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Review

Probiotics as Antibiotic Alternatives for Human and Animal Applications

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Abstract: Probiotics are live microorganisms recognized as natural candidates to substitute antibiotic substances, usually used to treat bacterial infections responsible for numerous human and animal diseases. Antibiotics are mostly prescribed for treating infections caused by bacteria. However, their excessive and inappropriate use has resulted in the increase of bacterial antimicrobial resistance (AMR) and host microbiota imbalance or dysbiosis phenomena. Even though antibiotics are the most well-known lifesaving substances, the AMR within the bacterial community has become a growing threat to global health, with the potential to cause millions of deaths each year in the future. Faced with these worldwide issues, it is high time to discover and develop antibiotic alternatives. There exists some evidence of probiotic roles in antagonizing pathogens, modulating immune systems, and maintaining general host health by restoring the gut microbiota balance. The multi-antimicrobial action mechanisms of such beneficial living microorganisms are one approach to practicing the "prevention is better than cure" concept to avoid antibiotics. The current review proposes a comprehensive description of antibiotic-related AMR issues and the potential of probiotics as antibiotic alternatives, while discussing pros and cons, as well as some evidence of beneficial uses of probiotics for human and animal health protection through recent results of experimental models and clinical trials.

Keywords: antimicrobial resistance; immunomodulation; gut microbiota; bacteriocins; human health; animal health

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1. Introduction

The use of antibiotics has a long history of applications in bacterial infection treatment, owing to their ability to inhibit the growth of or kill living microorganisms [1]. However, the current dissemination of antibiotic resistance genes into pathogenic bacteria has raised concern about the effectiveness of today's antibiotic repertoire in the near future. Antimicrobial and antibiotic resistance problems have spread worldwide and have prompted the World Health Organization to classify such issues as an unpredictable global health threat with broad, multiple-sector impacts to human, animal, food, and environment safety [2]. Antibiotic-resistant pathogen-related deaths are projected to rise to 10 million per year worldwide by the year 2050 [3]. Therefore, alternative approaches to target bacterial pathogens have been advocated, such as directly treating diseases with therapeutic agents or indirectly modulating the gut microbial community with beneficial live microorganisms, the so-called probiotics [4]. In fact, probiotics play a key role in the microbiota equilibrium by re-populating, for instance, a gut in dysbiosis [5].

The mammalian gut microbiota confers health-promoting benefits to the host by modulating the immune system, by increasing the efficiency of nutrient utilization, and by eliminating the presence of pathogens [6]. An overall balance in the proportion of gut

microbiota is essential in maintaining the healthy condition of the host [7]. The intestinal microbiome is unique in each individual and may be affected by genetic and environmental factors. Inappropriate and systematic administration of antibiotics is one of the environmental factors that cause alteration of gut microbiota (dysbiosis), leading to a deficiency of beneficial microorganisms in favor of potentially harmful microorganisms, as well as lower microbial diversity [8].

Probiotics are well-known as "good microorganisms" as opposed to "bad or harmful microbes" like pathogens. The term probiotic comes from the Latin "pro" and Greek "bios", literally meaning "for life", whereas antibiotic signifies "against life". The most common probiotic definition is a live microorganism with beneficial effects when provided in appropriate conditions to a host. [9]. By possessing antagonistic properties, probiotics have been found to hinder the growth of gut pathogens through (i) the production of bioactive metabolites such as bacteriocins, hydrogen peroxide, organic acids, antioxidants, and antimicrobial peptides [10,11]; (ii) competition for nutrients and attachment sites [12]; and (iii) the modulation of immune system functions [13]. The first antimicrobial activity mechanism of probiotics is comparable to the direct antibiotic molecular reactivity against pathogens, whereas the second and third ones are inherent to probiotic cells, owing to their adhesion and colonization capacities, and indirect mechanisms through immune cells, respectively. By developing multi-antimicrobial mechanisms, probiotics induce low risks of resistance to pathogens, aside from transferring resistance genes which are normally verified before any microorganisms are recognized as probiotics. Some experimental studies and clinical trials on humans and animals have been reported in the literature, indicating some evidence of probiotic applications as alternatives of antibiotics to inhibit or/and destroy pathogens responsible for various diseases [14,15].

This review proposes a comprehensive description of antibiotic-related antimicrobial resistance issues, states the potential of probiotics as antibiotic alternatives while discussing pros and cons of their uses, and illustrates with recent examples some evidence of probiotic applications instead of antibiotics in human and animal health protection.

2. Antibiotics: Antimicrobial Resistance Causes and Potential Alternatives

2.1. Basic Concept of Antibiotics

Etymologically, the notion of antibiotics comes from "antibiosis", which describes antagonistic effects among microorganisms [16]. The term "antibiotics" refers to naturally derived substances that inhibit or kill bacteria [17], whereas "antimicrobials" emerged with the development of natural, semi-synthetic and synthetic substances capable of inhibiting the proliferation of bacteria, viruses, fungi, and parasites [1]. According to Smith et al. (1998), antibiotics are low-molecular-weight substances produced by live microorganisms and plants, capable of selectively killing or hindering the growth of other organisms at low concentrations. These include synthetic organic compounds with identical antimicrobial activities [18].

Antibiotics can be classified according to their molecular structures, action mode, activity spectrum, origins, or administration route [17]. Most antibiotics are produced by filamentous actinomycetes (*Streptomyces* spp.). Other bacteria (*Bacillus* and *Pseudomonas*) and fungi (*Penicillium*) also synthesize antibiotic molecules [19]. A list of the major classes of antibiotics is provided in Table 1.

Table 1. Main classes of antibiotics and their sources.

Antibiotics	Example	Source	Reference
Aminoglycosides	Streptomycin	*Streptomyces griseus*	[20]
B-Lactams	Penicillin	*Penicillium griseofulvum*	[21]
Glycopeptides	Vancomycin	*Amycolatopsis orientalis*	[22]
Lipopetides	Daptomycin	*Streptomyces roseosporus*	[23]
Macrolides	Erythromycin	*Streptomyces erythreus*	[24]

Table 1. *Cont.*

Antibiotics	Example	Source	Reference
Oxazolidinones	Linezolid	Chemical synthesis	[19]
Phenicols	Chloramphenicol	*Streptomyces venezuelae*	[25]
Polypeptides	Gramicidin	*Bacillus brevis*	[26]
Polymixin	Colistin	*Paenibacillus polymyxa*	[27]
Quinolones	Ciproxacin	Chemical synthesis	[19]
Sulfonamides	Mafenide	Chemical synthesis	[19]
Tetracyclines	Oxytetracyclines	*Streptomyces rimosus*	[28]

Antibiotics are currently used to treat infections and inhibit the growth of pathogenic microbes in the context of human health. The main antibiotic action mechanisms include cell wall synthesis inhibition, cell membrane structure or function breakdown, nucleic acid structure and function inhibition, protein synthesis inhibition, and key metabolic pathway blockage of folate synthesis [29].

2.2. Antimicrobial Resistance (AMR) Issues

AMR is the ability of microorganisms to resist and grow in the presence of antimicrobial agents [30]. The emergence of antibiotic resistance is a major global health challenge. The possible causes of its apparition include poor hygiene and misuse and overuse of antibiotics [31]. Moreover, animal farms have been identified as a potential source of antibiotic resistance genes (ARGs) and antibiotic-resistant bacteria (ARB) [32]. Therefore, the consumption of antibiotic-treated animal products constitutes a potential risk of resistant bacteria transfer [33]. For example, methicillin-resistant *Staphylococcus aureus* (MRSA) has been detected in farm equipment, livestock, and dairy farmers [34]. Bacteria can insert their genetic information into another organism via horizontal gene transfer mechanisms such as conjugation, phage transduction, plasmid mobility, and natural transformation, which facilitate bacteria niche expansion and functional diversification [35]. Human-associated bacteria have been found to have a 25-times higher chance of exchanging genetic material than bacteria from other environments [36]. Under the selective pressure exerted by antibiotic treatment, evolving microbial communities result from the altered population structure of the indigenous microbiota, which have endured stress perturbation and acquisition of resistance enrichment. Antibiotics also favor antibiotic-resistant communities, enriching the presence of resistance genes in the microbiome. For instance, a study has showed an increased exchange of integrating conjugative genes that encode multidrug resistance by interspecies DNA-synthesis-inhibiting antibiotics. The ability of commensals to outcompete pathogens for space and nutrients, as well as enhancing the host defense of the colonic epithelium, actively protect the host against infections [37,38]. Administration of antibiotics can disrupt the population structure of the gut environment, which then compromises the defenses, thus opening new niches for intrusion. The mobility of antibiotic-induced resistance genes encourages co-localization of pathogenic and commensal bacteria, which thus provides opportunities for the transfer of resistance to harmful pathogens [35]. This can be exemplified by methicillin-resistant *S. aureus* (MRSA), which acquired a gene that improved its colonization in the host from *Staphylococcus epidermis* [39].

The main AMR mechanisms developed by resistant pathogens (Figure 1) include the presence of resistance genes in transposable elements such as in plasmids, reduction in uptake of antimicrobial agents (efflux of the antibiotic from the cell, biofilm formation, and permeability reduction), the presence of factors that affect the target antibiotic like enzymes, and mutation or alteration in the target site of antibiotics [40]. Table 2 lists the action modes and the resistance mechanisms of principal antibiotic classes.

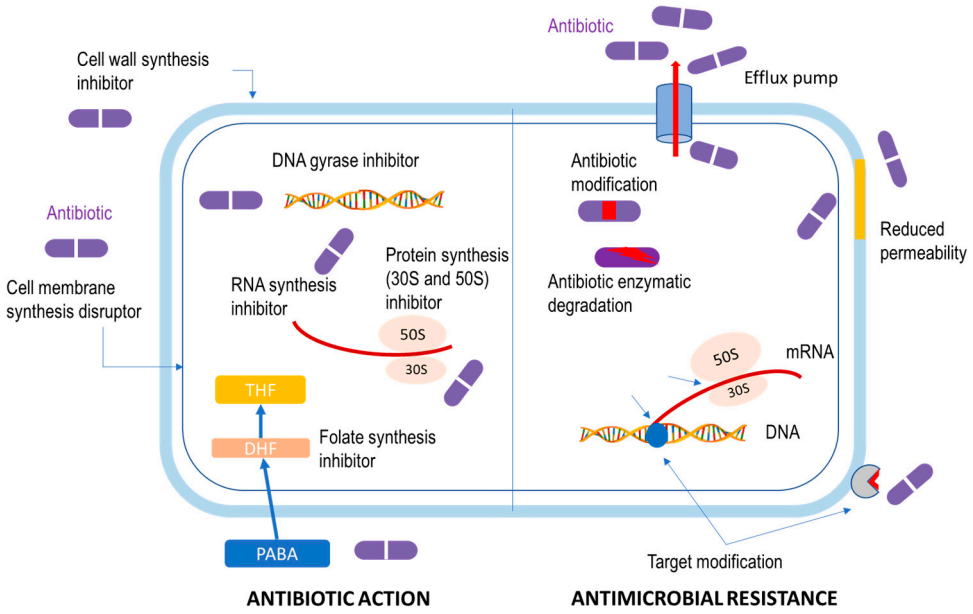

Figure 1. Illustration of antibiotic action modes (**left side**) and antibiotic resistance mechanisms (**right side**) of pathogens.

Table 2. Action modes and resistance mechanisms of main antibiotic classes.

Class	Mode of Action	Resistance Mechanism	Reference
Aminoglycosides	Inhibition of protein synthesis (30S ribosomal subunit inhibitor)	Binding inhibition by phosphorylation, adenylation, and acetylation of aminoglycosides Aminoglycoside-modifying enzymes (e.g., acetyltransferases, phosphotransferases) 16S rRNA methylation Efflux-mediated resistance	[41–43]
β-Lactams	Inhibition of cell wall synthesis (peptidoglycan)	Production of β-Lactamases Permeability change (Efflux)	[41,42,44]
Glycopeptides	Inhibition of cell wall synthesis (peptidoglycans)	Intrinsic resistance in Gram-negative cells by impermeable outer membrane Presence of enzymes that modify and hydrolyze peptidoglycan precursors Low permeability	[41,42,45]
Fluoroquinolones	Inhibition of nucleic acid synthesis	Mutations in DNA gyrase or topoisomerase IV	[41,42,46]
Sulfonamides	Blockage of key metabolic pathways (folate synthesis inhibitors)	Mutations in folP gene encoding dihydropteroate synthase, *sul1*, *sul2* genes, sulfonamide monooxygenase gene *sulX*	[41,42,47]
Tetracyclines	Inhibition of protein synthesis (30S-ribosomal subunit inhibitor)	Enzymatic inactivation Binding site mutation	[41,42,48]
Chloramphenicols	Inhibition of protein synthesis (50S-ribosomal subunit inhibitor)	Mutations within 23S rRNA of the 50S ribosomal subunit Enzymatic inactivation via acetyltransferases Active efflux	[41,42,49]

2.3. Alternatives to Antibiotics

Considering the alarming consequences of AMR, new antibiotic alternative treatments which are more specific while eliminating deleterious side effects on the gut microbiota are crucial. These alternatives aim at maximally reducing the inappropriate and excessive use of antibiotics and should produce the same beneficial effects of such active molecules.

Among the alternative candidates include molecular substitute classes such as bacteriocins, antimicrobial peptides, medicinal plants, and nanoparticles, which directly act by inhibiting or destroying pathogens, and microbial-based substitute classes such as bacteriophages, probiotics, and some vaccines [50]. The antibacterial mechanisms of the latter are based on either direct or indirect activities. For instance, bacteriophages are viruses that release their genetic material into bacteria, degrading the bacterial DNA, and ultimately killing them. Probiotics may directly act through antibiosis by producing metabolites such as bacteriocins, organic acids, antioxidant compounds, and nutrient-space competition, or indirectly by modulating the host's gut microbiota and immune system, and can in this way reduce dysbiosis and bacterial infections, respectively. Figure 2 summarizes the main potential alternatives that have been considered to reduce the use of or even replace conventional antibiotics, and thus fight against AMR phenomena. Two alternative groups are distinguished according to their functions: (i) disease prevention through gut microbiota and immune system modulation (e.g., probiotics) and immune stimulation (e.g., vaccines), and (ii) disease treatment by reducing or suppressing bacterial infections (e.g., phage therapy, bacteriocins, nanoparticles, antibodies, and quorum-sensing anti-virulence inhibitors) [50].

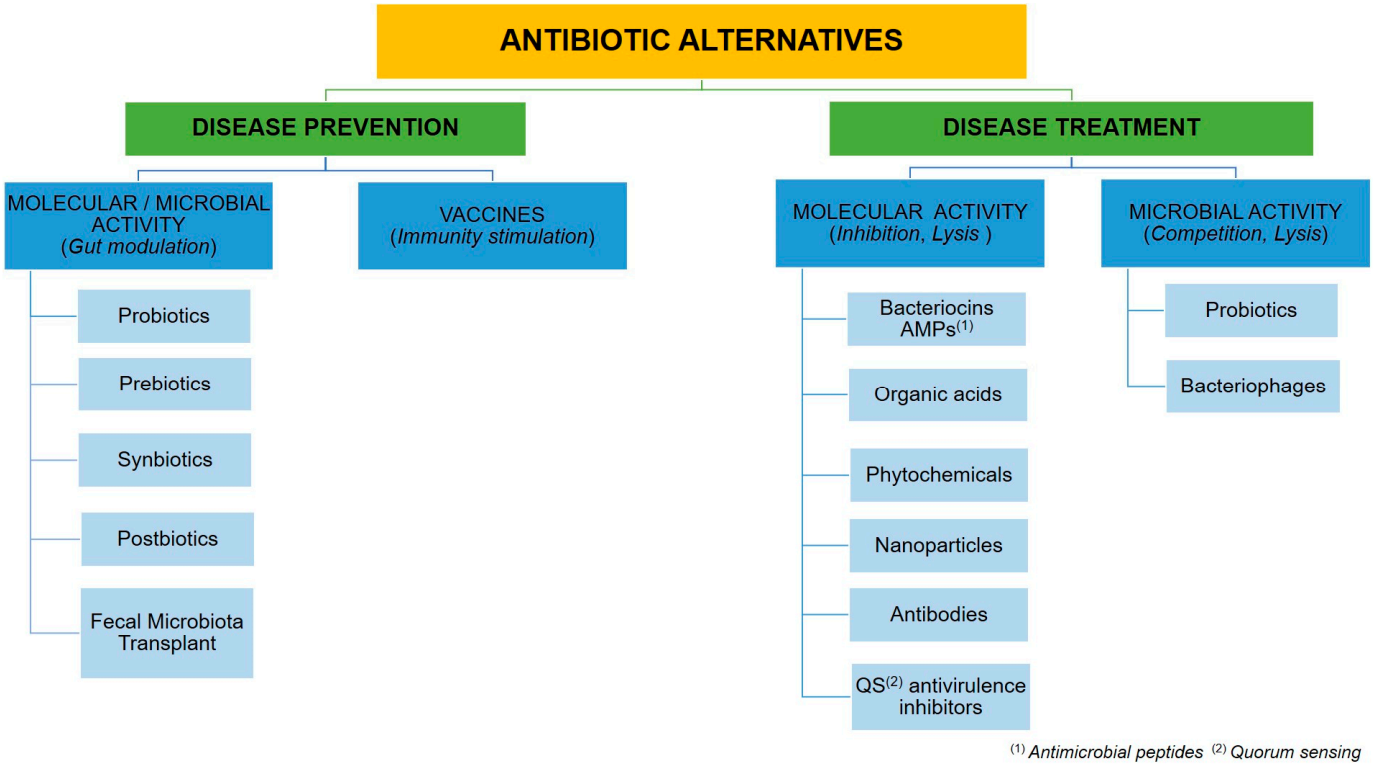

Figure 2. Antibiotic alternative classes.

3. Probiotics as Potential Alternative to Antibiotics

The probiotic-based approach represents a potential effective strategy to counter the emergence of antibiotic-resistant bacteria [51]. Probiotics consist of live microorganisms that are beneficial to the host when used under adequate conditions [9].

There exists evidence to support the idea that probiotics can be used for treating and preventing infectious diseases in human and animal health [4,52]. For instance, several clinical trials demonstrate the positive effect of the probiotic yeast *Saccharomyces boulardii* on *Candida* infection complications [53]. *Lacticaseibacillus casei* ATTC334, *Bifidobacterium breve* JCM1192, and *Bifidobacterium infantis* BL2416 are able to decrease the harmful effects and mortality in chicks due to *Salmonella* infections by competitive exclusion and cytokine release promotion mechanisms [54].

The main antimicrobial mechanisms of probiotics include competitive exclusion, intestinal barrier function improvement by enhancing mucin and tight junction protein expression, antimicrobial molecule secretion, and immune system regulation [55]. Figure 3 outlines the principal antimicrobial mechanisms employed by probiotics.

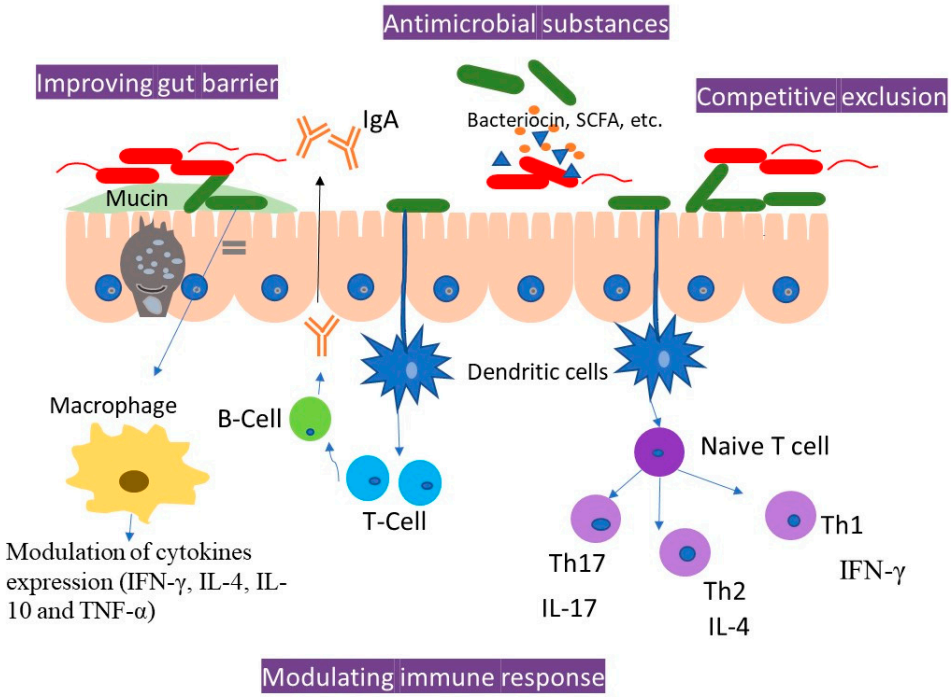

Figure 3. Antimicrobial mechanisms of probiotics against pathogens.

3.1. Competitive Exclusion of Pathogens

The establishment of a probiotic bacterial population in the gastrointestinal tract creates competition for nutrients or adhesion sites to prevent the overgrowth of potential pathogens. Two competitive strategies, namely, exploitation and interference competition, exist [12]. Exploitation competition for both nutrients and space is an indirect mechanism. It results from rapid nutrient consumption due to the secretion of extracellular molecules (e.g., proteases, iron-chelating siderophores), which are able to hydrolyze complex macromolecules, thus restricting resources for competitors. Probiotics also can rapidly colonize uninhabited niches or compete with pathogens through the production of adhesins and receptors that bind to specific surface features [56]. Several experimental studies reported the antagonistic effects of lactic acid bacteria (LAB) on the adhesion of pathogens [57–59].

Interference competition acts directly on potential pathogens by the production of antimicrobial compounds, for example, bacteriocins that harm pathogens. Furthermore, it reduces antibiotic-induced superinfections and aids in the restoration of the desired microbial numbers inside the body [7]. Probiotic *Lactiplantibacillus plantarum* strains effectively compete with, exclude, and displace the adhesion of pathogenic *Escherichia coli* and *Salmonella enterica* [60].

3.2. Improvement of Intestinal Barriers

The intestinal barrier has a fundamental role in health and disease. It constitutes an important line of defense in order to maintain intestinal homeostasis by ensuring mechanical, chemical, immune, and microbial barrier functions. These functions can be compromised when the mucosa suffers structural damage and dysregulation [61]. The use of probiotics represents a potentially effective strategy for the mucosal barrier function to out-compete pathogenic organisms. The mechanical barrier is ensured by the intestinal epithelial cells (IECs) and intercellular junction complexes. The tight junctions (TJs) at the

IECs' apical side regulate small and ionic molecules to maintain normal intestinal barrier function with regard to pathogenic bacteria and harmful substances [62]. Probiotics are able to restore the gut barrier by enhancing the expression of genes and proteins involved in tight junction (TJ) signaling and regulating the intestinal epithelial cells' apoptosis and the proliferation of IECs. As an example, *Lactobacillus acidophilus* causes a strain-specific and rapid enhancement of intestinal epithelial TJ barrier function, mediated by the Toll-like receptor-2 (TLR-2) heterodimeric complexes TLR-2/TLR-1 and TLR-2/TLR-6, which leads to protection against intestinal inflammation [63].

Moreover, a mucus layer is secreted by goblet cells in the intestinal epithelium. The mucus, mainly composed of high-molecular-weight glycoproteins called mucins, enhances nutrient uptake, provides adhesion sites for resident bacteria, and prevents microbial penetration [61,62,64].

Probiotics are also able to elicit mucin expression and mucus secretion from the goblet cells. Treatment of mucus-secreting colon epithelial cells (HT29-MTX) with probiotic mix yogurt supernatants (*Streptococcus thermophilus*, *Lactobacillus bulgaricus*, and *Bifidobacterium bifidum* (C-Bb); *S. thermophilus*, *L. bulgaricus*, and *L. acidophilus* (C-La); and *S. thermophilus*, *L. bulgaricus*, and *Lactobacillus gasseri* (C-Lg)) increased the expression of MUC2 and CDX2, as well as the production of mucin proteins. MUC2 is a major mucin protein in the mucus layer, whereas CDX2 regulates the expression of MUC2 [65].

3.3. Secretion of Antimicrobial Peptides (AMPs)

Probiotic bacteria can produce and release antimicrobial molecules such as organic acid compounds [66,67], diacetyl [68], hydrogen peroxide [69], and peptides [70], which have selective activity against numerous strains of microbes commonly found in the gut. Bacterial AMPs are often referred to as bacteriocins, which are a heterogenous group of ribosomally synthetized peptides. These peptides directly kill or inhibit the growth of pathogens in the lumen [71]. Bacteriocins are generally categorized into three classes: (1) heat-stable peptides of class I are lantibiotics with characteristic polycyclic thioether amino acids (e.g., lanthionine, <5 kDa), with linear (A-lantibiotics) or globular (B-lantibiotics) structures; (2) heat-stable peptides of class II are bacteriocins containing no lanthionine (<10 kDa); and (3) heat-labile high-molecular-weight molecules are class III bacteriocins (>30 kDa) [72].

The antimicrobial mechanisms of probiotic bacteriocins are structure-dependent (e.g., amino acid sequence and net charge) and include pore formation and enzyme activity modulation, as well as quorum sensing, i.e., the ability to detect and respond to cell population density with gene regulation [73].

Bacteriocins of class I have detrimental effects on cell integrity, owing to their ability to enter the cell membrane. Another action mechanism of class I bacteriocins is cell wall synthesis inhibition. Those of class II have the ability to depolarize cell membranes by binding to the membrane pore receptor system, such as mannose phosphotransferase, while those of class III directly lyse cells [74].

The AMP named nisin is, for instance, able to interact with membrane-bound lipid II proteins and cause pore formation in the cell membrane, leading to the lysis of the bacterium [75,76]. Such bacteriocins are produced by *Lactococcus lactis* and belong to the class of A-lantibiotics with a positive charge.

The class I B-lantibiotic named mersacidin from *Bacillus* spp. is a globular-shaped and neutral or negatively charged peptide that is able to interfere with cell wall biosynthesis [77].

The class II bacteriocin named pediocin from *Pediococcus pentosaceus* GS4 (MTCC 12683) has antibacterial and antagonistic potential against *S. aureus* (ATCC 25923), *E. coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 25619), and *Listeria monocytogenes* (ATCC 15313) [78].

The AMPs colicin, megacin, klebicin, helveticin I, and enterolysin from *Bacillus megaterium*, *Klebsiella pneumonia*, *Lactobacillus helveticus*, and *Enterococcus faecalis*, respectively, are categorized as class III bacteriocins. They are able to catalyze cell wall hydrolysis [73]. A few examples of probiotic bacteriocins and their target microorganisms are listed in Table 3.

Table 3. Antimicrobial activity of some probiotic bacteriocins.

Bacteriocins	Probiotic	Target Microorganisms	Reference
Bacteriocin	*L. acidophilus* KS400	*Gardnerella vaginalis*, *Streptococcus agalactiae*, *P. aeruginosa*	[79]
Enterocin M	*Enterococcus faecium* AL41	*Campylobacter* spp. *Clostridium* spp.	[80]
Nisin-like bacteriocin	*L. lactis* C15	*E. coli*	[81]
Pediocin	*Ped. pentosaceus* GS4 (MTCC 12683)	*S. aureus* (ATCC 25923), *E. coli* (ATCC 25922), *P. aeruginosa* (ATCC 25619), and *L. monocytogenes* (ATCC 15313)	[78]
Plantaricin P1053	*L. plantarum* PBS067	*S. aureus* and *E. coli*	[82]
Subtilin-like bacteriocin—Subtilin JS-4	*Bacillus subtilis* JS-4	*L. monocytogenes*	[83]

3.4. Modulation of Host Immune System

Probiotic bacteria may exert their immunomodulatory effect by increasing the growth of healthy components in the gut microecology. By restoring the normal ecological niche, a probiotic can give rise to better nutritional and environmental proto-cooperation that enables the body to regulate all the specific and nonspecific immune responses [84].

The nonspecific immune response (innate immunity) is the first line of defense and is composed of chemical and physical barriers (skin and mucous membranes), immune cells (dendritic cells, macrophages, monocytes, neutrophils, and natural killers), and immunomodulatory agent cytokines.

The specific immune response (adaptive immunity) is induced toward offensive targets by lymphocytes (B and T cells) and through antibody responses, immunoglobulin production, and the cell-mediated immune response [85].

Probiotics have an impact on innate immunity by enhancing the cytotoxicity of natural killer (NK) cells and the phagocytosis of macrophages. They modulate the adaptive immunity by interacting with intestinal immune cells such as enterocytes, dendritic cells, and regulatory T cells [13].

The replenishing of the gut population through probiotics has gone beyond the benefits of maintaining a balanced gut ecosystem by recuperating the immune system. Probiotics affect the host defense mechanisms in several ways such as the stimulation of phagocytic activity, balancing pro-inflammatory and anti-inflammatory cytokines, and enhancing the production of cytokines and immunoglobulin IgA.

3.4.1. Stimulation of Phagocytic Activity

Probiotic bacteria are able to enhance nonspecific immune responses. Among the possible mechanisms is the promotion of phagocytic activity through macrophage activation [86]. Activated macrophages enhance phagocytosis by promoting the production of cytotoxic molecules such as nitric oxide (NO) and secrete immunoregulatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, IL-10, and interferon-γ (IFN-γ) in order to initiate the destruction of pathogens [87]. At the same time, they express receptors for a variety of cytokines such as IFN-γ, IL-4, IL-10, and TNF-α [88].

Specific receptors (pattern recognition receptors, or PRRs) of macrophages can bind to the surface components of probiotic LABs, such as flagella, proteins, capsular polysaccharides (CPSs), lipopolysaccharide (LPS), and peptidoglycan (PG), which represent microbial-associated molecular patterns (MAMPs) [89].

The probiotic strains *Lacticaseibacillus rhamnosus* GG, *L. rhamnosus* KLDS, *L. helveticus* IMAU70129, and *L. casei* IMAU60214 have been shown to stimulate inflammatory responses and activate human macrophages. Pretreatment with *Lactobacillus* enhanced phagocyto-

sis and the antimicrobial activity of macrophages against *S. aureus*, *S. typhimurium*, and *E. coli* [90].

It has been proposed that consumption of fermented milk containing *Lactobacillus johnsonii* and *S. thermophilus* enhances the phagocytic activity of peripheral blood leukocytes in healthy adult volunteers [91]. In another study, an improvement of phagocytic activity of peritoneal macrophages in a murine model was shown after feeding with fermented fish protein concentrate (FPC) at 0.3 mg/mL for 7 consecutive days. This finding indicates that fermented fish proteins regulate nonspecific host defense mechanisms by enhancing the phagocytosis of pathogens [88].

3.4.2. Balancing of Pro- and Anti-Inflammatory Cytokines

Cytokines are small proteins released by immune cells such as macrophages, T cells, B cells, and natural killers in order to regulate and influence the immune response [92]. Cytokine production can lead to the modulation of the host immune system, as it is involved in the regulation of cell activation, growth, and differentiation, as well as inflammation [86]. The inflammatory process depends on the balance between pro-inflammatory and anti-inflammatory cytokines. Interleukin-1 (IL-1), IL-2, IL-6, IL-12, IL-18, gamma interferon (IFN-γ), and tumor necrosis factor alpha (TNF-α) are involved in pro-inflammatory action. The anti-inflammatory cytokines such as IL-10, transforming growth factor-β (TGF-β) produced by monocytes, T cells, B cells, macrophages, natural killer cells, and dendritic cells inhibit pro-inflammatory cytokines, chemokines, and chemokine receptors [93].

Probiotics regulate the innate and adaptive immune systems by interacting with enterocytes and dendritic cells, Th1, Th2, and Treg cells in the intestine, thus inducing the release of cytokines [13]. *Streptococcus thermophilus* ST285 has been shown to significatively increase the expression of anti-inflammatory IL-4, IL-5, and IL-10 cytokines, and decrease the secretion of pro-inflammatory IL-1β and IFN-γ, thus altering pro-inflammatory secretion to anti-inflammatory secretion against multiple sclerosis peptide in mice [94].

Moreover, *S. thermophilus* ST285 increased the anti-inflammatory cytokine production by human monocytes (IL-4, IFN-γ, and TNF-α) [95].

As the most generally accepted cultured dairy product, yogurt has been amended with specific strains of lactic acid bacteria to stimulate cytokine production, such as interferon γ (IFN-γ) by human blood mononuclear cells and also by monocytes [96].

Probiotic *Lactobacillus kefiri* CIDCA 8348 isolated from kefir induced immunomodulatory effects on CD4+ T lymphocytes from the lamina propria of intestinal bowel disease (IBD) patients. *L. kefiri* decreased the secretion of IL-6 and IL-8 from inflamed biopsies ex vivo and reduced the secretion of TNF-α, IL-6, IFN-γ, and IL-13. In addition, *L. kefiri* induced an increased frequency of activated CD4+ with high levels of IL-10 [97].

3.4.3. Enhancing Immunoglobulin A (IgA) Production

IgA is produced by the plasma cells while representing the first-line defense against infection in the digestive tract. Secretory IgA (SIgA) protects against the adhesion of pathogens and their penetration into the intestinal barrier. In contact with bacteria present in the digestive tract, SIgA traps pathogens and pathogenic material through agglutination, disrupting adhesive complex substances, and also by setting adhesive proteins on the surface of bacteria [98].

Probiotics are able to improve host defense by enhancing the production of specific antibodies against pathogens and total IgA. It has been demonstrated that LABs induced IL-6 and IL-10 production by dendritic cells, which contribute to upregulating the secretory IgA concentration at mucosal sites in humans [99]. For example, *L. gasseri* SBT2055 induced TGF-β expression in dendritic cells and activated TLR2 signaling to produce IgA in the small intestine [100].

Evidence of the immune-stimulating effect of fermented milk kefir made with a wide variety of bacteria such as lactobacilli, lactococci, leuconostocs, aceterobacteria, as well as some potentially beneficial yeast has been reported. After the ingestion of kefir by

young and senescent rats, a significant increase in IgA antibody titers in young rats was noticed [101]. Furthermore, it has also been shown that IgA production by plasma cells can be altered in a dose-dependent manner by consuming yogurt [102].

Administration of viable (*L. salivarius* subsp. *salicinius* AP-32, *B. animalis* subsp. *lactis* CP-9, and *Lacticaseibacillus paracasei* ET-66) and heat-killed (*L. salivarius* subsp. *salicinius* AP-32 and *L. paracasei* ET-66) probiotics in healthy adults increased salivary IgA levels after 6 weeks and inhibited oral pathogens such as *S. mutans*, *P. gingivalis*, *F. nucleatum* subsp. *polymorphum*, and *A. actinomycetemcomitans* [103].

A study conducted on children with acute rotavirus diarrhea showed that administration of *L. rhamnosus* GG fermented milk product caused stimulatory effects on IgA-specific antibody-secreting cells [104]. Table 4 lists recent in/ex vivo studies on probiotic effects on the immune system.

Table 4. In/ex vivo immunomodulation effects of probiotics.

Probiotics	Studied Model	Effects on Immunity	Reference
Bifidobacterium longum Bar33 and *L. helveticus* Bar13	Older adults (over 75 years)	Increase naive T cells Increase activated memory, regulatory T cells, B cells, and natural killer (NK) activity Decrease memory T cells	[105]
L. paracasei SD1	Children	Decrease of *Streptococcus mutans* pathogens Increase of salivary IgA	[106]
Limosilactobacillus reuteri D8	Piglets	Increase of goblet cells and antimicrobial peptides (AMPs), expressions of Muc2, Lyz1, and porcine β-defensins 1 (pBD1) Increase of CD3+ T cells, combined with increased expression of IL-4 and IFN-γ	[107]
Lactobacillus fermentum UCO-979C	Mice	Increase the production of intestinal IFN-γ, stimulate intestinal and peritoneal macrophages, increase the number of Peyer's patches CD4+ T cells Increase intestinal IL-6, intestinal IgA, and the number of mature B cells	[108]
L. acidophilus and *L. plantarum*	Freshwater crayfish	Upregulation of cytokine gene families (IL1β, IL8, IL10, and IL17F), proPO, and cytMnSOD	[109]
L. acidophilus	Broilers challenged with *E. coli*	Reduce the mortality rate caused by *E. coli* challenge Decrease the serum C-reactive protein, diamine oxydase, and endotoxin lipopolysaccharide levels at 14 days and 21 days Upregulate the mRNA expression of occludin and zona occludens protein 1 (ZO-1) in the jejunum and ileum (tight junction) Downregulate the mRNA expression of inducible nitric oxide synthase (iNOS), IL-8, and IL-1β in the jejunum in *E. coli* challenged birds at 21 days	[110]

4. Advantages and Disadvantages of Probiotics as Antibiotic Alternatives

While antibiotics are active substances directly used to fight pathogens, probiotics are live microorganisms that can act directly by producing antimicrobial metabolites and competing microbes for sites/nutrients, or/and indirectly by stimulating host immune systems. In addition, probiotics help to repopulate the gut with healthy microbiota and reduce dysbiosis caused by antibiotics. In this situation, probiotics can compensate for antibiotic side effects. Moreover, probiotic activities are multiple and may include antibacterial, antifungal, and antiviral effects, whereas those of antibiotics are only intended to inhibit or destroy bacteria [17,111–113]. Other aspects distinguishing them arise from their status. Antibiotics are used as drugs requiring medical prescription, while probiotics are freely available and mainly consumed as diet supplements or through fermented products, even if some strains are prescribed as drugs, such as *S. boulardii* as an antidiarrheal [114]. In terms of dose, effects, and treatment duration, an effective antibiotic is a short-time

and low-dose-acting antimicrobial, but it might cause progressive antimicrobial resistance and host microbiota imbalance by inducing a pathogen's defense mechanisms and killing also good microbes. Conversely, the positive effects of probiotics are often perceptible after long-term uptake, without the side effects observed after antibiotic treatment. In fact, probiotics can control pathogenic targets through competitive exclusion of nutrients and space, and ensure the host's microbiota balance. Among probiotics' disadvantages are their sensitivity under extreme stress conditions (e.g., temperature, acidity, moisture, etc.), which reduce their survival rate and therefore their capacity to colonize the gut. Table 5 compares the strengths and weaknesses of antibiotics and probiotics regarding their usage for fighting pathogen growth and infections.

Table 5. Comparison between antibiotics and probiotics: characteristic features, action mechanisms, strengths, and weakness.

	Antibiotic	**Probiotic**
Characteristic features	Active substance Natural or synthetic One function Non-growth over time (static process)	Live microorganism Natural Multifunction Growth over time (dynamic process)
Action mechanisms	Cell membrane breakdown Cell wall synthesis inhibition Nucleic acid structure/function and protein synthesis inhibition Key metabolic pathway blockage	Gut barrier protection Nutrient/space competitive exclusion Antimicrobial substance secretion Immunomodulation
Strength	Specificity Short-time treatment	No side effects Antibacterial and antiviral properties Generally recognized as safe (GRAS) Natural and biodegradable
Weakness	Destroy beneficial microbes Antimicrobial resistance induction Not effective on viruses Low biodegradability for synthetic compounds	Cell viability maintaining challenge Long-term treatment Sensitivity under stress conditions Antimicrobial resistance risk if genes transfer

5. Human Applications

The potential use of probiotics as antibiotic alternatives for human applications has been shown through many in and ex vivo experiments reported in the literature, as illustrated in Table 6. For instance, lactic acid- and soil-based bacteria are capable of exerting bacteriostatic and bactericidal activities to certain pathogens such as *S. aureus*, *L. monocytogenes*, *P. aeruginosa*, and *Candida albicans*, reducing their colonization of the human body. Some clinical trials have also proven their efficacy for disease treatments (Table 7). However, it is important to distinguish different scenarios where probiotics are used for supporting antibiotics from other situations where they are used as substitute options. For many situations in human health, the use of antibiotics remains the first choice for controlling bacterial infections, and probiotics are useful for repopulating the gut microbiota [115]. Other situations indicate no clear or controversial use of antibiotics, whereas the use of probiotics may constitute an alternative in cases such as periodontal disease, acne, recurrent infections with *Helicobacter pilori*, and bacterial vaginosis [116–119]. Finally, there are other situations for which the antibiotic use is non-indicated and probiotics appear as an appropriate option, such as in the case of acute and *Clostridium difficile*-associated diarrhea [120,121].

Table 6. In vivo antimicrobial activity of probiotics against human pathogens.

Probiotics	Pathogens	Observation	Reference
B. subtilis MB40	*S. aureus*	Significant reduction of *S. aureus* colonization in body human without modification of microbiome	[122]
L. casei	*C. albicans*	Fungicidal effect in vulvovaginal candidiasis (VVC) murine model	[123]
L. reuteri DSM 17938	*S. aureus*, *S. pyogenes* M1, *Cutibacterium acnes* AS12, *P. aeruginosa*	Antimicrobial action against pathogenic skin bacteria and reduction of proinflammatory IL-6 and IL-8 in reconstructed human epidermis and native skin models	[124]
Pediococcus acidilactici HW01	*P. aeruginosa*	Inhibition of biofilm formation by bacteriocin and decrease of the production of virulence factors, such as pyocyanin, protease, and rhamnolipid	[125]
Ped. acidilactici HW01	*L. monocytogenes*	Inhibition of biofilm formation, adhesion, and invasion of HT-29 cells (human-intestinal-epithelial cell line) by bacterial lysate	[126]

Table 7. Some clinical trials and uses of probiotics in human health.

	Disease	Probiotics	Outcome	Reference
Oral and dental health	Chronic periodontitis	*B. animalis* subsp. *lactis (B. lactis)* HN019	Decreasing significantly the periodontal pathogens of red and orange complexes; reducing proinflammatory cytokine levels; promoting clinical, microbiological, and immunological benefits in the treatment of chronic periodontitis	[127]
Skin	Atopic dermatitis	*L. plantarum* PBS067 *L. reuteri* PBS072 *L. rhamnosus* LRH020	Improvement in skin smoothness, skin moisturization, self-perception, and decrease in scoring atopic dermatitis (SCORAD) index and levels of inflammatory markers	[128]
	Acne vulgaris	*B. lactis* W51, *B. lactis* W52, *L. acidophilus* W55, *L. casei* W56, *L. salivarius* W57, *L. lactis* W58 combined with rice starch and maltodextrin	Increasing serum IL-10 levels after oral probiotic in acne vulgaris	[129]
	Surgical wound infection	*L. acidophilus* BCMC® 12130 *L. lactis* BCMC® 12451, *L. casei* subsp BCMC® 12313, *B. longum* BCMC® 02120, *B. bifidum* BCMC® 02290, and *B. infantis* BCMC® 02129	Reduction of pro-inflammatory cytokines (except for IFN-gamma) in colorectal cancer patients after consumption for 4 weeks	[130]
Respiratory tract	Ventilator-associated pneumonia (VAP)	*L. acidophilus* LA-5, *L. plantarum* UBLP-40, *B. animalis* subsp. *lactis* BB-12, and *S. boulardii*	Decreasing the incidence of VAP induced by *Acinobacter baumannii* and *P. aeruginosa* in patients subjected to prolonged mechanical ventilation for severe multiple trauma, including brain injury	[131]
	Acute respiratory tract infection	*B. lactis* Probio-M8	Reducing antibiotic prescription, preventing antibiotic new prescription in non-prescribed patients, decreasing oral cytokine levels of TNF-α, and increased IL-10 (over 4 weeks post-discharge)	[132]
	Virus associated respiratory tract infection	*L. plantarum* HEAL9 *L. paracasei* 8700	No effect on symptom severity but significantly fewer colds	[133]

Table 7. *Cont.*

	Disease	Probiotics	Outcome	Reference
Stomach	*Helicobacter pylori* infection, gastritis	*L. reuteri* DSM 17648	Effectively reducing *H. pylori* load and improving gastrointestinal symptoms in adults and children	[134]
Intestines	Inflammatory bowel syndrome (IBS)	*L. paracasei*, *L. salivarius*, and *L. plantarum*	Effective global relief of IBS symptoms and abdominal pain without significant adverse events	[135]
	C. difficile-associated diarrhea (CDAD)	*L. casei*	Reduction of the incidence rates of CDAD	[121]
	Acute diarrhea	*S. boulardii* combined with *bifidobacterium*	Shortening the duration of diarrhea and hospital stay, reducing the number of diarrhea, enhancing cellular immune function	[136]
Female urogenital tract	Bacterial vaginosis	*L. crispatus* CTV-05 (Lactin-V)	Prevention of the recurrence of bacterial vaginosis	[137]

6. Animal Applications

Antibiotics are often used in animal farming as antimicrobial agents for enhancing animal growth and production, as well as controlling diseases [138]. An evident use of probiotics instead of antibiotics is supported in the case of promoting animal growth, for which the goal consists of health development without specific infection targets [139,140]. A considerable number of probiotic strains are also capable of inhibiting diverse animal pathogens and may be potentially used as antibiotic alternatives in the farming sectors of poultry, swine, cattle, and others for enhancing immune function and disease prevention [10]. The benefits and inputs from probiotics as alternatives to antibiotics in animal health are outlined in Figure 4.

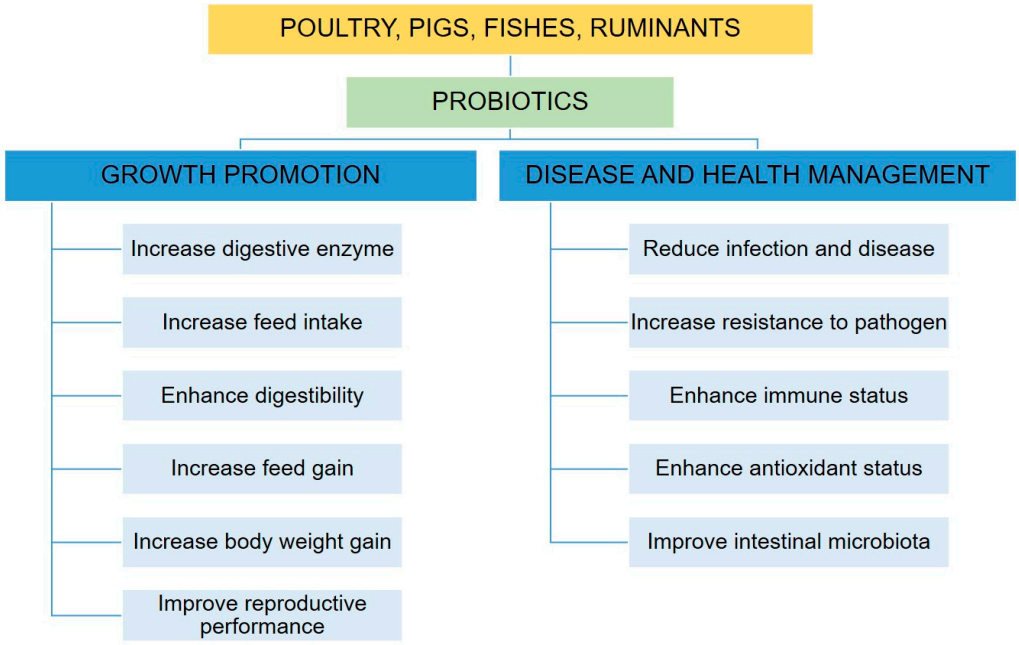

Figure 4. Impacts of probiotics as antibiotic alternatives in animals.

Table 8 illustrates some recent examples of animal feed being supplemented with lactic acid and soil-based bacteria, the form of administration, and the probiotic strain effects. The use of probiotics as feed supplements in animal farming allows not only the reduction of AMR apparition due to the excessive use of antibiotics, but also the diminution of the residue transfer risk to animal products such as eggs, milk, and meat.

Table 8. Animal applications of antimicrobial probiotics.

Animals	Probiotics	Form of Administration	Effects	Reference
Poultry				
Broilers	*L. casei*, *L. acidophilus*, and *Bifidobacterium*	Supplementing 1% of probiotics in water	Increasing growth performance, carcass traits, immune function, gut microbial population, and antioxidant capacity	[139]
Laying hens	*Bifidobacterium* spp. and *L. casei*	Feeding	Improving the growth performance, increase of egg weight, and feed efficiency	[140]
Newly hatched chicks	*L. plantarum* LTC-113	Oral vaccination	Protection from *Salmonella* colonization by regulating expression of tight junction genes and inflammatory mediators	[141]
Chickens	*L. paracasei* ssp. *paracasei* and *L. rhamnosus*	Feeding	Improving growth performance	[142]
Broiler	*L. johnsonii* BS15	Feeding	Preventing subclinical necrotic enteritis	[143]
Chickens	*Bacillus licheniformis*	Feeding	Alleviating intestinal damage caused by SNE challenge, modulating intestinal microflora structure and barrier function, and regulating intestinal mucosal immune responses	[144]
	C. butyricum	Feeding	Promoting anti-inflammatory expression and tight junction protein genes Inhibiting pro-inflammatory genes in *C. perfringens*-challenged chickens	[145]
Swine				
Weaning piglets	*B. subtilis*, *E. faecium*	Liquid feed	Improve growth performance	[146]
Piglets	*L. plantarum* (strains 22F and 25F) and *Ped. acidilactici* (strain 72N)	Feeding	Reducing the infection severity with enterotoxigenic *E. coli* (ETEC) in weaned pigs	[147]
Cattle				
Cattle	*L. gallinarum* JCM 2011(T), *S. infantarius* subsp. *coli* HDP90246 (T), *S. salivarius* subsp. *thermophilus* ATCC 19258(T), and *S. equinus* ATCC 9812(T)		Improving the growth and haemato-biochemical parameters of growing cattle	[148]
Dairy cows	*Saccharomyces cerevisiae S. cerevisiae*, *B. subtilis*, *B. lichenformis*, *E. faecium*, *L. acidophilus*, *L. plantarum*, *B. tedium* and calcium carbonate	Feeding	Improving reproductive performance Increasing milk yield and milk fat and protein percentage	[149]
	L. rhamnosus, *P. acidilactici*, and *L. reuteri*	Ex vivo bovine endometrial explants	Reducing acute inflammation under *E. coli* infection, decreasing IL-8, IL-1β, and IL-6	[150]
Sheep				
Sheep, Lamb	Enzimsporin™ (*B. subtilis* B-2998D, B-3057D, and *B. licheniformis* B-2999D)	Feeding	Increasing body weight gain and improving intestinal microbiota	[151]
Fish				
Nile Tilapia (*Oreochromis niloticus*)	*S. cerevisiae*	Feeding	Increasing growth performance and feed utilization indices	[152]
Nile Tilapia (*Oreochromis niloticus*)	DBA® (*B.* sp., *L. acidophilus* and *E. faecium*)	Feeding	Protection against *A. hydrophila* infection without growth reduction	[153]
Common carp (*Cyprinus carpio*)	*Ped. pentosaceus*	Feeding	Improving growth performance, digestive enzyme activity, and haemato-immunological responses	[154]
Rohu fingerlings (*Labeo rohita*)	*B. amyloliquefaciens* BN06, *B. subtilis* WN07, and *B. megaterium*	Feeding	Improving growth and haemato-immunological parameters	[155]

Table 8. *Cont.*

Animals	Probiotics	Form of Administration	Effects	Reference
Shrimp				
Whiteleg shrimp, (*Litopenaeus vannamei*)	*B. subtilis*, *Ped. pentosaceus*, and *L. lactis*	Feeding	Improving growth, immunity, histology, gene expression, digestive enzyme activity, and disease resistance	[156]
Pacific white shrimp (*Litopenaeus vannamei*)	*B. subtilis* AQAHBS001	Feeding	Improving the growth performance, immune response, and resistance to *Vibrio parahaemolyticus*	[157]

7. Conclusions

Inappropriate and excessive use of antibiotics increases pathogen resistance cases and dysbiosis phenomena, which constitute a real threat to human and animal health and wellbeing. As alternatives, probiotics appear to be reliable candidates, owing to numerous features and functions that these live and multifunctional microorganisms possess compared to antibacterial substances. In addition to their capacity to produce multiple antimicrobial metabolites comparable to antibiotics, probiotics have other mechanisms of action against pathogens, including nutrient competition and space exclusion, as well as immunomodulation activities. Such multi-action mechanisms minimize the risk of pathogen AMR and increase the potential for the use of probiotics as substitutes for antibiotics. Moreover, the use of probiotics as antimicrobials is not limited to bacteria but is also applicable to viruses. Plentiful evidence indicates their efficacy in inhibiting human and animal pathogens through experimental models and clinical trials and confirms their potential applications to prevent diseases, treat infections, and promote growth performance, immune systems, and nutrient efficiency. Despite such advantages, the maintenance of cell viability and dose optimization remain industrial challenges to achieving high specificity and short-time treatment with probiotics compared to antibiotics.

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