Original Article

Ecofriendly Alternatives to Antibiotics for Improving Growth Performance in Poultry

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Abstract

Background: Poultry farming has become an integral part of animal husbandry and has been developed rapidly during the last few decades. Antibiotics have been used and adopted as growth promoters for improving feed efficiency and performance in poultry industry. The prolonged use of antibiotics has led to the development of resistant bacteria and destruction of beneficial bacteria. Search on additives that can replace antibiotics without causing any negative impact in productivity and quality has been progressed. **Objective:** To review the various growth promoters available alternate to antibiotic, that can perform better in the existing condition according to their genetic potential and keep up health, growth, and performance of poultry. **Materials and Methods:** Our study relies on the literature analysis; clinical and biological data were collected from different literatures and reports. **Result of Study:** A brief description of alternatives and their efficaciousness, use, and advantage for enhancing production and safeguarding the health of poultry is presented. Although the beneficial activities of the developed alternative are well demonstrated, their mode of actions is not well defined. **Conclusions and Recommendations:** The article is useful to the researchers to enhance their idea on poultry birds and perform further research on antibiotics and other alternatives without sacrificing birds.

Keywords: Alternatives, antibiotics, applications, poultry

Introduction

Over more than six decades, dietary antibodies are used not solely to regulate infectious disease but conjointly to improve growth performance and feed potency.[1] They are accountable for building the immunocompetence of poultry against several infectious diseases. However, the use of antibiotics as feed additives, in the long run, can lead to the development of bacteria resistant to drugs that are used to treat infections. Later on, they are of potential risk if they are transferred to humans.[2] In-feed antibiotic (IFA) has played a substantial role in the advancement and prosperity of the poultry industry since its discovery.[3] When antibiotic is administrated, it impacts the entire population of the body. Among the bacteria, some are susceptible to the antibiotics that die, but some bacteria may thrive, and they begin to multiply. Sometimes, these remaining bacteria are resistant to many antibiotics, and many large problems can develop.[4] There exist significant concerns about the use of an IFA, which leads to the development of antimicrobial resistance, creating a potential menace to human health.[5] Figure 1 shows the effect of antibiotics on different aspect of environment. Due to the negativity and debate on the role of IFA use, the European Union banned the approval of antibiotics as growth promoters since January 1, 2006, on preventive grounds.[6] The reduction in the use of antibiotic growth promoters (AGPs) in the future seems inevitable, and the practice of using antimicrobials may prove economically illogical because of market limitations and export restrictions.[7] The number of scientific papers, researches, and analyses has been increasing, which is concerned with growth promoter and feed additives to push growth, enhance gut health, and reduce the utilization of antibiotics in animal production. Several antibiotic alternatives are available, which are used to increase productivity and create a suitable environment

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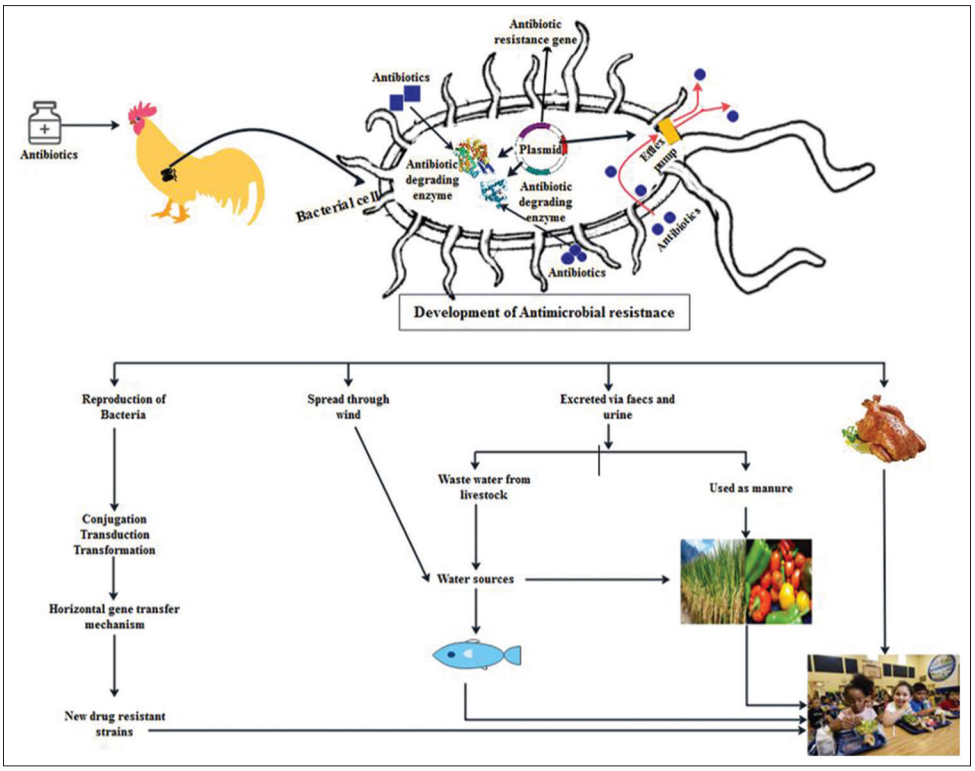

Figure 1: Antibiotics resistance and its effect on different aspects of environment

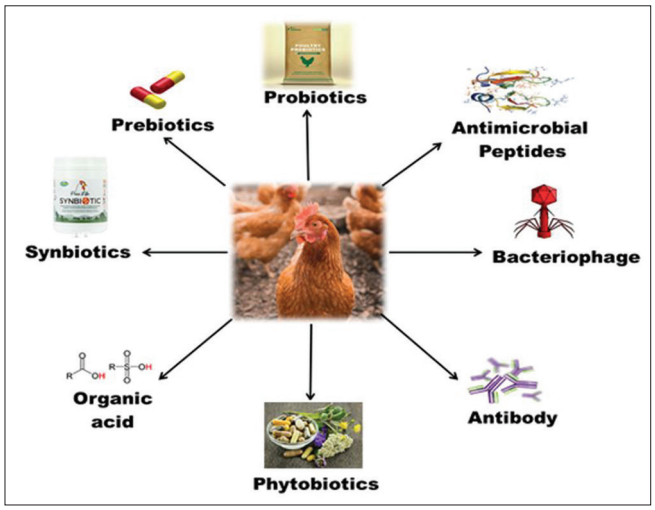

Figure 2: Various types of alternatives to antibiotics in poultry production

for animals to perform higher in keeping with their genetic potential under commercial conditions. The additives may include probiotics, prebiotics, organic acids, synbiotics, phytogenics, enzymes, antimicrobial peptides, hyperimmune egg antibodies, bacteriophages, clay, and metals [Figure 2].[1] The target of this review is to search out the other alternatives for antibiotics for better growth performance and to extend the feed potency in poultry.

Methodology

Our study was based on the literature and report analysis. Precise study was done in line with the topic of the study; relevant information and clinical and biological data related to antibiotics and different growth promoter were collected from journals available on Web of Science, PubMed, and other related sites. Reports from the World Health Organization (WHO), North American Meat Institution, and other organizations were studied to understand the role of food additives, antibiotics, and their impact on health of both bird and human.

Characteristics of antibiotic growth promoter alternatives

An alternative to growth promoter ought to have beneficial features as AGPs. However, the explicit beneficial action of the AGP is not well understood how it works. The most accepted mechanism is that the AGPs have an antibacterial activity that supports the performance in numerous ways: it reduces the incidence and severity of subclinical infections, reduces the microbial uses of nutrient, improves the absorption of nutrient due to the thinning of the intestinal wall, and lowers the amount of growth-depressing metabolites produced by the Gram-positive bacteria.[8] Numbers of scientists have postulated the mechanism of its action at different times. No matter the mechanism, the most important thing is that the selected alternative must improve the performance at least as AGPs. There are many possible ways that microbiota-modulating compounds could alter the intestinal microbiota population without adding AGPs to the feed. The most apparent method is therapeutic doses of antibiotics under prescription, a practice that will undoubtedly increase and possibly raise the probability of the emergence of resistant human pathogens.

For the complete loss of AGPs, none of the nonantibiotic AGP alternatives are likely to remunerate. It must be emphasized that some strategies will only help compensate partially but will not replace AGPs and will work through an indirect mechanism.[9]

Classes of alternatives

Several antibiotic alternatives have been proposed and demonstrated in poultry production, including probiotics, prebiotics, synbiotics, organic acids, enzymes, and phytogenics. Newly developed modern alternatives such as bacteriophages, antimicrobial peptides, hyperimmune egg yolk, AMP, and clay have come into practice in recent years.

Probiotics

Probiotics are microbial feed supplements that have a contrasting mode of action, and it improves the microbiota balance in the intestine, inhibiting the growth of pathogenic bacteria, promoting digestion, lowering cholesterol level, and boosting the immune system.[10] There are several sources of probiotics such as live bacteria (*Bacillus subtilis*, *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*), yeast (*Saccharomyces cerevisiae*, *Saccharomyces boulardii*, and *Candida*), and fungi (*Aspergillus*). Probiotics can follow various mechanisms based on inhibition of all pathogens via producing organic acids and antibacterial substances, i.e., hydrogen peroxide, bacteriocins, and defenses, blockading of pathogenic bacteria adhesion to intestinal epithelial binding sites using competitive inhibition.[11] The majority of the conducted research aims to investigate the effects of probiotics in reducing the number of pathogenic microorganisms in the gastrointestinal (GI) tract. A single strain of *Lactobacillus* sp. (*Lactobacillus casei*, *Lactobacillus fermentum*, *Lactobacillus bulgaricus*, *Lactobacillus*. *reuteri*), when given with diet, had shown to improve body weight and feed efficiency in broilers.[12] Such type of results was also shown when broilers got multiple strains of *Lactobacillus* sp.[13] The application of several other bacteria such as *Enterococcus faecium*, *Clostridium butyricum*, and *Rhodopseudomonas palustris* also significantly increased the daily weight gains with decreased feed conversion ratio (FCR).[1] Lei *et al*. in 2013 reported that the inclusion of *Bifidobacterium licheniformis* improved laying performance and egg mass.[14] Lactic acid bacteria, when supplemented to broilers' feed, the cholesterol content of meat, were significantly reduced.[15] The addition of probiotics with diet also reduced the number of gut pathogens such as *Salmonella enteritidis*, *Salmonella gallinarum*, *Salmonella typhimurium*, and *Campylobacter jejuni*.[16] When laying hens were given a diet supplemented with different strains of probiotics, it significantly improved gut microbial balance, blood and yolk cholesterol levels, egg production, and egg quality. *Lactobacillus* improved the equilibrium of gut microbiota by increasing the population of Bifidobacteria and decreased potentially harmful bacteria.[17] Not all strains exhibit all of the above properties; hence, due care must be taken to select the strains and their combinations to achieve maximum beneficial effect *in vivo* in poultry. It can be concluded that probiotics can be a potential alternative to antibiotics for increasing poultry growth and performance.

Prebiotics

Prebiotics are those macromolecules that are derived from plants or synthesized by microorganisms. They are fermentable feed additives that can support (directly or indirectly) a healthy intestinal microbiota. They have a beneficial action on GI microbiota and also promote the growth of animals.[18] Mechanisms by which probiotics regulate the ecosystem of the gut include improvement of the epithelium, alternation of the intestinal microbiota, and stimulation of the immune system.[19] The functions of prebiotics include alteration of GI microflora, immune stimulation, prevention colon cancer and reduction of pathogen invasion, reduction of cholesterol and odor compounds, improve gut health through intestinal microbial balance, reduction in ammonia and phenol products promotion of enzyme reaction, and ultimately reduction production cost.[17] Prebiotics include a variety of nonstarch polysaccharides (NSPs) or oligosaccharides, fructooligosaccharides (FOSs), Mannan oligosaccharides (MOSs), oligofructose, inulin, galactooligosaccharides, lactulose, maltooligosaccharides, isomaltooligosaccharide (IOS), lactitol, xylooligosaccharide, glucooligosaccharide, soya-oligosaccharide, and pyrodextrins.[1] The significant characteristics of being good prebiotics include: it should neither be hydrolyzed nor be absorbed in the upper part of the GI tract, and it is easy to process in a larger scale too and induces systemic effect to enhance the health of the host and palatable as feed ingredient.[20]

The addition of various levels of MOS to the broilers diet significantly improved feed conversion efficiency along with intestinal villi height and increased body weight.[21] Specific benefits of the prebiotics were found in reducing blood cholesterol and increasing lactic acid-producing bacteria in broilers.[10] It is reported that when broilers were supplemented with prebiotics, it improved body weight by 5.41%, decreased FCR by 2.54%, and reduced mortality rate by 10.5%.[22] Prebiotics, when used in the layers, improved feed intake, body weight gain, egg production from 20 to 36 weeks of age, FCR, egg weight, egg mass, and egg size from 20 to 52 weeks of age.[23] It is found from various studies that prebiotic supplementation improves meat quality of the produced broilers and egg quality of layers.

Synbiotics

Prebiotics and probiotics serve as an essential product for the development of healthy intestinal microflora. Prebiotics and probiotics act through different mechanisms and in separate compartments of the intestine. Therefore, they can be combined into one synergistic compound called synbiotics.[24] Synbiotics are used as an useful feed additive to improve the meat quality, productive performance, and ammonia reduction and also to decrease the microbial population of broiler chicks.[25] Supplementation of diet with synbiotics showed a significant increase in body weight, average daily gain, feed efficiency, and carcass yield percentage compared to control or probiotics only.[26] Another study showed that a combination of yeast-derived carbohydrates and probiotics increased body

weight gain faster than the controls or prebiotics supplements in pullet.[27] Feeding of the symbiotic named Biomin ®IMBO at 0.1%, 0.15%, and 0.125% of the diet to broilers improved body weight gain and feed efficiency in the starter period and have no detrimental effect on their performance.[28] The addition of GOS and *B. subtilis* to broiler diet showed that it improves the ADG and FCR and also reduces the incidence of diarrhea and mortality. Synbiotic containing a combination of *E. faecium* and prebiotics derived from chicory and sea algae significantly improved a live weight, ADG, carcass yield, and also FCR. By the combination use of probiotics and prebiotics, it could represent a synergistic strategy to improve poultry intestinal health and also reduce the spread of pathogens in the environment.[16] The use of synbiotics has gained considerable attention in the poultry industry as it can promote healthy intestinal function, improve performance, and keep pathogens in check. The number of research is still inadequate regarding the issue of their working mechanism. If further research is progressed, it can play a pivotal role in poultry to act as an alternative to antibiotics.

Organic acids

Organic acids are either simple monocarboxylic acid such as formic, acetic, propionic, and butyric acid or carboxylic acid having a hydroxyl group such as lactic, malic, tartaric, and citric acid.[29] They are added in the feed or drinking water and can be used either individually as an organic acid or as their salt (sodium, potassium, or calcium) or as blends of multiple acids or their salt.[9] They show their antibacterial nature by decreasing the pH of drinking water and reducing the buffering capacity of the feed that affect the physiology of the crop and proventriculus, which can improve the quality of the egg.[30] Organic acid also ameliorates the quality of the egg, i.e., yolk index, albumen index, shell hardness, and resistance to breakage.[31] The number of researchers delineates the numbers of mechanisms, but it is not clearly understood.

Organic acid alters the gut microflora either by directly killing or through cell wall penetration or indirectly modifies the pH and reduces pathogenic bacteria. At the same time, it increases the acid-tolerant beneficial species such as *Lactobacillus* spp. so that it reduces the competition for nutrients by altering microbes.[32] It is found that organic acid increases nutrient digestibility by increasing protein and dry matter retention and improving mineral absorption and phosphorous utilization.[33] Several trials and researches have shown that a diet containing organic acid has significantly increased the villus height and area in the duodenum, jejunum, and ileum of chicks.[34] Supplementation of fumaric acid to broiler chicken had shown to improve weight gain and feed efficiency.[35] A similar result was found by using other organic acids such as citric acid and acetic acid in further researches and findings. At the same time, research showed that supplementation of organic acid as the blend was found to be more beneficial than a single acid. Various organic acid blends were tested and found to improve the FCR in broiler chickens.[36] The beneficial effect of organic acid can be summed as it significantly increases villus width, height, and area of the duodenum, jejunum, and ileum of broilers, thus boosting the performance of broilers. It improves the digestibility by reducing the microbial competition with the host for nutrients. They lower the incidence of subclinical infection by secretion of immune mediators, reducing the promotion of ammonia and other growth-depressing microbial metabolites.

Phytobiotics or botanical supplements

Plant extracts are complex compounds containing the different compositions of many active components. Generally, they contain protein, peptides, oligosaccharides, fatty acid, vitamins, and minerals.[37] Many plants and their extract have been used and reported to possess beneficial multifunctional properties due to which it is used as feed additives in the farm from ancient cultures.[9] Plant-derived products are natural, less toxic than antibodies and typically residue-free. Phytobiotics has established a positive effect in the animlas due to the presence of different plant constituents like:glycosides, terpenoids (monoterpenes and sesquiterpenes, steroids), phenolics (tannins), alkaloids (present as alcohols, aldehydes, ketones, esters, ethers, and lactones), flavonoids, and glucosinolate.[38] The coherent mechanism of its mechanism is still not understood, But their features are responsible for the disruption of the cellular membrane of pathogens, protection of intestinal mucosa from bacterial pathogens colonization, promoting the growth of beneficial bacteria such as Lactobacilli and Bifidobacteria, stimulation of immune system especially activation of lymphocytes, macrophages, and NK cells.[39] A wide variety of herbs and spices such as oregano, rosemary, marjoram, garlic, ginger, thyme, turmeric, green tea, black cumin, and coriander have been used in poultry as an AGP alternative. When broilers were given diets supplemented with a mixture of 14 herbs, they showed a significant increase in body weight gain and improvement in feed efficiency.[40] There are several classes of plant products based on physical characters and appearance, which include essential oil, crude or processed plant parts, processed extracts, mixtures of powders or extracts, and phytochemicals used for the prevention and treatment of various diseases in farm animals.[41] Extract from black pepper, cinnamon, and turmeric improves the immune system and reduces serum cholesterol and liver enzymes as well as enhances performance and overall health status of poultry.[37] Botanical or herbal extracts, flavors, and essential oils (EOs) are beneficial in the poultry farm. Use of asthma plant (*Euphorbia hirta*) increased villus height, crypt depth, and the ratio of villi to the crypt and enhanced the maintenance and functions of the small intestine.[42] Use of 240 ppm dose of ginger rhizome powder enhanced the nutrient digestion and absorption in poultry because of its positive effect in gastric secretion and enterokinase. The experiment done by the use of an extract of Babylon willow (*Salix babylonica*)[43] and black poplar (*Populus nigra*)[44] showed that they improve heat tolerance, weight gain, and FCR in poultry. Along with extract and powder, EOs (volatile lipophilic substances obtained by cold extraction or by steam or alcohol

distillation)[45] from clove, coriander, star anise, ginger, garlic, rosemary, turmeric, basil, caraway, lemon, and sage have been used either individually or as blends for the betterment of health and performance. The use of EO of garlic (*Allium sativum*) improved the growth performance and essential microbial population.[46] Another study shows that the EOs of rosemary (*Rosmarinus officinalis*) and laurel (*Laurus nobilis*) improve the gut health and act as an antioxidant,[47] and EO supplementation was also shown to improve feed efficiency as seen by reduced FCR. A meta-analysis study of broiler chicken by the inclusion of a commercial blend of phytonutrients containing carvacrol, cinnamaldehyde, and capsicum oleoresin, in feed, increased body weight gain and decreased FCR and mortality.[48] Herbs, spices, and various other plants extracts, including EO, are used as alternatives to antibiotics, while some do have growth-promoting effects, antimicrobial properties, and other health-related benefits.[38]

Antimicrobial peptides

Antimicrobial peptides (AMPs) are the small biological components having a broad-spectrum effect against bacteria, fungi, protozoa, and some of the viruses.[49] Due to the broad-spectrum activity of AMPs, they can be developed as one of the better alternatives to antibiotics.[50] Most AMPs can interact with bacterial membranes. They decrease the pathogen count[51] and also increase the beneficial bacteria, nutrient absorption, weight gain, and FCR.[52] It is generally hypothesized that three main mechanisms could account for peptide permeation of the membrane of the target cell. First, they are responsible for the disruption of DNA, transcription, and translation. They also alter membrane permeability, which leads to cell lysis by the formation of the transmembrane pore. The introduction of AMPs also inhibits cell cycle, activates lytic enzymes, and produces free radicals. Due to this, the production of cytokines occurs by the proliferation of immune cells and they also induce wound repair mechanisms.[53] Along with directly attacking microbes, they also accord protection by the alternative mechanisms such as maintenance of normal gut homeostasis and modulation of host inflammatory response.[49] The application of AMPs has been mostly focused on the pathogens causing infectious diseases rather than growth-promoting activities. Several types of researches have been conducted on its beneficial effect on growth performance, gut microbiology, and intentional morphology. Supplementation of cecropin A(1-11)-D(12-37)-Asn (CADN) in poultry diets increased weight gain, feed intake, and intestinal villus height.[54] Naturally synthesized AMPs, from swine gut and rabbit, administrated in birds improved growth performance, intestinal ability to absorb nutrients, and mucosal immune parameters.[54,55] Based on the origins of AMPs, there is a particular group of AMPs called bacteriocins; these are commonly described as small ribosomally synthesized peptides that are secreted by bacteria and inhibit the growth of closely related species and found to be potential food additives.[56] Bacteriocins, produced by *Ruminococcus albus* 7 called Albusin B, were supplemented to poultry feed and showed improved growth performance, increased intestinal absorption, and *Lactobacillus* counts, and modulated lipid metabolism.[52]

Researchers have concluded that antimicrobial peptides, along with bacteriocins, improve growth performance, gut health, and immune function, and promote nutrient digestibility in poultry. The beneficial effect is due to their antimicrobial and immunomodulating activity. Their potential can be improved further if the number of obstacles such as high production cost, resistance development, and instability of the AMPs is addressed in the future.

Bacteriophage

Bacteriophages are highly species-specific viruses that kill bacteria by the producing endolysins and the subsequent lysis of the bacterial cells. Bacteriophages can be considered safe antibiotic alternatives as they exhibit no activity against animal and plant cells.[57] Phage therapy exploits the therapeutic potential of lytic phage. Bacteriophage binds to the specific receptors on the bacterial cell surface, releases their genetic material into the cell, and uses the host cell machinery to synthesize multiple virion particles. When the virus is matured, the cell wall is lysed and finally releases progeny phages.[58] Not only the whole phages but also phage-encoded enzymes have been found to have antibacterial properties. They are classified into peptidoglycan hydrolases (VAPGH) and endolysins. VAPGH disturbs the peptidoglycan layer of the bacterial cell wall after phage absorption. They produce a small hole in the cell wall to facilitate the transfer of viral DNA into the cytoplasm.[59] Endolysins have a cell wall binding domain which cleaves the specific bonds in the peptidoglycan.[60] Incorporation of 0.035% or 0.05% of bacteriophage in the feed of laying hens significantly improved egg production.[61] It is also reported that supplementation of 0.1% and 0.15% of bacteriophage increased body weight gain and also reduced the FCR.[62] The number of pathogens (*Campylobacter* spp.) was reduced in broilers when phage was administrated by mixing with drinking water.[63]

Limited number of research has been carried out under the use of bacteriophage as an alternative to antibiotics, and some drawbacks have been found by the use of phage. The development of bacterial resistance is one of the major issues. Numbers of mechanisms have been postulated to discuss this issue such as blocking of viral adsorption on surface receptors, degradation of viral genome by restriction–modification systems, and phage superinfection exclusion, but this can be prevented by using a bacteriophage "cocktail,"[53] but the resistance to bacteriophage is not considered as a serious threat as the number of bacteriophages is specific for the host is not limited.[64] Furthermore, research is needed to establish the performance effects of bacteriophages and make their use practical in poultry production systems.

Antibody

Supplementation of antibodies orally is an upcoming approach for the treatment of pathogens in humans as well as

in animals.[53] In the case of poultry, hyperimmune egg yolk antibodies (IgYs) are essential antibody as an alternative. IgYs are produced by repeated immunization of hens with specific antigens, and collection of antibodies, thereafter from their egg yolks, has been commonly employed in the prevention and treatment of various enteric diseases and can be utilized as a feed additive.[65] Mainly, two mechanisms of action have been described as the action of the antibody. First, IgY binds to the bacterial structure such as flagella and pili which prevent the adhesion to and colonization of intestinal epithelium by the bacteria. Second,on binding there is increase on pathogen agglutinates, that lead to changes in structure on cell surface which lead to increase phagocytic activity and toxin neutralization.[66] On the 1990s, progeny from hens injected with jack bean urease improved body weight at 3 weeks of age and was proposed that urease antibodies maternally transferred to the progeny decreased ammonia production in the intestinal tract by inhibiting bacterial urease enzyme and improving growth.[1]

Several studies have reported the efficacy of IgY against *E. coli*, *Clostridium*, *Campylobacter*, and *Salmonella*.[67] Supplementation of diet with egg powder containing CCK antibodies at 0.25 g/kg increased the feed conversion efficiency as compared to that of birds fed with egg powder from unimmunized hens. Weight gain and FCR at 3 weeks of age were increased by 9% and 8%, respectively, using the yolk antibody.[68] Oral administration of IgY against *E. coli* O78:K80 via egg yolk powder found to improve intestinal health and broiler's performance.[69] Other many IgYs are used in poultry to improve feed efficiency and as an excellent alternative to antibiotics. Large amount of antibodies can be produced in laying hens via eggs and can be collected noninvasively. They are environment-friendly and less toxic. Although bacteria cannot develop resistance to antibodies, their most significant drawback is proteolytic degradation in the gut as well as their expensive in large-scale production.[65] Although the existing results seemed encouraging and more advantageous, much more research is needed on using egg antibodies for growth promotion by making it cost-effective method for IgY production for higher production in poultry.

Conclusion

Probiotics, prebiotics, and synbiotics interact directly with host gut epithelium, and pathogen colonization is prevented. Organic acid decreases the pH of water intake and has a successive effect on the physiology of the crop and proventriculus by reducing the buffering capacity of feed. Phytobiotics show antioxidant and antimicrobial activity,but the mechanism of its action is not clearly understood, so further study is necessary. AMP is a broad spectrum in nature and binds the cell surface by electrostatic attraction rather than to a specific receptor. A limited number of researches have been carried out in the case of antibody and bacteriophage. There is a great need for the development of antibiotic alternatives that can improve performance and maintain the optimum health of animals. They are used to replace AGPs whose primary function is to decrease the microbial population and promote the growth by a different mode of action, which includes exclusion and inhibition of pathogens in the intestinal tract, improvement of gut integrity, improvement in digestion, and absorption of the nutrient. A variety of alternatives have been used as antibiotics in the poultry industry. Many research results indicated that especially prebiotics, probiotics, synbiotics, organic acids, and phytobiotics showed similar effects to antibiotics in poultry. Besides, appropriate doses and the method of application for these alternatives to antibiotics are important for them to be more effective in poultry. During the selection of alternatives, well care should be taken in such a way that it fits the need of the individual production without affecting the welfare of the poultry. Further research is needed about the mechanism of action and the means to standardize the effects. Combined use of two alternatives with proper management, dose and delivery method, can be practiced for reducing the use of antibiotics and improving the performance of animals. Due to the development of resistance in bacteria by the use of antibiotics, it is essential to develop alternatives with multiple targets for antibiotic activity so that it is hard to develop an effective resistance mechanism against it. The elimination of antibiotics may harm the production, so advanced research is essential to provide new opportunities for developing alternatives to ameliorate the production and health of poultry. During the development, the selection of multiple products that can wok synergetically and act on numerous pathogens simultaneously is required. The number of scientific studies under field conditions on the target animal species is needed to determine the efficacy and safety of alternative products. In course of studies' integration of nutrition, health and disease are vital. The linkage between researchers, feed industry, pharmaceutical industries, poultry industry and regulatory agencies is essential so that it can define the scope of future research, development, and applications for alternatives products to antibiotics.

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Conflicts of interest

There are no conflicts of interest.

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