



Benefits and Inputs From Lactic Acid Bacteria and Their Bacteriocins as Alternatives to Antibiotic Growth Promoters During Food-Animal Production

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Resistance to antibiotics is escalating and threatening humans and animals worldwide. Different countries have legislated or promoted the ban of antibiotics as growth promoters in livestock and aquaculture to reduce this phenomenon. Therefore, to improve animal growth and reproduction performance and to control multiple bacterial infections, there is a potential to use probiotics as non-antibiotic growth promoters. Lactic acid bacteria (LAB) offer various advantages as potential probiotics and can be considered as alternatives to antibiotics during food-animal production. LAB are safe microorganisms with abilities to produce different inhibitory compounds such as bacteriocins, organic acids as lactic acid, hydrogen peroxide, diacetyl, and carbon dioxide. LAB can inhibit harmful microorganisms with their arsenal, or through competitive exclusion mechanism based on competition for binding sites and nutrients. LAB endowed with specific enzymatic functions (amylase, protease...) can improve nutrients acquisition as well as animal immune system stimulation. This review aimed at underlining the benefits and inputs from LAB as potential alternatives to antibiotics in poultry, pigs, ruminants, and aquaculture production.

Keywords: probiotics, animal health, lactic acid bacteria, antibiotic alternatives, microbiota, immunity

INTRODUCTION

Livestock production is one of the fastest growing aspects of the agricultural sector. During the last decades, production, and consumption of animal products have largely increased (Speedy, 2003). This increase will continue in the near future in order to satisfy the high demand for livestock products, such as meat, milk, eggs, and fish, especially in industrialized countries (OECD/FAO, 2018). The dominant livestock types are pig with 112.33 million of tons (MT), poultry (109.02 MT), and cattle, which includes beef and buffalo meat (67.99 MT) representing 91.80% of meat production in the world (FAOSTAT, 2013). While fish captures, and aquaculture production reached 158 MT (FAOSTAT, 2013).

In veterinary medicine, antibiotics are used to fight clinical and subclinical infectious diseases. Notably, in some countries, they are also used as antimicrobial growth promoters (AGPs). To this end, antibiotics are supplied in subtherapeutic doses to provide benefits for livestock by improving growth rate, reducing mortality, and enhancing animal reproductive performance (Marshall and Levy, 2011). Antibiotics mostly used for AGP applications include tetracyclines, ionophores, and penicillins (American Meat Institution, 2013). In Europe, different antimicrobials have been used (Butaye et al., 2003), but the Regulation (EC) No 1831/2003 stated that “Antibiotics, other than coccidiostats or histomonostats, shall not be authorized as feed additives” and these are now banned in the EU. Global antibiotic consumption in livestock was estimated to be approximately 63,000 to over 240,000 metric tons yearly (World Bank, 2017), and these quantities may certainly increase because of the high consumption level registered in the emerging economies (World Bank, 2017). However, a substantial decline of the sales of antimicrobials for food-producing species has been observed in some countries (ESVAC, 2017). As a consequence, this overuse of antibiotics will contribute to spreading antimicrobial resistance worldwide.

Antibiotics can affect the intestinal microbiota and host physiology by (i) preventing pathogen colonization, (ii) impacting the immune system, (iii) increasing fat absorption by decreasing the hydrolysis of conjugated bile salts, and (iv) enhancing the use of nutrients as a result of an alteration of the intestinal wall and lamina propria (Niewold, 2007; Lee et al., 2011). The balance existing between beneficial and non-beneficial bacteria in the gastrointestinal tract (GIT) of a healthy animal can be modified upon alteration of the bacterial proportions causing pathogen infections from different external sources (Kers et al., 2018; Pluske et al., 2018). Pathogenic bacteria can negatively act on the animal health and welfare, as well as on their growth and reproduction performances. Some of these can reach the human gastrointestinal tract through the food chain (Newell et al., 2010), which meanwhile can lead to antibiotic resistance transmission (Soucy et al., 2015). Resistance to antibiotics is a serious concern for humanity. To reduce this phenomenon, the EU ban of antibiotics as growth promoters, should be globalized worldwide. Consequently, some countries such as Mexico, New Zealand, and South Korea have adopted the EU approach. Other countries such as United States, Canada, or Japan have established guidelines and recommendations to reduce the use of AGP in animal productions (Laxminarayan et al., 2015; Brown et al., 2017; Liao and Nyachoti, 2017). To help fighting against antibiotic resistance, the international organizations have ruled through global action plans aimed at ensuring treatment and prevention of infectious diseases with safe and effective medicines (WHO, 2015).

Ban of antibiotics as AGPs is economically and negatively impacting the livestock sector because of different and uncontrolled bacterial diseases (Laxminarayan et al., 2015). To help control increasing resistance to antibiotics, innovative alternatives are urgently needed for food-animal production (Seal et al., 2013; Cheng et al., 2014; Kogut, 2014; Czaplewski et al., 2016). Related to that, the EU has recently recommended

the use of alternative strategies in food-producing animals to limit antimicrobial resistance (AMR), and this resulted in temporarily and satisfactory achievements as observed in some EU countries. The strategies adopted included (i) national reduction targets, (ii) benchmarking of antimicrobial use, and (iii) controls on prescription and restrictions on use of specific critically important antimicrobials, together with improvements to animal husbandry and disease prevention and control measures (Murphy et al., 2017). According to studies by Allen et al. (2013), Czaplewski et al. (2016), Seal et al. (2018), additional means expected to replace AGPs in livestock sector are prebiotics, antimicrobial peptides (AMPs), bacteriophages and their gene products, antibodies, vaccines, and natural compounds such as polyphenols and particularly probiotics. The current adopted definition of probiotics from FAO/WHO (2002) states that probiotics are “live microorganisms, providing health benefits for the host, when they are administered in adequate amounts.” Microorganisms with probiotic grade must be devoid of any adverse effects (cytotoxicity, antibiotic resistance, hemolysis), and endowed with beneficial claims. Probiotics are known to act in strain-dependent manner and inhibit pathogenic bacteria through different mechanisms as reported in different studies (Kabir, 2009; Alloui et al., 2013; Pandiyan et al., 2013; Dowarah et al., 2017). Regarding to the functions allocated to probiotics, it has been established that numerous phylogenetic analyses associated to experimental data have revealed some paradigm for host-adaptation (Frese et al., 2011).

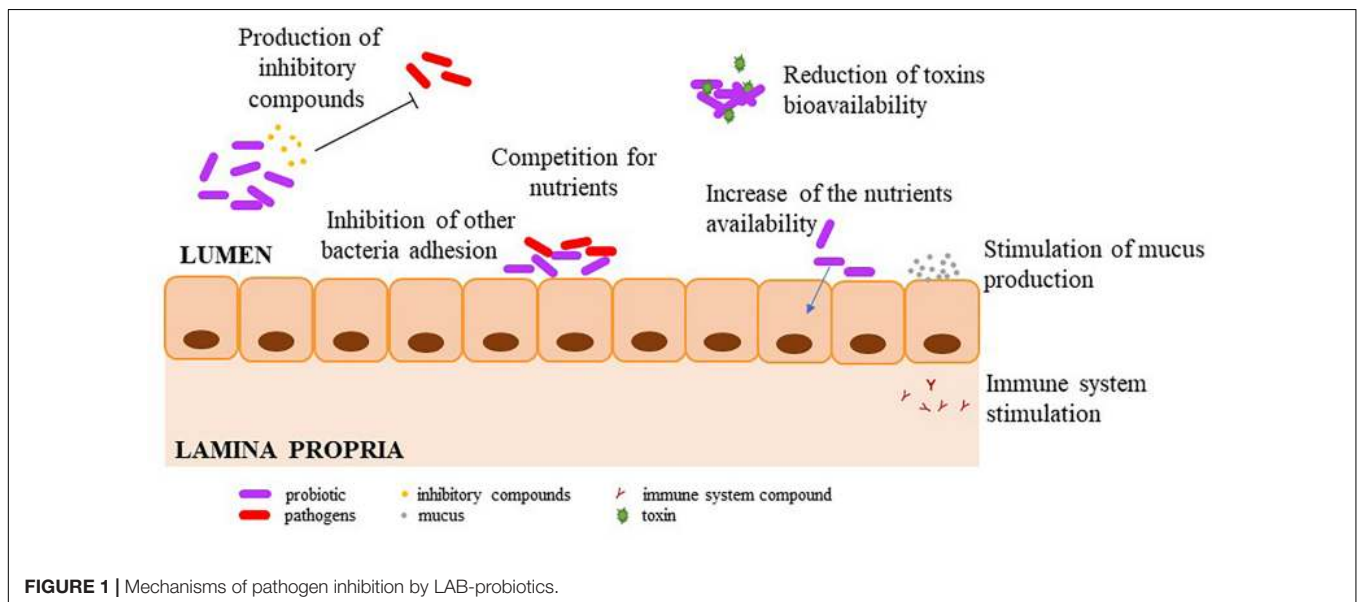
According to Krajmalnik-Brown et al. (2012), the animal intestinal microbiota is a key organ, which plays a determinant role in the harvesting, storage, and expenditure of energy obtained from the diet. Notably, these functions can influence the health and weight modification of the animal (Krajmalnik-Brown et al., 2012). Note therefore, that another report from FAO (2013) reported the possibility of probiotics application for animal nutrition as gut ecosystem enhancers. Interestingly, Yirga (2015) and Seal et al. (2018) reported and argued on the use of lactic acid bacteria (LAB)-probiotics in promoting the growth and reproduction performances and the survival rate and health status of animals. Related to LAB-probiotics, **Table 1** shows the list of these strains potentially usable as antibiotics replacers because of their multifaceted functions.

Lactic acid bacteria are suitable for livestock as probiotics because of their capabilities to modify the environment, in which they have been delivered, by producing different metabolites among which a wide range of inhibitory substance and even competitive exclusion (Gaggia et al., 2010; FAO, 2016). It should be noted that LAB-probiotics belong to *Lactobacillus* (*Lb.*), *Pediococcus* (*Ped.*), *Lactococcus* (*Lc.*), *Enterococcus* (*Ent.*), *Streptococcus* (*Str.*), and *Leuconostoc* (*Leuc.*) species. Nevertheless, *Lactobacillus* species remain the upmost studied and used ones (Martínez Cruz et al., 2012). Mechanisms of pathogens inhibition by LAB-probiotics include (i) production of inhibitory compounds, (ii) prevention of the pathogens adhesion, (iii) competition for nutrients, (iv) modulation of the host immune system, (v) improvement of nutrient digestibility, feed conversion, and (vi) reduction of toxin bioavailability (**Figure 1**).

TABLE 1 | Probiotic genera used in animal farming*.

Animal	Yeast	Bacteria		Fungi	Microalgae
		LAB	Non-LAB		
Poultry	<i>Candida</i> , <i>Saccharomyces</i> <i>Kluyveromyces</i>	<i>Lactobacillus</i> <i>Streptococcus</i> <i>Pediococcus</i> <i>Enterococcus</i> <i>Weissella</i>	<i>Bacillus</i> <i>Bifidobacterium</i>	<i>Aspergillus</i>	–
Pig	<i>Saccharomyces</i> <i>Kluyveromyces</i>	<i>Lactobacillus</i> <i>Pediococcus</i> <i>Enterococcus</i> <i>Weissella</i>	<i>Clostridium</i> <i>Bacillus</i> <i>Bifidobacterium</i>	–	–
Ruminant	<i>Saccharomyces</i> <i>Trichosporon</i> , <i>Kluyveromyces</i>	<i>Lactobacillus</i> <i>Enterococcus</i>	<i>Megasphaera</i> <i>Bacillus</i> <i>Prevotella</i> <i>Propionibacterium</i> <i>Bifidobacterium</i>	<i>Aspergillus</i>	–
Aquaculture	<i>Saccharomyces</i> <i>Debaryomyces</i>	<i>Lactobacillus</i> <i>Lactococcus</i> <i>Leuconostoc</i> <i>Enterococcus</i> <i>Pediococcus</i> <i>Carnobacterium</i> <i>Weissella</i>	<i>Bacillus</i> <i>Enterobacter</i> <i>Pseudomonas</i> <i>Streptomyces</i> <i>Alteromonas</i> <i>Clostridium</i> <i>Roseobacter</i> <i>Eubacterium</i> <i>Brevibacterium</i> <i>Microbacterium</i> <i>Staphylococcus</i> <i>Streptomyces</i> <i>Micrococcus</i> <i>Psychrobacter</i>	<i>Aspergillus</i>	<i>Tetraselmis</i> , <i>Phaeodactylum</i>

*Data summarized from (Kabir, 2009; Seo et al., 2010; Hai, 2015; FAO, 2016; Banerjee and Ray, 2017; Carnevali et al., 2017; Liao and Nyachoti, 2017).



PATHOGEN INHIBITION

The commonly encountered pathogenic or zoonotic bacteria in food-animal farming are *Escherichia coli*, *Salmonella*

enterica, *Campylobacter jejuni*, *Vibrio anguillarum*, *Clostridium perfringens*, *Aeromonas salmonicida*, *Pseudomonas* spp., and *Edwardsiella* spp. (Table 2). Whilst some of these pathogens, such as *V. anguillarum*, and *C. jejuni* are most often encountered

TABLE 2 | Most frequently encountered bacterial infections among producers in animal production*.

Animal	Potentially reported as pathogenic or zoonotic bacteria
Poultry	<i>Escherichia coli</i> <i>Salmonella enterica</i> <i>Clostridium perfringens</i> <i>Campylobacter jejuni</i>
Swine	<i>Streptococcus suis</i> <i>Pasteurella multocida</i> <i>Escherichia coli</i>
Ruminants	<i>Salmonella abortusovis</i> <i>Brucella ovis</i> <i>Campylobacter</i> Enterotoxigenic <i>Escherichia coli</i>
Aquaculture	<i>Aeromonas salmonicida</i> (Furunculosis) <i>Vibrio anguillarum</i> (Vibriosis) <i>Pseudomonas</i> spp. <i>Streptococcus</i> spp. <i>Edwardsiella</i> spp.

*Data obtained from OIE – World Organization for Animal Health (<http://www.oie.int/en/animal-health-in-the-world/oie-listed-diseases-2006/>).

in fish and poultry, respectively, other bacteria can affect various hosts provoking different pathologies in several food-producing animals. These are the cases of *E. coli* and *S. enterica* which can afflict poultry, swine, ruminants, and humans (Table 2). As above-cited, LAB-probiotics can limit the dissemination of pathogenic bacteria by mechanisms involving production of inhibitory compounds and competitive exclusion.

Production of Inhibitory Compounds

The LAB can produce a wide range of inhibitory compounds to reduce pathogens invasion (Table 3). These include AMPs such as bacteriocins, organic acids, ethanol, diacetyl, carbon dioxide, and hydrogen peroxide (Liao and Nyachoti, 2017).

Bacteriocins are ribosomally synthesized AMPs produced by both Gram-negative and Gram-positive bacteria (Drider and Rebuffat, 2011). Bacteriocins produced by LAB referred here as LAB-bacteriocins are most often devoid of cytotoxic traits (Belguesmia et al., 2010), and endowed with antagonistic functions as well as additional beneficial attributes (Drider et al., 2016; Chikindas et al., 2018). LAB-bacteriocins are emerging as a novel wave of antibiotics with potent *in vitro* and *in vivo* activities (Stern et al., 2008; Rihakova et al., 2010; Al Atya et al., 2016; Jiang et al., 2016; Caly et al., 2017; Seddik et al., 2017). In contrast to traditional antibiotics, LAB-bacteriocins target specific species and do not affect other population within the same ecosystem. LAB-bacteriocins are known to exert either bacteriostatic or bactericidal activity toward sensitive organisms. Their modes of action have been widely but not thoroughly investigated. Recent insights on modes of action are reviewed elsewhere (Cavera et al., 2015; Drider et al., 2016; Woraprayote et al., 2016; Ben Lagha et al., 2017; Perez et al., 2018). Combinations of LAB-bacteriocins and antibiotics are emerging as novel therapeutic options for food-producing animals (Naghmouchi et al., 2010, 2011, 2013; Al Atya et al., 2016). Different reports have established the main advantages and

synergistic actions of LAB-bacteriocins with other biomolecules. These are the case of enterocin AS-48 and ethambutol against *Mycobacterium tuberculosis* (Aguilar-Pérez et al., 2018), nisin and citric acid against *Staphylococcus aureus* and *Listeria monocytogenes* (Zhao et al., 2017), nisin and beta-lactams against *Salmonella enterica* serovar Typhimurium (Rishi et al., 2014; Singh et al., 2014), and Garvicin KA-farnesol against a set of Gram-positive and Gram-negative bacteria (Chi and Holo, 2018). Orally administration of these substances is a challenge because of their enzymatic degradation. This case was reported *in vivo* for lactacin 3147 and nisin (Gardiner et al., 2007; Gough et al., 2018).

Organic acids, including short chain fatty acids, lactic and formic acids, were shown to inhibit potentially pathogenic bacteria of importance for livestock animals. LAB are producing lactic acid as the main product of sugar metabolism (Russo et al., 2017). However, LAB metabolically known as heterofermentative species can concomitantly produce other end-products such as acetic acid (Oude Elferink et al., 2001; Schnürer and Magnusson, 2005). Organic acids are known to act by reducing the intracellular pH and inhibiting the active transport of excess internal protons which requires cellular adenosine triphosphate (ATP) consumption leading to cellular energy depletion (Ricke, 2003). The main targets of organic acids are the bacterial cell wall, cytoplasmic membrane, and specific metabolic functions (e.g., replication and protein synthesis) of pathogenic microorganisms leading to their disturbance and death (Surendran Nair et al., 2017; Zhitnitsky et al., 2017). Lactic acid produced by LAB induces an unfavorable local microenvironment for pathogenic bacteria (Dittoe et al., 2018). Wang C. et al. (2015) showed that concentrations of 0.5% (v/v) lactic acid could completely inhibit growth of pathogens such as *Salmonella* spp., *E. coli* or *L. monocytogenes*. Nevertheless, these acids do not affect animal epithelial cells because of the mucus layer that creates a gradient of pH (Allen and Flemström, 2005). Feeding with organic acids such as propionic has some limits because their dissociation before they reach the small intestine (Hume et al., 1993).

Ethanol produced by hetero-fermentative LAB is generated from the glycolysis pathway (Elshaghabee et al., 2016). Ethanol affects the membrane fluidity and integrity resulting in bacterial cell death due to plasma membrane leakage (Ingram, 1989). Oh and Marshall (1993) reported that ethanol concentration at 5% inhibited *L. monocytogenes* replication.

Diacetyl is produced from citrate uptake and metabolism in LAB. Notably *Lb. plantarum*, *Lb. helveticus*, *Lb. bulgaricus*, *Ent. faecalis*, and mainly *Leuc. mesenteroides* and *Lc. lactis* biovar diacetylactis are the most commonly known LAB species producing diacetyl (García-Quintáns et al., 2008; Singh, 2018). Diacetyl interferes with arginine utilization by reacting with the arginine-binding protein of Gram-negative bacteria (Lindgren and Dobrogosz, 1990), while carbon dioxide liberated in the near environment by LAB creates an anaerobic environment where aerobic bacteria cannot grow (Singh, 2018).

Some species of LAB are able to produce hydrogen peroxide (H₂O₂) and can inhibit pathogenic bacteria devoid of catalase (Mitchell et al., 2015), through superoxide anion chain reaction enhancing toxic oxidation. H₂O₂ bactericidal

TABLE 3 | Examples of antimicrobial compounds produced by LAB.

Molecule	Examples	Producers	Spectrum	Reference
Bacteriocins	Nisin	<i>Lc. lactis</i> subsp. <i>lactis</i>	Broad spectrum: Gram-positive bacteria without nisinase	Juncioni de Arauz et al., 2009
	Pediocin PA-1	<i>Ped. acidilactici</i>	Broad spectrum: Gram-positive bacteria	Rodríguez et al., 2002
	Enterocin AS48	<i>Ent. faecalis</i>	Gram-positive bacteria and <i>E. coli</i> , <i>Salmonella enterica</i> , <i>Bacillus subtilis</i> , <i>B. cereus</i> , <i>B. circulans</i> , <i>Corynebacterium glutamicum</i> , <i>C. bovis</i> , <i>Mycobacterium phlei</i> , <i>Nocardia corallina</i> , <i>Micrococcus luteus</i> , <i>Micrococcus lysodeikticus</i> , <i>S. aureus</i> , <i>Enterococcus faecalis</i> , <i>Ent. faecium</i> , <i>Enterobacter cloacae</i> , <i>E. coli</i> , <i>Klebsiella pneumoniae</i> , <i>Proteus inconstans</i> , <i>Salmonella</i> Typhimurium, <i>Shigella sonnei</i> , <i>Pseudomonas fluorescens</i> , <i>P. aeruginosa</i>	Karpiński and Szkaradkiewicz, 2013; Grande Burgos et al., 2014
	Enterolysin A	<i>Ent. faecalis</i>	<i>Lb. sakei</i> , <i>Lb. brevis</i> , <i>Lb. curvatus</i> , <i>Lc. cremoris</i> , <i>Lb. lactis</i> , <i>Ped. pentosaceus</i> , <i>Ped. acidilactici</i> , <i>Ent. faecium</i> , <i>Ent. faecalis</i> , <i>L. innocua</i> , <i>L. ivanovii</i> , <i>Bacillus subtilis</i> , <i>B. cereus</i> , <i>S. carnosus</i> , <i>Propionibacterium jensenii</i>	Karpiński and Szkaradkiewicz, 2013
Bacteriocin-like inhibitory substance (BLIS)		<i>Ped. acidilactici</i> Kp10 <i>Leuc. mesenteroides</i> 406 <i>Lc. lactis</i> subsp. <i>lactis</i> CECT-4434	<i>L. monocytogenes</i> <i>L. monocytogenes</i> <i>Staphylococcus aureus</i>	Wong et al., 2017; Arakawa et al., 2016; Souza Vera et al., 2018
Antibiotic	Reutericyclin	<i>Lb. reuteri</i>	Gram-positive bacteria (<i>Lactobacillus</i> , <i>Bacillus</i> , <i>Enterococcus</i> , <i>Staphylococcus</i> , and <i>Listeria</i>)	Rattanachaiyonsopon and Phumkachorn, 2010; Singh, 2018
	Reuterin	<i>Lb. reuteri</i> DSM 20016	Gram-positive (<i>Clostridium</i> and <i>Staphylococcus</i>) and Gram-negative (<i>Escherichia</i> , <i>Salmonella</i> , <i>Shigella</i>) bacteria, against the yeast, <i>Saccharomyces cerevisiae</i> , and against the protozoan, <i>Trypanosoma cruzi</i>	Stevens et al., 2011
Organic acids	Lactic acid, Acetic acid	LAB	Broad spectrum: bacteria affected by pH	
Hydrogen peroxide		<i>Ped. acidilacti</i> <i>Leuc. mesenteroides</i> <i>Lb. brevis</i> <i>Lb. plantarum</i> <i>Lb. casei</i>	Broad spectrum: Catalase negative bacteria	Whittenbury, 1964
Others	Ethanol	<i>Bifidobacterium longum</i> <i>Ent. faecalis</i> <i>Lb. acidophilus</i> <i>Lb. fermentum</i> <i>Lb. plantarum</i> <i>Weissella confusa</i>	Broad spectrum: bacteria affected by membrane dissociations	Eshaghabe et al., 2016
	Diacetyl	<i>Lb. plantarum</i> <i>Lb. helveticus</i> <i>Lb. bulgaricus</i> <i>Ent. faecalis</i> <i>Leuc. mesenteroides</i>	<i>Listeria</i> , <i>Salmonella</i> , <i>Escherichia coli</i> , <i>Yersinia</i> , and <i>Aeromonas</i> .	Singh, 2018
	Carbon dioxide	Heterofermentative LAB	Broad spectrum: Aerobic bacteria	Singh, 2018

action depends on the concentrations and environmental factors such as pH and temperature (Surendran Nair et al., 2017). *Lc. lactis* and *Ent. faecium* species were reported to produce H₂O₂ with strong antimicrobial effects (Yang et al., 2012).

Reuterin, is a secondary metabolite associated with glycerol metabolism by *Lb. reuteri*. This potent inhibitory compound has a broad spectrum of activity exerted in a pH-independent manner. Reuterin is known to inhibit DNA replication and is resistant to proteolytic and lipolytic enzymes (Singh, 2018). In terms of spectrum of activity, reuterin was shown to

be active against *E. coli*, *Staphylococcus aureus*, and *Candida* spp. (Helal et al., 2016).

Competitive Exclusion

Competitive exclusion (CE) can occur after addition of any culture containing at least one non-pathogenic bacteria to the gastrointestinal tract of animals. This will decrease the number of pathogenic bacteria, through direct or indirect competition for nutrients and adhesion for sites in the gut (Callaway et al., 2008). These LAB-probiotics are able to form biofilms and communicate through Quorum Sensing (QS) upon producing and releasing of

autoinducers (Tannock et al., 2005). Pathogens are not able to adhere to the intestinal mucosa, which blocks the development of their population by the constant flow of digesta (Callaway et al., 2008; Yirga, 2015; Liao and Nyachoti, 2017). Some studies aimed at highlighting this mechanism are briefly described below. Carter et al. (2017) reported the protective effect exerted by the combination of 5×10^7 CFU/mL of *Lb. salivarius* 59 and *Ent. faecium* PXN33 by reducing *Salmonella* Enteritidis S1400 colonization in chicks. Penha Filho et al. (2015) reported the effect of 1×10^5 CFU of a *Lb.*-based probiotic suspension on reducing *Salmonella* colonization when this strain was provided to chicks from 1 to 7 days of age. Arruda et al. (2016) showed that a commercial probiotic of *Lactobacillus* spp. decreased prevalence of *Clostridium difficile* infections in pigs when administrated at a concentration of 7.5×10^9 CFU. Sha et al. (2016a) showed through feeding trial assays that 1×10^9 CFU/mL of *Lb. pentosus* HC-2 strongly inhibited the growth of *Vibrio parahaemolyticus* in the intestine of shrimp.

Modulation of the Host Immune System

Lactic acid bacteria have been widely described for their capabilities to enhance the animal immune system, by positively affecting the innate and adaptive immune response (Tellez et al., 2012; Tsai et al., 2012; Ashraf and Shah, 2014) by helping protect from pathogen disorders (Ashraf and Shah, 2014). The innate immune system induces immediate defense against infection, but also activates a long-lasting adaptive immunity. Components of the innate system recognize the molecular patterns associated with pathogens through pattern recognition receptors (PRRs). The recognition of these patterns by PRR leads to the induction of inflammatory responses and innate host defenses. In addition, the detection of microbes by PRR expressed in antigen-presenting cells, particularly dendritic cells (DC), leads to the activation of adaptive immune responses, by means of T and B cells (Iwasaki and Medzhitov, 2015). Various immune cells types, including granulocytes, macrophages, DCs, and T and B lymphocytes, are involved with inflammatory responses which are mediated by several cytokines like TNF α , IL-1 β , IL-6, IL-8, and IL-15 interleukins. The anti-inflammatory/suppressive responses are mediated for their part by IL-10, IL-12, and TGF β (Hardy et al., 2013). LAB have different immunomodulatory properties associated with their capabilities to induce cytokine production, impact immunomodulation by innate or adaptive immune responses (Kiczorowska et al., 2017a). Those immunomodulation abilities are considered as a crucial criterion for probiotic assessment, through various mechanisms (Wells, 2011; Hardy et al., 2013).

Enhancing Innate Immune Response

The primary mechanism of innate immunity stands as physical and chemical barriers such as the intestinal epithelial cells (IECs), which prevent pathogens spreading and subsequent infections (Riera Romo et al., 2016). Depending on the presence of changing mucus layer, probiotics will be able to interact with IECs and DCs (Lebeer et al., 2010). IECs are the first defense barriers (Dowarah et al., 2017) and they are supposed to be the first and most important target cells for probiotic action (Lebeer et al.,

2008). Probiotic strains have been shown to have beneficial effects related to the nutritional function of the intestinal epithelium (Lebeer et al., 2008). They also improve intestinal barrier function by stimulating: (i) the production of antimicrobial mucus and peptides such as defensins (Yang et al., 1999; Schlee et al., 2008), (ii) increased immune responses, (iii) improved expression and/or localization of tight junction proteins, (iv) preventing apoptosis of epithelial cells, and (v) induction of cytoprotective molecules (Ewaschuk et al., 2008; Anderson et al., 2010; Mathias et al., 2010; Madsen, 2012). In chicks, *Lb. plantarum* LTC-113 (1×10^9 CFU) can up-regulate cellular junctions to impede pathogens colonization as *Salmonella* (Wang et al., 2018).

In addition, other cellular components of the innate immune system such as monocytes and macrophages, prevent the invasion of pathogens by secreting pro-inflammatory cytokines and cytotoxic molecules. Natural Killer (NK) cells produce cytokines such as interferon (IFN- γ) and various interleukins (IL): IL-10, IL-3, etc. (Vivier et al., 2011). In weaning pigs, administration of *Lb. brevis* ZLB004 (2×10^9 CFU/kg of feed) increased the level of IFN- γ (Liu et al., 2015). Lactobacilli strains as *Lb. fermentum*, *Lb. salivarius*, *Lb. crispatus*, and *Lb. gasseri* have been reported to modulate positively the secretion level of the pro and anti-inflammatory interleukins IL-6, IL-8, and IL-10 in order to regulate the inflammation and restore the physiological equilibrium of food-producing animals (Pérez-Cano et al., 2010; Luongo et al., 2013; Sun et al., 2013; Rizzo et al., 2015). IL-8 is a pro-inflammatory cytokine which directly recruits macrophages and leukocytes into inflammatory regions by chemosensing (Riera Romo et al., 2016). A *Lb. acidophilus* strain stimulated anti-inflammatory properties in enterotoxigenic *E. coli* (ETEC) infected piglets when administered at 1×10^8 CFU in the feed. This strain was also able to down-regulate pro-inflammatory cytokines IL-8 and TNF- α *in vivo* based on animals experiments (Li et al., 2016). The same trend in IL-8 levels was also observed in *Aeromonas hydrophila* infected carp (*Cyprinus carpio* Huanghe var.) when fed with 1×10^7 CFU g/L *Lb. delbrueckii* strain (Zhang et al., 2017). Conversely the combination at 1×10^7 CFU each/g feed pellet of *Lc. lactis* BFE920 and *Lb. plantarum* FGL0001 induced IL-8 and IL-6 increase in *Streptococcus iniae*-infected Japanese flounder fish (Beck et al., 2015). Walter (2008) and Brisbin et al. (2011) support that discrepancies in the immunomodulation effects were ascribed to the *Lactobacillus* strains selected, their dosage, and also to the animal conditions. Zhang et al. (2017) established that *Lb. delbrueckii* at 1×10^7 CFU g/L increased levels of anti-inflammatory cytokines IL-10 and TGF- β in the intestine and enhanced immunity of *A. hydrophila*-infected *Cyprinus carpio* Huanghe var.

Enhancing Adaptive Immune Response

The adaptive immune response depends on B- and T-lymphocytes, which induce antigen-specific response. Association of *Lb. plantarum* (1×10^7 CFU/kg of feed) and *Clostridium butyricum* (1×10^6 CFU/kg of feed) on production performance and immune function in broilers revealed the increase of IgG and IgA levels in chickens fed with these beneficial probiotics (Han et al., 2018). In direct line, *Lb. plantarum* B2984 was shown to stimulate immunoglobulin

production (IgM and IgA) against *Salmonella* infection in pigs during orally challenged animal trials (Naqid et al., 2015). Feeding piglets with a strain of *Lb. rhamnosus* ATCC 7469, at a concentration of 10^9 CFU/mL, prevented acute infectious diarrhea by stimulating the adaptive immune system subsequently to produce an increase in the concentration of lamina propria CD3⁺ CD4⁺ CD8⁻ T cells (Zhu et al., 2014). In chicken, feed supplementation with 1×10^9 CFU/kg of *Lb. acidophilus* LA5 increased the production of CD4⁺, CD8⁺, and TCR1⁺ T cell in GI tract but also in peripheral blood (Asgari et al., 2016). The administration of 10^{10} CFU/mL *Lactobacillus* spp. could efficiently activate the immunity of mucosa in chickens by increasing the levels of IgA and IgG (Rocha et al., 2012). In young calves, administration of 1.85×10^7 CFU/L of *Lactobacillus* species has been shown to improve weight gain and immunocompetence (Al-Saiady, 2010). In summary, LAB were reported to improve the host resistance and production performance as delineated in Section “Production Performance,” by enhancing the immune response (Kiczorowska et al., 2017a).

Improvement of Nutrient Digestibility and Feed Conversion

Feed digestibility reflects the amount of absorbed feed and the nutrient's availability used for the animal growth and reproduction (ILCA, 1990). It is possible to measure the apparent or real digestibility by comparing nutrients contained in the feces from nutrients contained in the dietary intake, or adding external markers (such as titanium dioxide, chromium oxide and rare-earth elements) into feed (ILCA, 1990; Safwat et al., 2015). The improvement of this nutrient digestibility is measured by an indirect method: feed conversion ratio, a correlation between weight of feed administered over the lifetime of an animal and weight gained, which is a valuable indicator of feeding systems efficiency (Wenk et al., 1980; Fry et al., 2018). LAB-probiotics improved nutrient digestibility because of their highly fermentative activities. Indeed, they can enhance the whole digestive process, the metabolic utilization of nutrients, and improve the feed efficiency by producing digestive enzymes (e.g., amylases, chitinases, lipases, phytases, proteases) or by just generating volatile fatty acids and B-vitamins: riboflavin, biotin, B12 vitamin (Russo et al., 2014; Liao and Nyachoti, 2017; Sharifuzzaman and Austin, 2017). In addition, LAB-probiotics can indirectly modify the gut microsystem (FAO, 2016) by helping in the assimilation of nutrients through activation of the host immune cells and increasing the number of antibodies leading to animal welfare improvement (Forte et al., 2016).

Reduction of Toxin Bioavailability

Protective effects of LAB-probiotics can result in inhibition of toxin expression in pathogens (Liao and Nyachoti, 2017). It was also reported that LAB can constitute natural barriers against mycotoxins considered as potentially harmful compounds for animals (Tsai et al., 2012; Peng et al., 2018). Several investigators reported that *Lb. plantarum*, *Lb. acidophilus*, *Lb. paracasei*, and *Ent. faecium* could mitigate the effect of aflatoxins for improving

human and animal health (Gratz et al., 2007; Ahlberg et al., 2015; Abbès et al., 2016; Damayanti et al., 2017; Li et al., 2017).

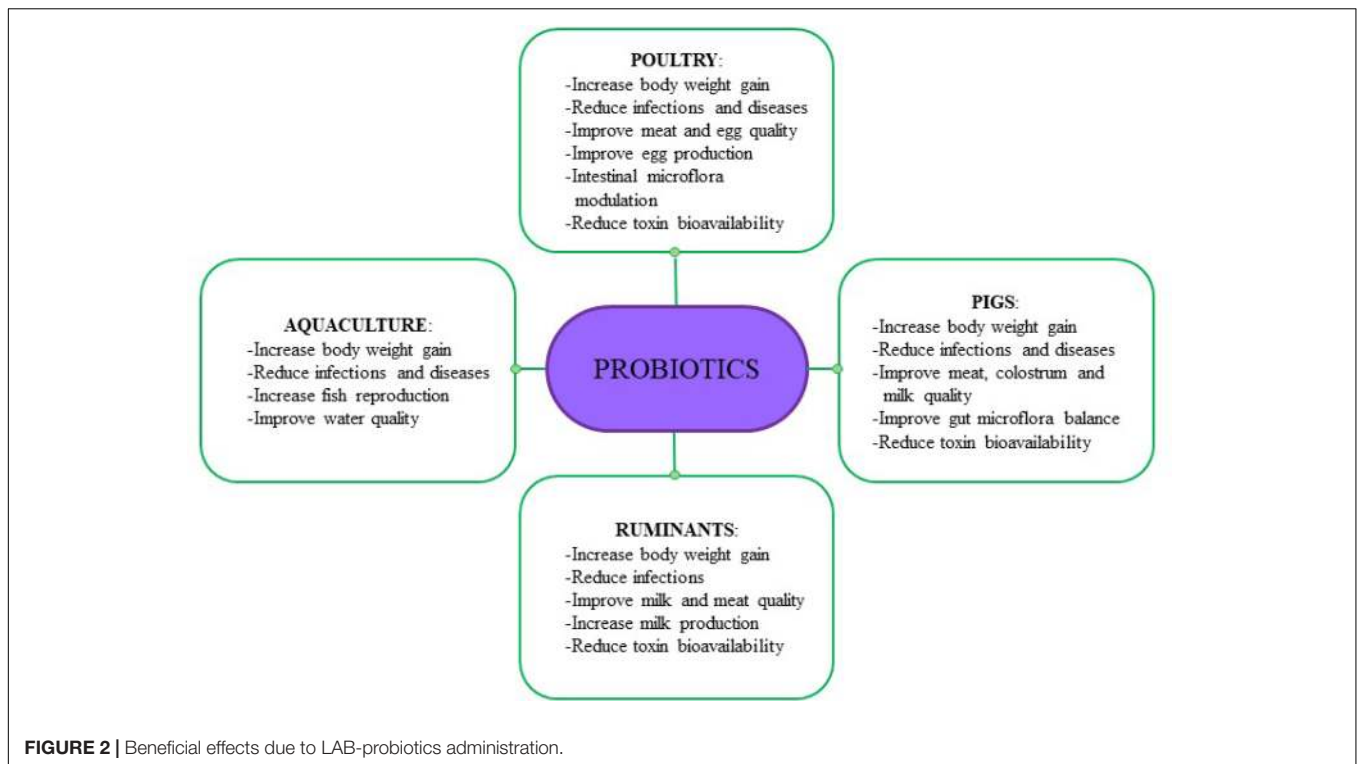
Lactic acid bacteria act as a biological barrier in the intestinal tract, decreasing availability of ingested mycotoxins and neutralizing their adverse effects. Detoxifying capabilities of LAB are associated with their capacities to bind and sequester mycotoxins, boosting their excretion by digestive system in the feces (Zoghi et al., 2014; Damayanti et al., 2017; Li et al., 2017). Mycotoxins can bind to viable and non-viable bacterial surface by adhesion to their cell wall components (Damayanti et al., 2017; Li et al., 2017), and aflatoxin B1 (AFB1), for example, was bound to LAB by non-covalent interactions (Haskard et al., 2001). Tests aimed at controlling mycotoxins have been carried out with *Lb. casei* DSM20011, *Lb. casei* Shirota (Liew et al., 2018), *Lb. rhamnosus* strains LGG and LC 705 (El-Nezami et al., 1998, 2002; Nybom et al., 2007), *Lb. acidophilus* 24 (Pizzolitto et al., 2012), and *Lb. plantarum* *Lb. brevis*, *Lb. sanfranciscensis*, from LOCK collection (Piotrowska, 2014). Piotrowska (2014) suggested that the binding to mycotoxins, particularly to ochratoxin was ascribed to hydrophobic properties of the cell wall, and also by electron donor-acceptor and Lewis acid-base interactions. LAB have additional anti-mycotoxin mechanisms based on a study performed on mice wherein the diet was supplemented with *Lb. plantarum* C88 (1×10^{10} CFU/mL). This supplementation weakened oxidative stress induced by aflatoxin AFB1. Likewise, this strain decreased lipid peroxidation in serum and the liver due to hepatic damage caused by AFB1 toxicity (Li et al., 2017). LAB produce exopolysaccharides, which are important compounds capable of inhibiting bacterial toxins as reported by Ruas-Madiedo et al. (2010) for the interactions between *Lb. rhamnosus* GG against *Bacillus cereus*. Further mechanisms including pH decrease and blockage of QS have been reported during co-existence of *C. perfringens* type A and LAB particularly *Lb. acidophilus* CGMCC 11878 and *Lb. fermentum* CGMCC12029 (Guo et al., 2017).

BENEFITS FOR ANIMALS AND FOOD CHAIN

In addition to the above listed positive effects attributed to LAB potentially utilizable as probiotics, we noted further beneficial effects on the health of various livestock animals and quality of animal products. These effects are animal-dependent and consist of enhancing body weight gain, improve gut microbial balance, improve reproductive performance, and increase overall productivity (Figure 2).

Disease Management

Different investigators have reported the potential effect of LAB to decrease the risk of infections and intestinal disorders associated with pathogens such as *Salmonella* spp., *E. coli*, *Campylobacter*, or *Clostridium* spp. LAB-probiotics were used preventively and therapeutically to treat infections by these pathogens (Tellez et al., 2012; Layton et al., 2013; O'Bryan et al., 2014; Gómez et al., 2016; Park et al., 2016).



Poultry

Many studies were dedicated to LAB used in poultry. Indeed, Wang et al. (2018) inoculated hatched chicks with 1×10^9 CFU *Lb. plantarum* LTC-113 strain, which provided anti-*Salmonella* Typhimurium protection by limiting the gut colonization and stabilizing the expression of tight junction genes in intestinal epithelial cells among treated chickens making them more resistant to the infection. As previously mentioned, CE is an effective mechanism protecting newly hatched birds from enteropathogen colonization in poultry (Kabir, 2009). Similarly, Olnood et al. (2015) showed that 5×10^8 CFU of *Lb. johnsonii* reduced numbers of *Salmonella enterica* serovar Sofia and *C. perfringens* in challenged 1-day-old Cobb broilers (Olnood et al., 2015). Another study reported that administration of 1×10^9 CFU (50:50) *Lb. salivarius* 59 and *Ent. faecium* PXN33 in combination decreased the levels of colonization in birds by *Salmonella* (Carter et al., 2017). On the other hand, strains of *C. perfringens* are responsible for production of the necrotic enteritis toxins and/or enzymes. Colonization of poultry mucosa by *C. perfringens* occurs during the early life of the birds (M'Sadeq et al., 2015). Several *Lactobacillus* (*Lb. acidophilus*, *Lb. fermentum*, *Lb. plantarum*, *Lb. reuteri*, and *Lb. salivarius*) and *Enterococcus* strains (*Ent. faecium* and *Ent. faecalis*) can inhibit *C. perfringens* *in vitro* (Caly et al., 2015). The administration of certain LAB strains do not generate systematically benefits for poultry, as underpinned for *Lb. plantarum* PCS 20 against *Campylobacter jejuni* (Santini et al., 2010), or *Lb. johnsonii* FI9785 against *Salmonella* Enteritidis (La Ragione et al., 2004). Therefore, the screening has to be performed in defined conditions and the results are strictly strain-dependent.

Lactic acid bacteria-bacteriocins improve growth performance of *C. perfringens*-challenged chickens allowing weight to recover at similar levels of healthy birds. For instance, this effect was observed when chickens challenged with *C. perfringens* were treated with pediocin A from *Ped. pentosaceus* (Grilli et al., 2009), or when *E. coli* infected chickens were receiving plantaricin from *Lb. plantarum* F1 (Ben Lagha et al., 2017). Notably, anti-*C. perfringens* divercin bacteriocin, produced by *Carnobacterium divergens* AS7 improved growth performance and welfare in treated chickens (Józefiak et al., 2012).

Swine

Numerous benefits have been described in pig upon LAB administration specifically with lactobacilli (Yang F. et al., 2015; Valeriano et al., 2016; Dowarah et al., 2017). For pigs, the highest death loss is due to diarrhea caused by ETEC and *Salmonella* (Liao and Nyachoti, 2017). Feed supplementation with various species of *Lactobacillus* including *Lb. johnsonii*, *Lb. mucosae*, and *Lb. plantarum* improved the gut microbial profile and microbial metabolites production, leading to gut health improvement, and reduced pathogens colonization of intestinal mucosa (Dowarah et al., 2017). Subsequently, these investigators showed that weaned piglets treated with 2×10^9 CFU/g of *Ped. acidilactici* FT28 rather than *Lb. acidophilus* NCDC-15 resulted in the reduction of diarrhea due to dietary and environmental changes (Dowarah et al., 2018). Decrease of ETEC number was observed when a fermented food from reuteran-producer *Lb. reuteri* LTH5794 at a concentration of 1×10^7 CFU/g was administered to weaning pigs. The studied strain was able to produce exopolysaccharides such as reuteran or levan

impeding ETEC adhesion to the mucosa (Yang Y. et al., 2015). However, a study from Andersen et al. (2017) showed that no protective effect was observed in newly born piglets treated with commercially available probiotic *Lb. paracasei* F19 strain (2.6×10^8 CFU/kg) and a newly characterized *Ped. pentosaceus* (1.3×10^{10} CFU/kg) developed to inhibit *E. coli* F18-inducing diarrhea (Andersen et al., 2017).

Streptococcus suis is involved in a wide range of infections in pigs such as meningitis, arthritis, endocarditis, pneumonia, and septicemia (Ben Lagha et al., 2017). This bacterium has been reported to be sensitive to nisin, a well-known and the only bacteriocin marketed now (Lebel et al., 2013).

Ruminants

Administration of LAB can prevent development of ruminal acidosis by creating optimal conditions for lactic acid consuming bacteria such as *Megasphaera elsdenii* or *Propionibacterium* spp. (Chaucheyras-Durand and Durand, 2010). Addition of *Lb. acidophilus*, *Lb. salivarius*, and *Lb. plantarum* at concentrations of 10^7 – 10^8 CFU/g, reduced the incidence of diarrhea in young calves (Signorini et al., 2012). LAB species including *Lb. paracasei* and *Lb. plantarum*, and those isolated from honey like *Lb. kunkeei*, *Lb. apinorum*, *Lb. mellis*, *Lb. mellifer*, *Lb. apis* had *in vitro* activities against mastitis pathogens such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus uberis*, or *E. coli* (Piccart et al., 2016; Diepers et al., 2017). LAB-probiotics were also successfully used to relieve symptoms of diseases such as coccidiosis, an important parasitic disease of young ruminant livestock, caused by *Eimeria*. These LAB-probiotics minimized the impact of this disease by reducing the risk of dissemination of this parasite (Giannenas et al., 2012). On the other hand, Cao et al. (2007) reported on the effectiveness of intra-mammary infusion of nisin for treating mastitis caused by *Staphylococcus aureus* in dairy cows.

Aquaculture

In aquaculture, *Lb.* strains such as *Lb. murinus* or *Lb. pentosus* displayed antagonism against *V. harveyi* and *V. parahaemolyticus*. Other potential LAB-probiotics such as *Ent. faecium* NRW-2 (1×10^7 CFU/g of feed) were reportedly active against *Vibrio* spp. strains through their highly elevated capacities of adhesion and competition for nutrients. These bacteria were reported to decrease the presence of *Vibrio* in shrimp (Sha et al., 2016b). Fish fed with *Lb. delbrueckii* became more resilient to *Aeromonas* infections. It was suggested that 1×10^6 CFU/g of *Lb. delbrueckii* action was linked to their stimulation properties of the shrimp larval gut immune system (Zhang et al., 2017). Araújo et al. (2016) isolated several strains of *Ped. acidilactici* from rainbow trout (*Oncorhynchus mykiss*) feed and larvae. Some of these strains have wide action spectra and showed antagonistic activities against several fish pathogens including *Lc. garvieae*, *Streptococcus iniae*, *Carnobacterium maltaromaticum*, and *A. salmonicida*.

Nisin Z-producing *Lc. lactis* WFLU12 provided protection against infections caused by *Streptococcus parauberis* in olive flounder fish (Nguyen et al., 2017). While *Lb. pentosus* 39 produces a bacteriocin active against the fish pathogen

A. hydrophila, suggesting this LAB could be used as a natural biopreservative agent (Anacarso et al., 2014).

LAB-Probiotics in Treatment of Viral Infections

Lactic acid bacteria-probiotics were described as potent organisms to treat viral infections (Al kassaa et al., 2014; Arena et al., 2018a,b). Leyva-Madrigal et al. (2011) reported the capabilities of *Ped. pentosaceus* and *Staphylococcus haemolyticus* (1×10^6 CFU/g feed) to treat white spot syndrome virus (WSSV) in white leg prawns (*Litopenaeus vannamei*). A modified *Lb. plantarum* conferred resistance to yellow head virus in shrimps (Thammasorn et al., 2017). In piglets, *Lb. plantarum* N4 was shown to be active against transmissible Gastroenteritis Virus when provided in a preventive manner (Yang Y. et al., 2017) and *Lb. plantarum* 25F, reduced viral infectivity of Porcine Epidemic Diarrhea Virus (PEDV) (Sirichokchatchawan et al., 2018). The effects of *Lb. casei* CMPUJ 415 and *B. adolescentis* DSM 20083 on rotavirus has been demonstrated by a reduction on the production of a viral enterotoxin protein (NSP4) (Olaya Galán et al., 2016). Roselli et al. (2017) listed numerous examples of LAB-probiotics with antiviral activities such as *Lb. casei* MEP221106 or MEP221114, *Lb. rhamnosus* CRL1505. Nevertheless, Sachsenrödder et al. (2014) hypothesized the administration of probiotics as *Ent. faecium* NCIMB10415 do not have an effect on the virus composition present in the pigs' gut. For this reason, several studies focus on producing recombinant LAB for vaccination as it is the case of recombinant *Lb. casei* ATCC 393 against PEDV (Wang X. et al., 2017) or *Lb. plantarum* NC8 against H9N2 avian influenza virus (Yang W. et al., 2017) boosting the immune system presenting antigens.

Production Performance

Lactobacilli produce lactic acid and proteolytic enzymes, which enhance nutrient digestion in the GIT and feed supplementation with *Lactobacillus* strains can induce weight gain in livestock animals (Angelakis, 2017), in a strain strain-specific dependent manner (Drissi et al., 2017). For instance, *Lb. delbrueckii*, *Lb. acidophilus*, *Lb. casei*, *Lb. agilis*, *Lb. salivarius*, *Lb. fermentum*, and *Lb. ingluviei* were described as weight enhancers (Drissi et al., 2017). The last two species were associated with a substantial weight gain effect in ducks and chicks (Million et al., 2012; Drissi et al., 2017). LAB-probiotics improved the feed conversion efficiency by modifying the intestinal microbiota, limiting the growth of pathogens, promoting non-pathogenic bacteria, and enhancing nutrients use and digestion (Yang Y. et al., 2015). Some LAB-probiotics provided similar benefits as antibiotics in terms of weight gain, feed intake, and feed efficiency, as in the case of *Lb. plantarum* P-8 (2×10^6 CFU/mL) (Wang L. et al., 2015).

Baldwin et al. (2018) showed that a LAB-probiotics consortium containing *Lb. ingluviei*, *Lb. agilis*, and *Lb. reuteri* strains improved weight gain when they were inoculated early at the hatchery, modifying intestinal microbiota and decreasing the pathogenic taxa numbers in chicks (Baldwin et al., 2018). On the other hand, a feed supplementation with 1×10^6 CFU/g feed *Lb. johnsonii* BS15 in broilers enhanced digestive abilities, promoting growth performance, and lowering body fat content (Wang H. et al., 2017).

Another study carried out on pigs fed with *Lb. plantarum* ATCC 4336, *Lb. fermentum* DSM 20016, and *Ent. faecium* ATCC 19434 at concentrations of 10^{11} CFU/kg resulted in a weight gain due to the ability of these strains, mainly *Lb.* ones, to produce enzymes enhancing feed digestion, besides lactic acid production (Veizaj-Delia et al., 2010). Lan et al. (2016) showed that a strain of *Lb. acidophilus* increased digestibility in weaning piglets of 14 days-old and improved their growth performance.

However, supplementation of feed with LAB-probiotics did not induce any effect on the animal weight in all cases. Wang et al. (2012) showed that *Lactobacillus* or *Pediococcus* fermented maize feed can modify the microbiota but did not affect pig's production performances. This variability is related to a heterogeneity between trials. Nonetheless, for pigs, environmental factors such as pen, litter. . . the sow and piglet are closely related according to Zimmermann et al. (2016).

Concerning ruminants, calves fed with a mixture of 1×10^9 CFU of *Lb. casei* DSPV 318T, *Lb. salivarius* DSPV 315T, and *Ped. acidilactici* DSPV 006T exhibited higher daily weight gain, total feed intake, and starter diet intake (Frizzo et al., 2010). Furthermore, calves fed with 6.8×10^8 CFU of *Lb. acidophilus* and *Lb. plantarum* fortified milk (Gupta et al., 2015) or 1×10^{10} CFU of *Lb. plantarum* DSPV 354T (Soto et al., 2014) consumed more milk, in addition to body weight gain and growth performance. A similar effect has been reported for post weaning lambs. When they were fed with *Pediococci* (1×10^6 CFU/g) an increased intake of dry matter feed and better growth performances were shown (Saleem et al., 2017).

In the aquaculture sector, Zheng et al. (2017) showed a size improvement in white shrimps (*Litopenaeus vannamei*) when their diet was supplemented with 1×10^9 CFU/mL of *Lb. plantarum*. Furthermore, *Lb. delbrueckii* also enhanced the production performance of *Cyprinus carpio* Huanghe var., when added at a concentration of 10^{6-7} CFU/g in feed (Zhang et al., 2017). In abalones (*Haliotis discus hannai* Ino) feed intake and growth increases were observed when *Lb. pentosus* was supplied at concentration of 10^{3-5} CFU/g (Gao et al., 2018).

Improvement of the Quality of Livestock Products

There are several examples of *Lactobacillus* spp. as probiotic improving meat quality in chickens, including tenderness, appearance, texture, and juiciness among other parameters (Park et al., 2016). It is known that addition of LAB to broiler's feed reduced the cholesterol content of meat (Popova, 2017). Administration of *Lb. salivarius* SMXD51, at a concentration of 10^7 CFU/mL, can partially prevent the impact of *Campylobacter* in chickens due to ability of this strain to produce an anti-*Campylobacter* bacteriocin with strong activity against four tested *Campylobacter jejuni* strains (Messouadi et al., 2012; Saint-Cyr et al., 2017). In addition, the probiotics can improve the production and quality of eggs. Thus, the supplementation of *Ped. acidilactici* MA 18/5M (10^8 CFU/kg feed) to the chicken feed revealed an effect on the eggs' quality by increasing their weight, eggshell thickness and decreasing cholesterol on the egg yolk (Mikulski et al., 2012).

In pigs, *Ped. acidilactici* was shown to improve meat quality (Dowarah et al., 2018). Kiczorowska et al. (2017b) compared four groups of cows and demonstrated that cows under an intensive production system receiving a probiotic treatment [*Lb. casei*, *Lb. plantarum* (5×10^6 CFU/mL)], and *S. cerevisiae* (5×10^3 CFU/mL) produced higher milk quality with higher protein content and fat that contained a higher amount of unsaturated fatty acids conversely to cows in intensive production system. It was shown that supplementation of feed with 4×10^9 CFU *Lb. acidophilus* NP51 and *Propionibacterium freudenreichii* NP24 increased milk production and improved apparent digestibility of dietary nutrient (Boyd et al., 2011).

Fish Reproduction

Probiotics are associated with fish reproduction by enhancing their fecundity rate (Banerjee and Ray, 2017; Carnevali et al., 2017). The direct effects are reportedly due to increasing expression of genes encoding several hormones and enhancing gonadal growth, fecundity, and embryo survival (Gioacchini et al., 2010, 2012). Probiotics also enhance follicles maturation and development, and embryo quality. For example, several strains of *Lb. rhamnosus* can improve the fecundity in zebrafish (*Danio rerio*) model (Hai, 2015; Banerjee and Ray, 2017).

Water Quality

The quality of water on the fish farms is clearly an important factor to avoid the spread of diseases. The parameters to measure this quality are based on the pH of the water and the amounts of CO₂, ammonia, nitrate, and phosphorus found in it. *Lb. plantarum* and *Lb. casei* reportedly maintained or improved water quality during fish production (Banerjee and Ray, 2017).

A major concern is related to water pollution with heavy metals provoking fish diseases. This can be avoided by the use of some LAB-probiotics such as *Lb. plantarum* CCFM639, which restored the integrity of damaged tight junction proteins and maintained intestinal permeability leading to decrease of aluminum-induced gut injuries (Yu et al., 2016). Yu et al. (2017) also reported reduction of aluminum accumulation in tilapia tissues and lower death rate upon incorporation of 10^8 CFU/g *Lb. plantarum* to the feed.

SYNBIOTICS

Synbiotics are defined as combination of probiotics and prebiotics that beneficially affect the host by improving survival and settlement of live microbial dietary supplements in the gastrointestinal tract. This happens by selectively stimulating the growth and/or by activating the metabolism of one or a limited number of health-promoting bacteria, and thus improving host welfare (Gibson et al., 2004). A prebiotic that confers gastrointestinal health benefits could support the growth of a probiotic which has activity against a potential pathogen (Allen et al., 2013).

Guerra-Ordaz et al. (2014) reported a synergistic effect when *Lb. plantarum* (2×10^{10} CFU) and lactulose (10 g/kg feed) were concomitantly used to treat colibacillosis in pigs, reducing

diarrhea and improving the average daily weight gain. Yasuda et al. (2007) showed that *Lb. casei* subsp. *casei* (1×10^7 CFU/kg feed) and dextran (5%, w/w) in combination improved the milk yield and milk components in cows, and they hypothesize the symbiotic association had a prophylactic effect inhibiting mastitis development. Data from Naqid et al. (2015) suggested caution on the use of synbiotics because intra-interaction can occur within the combination and reduce the expected activity. Mookiah et al. (2014) showed same body weight increase in chickens treated with multi-strain *Lactobacillus* probiotic at 1×10^9 CFU/g or prebiotic (isomalto-oligosaccharides; 5 or 10 g/kg of feed) separately or their association as synbiotic. Szczurek et al. (2018) showed that synbiotic composed of whey lactose and *Lb. agilis* did not show any advantage when compared to each compound alone.

In fish, the administration of *Ent. faecalis* and mannan-oligosaccharides enhanced growth, immune response, and survival of Rainbow trout (*Oncorhynchus mykiss*) to the infection of *A. salmonicida* (Rodríguez-Estrada et al., 2013). In Tilapia, there is an effect against *A. hydrophila* when the combination of 1×10^8 CFU *Lb. brevis* JCM 1170 or *Lb. plantarum* JCM 1149 and fructo-oligosaccharides (1 g/kg feed) were added to the feed, but the same combination did not improve animal growth or feed conversion (Liu et al., 2017).

CONCLUSION AND FUTURE DESIGN OF LAB-PROBIOTICS

This review highlighted numerous advantages from LAB-probiotics used in animal farming and production. After the indiscriminate use of antibiotics in livestock to increase the animal performance, resistance to these molecules has dramatically escalated. To help reduce this worldwide concern, the use of LAB-probiotics stands as an efficient and promising alternative. Different benefits have been observed in animals fed with various LAB-probiotics. As supported by a variety of studies, LAB-probiotics can control the development of bacterial diseases, increase weight gain in healthy and affected animals, stimulate the quality of the (by-) products of this industry or even improve aquaculture water quality. LAB-probiotics can control bacterial infections by excretion of inhibitory compounds, or by other mechanisms including competitive exclusion, decreasing bioavailability of toxins, strengthening

intestinal barrier or positively stimulating the immune system. Their actions are exerted in strain and host-specific manners. Finally, there are a variety of synergistic effects when combining LAB with other probiotic species, prebiotics, or enzymes. In terms of future design, recombinant LAB-probiotics may offer additional advantages. Pioneering studies have already opened this avenue. Indeed, it has been reported that *Lb. plantarum* NC8 can produce a recombinant dendritic cell-targeting peptide with activity against H9N2 avian influenza virus in chickens (Shi et al., 2016; Wang X. et al., 2017). Also, this recombinant dendritic cell-targeting peptide can be used synergistically to enhance vaccine humoral immune responses and to reduce viral replication in chicken lungs (Shi et al., 2016).

ETHICS STATEMENT

All authors of this paper have read and approved the final version submitted. The contents of this manuscript have not been copyrighted or published previously. No procedures performed in these studies have been conducted in human participants and/or animals.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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