

Review

Antilisterial Potential of Lactic Acid Bacteria in Eliminating *Listeria monocytogenes* in Host and Ready-To-Eat Food Application

Phui-Chyng Yap¹, Nor-Aziah MatRahim^{1,2}, Sazaly AbuBakar¹ and Hai Yen Lee^{1,*} 

- ¹ Tropical Infectious Diseases Research and Education Centre (TIDREC), Level 2, High Impact Research Building, Universiti Malaya, Kuala Lumpur 50603, Malaysia; phuichyng.yap@gmail.com (P.-C.Y.); aziyahrahim@yahoo.com (N.-A.M.); sazaly@um.edu.my (S.A.)
- ² Virology Unit, Institute for Medical Research, National Institutes of Health (NIH) Complex, Jalan Setia Murni U13/52, Seksyen U13, Setia Alam, Shah Alam 40170, Malaysia
- * Correspondence: leehaiyen@um.edu.my; Tel.: +60-03-79676670

Abstract: Listeriosis is a severe food borne disease with a mortality rate of up to 30% caused by pathogenic *Listeria monocytogenes* via the production of several virulence factors including listeriolysin O (LLO), transcriptional activator (PrfA), actin (Act), internalin (Int), etc. It is a foodborne disease predominantly causing infections through consumption of contaminated food and is often associated with ready-to-eat food (RTE) and dairy products. Common medication for listeriosis such as antibiotics might cause an eagle effect and antibiotic resistance if it is overused. Therefore, exploration of the use of lactic acid bacteria (LAB) with probiotic characteristics and multiple antimicrobial properties is increasingly getting attention for their capability to treat listeriosis, vaccine development, and hurdle technologies. The antilisterial gene, a gene coding to produce antimicrobial peptide (AMP), one of the inhibitory substances found in LAB, is one of the potential key factors in listeriosis treatment, coupled with the vast array of functions and strategies; this review summarizes the various strategies by LAB against *L. monocytogenes* and the prospect in development of a 'generally regarded as safe' LAB for treatment of listeriosis.

Keywords: infectious diseases; listeriosis; antilisterial; lactic acid bacteria; vaccine development; immunity; hurdle technology



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1. Introduction

Listeria monocytogenes is well known for its tolerance of low pH (4.5), high salt conditions (10% NaCl), low temperature (−1 °C), and acid tolerance response (ATR) [1–4], which contribute to its common contamination of food. *Listeria* contamination is commonly reported in dairy products, ready-to-cook fish, and meat products such as smoked salmon and sausage, therefore, they are considered as high-risk foods. Despite the conditions of food storage and processing, such as high salt and low temperature, *L. monocytogenes* can survive and multiply to an infectious dose because of its halotolerance and psychrotolerance ability [2,3,5–8]. A susceptible population, e.g., immunocompromised and immunosuppressed individuals, is at a higher risk and could develop a more severe *Listeria* infection after consuming *Listeria*-contaminated food [1,9]. Although *L. monocytogenes* can be inactivated by pasteurization or heating procedure in food processing, there is a possibility of recontamination or cross-contamination at the post-food-processing line such as during preparation, cooking, and storing [1,2,8,9]. Consumption of food contaminated with *L. monocytogenes* at an infectious level could lead to the development of a life-threatening foodborne disease, known as listeriosis. Listeriosis is developed through the production of several virulence factors, including listeriolysin O (LLO), transcriptional activator (PrfA), actin (Act), internalin (Int), etc. [10,11]. Table 1 summarizes the proteins involved in pathogenesis of *Listeria*. Upon

entry of *L. monocytogenes* into host cells, PrfA is highly activated and leads to the synthesis and secretion of virulence factors [11–13]. The virulence of *L. monocytogenes* is associated with pathogenic characteristics that support and promote intracellular survival by cell entry, escape from host vacuole, replication, and spreading to adjacent cells. The survival and multiplication of *L. monocytogenes* in host cell cytosol enable it to damage the host cell, which is crucial in pathogenesis, instead of killing it [14–16]. The major virulence factor, LLO, is a crucial protein to allow the escape of *L. monocytogenes* from the host vacuole and grow intracellularly in the targeted cell. Thus, LLO-deficient *L. monocytogenes* are not pathogenic and poorly immunogenic even at high concentrations because of the lack of the gene that encodes the LLO toxin (*hly* gene). The absence of LLO will prevent *L. monocytogenes* from escaping the vacuole and therefore, it will not be able to infect other cells [15].

Listeriosis has a high mortality rate (about 20–30%) compared with other pathogenic microorganisms such as *Campylobacter* species and *Salmonella* species [5,17]. *Listeria* infection causes high hospitalization rates (91%) and large outbreaks of human illness worldwide, with approximately 500 deaths reported annually in the United States [5]. The food previously reported to cause *Listeria* outbreaks (from 2010 to 2015) in the U.S. includes cold cuts, raw vegetables, ice-creams, and ready-to-eat foods [2,6]. The European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control has reported that listeriosis was the most frequent cause of death related to the foodborne outbreak in Europe from 2008 to 2012 [5]. It has been reported that listeriosis is considered one of the etiological factors in pregnancy infection and fetal infection in India, especially during the perinatal period [8,18,19]. Listeriosis can have devastating effects in immunocompromised individuals. The elderly (60 years and above), pregnant women, HIV/AIDS patients, and chronic lymphocytic leukemia patients have 2.6- [20], 20- [21], 300- [21], and 1000-fold [22] greater risk of acquiring listeriosis, respectively, compared with the healthy population. However, the prevalence of listeriosis in healthy individuals is low, with an estimated rate of 0.7 cases per 100,000 people compared with immunosuppressed individuals with 100 cases per 100,000 people [3].

Because listeriosis is a type of bacterial infection, it is often treated with antibiotics. Antibiotics such as ampicillin or penicillin combined with aminoglycosides such as gentamicin [1] and trimethoprim, or in combination with sulfamethoxazole [3] are common antibiotics of choice in the treatment of listeriosis. However, antibiotics ampicillin and penicillin are only bacteriostatically effective against *L. monocytogenes* and not suitable for β -lactam allergy individuals [1]. Although trimethoprim–sulfamethoxazole is bactericidal, it is not suitable for sulfur allergy individuals, and carries the risk of kernicterus and teratogenic effects such as neural tube defects [9]. The use of antibiotics in food products has been banned in Europe because the overutilization of antibiotics can contribute to the emergence and dissemination of antimicrobial resistance among bacterial pathogens or directly to humans and animals, via horizontal gene transfer, increasingly becoming a threat to global public health [23,24]. To reduce the risk of listeriosis, the food industry implemented Good Hygiene Practices, Good Manufacturing Practices, and Hazard Analysis Critical Control Points, ensuring the hygiene and safety of food production. Some commercial microbial agents against *L. monocytogenes* that have been approved by the U.S. Food and Drug Administration (U.S. FDA) as food-grade preservatives include PhageGuard Listex™, LMP 102, and Nisaplin® [25], which can be applied in food processing.

Table 1. Proteins involved in *Listeria* pathogenesis [10–13,16,26,27].

Protein	Function
Positive regulatory factor A (prfA)	Expresses the secretion of other virulence factors
Listeria adhesion protein (LAP)	Facilitates the interaction between <i>L. monocytogenes</i> and host cell receptor, e.g., E-cadherin and mesenchymal epithelial transition factor (c-Met) found in adherens junction of epithelial tissue
Invasion associated protein (IAP), e.g., p60	Adheres and invades host cells
Pore-forming hemolysin, e.g., Listeriolysin O (LLO)	Binds to cholesterol on host cell membranes for pore formation leading to rapid Ca ²⁺ influx and K ⁺ efflux, triggering histone modification that modulates gene expression, damage of cell membrane, induce mitochondrial fragmentation, and alteration of immune cell function that enhances bacterial internalization
Hydrolytic enzymes, e.g., phosphatidylinositol-specific phospholipase (PI-PLC), phosphatidylcholine-specific phospholipase (PC-PLC)	Disrupts host cell vacuolar membrane and escapes to the cytoplasm
Surface actin assembly-inducing protein, e.g., Actin A (ActA)	Promotes movement of <i>L. monocytogenes</i> towards host cell surface and invades neighbor cells through disruption by LLO and p60
Internalin A (Inl A)	Adheres to E-cadherin and mediates <i>L. monocytogenes</i> internalization into the host cell
Internalin B (Inl B)	Adheres to c-Met causing phosphorylation of Met and promotes <i>L. monocytogenes</i> entry to host cell

Novel approaches have been widely explored in the employment of lactic acid bacteria (LAB) in food application for food safety, quality improvement, and shelf-life extension, by utilizing nutrient or attachment sites on gastrointestinal tract (GIT) competition, or through the production of antimicrobial compounds such as organic acids, ethanol, hydrogen peroxide, bacteriocin, etc. [28–32]. LAB are also found to promote health benefits such as enhancing gastrointestinal barrier function and serum cholesterol reduction [28,29] with the advantage that LAB have shown no activity or toxicity toward eukaryotic cells and are sensitive to digestive proteases, which ensures no negative impact or only little effect on gut microbiota [28,32,33]. Because of the safety recognition of LAB such as Generally Recognized As Safe (GRAS) by the U.S. FDA and Qualified Presumption of Safety status by the EFSA [24,34–36], the application of LAB as natural preservatives in the food industry is preferable and acceptable by consumers and because several detrimental effects have been reported on the use of chemical preservatives [28–30], degradation of food nutrients, and the expansion of antibiotic resistance by bacteria [29,37,38]. The capability of antimicrobial substances produced by LAB during food processing, as a biocontrol, has directed food manufacturers' attention to LAB's application in food processing. Several studies have demonstrated the antilisterial effects of LAB bacteriocins or enzymes in food products such as fresh and cooked meats, vacuum packaged meat, and dairy products [29,31,33,37], suggesting that LAB or their metabolites are potential agents to restrain *Listeria* activity. LAB bacteriocin can be used as a bioactive compound in food preservation and food safety, either solely or in combination with plant extracts such as essential oils or phytochemicals, or other treatments such as heating, irradiation, high pressure, etc., therefore act as part of hurdle technology [28,30]. The mechanism of action of LAB against *L. monocytogenes* is detailed in the following section.

2. Mechanisms of Lactic Acid Bacteria (LAB) against *L. monocytogenes*

2.1. Production of Inhibitory Substances

2.1.1. Organic Acids

LAB produce a wide range of microbial inhibitory compounds, including organic acids as a major product, ethanol, diacetyl, carbon dioxide, hydrogen peroxide, and bacte-

riocin. The main antimicrobial compound responsible for LAB's activity against pathogens is production of organic acids, mainly lactic acid and acetic acid, which have been proved to show a strong inhibitory effect against pathogenic bacteria [39,40]. Organic acids are known to acidify intracellular pH, generating a selective barrier by inducing an unfavorable microenvironment for nonacidophiles. This leads to interference with the membrane potential and disruption of the cytoplasmic membrane, reduces nonacidophiles' cytoplasmic pH and alters cell metabolism, including inhibition of protein synthesis and nutrient absorption, genetic material demolition, damaging enzymes, or energy depletion due to counteraction of the microenvironment alteration, hence resulting in cell death [39,41]. However, this may not apply to *L. monocytogenes* [42] due to its behavior of ATR by importing and decarboxylation of glutamate and catabolism of arginine to ornithine, which involves the consumption of protons and thus an increase in intracellular pH that plays a critical role in *Listeria* virulence [43,44]. Based on Rios-Covian et al. [45], *L. monocytogenes* produces lactic acid as the main product under anaerobic metabolism and co-culture of *L. monocytogenes* anaerobically with *Bifidobacterium breve*, which produces lactic acid and acetic acid as by-products. Hemolytic activity of *L. monocytogenes* was found to be increased due to activation of LLO function in an acidic environment, which indicated that organic acid inhibitory activity is *L. monocytogenes*-strain dependent. On the other hand, several studies reported antilisterial activity by organic acids (not produced from the LAB) including undissociated lactic acid as the essential factor for *L. monocytogenes* inhibition and have proven the inhibitory effect of lactic acid against *L. monocytogenes* in Gouda cheese [46]; acetic acid showed a significant inhibitory effect on *L. monocytogenes* present in cold-smoked salmon and poultry, yet the quality and sensory properties of the food products were not adversely affected [47,48]. This suggested that the antilisterial activity of organic acids is highly dependent on *Listeria* strains. Short-chain fatty acids (SCFAs) such as butyrate produced by LAB in food fermentation or gut microbiota have been reported to induce epithelial cell differentiation and enhance barrier integrity, prevent adhesion of pathogenic bacteria, or indirectly inhibit the virulence gene expression at the transcriptional level, as reported in *Salmonella typhimurium* and *L. monocytogenes* by changing bacterial membrane fatty acids composition [44,49].

2.1.2. Bacteriocin

Bacteriocin is a ribosomally synthesized polypeptide, exerting bactericidal or bacteriostatic activity toward sensitive bacteria produced by various bacterial species, including LAB [28,39,50,51]. LAB bacteriocins' potential is emerging as a novel substitute for antibiotics due to its broad-spectrum or specific cytotoxicity and antagonistic activity against targeted pathogenic bacteria. Most importantly, their nature is produced by GRAS bacteria with no associated health risks [25,34,52]. Bacteriocin classification is complex because they can be classified according to their molecular weight, mode of action, chemical structure, etc. [29,40,53]. Class IIa bacteriocins such as pediocin PA-1 (*Pediococcus acidilactici*), enterocin A (*Enterococcus faecium*), and sakacin A (*Lactobacillus sakei*), which are classified based on biochemical and genetic properties, consist of a highly conserved hydrophilic N-terminal domain with consensus motif YGNGYV (tyrosine, glycine, asparagine, glycine, tyrosine, valine), known as the pediocin box that is responsible for activity against *L. monocytogenes* [28,50,53–55]. Their cationic terminal interacts with anionic lipids present in the targeted bacterial cell membrane via electrostatic interaction or specific receptors such as the mannose phosphotransferase (Man-PTS) system on targeted specific bacterial species but not other populations within the same ecosystem [42], ensuring a limited spectrum of inhibition to the targeted bacterial species [39,56]. The electrostatic interaction and/or Man-PTS system interference led to inhibition of peptidoglycan cell wall biosynthesis of targeted bacteria and depolarization of the cellular membrane potential. The membrane permeabilization causes dissipation of proton motive force and water potential, ATP depletion, leading to cell lysis and leakage of nutrients and intracellular metabolites [25,28,30,51]. The electrostatic interaction's antilisterial efficiency is highly dependent on the presence of

charged ions or net charges of bacteriocin molecules [57]. LAB bacteriocins may act through both mechanisms, cell wall inhibition and pore formation, which act as an added potential in preventing bacteriocin resistance development [28]. The antilisterial activity of LAB bacteriocins was also reported to reduce virulence gene expression or protein production. Several studies have shown bacteriocin's capability in *L. monocytogenes* inhibition—150 AU/mL and 300 AU/mL rhamnocin 519 derived from *Lactobacillus rhamnosus* CJNU 0519 decreases by 0.33 log CFU/mL and no viable cells of *L. monocytogenes* detected at 3 h of incubation, respectively [54]; sakacin A produced by *L. sakei* DSMZ 6333 was shown to permeabilize *Listeria* cells' membrane, dissipating both transmembrane potential and transmembrane pH gradient, leading to the leakage of cellular materials [55]; pediocin PA-1 produced by *P. acidilactici* UL5 induced elimination of *Listeria*, approximately 5 log reduction within 5 h in the ileum [56]; *Lactobacillus reuteri* INIA P572 produces reuterin with a strong antilisterial effect [58]; 2.5 mg/L of nisin suppressed growth of *L. monocytogenes* for up to eight weeks in chilled conditions, and 12,800 AU/g of enterocin reduced *L. monocytogenes* by 1.67 log cycle in salami [59]. It is possible for *Listeria* to become immune to bacteriocins such as nisin (Class I bacteriocin) or Class IIa bacteriocin as reported via the production of the enzyme nisinase, which degrades nisin [29], altering the fatty acid composition, thickness, charge, or fluidity of its cell membrane [25,29,51], preventing the binding of nisin to lipid II; through a spontaneous bacteriocin resistant mutant outgrowth [42,60]; cross-resistance to other antimicrobial compounds [42,51] or other classes of bacteriocins [25,29]. Besides, the presence of genes, e.g., cell wall synthesis gene *dltA* and penicillin-binding protein gene *lmo2229* or increased expression of β -glucoside-PTS involved in *mptACD* gene downregulation causing the absence of Man-PTS permease has been reported as resistant against class I and class IIa bacteriocins, respectively [25,61]. Immunity proteins produced by *L. monocytogenes* may either bind to bacteriocin for immobilization or the Man-PTS of the listerial cell membrane as a competitive site, leading to the inability to form pores and *Listeria* remains intact. As a result, bacteriocins fail to exert their antilisterial function effectively despite efficient production [25].

Production of bacteriocin is inducible by gene expression, which requires the presence of an auto-inducer and is dependent on their growth phase, culture media components such as carbon and nitrogen sources, and environmental factors such as temperature, pH, and incubation atmosphere [30,52,57,62]. The common commercial culture media for LAB include de Man, Rogosa and Sharpe (MRS), brain heart infusion (BHI), tryptic soy (TS), M17 media, and sodium lactate (NaLa), which support the rapid growth of LAB, yet are eminently strain-dependent. Nonetheless, high LAB bacteriocin production and activity are not inevitably based on cell yield, optimal growth, and LAB viability [52,62]. Certain LAB may produce bacteriocin during the log growth phase and stop at the stationary phase or only start producing during the stationary phase; insufficient nutrients or oversupply of nutrients can negatively affect LAB growth because excess insoluble nutrients in broth further affect the stability of bacteriocin production. Optimal growth temperature may not be similar to optimal bacteriocin production temperature because suboptimal growth temperature slows LAB growth rate and maximizes availability of essential metabolites. The pH of the culture media greatly affects LAB growth, cell aggregation, proteolytic degradation, protein solubility, biosynthetic gene regulation, and/or enzymatic reaction, influencing bacteriocin activity and stability; oxygen availability influences bacteriocin production, especially the facultative anaerobic nature of LAB; and agitation contributes to the introduction of an oxygen supply but could reduce bacteriocin activity due to shear effect, chemical degradation, and gene regulation [52,62]. The maximum bacteriocin production of *P. acidilactici* kp10 was obtained in M17 media (43.7 AU/g cell/h), followed by TS broth (26.70 AU/g cell/h), nutrient broth (NB) (11.21 AU/g cell/h), and MRS broth (7.46 AU/g cell/h), suggesting the rich nitrogen sources in M17 contribute to high bacteriocin production [63]. *Lactobacillus curvatus*, *E. faecium*, *Lactobacillus paracasei* subsp. *paracasei*, and *Streptococcus thermophilus* have grown well in MRSB and BHI ($>10^8$ CFU/mL). However, the bacteriocin production in BHI culture (<70 AU/mL) is much lower than

in MRSB culture (>340 AU/mL). Higher bacteriocin activity was demonstrated by LAB cultivated at pH 5.5 in BHI instead of pH 6.2; the latter had better growth [62].

Class IIa bacteriocin is known for its active inhibition activity against *L. monocytogenes*, suggesting its production is based on antilisterial gene expression. The gene expression is often regulated by a two-component regulatory system or three-component regulatory system that includes an inducer peptide (prepeptide), transmembrane histidine protein kinase (inducer peptide receptor), and cytosolic response regulator [30,64]. Depending on the bacteriocin, the inducer peptide could be the bacteriocin itself such as nisin and brevicin 174A, whereas some other bacteriocins, such as lactococcal bacteriocin LsbB, regulate their expression by stabilizing RNA [30]. The inducer peptide contains an amino acid leader sequence at the N-terminus, which serves a critical role in bacteriocin gene expression to maintain the inactive status of the inducer peptide to protect itself from the high concentration of active peptides in the host cell. The amino acid leader sequence is cleaved and removed by a proteolytic domain in transport systems such as ABC transporter or sec-dependent transporter to undergo modification by the regulatory system [64,65], thereby coordinating the translocation of inducer peptides to the transport system, which allows excretion of mature bacteriocin. The gene encoding for LAB immunity proteins or the regulation protein involved in bacteriocin production is located in a gene cluster responsible for the bacteriocin structural gene, causing the immunity protein genes to be co-transcribed with bacteriocin structural genes. Therefore, the immunity protein production is reduced with bacteriocin production, protecting itself from its bacteriocin activity [64,66,67]. Other than bacteriocins, other compounds produced by LAB also possesses antimicrobial properties and is summarized in Table 2.

Table 2. Mechanisms action of other antimicrobial substances produced by LAB [29,34,35].

Antimicrobial Substances	Source	Mechanisms of Action
CO ₂	A by-product of fermentation from heterofermentative LAB	<ul style="list-style-type: none"> - Interacts with cell membranes by reducing internal and external pH. - Inhibit enzymatic decarboxylation by an accumulation of CO₂, creating an anaerobic environment that effectively prevents aerobic microbial growth by causing dysfunction in permeability and produces carbonic acid.
H ₂ O ₂	Metabolites produced by LAB in the presence of oxygen	<ul style="list-style-type: none"> - A powerful oxidizing agent that oxidizes sulfhydryl groups and destroys the bacterial enzymatic activity. - Causing peroxidation of membrane lipids and cell proteins, hence increasing cell membrane permeability, losing components, and cell death. - Acts as a precursor for bacterial free radicals such as superoxide (O⁻²) and hydroxyl (OH⁻) radicals, which damage DNA.

2.2. Competitive Exclusion

Competitive exclusion is defined as the presence of at least one nonpathogenic bacterium that reduces the number of pathogenic bacteria, either directly or indirectly via different types of mechanisms such as competition for nutrients or receptor sites in the GIT [39]. In general, nonpathogenic bacteria and pathogenic bacteria compete against each other in a host for available nutrients, causing depletion of the nutrient supply to an opponent and cell death, hence effectively excluding the host's population. The growth rates of pathogenic bacteria and nonpathogenic bacteria present in the microenvironment are important for nutrient competition. A faster-growing bacterium leads to faster uptake of nutrients and inhibits opponents due to insufficient available nutrients in the microenvironment [68,69]. Pathogenic bacteria could also be excluded by nonpathogenic bacteria through the competition for adhesion receptors expressed on host cells [41]. Biofilm formation of

bacteria through quorum sensing plays an essential role in colonization in a host, which aids in the prevention of the attachment of opponent cells [39,40,70]. The competition for nutrients and attachment sites was suggested to co-occur. The sequence of bacterial treatment in both competition for nutrients and attachment sites significantly affects bacterial dominance in the microenvironment. LAB have been suggested to be better than the pathogen in attachment competition. This is because certain LAB are able to modify the microenvironment to be unfavorable for *L. monocytogenes* survival through the production of antimicrobial substances [39,49], or to attach specifically onto host cells through the production of other molecules such as lipids or free proteins that facilitate close contact to host cells [71].

2.2.1. Competition for Nutrients

All microorganisms require different compositions and concentrations of nutrients for survival and growth. The metabolic activity of *L. monocytogenes* may not be influenced by antimicrobial substances, e.g., organic acids and bacteriocin produced by LAB, due to their acid tolerance properties and production of proteolytic enzymes. Thus, the LAB's growth rate plays a critical role in presiding in the microenvironment to compete for nutrients with *L. monocytogenes*. Inhibition of *L. monocytogenes* by *Carnobacterium piscicola* has been reported. This dual bacteriocin-producing strain has a higher growth rate at chilled temperatures, via nutrient competition, than bacteriocin [60]. According to Saraoui et al. [68], *Lactococcus piscium* was faster growing than *L. monocytogenes*, which may result in quicker uptake of nutrients, and this competition may involve a partial inhibition mechanism but is bacterial-concentration dependent. However, the limited nutrients present in the host cell after LAB consumption may stress *L. monocytogenes* for survival and replication, causing stimulation of virulence gene expression [72]. PrfA, which plays a role in activating virulence factors, is positively regulated by the stress-responsive sigma B factor (σ^B). Therefore, under stress conditions such as insufficient nutrients or acid or oxidative stresses, *L. monocytogenes* may express its virulence factors such as protein InlA and InlB or immune response to counteract the stresses. The InlA and InlB were reported to be also co-activated by both σ^B and PrfA, suggesting the effectiveness of virulence gene expression under stress conditions [72,73]. Similarly, the LAB may also struggle with limited nutrients and induce bacteriocin to overcome survival stress.

2.2.2. Niche Competition

Adhesion of *L. monocytogenes* on host cells is crucial for their invasion and virulence [74,75]. For instance, heparin and heparin sulfate expressed on epithelial host cells act as the receptor for bacteria attachment such as di-glucosyl-di-acyl-glycerol/lipoteichoic acid of *E. faecium* and ActA of *L. monocytogenes* [76]. LAB surface adhesins embedded in the cell wall or anchored in the cell through lipid moiety, e.g., mucus adhesion-promoting protein) and mucus-binding protein produced by *L. reuteri* and *Lactobacillus fermentum*, potentiate their attachment to the host cell by facilitating close contact and colonization through the degradation of the extracellular matrix of cells [49]. LAB can prevent the attachment of *L. monocytogenes* on host cells through (i) colonization on host cells and (ii) saturation of *L. monocytogenes* attachment receptor.

The sequence of bacterial treatment affects the degree of *L. monocytogenes* attachment inhibition by LAB via different mechanisms: direct competition, displacement, and exclusion. Studies have shown that pretreatment of LAB on intestinal epithelial cells significantly reduced *L. monocytogenes* invasion by up to 90% [77]; pretreatment of LAB on abiotic surfaces effectively prevented the attachment of the incoming *L. monocytogenes* by reducing attachment of *L. monocytogenes* 2.82 log and 3.81 log after 24 h and 72 h, respectively [69]; the simultaneous treatment of LAB and *L. monocytogenes* that enables direct cell-to-cell competition to the available attachment sites effectively reduced *L. monocytogenes* attachment by 4.38 log and 3.22 log after 24 h and 72 h, respectively, with LAB concentration as low as 10^6 CFU/mL [69]. LAB's degree of inhibition of *L. monocytogenes* on both abiotic surfaces and epithelial cells is highly dependent on cell concentration, cell hydrophobicity, and

extracellular polysaccharide substances (EPS). Wang et al. [70] reported an *L. rhamnosus* GC mutant that produced low capsular polysaccharide, possessing a weak biofilm-forming capacity and adhesion. In the event where *L. monocytogenes* have occupied the attachment site, LAB inhibit *L. monocytogenes* invasion by inhibiting their access to the available nutrients.

Nevertheless, it is notable that *L. monocytogenes* invasion can occur via the production of proteolytic enzymes or immunity protein that could defend against LAB and/or LAB inhibitory compounds. Specific molecules present on the LAB surface or their metabolites act as ligands binding to *L. monocytogenes* attachment receptors [71,78]. As a result, *L. monocytogenes* receptor sites that are responsible for gastrointestinal cell attachment were altered and malfunctioned. These LAB metabolites and surface molecules involved in the adhesion and co-aggregation of *L. monocytogenes* that interfere with their attachment are related to bacteria specificity. According to Saraoui et al. [68], the cell-to-cell contact is vital for LAB to inhibit *L. monocytogenes* from exchanging information such as genetic materials through conjugation, transport of DNA, proteins, or molecules through secretion system pathway IV, which is also supported by Zilelidou et al. [72], who declared that cell contact enables bacteria to deliver toxic compounds to an antagonist in close vicinity. In contrast, Corr and co-workers [77] showed that the invasive activity of *L. monocytogenes* is independent of cell-to-cell contact with LAB and suggested that the inhibition of *L. monocytogenes* invasion was mainly due to inhibitory substances secreted by LAB, which was supported by Rios-Covian et al. [45].

2.3. Reduction of *L. monocytogenes* Virulence Availability by LAB

A new approach of utilizing LAB to reduce the virulence expression of pathogens has been reported in several studies via modulation of gene or protein expression through bacterial signaling mechanisms. Upadhyay et al. [79] showed that LAB, including *L. reuteri*, *L. fermentum*, *Lactobacillus plantarum*, and *Lactococcus lactis*, significantly reduced *L. monocytogenes* adhesion and invasion of Caco-2 cells (approximately 1.5 to 2 log CFU) and downregulated most *L. monocytogenes* virulence genes, including *prfA*, *plcA*, *plcB*, *hly*, *actA*, *inlA*, *inlB*, and *iap*, up to sixfold change, but the degree of reduction is LAB-strain dependent. These reduction activities are enhanced with the combination of eugenol extracted from clove oil, suggesting LAB's potential as part of hurdle technology. Another study by Winkelströter and De Martinis [80] demonstrated that bacteriocins derived from *E. faecium*, *Leuconostoc mesenteroides*, and *L. sakei* significantly decreased the expression of *inlA* from different sources of *L. monocytogenes*. Food-isolated *L. monocytogenes* reduced their adhesive and invasive properties on Caco-2 cells. Interestingly, adhesion of *L. monocytogenes* isolated from a food-processing environment is inversely proportional to invasion of Caco-2 cells when treated with LAB bacteriocins. This suggested that *L. monocytogenes* adhesion was independent of invasion of Caco-2 cells. The adhesion and invasion of *L. monocytogenes* on Caco-2 cells and inhibitory effect of LAB are interrelated to *L. monocytogenes* strain, LAB strain, and environmental conditions. According to Rios-Covian et al. [45], co-culture of *Bifidobacteria* with *L. monocytogenes* caused overexpression of the *hly* gene and *luxS* gene, which are involved in the regulation of biofilm formation. The early expression of the *hly* gene extracellularly causes energy dissipation and disrupts virulence efficacy, whereas the expression of the *luxS* gene repressed *L. monocytogenes* biofilm formation and weakened the adhesion of *L. monocytogenes* onto host cells. Similar studies were reported on the lower virulence gene expression of non-*Listeria* species. For instance, expression virulence genes of *Salmonella enterica* (SPI-1 and SPI-2), *Clostridium difficile* (*tcdA* and *tcdB*), and *Clostridium perfringens* (*cpb2*) were downregulated by LAB, e.g., *Lactobacillus bulgaricus*, *L. paracasei*, *Lactobacillus acidophilus*, and *L. fermentum*, instead of bacteriocin-like inhibitory substances, reducing the pathogenicity [38,81,82]. Nevertheless, the pathogenicity of *L. monocytogenes* and antagonistic effect of LAB involved several factors and regulatory mechanisms; thus, more studies are required to discover their roles in listeriosis.

3. Role of LAB in Host Cells against *L. monocytogenes* Infection

3.1. Protection of Gastrointestinal Tract from *L. monocytogenes* Invasion

The GIT is a complex microecosystem consisting of diverse microbiota, e.g., *Lactobacilli* and *Bifidobacteria* that influence host physiology and immunological development [74,77]. Gut microfloras activate the host immune system to react promptly against pathogenic infection and act as antagonists to compete for essential nutrients and colonization spaces. Intestinal epithelial cells (IECs) serve as the main target site of *L. monocytogenes* pathogenesis associated with the capability of attachment, invasion, and resistance of host immunity [77,83]. IECs are also said to be the first-line defense mechanism against *L. monocytogenes* invasion, which consist of three physical barriers, namely, single-layer epithelial cells, enteric mucosal surface layer, and epithelial junction adhesion complex with glycocalyx, which consists of mucin that aids in strengthening epithelial physical barrier function and epithelial integrity against *Listeria* invasion [39,84]. The antibacterial mechanisms possessed by microfloras could be reinforced by inoculating LAB in the microenvironment to maintain intestinal microbial balance. LAB enhances IECs' functions, regulates intestinal immune cell responses, eliminates gastrointestinal pathogens, and prevents postinfectious inflammation or overreaction of adaptive immunity [41,84,85]. The protection of GIT by LAB has been consistently reported on its effectiveness in the early control of *L. monocytogenes* infection [43,86].

Among the three physical barriers of IECs, the mucus layer is the frontline of host intestinal defense that protects IECs from pathogens' adsorption and invasion, chemical, enzymatic, mechanical, and microbial damage [41]. The primary constituent of mucus, mucin, especially mucin2 (MUC2), and other antimicrobial peptides (AMPs), e.g., Trefoil factor 3 (TFF3) and resistin-like molecule-beta are secreted by goblet cells via transcription factor Krueppel-like factor 4 (KLF4), under normal physiological conditions. Gene expression of these mucus constituents is augmented by goblet cells to replenish and conserve the integrity of the mucus layer by increasing its viscosity [49,87,88] because the presence of the toxin, food components, cytokines, and microbial colonization, or flow of digesta may cause depletion of the mucus layer [89,90]. Mucin sulfation is a crucial process that requires galactose-3-O-sulfotransferase 2 (GAL3ST2) and carbohydrate sulfotransferase 5 (CHST5) to reinforce the protective effect of the mucus layer against pathogenic infection and inflammation in the intestine [88]. A recent study by Ren et al. [88] showed that the upregulation of *MUC2*, *TFF3*, *RETNLB* (gene encoded for resistin-like beta protein), *CHST5*, and *GAL3ST2* genes depended on LAB species and strains, incubation time, and the presence of cytokines, e.g., tumor necrosis factor- α (TNF- α) and interleukin-13. For instance, *Lactobacillus casei* and *L. reuteri* only significantly elevated *MUC2* and *TFF3* genes' expression, respectively; *L. rhamnosus* significantly augmented *MUC2* and *GAL3ST2*; *L. fermentum* expressed the *TFF3* gene to peak at 24 h. Besides, certain cell-free supernatants (CFS) of LAB were also shown to upregulate these genes' expression, illustrating that specific compounds produced by LAB may be involved in goblet cell function modulation, which is supported by Caballero-Franco et al. (2007) [91]. It is also in line with Fernandez et al. [92], who reported that lactate produced from *S. thermophilus* was suggested to upregulate KLF4 protein involved in goblet cell differentiation maturation, despite weak adhesion of *S. thermophilus* onto the mucus layer of HT-29 cells. Interaction of lactate and Gpr81 (G-protein-coupled receptor) in the intestine stimulates intestinal stem cells, thereby maintaining IECs' integrity [93]. Soluble protein p40 produced by *L. rhamnosus* GG induced *MUC2* gene expression and mucin secretion by activating epithelial growth factor receptor (EGFR) through secretion of epithelial growth factor (EGF) without promoting goblet cell differentiation and proliferation [91,94] has also been reported. These results suggested LAB metabolites' potential involvement in diverse signaling cascades activation, supporting the growth and maturation of goblet cells or mucin production [93]. Goblet cell function is influenced by the presence of cytokines and mucus integrity, which both could be augmented or attenuated by LAB species and strain, e.g., *B. breve* is a mucus degrader [88,95]. An in vivo study has demonstrated where the addition of LAB in animal diet significantly augmented *MUC2* gene expression and increased goblet cell number

and density, and villus length of chickens [87]; the number of intraepithelial lymphocytes, CD3+ (cluster of differentiation) cells density in Peyer's patches and lamina propria of piglets [93] compared with the normal diet. It has been suggested that Nucleotide-binding and oligomerization domain (NOD) proteins, e.g., NOD1 and NOD2, are the critical receptors for LAB to stimulate goblet cells and MUC2 production because NOD1 and NOD2 ligands have been shown to upregulate β -1,3-*N*-acetylglucosaminyltransferase 3 (C3GnT), which is involved in mucin synthesis and increases goblet cell numbers [96,97]. Even so, pathogens may not be eliminated by the mucus layer due to their high binding affinity to glycoproteins or glycolipids of IECs [74]. *L. monocytogenes* encode several proteins, e.g., lmo0576 (containing a mucin-binding protein, MucBP domain) which is also found in the MUCB protein of *L. reuteri* [98], and internalin has binding ability onto mucin and adheres to the mucus layer of IECs [43]. However, interestingly, under anaerobic conditions and the presence of SCFA, LLO production is increased without immediately triggering LLO activity, instead of increased mucin production and thereby enhancing the IECs barrier against *L. monocytogenes* infection [43,99].

The tight junction of IECs that comprise several transmembranes and adaptor proteins is a pivotal barrier in regulating paracellular permeability and preventing invasion by *L. monocytogenes*. Notably, the virulence factor, LAP, e.g., alcohol acetaldehyde dehydrogenase (Aad or *lmo1634*), is crucial for *L. monocytogenes* to disrupt a tight junction actively by recognizing the epithelial receptor, heat shock protein 60 (Hsp60). This interaction activates nuclear factor-kappa B (NF- κ B) and stimulates myosin light-chain kinase (MLCK), which mediates remodeling of epithelial junction proteins including tight junction proteins, e.g., claudin-1 and occludin, and adherens junction protein (E-cadherin). Restructuring of these proteins leads to E-cadherin exposure on epithelial apical sites, especially in villus tips, causing IECs to be susceptible to *L. monocytogenes* invasion by InlA into the lamina propria [100,101]. Activation of c-Met by InlB has also been proposed to expose E-cadherin on the apical surface either through manifestation or stimulation of hepatocyte growth factor because c-Met signaling is involved in junction assembly. However, the mechanism is not known because c-Met is also a basolateral receptor [100]. LAP-deficient *L. monocytogenes* significantly reduced adhesion, invasion, and transepithelial translocation properties through Caco-2 cells [102–104], and *L. monocytogenes* translocation through IECs is dependent on the concentration of secretory LAP and transport protein, SecA2 [102]. It has been reported that short hairpin suppression of epithelial Hsp60 [104] and E-cadherin saturation by antibody [101] significantly dampened *L. monocytogenes* adhesion and invasion of IECs, suggesting the importance of Hsp60 in LAP-mediated invasion and E-cadherin receptor for *L. monocytogenes* invasion. Other than MLCK stimulation, LAP-mediated NF- κ B activation independent of invasion stimulates pro-inflammatory cytokines, e.g., TNF- α and IL-6, and induces epithelial barrier disturbance, facilitating *L. monocytogenes* translocation without triggering innate immune response [101]. However, LAB's potential to antagonize LAP or epithelial Hsp60 is poorly known although *L. rhamnosus*, *L. acidophilus*, and *L. paracasei* have been reported to carry a LAP homolog, showing neither interaction with purified Hsp60 protein nor anti-LAP antibody [103]. Instead, probiotic bioengineering is applied by developing recombinant LAB-expressing LAP without negative impact such as cytotoxic response [105]. Surprisingly, strong interaction between Hsp60 with recombinant LAB including *L. paracasei* expressing LAP (Lbp^{LAP}) [103]; *L. casei* expressing inlAB (Lbc^{InlAB}) and LAP (Lbc^{LAP}) [105], were even stronger compared with wild-type *L. monocytogenes* and wild-type LAB, resulting from high plasmid copy number in the LAB recombinants [105], hence, enabling a higher reduction of *L. monocytogenes* adhesion, invasion, and translocation through IECs. Prolonged exposure of Caco-2 cells to recombinant LAB exhibited *L. monocytogenes* adhesion, invasion, and translocation inhibition ($\geq 30\%$), and protection of Caco-2 cells from *L. monocytogenes* cytotoxicity up to 79% after 24 h [103,105]. Lbc^{LAP} and Lbc^{InlAB} were also shown to lower transepithelial/transendothelial electrical resistance) reduction by <10% and <15%, respectively [105], suggesting LAP of recombinant LAB plays the leading role in conserving Caco-2 cells' integrity. Koo et al. [103] suggested that

the enhancement in Caco-2 cells' integrity by Lbp^{LAP} was due to suppression of TNF- α and interferon- γ (IFN- γ), and subsequent regulation of tight junction protein expression.

3.2. LAB as an Immunoadjuvant in Immunomodulation of *L. monocytogenes* Infection

The innate immune system plays an important role in inducing immediate defense against acute inflammation and in activating long-lasting adaptive immunity. Innate immunity is activated via the engagement of pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) that are expressed on IECs' apical site or endosome, or cytosolic NOD-like receptors (NLRs) with pathogen-associated molecular patterns (PAMPs) in the majority of pathogens [49]. PRRs including TLR2, NOD1, NOD2, and NACHT, LRR and PYD domains-containing protein 3 (NALP3), e.g., cryopyrin and IL-1 β -converting enzyme, ICE-protease activating factor (IPAF) are crucial in defending against *Listeria* infection, which recognizes *L. monocytogenes* lipoproteins, lipoteichoic acid, peptidoglycan components, e.g., meso-diaminopimelic acid and muramyl dipeptide, DNA, or toxin, e.g., LLO and p60 [85,86,106–108]. The recognition by these PRRs of *L. monocytogenes* is greatly dependent on the *lgt* gene encoded for prolipoprotein and type of *L. monocytogenes*, e.g., noncytosolic *L. monocytogenes* (LLO-deficiency) lead to inability to secrete IL-1 β and IL-18 [106]. Interactions of these PRRs and PAMPs activate transcriptional factors, e.g., Myeloid differentiation primary response 88 (MyD88), NF- κ B, and interferon regulatory factor 3, and induce proinflammatory cytokines and chemokines, e.g., TNF, IL-6, IL-12, IL-1 β , IL-18, and type-I IFNs, e.g., IFN- $\alpha\beta$ [85,86,106,107,109,110]. Type-I IFNs are well known for their potential in antitumor and antiviral functions that cause apoptosis, autophagy, or mediate inflammation and autoimmunity. However, these IFNs possess an opposite effect against bacterial infection, including *L. monocytogenes* [106], suggested to downregulate immune response or enhance bacterial growth directly. IFN- $\alpha\beta$ was also reported to suppress IFN- γ (type-II IFNs) which are produced by natural killer (NK) to activate macrophages for phagocytosis in conjunction with TNF α signaling or via Janus kinases, and signal transducer and activator of transcription protein (JAK-STATs) pathway [108,109]. Patients or mice associated with a deficiency in IFN- γ and TNF α receptors and/or gene mutations are highly susceptible to *L. monocytogenes* infection [108,109] whereas a deficiency in type-I IFN receptors and transcriptional factor IFN-regulatory factor 3 are resistant to *Listeria* infection [107,109], suggesting that IFN- γ and TNF α are essential for primary antilisterial defense. The immunomodulatory activity exerted by LAB includes the downregulation of pro-inflammatory cytokines and upregulation of anti-inflammatory cytokines; modulation of the signaling pathway, e.g., NF- κ B, mitogen-activated protein kinases (MAPK) and phosphatidylinositol 3-kinase (PI3K) [110]. An increase in the IFN- γ RNA level was shown with the administration of *Lactobacilli* in mice, which stimulated the proliferation of CD4⁺ T cells [111]. Antilisterial-acting IFN- γ plays a critical role in adaptive immunity against *Listeria* infection by increasing the expression of costimulatory molecules and major histocompatibility complex (MHC), thus enhancing T cells [107–109]. Other than competing for adhesion sites with *L. monocytogenes*, EPS of LAB, e.g., polysaccharide-peptidoglycan administration by mice, has been shown to improve their survival rate from *Listeria* infection mainly via activation of macrophages [70]. The interplay of these active receptors and adaptor proteins is critical in triggering host immunity by producing various IL and IFN from innate cells, e.g., monocytes, macrophages, and NK cells can respond promptly, for the effective removal of *L. monocytogenes* in IECs.

The production of AMPs, e.g., defensin (cryptidin), lysozyme, phospholipase A2, cathelicidin, matrix metalloproteinase 7, and regenerating islet-derived protein 3- γ (RegIII γ) from Paneth cells may be stimulated upon production of proinflammatory cytokines [89] and/or dependent on microbial stimulation including exposure to bacterial membrane proteins [43,89,96,112]. LAB have been demonstrated to increase Paneth cell number and/or stimulate AMPs, depending on the type of LAB strains and epithelial environment context [89,96]. AMPs such as α -defensin and cathelin-related antimicrobial peptides have been demonstrated to provide effective protection to host cells against *L. monocytogenes*

and exert a synergistic effect with macrophages to limit the secretion of LLO and subsequent intracellular proliferation of *L. monocytogenes* [113,114]. Cathelicidins and defensins bind to the phospholipids group of *Listeria* membrane, e.g., lipid II through electrostatic force can create pores, e.g., Human Neutrophil α -defensin 2 dimer forms multimetric pores, impedes peptidoglycan formation, and alters *Listeria* integrity [41,49,112,115,116]. The release of AMPs is partially dependent on NOD2 [49,110], the molecule particularly highly expressed on Paneth cells, and thus was suggested to be crucial to regulate Paneth cells' antimicrobial activity [96,117], or initiated by TLRs [115]. Similar to the nature of *L. monocytogenes*, LAB as Gram-positive bacteria consist of a peptidoglycan cell wall, lipoteichoic acid, and teichoic acid, act as microbe-associated molecular patterns (MAMPs) recognized by PRRs, e.g., TLRs and NLRs to mediate immune regulation [70,89,118]. The interaction of several LAB peptidoglycans with NOD or TLRs was suggested to stimulate these AMPs [96,115,116], particularly defensin via subsequent MAPK, NF- κ B, or Activator protein 1 (AP-1) signaling pathway [77,89]; lysozyme via Receptor-interacting serine/threonine-protein kinase 2 (RIPK2) pathway [90,116]; or RegIII γ via TLRs/MyD88 signaling pathway to disrupt glycosidic linkage of peptidoglycan via enzymatic reaction, promoting mucosal barrier function [115,116]. *L. helveticus* membrane protein was reported to have a greater extent in human beta-defensin-2 (hBD2) expression compared with cells. The membrane protein as TLR2 antagonist activates TLR2 downstream signaling, including MAPK, NF- κ B, and mainly c-Jun N-terminal kinase signaling, mediating the upregulation of hBD2 as suggested [119]. However, the exact role of NOD in AMPs' expression is poorly known because there are conflicting reports, suggesting the possibility of an additional function of NOD in Paneth cells beyond regulation of AMPs' secretion and activity [43,48,90,115,117,120]. AMPs perform different functions through different mechanisms in exerting an antipathogenic effect, including enzymatic or nonenzymatic reaction, or interaction with the intracellular component to inhibit DNA and protein synthesis, and protein folding [113]. In short, every AMP plays a crucial and specific role in protecting host cells from pathogenic infection [43,114–116].

Early or excessive production of proinflammatory cytokines that trigger an inflammatory response has been shown to cause a negative impact on the host, including tissue damage, intestinal disorder, and IECs or leukocytes' apoptosis that promote pathogen virulence [49,120]. Upon phagocytosis, the close contact of dead phagocytes or secreted apoptogenic compounds with leukocytes leads to its apoptosis independently of *L. monocytogenes* infection. This cytokine-induced cell apoptosis event is increased with LLO-producing *L. monocytogenes* with concentrations ranging from 0.4 to 4 nM [121]. Notably, LLO potentiates the imitation of perforin to cooperate with granzyme (serine protease) stored in cytotoxic lymphocytes (CD8⁺ T cells), inducing autologous apoptosis instead of target cells [15,121,122]. A report has shown that IL-18 and TNF-related apoptosis-inducing ligand deficient mice have reduced susceptibility to *L. monocytogenes* infection due to less apoptosis of leukocytes and IECs, resulting in a higher number of leukocytes including macrophages, dendritic cells (DCs), and NK cells after *Listeria* infection compared with wild-type mice [107,120]. Therefore, the production of proinflammatory cytokines, e.g., TNF- α and IFN- γ , needs to be regulated because an adequate amount is essential for primary antilisterial defense and required for activation of T cells involved in adaptive immunity whereas an excessive amount can cause detrimental effects.

LAB's potential in reducing cytokine-induced apoptosis, protecting IECs from inflammation and injury, has been widely reported. For instance, *L. rhamnosus* GG and *L. acidophilus* have been demonstrated to alleviate IECs' apoptosis, e.g., TNF- α -induced Zonula occludens-1 disruption, which plays a critical role in preserving tight junction integrity in a cell-contact-dependent manner [110,123]. LAB metabolites, e.g., soluble proteins p40 and p75, potentiate the stimulation of serine-threonine kinase to induce secretion of EGF through MMP activation, transactivation, and interaction with EGFR [110,124]. The subsequent activation of anti-apoptotic PI3K-downstream substrate, serine/threonine kinase (Akt/PKB), and inhibition of proapoptotic mitogen-activated protein kinase (p38/MAP

promote IECs' homeostasis. Hence, minimizing IECs' apoptosis and cytokine-induced apoptosis protects host cells from injury and inflammation [125,126]. TLR1 and TLR6 are indispensable for the activation of TLR2 signaling by forming heterodimers and are critical for GIT immune homeostasis maintenance. Activation of TLR2/TLR1 induces pro-inflammatory cytokines as demonstrated by *L. monocytogenes*, whereas activation of TLR2/TLR6 induces tolerogenic cytokines, e.g., IL-10 stimulated by regulatory T (Treg) cells which was demonstrated by LAB to possess immunological tolerance to abolish intestinal inflammation [118,127]. Nevertheless, excessive TLRs signaling stimulation can cause several diseases. *L. plantarum*, *L. casei*, *L. reuteri*, *L. acidophilus*, *L. rhamnosus*, *Lactobacillus brevis*, and *S. thermophilus* and their CFS were shown to induce anti-inflammatory IL-10 production by NF- κ B/AP-1 through MyD88/AP1-dependent signaling, in which TLR2 acted as the PRR. The characteristic of heat-stable, DNase, RNase, and proteinase sensitive LAB CFS suggests the potential compounds to be proteins or nucleic acids, or possibly ligands expressed on cell surfaces. Nuclease-treated *L. plantarum* CFS was reported to improve TLR2 activation by the degradation of nuclease-sensitive molecules. These molecules may aggregate with MAMPs, limiting their interaction with TLR2. Therefore, removal of the molecules through enzymatic treatment will improve the accessibility of TLR2 binding sites by the MAMPs, suggesting nuclease as an auxiliary to promote LAB-produced bioactive compounds in TLR2 activation [127,128]. Other than an attachment, EPS of *L. casei* Shirota and *Lactobacillus delbrueckii* subsp. *bulgaricus* modulate host immune response by preventing pro-inflammatory IL-6 and IFN- γ production that causes inflammation [70]. Corr et al. [77] demonstrated that *L. acidophilus*, *L. casei*, and *Lactobacillus salivarius* have significantly reduced pro-inflammatory cytokines (IL-8) and increased the production of anti-inflammatory cytokines (IL-10), approximately threefold reduction and 1.5-fold increase, respectively. Interestingly, there was no detectable IL-8 and IL-10 production in the absence of *L. monocytogenes* despite LAB's presence, suggesting the importance of innate immune response activation via the recognition of PRRs with PAMPs.

Although innate immunity is crucial for early control of *L. monocytogenes* infection by limiting their exponential growth, the importance of adaptive immunity in the final elimination of the pathogens is also indispensable, providing effective sterilizing protection [85,86,129]. The innate immune response follows an adaptive immune response, mainly triggered through the interaction of cytosolic NLRs, e.g., NOD2 with PRRs [130] and stimulated by activated DCs through recognition of PAMPs to its PRRs, leading to the expression of costimulatory molecules, e.g., TNF and cytokines [4,39,86]. As compared with humoral immunity, cell-mediated immunity involving CD4⁺ and CD8⁺ T cells contributes to major protection from *L. monocytogenes* infection, which is activated by the degraded *Listeria* peptides presented on MHC class II and class I, respectively. CD8⁺ T cells have contributed substantially and effectively in mediating adaptive immunity from *Listeria* infection, stimulated by endogenous listerial antigen, e.g., LLO or p60 protein loaded on MHC class I molecules. CD4⁺ T cells' role is relatively less well defined in defending against *Listeria* infection, probably in protective immunity [86,107,129] due to the kinetics and magnitudes of CD4⁺ T cells, accumulation of CD4⁺ memory T cells is tissue-specific and dependent on infection route [129]. CD8⁺ T cells possess cytoplasmic granules containing perforin and granzymes, which lyse infected cells and expose intracellular bacteria for subsequent killing by neutrophils and activated macrophages via phagocytosis [85,86,129]. As mentioned above, LLO may mimic perforin and cause unwanted apoptosis of uninfected cells, thereby impairing antilisterial immunity. Humoral immunity involving antibodies did not show a significant elimination in *L. monocytogenes* infection, although anti-LLO monoclonal antibody has been shown to neutralize LLO [86,108,129]. However, B cells are essential in the efficient formation of long-lasting memory CD8⁺ T cells that differentiated from cytotoxic CD8⁺ T cells together with CD4⁺ T cells [108], which react promptly and protect the host from subsequent exposure to *Listeria* infection.

Although the immunomodulation of LAB against *L. monocytogenes* is mainly based on activation of the innate immune response, LAB plays a minor role in triggering adaptive

immunity through innate immune response, stimulating the production of cytokines from Treg cells, e.g., IL-10 to activate DCs or specifically INF- γ and TNF- α from T cells that are important for complete *L. monocytogenes* clearance [70,84,108,109]. LAB, e.g., *L. paracasei* subsp. *paracasei* NTU 101 or LAB-expressing antigen have been proved to upregulate the expression of surface proteins, e.g., CD40, CD80, CD86, and MHC class II on antigen-presenting cells (APCs) via interaction with APCs' surface peptide which activates APCs or CD154 on CD4⁺ T cells, providing costimulatory signaling for T cells' activation, proliferation, and differentiation to trigger costimulatory molecules and cytokines' secretion, inducing an adaptive immune response [118,125,131]. *L. paracasei* subsp. *paracasei* NTU 101 and *L. rhamnosus* GG augmented DC-T cells' interaction via STATs signaling that led to an increase in B cell number [41,109,125]. Wells (2011) [118] suggested the antilisterial genes present in LAB, e.g., plantaricin from *L. plantarum* are involved in immune response to DCs in cytokines' production because deletion of genes was found in the locus responsible for plantaricin biosynthesis and secretion (*lp_0403* to *lp_0431*) when co-cultured with DCs [118]. Regulation of the TLR signaling pathway by LAB also mediates the differentiation of effector T cells or stimulation of macrophages and DCs [70,111], e.g., (i) *L. casei* upregulates expression of TLR2 and mannose (CD206) on APCs [84], (ii) *B. breve* BbC50SN promotes expression of CD83, CD86, and HLA-DR via activation of the TLR2 signaling pathway, which is involved in DCs' maturation [70] later stimulation of adaptive immunity, suggesting the importance of TLRs in both innate and adaptive immunity. A remarkable increase in the number of effector T cells, including helper CD4⁺ and cytotoxic CD8⁺, and NK cells, has been reported in several case studies in LAB consumption as probiotic supplements [70]. Nevertheless, solely enhancing the CD4⁺ and CD8⁺ T cells' levels may cause induction of inflammatory response and overstimulation of mucus; thus, their levels should be optimal [74].

4. LAB as a Vaccine Vector against *L. monocytogenes*

The potential of LLO in antitumor vaccine development is due to their features of (i) ability to live inside the host cell, which is not possessed by other CDC-producing bacteria [132], (ii) ability to provide cytosolic access for antigens in APCs by pore formation [133]. Because infection by *L. monocytogenes* is closely related to contaminated food products, and the bacterium is able to bypass the mucosal barrier, mucosal vaccines may offer more advantages than vaccines delivered via the parenteral delivery route and whereby it has been demonstrated to be able to induce both mucosal and systemic immune response [134]. However, antigen delivered via mucosa induces low immune responses, probably due to rapid degradation in the mucosal secretion, poor microbial adsorption, and induction of mucosal tolerance [134,135]. LAB have a long track record for safe oral consumption, and some strains possess probiotic properties. The increasing interest in using LAB as a live vector has heightened the development of a vector for LAB, especially for *Lactobacilli* with probiotic properties [136]. Perhaps synergistic effects between the immunomodulatory properties are conferred by LAB, and the potential antigen could elicit a better immune response at lower vaccine dosage and confer more effective protection against the infection. However, different strains of LAB demonstrated differences in their activities. Some bacteria maintain homeostasis of the intestinal microbiota, and some strains induce the immune system and repress the allergic reactions. Other probiotic strains render protection against pathogenic bacteria either by competing for the colonized surface, producing inhibiting compounds against the growth of pathogens, or by inducing mucus AMP production by the mucosal epithelial cells [136]. Among the LAB, *L. lactis* has been highlighted as potentially the best vaccine vehicle due to its safety and sequenced complete genome [137]. The potential of *L. lactis* as a vector for DNA plasmid transfer for *L. monocytogenes* LLO expression intracellularly and extracellularly has been demonstrated. The plasmid transfer ratio in *L. lactis* is low, however, with the recombinant *L. lactis* expressing the mutated InIA and LLO of *L. monocytogenes* with observed increase in the production of the gene of interest [138]. Besides functioning as a carrier for plasmid DNA, the potential of *L. lactis* in the expression of various antigen

intracellularly and extracellularly has led to the development of an inducible expression system for *L. lactis*. The availability of such a system enabled the intracellular expression of many antigens in *L. lactis* such as tetanus toxin fragment C and 28-kDa immunogen from *Schistosoma mansoni* [135,139]. In the context of a vaccine for *L. monocytogenes*, the *L. lactis* expression system could be employed for the expression of listerial antigens for oral route delivery. A study by Jensen et al. [140] demonstrated that the production of IFN- γ within the animal group subcutaneously inoculated with vaccine candidate containing LLO and p60 in replication-deficient adenovirus-based vaccine contributed toward protective immunity against *Listeria* infection. Because *L. lactis* is also reported as an effective vehicle for cytokine delivery [134], an oral vaccine for *L. monocytogenes* could be developed using *L. lactis* for expression of listerial antigens with co-expression of cytokine (i.e., IL-12, IL-2, or IL-6). This approach perhaps could lead to effective protection against the infection, possibly similar to that reported by Jensen et al. [140] or could be better. LAB have also been demonstrated to be utilized to display a single-chain antibody fragment (ScFv) that could be used for the generation of passive immunity [141,142]. Such an approach could be developed to treat *L. monocytogenes* because it might provide a more direct and fast response. The beneficial effects, robustness, and encouraging results on LAB's capability as a delivery system are likely to play a crucial role in future vaccine development [136]. Nevertheless, some concerns remain to be addressed. Among them is the horizontal transfer of plasmid carrying antibiotic resistance marker to the environmental and host microfloras [137]. It is also important to understand the immune response in relation to the route of administration and the level of in vivo antigen production to stimulate further vaccine development using the LAB system [135].

5. LAB/LAB Bacteriocin as Part of Hurdle Technology

The common food preservation technologies implemented in the food industry include heat treatment, e.g., Ultra-High-Temperature, High-Temperature-Short-Time pasteurization; dehydration, e.g., smoking, freeze-drying; pickling, and salting by addition of vinegar, sugar, and salt; addition of chemical preservatives; and prevention of oxidation or oxidative rancidity by addition of antioxidants [143,144]. Although these food preservation techniques effectively extend the food shelf life, they may result in food quality deterioration such as loss of nutrients and sensory attributes, and adverse health effects resulting from chemical preservatives. Thus, hurdle technology has been developed to inaugurate a series of selective protection aspects to provide a hostile environment that coerces multi-stress reactions to foodborne pathogens and spoilage microorganisms [32,143–145], minimizing food deterioration while maintaining the expected organoleptic quality through the implementation of more than one barrier including existing (temperature, pressure, pH, etc.) and novel (antimicrobial compounds and physicochemical treatment) preservation techniques [25,144]. Hurdles interfere with microbial homeostasis by affecting their physiological processes, which lead to microbial metabolic exhaustion [25].

LAB/LAB bacteriocin is being implemented as a natural preservative in food application. Because food is the main source of listeriosis, the effectiveness of LAB/LAB bacteriocin antilisterial activity in food applications should be widely explored. The interaction between *L. monocytogenes*, LAB/LAB bacteriocin, and food matrix may lead to alteration in survival or replication of *L. monocytogenes*/LAB, *L. monocytogenes* virulence gene expression, or antilisterial activity functionality of LAB/LAB bacteriocin [7,25,29,72]. Application of bacteriocins individually in food is unlikely to ensure complete safety [57,146], for instance, LAB bacteriocin is degraded by the enzymatic activity of food proteolytic enzymes, thus losing LAB bacteriocin functionality [147]. Therefore, the introduction of LAB/LAB bacteriocin in hurdle technologies with other preservation techniques reduces the application and severity of physical hurdles. This lowers the risk of LAB bacteriocin resistance by undesirable microbes and maintains food quality in safety, organoleptic, and nutrition while reaching higher lethality [7].

Nevertheless, several factors should be considered for incorporating LAB/LAB bacteriocin as a hurdle, including their stability in terms of temperature, wide range of pH, tonicity, adaptability in the food matrix, and concentration [32]. Thus, appropriate intensity and a proper combination of hurdles need to be established to maximize food shelf life and quality [25,145]. Notably, safety concern or spoilage of hurdle-treated food may arise due to post-contamination or improper storage affected by extrinsic factors such as light [7,25,144].

Nisin is the only bacteriocin approved by the FDA and World Health Organization (WHO) in food application, for example, the commercially available Nisaplin[®] product is a good role model of LAB bacteriocin involving hurdle technology, which employs nisin (2.5% *w/w*) with the combination of NaCl (77.5% *w/w*), protein (12% *w/w*), and carbohydrates (6% *w/w*) [25,148]. Nisin also has been documented to improve thermal inactivation of bacteria, which reduces treatment time and degree, preserves food quality, with cost savings. The bactericidal effect of nisin against *L. monocytogenes* was found to be enhanced with the addition of NaCl together with vacuum packaging and is active at low pH [7,25,57,149], suggesting their suitability in acidic foods' applications. Nevertheless, some studies reported that nisin is slightly inactive against *L. monocytogenes* because it is not a class IIa bacteriocin and has weak antilisterial activity when applied in meat due to high pH, interference with meat components, and uneven distribution [29,51,60]. Thus, the study of antilisterial bacteriocin purified from LAB is encouraged and applied in food technology and preservation to reduce listeriosis risk.

5.1. Encapsulation of LAB/LAB Bacteriocin

Because LAB bacteriocin is a biosynthesized peptide, its structure and function are easily degraded or inactivated by the food matrix, e.g., polar and nonpolar food components, and food processing, e.g., heat or diluted below appropriate concentration resulting from migration into the food matrix [146]. Bacteriocin is incorporated in biocompatible films or nanovesicles, e.g., alginate, gelatin, starch, guar gum, xanthan gum, or liposomes, to overcome this problem, which is known as encapsulation [150–152]. Theoretically, the thin layer of encapsulant protects LAB/LAB bacteriocin from the fluctuating and dynamic food processing, and against other microbial competitors, thus increasing their viability, stability, and distribution. Indirect contact of encapsulated LAB/LAB bacteriocin allows them to adapt to the food matrix environment by controlling their release rate [7,150,151], reducing the risk of malfunction, and ensuring their antilisterial efficacy. Several studies had proven that encapsulated LAB/LAB bacteriocin in phosphatidylcholine-liposomes (4–250 µg/mL) [153,154], and the combination of alginate (2.5% *w/v*) [152] and gelatin (6.0% *w/v*) significantly slows the growth or reduces the number of *L. monocytogenes* (CFU/mL) compared with free LAB/LAB bacteriocin in dairy products, e.g., milk and cheese, and meat under refrigeration for up to at least 21 days. Notably, free bacteriocin demonstrated lower antilisterial activity due to their interaction with fat globules in milk [153], and the number of *L. monocytogenes* was found to increase slowly from an undetectable level after a few days under refrigeration storage, which was suggested as due to resistance of *L. monocytogenes* to LAB bacteriocin [154]. However, it has been reported that free nisin has better antilisterial activity than soy lecithin-encapsulated nisin (250 µg/mL), possibly resulting from the inhibitory effect of lecithin on nisin through complex formation. However, the encapsulated nisin possessed bacteriostatic properties toward *L. monocytogenes* [155]. Martinez et al. [148] reported that both free and encapsulated nisin showed a significant reduction of *L. monocytogenes* in milk. Their combination exerted a more substantial antilisterial effect, hypothesizing initial action by free nisin followed by encapsulated nisin. Barbosa et al. [156] reported that the encapsulation of bacteriocin-producing *L. curvatus* MBSa2 slightly improved their survival in salami, in which their count was maintained at 8 log CFU/mL for 30 days compared with free cells, and encapsulated *L. curvatus* MBSa2 showed a better reduction of *L. monocytogenes* in salami. In encapsulation, the encapsulant properties such as polydispersity, zeta potential, size, entrapment encapsulation, and concentration are the important factors that could influence the encapsulated antimicrobial compound

function [153,154]. Le et al. [152] explained that the concentration of gelatin in the capsule influenced its viscosity and the fertility of LAB antimicrobial compounds. The highest inhibitory effect (68.69%) against *L. monocytogenes* was found when encapsulated in 2.5% (*w/v*) alginate with 6.0% (*w/v*) gelatin *L. plantarum* SC01. Besides, internal factors, e.g., composition and pH of food products, concentration and type of LAB/LAB bacteriocin, and external factors, e.g., storage temperature and time are critical in antilisterial activity.

5.2. Active Packaging

Food packaging is intended to protect food from physical damage, unwanted physiological and chemical changes, environmental factors, e.g., light, dust, and pests, and ease of transportation [144,157], especially post-processed food for long-term storage. Active packaging, e.g., vacuum packaging, modified atmosphere packaging (MAP), active scavenging, or active releasing system, were developed to enhance the strength of normal packaging and is widely used for highly perishable food, including fresh produce, meat, and fish to preserve their appearance, which is easily discolored from enzymatic reaction or oxidation [36,144,146,158,159]. The alteration of the external food environment promotes retardation of microbial growth, e.g., CO₂ (active releasing system) inhibits aerobic bacteria and reduces ethylene sensitivity, thus inactivating or slowing enzymatic reaction [144]. Slow migration of antimicrobial agents from food packaging material to the food matrix provides a consistent exposure of antimicrobial compounds to bacteria, maintaining a high concentration where required and protecting loss of antimicrobial functionality resulting from interaction with the food matrix [146,158]. Antimicrobial packaging by incorporating LAB bacteriocin is an alternative strategy to extend the shelf life of food products while improving LAB bacteriocin stability and antilisterial properties in the complex food environment [51]. The introduction of LAB/LAB bacteriocin in active packaging, e.g., alginate film [160], starch/halloysite nanocomposites film [159], bioactive plastic pouches [161], and edible pullulan film [162], has been widely studied and proved to be effective against *L. monocytogenes* in chilled food for up to a month. Antilisterial activity of LAB/LAB bacteriocin in active packaging was reported to be augmented with a combination of LAB and LAB bacteriocin in the film [160], improved with a higher concentration of bacteriocin [159], enhanced with vacuum packaging and MAP (60:40 N₂:CO₂) [161], or addition of lauric arginate, an approved synthetic preservative [162]. Spraying *L. piscium* EU2241 and *Leuconostoc gelidium* EU2247 onto shrimp before vacuum packaging slowed the growth of *L. monocytogenes* and their count was reduced by up to 2 log at 8 °C and 20 °C [163]. Similar to encapsulant, the effectiveness of LAB/LAB bacteriocin in the film is greatly affected by the concentration of the film nanocomposites because a higher concentration of nanocomposites delayed the bacteriocin diffusion. It is also notable that the growth of *L. monocytogenes* slowly increased during storage caused by the development of bacteriocin resistance. Therefore, an amalgamation of LAB/LAB bacteriocin with encapsulation or active packaging is suggested to delay bacteriocin resistance [148,160]. It has also been suggested not to apply LAB cells alone because it may not ensure complete elimination of *L. monocytogenes* and outgrowth of LAB may cause an undesired quality of food such as acid production that may influence the sensory attributes of food [40].

6. Conclusions and Future Perspective

An established and balanced gut microbiota composition can greatly benefit host immunity by maintaining host homeostasis and health. Disturbances in gut microbiota and immunity interaction can ease the translocation of a pathogen to host cells and expose the host to pathogenic infection, particularly intracellular *L. monocytogenes* due to immune dysregulation and subsequent autoimmune disorder. Because nisin is the only approved bacteriocin launched in the market, the advanced properties of LAB, such as antilisterial gene and gastrointestinal function and GRAS status, should attract more efforts to potentiate their role as antibiotic substitution, nutrient supplements, or biopreservatives in listerial treatment and prevention or food application. The colonization of gut microbiota in the

host is critical and greatly augmented with LAB administration, which aids in reinforcing gut barrier function to prevent invasive *L. monocytogenes* and modulate host immune response to prevent cell injury or tissue damage.

Despite the potential of LAB in competing for host colonization with *L. monocytogenes* and preventing their internalization from hosting cells, the mechanism of downregulation or suppression of *L. monocytogenes* virulence factors gene or production is poorly understood. Gene cloning of *L. monocytogenes* virulence factors, e.g., LLO, LAP, and p60 in LAB could be developed for listeriosis vaccination. *L. monocytogenes* virulence factors' production is triggered by environmental stress or as metabolites. In the absence of stress or limiting nutrients for metabolism, virulence factors may still exist but are hidden or under control. *L. monocytogenes* and LAB's metabolic study could further identify their interaction in the host cell or food matrix that provides nutrients. However, LAB's effect in *L. monocytogenes* defense is greatly dependent on several factors, including LAB strains and dosage, host physiological status, type of listeriosis, or in prevention including food components' environmental factors, e.g., temperature, pressure, and light exposure. In addition, avirulent *Listeria* spp., e.g., *L. innocua* should not be overlooked because the virulence factor could be transferred readily between each other. Overall, LAB present a great potential to be used for controlling and combating listeriosis through direct inactivation to immunomodulation prospects and can also be developed into a multiprong approach against *L. monocytogenes*.

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