleeding (Zou et al., 2024), acute abdomen, perforated gastrointestinal tract, rupture in appendicitis, fistula of intestine and intestinal vessel (Doron and Snydman, 2015; Sadanand et al., 2019). Another important reason is a previous history of gastrointestinal surgery that changes the gut structure, particularly multiple abdominal surgeries, gastrostomy, jejunostomy, or total colectomy (Shimura et al., 2021; Mikucka et al., 2022; Ramos-Coria et al., 2021). The abnormal structures may lead to weak connections, offering chances for microorganisms to deeply invade.

Functional abnormalities are associated with disease adverse effects on the normal physiology of the gastrointestinal system, even in the presence of pathologic structural changes. Common relevant conditions include severe intestinal inflammation, autoimmune disorders such as leaky gut, inflammatory bowel disease (IBD), Crohn's disease, and ulcerative colitis (Mu et al., 2017; Camilleri, 2019; Paray et al., 2020; Twardowska et al., 2022), and intestinal cancer (Redman et al., 2014). These conditions can increase intestinal permeability, allowing toxins and undigested food particles to enter the bloodstream, thereby elevating the risk of systemic infections (Dore et al., 2019; Vahabnezhad et al., 2013). For instance, rates of worsening IBD activity after fecal microbiota transplant (FMT) have been reported as high as 25 % (Cheng et al., 2019), and cases of *Lactobacillus* bacteremia have been documented in patients with Crohn's disease and HIV infection following the consumption of probiotic-containing yogurt (Haziri et al., 2021). Meanwhile, disruptions in normal intestinal flora due to broad-spectrum antibiotic use, infectious diarrhea, or severe diarrhea leading to neutropenia can further compromise gut barrier function and increase susceptibility to infections (Kothari et al., 2019; On behalf of the Yokohama Cooperative Study Group for Hematology (YACHT) et al., 2019). Additionally, patients requiring enteral or parenteral nutrition are also at heightened risk, as these individuals often have significantly impaired gastrointestinal function (D'Agostin et al., 2021; Acuna--Gonzalez et al., 2023; Vinayagamoorthy et al., 2023). Furthermore, specific cases, such as *Lactobacillus* bacteremia and liver abscess following probiotic use in *C. difficile* colitis (Sherid et al., 2016) and *C. butyricum* bacteremia in patients with damaged intestinal barriers after major hepatectomy (Shimura et al., 2021), highlight the potential risks of probiotics in individuals with compromised gut integrity.

The liver also has a close relationship with gut microbiota (Fukui, 2015). Liver disease may alter the gut microbiome, a condition known as dysbiosis. Administration of probiotics in such an imbalanced environment may lead to unpredictable and potentially harmful changes in the gut flora (R. Wang et al., 2021). Naqvi et al. report that a 36-year-old woman died due to *L. rhamnosus* endocarditis, and had a history of complicated cirrhosis and *C. difficile* colitis (Naqvi et al., 2018). In cases of advanced liver disease, particularly cirrhosis, there is an increased risk of bacterial translocation from the gut, whereby bacteria, including probiotic strains, are more likely to cross the gut barrier and cause infections (Obeidat et al., 2020; Antoun et al., 2020).

Certain transplants could significantly additionally affect the gastrointestinal tract. For instance, autologous and allogeneic hematopoietic stem cell transplants both may lead to chemotherapy-induced mucositis, GI graft-versus-host disease (GVHD), and *C. difficile* infection, causing dysbacteriosis and decreased diversity of intestinal flora, and impair or incomplete mucosa and alter barriers of mucosal immune, which increase the risk of bacterial translocation, contributing to bacteremia (Carretto et al., 2001; Sadanand et al., 2019; Taur et al., 2014).

4.2.2. Probiotics may enter the blood through the oral cavity, and probiotic-associated endocarditis

It is worth noting that the oral cavity can serve as an entry point for microbes, including probiotics, to invade the circulatory system, particularly through open wounds or dental procedures (Antoun et al., 2020). Several studies have highlighted the association between *Lactobacillus* endocarditis and dental conditions. For instance, approximately 34–75 % of *Lactobacillus* endocarditis cases are linked to dental procedures or pre-existing dental conditions, such as gingival cuts, dental abscesses, or a history of dental disease (Bapna et al., 2023; Campagne et al., 2020; Cannon et al., 2005; Mackay et al., 1999). Notably, even

healthy individuals who regularly consume probiotics may be at risk if they experience oral trauma, as demonstrated by a case where a patient developed *Lactobacillus* endocarditis following a gingival cut that bled for four days, despite a decade-long history of probiotic use (Pasala et al., 2020). Similarly, *Lactobacillus* endocarditis has been reported in patients with dental abscesses, further underscoring the role of oral health in facilitating bacterial entry into the bloodstream (Stroupe et al., 2017). Therefore, probiotics-associated endocarditis is associated with dental conditions to some extent.

Cardiac risk factors of probiotic-associated endocarditis include structural heart disease or heart valve disease (case reported with mitral or tricuspid regurgitation), the presence of a cardiac device or a prosthetic valve (tricuspid valve repair or replacement), infective endocarditis history, or patients after cardiac surgery (Tang et al., 2021; Kim et al., 2023; Ajam et al., 2019; DeMarco et al., 2023; Rahman et al., 2023; Guzek et al., 2023; Husni et al., 1997). Pathogenic relevance of *Lactobacillus*: A retrospective review of over 200 cases made by Cannon et al., indicates that in 73 endocarditis cases, 63 % of patients with structural heart disease and 12 % of them having a history of endocarditis (Cannon et al., 2005). Case reports and reviews about *Lactobacillus* endocarditis by Antoun et al. suggest that 63 % of patients have structural heart disease (Antoun et al., 2020). Guzek et al. present a 63-year-old patient who develop *L. casei* bacteremia with septic shock, after cardiac surgery of implantable cardioverter-defibrillator (ICD) electrodes removal (Guzek et al., 2023). DeMarco et al. describe a rare case of an immunocompetent female with uncontrolled diabetes, non-ischaemic cardiomyopathy, and ventricular issues, who developed meropenem-resistant *Lactobacillus* endocarditis after taking *Lactobacillus* probiotics, despite having a biventricular AICD (DeMarco et al., 2023). Heart valves are connective tissues, mainly composed of extracellular matrix components such as collagen, elastin, and glycosaminoglycans. Heart valve abnormalities lead to exposed extracellular matrix (Pasala et al., 2020), and *Lactobacillus* could break down a part of them, which is conducive to the colonization and reproduction of pathogenic microorganisms (Campagne et al., 2020).

4.2.3. Probiotics may enter blood due to medical invasion

Invasive medical operations, especially central venous catheter (CVC), surgery and perioperative period, and even endoscopy and peritoneal dialysis, will directly expose tissues or blood to the environment. This direct access, while beneficial for treatment purposes, also presents a potential pathway for organisms including probiotics in the case of non-standard operation, to enter the bloodstream, leading to bacteremia or even sepsis (Olano et al., 2001).

Catheter-related infections pose a significant risk for probiotic-associated bacteremia, particularly in vulnerable patient populations. Statistical data indicate that intravenous catheters, central venous catheters, urinary catheters, and prior surgical or endoscopic procedures are strongly associated with *Lactobacillus* bacteremia (Salminen et al., 2004). Aaron et al. report a *L. rhamnosus* endocarditis case after upper endoscopy, who often consume yogurts with *Lactobacillus bulgaricus*, *Lactobacillus acidophilus*, and *L. casei* (Aaron et al., 2017). Of greatest concern are catheter-associated infections caused by probiotics. D'Agostin et al. count 1537 studies, 49 pediatric patients have infection due to probiotics, and 51 % of these cases with intravenous catheter use (D'Agostin et al., 2021). The results of Gouriet et al. indicated that nosocomial *L. rhamnosus* bacteremia is relevant to catheters (83 %) (Gouriet et al., 2012). Mayer et al. suggest that the use of probiotics in ICU patients with CVCs is linked to a high incidence of probiotic-related bloodstream infections, which could lead to a rise in mortality rates. In these patients, the risks of probiotic-related bloodstream infections and mortality outweigh any potential advantages of probiotic treatment (Mayer et al., 2023). Carretto et al. report that a single-lung transplant recipient with bad physical status, developed catheter-related *L. rhamnosus* bacteremia, due to the prolonged period of a femoral catheter, which may offer *Lactobacillus* chances to enter blood and catheter adhesion (Carretto et al., 2001). A 73-year-old patient had *S. boulardii* fungemia in the CVC, during the period of chemotherapy. The probiotic *S. boulardii* is used to treat antibiotic-associated pseudomembranous colitis (Appel-da-Silva et al., 2017). There is even an immunocompetent patients, a 56-year-old female with multi-traumatized, had probiotic *L. rhamnosus* GG infection after indwelling catheters (Rubin et al., 2022). In addition, powdered probiotic formulations are more likely to cause bloodstream infections compared to non-powdered forms (Mayer et al., 2023).

Though probiotic is a useful and wide way to prevent surgical infection during the perioperative period, Shimura et al. describe two cases of biliary cancer developed probiotic-related bacteremia after major hepatectomy (Shimura et al., 2021). Guzek et al. describe a patient who presented *Lactobacillus* casei bacteremia, who consumed the Actimel Danone® products, including *L. casei*, after cardiac surgery, and *L.* casei was cultured from a dialysis catheter (Guzek et al., 2023). Bapna et al. suggested that continuous peritoneal dialysis may be a risk factor for disseminated *Lactobacillus* infections (Bapna et al., 2023). Ohishi et al. describe a *Bifidobacterium* septicemia case, a neonate with omphalocele, after conventionally postoperative probiotic *Bifidobacterium breve* BBG-01 (Ohishi et al., 2010). Shareef et al. report that an immunocompetent case presented persistent *Lactobacillus* bacteremia, due to endovascular infection of transjugular intrahepatic portosystemic shunt (TIPS) stent (Shareef et al., 2023). Hori et al. report a 46-year-old female developed *Lactobacillus* pyelonephritis after total thyroidectomy due to papillary thyroid cancer (Hori et al., 2022). The above cases suggest that probiotics are not without side effects after surgery and deserve serious consideration by doctors.

4.2.4. The host's dysfunctional immune system makes invading probiotics more likely to cause disease

Host immunity plays a critical role in the safe use of probiotics. In most cases, even if the probiotics enter the bloodstream, the normal immune system functions can eliminate them. A robust immune system significantly reduces the likelihood of normal flora or probiotics turning into opportunistic pathogens; conversely, a compromised immune system heightens this risk. Gouriet et al. reported that nosocomial *L. rhamnosus* bacteremia is closely associated with immunosuppression (66 %) (Gouriet et al., 2012). Individuals with HIV/AIDS (Haghighat and Crum-Cianflone, 2016; Haziri et al., 2021), hematologic malignancies (Omar et al., 2019) such as multiple leukemia (D'Agostin et al., 2021; Ambesh et al., 2017; Avcin et al., 2023), organ transplant recipients (Cheng et al., 2019), including lung (Carretto et al., 2001), kidney (Sendil et al., 2020; Vanichanan et al., 2016), autologous stem cell (On behalf of the Yokohama Cooperative Study Group for Hematology (YACHT) et al., 2019), and hematopoietic stem cell transplantation patients (Robin et al., 2010; Sadanand et al., 2019), as well as those undergoing immunosuppressive therapies like corticosteroids, radiotherapy, and specific chemotherapies (Redman et al., 2014; Shimura et al., 2021), or those with a history of COVID-19 infection (Shareef et al., 2023), and even drug abusers (Obeidat et al., 2020), are all at risk of immunodeficiency or immunocompromise (Redman et al., 2014). Symbols of such compromised states include low leukocyte counts, neutropenia, and elevated inflammatory markers. Rahman et al. described a case where a patient, immunocompromised by prednisone and golimumab, developed *Lactobacillus casei* endocarditis after consuming a 2g daily dose (600 billion CFUs) of over-the-counter probiotics for several months to improve gut health (Rahman et al., 2023). Similarly, Haghighat and Crum-Cianflone reported an AIDS patient who developed *Lactobacillus acidophilus* bacteremia after excessive consumption of probiotic-enriched yogurt (Haghighat and Crum-Cianflone, 2016).

Another associated problem is that probiotics may be relevant to nosocomial infections. Nosocomial infection refers to these infections due to medical invasion, hospitalization, antibiotic overuse, and immunosuppressor administration. Medical invasion and

immunosuppressor administration have been discussed earlier. Patients with various diseases in the hospital have varying degrees of impairment and deficiencies in their immune defense functions, and hospitals have multiple microorganisms.

The frequent use of broad-spectrum antibiotics has been linked to an increase in the side effects associated with probiotics, especially when immune function is abnormal (Sendil et al., 2020). Shimura et al. report 2 cases present postoperative *C. butyricum* bacteremia from probiotic *C. butyricum* MIYAIRI 58, during the broad-spectrum antibiotics treatment of sepsis (Shimura et al., 2021). Gurley et al. describe a 59-year-old woman with abnormal genitourinary tract anatomy and frequently accepted broad-spectrum antibiotic treatment, who developed *L. lactis* bacteremia after using probiotic therapy (Gurley et al., 2021). Excessively frequent use of broad-spectrum antibiotics, especially in patients with a history of recurrent infections, may indiscriminately kill both harmful and beneficial bacteria, disrupting gut microbiota. The dysbacteriosis could lead to an increased susceptibility to infections, including those caused by antibiotic-resistant bacteria. In addition, Olano et al. suggested that excessive antibiotic administration may break mucous integrity (Olano et al., 2001). When probiotics are introduced into this imbalanced environment, in rare cases these probiotics may either fail to colonize effectively or overgrowth contributing to the complexity of the microbial environment, potentially leading to adverse effects (Olano et al., 2001; Joshi et al., 2019). Moreover, the use of probiotics in environments with high antibiotic pressure could be selected for mutants with increased resistance as well (Crits-Christoph et al., 2022), which is discussed earlier.

Furthermore, the nosocomial transmission of a probiotic strain is rather rare, but not absolutely impossible. Gün et al. report a 6-month-old boy in a pediatric intensive care unit without probiotic administration had a fever spike due to *Saccharomyces* fungemia after a neighboring patient started administration of probiotics containing *Saccharomyces* (Gün et al., 2022). Hennequin's group conducted simulation tests, proving *S. boulardii* could disseminate in the surroundings simultaneously when opening the package, contaminating nearby possible inert surfaces and skin, even air. Therefore, either the opening of the packet or hand-related transmission, and air or nearby patient use could lead to transmission of probiotics (Hennequin et al., 2000).

4.3. Improper use of probiotics could cause harm

The function of probiotics in the body involves a series of complex interactions, and the overall function of the host could affect the corresponding therapeutic effect. When it comes to serious underlying diseases, critical illness, ICU patients, or newborn infants, it is crucial to weigh the pros and cons of probiotic administration, cautiously considering the risk-reward ratio (Kothari et al., 2019).

4.3.1. Cautious administration of probiotics to serious underlying diseases, critical illness, or ICU patients

Probiotics for patients with weak basal status should be used with caution. For instance, a study at Boston Children's Hospital revealed that ICU patients administered *L. rhamnosus* GG probiotics had a significantly higher likelihood of developing *Lactobacillus* bacteremia compared to those not receiving probiotics (Yelin et al., 2019). Similarly, in a randomized controlled trial involving 296 patients with severe acute pancreatitis, the probiotic intervention group exhibited higher mortality rates (16 % versus 6 %), and increased prevalence of bowel ischemia compared to the placebo group. Urine analysis in these patients revealed elevated levels of intestinal fatty acid-binding protein, indicating intestinal mucosal injury (Besselink et al., 2008). Other case studies further highlight the risks: a 34-year-old burn patient developed *Saccharomyces* fungemia after nearly two months of *S. boulardii* supplementation to improve enteral feeding tolerance (Stefanatou et al., 2011), while a 74-year-old man with multiple comorbidities, including obstructive jaundice and cardiovascular disease, developed acute cholangitis following the use of an *S. boulardii* probiotic supplement (Fadhel et al., 2019). Additionally, *B. breve* was linked to necrotizing fasciitis and bacteremia in a 43-year-old female with uncontrolled type 2 diabetes (Wakabayashi et al., 2022). These adverse events may be exacerbated by underlying conditions such as diabetes, which is associated with heightened vascular permeability and endothelial cell damage due to metabolic changes and basement membrane glycosylation, potentially facilitating bacterial translocation (Rossi et al., 2022). Based on the above research, severe dysfunction of the body increases the potential for normal gut flora and probiotics to become opportunistic pathogens and leading bloodstream infection, even death, which may further beyond probiotic administration benefits (Mayer et al., 2023; Gün et al., 2022).

4.3.2. Cautious administration of probiotics to newborn infants

Many researchers suggest probiotics could be used in newborns, and hospitals have begun to often use probiotics for infants, a part of whom do get favorable effects (Barbian et al., 2019). However, several studies have reported that the use of probiotics has not produced significant results. In the study by Hays et al., premature infants who were given *Bifidobacterium* supplements did not show improved postnatal growth compared to those who received a placebo. There were no negative effects linked to the use of probiotics. The group that received a combination of probiotics did not experience any advantages, and there was even a trend toward a higher incidence of necrotizing enterocolitis in this group (Hays et al., 2016). Granger et al.'s study in the UK examined the occurrence of necrotizing enterocolitis (NEC), late-onset sepsis (LOS), focal intestinal perforation (FIP), and mortality in infants from a neonatal unit before and after the introduction of routine probiotics. The results showed that the use of probiotics at this facility did not decrease the overall mortality rate or the incidence of NEC, LOS, or FIP (Granger et al., 2022). Meanwhile, given the potential risks of infections such as septicemia, the administration of probiotics should be cautious for newborn infants, especially preterm neonates, and very low birth weight infants (Dani et al., 2016). Probiotic sepsis in preterm neonates—a systematic review, made by Kulkarni et al., indicated that the occurrence of sepsis caused by the probiotic strain used poses a challenge to the widespread use of prophylactic probiotic supplements in premature infants to prevent necrotizing enterocolitis. Probiotic-related sepsis is not frequently seen in premature infants, and most cases could be successfully treated with antibiotics or antifungal medications (Kulkarni et al., 2022).

Infants' bodies are in rapid development, producing dramatic changes. The underdeveloped immune system and gastrointestinal tract are not capable of forming structural and functional barriers, which may increase the likelihood of translocation after administration of probiotics. Infants with other risk factors are also easier to lead to adverse effects (Kullar et al., 2023; Kunz et al., 2004). In addition, premature or prolonged exposure to probiotics, during the period of neonatal microbiota establishment, may disrupt normal processes, leading to permanent impact (Merenstein et al., 2023). Other study shows probiotics could affect neonate gut microbe colonization but not overall longitudinal alternation (Hui et al., 2021). Furthermore, infant feeding patterns and enough nutrients, especially proteins, are significant, and are responsible for normal development (Jacobs et al., 2013; Westaway et al., 2022). Hence, the use of probiotics for infants should have comprehensive consideration of the individual and follow-up for infants with risk factors that received probiotics.

5. Some recommendations for better use of probiotics

The correct methods of probiotic administration need to consider the host's health status (Hill et al., 2014), probiotic strains, dosage (Dore et al., 2019), starting time, and duration (Shimura et al., 2021). Healthcare providers also need to consider probiotics as a potential cause when systemic infection symptoms, metabolic dysfunction, and

hemodynamic instability arise post-probiotic administration, especially in the absence of identifiable pathogens. Stroupe et al. reported a heart valve infection from a dental abscess caused by *Lactobacillus*, which was misidentified as *Corynebacterium*, leading to ineffective treatment (Stroupe et al., 2017). As Obeidat et al. proposed, this underscores the need for recognizing usually harmless strains, like *Lactobacillus*, as potential infectious agents. Even in *Lactobacillus*-related bacteremia, *Lactobacillus* should no longer be dismissed as mere contaminants. While not all probiotic infections exhibit antibiotic resistance or require antibiotics, infections sometimes resolve after discontinuing the probiotics. Nevertheless, in cases with infection-related symptoms, especially in at-risk populations, prompt collection of samples from various sites and times is essential. Identifying strains quickly, conducting susceptibility tests, and providing timely treatment can improve patient outcomes (Cannon et al., 2005; Kullar et al., 2023), as reliance solely on empirical therapies might worsen conditions.

As sequencing technology becomes increasingly accessible, safety analysis based on whole genome sequencing holds significant potential for advancing the probiotic industry. Several studies suggest feasibility and necessity (Jiang et al., 2023; Peng et al., 2023; Y. Wang et al., 2021; L. Zhao et al., 2023). Developing safer probiotic strains through genetic engineering or selective breeding is crucial, and genome analysis can help identify potential safety risks, providing a scientific basis for screening probiotic candidates. Furthermore, advancements in genomic and metagenomic analysis techniques offer powerful tools for gaining deeper insights into probiotic functions and their interactions within the human microbiome. However, the presence of genes does not necessarily guarantee their expression in vivo, as gene expression is also significantly influenced by environmental conditions (Merenstein et al., 2023). Therefore, functional testing and monitoring probiotics in living organisms are equally important to ensure their safety and efficacy.

Based on these, personalized probiotic therapy represents a promising area. Recognizing that individuals may respond differently to specific probiotic strains, future efforts could focus on tailoring probiotic treatments based on a person's genetic makeup, microbiome composition, and specific health conditions. By analyzing an individual's microbiome, tailored probiotic supplements could be developed to address specific health issues or to optimize individual health outcomes, especially for individuals with compromised immune systems, underlying diseases, and those undergoing medical interventions. This personalized approach could significantly enhance the effectiveness of probiotic interventions, which research of potential risk factors of probiotics could also promote.

6. Conclusion

Probiotics, as a cornerstone of human health practices, hold remarkable potential for enhancing physical, mental, and social well-being. However, this review has highlighted the need for a balanced perspective on probiotic use, acknowledging both their therapeutic benefits and the risks associated with their use. It is crucial to recognize the intrinsic and extrinsic factors that could transform probiotics into opportunistic pathogens. The intrinsic risks associated with probiotics are multilayered, encompassing the potential for toxigenicity, invasive capabilities, and metabolic complications. Extrinsic risks involve factors outside the probiotic strains themselves, such as the host's health status and the regulatory environment.

The growing demand for comprehensive research is evident, particularly in understanding how the substances of probiotics exert their functions, including the genetic basis of these processes and their interaction with the host. Such knowledge is essential for optimizing the use of probiotics. As the field of probiotics continues to advance, a personalized approach to probiotic therapy, tailored to an individual's unique genetic and microbiome profile, presents a promising avenue for maximizing health outcomes. Future research should prioritize understanding how to effectively and safely harness the potential of probiotics, thereby contributing to the advancement of personalized medicine and the broader goal of human wellness.

CRediT authorship contribution statement

Ruiyan Xu: Methodology, Formal analysis, Investigation, Writing – original draft, Visualization, Writing – review & editing. **Yifeng Yu:** Supervision, Writing – review & editing. **Tingtao Chen:** Conceptualization, Writing – review & editing, Supervision, Project administration.

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Declaration of competing interest

There is no competing interest or conflict that needs to be declared.

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Data availability

data sharing is not applicable to this article, because no new data is made.

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