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Review Article

Potential Probiotics Role in Excluding Antibiotic Resistance

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Background. Antibiotic supplementation in feed has been continued for the previous 60 years as therapeutic use. They can improve the growth performance and feed efficiency in the chicken flock. A favorable production scenario could favor intestinal microbiota interacting with antibiotic growth promoters and alter the gut bacterial composition. Antibiotic growth promoters did not show any beneficial effect on intestinal microbes. *Scope and Approach*. Suitable and direct influence of growth promoters are owed to antimicrobial activities that reduce the conflict between host and intestinal microbes. Unnecessary use of antibiotics leads to resistance in microbes, and moreover, the genes can relocate to microbes including *Campylobacter* and *Salmonella*, resulting in a great risk of food poisoning. *Key Findings and Conclusions*. This is a reason to find alternative dietary supplements that can facilitate production, growth performance, favorable pH, and modulate gut microbial function. Therefore, this review focus on different nutritional components and immune genes used in the poultry industry to replace antibiotics, their influence on the intestinal microbiota, and how to facilitate intestinal immunity to overcome antibiotic resistance in chicken.

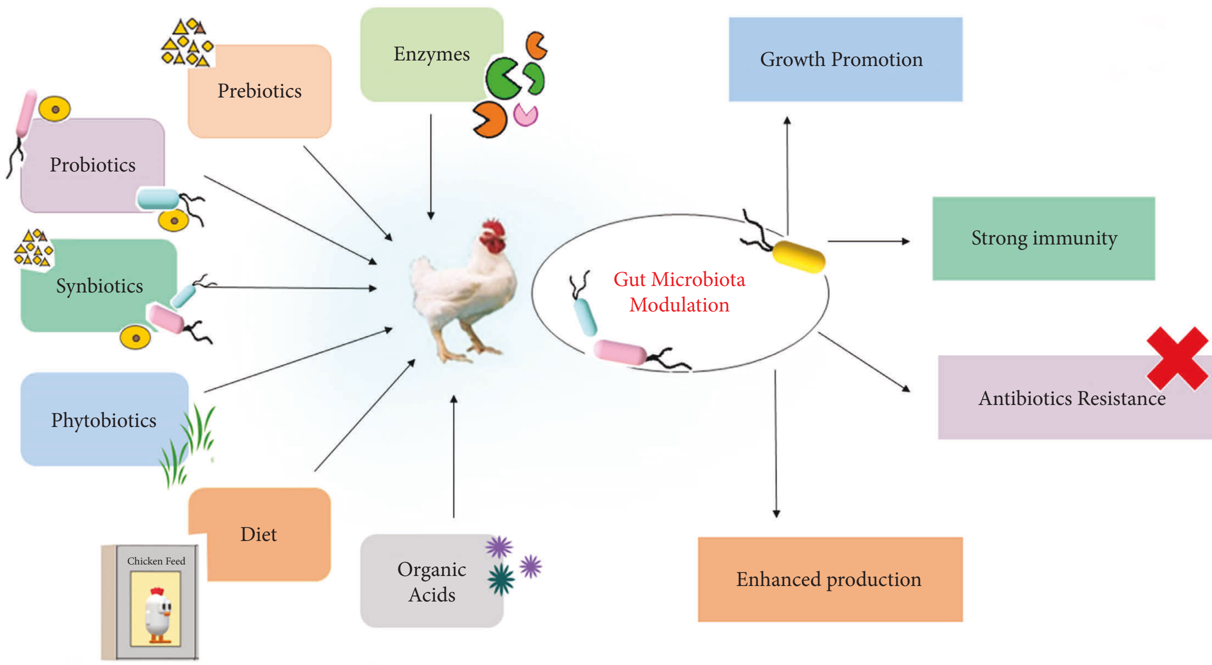


Figure 1: A schematic diagram of gut microbiota and introduction of different regulators involved in different functions.

1. Introduction

Bacterial resistance is a serious problem all over the world, especially in medical and agriculture fields. Bacteria displayed resistance to antibiotics and resulted in enhancing threats to human and animal health. Identifying mechanisms of resistance and investigating all the identified antimicrobial agents for clinical use are important. Curative and subtherapeutic uses of antimicrobials for animals are of increasing interest regarding the disclosure and distribution of resistant zoonotic bacterial pathogens [1]. A serious threat emerges due to antibiotic resistance with global deaths estimated by 2050 to reach 10 million people every year, but it is challenging to quantify the associated excess morbidity and mortality [2]. Due to disease problems and social pressure, there is a need to make important regulations on how to use particular antibiotics in livestock and poultry production. Potential alternatives need to implement to control different diseases and improve the quality of food through animal production and meat quality.

Supplementation of antibiotics is useful for stabilizing gut health, increasing growth performance, and preventing intestinal pathogens. Due to antibiotic resistance, the European Commission has banned the production and supplementation of antibiotics as growth promoters in the feed [3]. Different alternatives of antibiotics have been introduced including enzymes, organic acids, prebiotics, probiotics, and herbs to control pathogens by stimulating intestinal microflora in poultry production. The purpose of antibiotics alternatives is for feed preservation and antimicrobial activity [4–6]. The interaction of intestinal microbiota and the immune system through the use of antibiotic alternatives will be discussed in more detail in this review. Gut microflora plays a significant role in the chicken's physiological health, immunity, and nutrition. Schematic Figure 1 displayed different functions related to the use of gut microbiota. Different changes arise in gut microflora that can influence the feed efficiency accompanying bird status during health and disease. There are two subclasses of gut microbiota including the luminal microbiota and mucosa-attached microbiota. These could be affected by the nutrient availability, effects of antimicrobial substances, and the passage rate of diet [7, 8].

2. Morphological and Functional Development of the Small Intestine

Hatching results in maximum morphological changes in the small intestine. The intestine attains more weight as compared to whole body weight gain. The absence and presence of the feed are most important for small intestine development, but maximum and relative growth is less in the absence of feed. After 2–3 days posthatch, the crypts begin to form and reach a plateau. During the first 2 days, villi increase in length rapidly; a plateau reaches at first 10 days posthatch in the jejunum [9, 10]. The width of the jejunal villi increases marginally, and the optimum width was reached at 7 days posthatch. The density of jejunal villi reaches a constant level at 9 days posthatch [11]. The cell death or apoptosis occurs at the villi tips, which correspond to the physiological turnover. Dead epithelial cells and macrophages peel from villi into the lumen. Aberrant cell proliferation and maximum apoptosis occur due to contortion in the lumen of the intestine. More apoptosis is observed in the villus tip as compared to the villi tips of healthy chickens during the malabsorption syndrome, whereas acute inflammation arises due to infiltration of intestinal tissue/villi by heterophils, which provoke the production of cytokines in the affected villi epithelium [12, 13].

The capacity of the birds to absorb carbohydrates is detectable during the 18th embryonic day. A moderate level of absorbable capacity is in the hatch birds and then becomes maximum after a few days. With the increase of intestinal surface area, the absorptive capability also increases that occurs during morphological development. That is why enhancing the absorption surface results in the high uptake of nutrients that is significant for the synthesis and growth of tissues and organs. The regional activity of mucosal enzymes is linked with the digestive capability in particular intestinal regions. Mucin protein that is acidic in nature expressed from 17 days of eggs incubation to 3 days posthatch [14–16]. The production of neutral mucin that is linked with the mucus layer coordinates with the colonization of the intestine by microbes. *In vitro* studies on chickens and rats have proved that bacteria, for example, *Lactobacillus* strains, attach to the intestinal mucin and conflict for adhering to the epithelial or mucin layer happened between commensal bacteria and pathogens [17, 18].

3. Intestinal Microbiota

Colonization or aggregations of bacteria, viruses, and fungi in the skin, gut, genital, and respiratory tracts are described as microbiota. The microbiota has an important role in the suitable functioning of various physiological processes including host tissue development, nutrient absorption, and metabolism including immune system development [19]. Gut microbiota are closely associated with the lives of livestock, poultry, and of course human being due to their importance in overall health, well-being, and productivity. The gut environment's effects on the growth of normal intestinal bacteria have increasing commensal components that are accompanied by food-producing animals [20]. Intestinal epithelial cells, the immune system, and a microbial bunch are three important parts of the gastrointestinal tract (GIT) ecosystem [21]. Microbiota and host interlinking is very crucial for regular immune functioning. Microbiota regulates the growth of immune cells, the production of different molecules that facilitate the immune system including antibodies, host defense peptides (HDPs), and intestinal villi length and width [22]. Microbiota in GIT not only affects the host as a source of providing digestive enzymes but also increases nutrient absorption, defense, and destruction of pathogens and facilitates the growth of a healthy immune system. Irregular maturation of microbiota can result in the form of alternating of intestinal microbial colonization correlated with sensitivity, diabetes, obesity, diabetes, and abnormal immune defense system or responses [23]. The newly hatched chicks have differences in intestinal microbiota development; that is why there will be different responses to antibiotic treatment and diseases. Moreover, in animal kingdom, the growth and development of healthy gut microbiota is a very important stage in the beginning days after hatch that affects future growth and fitness [24, 25]. Initial days of chicks after hatching are very important for developing the normal microbial community. It shows that before going out of hatchery, young chicks have the most advanced stable microbiota [26]. The development of GIT is much faster than the development of other organs during the first week after hatching, and it is crucial for chicks to achieve genetic potential [27].

The primary and foremost assignment of the gut is the absorption of nutrients from feed and the expulsion of feces and urine. Moreover, chicks have a distinctive microbiota community that could be modulated by host secretions, dietary nutrients, and the host systemic responses [28]. Microbes regulate the various host physiological metabolisms in the gut and interact with each other and also with the host. Different genera that are associated with effective performance are *Lactobacillus*, *Clostridium*, and *Ruminococcus* [26]. There are two clusters of *Clostridium* species including IV and XIV, which are prominent in the microbiota of avian cecal, which is important butyric acid producers regarding growth booster function. Butyrate for epithelial cells is a crucial energy source in ceca and prohibits the inflammatory responses by a substitute on proinflammatory cytokines [29, 30]. There are more than 200 nonstarch polysaccharides enzymes (NSPs) and various pathways linked with the production of short-chain fatty acids (SCFAs) identified in a metagenomics analysis of cecal microbiota. These SCFAs provide energy to the chickens and decrease the cecal pH that inhibits pathogen growth and increases mineral absorption and ultimately growth performance [31].

4. Negative Impact of Antibiotics on Intestinal Microbiota

The basic purpose of antibiotics usage as therapeutics and growth promoters in animals and humans since the 1940s is to save lives and eradicate the uncountable microbes that cause diseases [32, 33]. It was reported that the United States utilizes an estimated 24.6 million dollar antibiotics annually as growth promoters. Antibiotics are obtained from either natural resources or synthetic drugs that play a critical role in the gut. Antibiotics have been widely associated with the poultry industry for decades, but there is the reduction in gut microbes and their toxic metabolites due to antibiotics [34]. Concurrently, overuse and irregular antibiotics supplementation have been declared to be notable bacterial resistance development. There is a threat to animal and human treatments due to bacterial resistance as they spread to genes for antibiotic resistance or may also interchange plasmid with intra- or interspecie [35, 36]. Antibiotic prophylactic usage in animal feed has been banned in the European Union (EC Regulation, No. 1831/2003). There has been a great challenge to nutritionist and poultry farmers due to this prohibition. There is an example of necrotic enteritis in poultry that is controlled with antibiotic growth promoters (AGPs) added in feed. Due to the prohibition of AGPs, there has been a great incidence of necrotic enteritis cases in poultry. Therefore, there is prompt demand for discovering antibiotics alternatives to regulate and maintenance of gut ecosystem balance and improve the overall performance of the birds [37].

Therapeutic and nontherapeutic usage of antibiotics causes the selection pressure for potential exits for *Salmonella* to obtain antimicrobial resistance genes from resident poultry microbiota. Previously, the abundance and diversity of antibiotic resistance genes (ARGs) were underestimated based on bacterial culture and ARGs identification that were intensified by the increase of sequence-novel ARGs [38, 39]. Recently, different approaches including metagenomics have been utilized for bacterial communities analysis and ARGs in bird diet [40]. The ARGs-harboring bacterial hosts were significantly influenced by bacterial colonization alteration due to antibiotics [41, 42]. Interaction between factors affecting the gut microbiota is shown in Figure 1.

5. Immune System

Biological structures, metabolism, and hemostasis that can protect the birds from different harmful organisms including bacteria, viruses, and protozoa are the immune system. The innate and adaptive are two types of the immune system. The innate immune system contains physical and chemical barriers including blood proteins, phagocytic cells, and blood complement serum proteins that function with antibodies to help the destruction of target cells. Whenever the innate immune system fails to invade pathogenic organisms, the adaptive immune system responds to counteract by recognizing the specific molecular functions on the outer surface of the pathogens. This system includes B and T cells and humoral immunity [43]. The immune system and physiology in birds also seem to parallel that of mammals due to the origin of the common reptilian ancestor and the lymphomyeloid tissues that are full of hematopoietic cells that evolved from epithelial or mesenchymal enlarge [44]. In the avian immune system, immune organs including the bursa of Fabricius, thymus, spleen, and lymphoid organs are fully developed when hematopoietic stem cells enter the bursal or thymic analogs and become efficient B and T cells [45]. The subtherapeutic doses of antibiotics were used since the 1950s in feed to improve growth performance in broiler chickens [46]. The increased knowledge of this concern with the antibiotic resistance development and the prevalence of its transfer to human pathogens has led to a European ban on the utilization of antibiotics in animal feed as growth promoters. Alternative ways are required to control microbial outgrowth and to prevent microflora imbalances in poultry. An alternative strategy is to modulate the expression of antimicrobial proteins (AMPs) such as β-defensin gallinacin-6 on the surfaces of the mucosa of chicken GIT [47]. Currently, several chicken antimicrobial peptides, belonging to the cathelicidin, liver-expressed antimicrobial peptide (LEAP), and β-defensin families, have been discovered. These are synthesized, are available after detecting the invading microbes, and rapidly neutralize a large range of microbes. AMPs have similarities among themselves regarding biophysical properties due to different species but their sequence is rarely similar. But some particular degree of identity is present either in the sequence of amino acids or the pre-region such as in cathelicidins. The AMPs possess a net positive charge that can attach to the negatively charged phospholipids groups on the bacterial membrane through electric interactions [48].

Recent studies have reported that beta-defensin family is involved in a crucial function in avian immunity, defending as the first line of defense against pathogens [49]. In the avian genome, only the beta-defensin family is present, also known as gallinacin or avian β-defensins (AvBDs) [50]. Avian β-defensins attach to a huge number of microbes including Gram positive, negative bacteria, yeast, and fungi [51]. Due to the response of multiple factors, beta-defensin is expressed and upregulated in the dendritic cells, keratinocytes, peripheral blood cells, epithelial cells lining the respiratory, gastrointestinal, and urogenital tracts including cytokines (interleukin) IL-1α, IL-1β, tumor necrosis factor-alpha (TNF-α), interferon-γ (IFN-γ), insulin-like growth factor1 [52], bacteria, lipopolysaccharides [53], yeast [54], and other stimulants such as PMA, isoleucine, and 1,25-dihydroxy vitamin D3 [55].

6. Regulation of Beta-Defensin in GIT

Microbial colonization of the avian gut possesses coincidence with gene expression of defensin, which plays a role as peptides defending against a huge number of microbes [56]. The responses of the gut defensin seem less predictable to the acute microbial challenges in down- and upregulation of the avian genes. Moreover, there are multiple factors challenged by microbes that could have an effect on GIT gene expression as well as the breed and age of the birds. The gene expression of avian β-defensin-1 (AVBD-1) and 4 in the duodenum were recorded elevated in the hatch and 7-day-old birds kept the low hygienic environment as compared to birds kept in the high hygienic environment due to potent gut antimicrobial activity, while AVBD-10 was found to maintain in all ages and environments [57, 58]. Figure 2 shows the antibacterial activity of sAVBD-6 against *Clostridium perfringens*.

AVBD 12 possesses a unique feature as a chemoattractant for avain immune cells and dendritic cells that can be related to the AvBDs application as a chemotherapeutic agent in the mammalian host. This is the reason that analogs of AVBD 12 were used to investigate the chemotherapeutic feature [59]. It has been proven that the antibacterial activity of avian β-defensin 7 plays an effective role to control the multidrug-resistant *Salmonella* strain after incubation with infected macrophages in the mouse. There was a significant reduction in the liver bacterial load that causes a significant increase in survival affected with a systemic lethal *Salmonella* infection. This can indicate that AVBD-7 could be used as a candidate of interest alternative to conventional antibiotics against bacterial infections [60].

7. Regulation of Cathelicidins in GIT

Four cathelicidins have been reported in the chickens until now including cathelicidin-1 (CATH-1), CATH-2, CATH-3, and CATH-B1 [61]. Cathelicidins possess a strong antimicrobial activity against various types of microbes including enveloped viruses, bacteria, and fungi at low

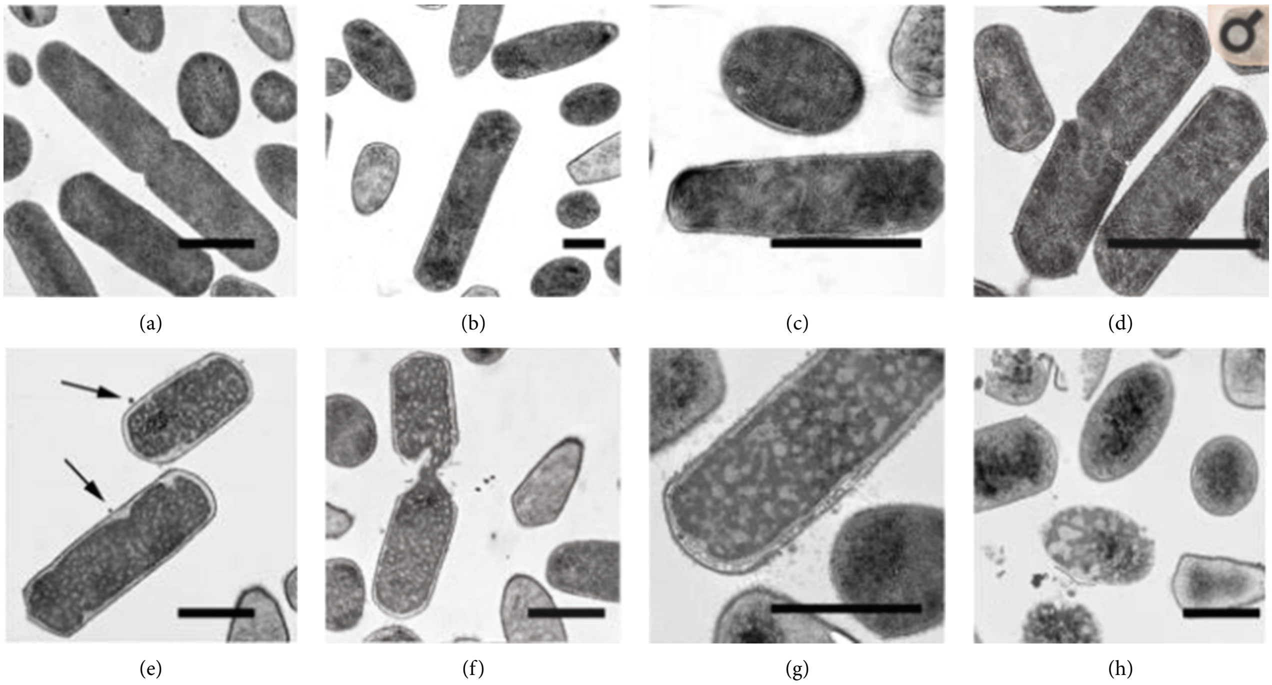


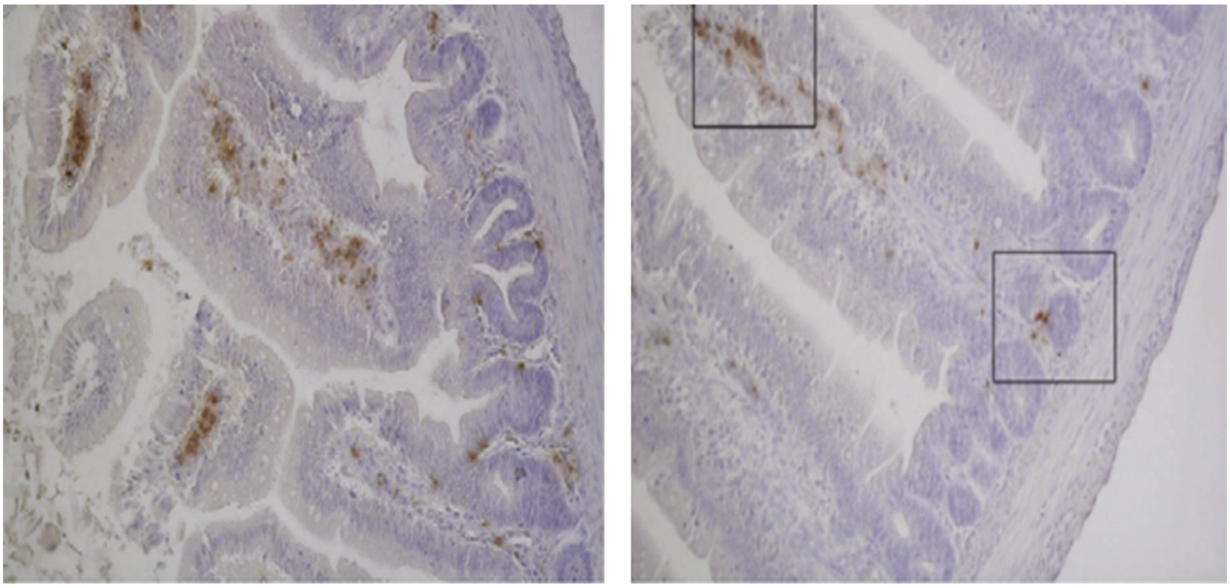
Figure 2: Transmission electron microscopy of *C. perfringens* cells incubated with synthetic AvBD-6. Bacteria incubated in a minimual medium for 30 min were undamaged. In contrast, bacteria incubated for 30 min with an increasing concentration of sAvBD-6 exhibited dose-dependent changes in the ultrastructure (a). Granulation of the intracellular material was already observed at 1.56 μm/ml (b). Irregular septum formation in dividing cells was observed at 1.56 μm/ml (c) and 6.25 μm/ml (d). At 12.5 and 25 μm/ml, cells exhibited retracting cytoplasm (e), lysis at the septa of dividing cells (f), cytoplasmic membrane degradation (g), and complete cell lysis (h) [47].

concentrations. Due to the cationic property in CATH molecular structure, it binds with the bacterial or fungal membranes containing negatively changed components. That is why the hydrophobic side chains are a lipid bilayer and disturbance resulting in pore formation. There are different models including carpet, barrel stave, and aggregate channel models of pore formation. Microbial exposure to the low concentration of peptides causes membrane permeability and proton motive force losses during complete lysis at high concentrations. There is another possibility that the negatively charge nature of the DNA, RNA, or proteins could lead to the prevention of DNA replication, protein synthesis, and function [62]. There was local infiltration of mature CATH-2 that was shown from heterophils after 8 and 48 h stimulation of *Salmonella enteritidis* in jejunum villus lamina propria of broilers of 4 days of age as shown in Figure 3 after immunohistochemistry. Moreover, CATH-2 could not express in intestinal epithelial cells from control or *Salmonella*-challenged broilers. CATH-2 exhibited dominant fungicidal and bactericidal activity against many microbes including specific chicken *Salmonella* isolates. CATH-1-3 has been reported to stop the LPS-induced cytokines to release from mouse macrophage cell line. Unlike CATH-1 and CATH-3, CATH-2 possesses a single proline residue at its center that can destabilize helical conformation and might be important for its interaction with biological membranes [63]. Enormous infiltration of CATH-2 positive cells eventuated in jejunal villi lamina propria of infected chickens at 8 h (a) and lesser extent at 48 h (b) as shown in Figure 3.

A moderate level of CATH-1 was expressed in the gizzard, small and large intestine, while CATH-2 expression was reported moderate in the cecal tonsil tissues and there was a low expression level throughout the intestinal tract [64]. Chicken CATH-B1 was expressed in the bursa of Fabricius and restricted to secretary epithelial cells due to the close proximity of M cells [65]. The highest expression level of CATH-1, CATH-2, and CATH-3 was found in the large intestine of the Baladi (local) breed, while only CATH-2 showed moderate expression levels in the duodenum [66].

8. Probiotics

Microbes fed directly or probiotics have been previously defined as "live microbial feed supplement with beneficial effect to host animal by improving its intestinal balance" [67]. Currently, bacterial species that are used as lactic acid producing (*Lactobacillus bulgaricus*, *Lactococcus lactis*, *Lactobacillus acidophilus*, *Lacticaseibacillus casei*, *Lactiplantibacillus plantarum*, and *Ligilactobacillus salivarius*), *Streptococcus thermophiles*, *Enterococcus faecium*, *Enterococcus facecalis*, *Bifidobacterium* sp., fungi (*Aspergillus oryzae*), and yeast (*Saccharomyces cerevisiae*) are used as probiotics [68, 69]. It is suggested that probiotics, when fed early in life, can influence the intestinal environment and



(a) (b)

Figure 3: Localization of CATH-2 in jejunal tissues of *S. enteritidis*-infected chicken. Chickens were infected with 1 × 104 CFU nalidixic-resistant *S. enteritidis* PT4. Jejunum tissue sections from infected and control chickens were taken 8 and 48 h after infection and were applied with Giemsa stained followed by immunostaining with anti-CATH-2 antibody. Massive infiltration of CATH-2 positive cells occurred in jejunal villi lamina propria of infected chickens at 8 h (a) and lesser extent at 48 h (b) [63].

favor the establishment of beneficial bacteria, thus reducing the likelihood of pathogenic colonization [70, 71]. The proposed mechanism of probiotics include: (a) competitive exclusion and antagonism of pathogens through the maintenance of beneficial commensals, (b) altering metabolism decreasing bacterial ammonia production and enzyme activity while increasing digestive enzyme activity, (c) boosting feed intake and digestion, (d) neutralizing enterotoxins, and (e) stimulating immune system [72]. There are some possible mechanisms that may be responsible for the competitive exclusion of pathogens. These include competition for binding sites of the mucosa, nutrients, or inhibitory substances production like volatile fatty acids or bacteriocin, which are antibacterial for pathogenic bacteria. Preparations are normally fed orally to newly hatched chicks in order to prevent colonization by pathogens in the rearing environment [73, 74]. Interestingly, some studies reported that undefined preparations have a beneficial influence on the necrotic enteritis prevalence including reduced mortality and cecal colonization, for example, demonstrated the lowering in the colonization of *C. perfringens* and subsequent reduction in the incidence of necrotic enteritis [75]. Another field study found that the use of undefined microflora preparations delayed the intestinal proliferation of *C. perfringens* and the presence of necrotic lesions [76], while the performance of probiotics depends on the blocking receptor sites of pathogen adhesion, production of antimicrobial peptides, transfers in the intestinal microbial structure, and immunomodulation in chickens [77].

There are many probiotics that are available with various commercial names in the market. But *Lactobacillus acidosis* is an important bacterial organism that provides the best acidic environment (pH 5–6.5) for the growth of villi in the intestinal wall to increase the surface for nutrient absorption [78]. Additionally, five effective strains *Pediococcus acidilactici* (*P. acidilactici*), *Enterococcus faecium* (*E. faecium*), *Bifidobacterium animalis*, *Lactobacillus reuteri*, and *L. salivarius* were investigated that these strains can inhibit a range of common pathogens in *in vitro* condition [79]. Lactic-acid-producing bacteria produce bacteriocins, lactic acid, peroxides, and antibiotics. These factors play an important role in the colonization of intestinal mucosa by probiotic bacteria by preventing the binding of pathogens and hence competition for attachment sites. Different beneficial bacteria produce different antibodies. The bacteriocin is produced from the bacterial genus *Enterococcus*, which possesses an inhibitory influence on pathogens *Clostridium* and *Listeria* spp. in broilers [80]. Acidophilin, lactocidin, and acidolin are produced from *Lactobacillus acidophilus*, while lactolin is produced from *L. plantarum*. Additionally, the lantibiotic nisin is produced by different *Lactococcus lactis* spp. Bacteriocin-like inhibitory substances are produced from *Bacillus cereus*, which has an inhibitory effect on *Staphylococcus aureus* and *Micrococcus luteus* with activity in the range of pH 2–9 [81]. Acidophilin, acidolin, lactobacilli, and blasticidin show *in vitro* inhibitory activity against *Klebsiella, Proteus*, *Salmonella*, *Shigella*, *Vibrio*, *Staphylococcus*, *Pseudomonas*, and *Escherichia coli*. Due to the supplementation of probiotics, there are a large number of goblet cells in the avian intestinal villi that suggested the substances produced during bacterial fermentation may take part in the development and maturation of goblet cells. The second mechanism is known as a tight junction a unique structure that establishes the epithelial barrier integrity,

Table 1: Probiotics and beneficial effects.

Probiotics	Biological functions	Reference(s)
E. faecium NCIMB 10415	Supplementation increases chicken body weight and FCR	[82]
Probiotic-FMB11(*Lactobacillus*)	Increase body weight and reduce cost of production	[83]
Lactobacillus (2 strains), *Bifidobacterium*, *Enterococcus*, *Pediococcus*	Increase more growth and no residual effect as compared to avilamycin-containing product	[84]
CE and MCE cultures	Feed CE and lowering colonization of *S. typhimurium* and *Campylobacter* as compared to the MCE	[85]
Probiotic Bio Plus 2B (*B. licheniformis*, *B. subtilis*)	Enhance egg production, reduce the ratio of damaged eggs, and reduce serum and egg yolk cholesterol and triglyceride levels, effective on FCR	[86]
Saccharomyces cerevisiae	Regulate intestinal microflora balance and humoral immune responses and also upregulate the expression of IL-1β and downregulate the TLR-4	[82, 87]

which inhibits the entrance of pathogenic bacteria and macromolecules. These are dynamic protein structures that can regulate their function [81]. Different probiotic strains and beneficial effects are shown in Table 1.

9. Prebiotics

Yeast cell walls (YCW) consist of mannoproteins, β-1,3-glucan, β-1,6-glucans, chitin glucans, and glucophospholipid surface proteins that are related to the plasma membrane. YCW is well-known possessing prebiotic properties with efficacy for regulating the immune system and intestinal microbiome [88]. Prebiotics with the proinflammatory response were investigated to inhibit the disease, as inflammation stimulates the host immunity against the disease [89]. The utilization of prebiotics, such as *Saccharomyces cerevisiae,* mannan-oligosaccharides (MOS), fructooligosaccharides (FOS), and beta-glucan has been applied in many experiments in chickens [90–92]. The Actigen™ (prebiotic) or MOS is second-generation yeast developed by using a technology called nutrigenomics that deals with changes in the gene expression of intestinal cells. Basically, Actigen™ is mannan-oligosaccharides a specific product that has been acquired from the outer cell of yeast (*Saccharomyces cerevisiae* var.),which improves growth performance [93]. The uses of MOS improve and maintain intestine health, hence leading to efficient absorption and conversion of nutrients into body weight [54]. The β-glucan is a long-chain polysaccharide and prebiotic that is extracted from yeast or fungal cell wall. Receptors of β-glucan recognition are present on sentinel cells, stimulating the production of cytokines and expansion of lymphocytes [94]. There are three major types of lymphocytes including NK cells, T cells, and B cells that play an important role in innate immunity, regulation of adaptive immunity, and production of antibodies against antigens [53]. Chitosan oligosaccharides that consist of 1–4 β-linkage with 2–10 sugar units of glucosamine 2–10 sugar, extracted from chitin, reported that supplementation in a broiler diet could regulate the immune system and increase nutrient availability, digestibility, and feed conversion ratio [54]. There is an increase in body weight gain of broilers 34 days after hatching due to the *in ovo* injection and also affected the intestinal microbiota [95]. But *in ovo* supplementation of GOS could replace prolonged water supplementation [96]. There are some novel extracted prebiotics that are acquired after processing of the softwood trees including galactoglucomannan oligosaccharides-arabinoxylans (GGMO-AX) and galactoglucomannan oligosaccharides (GGMO). Moreover, these contain glucose, galactose monomers, and mannose [97]. *In vitro* conditions investigated that *Lactobacillus* could grow faster on GGMO than MOS. It is reported that *Lactobacillus* could grow faster on GGMO than MOS. It has been described that colonization of *Salmonella typhimurium* in the liver, ceca, and ileum when supplemented with 0.2% GGMO in a broiler diet and enhances the growth performance and healthy intestinal morphology by clearing *S. typhimurium* as compared to the control treatment [98].

Xylan is the main part of cereal fiber such as corn cobs, hulls, straws, bran, and raw source of xylo-oligosaccharides (XOS). By the degradation of xylan from xylanase of fungi, steam or mineral acids diluted solutions can produce the XOS [99]. XOS might enhance growth performance, intestinal villus height, the proportion of *lactobacillus*, and levels of organic acids including butyrate, acetate, and lactate in the ceca of chickens. There is an increase in antibody titer against influenza H5N1 and thus improve humoral immunity in chickens by XOS supplementation [100, 101]. The supplementation of autolyzed yeast in the broiler diet would help provide cellular components and cell wall carbohydrates. *Saccharomyces cerevisiae* (an autolyzed yeast) contains 29–64% β-glucans, 13% protein, 9% lipids, and 31% mannan-oligosaccharides. Supplementation of yeast in ruminant feed depends on the enhanced rumen cellulolytic bacteria, energy delivered from diet, and finally the performance of the animals [102]. Fructooligosaccharides (FOS) and mannan-oligosaccharides (MOS) are two important beneficial bacterial groups that can cause the proliferation of *Lactobacillus* and *Bifidobacterium* and limit the number of *Salmonella* and *E. coli* (Table 2). These bacteria bind with MOS through the fimbriae, not with epithelial cells, which cause the bacteria to expel out with the feces [91]. FOS decreased the *S. enteritidis* in the excreta and colonization in the ovaries of layers. However, FOS upregulated the toll-like receptor-4 (TLR-4) and enhanced IgA-positive cells in the ileal mucosa. YCW exhibited strong anti-inflammatory effects than antibodies or a control diet, which causes lowering the liver relative weight because of systemic inflammation [103]. It was reported that the heterophil: lymphocyte ratio (H:L ratio) and basophil counts were

Table 2: Prebiotics and their biological functions.

Prebiotics	Biological functions	Reference(s)
FOS (fructooligosaccharide) or fructans	Create positive effect on the growth of *Bifidobacterium* and *Lactobacillus* bacteria and reduce pH that results in inhibition of *E. coli*.	[91]
Chitosan oligosaccharides (COS), extracted from chitin	Increase the weight of the bursa, thymus, IgG, IgA, and IgM in the serum and antibody titers against NDV and also, improve ileal digestibility.	[54, 106]
IMO	Increase the *Bifidobacterium* count in the gut and decrease the *S. typhimurium* count.	[107]
Mannan-oligosaccharide (MOS)	Inhibit the adhesion of bacteria with gut epithelial cells and improve intestinal immunity and microflora.	[82]
Yeast β-D-glucan	Trigger macrophage proliferation, production of inducible nitric oxide synthase causing nitric acid production that can kill *Salmonella enterica*, and regulate macrophage gene expression of interleukin-1(IL-1), IL-18, and TNF-α (tumor necrosis factor-α).	[54]
Galacto-oligosaccharides (GOS)	Inhibit the *Lactobacillus intestinalis* and *Faecalibacterium prausnitzii* in the broilers ceca and also enhance the concentration of *bifidobacteria* and lactobacillus in feces.	[96]
Xylo-oligosaccharides (XOS)	Lactate produced from *L. Crispatus* that could be used by butyric acid-producing bacteria. In response to this, butyrate can trigger MUC-2 gene expression, exert anti-inflammatory effects, and prevent necrotic enteritis.	[99]

higher in birds fed antibiotic-free control and 0.5% FOS diets than in birds fed antibiotics or other prebiotics-added diets [104]. Results from pathogen-challenged animal models in evaluating the effect of FOS supplementation on pathogen colonization suggested a reduced susceptibility to either *Salmonella* spp. or *E. coli* infection in broiler chickens [105]. These results suggest that the FOS supplementation in broiler diets may reduce the susceptibility to *Salmonella* colonization.

Supplementation of yeast β-d-glucan and *S. enteritidis* have interaction effects on AvBD-1 mRNA expression (at 15 day postinoculation (DPI), $P = 0.004$), AvBD-10 (at 7 DPI) and liver-expressed antimicrobial peptide-2 (LEAP-2; at 15 DPI $P < 0.001$) in jejunum. It was found that LEAP-2 showed higher expression in the SE-infected group as compared to the other groups at 15 days postinoculation (DPI) while in early infection found lower expression levels in the spleen. AvBD-1 exhibited the highest expression level in the glucan-supplemented and SE-infected birds. AvBD-10 gene showed higher mRNA expression in the jejunum at 7 DPI in birds infected with S*almonella* with no beta-d-glucan supplementation as compared to the control birds. AvBD-10 mRNA gene expression in the jejunum at 7 DPI was found to be lower in the birds given glucan and *Salmonella* infected as compared to the glucan-treated and uninfected birds. By the use of yeast β-D-glucan, the overall growth performance of broilers was affected but has a strong response of protective way against *Salmonella* infection (Table 2). *Salmonella* infection causes decreasing growth performance in birds due to the disruption of the intestinal mucosa and strong inflammatory responses [53]. *S. enteritidis* colonization in the intestine could be inhibited by the supplementation of yeast β-D-glucans causes the production of β-defensin in intestine mucosa. Moreover, there may be two reasons in the spleen: (1) during the early stage of infection with local infection of *S. enteritidis* in the intestine, there might be not enough stimulants for the origination of immune response in the spleen. The cells are stimulated due to infection started circulating in the body and enter into spleen and (2) the higher *Salmonella* load in the spleen in early infection period causes lower AvBDs gene expression which could be compromised to the production of defensin through immune evasion mechanism[53].

10. Synbiotics

When probiotics are combined with prebiotics, then they form synbiotics. As mentioned earlier that probiotics and prebiotics have been described to provide a positive influence on GIT of the birds [37]. The development of gut morphology and nutrient absorptions are contributed to enhancing the growth performance of chickens due to feeding synbiotics [108, 109]. A probiotic and FOS when used singly reduce the colonization of *S. enteritidis* in the intestine but show more effective utilization when used in combination [110]. In contrast, using in combination of multiple strain probiotics (containing 11 *Lactobacillus* strains) or prebiotics such as isomalto-oligosaccharide (IMO) alone for the purpose of cecal bacterial microflora and the concentration of ceca volatile fatty acids (VFAs) and non-VFA of the chickens, synbiotics does not exhibit 2-fold synergic effects [108]. Synbiotics have the great potential to be utilized as antibiotics alternatives for improving overall growth and decreasing pathogenic load in the chickens [111, 112].

There were histomorphological changes that occurred in the small intestine of chickens when synbiotics were used in the ovo stimulation. On day 1, both *L. salivarius* and *L. plantarum* enhanced the villi height, width, and surface of the duodenum of the chickens. Moreover, Brudnicki et al. showed that RFO prebiotics with ovo stimulation of broiler chickens enhanced the absorption rate of yolk sacs in the day-old chicks (Table 3) [96]. The retention of yolk sac in the population at the end of 14 days of posthatching was 0% in

Table 3: Synbiotics and their biological functions.

Synbiotics	Biological functions	Reference
Lactobacillus spp., lactose	Improved FCR and body weight	[114]
B. subtilis, FOS	Reduced incidence of diarrhea and mortality	[68]
A prebiotic fructooligosaccharide and four probiotic bacterial strains (*Lactobacillus reuteri, Enterococcus faecium, Bifidobacterium animalis, and Pediococcus acidilactici*)	More hen day egg production in supplemented hens than in nonsupplemented	[115]

the *in ovo* stimulated group as compared to 30% in the control group. From this, it is concluded that the major source of immunoglobulins contribution to the passive immunity in newly hatched chicks and initiation of early growth posthatching is the yolk sac, and faster yolk sac resorption results in the greater shifting of maternal antibodies into chicken's bloodstream [113]. For early colonization of the embryonic gut with benefit microbes, *in ovo* stimulation is a powerful and effective tool that can result in improved health, performance, and welfare of the chickens.

11. Organic Acids

Organic acids are carboxylic and fatty acids that possess a chemical structure R–COOH. Acetic acids, formic acid, propionic acid, butyric acid, lactic acid, malic acid, fumaric acid, and citric acid have been used in the poultry industry due to the importance of their physiochemical properties (Table 4). The utilization of an organic acid mixture in poultry feed not only improves the growth performance but also better carcasses characteristics [116]. It has been described that (formic, phosphoric, formic, tartaric, malic acid citric, and lactic acids (an acidifier mixture) were added to the chicken feed at the rate of 0.15%, and body weight gain was achieved. This improved performance may be due to the reduction of pH values in the gut, decrease in the number of pathogens that are tactful to lowering pH, or increase in the number of acid-loving *Lactobacillus* and exert direct antimicrobial effects [117]. The fundamental interest in organic acids usage instead of the use of antibiotics is that there are no residues in the meat or environment and any microbial resistance [118]. Many research work have described that organic acids in the diet have affected the height and area in the duodenum, jejunum, and ileum of chickens significantly [119]. There has been an increase in villi height, crypt depth, and surface area in the colon and jejunum of rats by supplementation of butyrate [120]. Broilers fed a diet having formic acid have the longest villi (1,273 μm) as compared to control (1,088 μm), whereas birds fed the organic acids possess deeper crypts in jejunum as compared to antibiotic-fed birds (266 vs. 186 μm) [121]. It has been described that to boost the normal crypt cell proliferation. There will be an increase in fast-growing tissues and maintenance. Butyrate concentrations (0.2%, 0.4%, or 0.6%) in broiler feed had improved the villi length and crypt depth in the duodenum and might be highly beneficial to young birds in intestinal development [122]. Supplementation of 3% butyric acid and fumaric acid and 2% formic acid mixed in the bird feed was experienced the highest duodenal, jejunum, and ileal villus height, respectively. The development in villi height of different parts of the small intestine might be attributed to the contribution of the intestinal epithelium as a natural barrier against pathogenic bacteria and toxic substances. These pathogenic substances cause a disturbance in the normal microflora or may change the permeability of intestinal epithelium and facilitate the takeover of the pathogen resulting in alteration of the ability to digest and absorb nutrients that leads to chronic inflammatory processes in the intestinal mucosa [81]. Due to the property of low pH organic acids, it may be helpful in preventing the transfer of bacteria from the diet or environment [123]. However, the reduction in the *Coliform* or *E. coli* count was more enormous than those of lactic acid-producing bacteria or *Lactobacilli* count in the ileum or the cecum. Less susceptibility to pH changes may be the reason for higher *Lactobacilli* that confirms that *Lactobacilli* in the gut are less sensitive to pH changes or reduction [122]. The *Lactobacilli* growth will be a boost in response to acidic pH and early growth of chickens.

12. Enzymes

Corn starch comprises amylose and amylopectin. Most starch sources are composed of 70–80% of amylopectin. Amylopectin contains α-1,4 and α-1,6 glucosidic bonds. α-amylase can degrade α-1,4 glucosidic bonds, but amylopectase is needed to degrade amylopectin [127]. Moreover, high concentrations of insoluble nonstarch polysaccharides (NSPs) are present in the corn including xylan and cellulose that have the ability to decrease digestive enzymes activity [128]. There is a large amount of native trypsin inhibitors in the corn, ranging from 0.56 to 1.87 mg/g dry matter, which inflict restriction on the enzyme to access the substrate associated with high digesta viscosity in chickens. The growth of *C. perfringens* has a much friendlier environment in the upper gut of chickens due to slow digestion passage rate, impaired nutrient digestion, and increased water intake that affect negatively on gut health [129]. The new season grains diets starch could be hydrolyzed by the supplementation of NSP-degrading enzymes that can reduce digesta viscosity and increase nutrient digestibility of the chickens fed a corn-based diet [130].

The supplementation of multienzyme (xylanase, amylase, protease, and phytase) enhances the optimum utilization of fibers and increases intestinal microbiota leading to the availability of important minerals and better growth performance of broiler chickens [128]. For degradation of NSPs in barley based diet, exogenous enzymes are used that can cause significant variation between gut microbial communities except between duodenum and jejunum. *Salmonella* that can be transmittable horizontally can be

Table 4: Functions of different organic acids in intestinal microbiota.

Organic acids	Biological functions	Reference
Butyric acid, acetic acid	Acting as the fuel of intestine, energy generation enhances development of host epithelial cells and villi height and is in the duodenum.	[8]
Citric acid	Lower the pH and cause increasing acid-loving lactobacillus	[117]
Fumaric acid	Increase Jejunum villus height	[124]
Formic acid	Decrease *Clostridium* count in the ileum	
Propionic acid	Directly act on the cell wall of Gram negative and result in lowering the pH in the GIT	[126]

controlled by the application of exogenous enzymes. The effectiveness of exogenous enzymes depends on different factors including animal strain, digesta viscosity rate, sex, diet composition, and type of supplemented enzyme [131, 132]. Yadav and Jha demonstrated the linking of growth-promoting effects of enzymes with mucosal morphology of the small intestine [133]. Moreover, the increase in the membrane enzyme activity and role in the last step of digestion cause the reduction in crypt depth of jejunum, ultimately improving growth performance in chickens by xylanase supplementation in diet [134]. Exogenous protease plays an important role by reducing the undigested protein from diet or caudal gut inflammation reduction and maintaining tight junction integrity [135].

The use of exogenous enzymes (xylanase, β-glucan, amylase, protease, phytase, lipase, and α-galactosidase) is important in poultry diets, which is composed of corn and soybean meal because these contain various anti-nutritional factors including NSPs and protein inhibitors that can disturb the normal digestion and nutrients absorption in the gut [136, 137]. Phytic acid is a crucial anti-nutritional factor due to the property of bonding with proteins, minerals, and starches prohibiting them to dissolve in GIT and thus not being available for chickens [138]. In chickens, the activity of phytase at the brush border of GIT is very low; this is the reason for supplementation of phytase in the feed for maximizing phytase activity for the availability of phosphorus and energy contents [139]. Dersjant-Li et al. reported that crop is the primary site for the bacterial phytase [140]. Maximum phytase utilization in chicken GIT will ensure the reduction of phytate phosphorus pollution in the environment when manure mix with the land and chicken will not face phosphorous deficiency problems. The reduction of digesta viscosity and FCR of chickens provided with different varieties is caused due to the proper use of exogenous microbial xylanase [141]. A most important factor in exogenous enzyme supplementation in the wheat-added feed is a significant level of arabinoxylans [142]. The most positive effects of xylanase supplementation on the growth performance of broilers in this research seemed to be related to improved nutrient digestibility, decreased viscosity of digesta, longer villi, as well as increased villus length-to-crypt depth ratios [143]. Supplementation of exogenous xylanase led to increasing numbers of *Lactobacilli*, which was confirmed by Nian et al., leading to the reduction of *Coliform* in the ileal contents, but *Salmonella* was not detected, while in cecal content, *Coliform* and *Salmonella* were increased simultaneously [144].

13. Herbal Extracts or Phytobiotics

Plant-derived compounds added into the diet to improve livestock productivity by melioration of feed properties, improvement of nutrient digestibility, absorption, and elimination of pathogens in the gut are phytogenic feed additives. According to their origin and treatment, a variety of plant derivatives used as nonwoody, herb flowering, spices (herbs with concentrated smell or taste commonly added to human food), like cinnamon, corridor, pepper, chili, oregano, and garlic (Table 5). Some are extracted from the fruits such as flavonoids that are water-soluble used in poultry feed as additives [145]. Phytobiotics possess many properties in poultry feed including palatability and quality (taste), growth promotion, gut function (improve health and absorption), carcass meat safety, and reduced microbial loads [84]. Different phytobiotics perform different functions including triggering the favorable bacterial growth including *Lactobacilli* and *Bifidobacteria*, acting as immune-stimulatory substances, and acting as protective shield against microbial attack in intestinal tissues, by decreasing virulence properties by enhancing microbial species hydrophobicity [146].

Essential oils from anise, citrus peels, and oregano along with antibiotic growth promoter reduced microbial activity in the cecum, colon, and terminal ileum, decreased chyme contents of volatile fatty acids and reduced bacterial colony count as well as biogenic amines. Relief from antimicrobial activity and its related product in small intestine results in volatile fatty acids counteracts intestinal pH stabilization and helpful for digestive enzyme activity. The formation of biological amines is causing toxicity by decarboxylation of limiting essential amino acids such as cadaverine from lysine and skatole from tryptophan [147, 148]. Using these feed additives can alter morphological changes in intestinal tissues and benefits the digestive tract by increasing villi length and reducing crypt depth in the jejunum and colon in broilers [149]. Hydrophilic extract of liquid fresh green tea at the level of 0.1 or 0.2 g/kg in a broiler diet can increase body weight gain, carcass weight, feed efficiency, and dressed weight, reducing the cholesterol content in serum and yolk [147]. The inclusion of ginger powder (0.5, 1, 1.5%), in a broiler diet, showed increased breast and thigh muscle yield and reduced abdominal fat content at a 1.5% ginger powder inclusion level due to the anti-cholesterimic effect. Thyme and cinnamon at 0.5 and 1% inclusion rate favorably changed antimicrobial balance (reduced total bacterial count and *E. coli* form group in jejunum and large intestine) in broiler's gastrointestinal tract [150].

14. Feed and Nutritional Management

The fibrousness, hardness, and coarseness of feed particles are referred to as the diet texture. The presence of these particles in the diet contributes to benefits to the digestive system of birds. In a broiler diet, lack of structure or texture affects the bird growth performance in modern commercial poultry production [160, 161]. Feed intake can be affected due to feed particle size and grain type being used and vary with the age of birds. Beak pasting from the fine grinding of wheat is an important reason results due to wheat gluten and enhances digesta viscosity with associated depression in feed intake [162]. It was reported that whatever the method of grinding (hammer or roller mill) of sorghum, broiler consumed feed according to the coarseness of feed and surface of ground grain is inversely related to the feed intake [163]. Pelleting feed positively affects feed intake and improves feed consumption due to the complete balance of nutrients available to chickens [164]. The high feed consumption has

Table 5: Effects of different phytobiotics on intestinal microbiota.

Phytobiotics	Biological functions	Reference
Chinese herbal polysaccharides (astragalin and achyranthan)	Enhance hemagglutination inhibition antibody titers, bursa of Fabricius index, and splenocyte proliferation	[151]
Essential oil of *Oreganum aetheroleum*	Increase humoral immune responses against *E. coli*	[137]
Garlic (*Allium sativum*)	Lower the lipid content and cholesterol in plasma, broad-spectrum antibacterial properties acting against Gram positive and Gram negative	[152]
Turmeric (*Curcuma longa*)	Enhance levels of serum antibodies to an Eimeria microneme protein, MIC2, and enhanced cellular immunity as measured by concanavalin A-induced spleen cell proliferation	[153]
Black cumin (*Nigella sativa* L. powder)	Enhance immune cells and intestinal health against Newcastle disease and significant decreased total counts of *Coliform* bacterial in the jejunum	[137]
Moringa oleifera	Reduce the activity of pathogenic bacteria and molds and improves the digestibility of other foods, helping chickens express their natural genetic potential	[154]
Ginger	Increase the absorptive surface area of the intestine and thus increase the absorptive capacity, resulting in higher body weight gain and lower FCR	[155]
Euphorbia hirta	Improve the microflora balance, decrease *E. coli* and *Salmonella* population, and stimulate the *Lactobacillus* spp. proliferation anti-dengue activity	[156]
Thyme (*Thymus vulgaris*)	Improve endogenous digestive enzyme secretion and activate immune response and antibacterial, antiviral, and antioxidant actions	[157]
Capsicum and *Curcuma longa* oleoresins	Reduce gut lesion scores in necrotic enteritis-afflicted birds, increase numbers of macrophages in the intestine, and regulate expression of genes associated with immunology	[158]
Cinnamaldehyde, a constituent of cinnamon (*Cinnamomum cassia*)	Increase 17 and 42% body weight gains following *Eimeria acervulina* and *E. max*ima infections and 2.2-fold higher *E. tenella*-stimulated parasite antibody responses, compared with the control	[159]

been observed in the pellet-fed birds due to an increase in the bulk density of pelleted feeds, which facilitates easy hold and an increase in feed intake (FI) was observed to vary from 2.8% to 64% resulting in increased growth performance and decreases the proportion of maintenance energy [165]. The application of whole grains to chickens has been widely used to lower feed handling and processing costs; improve foregut development, gut microflora, and prevention of coccidiosis; decrease ascites-related mortality; and enhance digestive enzymes secretion [166].

Mash pre-starter feed significantly affected the small intestine length. Digestion is associated with related enzyme proportion secreted from the pancreas and intestine that regulate digestion. The increase in weight of pancreas, protease, and amylase activity significantly ($P < 0.05$) was described in the response to feeding crumble pre-starter diet (CPD), but the activity of lipase was not affected. Birds fed with CPD exhibited greater body weight gain (BWG) than birds fed mash pre-starter diet (MDP) at 10 days of age [167]. In contrast, the activity of pancreatic enzymes was described as decreasing the pelleting of broiler feed. The amylase activity was decreased in crumble-fed chicks than mash feed fed chickens. Moreover, the increased villi height of chicks pelleted diet fed noticed enhanced growth performance and also increased the area of intestine for absorption [168]. Mash farm feed decreases the number of *Coliform* and *Enterococcus* while enhancing *C. perfringens* and *Lactobacillus* in the chicken's ileum as compared to pelleted feed [169]. The corn supports a low percentage of *Clostridia*, *Enterococci*, and *Lactobacilli* while wheat favors a high percentage of *Bifidobacteria* [170]. The low numbers of *Firmicutes* and *Bacteroidetes* from day one hatch to day 42 as birds are transferred from starter to finisher diet and for fermenting starch to sugars [171]. Gut microbiota are very important components in the gut for intestinal ecology that is why the gut is considered a forgotten organ. The composition of gut ecology, the effect of feed supplements on the gut microbiota modulation, and finally the harmful and beneficial effects of microbiota are all dependent on a better understanding and interactions of gut microbiota with other organisms. However, the most advanced technique is the only evidence available on how gut microbiota are affected by specific dietary components in the main parts of the gut including the small intestine, crop, and ceca. The role of microbiota cannot be negotiated in the different physiological, nutritional, immunological, and developmental processes in the chickens [133].

15. Age and Sex

The important factor that affects the gut cell density, bacterial composition, and metabolic function is the age of birds. With the advances in bird's age, there are sequential modifications in the composition of gut microbiota, due to the substitution and set up of more stable bacterial taxa [54]. Chickens are highly susceptible to pathogens during the neonatal period and relatively face problems after the rest of life. It was reported that *L. delbrueckii, C. perfringens*, and *Campylobacter coli* chicks at the age of 3rd day and *L. acidophilus, Enterococcus*, and *Streptococcus* chicks from 7 to 21 d of age, while *L. Crispatus* chicks at 28 and 49 days of age in the gut, different composition at different periods of age [172]. The main gizzard contains *Lactobacillus, Enterococci*, lactose-negative *Enterobacteria*, and *Coliform* [28]. The lowest bacteria density was found in the duodenum due to a dilution of the digest by bile secretion, containing *Clostridia*, *Streptococci*, *Enterobacteria*, and *Lactobacilli* and a short passage of time interval [173]. Ileal bacteria community was examined to 16S rRNA gene sequences, and *lactobacillus* (70%) as the major group, *Clostridiaceae* (11%), *Streptococcus* (6.5%), and *Enterococcus* (6.5%) were found [171]. The cecum as compared to the ileum possesses a wide range, rich, and steady microbiome community including anaerobes. There were significant changes observed at 6 weeks from day-old in the cecal microbiota community [174].

Male chickens exhibited a faster growth rate as compared to female chickens due to sexual differences in growth and development. This difference in growth rate may be associated with the difference in gut microbiota between sexes that can affect significantly nutrient digestion, absorption, and metabolism, which are associated with the immune and health status of birds. Alternation of the gut microbiome is directly related to the body weight of animals including pigs, chickens, and humans [21]. Lee et al. investigated that female broiler chickens harbor a number of *Bacteroidetes*, *Firmicutes*, and *Proteobacteria*. There are *Shigella* and *Moraxellaceae* associated with *Proteobacteria* causing relative abundance in female gut microflora, while male broiler chickens are associated with the enriched relative abundance of *Bacteroidetes* and *Firmicutes*, but the major difference between male and female growth in harboring microbiota are two genera *Bacteroides* and *Blautia* [7, 174]. It is concluded that biological processes such as sex hormones secretions differences cause the differences in microbiota in the ceca of male and female chickens [174].

16. Bacteriophages

Bacteria-eating viruses called bacteriophages are reported as an alternative to antibiotics in the resistance to bacterial diseases. Bacteriophages are particularly host-specific in nature, targeting a specific bacterial group, and did not affect the immune system of humans or animals, and normal gut microflora. These viruses increase in number inside the infected host cell or bacterial cell so-called lytic infection cycle and, by bacteriolysis, come out from the cells. Bacteriophages inject their DNA into the host cytoplasm and replicated utilizing the metabolic components of the infected host cell and encoding genes [175, 176].

It is investigated that bacteriophages were isolated and used in different experiments to decrease the colonization of *S. Typhimurium* and *S. enteritidis* in the cecum [177]. There is a decrease in the colonization of positive control groups. From the 7 DPI beginning of the experiment to the end at 15 DPI, all chicks exhibited no colonization of *Salmonella* in the cecum, which concluded that bacteriophage treatment is effective for *Salmonella* treatment. The use of antibiotics against the *salmonella* resistance strains results in high economic losses in the poultry industry. Uses of antibiotics kill the pathogenic bacteria and impact normal microflora and secondary infections. Bacteriophage supplementation has potential beneficial effects as compared to antibiotics supplementation due to the specific nature of bacteriophages. There will be a reduction of bacterial load in the intestine of newborn chicks if it could be possible to administer five succeeding dosages of bacteriophages orally [177]. By the combination of bacteriophage P22 and antibiotics inhibited the growth of *S. Typhimurium*. This combination of two factors reduces the development of antibiotic resistance in *S. Typhimurium*. There was a reduction in relative expression levels of genes regulating efflux pump (acrA, acrB, and tolC) and outer membrane (ompC, ompD, and ompF) [178]. Huang and Nitin grow bacteriophages that is based on edible antimicrobial coatings T7 phages (#BAA-1025-B2) on fish feed, a fish pathogen *Vibrio*, and a bacterium *E. coli* for treatment of human and fish pathogens, especially in a hydroponic system. This edible whey protein isolate coating was found to be beneficial in increasing the load of phages on fish feed pellets and decreasing the loss of phage activity during feed storage. This coating facilitates increased durability of phages in the stimulated gastric environment, and there is a significant reduction of bacteria in stimulated intestinal digestion [179].

17. Conclusions and Future Perspectives

The potentiality of these components as nutritional sources for the overall performance and prevention of enteric infections can improve the gut microflora and immune system in chickens. There are many natural sources that have been used as an alternative therapy against depression, osteoporosis, diabetes, and cancer. Rather than an antibiotic, there will be just another option to find new alternative sources from plants, animals, and other origins so that can be rich in nutrients and minerals to provide the nutrients to the broilers. In addition, the studies on the agonistic and synergetic effect of different feed additive sources are important to know so that the gap between information on their combined effects may be filled. The beneficial use of natural resource products in regulating the gut microflora population and immune system should be used in poultry against enteric infections to overcome antibiotic resistance. The nutrients may also encourage using these natural resources in the feed to improve the growth performance of poultry and alternately consumer, and human health.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Irfan Ahmed, Zhengtian Li, and Sharoon Shahzad contributed equally to this work.

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