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NON-ANTIBIOTIC GROWTH PROMOTERS IN POULTRY NUTRITION – A REVIEW

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Abstract

Poultry meat and eggs are considered as major sources of food for rapidly increasing human population across the globe. During the rearing of poultry, different antibiotics were included in poultry diets in sub-therapeutic doses to attain improvements in growth performance. Recently, the use of antibiotics in poultry production has been considered as one of the major reasons behind the emergence of antibiotic resistance in human and poultry pathogens. The pressing issue of antibiotic resistance led to complete or partial bans on the use of antibiotics as growth promoters in many parts of the world. Moreover, there have been increased concerns among the consumers about the antibiotic residues in poultry products. These administrative bans led to an increased incidence of bacterial disease outbreaks, thus compromising the poultry performance, welfare, and economic outcomes of poultry producers. This ultimately attracted the attention of researchers to find the alternative strategies that could replace the antibiotics and bring production, health, and food safety benefits to the poultry production systems. These non-antibiotic growth promoters mainly include probiotics, prebiotics, synbiotics, phytogenic substances, organic acids, antimicrobial peptides, enzymes, bacteriophages, and egg yolk antibodies. Inclusion of these non-antibiotic solutions in poultry diets demonstrates promising results in terms of production performance and birds' health. These promising results are demonstrated through improvements in nutrient absorption, proliferation of beneficial bacteria, reduction in pathogenic bacterial species, production of bacterial metabolites that serve as energy sources for intestinal epithelial cells of the host, and positive modulation of immune responses. Apart from reducing the colonization of bacterial species that are pathogenic for poultry, these alternative solutions have also exhibited satisfactory efficacy in reducing the colonization of foodborne pathogens like *Salmonella* and *Campylobacter jejuni* which cause illness in the human population. In this paper, we reviewed studies that evaluated the effects of non-antibiotic growth promoters on different types of poultry. A description of mechanism of action, advantages, disadvantages and effects on production performance, gut health and immune parameters are discussed in this paper.

Key words: non-antibiotic growth promoters, poultry, gut health

Meat is an excellent food source containing a substantial amount of protein percentage and a fair amount of essential amino acids and micro- and macro-nutrients in the form of minerals and vitamins (Geiker et al., 2021). Poultry meat consumption rate (46%) swiftly increased between 1961 and 2020 with a growth factor of 13 (van der Laan et al., 2024). Moreover, poultry meat consumption is expected to increase by 11.9% in the upcoming decade (OECD-FAO, 2022). Poultry meat has several nutritional superiorities over the rest of other meat types because of low fat percentage and majority of the fat being composed of polyunsaturated fatty acids (Brenes and Roura, 2010). The amino acid composition of the protein obtained from the chicken meat is also substantial. Moreover, the collagen content which is considered as incomplete protein is also low (Chmiel et al., 2019). On the other hand, the global egg production exceeded 86 million metric tons in the year 2020 (FAO, 2020). Poultry eggs are a source of essential and diverse nutrients having higher digestibility, making it basic food commodity for human consumption (Réhault-Godbert et al., 2019). The annual consumption of egg was 217 eggs per capita, with the higher consumption and production rates in developed nations (Gautron et al., 2022).

Antibiotics are substances that have the potential to mitigate the proliferation and survival of bacteria. These can be produced by natural, semi-synthetic and synthetic ways and are widely used to prevent and treat the bacterial infections. The first antibiotic ever discovered was penicillin that was developed by Alexander Flemming in 1928 (Mohr, 2016). Antibiotics are also being used in the food animal production sector to treat bacterial disease outbreaks and as growth promoting agents (Al Sattar et al., 2023). The efficacy of antibiotics in treating the bacterial infection and their cost effectiveness led to their indiscriminate usage in the food animal industry (Joerger, 2003). The application of antibiotics as growth promoters (AGPs) was initiated in 1951 with the approval of Food and Drug Administration (FDA) authority in the United States followed by the European Union (Castanon, 2007). Antimicrobial growth promoters are antimicrobial substances that are used in sub-therapeutic doses that exert their beneficial effects in terms of improvements in growth and performance by modulating the intestinal microbiota (Rushton, 2015). Apart from beneficial effects of AGPs, antimicrobial resistance in intestinal microbiota has also been reported with the use of AGPs (Luiken et al., 2019; Nazeer et al., 2021). Antimicrobial resistance is referred to as the inability of antimicrobials to eliminate or mitigate the proliferation of certain bacterial populations (Verraes et al., 2013). The administration of antibiotics leads to the elimination of susceptible bacterial populations, which in turn favors the proliferation of resistant bacterial strains. These resistant bacterial strains transmit their resistant bacterial genes to other bacterial populations that may be the isolates of the same species, or the other bacterial species. This phenomenon of transmission of resistant genes within the same bacterial species or among the different bacterial species can be observed in both commensal or pathogenic bacteria isolated from humans, animals and the environment (Founou et al., 2016).

Keeping in view the possible risk of antimicrobial resistance, the European Union imposed the ban on use of antibiotics as growth promoting agents (European Union, 2005). Similarly, the Food and Drug Administration Authority in the United States has also banned a wider variety of antibiotics as growth promoters to minimize the incidence of antibiotic resistance in poultry pathogens (Yang et al., 2019). Moreover, public concerns regarding the risk of antibiotic resistance in humans are also rising. There has been more emphasis on recent popular poultry production trends of "Antibiotic Free", "Raised Without Antibiotics" and "No Antibiotics Ever" (Marshall and Levy, 2011). All these possible risk factors and public concerns led to emphasized research on non-antibiotic strategies that could enhance poultry growth and mitigate the proliferation of pathogenic microbes (Upadhyaya et al., 2015; Ricke, 2018). The most commonly used non-antibiotic growth promoters are listed in Figure 1. In this paper, we reviewed studies that evaluated the effects of non-antibiotic growth promoters on different types of poultry. A description of mechanism of action, advantages, disadvantages and effects on production performance, gut health and immune parameters are discussed in this paper.

Probiotics

A probiotic is defined as live microbe preparation that exerts beneficial effects on the host by improving the balance of microbial populations across the gut (Fuller, 1992). Qualities of good probiotic preparation include the viability of probiotic bacteria in the acidic environment of the gut, microbes must adhere to the intestinal epithelium and maintenance of the microbiota at optimal levels (Kabir, 2009; Krysiak et al., 2021). Probiotics improve the process of digestion, balance the gut microbial communities, and promote the proliferation of beneficial bacteria in the gut (Mountzouris et al., 2010). Moreover, probiotics competitively exclude the pathogenic bacterial species (Tran et al., 2023), modulate the immune responses of the gut mucosal surfaces (Shini and Bryden, 2021). Probiotics have the potential to replace the use of antibiotics as growth promoters (Krysiak et al., 2021). Despite the beneficial effects of probiotics in poultry production there are certain limitations associated with their precise application (Pan and Yu, 2014). Probiotic efficacy is variable depending upon the taxonomic features of administered microbes, survival rate, stability after application of pelleting conditions, dosage level, diet, age of birds, biosecurity practices and environmental conditions (Mountzouris et al., 2010). The most widely used probiotic bacterial species in poultry nutrition include *Bacillus subtilis*, *Lactobacillus rohita*, *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus coagulans*, *Bifidobacterium rohita*, *Lactobacillus lactis*, *Escherichia coli, Clostridium butyricum*, *Methanobacterium*, and *Streptococcus* spp. (Koshchaev et al., 2020; Mortada et al., 2020; Hassan et al., 2022). Moreover, the application of some other bacterial preparations includes bacteria belonging to the Enterococci genus especially *Enterococcus faecalis* SF68 and *Saccharomyces cerevisiae,* which have also been reported (Smialek et al., 2018).

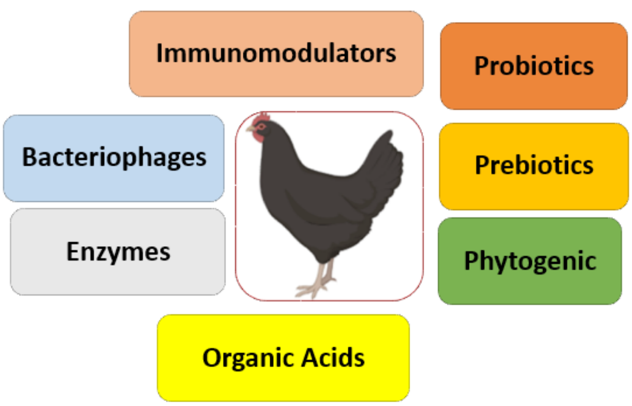

Figure 1. Non-antibiotic growth promoters in poultry nutrition

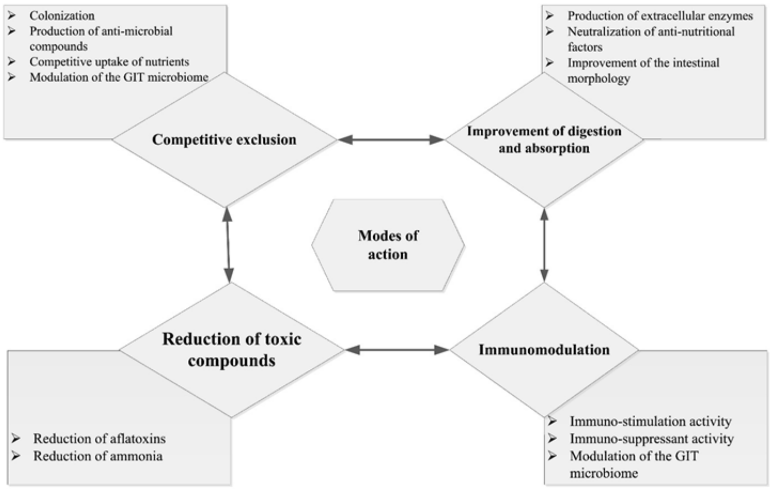

Figure 2. The mechanism of action of probiotics

Probiotics benefit the host health through a variety of mechanisms which include the enhancement of innate and acquired immunity (Cox and Dalloul, 2015). Immunomodulation is achieved by the enhancement in gene expression of interferons and interferon proteins in the spleen. Innate immunity is modulated by regulating the macrophages and leukocytes (Swaggerty et al., 2019). Probiotics also exhibit the potential to balance the intestinal microflora. This beneficial microbial balance can be achieved by mitigating the proliferation of pathogenic bacteria (Rodjan et al., 2018). Probiotics can also reduce the production of harmful microbial metabolites in the gut, e.g., ammonia, hydrogen sulfide, and indoles (Wu et al., 2019). The mechanism of action of probiotics is depicted in Figure 2 (adapted from Ramlucken et al., 2020).

Addition of *Bacillus amyloliquefaciens* probiotic in broiler diet improved the performance and reduced the mortality percentage. Feed conversion ratio (FCR) was lower in probiotic supplemented birds (1.26) whereas the control group had a value of 1.28 FCR. Moreover, the mortality rate was 1.56% in comparison with the control group where a mortality rate of 3.13% was noted (Horyanto et al., 2024). Feed supplementation of dual strain probiotics (*Enterococcus faecium* + *Streptococcus thermophiles*) at the inclusion level of 0.5% in Plymouth Rock chicks led to 17% improvement in body weight and decrease in FCR value. Enzymatic digestive activity was also enhanced with the application of probiotic spray. Moreover, the probiotic supplementation also resulted in increasing the abundance of beneficial bacteria (*Ruminococcaceae* and *Faecalibacteriumin*), whereas it reduced the population of harmful bacteria like *E. coli*, thus leading to better management of diarrhea (Mirsalami and Mirsalami, 2024). Cobb 500 broilers supplemented with *Bacillus subtilis* had better feed conversion ratio as compared to birds fed a basal diet supplemented with antibiotics. Moreover, the relative abundance of *Bifidobacterium, Intestinimonas* and *Ligilactobacillus* was also affected by the probiotic supplementation (Fonseca et al., 2024). A comparative study evaluating the different probiotic strains found that *Bacillus subtilis* KB41 (0.1%) improved the growth performance of broilers. The supplementation also resulted in increasing the *Lactobacillus* bacterial count in the ceca and interferon gene expression (IL-6 and IL-10) in the splenocytes (Popov et al., 2024). An *in vivo* experiment indicated that oral administration of *Bacillus velezensis* reduced the colonization of *Campylobacter jejuni* in the cecum, whereas the microbial diversity and richness in the ileum were improved (Cui et al., 2024). Feeding of compound duck probiotics (*B. fragile, B. sphaericus, B. subtilis, Bifidobacterium, Lactobacillus,* and *E. faecium*) fermented feed resulted in improvements in average daily gain and FCR. Moreover, the gut health parameters e.g., gut morphology, and tight junction proteins, were also improved with probiotic fermented feed (Li et al., 2024 a). Heat stressed broilers supplemented with liquid and lyophilized probiotic strains obtained from rye grass lactic acid bacteria had improved growth rate, hormonal concentration, gut health and microbial diversity. Thus, probiotics can be used to alleviate the negative impacts of heat stress (Hatipoglu et al., 2024). *In ovo* spray application of probiotics (*Lactobacillus rhamnosus* or *Lactobacillus paracasei*) led to a 5% improvement in the hatchability percentage of Ross 308 broilers. Hatch quality parameters like hatchling weight and yolk free body mass were also improved with probiotic application. The post hatch performance records indicated that hatchling weight was positively correlated with the post hatch performance of birds (Gao et al., 2024). Inclusion of *Saccharomyces cerevisae* fermentation product at the dose rate of 1.5 kg/ton in the broiler diets improved the feed intake, weight gain and feed conversion ratio of birds during the experimental period of 42 days. Moreover, the pathogenic bacterial counts (*E. coli, Enterobacteriaceae, Salmonella*) declined in the birds offered a yeast supplemented diet

(Soren et al., 2024). Supplementation of *Lactiplantibacillus plantarum* HJLP-1 (5×10^8 CFU kg^{-1}) in the basal diet of broiler chickens improved the average daily weight gain (52 vs 44 g) and reduced the overall feed conversion ratio (1.80 vs 1.70). The dietary manipulation also resulted in an increase in cecal acetic and butyric acid concentrations. Moreover, the abundance of bacteria belonging to genus *Ruminococcus* and *Lachnospiraceae* was also increased with probiotic supplementation (Yang et al., 2024 b).

Limitations of probiotics

Survival of live cells during processing and dose optimization in poultry feed processing remain the most important challenge with probiotic use in poultry diets (Salahi and Abd El-Ghany, 2024). Probiotic dose optimization in breeder flocks is another limitation as probiotic overdose may lead to semen quality deterioration in breeding roosters. The abundance of *Lactobacillus* species bacteria has direct relationship with semen quality of roosters. Prolonged duration of probiotic administration may lead to altering the cloacal microbial communities, thus impacting semen quality in breeding flocks (Haines et al., 2015; Kiess et al., 2016).

Prebiotics

Prebiotics are non-digestible fractions of carbohydrates that selectively promote the proliferation of beneficial bacteria in the host (Morgan, 2023). Prebiotics profit the host's health in a wider variety of ways: a) inhibition of pathogenic bacteria colonization in the gut by serving as selective nutrients for the beneficial bacteria (Ricke et al., 2020); b) production of short chain fatty acids, which serve as energy sources for birds and reduce the intestinal pH (Gibson et al., 2004); c) stimulation of gut mucosal immune system against pathogenic bacteria (Gibson et al., 2010). These summarized modes of activities lead to improved production performance and better gut health. In order to be categorized as a prebiotic, a feed ingredient must exhibit the following properties: a) it should not be hydrolyzed by the gastric enzymes and bile salts of the host; b) utilized by the enzymatic action of beneficial microbial communities; c) encourage the physiological pathways that benefit the host health (Liu et al., 2021 a, b). The most commonly used prebiotics in poultry nutrition are sourced from oligosaccharides. Oligosaccharides are made of 2–10 monosaccharide units that are either linear or branched and α- or β-glycosidic linkages are present to connect them (Patel et al., 2014). Prebiotics originating from the oligosaccharides class include xylo-oligosaccharides, fructo-oligosaccharides, and galacto-oligosaccharides. Prebiotic oligosaccharides can be obtained from plants or can be manufactured on industrial scale using physiochemical and biological methods (Morgan, 2023). The chemical process for oligosaccharides extraction include acid and alkali hydrolysis, oxidation and chemical modifications. Moreover, biological extraction processes involve enzymatic, fermentation and strain extraction method (Chen et al., 2024). The source of extraction and mechanism of action of prebiotics is depicted in Figure 3 (adapted from Fathima et al., 2022).

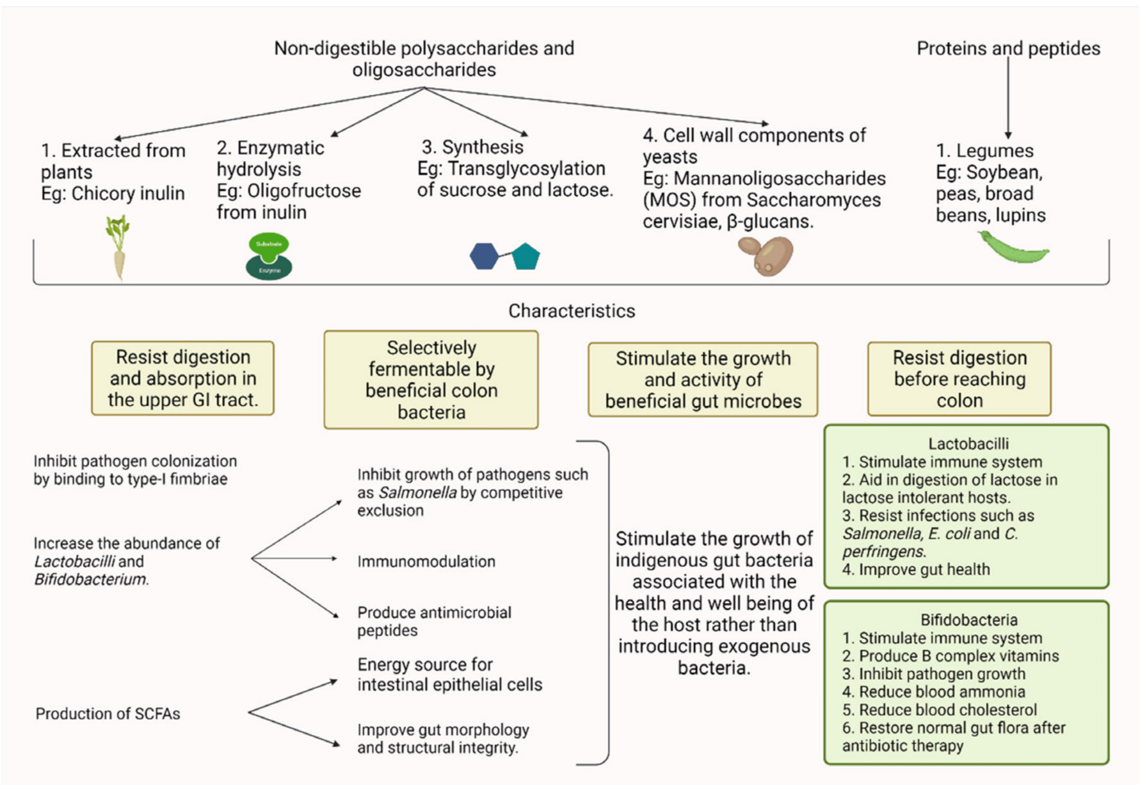

Figure 3. The source of extraction and mechanism of action of prebiotics

Inclusion of 0.05, 0.1, and 0.2% of xylo-oligosaccharides in the corn soybean meal-based diet of broiler chicken did not influence the production performance parameters. However, the gut histomorphology tended to be improved with the increase in villus to crypt ratio of jejunum at the inclusion levels of 0.05 and 0.2%. Moreover, the population of *Bifidobacterium* in the cecal content increased linearly with the increasing level of xylo-oligosaccharides, whereas a decline in the number of *Clostridium perfringens* was noted (Yadav et al., 2024). Supplementation of chitosan oligosaccharide at the inclusion levels of 200, 400 and 800 mg/kg in the diet of Arbor Acre broilers did not significantly improve the growth performance parameters. However, an increase in intestinal weight and improvements in gut morphology architecture were noted. Moreover, the gene expression of nutrient transporters (glucose, sodium-glucose cotransporter, peptide transporter) was enhanced with the chitosan oligosaccharide supplementation (Lan et al., 2024). Supplementation of yeast (*Saccharomyces cerevisiae*) cell wall at the inclusion levels of 0.25 and 0.5 g/kg improved the growth performance and carcass quality in necrotic enteritis challenged birds whereas the mortality rate declined. The gut histomorphological architecture also improved with increased villus height, surface area and height to crypt depth ratio. Moreover, the yeast cell wall supplementation increased the *Lactobacilli* count and decreased the *Clostridium perfringens* populations (Alqhtani et al., 2024). Broiler diets supplemented with xylo-oligosaccharides at the inclusion levels of 150, 300, or 450 mg/kg improved the growth performance, immune function and gut health of birds. Birds receiving the 150 and 450 mg/kg of xylo-oligosaccharides had higher body weight and average daily gain. The gene expression of intestinal tight junction proteins (claudin-1 and ZO-1) was higher in 150, 450 mg/kg of xylo-oligosaccharides treatment groups. Similarly, xylo-oligosaccharides supplementation increased the ileal villus height and villus height to crypt depth ratio (Rao et al., 2024). Feeding of broiler breeder pullets with hydrolyzed whole yeast (0–22 weeks of age) at the inclusion level of 0.05% resulted in non-significant effects on the growth, pre-lay body weight and uniformity. Similarly, no effects were found on serum antibody titers against Newcastle disease and infectious bronchitis, cecal short chain fatty acid concentration and leg bone morphometry (Maina et al., 2024). Supplementation of yeast derived mannan rich fraction (0.4–0.8 g/kg) in the diet of laying hens improved their productivity. Birds consuming yeast derived mannan rich prebiotic diet produced 6.79% more eggs and a 5.58% better FCR in comparison with the control birds. Flock uniformity also improved with prebiotic supplementation; however, egg quality parameters remained unaffected. From the food safety perspective, the colonization of *Campylobacter jejuni* declined in the birds consuming prebiotic added diet whereas bacterial populations producing butyrate and propionates increased in the ceca of laying hens (Leigh et al., 2024). Dextran sodium sulfate challenged laying hens supplemented with 5 g/kg of bamboo shoot extracted oligosaccharides improved the egg quality characteristics and gut microbiota diversity. Moreover, the recruitment of leucocytes and inflammatory cytokines was also enhanced with the bamboo shoot oligosaccharide supplementation (Sittiya and Nii, 2024). Reduced protein diets of laying hens supplemented with 0.15 and 0.2 g/kg of β-mannanase improved the productive performance parameters and decreased the anti-inflammatory factors. Moreover, the prebiotic supplementation was helpful in increasing the relative abundance of beneficial bacteria in gut (Liu et al., 2024). Supplementation of xylo-oligosaccharides at the inclusion level of 0.1 g/kg in the broiler diet improved the growth performance of birds during the first 4 weeks of broiler life. However, these improvements in terms of weight gain in broilers diminished at the 35th day of experiment. In addition to that, xylo-oligosaccharide supplementation enhanced the starch utilizing system of *Bacteroidetes* bacteria, thus improving the utilization of complex carbohydrates in the broiler diets (Amir et al., 2023). Supplementation of alginate oligosaccharide at the inclusion levels of 100, 200 and 400 mg/kg in diet of Arbor Acre broilers improved the growth performance and health of birds. Birds offered a 200 mg/kg alginate oligosaccharide diet had a higher average daily gain and feed intake. Intestinal villus height increased, and tight junction protein expression was enhanced with dietary manipulation. Additionally, the concentrations of acetate, isobutyrate, isovalerate, valerate, and total short chain fatty acids were higher in comparison with birds fed a basal diet. The bacterial population promoting the generation of short chain fatty acids was higher in alginate oligosaccharide supplemented birds (Zhu La et al., 2023). Dietary supplementation of mannan oligosaccharides at the inclusion levels of 0.1, 0.2 and 0.5 g/kg improved the immune status of Mandarah roosters and laying hens. Improvements in immune status were evident through the elevated levels of immunoglobulins (IgY and IgM) and enhanced antibody titers against avian influenza. Moreover, the prebiotic was effective in improving the histological architecture of testis and spermatogenesis (Youssef et al., 2023 a). Similarly, another study using chitosan oligosaccharide in Mandarah roosters and laying hens at the inclusion levels of 0.1, 0.2 and 0.5 g/kg improved the blood immunoglobulin and antibody titers against the Newcastle disease. Moreover, the improved hematological parameters (red and white blood cells, hemoglobin and hematocrit) were also noted in the supplemented group. The inclusion level of 0.1 g/kg showed improved growth of reproductive organs (Youssef et al., 2023 b). Dietary supplementation of chitosan oligosaccharides at the inclusion levels of 0.1, 0.2 and 0.5 g/kg improved the productive performance and egg quality traits of Mandarah roosters and laying hens. The highest laying percentage was observed in birds offered 0.1 g/kg of chitosan oligosaccharides. On the other hand, birds fed 0.2 g/kg of prebiotic exhibited best reproductive performance traits in comparison with other treatment groups (Youssef et al., 2024 a). Addition of 0.5% mannan oligosaccharides in the diet of female turkeys resulted in higher body weight as compared to birds fed a control basal diet. Moreover, the crude fat percentage also decreased with mannan oligosaccharides supplementation. Mineral elements (sodium and copper) in the breast and iron in the thigh muscle also increased with prebiotic feeding. Regarding bone health, bone weight, length, elasticity, breaking strength and phosphorus deposition were higher in prebiotic fed birds (Kwiecień et al., 2023). Inclusion of mannan oligosaccharide (0.97 kg/ton) in the diet of laying hens improved the egg production by 1.76%. Moreover, an increase of 2.39% in livability was also noted in prebiotic supplemented group (Salami et al., 2022).

Limitations of prebiotics

The outcomes of prebiotic use in poultry diets are dependent upon a wider variety of external factors which include dietary fiber source, inclusion level, birds' age, physiological status, dietary energy and protein percentage, and duration of prebiotic feeding. All these aforementioned external factors influence the microbial taxonomy in the gut which ultimately leads to variation in performance and health outcomes of poultry flocks (Leone and Ferrante, 2023).

Synbiotics

Synbiotics are the combinations of two different classes of feed additives (probiotics and prebiotics) benefiting host health through synergistic collaboration (Gibson and Roberfroid, 1995). Synbiotics are known to benefit the host through competitive exclusion, generation of antimicrobial compounds and immune response regulation. In addition to that synbiotics enhance the production of short chain fatty acids which serve as energy source for intestinal cells, thus maintaining intestinal health (Shanmugasundaram et al., 2020). The mechanism of action of synbiotics is summarized in Figure 4 (adapted from Fathima et al., 2022).

A study comparing different administration routes (spray, drinking water and mouth dripping) for synbiotic (*Enterococcus faecium*, *Bifidobacterium animalis*, *Pediococcus acidilactici*, *Lactobacillus reuteri* and *Lactobacillus salivarius*) in Mandarah male chicks found that provision of synbiotics through drinking water at the dose rate of 0.25 or 0.50 ml/L increased the lactic acid producing bacteria whereas *E. coli* population were reduced in the gut. Moreover, 0.50 ml/L of synbiotic through drinking water was helpful in improving the gut morphological parameters (Youssef et al., 2024 b). Hatchery and dietary administration of synbiotic (Inulin + *Enterococcus faecium* + *Pediococcus acidilactici* + *Bifidobacterium animalis* + *Lactobacillus reuteri*) had beneficial effects on the broiler immunity by reducing the mRNA abundance of Toll like receptors and interleukins. Birds subjected to 0.5 ml of oral synbiotic gel at hatchery, in feed at a level of 0.5 kg/ton or the combination of hatchery and feed synbiotic treatments had a lower feed conversion ratio on days 14 and 21 of age. However, no significant effects regarding body weight and feed conversion ratio were recorded during the whole experimental period of 35 days of age (White et al., 2024). A laying hen diet supplemented with synbiotic at the age of 50–60 weeks resulted in regulation of the neural pathways that connect gut microbiota and gastrointestinal system with brain (microbiota-gut-brain axis) as this was evident with behavioral changes in birds. Synbiotic supplemented birds spent less time exhibiting the undesirable activities like threatening, fighting, and pecking. The relative abundance of *Lactobacillus* and *Bifidobacterium* in the ceca was significantly higher in birds fed synbiotic supplemented diet. Moreover, differences in dopamine, serotonin and corticosterone concentrations were also noted among the synbiotic and control group laying hens (Johnson et al., 2024). A dietary synbiotic (*Bacillus subtilis* + *Saccharomyces cerevisiae* cell wall) reduced the enteric colonization of *Salmonella* Enteritidis in the infected Lohmann LSL chicks (Araba et al., 2024). Addition of 2 g/kg of synbiotic (*Bacillus licheniformis* + *Bacillus subtilis* + mannan oligosaccharides + 1,3 ß-glucan) in the diet of ISA Brown laying hens improved the production indices and egg quality. Egg production was 83% in synbiotic treated group whereas it was 67% in the control group. Similarly, egg mass also increased in the synbiotic supplemented group (54 vs 42 g). Egg shell calcium content and blood estradiol level increased with synbiotic supplementation (Salem and Abd El-Dayem, 2024). Synbiotic supplementation (1 g/kg) in necrotic enteritis challenged birds helped in alleviating the negative impacts of disease by reducing mid gut lesion score and altering the immune cell proliferating activity across the different time frames during the experiment (Shah et al., 2023). Synbiotic (PoultryStar Me) supplementation during *Campylobacter jejuni* challenge in broilers regulated the immune responses in a positive manner, decreased the colonization of *Campylobacter* in hind gut. Moreover, symbiotic supplementation increased the expression of intestinal tight junction proteins. Synbiotic was more effective in comparison with virginiamycin antibiotic in reducing the *Campylobacter* colonization (Cason et al., 2023).

Challenges in synbiotics application

Identification of a suitable synbiotic delivery system that ensures the maximum survival rate of probiotic in the product preparation remains the challenging factor. This problem can be resolved to a greater extent with the microencapsulation procedure that has higher success rate; however, methods other than microencapsulation are still in demand (Baffoni et al., 2012). Moreover, synbiotics being the combination of probiotic and prebiotic exert synergistic effects on gut environment. The mechanisms behind extensive alterations in gut microbial ecology and host health still need further investigation (Tabashsum et al., 2023).

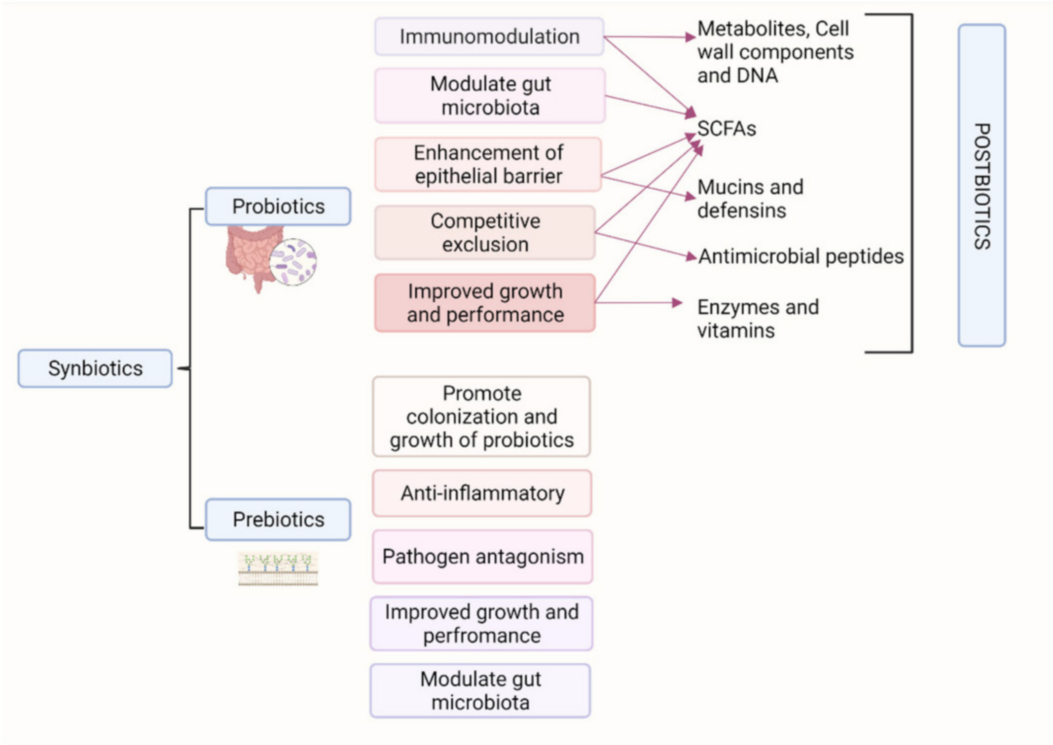

Figure 4. The mechanism of action of synbiotics

Phytogenics (herbs and plant extracts)

Phytogenics are the feed additives that are derived from the plant material and mainly include natural compounds, herbal and plant extracts and bioactive compounds that have the potential to improve animal health, performance and product quality. These are also commonly known as phytobiotics or phytochemicals (Hashemi and Davoodi, 2011; Yang et al., 2015). The major classes of phytobiotics include botanicals, essential oils, herbs, and oleoresins. Botanicals are plants that have been processed whole or in parts. Essential oils are volatile in nature, hence hydro-distillation is used to extract them (Pham et al., 2020). Herbs are non-woody, flowering and non-persistent plants (Puvača et al., 2015). Oleoresins are non-aqueous solvent extracts such as carvacrol, capsicum and cinnamaldehyde (Bravo et al., 2014). Each bioactive in phytogenic feed additives benefits the host in a versatile and complicated way, and the complete mechanism behind physiological alterations is still unknown. The proposed mode of action of phytogenic compounds includes: a) improvements in digestive function by affecting the release of gastric enzymes (Murugesan et al., 2015); b) presence of antimicrobial substances, e.g., hydroxyl group, which modulates gut microbiota (Bessam and Mehdadi, 2014; Rafeeq et al., 2023); c) modulation of mucin production and gut morphology, which affects the nutrient absorption capacity (Tsirtsikos et al., 2012; Shah, 2015); d) modulation of immune related functions by neutralizing the reactive oxygen species, thus minimizing the cellular damage and stabilization of inflammatory cytokines (Flora et al., 1998; Begum et al., 2014).

Arbor Acres broilers fed different levels of *Taraxacum monoglicum* plant extract (500, 1000, and 2000 mg/kg diet) improved the performance and health status of birds. Inclusion level of 1000 mg/kg proved to have more beneficial effects in terms of blood biochemical profile, gut morphology, and antioxidant activity. Plant extract was also helpful in enriching the gut with the beneficial microbial populations, e.g., *Alistipes* and *Lactobacillus,* whereas the harmful bacterial colonies were reduced in the gut (Dong et al., 2024). Addition of herbal blend (coriander, garlic, and fenugreek) at the inclusion levels of 1, 2, and 3% in the broiler diets revealed that birds fed the inclusion level of 1% had higher live and carcass weights. Supplementation at 1% also led to improvements in the nutrient digestibility, especially crude protein and fat. However, the mineral utilization was improved at the inclusion level of 3% in the broiler diet (Hafeez et al., 2024). A study conducted on the liver damaged broilers found that supplementation of a phytogenic feed additive (silymarin + betaine + curcumin extract) improved body weight gain and feed conversion ratio irrespective of CCl_4-induced liver damage. No interactions were found between presence of phytogenic feed additive and CCl_4-induced hepatic damage (Carpio et al., 2024). Supplementation of a Vencobb broiler diet with rosemary essential oil (100 mg free + 200 mg nano-encapsulated) improved the weight gain and feed efficiency (+8.47%) in comparison with other preparations of free and nano-encapsulated rosemary essential oil. Similarly, nutrient utilization (dry matter and crude protein) and carcass quality traits (dressing, breast, thigh %) were also increased with rosemary essential oil supplementation. Gene expressions for mucin protein, peptide transporters and IL-10 were enhanced whereas TNF-α were downregulated (Adil et al., 2024). Dietary supplementation of broilers with a commercial phytogenic product (encapsulated blend of kelp, thymol, eugenol and cinnamaldehyde micro-particles) at the inclusion level of 75 and 100 g ton for different time intervals resulted in 62 g higher body weight and 2.1 points lower feed conversion ratio in comparison with birds fed basal diet. Birds supplemented with 100 g/ton of phytogenic product (1–40 days) yielded higher carcass weight on processing. Dietary supplementation with phytogenic product reduced the incidence of femur and tibia lesions; however, the incidence of muscle myopathies was higher (Mullenix et al., 2024). Supplementation of 50 and 100 mg/kg of oregano and rosemary leaves extract to the heat stressed broilers improved the weight gain and feed conversion ratio of birds. Heat stressed birds supplemented with rosemary leaves extract had better total antioxidant capacity and higher thyroid hormone levels. The inclusion level of 100 mg/kg of oregano and rosemary leaves extract downregulated the gene expression of heat shock proteins (Madkour et al., 2024). Broiler birds supplemented with 20% oregano essential oil through drinking water (1 ml/5 liters for 8 hours daily) improved the weight gain and reduced the feed conversion ratio. Antibody titers increased against Newcastle disease virus and jejunum morphology was improved with an increase in villi height, villi width, crypt depth and villi to crypt depth ratio (El-Sayed et al., 2024). Sanguinarine-based isoquinoline alkaloid supplementation at the inclusion levels of 60 and 100 mg/kg in the basal diet of heat stressed Ross 308 broilers improved the performance parameters and reduced the mortality percentage. Promising cecum microbiome results were obtained with the increase in diversity of beneficial microbial populations (*Bacteroidetes* and *Cyanobacteria)* and decline in harmful bacteria (*Firmicutes* and *Proteobacteria*). The supplemented phytobiotic also enhanced the metabolism of essential amino acids. The effects of heat stress were alleviated with phytobiotic supplementation because of the increase in population of *Turicibacter sanguini* bacteria that promotes the serotonin biosynthesis (Khongthong et al., 2024). Supplementing broilers with a blend of microencapsulated essential oil and organic acid at the varying inclusion levels (200, 400, 600, and 800 mg/kg of diet) had beneficial effects on the performance and health of birds. Birds supplemented at 200 mg/kg level had higher daily gain and average body weight. The lipase activity in the duodenum and butyric acid concentration in ceca were enhanced with the supplementation of microencapsulated essential oil and organic acid. Lactic acid producing bacteria population increased in the cecal content of supplemented broilers (Huang et al., 2024). Broiler diets supplemented with 200 and 400 mg/kg of honokiol (*Magnolia officinalis* plant extract) increased the body weight gain and reduced the feed conversion value during the starter phase of production. Honokiol supplementation at 100 mg/kg improved the morphological architecture of small intestine by increasing villus height to crypt depth in the jejunum and ileum. Moreover, honokiol supplementation led to an increased population of *Firmicutes* and *Lactobacillus,* and an increased concentration of short chain fatty acids was detected in the cecal samples (Du et al., 2024). *Polygonatum sibiricum* polysaccharide supplementation at the inclusion level of 400 and 800 mg/kg in broiler diets linearly improved the body weight and feed conversion ratio. Gut morphological architecture (villus height and crypt depth) improved with polysaccharide supplementation. Changes in cecal microbial community were also noted with an increase in *Firmicutes* and *Verrucomicrobiota,* whereas *Euryarchaeota* and *Proteobacteria* were reduced (Yang et al., 2024 a). Supplementation of powdered *Artemisia annua* leaves at the inclusion level of 0.5 and 1% had ameliorative effects on productive performance and gut permeability in coccidiosis challenged Hy-line laying hens. The birds fed a 1% *Artemisia annua* supplemented diet had 8.1% higher egg production and 0.61 points lower feed conversion ratio in comparison with challenged birds fed basal diet. Similarly, intestinal lesion severity was reduced and intestinal villi recovered with 1% inclusion of powdered *Artemisia annua* leaves. Gut permeability was also reduced by 29% with *Artemisia annua* inclusion in comparison with challenged birds fed basal diet (Sharma et al., 2024). Intermittent supplementation (1 week on and 1 week off) of microencapsulated essential oil (eucalyptus, thyme, cinnamon, and mentha) in the diet of Hy-line Brown laying hens at the inclusion level of 300 and 500 mg/kg improved the laying performance and feed conversion ratio. Hens fed microencapsulated essential oil increased the breaking strength of eggs, shell thickness and Haugh unit. Improvements in immune responses were also exhibited with higher serum immunoglobulins and cytokines. Moreover, intestinal morphometry parameter and enhanced antioxidant capacity were evident (Xu et al., 2024). Supplementation of heat stressed breeding hens with a phytogenic product (clove + green tea pomace + Vietnamese coriander) alleviates the negative impacts of heat stress by increasing the egg production and hatchability percentage. Moreover, a decline in late stage embryonic mortality was also noted during incubation. The antioxidant capacity of liver, yolk and meat was also enhanced with phytogenic supplementation. Gene expression for pro-inflammatory cytokines and heat shock proteins were, however, downregulated in hens fed basal diet with phytogenic feed additive (Pasri et al., 2024).

Limitations of phytogenic compounds

Phytogenic compounds have very complex composition and may also contain toxic compounds, unpleasant odor and taste (Cheng et al., 2014). Due to their complex composition, it is also difficult to fully understand the mechanisms that bring health benefits to host (Niewold, 2007). Moreover, it is difficult to quantify and detect the phytogenic compounds in feed and animal tissue using the common analytical techniques (Yang et al., 2015). Use of phytogenic compounds in feed also yields variable results because of variation in composition. Various factors affect the composition of phytogenic compounds including herb or plant growth location, extraction or manufacturing technique, storage conditions etc. (Yang et al., 2009). Phytogenic compounds also exhibit volatile nature when exposed to higher temperatures (Lambert et al., 2001). This makes the stability of these volatile compounds questionable as mash feed is exposed to high pelleting temperature during feed processing (Si et al., 2006).

Organic acids

Organic acids are the organic compounds that possess acidic properties (Kim et al., 2015). A carboxylic group (COOH) is the part of the majority of organic acids. Organic acids can be categorized into short chain (≤C6), medium chain (C7 to C12) and long chain fatty acids (>C12). The most widely used organic acids in poultry production are short chain fatty acids e.g., formic, acetic, propionic, fumaric and lactic acid etc. (Salsinha et al., 2023). Organic acids exhibit the antimicrobial activity, used as alternatives to antibiotics and ensure food safety (Mani-López et al., 2012). Animals use organic acids as readily available source of energy which can affect metabolism and product quality (Wolfenden et al., 2007).

Modes of action of organic acids include a) reduction in pH of the crop, proventriculus, and gizzard (Kumar et al., 2022); b) reducing the gastric emptying time through the activation of zymogens, thus improving nutrient utilization (Dibner and Buttin, 2002); and c) inhibiting the growth of pathogens by penetrating their cell walls and blocking the normal cellular functions (Kim et al., 2009).

Supplementation of broilers with commercial organic acid blend improved the weight gain and feed conversion ratio. Organic acids supplementation reduced the colonization of *Clostridium perfringens*, *Escherichia coli*, and *Salmonella*, whereas the growth of beneficial bacteria like *Bacillus* was enhanced. With regard to gut morphology, intestinal lesion scores declined and villus height increased (Islam et al., 2024). A blend of short chain fatty acids (butyric + valeric acid) and oregano oil during the starter (500 g/ton) and finisher phase (250 g/ton) in the broiler diet was effective in improving the performance parameters of broilers. Birds receiving the supplemented diet had higher feed intake (104.7 vs. 103.1 g/day) and weighed 2.5% more in comparison with the birds fed the control diet. Moreover, the birds supplemented with short chain fatty acid blend and oregano oil exhibited a better feed conversion ratio (1.58 vs 1.60). The mortality percentage was 1.1% lower in the supplemented group during finisher production phase, however, the average mortality rate during the 42 days of experiment remained non-significantly different (Garcia et al., 2024). A blend of short and medium chain fatty acids (C4:0 to C9:0) in the diets of Ross 308 broilers at the inclusion level of 1.5 g /100 g on dry matter resulted in a 3.5% reduction in feed intake of birds, whereas the rest of performance parameters remained unaffected. Similarly, the blend of short and medium chain fatty acids was unable to introduce the microbial diversity in the ceca of birds (Daghio et al., 2024). Dietary inclusion of fermented calcium butyrate at the dose rate of 300 mg/kg improved the ovarian health and egg shell strength of Hy-line Brown laying hens. Moreover, serum immunoglobulin level (IgA), villus height and tight junction protein expression increased with organic acid supplementation. However, the organic acid supplementation did not alter the cecal microbiota composition (Zhang et al., 2024 c). Supplementation of sodium butyrate at dose rates of 300, 500 and 800 mg/kg in the diet of *Salmonella* Enteritidis challenged laying hens improved the egg production post *Salmonella* challenge. Sodium butyrate supplementation ameliorated the negative impacts of *Salmonella* challenge by improving the villi height, and villi to crypt depth ratio segments of small intestine. Inclusion levels of 500 and 800 mg/kg increased the butyric acid concentration in the cecum and the propionic acid content increased linearly with the increasing inclusion level of sodium butyrate. Moreover, the gene expression for gut tight junction proteins (ZO-1 and CLDN1) was enhanced with the sodium butyrate supplementation. Sodium butyrate helped in reducing the *Salmonella* and *E. coli* count, whereas number of *Lactobacilli* increased in the cecum of laying hens (Xiong et al., 2024). Aflatoxin intoxicated turkey poults (250 ng AFB_1/g of feed) supplemented with humic acid (0.25% w/w) improved the intestinal integrity, immune response and promoted the proliferation of beneficial bacteria in the gut. Moreover, the humic acid supplementation improved the gut morphological parameters and encouraged the proliferation of butyric acid producing bacteria in the gut irrespective of aflatoxin intoxication (Maguey-González et al., 2024). Addition of 1000 and 2000 mg/kg of benzoic acid in the diet of laying hens did not significantly affect the production performance indices. However, linear improvement in egg quality traits like albumen height and Haugh unit was noted. Supplementation at dose rate of 1000 mg/kg improved the microbial diversity and composition in the gut (Gong et al., 2021). The supplementation of organic acid blend (formic, acetic, fumaric, propionic and lactic acid) at the dose rate of 1 ml/liter of water reduced the foregut pH and the coliform and *E. coli* bacteria colonization. However, egg weight and quality parameters were not affected with organic acid supplementation (Bouassi et al., 2021). Commercial broilers fed different levels of organic acids (2, 3, 4 kg/ton of ammonium formate + ammonium propionate) and (2, 3, 4 kg/ton of calcium formate + calcium propionate) improved the body weight gain, carcass quality, gut morphology and reduced the total bacterial counts in the ceca (Saleem et al., 2020).

Limitations of organic acids

Organic acids are readily metabolized in small intestine which raises doubts regarding their activity in the lower intestinal tract (Jadhao et al., 2019). The outcome of organic acids use in poultry diets is dependent on a variety of factors, like the composition of gut microflora, organic acid product specifications, and health status of the flock. It is also reported that organic acids influence the presence of already inhabited lactic acid producing bacteria in the gut (Broom, 2015). Other disadvantages of organic acids are their pungent smell, instability and corrosive nature, which can deteriorate the feed milling equipment. Industrialists have combined organic acids with salts and prepared products in encapsulated and buffer form, which minimizes previously mentioned problems (Tabata et al., 2018). The bactericidal activity of organic acids depends on the acid concentration, gut pH and dissociation constant. Pathogens have the ability of developing resistant strains that adapt to the action of organic acids. Some bacteria especially *Salmonella* have the ability to survive extreme pH and acidic conditions (Foster, 1995).

Enzymes

Enzymes are protein molecules that serve as biological catalysts and accelerate chemical reactions. Enzymes have the ability to withstand high temperatures during feed pelleting and pH changes across the gut (Ravindran, 2013). Enzymes are the essential component to digest the nutrients in feed. Exogenous supplementation of enzymes improves the digestive efficiency and availability of nutrients (Llamas-Moya et al., 2020). As a part of enzymatic hydrolysis several metabolites are generated that support the growth of beneficial bacteria in gut (Munyaka et al., 2016). Plant sourced nonconventional feedstuffs are widely included in chicken diet to minimize the feed cost and improve the economic return (Iji et al., 2001). Such feed ingredients, however, contain anti-nutritional factors, e.g., phytic acid, non-starch polysaccharides, and enzyme inhibitors. Presence of these antinutritional factors contribute to decreased nutrient availability which ultimately hinders the growth and development of chickens (Woyengo and Nyachoti, 2011). In order to overcome these problems, exogenous enzyme preparations are added in poultry diets to improve nutrient digestibility and intestinal health which are helpful in improving the growth performance parameters and economic returns (Ravindran and Son, 2011; Leinonen and Williams, 2015). The most frequently added enzymes in poultry diets include xylanases, proteases and phytase. Xylanases have the ability to degrade nonstarch polysaccharides (Morgan et al., 2020). Phytase enzyme hydrolyzes phytate to inositol and improves the phosphorus availability (Cowieson et al., 2016). Protease preparations enhance the protein and amino acid digestibility, which ultimately reduces the excretion of nitrogen, ammonia, nitrate and nitrite into the environment (Cowieson and Roos, 2013).

Addition of β-mannanase (100 mg/kg) in low energy broiler diets proved helpful in supporting the immune function by enhancing the phagocytic activity of macrophages. β-mannanase supplementation increased the abundance of *Lachnospiraceae* family bacteria in the ceca of birds during the grower phase. Moreover, enzymatic supplementation also decreased the activity of glutaryl-CoA dehydrogenase, which is responsible for microbial fatty acid degradation (Zhang et al., 2024 a). Different levels of xylanase (50, 100, 150 mg/kg) supplementation in wheat-based broiler diets improved the nutrient digestibility, intestinal barrier, enzymatic activity, and promoted the beneficial bacteria proliferation in the gut. Birds fed xylanase supplemented at the inclusion level of 150 mg/kg had better feed conversion ratio in comparison with the control and rest of enzyme supplemented diets. Xylanase supplemented birds showed increased villus height and villus height to crypt depth ratio, thus improving the intestinal barrier function. Propionic acid production enhanced with xylanase supplementation which was linked with the proliferation of *Phascolarctobacterium* in the ceca (Wang et al., 2024). *Bacillus* derived alkaline protease supplemented at the doses of 100, 200, 300 and 400 g/ton improved the quality of breast muscles. Moreover, protease supplementation promoted the abundance of beneficial bacteria and reduced the level of metabolites like D-lactic acid and malonic acid (Yi et al., 2024 b). Basal diet of broilers having 50 kcal/kg reduced energy value supplemented with 100 mg/kg of mannanase resulted in higher body weight and reduced the production of inflammatory mediators in comparison with low energy non-supplemented diet. Mannanase supplementation increased the gene expression of intestinal tight junction proteins (claudin-1 and zonula occlundens-1). Moreover, mannanase supplemented birds had an increased level of isobutyric acid in cecal content. The energy metabolism and N-glycan synthesis were enhanced with mannanase supplementation through gut microbiota changes. Mannanase supplementation increased the colonization of *Lactobacilli,* and *Odoribacter* (Zhang et al., 2024 b). White feathered broilers supplemented with 100, 150, 200 and 250 g/ton of multienzymes (xylanase, mannanase, cellulase, amylase, and protease) linearly and quadratically influenced the feed conversion ratio. Nutrient utilization was also improved with multienzyme supplementation through efficient utilization of energy and fiber content of the diet. Additionally, expression for nutrient transporter gene was also enhanced with multienzyme inclusion in broiler diet (Yi et al., 2024 a). Dietary supplementation of xylanase enzyme derived from two different sources (*Aspergillus oryzae* and *Trichoderma bisset*) did not fully compensate for the weight gain and feed conversion losses associated with reduced energy and crude protein in broiler diets. Xylanase supplementation, however, increased the nutrient absorption surface area as this was evidenced with increased villus surface area. Additionally, xylanase supplementation increased the count of *Lactobacilli* and concentration of branched and short chain fatty acids in ceca of broilers (Ceylan et al., 2024). Addition of β-mannanase (0.15, 0.20 g/kg) in low energy laying hen diets improved the feed conversion ratio and reduced the average feed intake and restored the losses in egg quality parameters associated with consumption of low energy diets. Moreover, the enzyme supplementation was helpful in reducing the activation of pro-inflammatory cytokines in the gut. The proliferation of beneficial bacteria (*g_Pseudoflavonifractor, g_Butyricicoccus*, and *f_Lactobacillaceae*) was enhanced in the birds fed β-mannanase supplemented diets (Liu et al., 2024 a). Laying hens fed protease DE200 supplemented at the inclusion level of 100 and 200 g/ton improved the egg production, reduced feed intake and feed conversion ratio. Egg weight was not affected with protease supplementation, however, egg quality parameters like Haugh unit and egg breaking strength were improved. Regarding cecal microbial diversity, protease supplementation increased the abundance of *Bacteroidetes* and *Firmicutes,* whereas the proportion of *Fusobacteria* was reduced (Cai et al., 2024).

Limitations in feed enzymes application

Exogenous enzymes in feed are susceptible to denaturation with high temperature application during pelleting. Moreover, there are differences in the denaturation temperature of feed enzymes depending upon their origin of extraction. For example, fungal enzymes can withstand the pelleting temperature of approximately 80°C whereas enzymes of bacterial origin can withstand the pelleting temperature of up to 90°C (Spring et al., 1996; Boroojeni et al., 2016).

Egg yolk antibodies

Antibodies can be harvested using chickens as an immunization host. Egg yolk immunoglobulin (IgY) is classified as primary chicken immunoglobulin and possesses equivalent properties in comparison with mammalian IgG. Chickens transfer high concentration of maternal antibodies in their egg yolk (Tini et al., 2002). These maternal antibodies or the egg yolks obtained from pathogen specific immunized chickens can be utilized as feed additives to protect chickens from different pathogenic bacteria (Chalghoumi et al., 2009). The egg yolk antibodies minimize the colonization of bacterial pathogens through a) antigen antibody reaction, pathogen specific antibodies harvested from egg yolk can neutralize the enteric pathogens in the gut and can be used as a preventive measure to endure enteric pathogens (Abadeen et al., 2021); b) IgY binding to bacterial appendages such as flagella and pili which in turn hampers the capability of bacteria to adhere to the intestinal wall; c) neutralization of bacterial toxins, inhibition of bacterial enzymes and blocking the bacterial signaling cascades (Wang et al., 2011; Xu et al., 2011). Feeding of low (600 mg/kg of diet) and high levels (700 mg/kg of diet) of microencapsulated egg yolk derived IgY antibodies improved the average daily gain and reduced the feed conversion ratio. The weight of immune organs (thymus and spleen) increased with the egg derived IgY supplementation. A high level of microencapsulated IgY antibody improved the gut morphology by increasing the villi height and villus height to crypt depth ratio. Microencapsulated IgY supplementation reduced the *E. coli* and *Salmonella* populations, whereas enrichment of gut with lactic acid producing bacteria and *Bifidobacteria* were enhanced (Jin et al., 2023). Coccidiosis and *Clostridium perfringens* challenged broiler chickens supplemented with 1% of egg yolk IgY powder enriched with *C. perfringens* antigens (NetB toxin and elongation factor-Tu) increased the body weight gain, ameliorated the enteric lesions and reduced the serum NetB levels. In an *in vitro* experiment, IgY against NetB antigen was successful in reducing the hepatocellular cytotoxicity (Goo et al., 2023). Provision of 1 ml of egg yolk antibodies against *Clostridium perfringens* through oral route ameliorated the negative clinical and behavioral signs associated with *C. perfringens* infection. Moreover, the damages associated with necrotic enteritis on the organs like liver, kidney and jejunum were reduced with administration of egg yolk antibodies (Abadeen et al., 2022). Feeding of different concentrations of egg yolk IgY (1500, 3000, 4000 μg/ml) influenced the production performance and gut microbiota of broilers. Birds offered 4000 μg/ml had higher body weight during the grower phase, whereas birds consuming 3000 μg/ml had higher body weight during the finisher phase. Feed conversion ratio was lower in birds fed 3000 μg/ml of IgY. Inclusion levels of 3000 and 4000 μg/ml reduced the *E.coli* counts in muscle and cecal contents (Rehan et al., 2022). Chicks infected with *Salmonella* fed a diet supplemented with 5% egg yolk enriched with polyclonal IgY against *Salmonella* Enteritidis and *Salmonella typhimurium* resulted in a 37.48 and 38.54% reduction in cecal *Salmonella* counts (Karabasanavar et al., 2022). Oral route administration of 120 mg of hyper-immune egg yolk *Eimeria* species-specific IgY in the coccidiosis challenged White Leghorn laying hens resulted in increased weight gain and survival rate post coccidiosis challenge. Moreover, the egg yolk treatment reduced the rate of oocyst shedding in the feces and intestinal lesion scores in challenged birds (Juárez-Estrada et al., 2021). Addition of 12.8 g/kg of capsulated immune yolk containing IgY against *Salmonella enterica* subsp. *enterica* serovar Infantis reduced the colonization of *Salmonella* in the ceca and liver of challenged broilers soon after 2–3 weeks of dietary supplementation (Isfahani et al., 2020).

Limitations of egg yolk antibodies

Proteolysis through gastric enzymes is the limiting factor regarding the use of egg derived IgY antibodies. IgY antibodies exhibit resistance to the enzymatic activity of trypsin and chymotrypsin, however, these are prone to proteolysis with the action of the pepsin enzyme (Hatta et al., 1993). Microencapsulation procedures can resolve the gastric inactivation of IgY antibodies (Odenbreit et al., 1999). Moreover, the production of IgY antibodies using extraction and purification methods in specific pathogen free birds is also a challenging aspect in its application in human and animal medicine (Lee et al., 2021).

Antimicrobial peptides

Antimicrobial peptides are the defense mechanism product produced by the animals and plants and can be found on the surfaces that are exposed to the external environment. Antimicrobial peptides have low molecular weight and are hydrophobic in nature (Patyra and Kwiatek, 2023). Most of the antimicrobial peptides are composed of 12–50 amino acids (Hancock et al., 2006). Bacterial antimicrobial peptides are known as bacteriocins (Hernández-González et al., 2021). Antimicrobial peptides of plant origin are thionines, snakins, and defensins (Zhang and Yang, 2022). Similarly, human or animal origin antimicrobial peptides are defensins and cathelicidines which can be widely detected in blood constituents and mucosal surfaces (Doss et al., 2010). Insect derived antimicrobial peptides include cecropin, defensins, moricins, proline, and glycine rich peptides (Patyra and Kwiatek, 2023). The proposed mode of action of antimicrobial peptides include a) disruption in cellular metabolism (Ongey et al., 2018); b) targeting the activity of cytoplasmic components leading to cell lysis, c) gaining entry into the cytoplasm and disrupting expression, thus affecting proteins synthesis (Hernández-González et al., 2021).

Addition of 10, 20 and 50 mg/kg of the antimicrobial peptide Llv in the diet of female broilers produced beneficial effects on immunoglobulin levels and gut immune cells across the various time frames in the experiment (Liu et al., 2024 b). Supplementation of 100 and 200 mg/kg of Gal-13 antimicrobial peptide in the diet of broilers improved the production performance and gut health of birds. Inclusion level of 100 mg/kg of Gal-13 was effective in improving the weight and average daily gain of birds. Lactic acid producing bacteria count was higher in the Gal-13 supplemented group; whereas the number of *Enterococcus* sp. and *Escherichia coli* declined in the ileum and cecum. Moreover, the antibody titers against Newcastle disease were higher in the antimicrobial peptide group, however, gene expression for various inflammatory cytokines was downregulated (Wang et al., 2023). An *in vitro* study revealed that the antimicrobial peptide HJH-3 was effective against both the gram positive and negative bacterial strains. The lethal dose of HJH-3 against *Salmonella pullorum* was 100 µg/mL. In the second experiment involving a chicken infection model, it was found that HJH-3 was effective in ameliorating the negative impacts of *Salmonella pullorum* infection. HJH-3 supplementation was effective in reducing the bacterial counts in blood and spleen and minimizing the intestinal pathological lesions. The effects of HJH-3 were more pronounced pre-infection in comparison with post-infection. The mortality rate in HJH-3 supplemented infected chickens was also lower (30%) in comparison with control group, where no antimicrobial peptides were offered during infection (Xu et al., 2023). Maggot derived antimicrobial peptides in the yellow feather broiler diets at the inclusion levels of 100, 200 and 300 mg/kg influenced the performance traits and gut microbiota of broilers. Inclusion levels of 200 and 300 mg/kg increased the average daily gain in comparison with other treatments. The immunoglobulins (IgA and IgG) level was also higher in the antimicrobial peptide group. Moreover, dietary manipulation with antimicrobial peptide increased the population of *Bacteroides* in the cecum of birds (Gao et al., 2023). An *in ovo* injection of avian β-defensin 1 (300 µg/ml) had antimicrobial and immunomodulatory effects. Avian β-defensin 1 reduced the chick mortality percentage up to 44% in pathogenic *E. coli* induced yolk sac infection (Nguyen et al., 2021). Inclusion of 20 mg/kg of Mastoparan X antimicrobial peptide in the broiler diets improved the production performance, modulated the immune responses and gut microbial composition. The expression of inflammation mediated cytokines (IL-6 and LITNF) was reduced; whereas gene expressions for intestinal tight junction proteins (ZO-1, Claudin-1, Occludin, JAM-2 and MUC2) were upregulated with antimicrobial peptide supplementation. The microbiota analysis of cecal content of antimicrobial peptide supplemented birds at 14 and 28 days revealed that relative abundance of *Lactobacillus* and *Lactococcus* was enhanced (Zhu et al., 2022). Dietary supplementation of broiler diets with *Escherichia coli* derived Microcin C7 antimicrobial peptide at the inclusion levels of 2, 4 and 6 mg/kg reduced the feed conversion ratio and maintained the gut morphology. Microcin C7 inclusion modulated the immune responses by elevating the serum cytokine levels, immunoglobulins, and IgA secretion capacity of ileal cells. Moreover, mRNA expression for tight junction proteins (Occludin and ZO-1) were enhanced. Antimicrobial peptide C7 supplementation increased the *Lactobacillus* count; whereas reduced the *E. coli* count in ileal and cecal content. Short chain fatty acid and lactic acid concentrations increased with dietary Microcin C7 supplementation (Dai et al., 2022). A study investigating the inclusion of different levels of small peptides found that the supplementation level of 4.5 mg/kg of small peptides was effective in exerting the beneficial effects in Tianfu green shell laying hens. Small peptide supplementation improved the growth rate, gut permeability, antioxidant capacity, and elevated the level of serum immunoglobulins. The trigger for anti-inflammatory responses was reduced. Moreover, small peptide supplementation increased the relative abundance of *Firmicutes*, whereas the prevalence of *Bacteroidetes* declined (Zhao et al., 2022).

Challenges in antimicrobial peptides application

Antimicrobial peptides exhibit non-specific control activity against pathogens which reduces the chances of incidence of resistance in bacteria. Repeated exposure of bacteria to antimicrobial peptide, however, leads to the development of antimicrobial resistant bacterial strains (Li et al., 2018). Another limitation linked with antimicrobial peptides is their higher cost of production in comparison with antibiotics (Kumar et al., 2020). Additionally, antimicrobial peptides are more susceptible to denaturation when exposed to fluctuating temperatures and changes in pH across the gut (Li et al., 2018; Dijksteel et al., 2021). The *in vitro* efficacy of antimicrobial peptides does not guarantee the same antimicrobial efficacy when *in vitro* trials are conducted. These aforementioned drawbacks limit the wide range approval and application of antimicrobial peptides in animal production sector (Rodrigues et al., 2022).

Bacteriophages

Bacteriophages are the viruses that target the specific bacteria and utilize the bacterial biosynthetic machinery to replicate and form the bacteriophage progeny with or without lysis of targeted bacterial cell (Iqbal et al., 2016). The virus after gaining entry into bacterial cells depends on the tree life cycle modes (lytic, lysogenic and chronic) to produce bacteriophages. Lytic bacteriophages depend on the lysis cycle to reproduce in a continuous manner. The lysogenic bacteriophages merge their genes with the bacterial genome and proliferate with the bacterial division. On the other hand, the chronic bacteriophages keep replicating the genetic material and assembling the progeny bacteriophages without harming the host bacterial cell (Jiang et al., 2024).

Bacteriophage supplementation confers benefits to the host by a) regulating the intestinal microbial ecology by exerting antagonistic effects on non-host bacteria (Chatterjee et al., 2021); b) targeted inhibition of pathogen through degrading extracellular macromolecules which aids in injecting the bacteriophage nucleic acid into targeted bacteria (Pires et al., 2016); and c) modulation of immune responses through regulated inflammatory responses (Miernikiewicz and Dabrowska, 2022).

A study investigating the combination of bacteriophages (*Fletchervirus phage* NCTC 12673 and *Firehammervirus* phage vB_CcM-LmqsCPL1/1) and competitive exclusion product found that the combination was effective in reducing the colonization of *Campylobacter jejuni* 1.0 $\log_{10}$ in the cecum, colon, and cloaca (Peh et al., 2024). Wild type bacteriophages delivered through drinking water were not effective in reducing the *Salmonella* Heidelberg colonization in cecal samples of infected chickens. These non- significant results may have appeared because of bacteriophage-resistant bacterial mutants (Vaz et al., 2024). A recent *in vitro* study indicated that *Escherichia* phage VaT-2019a isolate PE17 and the *Escherichia* phage AG-MK-2022 showed high antimicrobial activity and killed approximately 95% of avian pathogenic *Escherichia coli* strains (Karami et al., 2024). A bacteriophage cocktail against poultry *Salmonellosis* exhibited lytic activity in a wide range of temperature and pH conditions under *in vitro* conditions. Moreover, when the same bacteriophage cocktail was included in the diet of broilers (10^9 PFU/kg of feed), it was effective in reducing the *Salmonella* colonization in crop, liver, spleen, and ceca of birds (Pourabadeh et al., 2024). Single dose oral route administration of *Salmonella* phage vB_SalS_JNS02 at the dose rate of 10^8 PFU/mL or 100 µL/chick in broilers was successful in increasing the production of secretory IgA. Moreover, the phage therapy also brought significant changes in the gut microbial community by increasing the abundance of beneficial bacteria, thus maintaining homeostasis across the gut barrier (Li et al., 2024 b). Broiler chickens challenged with nontyphoidal *Salmonella* species offered different levels of cocktail phage diet (10^5, 10^6 and 10^7 PFU/day) reduced the enteric colonization of *Salmonella* as evidenced by reduction in bacterial count in fecal samples. Moreover, birds fed a cocktail phage diet had higher weight gain in comparison with the control challenged group (Thanki et al., 2023).

Challenges in bacteriophage therapy

Bacteriophage therapy itself can lead to the development of antimicrobial resistance (Joerger, 2003). Spontaneous mutation remains the most common mechanism through which antimicrobial resistance can be developed. Spontaneous mutation alters the bacterial surfaces components (lipopolysaccharides, outer membrane proteins, cell wall teichoic acids, capsules and other bacterial appendices) that determine bacteriophage specificity (Oechslin, 2018). The narrow spectrum of bacteriophages against the bacteria is considered as another limitation in the use of bacteriophage therapy. Bacteriophages have the ability to lyse specific bacteria, thus limiting their use against a small number of bacterial species or genera (Hyman and Abedon, 2010). Keeping in view the specificity bacteriophage may fail to treat the illnesses that are caused by multiple bacteria, thus limiting desirable therapeutic outcomes (Gill and Hyman, 2010). This problem may be resolved through the use of bacteriophage cocktails, which broaden killing capacity and host range coverage. Moreover, bacteriophage cocktails may also limit the development of bacteriophage resistance (Chan et al., 2013). The use of both lytic and lysogenic bacteriophage may also spread harmful antibiotic-resistant gene and toxins into the environment that may pose a public health risk (Chen et al., 2022). Although bacteriophages are generally recognized as safe (GRAS), there is currently no regulatory pathway that can register bacteriophage product as a feed additive. This hampers the commercialization of bacteriophage products in some parts of the world (Abd-El Wahab et al., 2023).

Table 1. Non-antibiotic growth promoters in poultry nutrition

Author	Species	Product	Inclusion level	Results
1	2	3	4	5
Probiotics				
Horyanto et al., 2024	Broilers	*Bacillus amyloliquefaciens*	500 g/ton	• Decreased feed conversion ratio • Decline in mortality percentage
Mirsalami and Mirsalami, 2024	Plymouth Rock chicks	*Enterococcus faecium* + *Streptococcus thermophiles*	0.50%	• 17% improvement in body weight • Decrease in FCR value • Enhancement of enzymatic digestive activity • Increase the abundance of beneficial bacteria • Better diarrhea management
Fonseca et al., 2024	Broilers	*Bacillus subtilis*	226.8 g/ton	• Better feed conversion ratio • Affected the relative abundance of *Bifidobacterium*, *Intestinimonas* and *Ligilactobacillus*
Popov et al., 2024	Broilers	*Bacillus subtilis* KB41	0.10%	• Improvements in growth performance • Increase in cecal *Lactobacillus* count • Enhanced interferon gene expression (IL-6 and IL-10)
Cui et al., 2024	Broilers	*Bacillus velezensis*	10^8 CFU/bird	• Reduction in *Campylobacter jejuni* colonization • Improvements in microbial diversity and richness
Li et al., 2024 a	Muscovy duck	Compound Duck Probiotic	1.3×10^8 CFU/ml	• Improvements in average daily gain • Better feed conversion ratio • Gut morphology, tight junction proteins were also improved
Hatipoglu et al., 2024	Broilers	Liquid and lyophilized lactic acid bacteria	0.5 mL/L	•Improvements in growth rate, hormonal concentrations, gut health and microbial diversity
Gao et al., 2024	Ross 308	*In ovo* spray *Lactobacillus rhamnosus* or *Lactobacillus paracasei*	~9 log CFU/egg	• 5% improvement in the hatchability percentage • Improvements in chick quality
Yang et al., 2024 b	Broilers	*Lactiplantibacillus plantarum*	5×10^8 CFU/kg	• Improvements in average daily gain • Better feed conversion ratio • Increase in cecal short chain fatty acid content • Increase in abundance of *Ruminococcus* and *Lachnospiraceae* genus
Prebiotics				
Yadav et al., 2024	Broilers	Xylo-oligosaccharides	0.05, 0.1, 0.2%	• No significant influence on the production performance parameters • Improvements in gut morphology with 0.05 and 0.2% inclusion • Linear increase in the beneficial bacteria population
Lan et al., 2024	Broilers	Chitosan oligosaccharide	200, 400, 800 mg/kg	• No significant influence on the production performance parameters • Improvements in intestinal weight and morphology with 200 and 400 mg/kg • Enhanced gene expression for different nutrient transporters at different inclusion levels

Table 1 – contd.

1	2	3	4	5
Alqhtani et al., 2024	Broilers	Yeast cell wall	0.25, 0.50 mg/kg	• Improved production performance and carcass quality at 0.25 and 0.5 mg/kg in enteric challenged birds • Decline in mortality percentage at 0.25 and 0.5 mg/kg • Improved gut morphology at 0.5 mg/kg • Increase in *Lactobacilli* count and decline in *Clostridium perfringens* population at 0.25 and 0.5 mg/kg
Rao et al., 2024	Broilers	Xylo-oligosaccharides	150, 300, 450 mg/kg	• Higher body weight and average daily gain at 150 and 450 mg/kg • Increased gene expression for tight junction proteins at 300 and 450 mg/kg • Increase in villus height and villus height to crypt depth ratio at all given inclusion levels
Maina et al., 2024	Broiler breeder pullets	Hydrolyzed whole yeast	0.05%	• No significant effects on growth, prelay body weight and uniformity • No significant effects on immunity, bone morphometry • No influence on cecal short chain fatty acids
Leigh et al., 2024	Laying hens	Yeast derived mannan	0.4 mg/kg (0–34 weeks) 0.8 mg/kg (35 weeks – end of laying period)	• Supplemented birds produced 6.79% more eggs • Up to 5.58% better feed conversion ratio • Improvements in flock uniformity • Decline in *Campylobacter* colonization • Increase in population of butyrate and propionate producing bacteria
Sittiya and Nii, 2024	Laying hens	Bamboo shoot extracted oligosaccharides	5 g/kg	• Improvements in egg quality and gut microbiota diversity • Enhanced recruitment of leucocytes and inflammatory cytokines
Liu et al., 2024	Laying hens	**β-mannanase**	0.15 and 0.2 g/kg	• Improvements in productive performance and gut microbial diversity • Reduced anti-inflammatory factor production
Youssef et al., 2023 a	Mandarah roosters and laying hens	Mannan oligosaccharides	0.1, 0.2 and 0.5 g/kg	• Elevated levels of immunoglobulins (IgM and IgY) • Enhanced antibody titers against ND • Improved the histological architecture of testis and spermatogenesis
Youssef et al., 2023 b	Mandarah roosters and laying hens	Chitosan oligosaccharides	0.1, 0.2 and 0.5 g/kg	• Inclusion level of 0.1 g/kg improved the growth of reproductive organs • Enhanced antibody titers against ND
Youssef et al., 2024 a	Mandarah roosters and laying hens	Chitosan oligosaccharides	0.1, 0.2 and 0.5 g/kg	• Inclusion level of 0.1 g/kg showed the highest laying percentage • Inclusion level of 0.2 g/kg exhibited better reproductive performance
Amir et al., 2023	Broilers	Xylo-oligosaccharides	0.1 g/kg	• Improvements in growth during first 28 days • Non-significant effects on growth at 35th day of age • Improvements in starch utilization of gut bacteria
Zhu La et al., 2023	Broilers	Alginate oligosaccharide	100, 200, 400 mg/kg	• Higher average daily gain and feed intake at 200 mg/kg inclusion • Increased villus height and expression for gut tight junction proteins at 200 mg/kg inclusion • Increased concentration of cecal short chain fatty acids
Kwiecień et al., 2023	Female turkeys	Mannan oligosaccharides	0.50%	• Improvements in weight gain • Increase in level of minerals in breast and thigh cuts • Improved bone health
Salami et al., 2022	Laying hens	Mannan oligosaccharides	0.97 kg/ton	• An increase of 1.76% in egg production • Improvement of 2.39% in livability percentage

Table 1 – contd.

1	2	3	4	5
		Synbiotics		
Youssef et al., 2024 b	Mandarah male chicks	Probiotic bacteria + Fructo-oligosaccharides	0.25, 0.50 ml	• Increase in lactic acid producing bacteria if the given dose provided through drinking water • Reduced *E. coli* population in drinking water at all given levels • Improved gut morphology at 0.50 ml dose through drinking water
White et al., 2024	Broilers	Probiotic + Inulin	0.5 ml of oral synbiotic gel 0.5k g/ton in feed	• Improved immunity through reduced interleukins and toll like receptors in both oral gel and feed application method • No significant effects on production performance
Johnson et al., 2024	Laying hens	Probiotic bacteria + Fructo-oligosaccharides	1 kg/ton	• Regulated microbiota gut brain axis • Birds reduced the threatening, fighting, and pecking behavior • Increase in relative abundance of *Lactobacillus* and *Bifidobacterium* • Differences in dopamine, serotonin and corticosterone concentration
Araba et al., 2024	Laying hens	*Bacillus subtilis* + Yeast cell wall	635 g/ton	• Reduced enteric colonization of *Salmonella* Enteritidis
Salem and Abd El-Dayem, 2024	ISA Brown laying hens	Probiotic + Mannan oligosaccharides + 1,3 ß-glucan	2 g/kg	• Improved egg production percentage • Increased egg mass • Increased level of estradiol in blood • Higher egg shell calcium content
Shah et al., 2023	Broilers	4 live strain bacteria + Fructo-oligosaccharides	1 g/kg	• Reduced feed intake and feed conversion ratio • Enhanced immunity against necrotic enteritis
Cason et al., 2023	Broilers	Probiotic bacteria + Fructo-oligosaccharides	20 g/1,000 birds/day	• Enhanced immunity • Decrease in *Campylobacter* colonization • Increased expression for tight junction proteins
		Phytogenics		
Dong et al., 2024	Broilers	*Taraxacum monoglicum* plant extract	500, 1000, 2000 mg/kg	• Most significant beneficial effects in terms of blood biochemistry, gut morphology and healthy bacterial population noted at 1000 mg/kg
Hafeez et al., 2024	Broilers	Herbal blend (coriander, garlic, and fenugreek)	1, 2, 3%	• Higher live and carcass weight at 1% inclusion level • Improvements in nutrient digestibility especially crude protein and fat at 1% inclusion level • Improved mineral utilization at the inclusion level of 3%
Carpio et al., 2024	Broilers	Silymarin + Betaine + Curcumin extract	250, 500 mg/kg	• No interaction among phytogenic supplementation and hepatic damage

Table 1 – contd.

1	2	3	4	5
Adil et al., 2024	Broilers	Rosemary essential oil	100 mg free + 200 mg nano-encapsulated	• Improved weight gain and feed efficiency • Improved carcass quality and nutrient utilization • Increased gene expression for mucin and peptide transporters
Mullenix et al., 2024	Broilers	Kelp, thymol, eugenol and cinnamaldehyde micro-particles	75, 100 g/ton	• Higher carcass weight at 100 g/ton inclusion level • Decreased the tibia and femur lesion at all inclusion levels • Numeric increase in the incidence of muscle myopathies at all inclusion levels
Madkour et al., 2024	Broilers	Oregano and rosemary leaves extract	50, 100 mg/kg	• Inclusion of 50 mg/kg of oregano leaves extract improved the production performance, heat shock protein
El-Sayed et al., 2024	Broilers	20% oregano essential oil	1 ml/5 liters for 8 hours daily	• Improved the weight gain and feed conversion ratio • Higher antibody titers • Improved gut morphology
Khongthong et al., 2024	Broilers	Sanguinarine-based isoquinoline alkaloid	60, 100 mg/kg	• Improved the performance parameters with nonsignificant differences between different inclusion levels • Increase in cecal microbial diversity • Restored the heat stress losses
Huang et al., 2024	Broilers	Microencapsulated essential oil + Organic acid	200, 400, 600, 800 mg/kg	• Higher daily gain and average body weight at 200 mg/kg • Enhanced lipase activity in the duodenum at 200, 400 and 600 mg/kg inclusion level • Increased butyric acid concentration in ceca at 200 mg/kg • Increase in lactic acid producing bacteria at 400 mg/kg inclusion level
Du et al., 2024	Broilers	*Magnolia officinalis* plant extract	100, 200, 400 mg/kg	• Improved weight gain and feed conversion ratio at 200 and 400 mg/kg inclusion level • Improved gut morphology at 100 mg/kg inclusion level • Increased short chain fatty acids concentration at 100 mg/kg inclusion levels
Yang et al., 2024 a	Broilers	*Polygonatum sibiricum* polysaccharide	400, 800 mg/kg	• Linear improvement in body weight and feed conversion ratio • The inclusion level of 800 mg/kg showed improved growth, antioxidant capacity and gut morphology
Sharma et al., 2024	Laying hens	*Artemisia annua* leaves	0.5, 1%	• Improvements in productive performance, intestinal lesion severity, villi recovery at 1% inclusion level
Xu et al., 2024	Hy-line Brown laying hens	Microencapsulated essential oil	300 and 500 mg/kg	• Improved productive performance, egg quality, antioxidant capacity and immunity parameters at both inclusion levels
Pasri et al., 2024	Broiler breeders	Clove + Green tea pomace + Vietnamese coriander	1%	• Increase in egg production and hatchability percentage • Decline in late stage embryonic mortality • Enhanced antioxidant capacity of liver, yolk and meat • Decreased gene expression for pro-inflammatory cytokines and heat shock proteins

Table 1 – contd.

1	2	3	4	5
		Organic acids		
Islam et al., 2024	Broilers	Formic acid + Propionic acid + Ammonium formate + Ammonium propionate	200 mg/kg	• Improved the weight gain and feed conversion ratio • Reduced the colonization of *C. perfringens*, *E. coli* and *Salmonella* • Population of *Bacillus* was enhanced
Garcia et al., 2024	Broilers	Butyric + Valeric acid	500 g/ton = Starter 250 g/ton = Grower	• Increased feed intake and weight • Better feed conversion ratio • Mortality percentage was 1.1% lower during finisher phase
Daghio et al., 2024	Broilers	Blend of short and medium chain fatty acids (C4:0 to C9:0)	1.5 g/100 g on dry matter	• 3.5% reduction in feed intake • No significant effects on performance parameters • Nonsignificant effects on cecal microbial diversity
Xiong et al., 2024	Laying hens	Sodium butyrate	300, 500, 800 mg/kg	• Improved the egg production post *Salmonella* challenge at 800 mg/kg • Improved the villi height and villi to crypt depth ratio at all inclusion levels • Increased the butyric acid concentration in the cecum at 500 and 800 mg/kg inclusion • Gene expression for gut tight junction proteins (ZO-1 and CLDN1) were enhanced at inclusion level of 800 mg/kg • Reduced the *Salmonella* and *E. coli* count at inclusion level of 800 mg/kg • *Lactobacilli* increased in the cecum at inclusion level of 800 mg/kg
Zhang et al., 2024 c	Hy-Line Brown laying hens	Fermented calcium butyrate	300 mg/kg	• Improvement in ovarian health and egg shell strength • Elevated the IgA levels • Increased villus height and expression of tight junction proteins
Maguey-González et al., 2024	Turkey poults	Humic acid	0.25% w/w	• Encouraged the proliferation of butyric acid producing bacteria • Improved the intestinal integrity, immune response
Gong et al., 2021	Laying hens	Benzoic acid	1000 and 2000 mg/kg	• 1000 mg/kg dose rate improved the egg quality, gut morphology and microbial composition
Bouassi et al., 2021	Laying hens	Formic, acetic, fumaric propionic and lactic acid	1 ml/L	• Reduced the foregut pH and improved the beneficial bacteria colonization
Saleem et al., 2020	Broilers	Ammonium formate Ammonium propionate Calcium formate Calcium propionate	2, 3, 4 kg/ ton	• Improved the body weight gain, carcass quality, gut morphology • Reduction in total cecal bacterial counts
		Enzymes		
Zhang et al., 2024 a	Broilers	β-mannanase	100 mg/kg	• Enhanced the phagocytic activity of macrophages • Increased the abundance of *Lachnospiraceae* family • Decreased the activity of glutaryl-CoA dehydrogenase

Table 1 – contd.

1	2	3	4	5
Wang et al., 2024	Broilers	Xylanase	50, 100, 150 mg/kg	• Improved nutrient digestibility, intestinal barrier and enzymatic activity at inclusion level of 100 and 150 mg/kg • Inclusion level of 150 mg/kg had better feed conversion ratio • Increased villus height and villus height to crypt depth ratio • Enhanced total short chain fatty acids production at inclusion level of 150 mg/kg
Yi et al., 2024 b	Broilers	Alkaline protease	100, 200, 300, 400 g/ton	• Improved the quality of breast muscles at inclusion level of 200–400 g/ton • Promoted the abundance of beneficial bacteria at all inclusion levels • Reduced the level of metabolites like D-lactic acid and malonic acid
Zhang et al., 2024 b	Broilers	β-mannanase	100 mg/kg	• Reduced the production of inflammatory mediators • Increased the gene expression of intestinal tight junction proteins • Increased level of isobutyric acid in cecal content • Enhanced energy metabolism • Increased colonization of *Lactobacilli* and *Odoribacter*
Yi et al., 2024 a	Broilers	Xylanase + Mannanase + Cellulase + Amylase + Protease	100, 150, 200, 250 g/ton	• Linear and quadratic influence on feed conversion ratio • Improved nutrient utilization • Enhanced expression for nutrient transporter genes
Ceylan et al., 2024	Broilers	Xylanase	152 FXU/kg	• Enzyme supplementation did not compensate for weight gain and FCR losses associated with reduced energy and protein diet • Increased villus surface area • Increased count of *Lactobacilli* • Increased concentration of branched and short chain fatty acid
Liu et al., 2024 a	Laying hens	β-mannanase	0.15, 0.20 g/kg	• Improved the feed conversion ratio and reduced the average feed intake • Restored the losses in egg quality • Reduced the activation of pro inflammatory cytokines • Proliferation of beneficial bacteria
Cai et al., 2024	Laying hens	Protease DE200	100 and 200 g/ton	• Improved egg production, quality and abundance of beneficial bacteria at the inclusion level of 200 g/ton
Egg yolk antibodies				
Jin et al., 2023	Broilers	Microencapsulated IgY antibodies	600, 700 mg/kg	• Inclusion level of 700 mg/kg can be used to improve immunity, gut health and production performance
Goo et al., 2023	Broilers	*C. perfringens* antigens (NetB toxin and elongation factor-Tu)	1%	• Increased the body weight gain • Ameliorated the enteric lesions • Reduced the serum NetB levels

Table 1 – contd.

1	2	3	4	5
Karabasanavar et al., 2022	Broilers	Polyclonal IgY against *Salmonella*	5%	• *Salmonella* Enteritidis was reduced up to 37.48% • Reduction in cecal *Salmonella typhimurium* up to 38.54%
Abadeen et al., 2022	Broilers	Antibodies against *Clostridium perfringens*	1 ml	• Ameliorated the negative clinical and behavioral signs • Reduced damages associated with necrotic enteritis on the organs like liver, kidney and jejunum
Rehan et al., 2022	Broilers	Egg yolk IgY	1500, 3000, 4000 µg/ml	• Inclusion level of 3000 and 4000 µg/ml of IgY can be used to improve growth rate, behavior, gut health and meat quality of broilers
Juárez-Estrada et al., 2021	Laying hens	*Eimeria* species-specific IgY	120 mg	• Increased weight gain • Improved survival rate post coccidiosis challenge • Reduced oocyst shedding rate • Reduced intestinal lesion scores
Isfahani et al., 2020	Broilers	IgY against *Salmonella enterica*	12.8 g/kg	• Reduced the cecal colonization of *Salmonella*
Antimicrobial peptides				
Liu et al., 2024 b	Broilers	Antimicrobial peptide Llv	10, 50, 100 mg/kg	• Increased immunoglobulin levels and gut immune cells at inclusion level of 100 mg/kg
Wang et al., 2023	Broilers	Gal-13 antimicrobial peptide	100, 200 mg/kg	• Improved weight and average daily gain at inclusion level of 100 mg/kg • Increased beneficial bacteria count at 200 mg/kg • Higher antibody titers against Newcastle disease • Downregulated gene expression for various inflammatory cytokine
Gao et al., 2023	Broilers	Maggot derived antimicrobial peptides	100, 200, 300 mg/kg	• Improved production performance at inclusion level of 200 and 300 mg/kg • Higher immunoglobulins (IgA and IgG) levels at inclusion level of 300 mg/kg • Increased cecal population of *Bacteroides*
Xu et al., 2023	Broilers	HJH-3	200 µg/mL	• Exhibited antimicrobial activity against gram positive and negative bacterial strains • Lethal dose of HJH-3 against *Salmonella pullorum* was 100 µg/mL • Mortality rate reduced up to 30% in infected birds
Zhu et al., 2022	Broilers	Mastoparan X antimicrobial peptide	20 mg/kg	• Improved the production performance • Upregulated tight junction proteins • Reduced expression of cytokines • Enhanced relative abundance of *Lactobacillus* and *Lactococcus*
Dai et al., 2022	Broilers	Microcin C7	2, 4, 6 mg/kg	• Improved production performance at 4 mg/kg • Improved IgA secretion and short chain fatty acids production at inclusion level of 6 mg/kg
Zhao et al., 2022	Laying hens	Small peptides	4.5 mg/kg	• Improved the growth rate, gut permeability antioxidant capacity • Elevated serum immunoglobulins levels • Reduced trigger for anti-inflammatory responses • Increased the relative abundance of *Firmicutes* • Prevalence of *Bacteroidetes* declined

Table 1 – contd.

1	2	3	4	5
Nguyen et al., 2021	Broilers	Avian β-defensin 1	300 µg/ml	• Reduced the chick mortality percentage up to 44% in pathogenic *E. coli* induced yolk sac infection
Bacteriophages				
Peh et al., 2024	Broilers	*Fletchervirus phage* NCTC 12673 + *Firehammervirus* phage vB_CcM-LmqsCPL1/1	10^7 PFU/ml	• Reduced the colonization of *Campylobacter jejuni* by 1.0 $\log_{10}$ in the cecum, colon and cloaca
Vaz et al., 2024	Broilers	Wild type bacteriophages		• Not effective in reducing the *Salmonella* Heidelberg colonization
Karami et al., 2024	Broilers	*Escherichia* phage VaT-2019a *Escherichia phage* AG- MK-2022	10^9 PFU/ml	• Killed approximately 95% of avian pathogenic *Escherichia coli* strains
Pourabadeh et al., 2024	Broilers	Bacteriophage cocktail	10^9 PFU/kg	• Reduced *Salmonella* colonization • Exhibited antibacterial activity *in vitro*
Li et al., 2024 b	Broilers	*Salmonella* phage vB_SalS_JNS02	100 µL/chick	• Increased production of secretory IgA • Significant changes in gut microbial community
Thanki et al., 2023	Broilers	Cocktail phage	10^5, 10^6, 10^7 PFU/day	• All the inclusion levels in feed were effective in reducing *Salmonella* colonization and production gains

Conclusions

A wider variety of non-antibiotic growth promoters are being used in the poultry industry to improve the production, product quality, and health of birds. These improvements are achieved through mechanisms including enhancement of nutrient utilization, competitive exclusion of pathogenic bacteria, increase in nutrient absorption surface area, production of gut microbial metabolites and modulation of immune responses. The efficacy of these alternatives is also highly dependent on viability in feed manufacturing procedures, farm sanitation, biosecurity and management practices. More research is needed to find the other suitable alternatives, their combinations, and the optimal dosage. Little information is known about differences in digestive physiology and gut microbiota across the different types of poultry that will be helpful in optimizing the dose for different classes of poultry. Moreover, interaction about feed contaminants and alternative to antibiotics still needs to be explored. At the same time, awareness regarding the potential applications of alternatives to antibiotics is also required for the farmers and veterinarians.

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