Research Progress on the Probiotic Functions of Exopolysaccharides from Lactic Acid Bacteria: Postprint

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Abstract

Lactic acid bacteria are widely recognized as food-grade safety microorganisms. Their exopolysaccharides are carbohydrate compounds produced and secreted extracellularly during bacterial growth and metabolism, possessing multiple probiotic functions including immunomodulation, antitumor activity, antioxidant properties, and regulation of intestinal microecological balance. Currently, researchers worldwide have conducted extensive studies on the structure, function, and application of lactic acid bacteria exopolysaccharides. This review summarizes the research progress on the probiotic functions of lactic acid bacteria exopolysaccharides, provides a brief overview of their mechanisms of action, discusses existing challenges, and outlines future research directions, aiming to provide a theoretical reference for further research and production application of lactic acid bacteria exopolysaccharides in animal nutrition.

Full Text

Research Progress on the Probiotic Functions of Lactic Acid Bacteria Exopolysaccharides

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Abstract: Lactic acid bacteria (LAB) are widely recognized as food-safe microorganisms. The exopolysaccharides (EPS) produced by LAB are carbohydrate compounds synthesized and secreted during bacterial growth and metabolism, exhibiting diverse probiotic functions including immunomodulation, antitumor activity, antioxidant properties, and regulation of intestinal microecological balance. In recent years, scholars worldwide have conducted intensive investigations into the structure, function, and applications of LAB EPS. This review summarizes the international research progress on the probiotic functions of LAB EPS, outlines their mechanisms of action, discusses existing challenges, and identifies future research directions, aiming to provide a theoretical foundation for further research and industrial application of LAB EPS in animal nutrition.

Keywords: lactic acid bacteria; exopolysaccharides; probiotic function

Lactic acid bacteria (LAB) are generally recognized as safe (GRAS) microorganisms that are widely distributed in humans, animals, plants, and throughout nature [1]. Research has demonstrated that LAB primarily improve the intestinal microecological environment through colonization in the host gut and exhibit various physiological functions including antitumor, anti-inflammatory, anti-allergic, and immunomodulatory activities [2]. Current evidence suggests that these functions may be associated with EPS, a secondary metabolite produced by LAB. Numerous LAB strains produce EPS, with most studied isolates derived from milk and dairy products, traditional fermented foods, and animal intestines. In recent years, as consumer demand has shifted toward natural, residue-free, safe, and healthy foods, the properties and physiological functions of LAB EPS have attracted increasing attention. According to relevant reports, LAB EPS can be applied in yogurt, cheese, and other food products as prebiotics [3]. Additionally, LAB EPS serve as natural additives in food, chemical, pharmaceutical, and livestock industries [4]. This review focuses on recent advances in the probiotic functions and mechanisms of LAB EPS, with particular emphasis on their research progress in animal nutrition.

1. Introduction to Lactic Acid Bacteria Exopolysaccharides

Polysaccharides are natural macromolecular polymers composed of aldoses or ketoses linked by glycosidic bonds, widely distributed in animals, plants, fungi, algae, and bacteria. Based on their origin, they can be classified as animal polysaccharides, plant polysaccharides, or microbial polysaccharides (including fungal, algal, and bacterial polysaccharides). Microbial polysaccharides exist in three main forms: intracellular polysaccharides as cellular components, structural polysaccharides attached to cell surfaces that maintain cell morphology, and exopolysaccharides secreted into the culture medium [5]. As the primary research focus among bacterial polysaccharides, LAB EPS are polysaccharides and their mixtures synthesized and secreted extracellularly or into the culture medium during LAB growth and metabolism. They can be categorized as capsular polysaccharides or slime polysaccharides [6-7], and further classified as homopolysaccharides (HoPS) or heteropolysaccharides (HePS) [8]. The monosaccharide composition and ratios of LAB EPS are influenced by various factors including strain type, culture medium composition, and cultivation conditions. Extensive research has demonstrated that LAB EPS play crucial roles in helping microorganisms resist adverse conditions such as dehydration, nutrient deficiency, bacteriophages, osmotic pressure, antagonistic substances, and toxic compounds [9], while exhibiting physiological activities including antitumor, antimicrobial, antioxidant, and immunomodulatory effects [6].

2.1 Immunomodulatory Effects

The immunomodulatory functions of LAB EPS primarily involve activating immune cells (such as macrophages, B lymphocytes, and T lymphocytes), enhancing monocyte phagocytic capacity, and regulating the secretion of immune cytokines (including complement and interleukins) [10-11]. Kishimoto et al. [12] applied EPS produced by *Lactobacillus delbrueckii* to human intestinal epithelial Caco-2 cells and mouse macrophage RAW264.7 cells, observing substantial secretion of tumor necrosis factor-α (TNF-α) and various cytokines from both cell types. Morifuji et al. [13] conducted a study in which 9-week-old mice were orally administered fermented milk or EPS for 10 days before exposing their dorsal skin to ultraviolet radiation (20 $\mathrm{MJ/cm^2}$). The mice showed no skin damage, demonstrating that both fermented milk and EPS significantly attenuated UV-induced erythema formation, skin dryness, and epidermal proliferation. Molecular mechanism studies revealed that EPS isolated from LAB-fermented milk enhanced DNA repair mechanisms and improved skin immunity, thereby protecting against UV damage.

LAB EPS can also be classified as acidic EPS (APS) or neutral EPS (NPS) [14]. Nishimura-Uemura et al. [15] cultured mouse macrophage J774.1 cells with NPS and APS produced by *Lactobacillus bulgaricus* OLL1073R-1, evaluating macrophage morphology and nitric oxide (NO) and cytokine production. The results showed that APS stimulated macrophage activation in terms of cell morphology, while NPS had minimal effect. Neither NPS nor APS induced NO production, but APS-stimulated macrophages exhibited higher cytokine mRNA expression levels than those stimulated with NPS, demonstrating that APS from this strain promotes murine macrophage immune function.

The immunomodulatory effects of LAB EPS may also be related to their molecular structure. Studies have shown that EPS containing phosphate or sulfate groups can more effectively induce immune cell proliferation, activation, or cytokine secretion [16]. Laiño et al. [17] elucidated a novel molecular mechanism for EPS-mediated immune function using small intestinal epithelial cells as a model to investigate the molecular interactions between EPS from two LAB strains and host cells. The results showed that EPS from both strains reduced inflammatory factor expression in cells lacking Toll-like receptors (TLRs). While EPS can exert immunomodulatory effects through TLR2, TLR4, and negative regulation of TLR signaling pathways, this study further revealed that LAB and EPS reduce intestinal epithelial cell inflammation via the RP105/MD1 pathway.

Current research indicates that due to strain specificity, EPS from different LAB strains exhibit significant physicochemical differences in type, structure, and molecular weight, which directly contribute to their distinct functional properties. Therefore, investigating immunological activity is essential when screening newly isolated LAB EPS for functional properties.

2.2 Antitumor Function

Numerous LAB species produce EPS, with over 20 strains identified to date that generate EPS with antitumor activity, including *Lactobacillus acidophilus*, *Lactobacillus salivarius*, *Lactobacillus plantarum*, *Bifidobacterium bifidum*, and *Bifidobacterium longum* [18-19]. Researchers have investigated the antitumor and anticancer activities of specific LAB EPS. Wang et al. [20] examined the antitumor activity of EPS from *Lactobacillus plantarum* 70810 against tumor cells HepG-2, BGC-823, and HT-29, reporting high inhibition rates of $(56.34\$\pm1.07)\pm2.07)\pm1.97)^{\{2+\})levelsingastriccancerSGC7901cellsandcervicalcancerHelacells,observingacontinuousdynami}$ fluorescence intensity following EPS treatment. The mechanism may involve selenium modification of EPS, where selenylated EPS binds to tumor cell surface receptors, causing reduction of intracellular free Ca^{2+} and inducing varying degrees of apoptosis.

Ismail et al. [22] extracted EPS from *Lactobacillus plantarum* MTCC 9510 and applied it to breast cancer MCF-7 cells, demonstrating significant inhibitory effects and confirming the antitumor activity of EPS. Wang et al. [23] evaluated the antitumor activity of EPS from *Lactobacillus plantarum* YW32 against human colon cancer HT-29 cells using the MTT assay under various concentrations (50, 100, 200, 400, and 600 g/mL) and time points (24 and 72 h). The results showed concentration-dependent inhibition, with the highest inhibition rate (39.24%) achieved at 600 g/mL EPS. According to Leng et al. [24], the antioxidant capacity and reactive oxygen species (ROS) levels of LAB EPS may be closely related to cancer cell generation and transformation, with higher antioxidant capacity potentially enhancing antitumor activity. Wang et al. [23] speculated that the antitumor activity of EPS from *L. plantarum* YW32 may be associated with its scavenging capacity against hydroxyl and superoxide radicals, suggesting its potential as a natural health food for colon cancer treatment. Additionally, literature indicates that antitumor activity differences may be related to EPS composition, molecular weight, structure, and sulfate content [25-26].

The proposed antitumor mechanisms of LAB EPS include: (1) indirect antitumor effects through enhanced immunity and antioxidant capacity; (2) induction of tumor cell apoptosis; and (3) competitive exclusion of carcinogenic pathogens through increased LAB colonization in the intestinal lumen. Furthermore, EPS-producing LAB can reduce the activity of bacterial enzymes such as β-glucuronidase in the intestine, decreasing secondary bile acids with carcinogenic effects and reducing cancer risk [27].

2.3 Antioxidant Function

Oxidative stress occurs when the balance of reactive oxygen species is disrupted under adverse conditions such as pathogen infection, radiation exposure, or exogenous free radical invasion, leading to excessive ROS that attack cells, induce disease, and compromise health [28]. Zhang et al. [29] screened 36 LAB strains isolated from traditional fermented foods and identified 8 high-EPS-producing strains, evaluating their antioxidant activity by measuring total reducing power, 1,1-diphenyl-2-picrylhydrazyl (DPPH) scavenging capacity, ferrous ion (Fe^{2+}) chelating ability, and nitrite (NO_2^-) scavenging capacity. All eight EPS samples exhibited antioxidant activity. At 30 g/mL EPS concentration, the Fe^{2+} scavenging rates of EPS from strains SR2-2, SR8, and SR12-1 were 15.55%, 12.41%, and 53.21%, respectively. At 40 g/mL, the DPPH and NO_2^- scavenging rates for these strains reached 9.69% and 11.93%, 8.93% and 5.73%, and 7.82% and 3.82%, respectively. Li et al. [30] investigated the antioxidant activity of EPS from *Bifidobacterium bifidum* WBIN03 and *Lactobacillus plantarum* R315, demonstrating strong DPPH and superoxide radical scavenging capacities at high concentrations with dose-dependent antioxidant activity.

The antioxidant mechanisms of EPS remain inconclusive, but proposed mechanisms include: (1) direct action on free radicals through binding, decomposition into harmless products, or direct oxidation and scavenging; (2) chelation-catalysis by polysaccharide molecules that impedes free radical reactions; and (3) enhancement of endogenous antioxidant enzyme activity [31]. Additionally, some reports suggest that molecular weight may influence antioxidant activity, with lower molecular weight correlating with stronger antioxidant capacity [32].

2.4 Regulation of Intestinal Function

LAB EPS regulate intestinal function primarily by improving intestinal mucosal adhesion, modulating intestinal microecological balance, and providing energy to the intestine. Adhesion to intestinal epithelial cells depends on adhesins including lipoteichoic acid, intact peptidoglycan, surface layer proteins, and EPS, with EPS playing a significant role [33]. EPS-mediated adhesion facilitates intestinal colonization, enhances signal communication between LAB and intestinal cells, inhibits pathogen colonization, and improves host immunity [34]. The enhanced adhesion of probiotics involves both non-specific and specific pathways. Upon entering the intestine, LAB initially colonize through reversible non-specific adhesion, which is strengthened by secreted EPS. Following non-specific aggregation, bacteria then engage in specific recognition and adhesion with host cells [35].

Li et al. [35] investigated the effects of *Bifidobacterium bifidum* WBINO3 EPS on murine intestinal microbial diversity, showing significant increases in *Lactobacillus* and anaerobe populations while inhibiting enterobacteria, enterococci, and *Bacteroides fragilis*, thereby modulating intestinal microecological balance. Studies have shown that LAB EPS can be degraded by intestinal microbiota into short-chain fatty acids and lactate upon reaching the human colon. Bäckhed et al. [36] found that short-chain fatty acids derived from EPS degradation can provide approximately 10% of human energy requirements. Reports also indicate that high molecular weight EPS ($>10^6$ u) can resist degradation in simulated gastric and intestinal fluids and serve as fermentation substrates to provide energy to the colon [37-38]. Additionally, EPS can function as carbon sources for intestinal microbiota fermentation, providing nutrients to microbial communities [39].

3. Research Progress on Lactic Acid Bacteria Exopolysaccharides in Animal Nutrition

Compared with other polysaccharides, bacterial polysaccharides including LAB EPS offer broad development prospects and significant market potential due to their production through fermentation, short production cycles, and independence from temporal and spatial constraints [40]. Currently, various polysaccharide additives such as astragalus polysaccharides and ganoderma polysaccharides are widely used in livestock and aquaculture to enhance immunity and disease resistance. However, research on the physiological activities of LAB EPS has primarily focused on human, rodent models, or in vitro cell culture conditions, with limited studies in animal nutrition. The few existing studies mainly involve monogastric animals (pigs and chickens), with no reports in ruminants. Chen et al. [40] examined the regulatory effects of *Lactobacillus reuteri* EPS against enterotoxigenic *Escherichia coli* (ETEC) in piglets, demonstrating that EPS reduced ETEC colonization in the small intestine and alleviated diarrhea. Le et al. [41] fed weaned piglets with wheat fermented by *L. reuteri* and found that while fermented grains did not significantly affect intestinal morphology, small intestinal fermentation, growth performance, or nutrient digestibility, the EPS stimulated hindgut fermentation and improved health status. Lu [42] investigated the effects of selenium-enriched polysaccharides from *Enterobacter cloacae* Z0206 (Se-ECZ-EPS) on growth performance, carcass quality, immune function, and intestinal morphology and microbial diversity in broilers and weaned piglets, reporting enhanced immune function and improved growth performance. Although this study used EPS from *Enterobacter* rather than LAB, the research approach and methodology warrant consideration for future LAB EPS studies. Our research group has screened, identified, and purified high-EPS-producing LAB strains from plant sources, obtaining multiple superior strains and thoroughly investigating their immunomodulatory and antioxidant activities in mouse models. We plan to conduct application trials in young ruminants such as lambs and calves to provide a basis for the industrial application of LAB EPS.

4. Conclusions

Recent research on the physiological activities of LAB EPS has demonstrated multiple functions including antitumor, antioxidant, immunomodulatory, and probiotic effects. Theoretically, LAB could be applied in fermented foods such as yogurt to improve rheological properties, texture, and flavor while regulating intestinal function. They could also serve as feed additives to replace antibiotics and be utilized in medical and healthcare applications to promote human health. However, commercialization of LAB EPS has been achieved only in dairy fermentation and preparation, with industrial production in other areas facing numerous challenges, primarily low conversion rates and high production costs. Therefore, the key to current LAB EPS research is obtaining high-EPS-producing strains through modern molecular biology and bioinformatics techniques to achieve high-yield production for industrial applications. Furthermore, animal studies on LAB EPS have been limited to humans, rodents, and monogastric animal models, with virtually no research reported in ruminants. Future studies should investigate LAB EPS in young ruminants such as calves and lambs to expand their applications in animal nutrition and fully realize their potential as green feed additives.

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