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Probiotics: an Antibiotic Replacement Strategy for Healthy Broilers and Productive Rearing

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Abstract

Pathogens develop resistance to antibiotics at a rate much faster than the discovery of new antimicrobial compounds. Reports of multidrug-resistant bacteria isolated from broilers, and the possibility that these strains may spread diseases amongst humans, prompted many European countries to ban the inclusion of antibiotics in feed. Probiotics added to broiler feed controlled a number of bacterial infections. A combination of *Enterococcus faecium*, *Pediococcus acidilactici*, *Bacillus animalis*, *Lactobacillus salivarius* and *Lactobacillus reuteri* decreased the colonisation of *Campylobacter jejuni* and *Salmonella* Enteritidis in the gastro-intestinal tract (GIT) of broilers, whereas *Bacillus subtilis* improved feed conversion, intestinal morphology, stimulated the immune system and inhibited the colonisation of *Campylobacter jejuni*, *Escherichia coli* and *Salmonella* Minnesota. *Lactobacillus salivarius* and *Pediococcus parvulus* improved weight gain, bone characteristics, intestinal morphology and immune response, and decreased the colonisation of *S.* Enteritidis. *Lactobacillus crispatus*, *L. salivarius*, *Lactobacillus gallinarum*, *Lactobacillus johnsonii*, *Enterococcus faecalis* and *Bacillus amyloliquefaciens* decreased the *Salmonella* count and led to an increase in lysozyme and T lymphocytes. Probiotics may also improve feed digestion through production of phytases, lipases, amylases and proteases or stimulate the GIT to secrete digestive enzymes. Some strains increase the nutritional value of feed by production of vitamins, exopolysaccharides and antioxidants. Bacteriocins, if produced, regulate pathogen numbers in the GIT and keep pro-inflammatory and anti-inflammatory reactions in balance.

Keywords Probiotics · Poultry · Productive rearing

Introduction

The last 70 years of research on poultry has largely been devoted to genetic selection and improvement of feed compositions [1]. Less progress has been made on the control of microbial infections caused by *Staphylococcus*, *Pseudomonas*, *Escherichia*, *Salmonella*, *Streptococcus*, *Campylobacter*, *Yersinia*, *Clostridium*, *Bacillus*, *Mycobacterium*, *Klebsiella*, *Enterococcus* and *Proteus* spp. [2, 3]. Broilers are more susceptible to bacterial infections during the first few weeks when the immune system is not fully developed [4]. Furthermore, developing of a stable gut microbiome may take as long as 8 weeks [5]. The longer the delay in reaching bacterial homeostasis, the higher the risk of contracting bacterial infections [6]. To minimise the chances of contracting bacterial infections, broilers are housed in confined facilities [7]. In many cases, farmers are still supplementing feed with antibiotics [8]. The irresponsible, non-therapeutic, use of antibiotics in poultry (and other animal) feed has led to a rapid increase in bacterial species resistant to antibiotics [9, 10]. Staphylococci associated with poultry farms were reported resistant to oxacillin and tetracycline [3]. Strains of *Pseudomonas* isolated from poultry in Ghana were resistant to cephalosporins, carbapenems, penicillins, quinolones, monobactam and aminoglycoside [11]. *Pseudomonas aeruginosa* strains isolated from poultry in Nigeria were resistant to β-lactams, tetracycline, tobramycin, nitrofurantoin and sulfamethoxazole-trimethoprim [12], whereas strains isolated from chickens in Pakistan showed resistance towards ceftriaxone, meropenem, ciprofloxacin, erythromycin and colistin [13]. *Escherichia coli* strains isolated from broilers were resistant to tetracycline, sulfamethoxazole, streptomycin, trimethoprim, ciprofloxacin, ampicillin, spectinomycin, nalidixic acid, chloramphenicol, neomycin and gentamicin [14]. Similar reports of multi-drug resistance have been reported for *Salmonella* [15], *Streptococcus* [16],

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Campylobacter [17, 18], *Yersinia* [19, 20], *Clostridium* [21–23], *Bacillus* [24], *Mycobacterium* [25], *Enterococcus* [26, 27] and *Proteus* spp. [28].

To control the spreading of antibiotic-resistant bacteria, health authorities in many European countries have now restricted the use of antibiotics in poultry feed [29]. Sweden was the first to ban the use of antimicrobials for growth promotion (year 1986) and prophylactic use (year 1988) [30]. Denmark, The Netherlands, the UK and other European Union countries followed suit [30]. In 2011, these countries banned the use of all essential antibiotics as prophylactic agents [31]. Despite these regulations, at least 60% of all antibiotics currently produced are used in livestock production, including poultry [32, 33].

Since the banning of antibiotics, probiotics [34, 35], prebiotics [34], synbiotics [36, 37], phytobiotics [38], enzymes [39, 40], essential oils [41, 42] and fatty acids [43] were proposed as possible alternatives. Probiotics are live microorganisms that, when administered in adequate cell numbers, confer a health benefit to the host. *Enterococcus faecium*, combined with *Pediococcus acidilactici*, *Bacillus animalis*, *Lactobacillus salivarius* and *Lactobacillus reuteri* (commercially available as PoultryStar®) decreased the colonisation of *Campylobacter jejuni* and *Salmonella* Enteritidis [44, 45]. A probiotic containing *Bacillus subtilis* (CLOSTAT™) improved feed conversion, intestinal morphology, enhanced the immune response, and inhibited gastro-intestinal tract (GIT) colonisation by *C. jejuni*, *Escherichia coli* and *Salmonella* Minnesota [46–49]. A combination of *L. salivarius* and *Pediococcus parvulus* (Floramax® B11) improved weight gain, bone characteristics, intestinal morphology and immune response, and decreased the colonisation of *S.* Enteritidis [50, 51]. Neveling and co-authors [52] have shown that a combination of *Lactobacillus crispatus*, *L. salivarius*, *Lactobacillus gallinarum*, *Lactobacillus johnsonii*, *Enterococcusfaecalis* and *Bacillus amyloliquefaciens* inhibited the colonisation of *Salmonella* in the GIT of broilers. Broilers treated with the multi-species probiotic had higher levels of lysozyme in their serum and higher T lymphocyte responses compared to control birds.

The use of probiotics in poultry feed is, however, still far from being common practice. While the murine in vivo model is perhaps the most commonly used for mechanistic studies of probiotics, only a few reports have been published on the role these microorganisms play in keeping the GIT of poultry healthy [53–55], let alone the interactions amongst gut microorganisms and communication between probiotics and broiler gut epithelial cells [56]. Findings from these studies are difficult to compare. Apart from insufficient evidence-based trials, none of the methods used by the different authors have been standardised. In-depth research needs to be done on the gut microbiota of broilers and the inter-microbial- and microbiota-host interactions.

This review assesses the benefits of probiotic use as feed additives for broilers and discusses the mechanisms by which probiotics improve health and growth performance. The role of probiotics in digestion, followed by modulation of the microbiome and physiology of broilers are reviewed. The effect probiotics might have on meat quality is also addressed.

Role of Probiotics in Digestion

Probiotics convert less degradable compounds into more digestible forms, increasing the nutritional value of feed. This, in turn, causes a shift in the gut microbial population, alters the composition of the gut microbiota and modulates the immune system (Fig. 1). The digestion of feed is improved through production of hydrolytic enzymes (phytases, lipases, amylases or proteases) that increase nutrient uptake [57, 58], or by stimulating the host to increase the secretion of digestive enzymes [59]. Probiotics may also increase the nutritional value of feed by the production of vitamins, exopolysaccharides and antioxidants (Fig. 2). Some probiotics may also regulate the metabolism of cholesterol [60, 61]. Nutrients are digested and absorbed in the proventriculus and small intestine. Undigested carbohydrates and proteins are fermented in the ileum and colon [57, 62]. This is an important step in digestion, as undigested nutrients is a predisposing factor for dysbiosis [63]. Genera from the *Firmicutes* phylum (to which most probiotics belong), in addition to members of the *Actinobacteria* and *Verrucomicrobium* phyla, may aid in the digestion of amino acids [64].

Enzymatic reactions in the colon provides additional energy in the form of lactate, acetate, propionate and butyrate [65]. These short-chain fatty acids (SCFAs), produced by probiotic bacteria, are also converted to lipids and cholesterol [66]. Although SCFAs serve as additional energy, only a small proportion (up to 25%) is recovered [67].

Some strains of *Bifidobacterium* and *Lactobacillus* spp. synthesise vitamin K, biotin, cobalamin, folates, nicotinic acid, pantothenic acid, pyridoxine, riboflavin and thiamine [68]. These vitamins are essential micronutrients and play an important role in growth and reproduction. However, it is unclear if these bacterially produced vitamins are absorbed in the GIT [69].

Exopolysaccharides (EPS), as concluded with studies on other animals, not only protect cells against dehydration, phagocytosis, predation, bacteriophages, antibiotics and other toxic compounds [70], but facilitates adhesion of the cells to the GIT and supports biofilm formation [71]. Exopolysaccharides produced by probiotic bacteria modulate the innate and adaptive immune systems [72, 73], display antitumor properties [74], lower cholesterol levels [75], inhibit pathogens, promote the growth of beneficial bacteria and act as antioxidants [76].

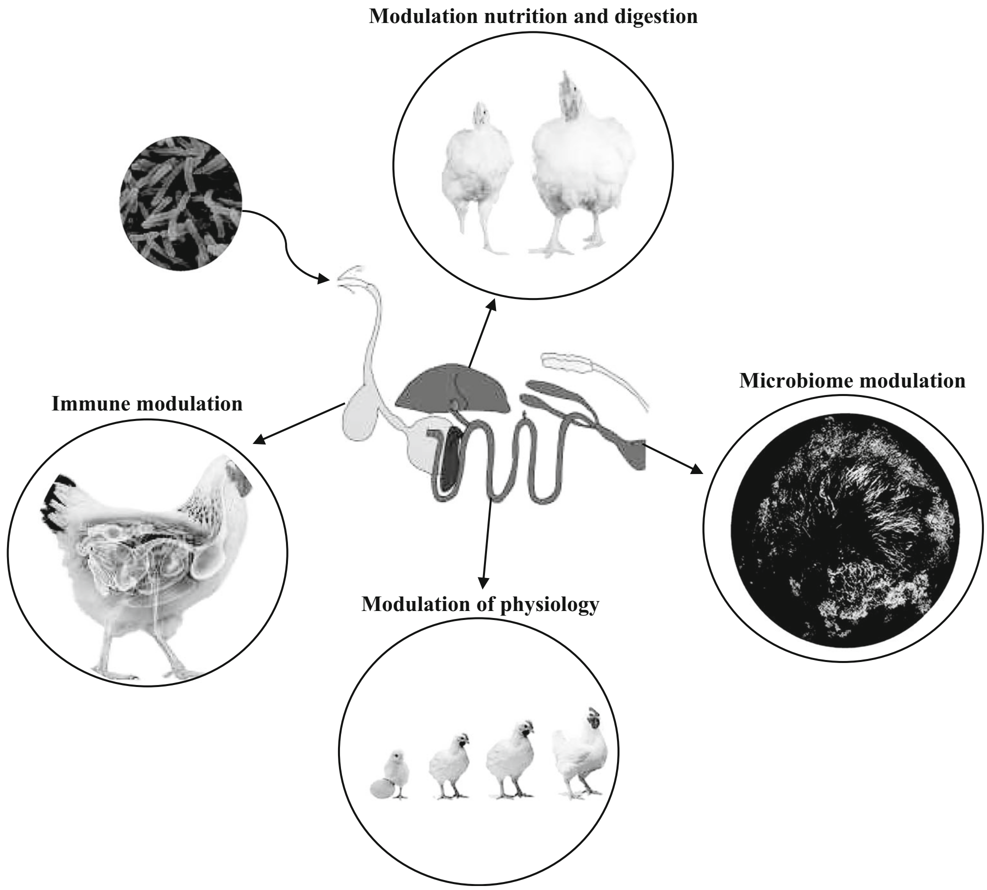

Fig. 1 General modes of action by which probiotics improve broiler health and performance

Anti-oxidative enzymes, such as glutathione S-transferase, glutathione reductase, glutathione peroxidase, superoxide dismutase and catalase, produced by probiotics scavenge reactive oxygen species (ROS) or prevents the formation thereof [77]. Strains of *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Bifidobacterium longum* and *Pediococcus pentosaceus* have been shown to possess antioxidative activity [77]. This is important, as ROS, often produced during stress, has a pronounced negative effect on the health and performance of broilers [78]. The presence of ROS may also lead to the development of chronic diseases and lipid peroxidation that may result in hyperlipidaemia and hyperglycaemia [79]. This results in an increase in the level of pro-atherogenic lipoproteins and a decrease in HDL (high-density lipoproteins) cholesterol levels [80].

Some probiotic bacteria regulate cholesterol homeostasis by hydrolysing bile acids, which prevents reabsorption in the intestine, indirectly lowering cholesterol levels [81, 82]. Members of the genera *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, *Clostridium* and *Bacteroides* frequently produce bile salt hydrolase [83]. The exact mechanism by which cholesterol is utilised is poorly understood. Probiotics administered to broilers decreased cholesterol levels in meat and blood [81, 82]. Probiotic bacteria may assimilate cholesterol during growth, bind cholesterol to their cell surfaces, incorporate cholesterol into the cell membrane, deconjugate bile via bile salt hydrolase (BSH) or co-precipitate cholesterol together with deconjugated bile [see review 84].

Microbiome Modulation

Interactions between the microbiota and host are important for development, health, nutrition and digestion and food safety [85]. Detrimental changes in the microbiota composition (dysbiosis) disrupts mutualistic interactions and can lead to disease [86]. Probiotics restore microbiota homeostasis by inhibiting pathogens and by promoting the growth of beneficial bacteria [87]. Immune activation or chronic inflammation induced by pathogens contributes to decreased health and growth in poultry. Probiotics and their metabolites induce shifts in the microbiota composition, from a predominant pathogenic microbiota to more beneficial microbiota [88]. This is primarily done by competitively excluding pathogens from the mucosal surface [89], competing for nutrients [90] and production of exopolysaccharides and antimicrobial compounds such as SCFAs, H_2O_2 and antimicrobial peptides (Fig. 3). Probiotics such as lactic acid bacteria (LAB) can also produce SCFAs (lactate, acetate, isovalerate, butyrate and propionate) which penetrate the cell wall of susceptible bacteria

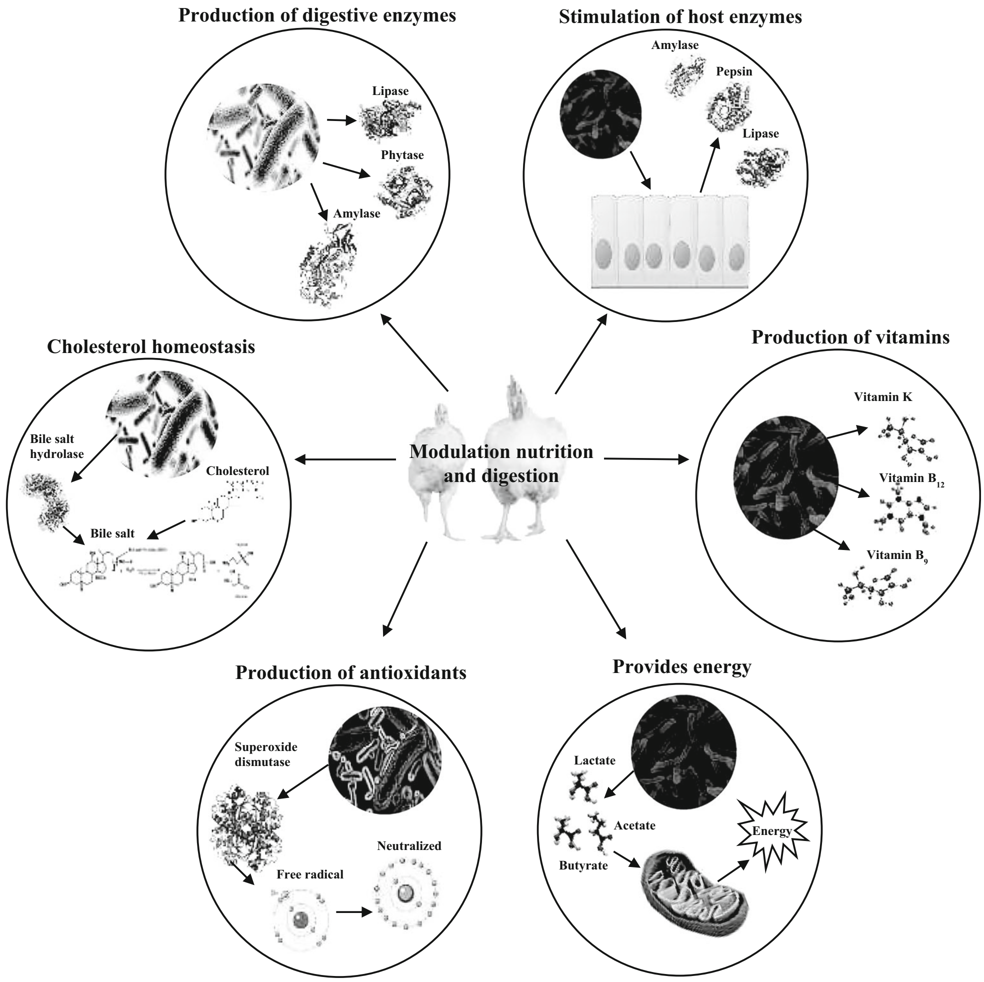

Fig. 2 Modes of action by which probiotics modulate broiler nutrition and digestion

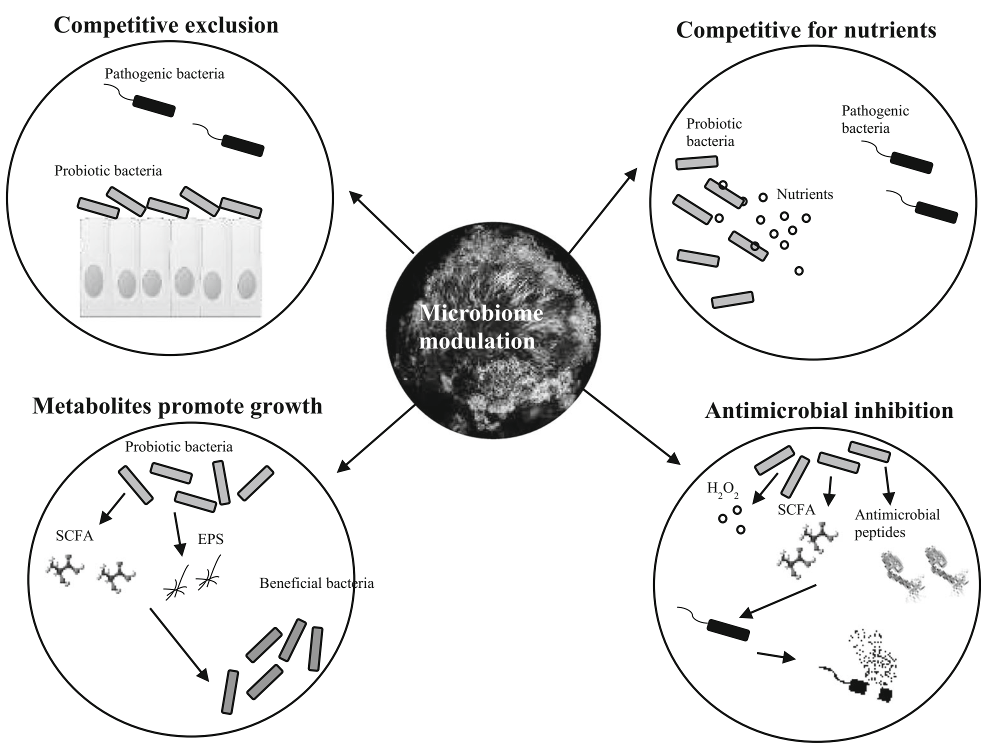

Fig. 3 Modes of action by which probiotics modulate the GIT microbiota composition

[91], decreasing the pH of the cytoplasm [92], leading to disruption of physiological reactions and the denaturation of proteins, enzymes, and nucleic acids [93], and subsequently cell death. Hydrogen peroxide produced by probiotic bacteria reacts with cellular components in the cytoplasm of susceptible prokaryotic cells, leading to apoptosis and destruction of the cell membrane [94].

Some probiotic bacteria produce antimicrobial peptides that may modulate the composition of the microbiota [95–100]. Bacteriocins are small, bacterially produced peptides that possess antimicrobial activity [101, 102]. The antimicrobial activity of bacteriocins has been well studied in vitro, but only a few reports of these peptides rendering protection against pathogens in the GIT have been published [103–105]. Some bacteriocins may also function as “colonizing peptides”, facilitating the introduction and dominance of the producing strain into an already occupied niche, as growth promoters regulating the microbiota composition [see review 106], or as signalling molecules that are used to communicate with other bacteria, or host cells [107]. In Gram-negative bacteria, (*N*-acyl) homoserine lactone typically serves as a signal molecule, while in Gram-positive bacteria, peptides, including some bacteriocins, are used as signalling molecules [see reviews 108, 109]. The production of EPS is equally important in modulating the gut microbiota, as shown with EPS-producing probiotic strains stimulating the growth of *Lactobacillus* and *Bifidobacterium* spp. [110, 111].

Although the microbiota of a broiler has been studied [112–114], much more research is needed to determine the role probiotics play in modulating the microbiota. First, we need to understand the role different members of the microbiota play in host physiology. This may be a challenge, since the gut microbiota of broilers is affected by a number of host and environmental factors [115]. Furthermore, little is known about how the avian microbiota develops, the factors responsible for early-life changes, and how these shifts in microbial populations relate to changes in metabolic functioning, health and growth [115]. It is, however, well known that probiotics assist in the establishment of a mature gut microbiota [116]. The potential role of probiotics in early-life includes the reduction of pathogen cell numbers, and an increase in feed conversion and growth [116]. Addressing these questions requires the developing of more advanced GIT investigation procedures and ultra-sensitive detection systems.

Modulation of Intestinal Barrier Integrity

With modulation of the gut microbiota, physiological changes in broilers are noted. These include changes in the integrity of the gut wall, the rate at which cells undergo apoptosis and, most probably, changes in the type of signals reaching the central nervous system via the enteric nerves (Fig. 4). All of these physiological alterations are observed as changes in bone health and meat quality [117, 118].

The epithelial monolayer forms a barrier between the luminal content and the interstitial tissue, which prevents diffusion of microbial cells and toxins from the lumen into the circulatory system and the tissue or organs [119]. Maintaining the integrity of the gut barrier is thus critical to prevent the translocation of pathogens into the intestinal lumen [120]. Probiotic bacteria regulate epithelial permeability by modulating tight junction (TJ) proteins (occludin, zonula occludens, claudins and junction adhesion molecules), which in turn inhibits pathogen colonisation, modulates cell proliferation and apoptosis, and controls mucin production [121–124]. Increased permeability leads to mucosal barrier dysfunction; however, probiotics can normalise TJ protein expression and localisation, restoring barrier integrity [125–127].

A balance exists between epithelial cell proliferation, differentiation and apoptosis [128]. Probiotics can modulate cell kinetics by regulating homeostasis of cell proliferation and apoptosis [88]. In addition, an increase in apoptosis over cell proliferation leads to increased susceptibility to pathogenic infections [129]. Numerous researchers have shown that probiotics regulate transcription of genes related to cell proliferation and apoptosis [88, 130, 131]. In the GIT of broilers, probiotic administration has been shown to regulate villus cell proliferation [132–134]. The structure and architecture of villi are important as their morphology regulates the capacity of nutrients absorption and defence responses against pathogens [132]. Probiotics regulate cytokine and oxidant-induced epithelial apoptosis by proteins p75 and p40 which activates anti-apoptotic Akt in a phosphatidylinositol-3′-kinase (PI3K)-dependent manner and inhibiting pro-apoptotic p38/MAPK activation [135, 136]. Reduced apoptosis improves barrier integrity and increases resistance to bacterial invasion [137]. In addition, numerous other studies have shown that probiotics decrease cell apoptosis by differentially expressing apoptosis inhibitor-related proteins, i.e. HIAP2/cIAP, TLR-2, COX2 and PGE2 proteins [138, 139].

Probiotic bacteria also contribute to intestinal barrier integrity by modulating mucin production [140–142]. Mucins are the major protein component coating the GIT. Probiotics normalise intestinal integrity through the restoration of the mucus layer by adjusting the mucin monosaccharide composition, mucus layer thickness and mucin gene expression [140–143]. The structural and functional properties of mucins influence bacterial adhesion to the mucosal surface. In broilers, probiotics modulate intestinal mucin monosaccharide compositions, subsequently influencing the GIT microbiota composition [140–142].

Until recently, the role probiotics play in bone health remained largely unknown [117, 118, 144]. Detrimental microbiota shifts in the GIT microbiota leads to dysbiosis which decreases bone density [145]. Probiotics are capable of

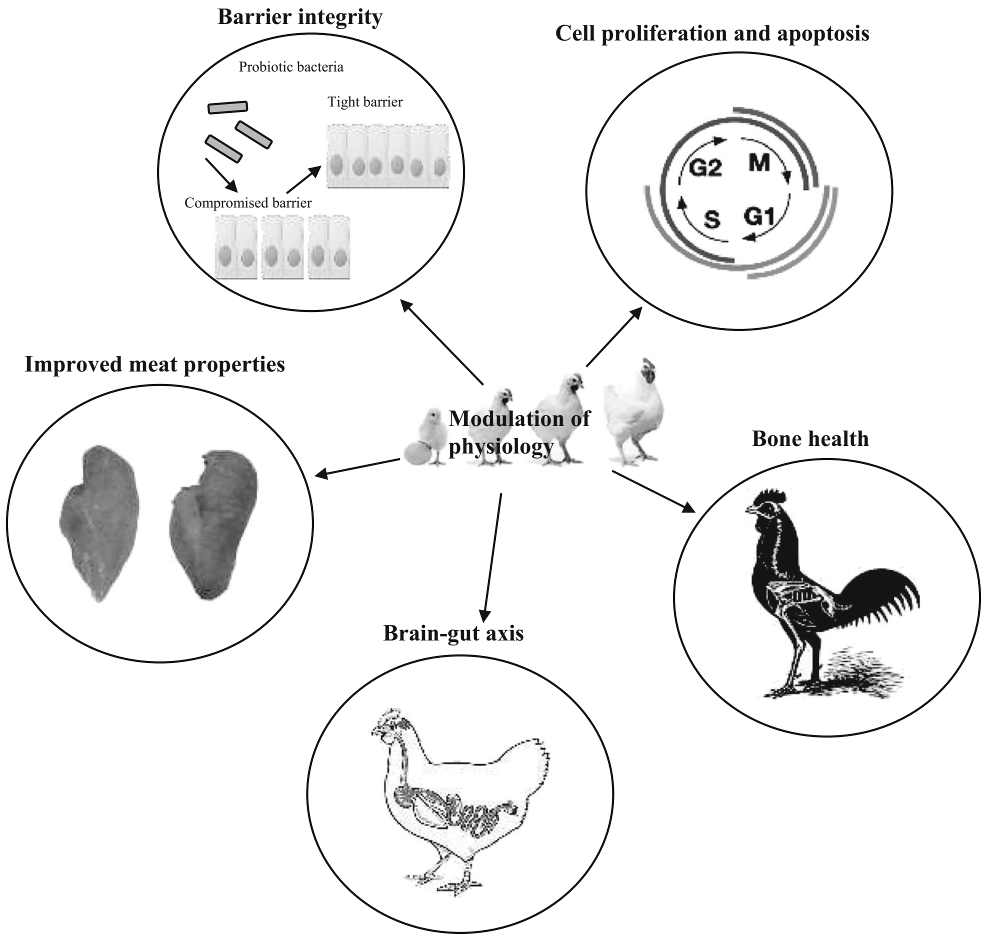

Fig. 4 Modes of action by which probiotics modulate broiler physiology

modulating bone mineralisation and development by impacting multiple aspects [147]. Probiotics modulate bone health by impacting nutrient acquisition important for bone growth (Ca^{2+} and P^{3-}), modulate barrier integrity and immune responses, and by the production of serotonin or oestrogen-like molecules [147, 148]. Probiotics indirectly modulate bone health by regulating microbiota health leading to increased intestinal absorption of minerals (Ca^{2+} and P^{3-}) important for bone health [149]. In addition, probiotics can also regulate bone health by neuroendocrine signalling pathways inducing intestinal cells to produces endocrine factors such as incretins, oestrogen-like molecules and serotonin which acts as signals for bone cells [147, 148]. In broilers, probiotics increase bone thicknesses and improve the mineral content and bone breakage strength [146].

Wang and co-workers [150] have shown that heat-stressed broilers fed a probiotic strain of *B. subtilis* coped better than broilers on a diet without the probiotic. Birds that received the probiotic spent less time in wing spreading, panting, squatting, drinking, sleeping, dozing and sitting. The probiotic-treated birds also had lower concentrations of hepatic IL-6, heat shock protein HSP70, cecal IgA and IgY.

Probiotics and Meat Quality

The role probiotics play in improving broiler carcass meat characteristics is highly debated. Some studies have reported improved meat attributes such as water-holding capacity, tenderness, lipid oxidation stability, sensory properties and microbial safety [151–155]. On the contrary, others have noted that there are no synergistic effects of probiotics on meat quality [156, 157]. Disagreements might be due to the differences in experimental conditions or probiotic compositions used. Probiotic administration in broilers improves the chemical, nutritional and sensorial characteristics of meat by increasing protein and free amino acid content, decreasing fat content and improving sensory properties [158, 159]. In broilers infected with pathogens, probiotic administration decreased pathogen-induced gut permeability [160].

Conclusions

Probiotics have a positive effect on feed digestion, regulation of GIT microbial communities, physiology and the immune system. However, in-depth research is required to understand the molecular changes brought about by probiotics and the crosstalk between probiotics, pathogens and epithelial cells. This will have to include metagenomic, proteomic and metabolomics studies. Elucidating these unknowns will provide greater insight into the role probiotics play in improving broiler health and growth.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interest.

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