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Review

Applications of Food-Associated *Lactobacillaceae* in Fermented Foods, Health, and Emerging Biotechnologies

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Abstract

The family *Lactobacillaceae*, reclassified in 2020 into 25 genera comprising 261 species, remains one of the most extensively studied groups of lactic acid bacteria (LAB) due to its wide distribution in fermented products, commensal presence in the gastrointestinal tract, and studied health effects. Long classified as "generally recognized as safe (GRAS)" by the U.S. Food and Drug Administration (FDA), these organisms not only contribute to the flavor, texture, and preservation of fermented foods and beverages but also provide important health benefits as probiotics. Their metabolic versatility allows them to produce lactic acid, bacteriocins, and other bioactive compounds that inhibit pathogenic microorganisms and enhance food quality. This review provides a comprehensive overview of the functional roles of members of the *Lactobacillaceae* family in the context of the food matrix in fermentation, health, and biotechnology, and examines recent advances in functional genomics, metabolomics, and extracellular vesicle research to highlight future directions for leveraging these microorganisms in sustainable and innovative applications.

Keywords: *Lactobacillaceae*; fermented foods; probiotics; gastrointestinal health; functional foods; gut microbiome

1. Introduction

Former members of the genus *Lactobacillus*, now regrouped into multiple genera within the family *Lactobacillaceae*, are inclusive of over 200 species that are Gram-positive, fermentative, facultatively anaerobic, and non-spore-forming micro-organisms [1,2]. Simply, *Lactobacillaceae* facilitate metabolic pathways that produce lactic acid from carbohydrates. *Lactobacillaceae* species are commonly found in human oral, urogenital, and gut microbiota and have been used in food and drink fermentation for centuries [1,3,4].

Lactobacillaceae species have been widely employed in food fermentation for their roles in microbial stabilization, development of flavor and aroma, and enhancement of nutritional properties; however, only specific, well-characterized strains are considered probiotics based on demonstrated health benefits [5]. Although *Lactobacillaceae* is a key player in many of these processes, it is commonly utilized synchronously with other bacteria and yeast. Since the passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994, *Lactobacillaceae* has increased in popularity as probiotics, with well-characterized strains (e.g., *Lactobacillus acidophilus* LA-5, *Lacticaseibacillus rhamnosus* GG) demonstrating beneficial effects on gut health, immune modulation, and other health outcomes [1,3,4,6].

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Lactobacillaceae has been classified by the U.S. Food and Drug Administration (USFDA) as "generally recognized as safe (GRAS)", allowing easier integration into our food processing [7]. *Lactobacillaceae* species, such as *Lactobacillus fermentum* and *Lacticaseibacillus casei*, have been used to extend food and drink shelf life, increase nutritional value, and modify gut microbiota [3]. Some traditional foods and beverages that utilize *Lactobacillaceae* fermentation are pickles, miso, buttermilk, sourdough bread, tempeh, kimchi, sauerkraut, yogurt, kombucha, and kefir [1,3,5,6,8–10]. This review focuses on food-associated members of the family *Lactobacillaceae*, emphasizing their roles in fermentation, bioactive compound production, and health-relevant functions across diverse food and beverage matrices [8,11,12]. Beyond strain selection alone, the food matrices in which *Lactobacillaceae* are delivered play a critical role in determining their functional outcomes. Unlike capsule-based probiotic formulations, food-delivered microorganisms are embedded within complex matrices containing proteins, fats, carbohydrates, fibers, and polyphenols that can enhance microbial stability, metabolic activity, and gastrointestinal survival [2,11,13,14]. Fermentation within these matrices not only improves organism viability but also leads to the in situ production of bioactive metabolites, including short-chain fatty acids, peptides, organic acids, and modified polyphenols, which may exert health effects independent of or synergistic with live cells [2,11,14–16]. Importantly, these effects are strain-dependent and matrix-specific, as identical strains can display distinct metabolic profiles and host interactions depending on the substrate and fermentation conditions [2,11,14,15]. Consequently, the strain and matrix interaction represents a key determinant of efficacy, underscoring the importance of evaluating health effects within food and beverage contexts rather than extrapolating findings from pharmacological probiotic preparations [11,14]. Beyond these applications, recent advances highlight the genus' broader biotechnological potential, including roles in agriculture, biotherapeutics, and mucosal vaccine delivery [11,17–24].

2. Health Effects of Food-Associated *Lactobacillaceae*

The human gut microbiome is home to bacteria, fungi, viruses, and archaea that collectively influence host physiology and immune regulation. Among one of its most influential constituents are probiotics, which are live microorganisms that, when administered in appropriate amounts, can bestow health benefits to the host [13]. A key concern for human health is dysbiosis, a state of imbalance in the gut microbiota that can result from factors such as diet, infections, underlying immune conditions, or antibiotic use [11].

Dysbiosis has been associated with several diseases, including viral infections, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), necrotizing enterocolitis, colorectal cancer, depression, diabetes, and obesity [11,25–27]. Collectively, *Lactobacillaceae* species help maintain a balanced gut microbiome by outcompeting harmful bacteria, strengthening the gut barrier, modulating both innate and adaptive immunity, and acidifying the intestinal environment, creating conditions that are inhospitable to pathogens [11,16,28]. These mechanisms enhance host defense against infections and help reduce inflammation [11,28,29].

Some members of the family *Lactobacillaceae*, including *Lactococcus lactis*, *Lacticaseibacillus salivarius*, *Levilactobacillus brevis*, and *Lactobacillus acidophilus*, produce bacteriocins (e.g., Lacticin, Nisin, Salivaricin, Brevicin, and Acidophilin, respectively), which are antimicrobial peptides that kill pathogenic bacteria through pore formation in their cell membranes [30,31]. A growing global health concern is the topic of antibiotic-resistant bacteria, which are responsible for over 700,000 deaths globally each year, a number projected to rise to 10 million annually by 2050 [32]. A notable advantage of bacteriocins is that they are degraded by proteases in the gut, which prevents pathogens from developing resistance [30]. However, this digestion also limits their systemic activity. As such, at

present, bacteriocins are primarily applied as natural food preservatives. For example, Nisin and Pediocin PA-1 are FDA-approved for inhibiting spoilage and pathogenic bacteria in foods [33]. Their antimicrobial activity within food matrices contributes to improved microbial safety, inhibition of spoilage organisms, and extension of shelf life, thereby reducing reliance on chemical preservatives [11,30,33]. Future studies should explore strategies to harness *Lactobacillaceae* bacteriocins with consideration of their role in preventing bacterial resistance. Such approaches could help ensure these compounds remain effective over time and may also limit the emergence of multidrug-resistant pathogens in the gastrointestinal tract, thereby reducing serious public health risks.

Lactobacillaceae also possesses strain-specific advantages. For instance, *Lactiplantibacillus plantarum* is particularly effective at supporting gut barrier integrity [11,12]. In a study by Yang et al., *Lactiplantibacillus plantarum* IDCC 3501 also demonstrated anti-inflammatory properties through inhibition of key pro-inflammatory mediators such as iNOS, COX-2, TNF-α, IL-1β, and IL-6, suggesting potential benefits in gut inflammation [29]. The strain also demonstrates a strong safety profile, with no virulence factors, minimal d-lactate production, absence of harmful enzymes, and susceptibility to most antibiotics [29]. These features, along with its postbiotic metabolites, make *Lactiplantibacillus plantarum* particularly valuable for supporting gastrointestinal health and preventing dysbiosis. Perhaps this is also why clinical trials [34,35] have demonstrated a significant reduction in IBS symptom severity (improved IBS-SSS and IBS-QOL scores [35]), restoration of beneficial gut bacteria, and a decrease in harmful, gas-producing bacteria such as *Methanobrevibacter*. These results posit *Lactiplantibacillus plantarum* as a promising adjunctive agent for managing IBS [34,35].

Lacticaseibacillus rhamnosus (GG) has demonstrated efficacy in IBD and pouchitis [36,37]. Multiple studies indicate that *Lacticaseibacillus rhamnosus* strains, including GG, CNCM I-3690, SHA113, and 1.0320, can alleviate IBD by modulating gut microbiota, restoring intestinal barrier function, and reducing inflammation [38–40]. In both cellular and animal models, treatment with these strains increased beneficial bacteria (such as *Bifidobacterium*, *Akkermansia*, and other SCFA-producers), upregulated tight junction proteins (including ZO-1, occludin, and E-cadherin), restored mucin production, and decreased pro-inflammatory cytokines (IL-1β, TNF-α), collectively improving disease symptoms [11,38–41]. Clinically, Gosselink et al. posit that prophylactic use of GG has translated to meaningful outcomes, reducing the 3-year cumulative risk of pouchitis from 29% to 7% ($p = 0.011$), highlighting its capacity to diminish disease-associated dysfunction and improve IBD prognosis [37].

Separately, one study suggests that *Lacticaseibacillus rhamnosus* may additionally influence the gut–lung axis [42]. Other research supports this possibility, hypothesizing that the effect could occur through stimulation of IgA or the migration of Th17 cells from the gut to the lungs, thereby modulating respiratory immune responses [31,42]. Randomized clinical trials have evaluated GG in pediatric respiratory diseases with significant improvements. In preterm infants and children in daycares, GG reduced the incidence and duration of respiratory tract infections, and in hospitalized children, it lowered both respiratory infections and gastrointestinal infection risk [43]. In children with cystic fibrosis, GG supplementation improved gut microbiota, reduced intestinal inflammation, and decreased pulmonary exacerbations and hospitalizations [42–49].

Several *Lactobacillaceae* species, including *Lacticaseibacillus rhamnosus* GG, *Lactobacillaceae acidophilus*, *Lactobacillus bulgaricus*, *Lacticaseibacillus casei*, and *Limosilactobacillus reuteri*, have been shown to effectively prevent antibiotic-associated diarrhea (AAD) through mechanisms such as competitive exclusion of pathogens and antimicrobial activity [4,50]. A meta-analysis by Sazawal et al., which included 34 randomized, placebo-controlled trials, reported an overall 52% reduction in AAD incidence among both adults and children, with a 57% reduction observed in healthcare settings for children under 18 years of age [50].

Limosilactobacillus reuteri, in particular, exhibits significant anti-inflammatory and antimicrobial activity against a wide range of enteric pathogens [51,52], including Gram-positive and Gram-negative bacteria, Candida species, and rotavirus [52]. This antimicrobial activity likely underlies its ability to significantly shorten the duration of pediatric diarrheal illnesses and to act as an effective prophylactic agent even in healthy children [52,53]. In the context of necrotizing enterocolitis (NEC), supplementation with *Limosilactobacillus reuteri* in very low birth weight infants has been associated with lower incidences of NEC, likely due to immunomodulatory effects and reinforcement of gut barrier function [18]. Moreover, *Limosilactobacillus reuteri* has shown an ability to inhibit colon cancer cells [20]. Importantly, these gut-protective effects highlight *Limosilactobacillus reuteri*'s clinical potential as a preventive strategy against serious gastrointestinal complications.

Beyond the gut, *Limosilactobacillus reuteri* also demonstrates antimicrobial activity against common clinical wound pathogens, including *Escherichia coli* and *Staphylococcus aureus*, through mechanisms such as nutrient competition and the production of antimicrobial compounds, including reuterin, reutericin 6, and reutericyclin [17]. Additionally, *Limosilactobacillus reuteri* and its vesicle-derived metabolites can modulate macrophage phenotypes and oxidative stress, promoting tissue repair and accelerating wound healing. These properties suggest that *Limosilactobacillus reuteri* could be employed as an adjunctive therapy in nonhealing or chronic wounds, particularly those complicated by multidrug-resistant (MDR) infections by reducing pathogen load and limiting infection progression through its anti-inflammatory properties [17,19].

This strain-specific functionality highlights the value of consuming a diverse array of fermented foods and beverages and underscores the importance of studying which strains are predominant in different products, as summarized in Table 1. Taken together, these findings support the multitude of promising applications of *Lactobacillaceae* in promoting gastrointestinal health and addressing various health-related conditions, while also paving the way for future research to optimize probiotic strategies for personalized nutrition and disease prevention.

Table 1. Summarization of applications of members of the *Lactobacillaceae* family in various health conditions.

Condition	Strains	Mechanism of Action/Clinical Application
Inflammatory bowel disease (IBD)/pouchitis	*Lactiplantibacillus plantarum*, *Lacticaseibacillus casei*, *Lacticaseibacillus rhamnosus* GG	Anti-inflammatory cytokine modulation, enhanced epithelial barrier, IBD symptom relief, Refs. [11,38–41] delay pouchitis [37]
Irritable bowel syndrome (IBS)	*Lactiplantibacillus plantarum*, *Lactobacillus acidophilus*	SCFA production, neuromodulation of gut–brain axis, reduce gas-producing bacteria [34,35]
Gastrointestinal infections (e.g., viral/bacterial diarrhea)	*Lacticaseibacillus rhamnosus* GG, *Limosilactobacillus reuteri*	Competitive exclusion, production of lactic acid and bacteriocins [28,51,53]
H. pylori infection	*Lactobacillus johnsonii* NCC 533, *Lacticaseibacillus casei Shirota*	Via various mechanisms: Produce bacteriocins, modifying *H. pylori* to dormant forms, inducing loss of flagellar motility, and reducing urease activity [25]
Antibiotic-associated diarrhea	*Limosilactobacillus reuteri*, *Lacticaseibacillus rhamnosus*, *Lactobacillus acidophilus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*	Restoration of microbiota balance, modulation of immune response [31]

Table 1. *Cont.*

Condition	Strains	Mechanism of Action/Clinical Application
Metabolic health (obesity, hyperlipidemia, diabetes mellitus)	*Lactobacillus gasseri*, *Lactiplantibacillus plantarum*	Improved gut barrier, modulation of lipid/glucose metabolism, enhances insulin sensitivity by decreasing PPARγ and via the glycerophospholipid metabolic pathway [11,12,25–27,29,54]
NAFLD/liver health	*Lactiplantibacillus plantarum*, *Lacticaseibacillus rhamnosus*, *Lactobacillus acidophilus*	Reduces hepatic inflammation, modulates lipid metabolism, reduces oxidative stress via the PPAR signaling pathway; separately, activates G protein-coupled receptors GPR41 and GPR43, which pushes peptide YY to decrease energy expenditure [4,11,54]
Gout/Hyperuricemia	*Lactiplantibacillus plantarum*, *Lactobacillus gasseri*	Enhances gut microbial community and subsequently hydrolase-based breaks of purine nucleosides, modulates purine metabolism, reduces uric acid levels [11,55]
Respiratory Illnesses	*Lacticaseibacillus casei Shirota*, *Lacticaseibacillus rhamnosus* GG	Immune stimulation, cytokine balance [42–49]

3. Role in Fermented Foods and Beverages

3.1. Mechanisms of Fermentation

Members of the family *Lactobacillaceae* are typically classified into three groups based on their metabolic traits and by-products: obligatory homofermentative, facultatively heterofermentative, and obligately heterofermentative (Figure 1) [1]. Obligate homofermentative species ferment via glycolysis typically utilizing the Embden–Meyerhof–Parnas (EMP) to produce lactic acid [1,4]. Facultative heterofermentative bacteria, under specific conditions, ferment carbohydrates to produce by-products including lactic acid, ethanol, acetic acid, and carbon dioxide dependent on carbohydrate availability. The obligate heterofermentative group—lacking fructose 1,6 aldolase—continuously ferments carbohydrates to produce lactic acid, ethanol, acetic acid, as well as carbon dioxide by way of the phosphogluconate and phosphoketolase pathways [1,4,5]. During these fermentative processes, *Lactobacillaceae* species maintain redox balance via NAD^+ regeneration, which influences lactic acid production and the generation of secondary metabolites [4,5,11]. Within the obligate homofermentative group, key species include *Lactobacillus acidophilus* and *Lactobacillus salivarius*, the facultatively heterofermentative group, *Lacticaseibacillus casei* and *Lactiplantibacillus plantarum*, and the obligate heterofermentative group, *Limosilactobacillus reuteri* and *Limosilactobacillus fermentum* [1,4,5].

In addition to carbohydrate metabolism, LAB are also capable of proteolysis via four amino acid pathways and lipolysis [56,57]. Proteolysis, necessary for bacterial growth, is responsible for generating peptides and amino acids [58]. The four amino acid pathways include the glutamate decarboxylase system, the branched chain amino acid metabolism, the aromatic amino acid metabolism, and the arginine deiminase pathway [57]. During lipolysis, LAB uses lipases and esterases to break down triglycerides, phospholipids, and cholesterol into free fatty acids (including saturated fatty acids and unsaturated fatty acids) [56,58]. These biochemical processes are essential components to fermented food and beverage texture, viscosity, aroma, and preservation.

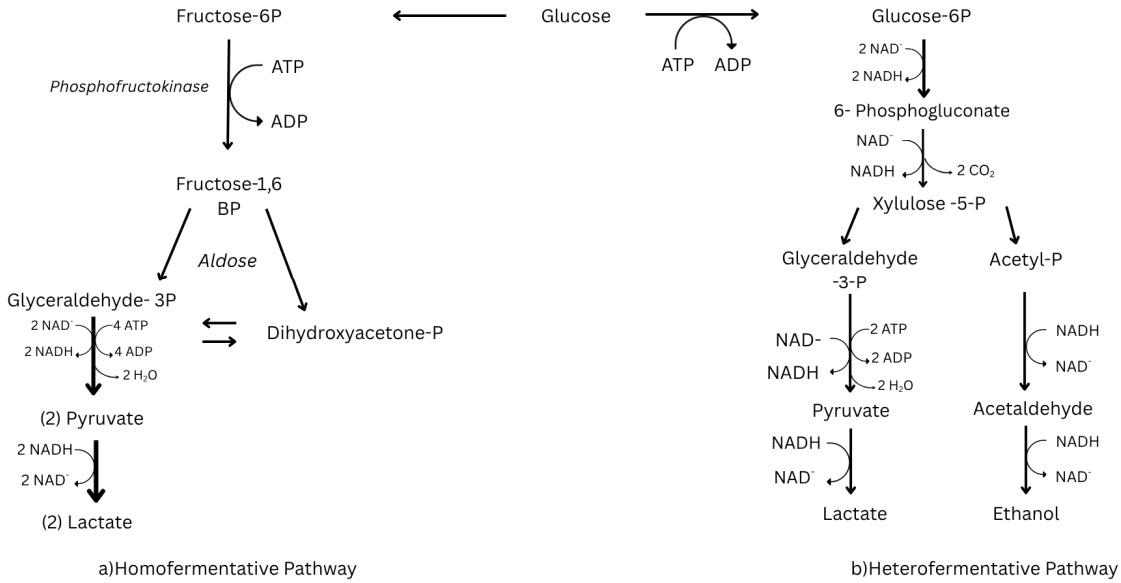


Figure 1. Metabolic pathways of members of the family *Lactobacillaceae*: (**a**) Homofermentative; (**b**) heterofermentative [1,4,5].

During fermentation, *Lactobacillaceae* species multiply rapidly, converting fermentable sugars into lactic acid, causing rapid acidification, and ultimately inhibiting food spoilage by lowering the pH. Maintaining the appropriate balance of beneficial microorganisms during fermentation is key to safety in fermented foods [59]. Well-known fermented foods and drinks include kefir, kombucha, sourdough bread, kimchi, and sauerkraut (Table 2).

Table 2. Some common *Lactobacillaceae* strains in fermented foods.

Strain	Food Source
Lactiplantibacillus plantarum	Sauerkraut, kimchi, pickles, dairy products [8,26]
Levilactobacillus brevis	Sauerkraut, kimchi [13,26]
Lacticaseibacillus rhamnosus GG	Yogurt, dairy drinks [2,26,29,30]
Lacticaseibacillus casei	Cheese, fermented milk [2,26,29,30]
Lactobacillus delbrueckii subsp. *bulgaricus*	Yogurt, kefir [2,10,26,29,30,60]
Limosilactobacillus reuteri	Sourdough, fermented milk [2,13,26,29,30]

Sauerkraut: Fresh vegetable, usually cabbage, fermented typically by *Levilactobacillus brevis* and *Lactiplantibacillus plantarum* [1,13].

Kimchi: Popular Korean dish with cabbage, radish, and hot peppers, with fermentation including *Levilactobacillus brevis* and *Lactiplantibacillus plantarum* [1,13].

Sourdough bread: Bread that utilizes yeast and fermentation, *Lactobacillaceae*, for leavening [1,5,13].

Kefir: A beverage made of fermented milk utilizing various *Lactobacillaceae* species [1,5,10,60].

Yogurt: Typically containing multiple strains of *Lactobacillaceae* and live cultures [3,5,6,13].

Kombucha: Popular fermented drink made from black tea, sugar, yeast, and *Lactobacillaceae*, amongst other fermentors [5,61].

3.2. Nutritional and Functional Improvements

Focused on benefits ranging from disease prevention to treatment, interest in members of the family *Lactobacillaceae* has increased over the last few decades. Some fermented

drinks and foods have been shown to have benefits to the immune system, gut microbiome, and psychological well-being [1,3–6,15,62].

Diving deeper into disease-controlling mechanisms, antimicrobial activity is shown by decreased colony formation, mycelia growth, and biofilm formation. Positive microbiota modulation occurs by increasing amounts of *Lactobacillaceae*, therefore decreasing pathogens, and increasing beneficial microbes. It has also been shown to decrease tumor cells and size while increasing survival. Immunomodulatory effects are seen by increasing anti-inflammatory cytokines and decreasing NF-κB translocation into the nucleus [1,4,6]. Furthermore, recent animal and in vitro studies have shown potential for decreasing liver disease, gout, and diabetes [55,63].

Kefir is thought to have originated in the Tibetan mountains thousands of years ago and is known for its antimicrobial, gastrointestinal health, anti-carcinogenic, immunomodulatory, wound-healing, anti-allergenic, and cholesterol metabolism properties [2,11,29]. Kefir is known to produce a bioactive compound, exopolysaccharides, which inhibit *Listeria monocytogenes* and *Salmonella enteritidis* [5,60]. Alongside kefir, studies show kombucha was found to have similar antimicrobial properties [15,61,62]. A recent randomized controlled trial by Kinoshita et al. in 2021 showed that women healthcare workers who consumed yogurt fermented with *Lactobacillus delbrueckii* subsp. *bulgaricus* OLL1073R-1 for 16 weeks showed improved quality of sleep, fatigue, constipation, and sense of general health [6].

3.3. Roles of Food-Associated Lactobacillaceae in Flavor Development and Bioactive Compound Formation

During flavor development many biochemical processes are happening sequentially and synergistically. When bioactive compounds are created, the quantity of compounds created and the sequence they occur in is key to adjusting flavors and aromas [64]. LAB are responsible for forming flavor profiles for many dairy products, cheeses, yogurts, bakery products, and beverages [56]. Major flavor profiles include alcohols, esters, ketones, organic acids, and sulfur compounds [56]. Aromas and flavor profiles are formed through primary metabolic pathways including glycolysis (carbohydrates), lipolysis (fatty acids), and proteolysis (amino acids) [59,64]. LAB, including *Lacticaseibacillus helveticus* and *Lactiplantibacillus plantarum*, produces volatile organic compounds (VOCs) through esterase and proteolytic activity increasing taste, aroma, and texture. *Lactiplantibacillus plantarum* and *Weisella* are the predominant LAB-producing organic acids that give fermented vegetables their sour taste [64].

Metabolites synthesized by LAB include vitamins, organic acids, enzymes, bacteriocins, amino acids and derivatives, and exopolysaccharides [57,59]. Key LAB species *Limosilactobacillus fermentum*, *Lacticaseibacillus casei*, and *Lactiplantibacillus plantarum* are known to produce B-group vitamins (B2, B12) and bioactive peptides [57,59]. Exopolysaccharides (EPSs) are known for texture enhancement of various yogurts and cheeses [5,59]. GABA is a naturally produced neuroinhibitory amino acid known to have antianxiety and antidepressive effects. LAB strains including *Lactiplantibacillus paraplantarum* and *Levilactobacillus brevis* have strategically been added to foods to produce GABA for its health benefits [5,59]. Metabolites are key participants of gut microbiota modulation leading to enhanced communication between the gut and brain [1,5]. Furthermore, these metabolites protect the intestinal epithelial barrier, ultimately increasing intestinal nutrition absorption and mucus secretion [5].

Building off of current food chemistry knowledge, new flavor profiles, textures, and aromas can be created. In collaboration with consumer feedback there are numerous avenues for new market research to create novel foods potentially linked with increased health benefits. However, challenges regarding food processing and storage leading to decreased

probiotic effects are of concern [59]. Efficient and accurate isolation and identification of LAB species present additional barriers to utilization of LAB probiotic and health benefits.

3.4. Safety and Quality Concerns

In addition to attaining GRAS status, most LAB species have the European Qualified Presumption of Safety (QPS) status, indicating that they are considered safe for use in the food industry and have a long history of consumption [7,11,65]. Some genera that are phylogenetically related to classical LAB, such as *Weissella* and *Periweissella*, still lack QPS and GRAS status and are therefore not approved for use in food applications [65]. This highlights that phylogenetic relatedness alone does not guarantee safety and that regulatory approval must be evaluated on a genus- and species-specific basis [1,2,7,65].

In addition, other concerns remain, particularly as some LAB (e.g., *Lactobacillus brevis*) are major producers of biogenic amines (BAs), which, if accumulated, can become toxic for humans depending on individual sensitivities [66,67]. BAs are produced by amino acid decarboxylation and can cause adverse symptoms including vomiting, diarrhea, and heart palpitations [66,68]. However, their extensive use as starter cultures in the fermentation of food products underscores their general safety and industrial importance. In fermented meat products, LAB such as *Lactobacillus sakei* and *Lactiplantibacillus plantarum* contribute to safety by rapidly lowering pH, producing antimicrobial compounds (e.g., bacteriocins), and outcompeting undesirable microbiota [30,69]. These mechanisms not only inhibit foodborne pathogens such as *Salmonella* and *Listeria* but also prevent the accumulation of potentially harmful biogenic amines (BAs), thereby enhancing both microbiological and chemical safety [33,66,67,69,70]. Furthermore, the use of starters helps standardize product properties and can reduce ripening times, illustrating the multifaceted industrial and safety advantages of LAB [69].

The USFDA oversees food products; however, probiotics are considered dietary supplements and are not comprehensively reviewed before being sold. Moreover, allergies and anaphylaxis are a growing concern as some probiotic products may include common allergens such as cow milk or chicken and egg protein derivatives [71].

Overall, the positive utility of *Lactobacillaceae* is extensive, with few side effects; however, it is important to acknowledge unwanted effects that have been discovered. *Lacticaseibacillus rhamnosus* can cause abscesses, bacteremia, and endocarditis [1,12]. Increased risk for opportunistic pathogenicity is seen in immunocompromised individuals (i.e., AIDS, organ transplants, or neutropenia) [1,12]. The PROPATRIA trial further emphasized these potential risks. In this study, 24 of 152 patients (16%) in the probiotic arm died, compared to nine of 144 (6%) in the placebo group, a statistically significant difference [50]. This finding underscores the need for caution when considering probiotic use in critically ill or immunocompromised populations [12,50].

3.5. Extracellular Vesicles Derived from Food-Associated Lactobacillaceae

In September 2021, The International Scientific Association of Probiotics and Prebiotics (ISAPP) published a consensus statement in regards to the definition and scope of postbiotics. Postbiotics were defined as a "preparation of inanimate microorganisms and/or their components that confers a health benefit to the host" [72]. Extracellular vesicles is a generic term that refers to extracellular membrane vesicles derived from probiotics in which exosomes are included [73]. In recent years extracellular vesicles (EVs) have increased in research and popularity to determine disease modification, health benefits, and ingesting and purification methods. Recently, extracellular vesicles (EVs) from Gram-positive bacteria, including members of the family *Lactobacillaceae*, have been termed membrane

vesicles (MVs). They are smaller (20–100 nm) than EVs (20–200 nm) typically produced by Gram-negative bacteria [74].

Most primary research has been conducted through animal models and in vitro testing [73,75] that shows MVs' ability to promote gut health and regulate immune response. Recent research attributes this regulation to balancing pro-inflammatory and anti-inflammatory signaling [73,75]. A 2023 study utilizing a piglet model with induced diarrhea found that *Limosilactobacillus mucosae*-derived EVs decreased diarrheal disease symptoms and improved gut homeostasis through macrophage phenotype modulation [76]. Another 2018 in vitro study found that *Lactiplantibacillus plantarum*-derived EVs were able to protect against atopic dermatitis induced by *Staphylococcus aureus* EVs by decreasing IL-6 production from keratinocytes and macrophages [77]. A more recent study found promising data suggesting prevention of colitis in mouse models with administration of MVs from *Lactiplantibacillus plantarum* [78]. Applications to disease modification and promotion of disease prevention are promising with current research.

Key concerns for EVs and MVs include appropriate identification of these vesicles along with isolation and purification once the vesicles are accurately identified. Furthermore, there is still debate on the amount needed to infer reproducible health benefits [73]. Finally, barriers to preservation and appropriate method of ingestion of EVs and MVs alone or through initial probiotics needs to be considered. More research is needed to understand the mechanisms of EVs/MVs on various cell types and in vivo. Future applications to disease prevention and disease modification are attainable with more research and clinical trials.

4. Role in Other Manufacturing Practices

Beyond human health, *Lactobacillaceae* species demonstrate utility in agriculture, livestock, and vaccine development—enhancing plant growth and pathogen resistance, improving animal gut health and productivity, and serving as safe mucosal vaccine vectors.

4.1. Agricultural and Livestock Applications

Lactobacillaceae can act as plant growth-promoting microorganisms (PGPMs) through production of gibberellins (GA4, GA7) and indole-3-acetic acid (IAA), enhancing wheat coleoptile growth and increasing dry matter in potatoes (via *Lactobacillus acidophilus*) and cucumbers (via *Lactiplantibacillus plantarum*), which improves not only yield but nutritional content [22–24,79,80].

Corn loss due to fungal infection may cost up to USD 40B annually [24,80,81]. *Fusarium* spp. alone can reduce corn yields by 30–50% [9,24,80,81]. Effectively, members of the family *Lactobacillaceae* have been shown to act as biocontrol agents against fungal pathogens like *Fusarium* spp., *Zymoseptoria tritici*, and *Botrytis cinerea* via organic acids, peptides, and reuterin [9,11,80].

Beyond plant protection, multiple LAB strains, including *Limosilactobacillus fermentum*, *Lactobacillus amylovorus*, and *Lacticaseibacillus casei*, promote animal health by preventing infections and enhancing immunity. Specifically, this has been noted through piglet diets with reduced pathogenic *E. coli* and *Clostridium perfringens*, lower diarrhea rates, and improved intestinal integrity and growth performance [82]. Furthermore, it has shown improved breeding success and faster growth in zebrafish via *Lacticaseibacillus rhamnosus* [83]. These results, in the promotion of vegetation and livestock, are a possible sustainable avenue of exploration to meet growing food demand and environmental concerns.

In addition, LAB are increasingly applied in agricultural systems through the production of soil amendments derived from food industry waste and by-products, contributing to waste valorization, improved soil health, and more sustainable farming practices [84,85].

Techno-economic analyses show that lignocellulosic waste-based processes can achieve production costs as low as USD 993–1123 per ton at a 100,000-ton annual scale, supporting the industrial feasibility of circular bioeconomy strategies [86]. By closing the loop between food processing, fermentation substrates, and agricultural inputs, this cyclic use of by-products further expands the role of *Lactobacillaceae* in environmentally sustainable food production systems through reduced environmental burden and chemical fertilizer dependency [11,22–24,84,85].

4.2. Innovative Uses: Vaccines and Beyond

Studies suggest that strains such as *Limosilactobacillus fermentum*, through their immunomodulatory effects and promotion of T-helper type 1 responses, may enhance the protective efficacy of influenza vaccines when co-administered orally [87]. This highlights the broader application and beckons further studies of probiotics to function as low-cost, orally deliverable adjuvants capable of strengthening mucosal and systemic immunity. LAB species, particularly *Lactobacillus casei* and *Lactobacillus plantarum,* have been explored as a potential mucosal vaccine vector, through its mechanism of delivering eukaryotic expression cassettes to epithelial cells, resulting in in situ IgA, IgM, antigen production, and Th1-skewed immune responses [88]. Recombinant invasive LAB expressing *Listeria*'s Internalin A further enhances DNA uptake and expression in host cells. Through decades of work with LAB species, researchers have developed efficient expression systems such as the nisin-controlled NICE system and vectors (pCYT, pSEC, pCWA) enabling intracellular, secreted, or surface-anchored antigen presentation [88]. Among these, cell-wall anchoring generally elicits the strongest immune responses. These modular systems provide precise control over antigen localization, which should be considered for further studies in recombination to guide the type and amplitude of immune response and minimize secondary effects. Various LAB such as *Lacticaseibacillus casei* have demonstrated protective effects against pathogens such as *Clostridium tetani* and human papillomavirus (HPV) in preclinical models; however, larger-scale studies are needed to confirm their efficacy [88,89]. Other *Lactobacillaceae* species, specifically *Lacticaseibacillus casei* and *Lactobacillus helveticus*, have shown anti-hypertensive effects via ACE inhibition [90]. *Lactiplantibacillus plantarum* has shown cholesterol-lowering effects through bile salt hydrolase activity [91]. Moreover, *Lactiplantibacillus plantarum*, *Lacticaseibacillus rhamnosus*, and *Lactobacillus acidophilus* have been shown to reduce hepatic inflammation and decrease oxidative stress via activation of the PPAR signaling pathway [54]. These strains can activate G protein-coupled receptors GPR41 and GPR43, leading to increased secretion of peptide YY, which promotes satiety and may reduce energy intake, contributing to improved metabolic homeostasis [4,11,54]. Separately, *Lactiplantibacillus plantarum* and *Ligilactobacillus gasseri* can modulate the gut microbiome in a strain-specific manner, enhancing the activity of microbial enzymes such as purine nucleoside hydrolases. This modulation of purine metabolism has been associated with decreased serum uric acid levels, suggesting a potential role in hyperuricemia and gout management [11,55]. Some *Lactobacillaceae* species, such as *Limosilactobacillus fermentum*, produce biosurfactants that prevent pathogen adhesion and biofilm formation [92]. Studies show efficacy against *S. aureus* on implants, *Candida* spp. on catheters, and multidrug-resistant urogenital pathogens [92], demonstrating further potential in functional foods, infection prevention, and therapeutic interventions (Table 3).

Table 3. Emerging applications of *Lactobacillaceae* in agriculture, livestock, and vaccination.

Application Area	Role/Function	Examples
Agriculture	Plant growth promotion (PGPM)	*Lactiplantibacillus plantarum* enhances wheat coleoptiles; *Lactobacillus acidophilus* increases dry matter vegetables via IAA, gibberellins, nitrogen fixation [23]
	Biocontrol of fungal pathogens	Inhibits fungal pathogens via organic acids, peptides, reuterin [80]
	Soil and environmental benefits	Promotes nitrification, reduces ammonia emissions; degrades organophosphates and cationic metals [84]
Livestock feeding and breeding	Infection prevention and immunity	*Limosilactobacillus fermentum*, *Limosilactobacillus amylovorus*, *Ligilactobacillus salivarius*, and *Lacticaseibacillus rhamnosus* reduce intestinal infections and boost innate immunity [82]
	Breeding optimization	*Lacticaseibacillus rhamnosus* improves fertility in zebrafish [83]; *Lactiplantibacillus plantarum*/*Lacticaseibacillus casei* enhance breeding environment quality [70]
Vaccine delivery	Vaccine vector	*Lacticaseibacillus casei* delivers eukaryotic expression cassettes to epithelial cells, resulting in antigen production and Th1-skewed immune responses [88,89]
Therapeutic intervention	Antihypertensives, lipid lowering agents, infection prevention	*Lacticaseibacillus casei* and *Lactobacillus helveticus*: anti-hypertensive effects via ACE inhibition [89]; *Lactiplantibacillus plantarum*: cholesterol-lowering effects through bile salt hydrolase activity [91]; *Limosilactobacillus fermentum*: prevents pathogen adhesion and biofilm formation, and studies show efficacy against *Staphylococcus aureus* on implants, *Candida* spp. on catheters, and multidrug-resistant urogenital pathogens [92]

5. Conclusions with Discussion on Challenges and Future Perspectives

The global probiotic market was valued at approximately USD 87.70 billion in 2023 and is projected to grow at a compound annual rate of 14.1% through 2030 [93], reflecting the expanding scientific and commercial interest in *Lactobacillaceae* and other lactic acid bacteria (LAB). *Lactobacillaceae* plays a central role in food and beverage fermentation, contributing to product preservation, flavor development, and nutritional enhancement [1,3–8]. Beyond industrial relevance, these microorganisms offer important health benefits through modulation of gut microbiota, enhancement of immune function, and maintenance of intestinal barrier integrity [11,38–41,50].

Despite encouraging preclinical data, translation into consistent human clinical outcomes remains limited. Individual variability in microbiome composition, strain-specific effects, and inconsistent metabolite production present major barriers. Additional challenges include strain standardization, gastrointestinal survivability, and the need for reproducible dosing and formulation strategies. Agricultural, livestock, and vaccine applications also

require rigorous investigation to address efficacy, biosafety, and ethical considerations. Future research should emphasize well-designed, large-scale clinical trials, standardized formulations, and precision strain characterization to fully realize the therapeutic potential of *Lactobacillaceae*. Advances in genetic engineering and microbiome-targeted technologies are expected to enable more personalized and efficient applications across human and animal health.

Emerging frontiers include the use of *Lactobacillaceae* as a live vaccine vector and immunomodulatory platform [89,90] Challenges in this domain involve ensuring mucosal immunogenicity, dose optimization, and biosafety compliance for genetically modified LAB. Optimizing LAB stability through encapsulation, freeze-drying, or bio-engineering could improve viability during storage and gastrointestinal passage [89]. Moreover, strain-specific immunomodulation may allow the design of *Lactobacillaceae*-based vaccines with adjuvant-like effects, potentially supporting single-dose, needle-free immunization.

Next-generation applications may involve co-delivery of antigens with immunostimulatory cytokines (e.g., IL-12) or checkpoint inhibitors for cancer immunotherapy [89,90]. The dual ability of LAB to induce mucosal tolerance and systemic immune activation also positions them as promising tools in allergy, obesity, and inflammatory bowel disease modulation [11,38–41]. Finally, synergistic use of LAB-based vectors alongside nanoparticle or viral systems in heterologous prime–boost strategies could enhance both mucosal IgA and systemic IgG responses [89].

Lactobacillaceae stands at the intersection of traditional fermentation and cutting-edge biotechnology. The literature remains constrained by strain heterogeneity, inconsistent food matrices, and limited mechanistic validation, underscoring the need for standardized, food-relevant study designs [14]. Hence, continued interdisciplinary research, including within microbiology, synthetic biology, and clinical science, will be crucial to harness its full potential for human health, sustainable food systems, and environmental resilience.

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