

Department of Animal Science

ALTERNATIVES TO ANTIBIOTIC GROWTH PROMOTERS IN BROILER PRODUCTION

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Demand for animal-origin food products continues to increase to meet the dietary needs of a growing world population and the rising financial capacities of the inhabitants of several countries who can now afford to purchase more animal protein products. The constant growing demand for animal food products has increased the expansion of intensive livestock farming worldwide to meet production needs. As a result, the poultry sector is one of the largest food production industries on the planet, at both the intensive and extensive level. A clear division has developed between intensive industrial-style production systems of large- and medium-sized poultry feeding operations with integrated value chains and extensive production systems that support livelihoods and supply product at the local level (FAO, 2022). The primary role of the former is to supply inexpensive, abundant and safe food to large populations far from the source of the supply, while the latter acts as a local livelihood safety net, often as part of a wide portfolio of income-generating sources. The role of each system is critical. Intensive systems allow much of the world population access to wholesome, nutritious animal protein at an affordable price. Extensive systems that are traditionally small-scale, rural, family-based poultry systems continue to play a vital role in sustaining livelihoods in developing countries, supplying poultry products in rural areas and providing important support to women smallholder farmers (FAO, 2022). This small-scale, extensive poultry production system will continue to offer opportunities for income generation and high-quality animal protein so long as there is rural poverty. In the U.S., with implementation of the Veterinary Feed Directive in 2017, medically important antibiotics are no longer available for growth promotion and finding alternatives continues to be a high priority for the livestock industry.

Decreasing antibiotic use and a look at alternatives

Antibiotics have been used for decades in the poultry industry to improve production, promote growth performance and protect flocks from pathogenic microbes. At least four modes of action have been proposed to explain the improved antibiotic-mediated animal growth performance:

- 1) Inhibition of sub-clinical infections
- 2) Reduction of growth-depressing microbial metabolites in the intestines
- 3) Increase in nutrient availability via reduction of microbes sharing the nutrients in the intestines
- 4) Improvement of uptake and use of nutrients through thinner epithelium tissues (Niewold, 2007; Broom, 2017).

Pathogenic gut bacteria decrease animal development either directly or indirectly via their metabolic activities. Rahman et al. (2022) indicated current evidence has diverged into two primary hypotheses: 1) bacteria-centric and 2) host-centric. The first proposes that the antimicrobial activity of antibiotics lowers the population or diversity of the gut microbiota, thereby reducing competition for nutrients. The second suggests that the anti-inflammatory role of growth-promoting antibiotics reduces wasted energy and directs it toward production (Butaye et al., 2003). We know there is a shift in microbiota composition (structure and diversity) when antibiotics are included in animal diets (Geng and Lin, 2016). The changes eventually contribute to an optimal and balanced microbiota that is less likely to elicit an inflammatory response, increases the nutrient energy harvest and allows animals to better reach their genetic potential (Rahman et al., 2022).

However, despite their important role in fighting diseases such as necrotic enteritis and coccidiosis, improper use of antibiotics in livestock production has been reported to increase antimicrobial resistance (Nhung et al., 2017; Christy et al., 2018) and residues in animal products, and cause environmental pollution (Gonzalez and Angeles Hernandez, 2017; Carvalho and Santos, 2018). Emergence and spread of antibiotic resistance have created a global concern. Because the use of antibiotics in any setting drives resistance expansion everywhere, it is important to minimize their use — a goal that depends on eliminating inappropriate uses and finding alternative means of preventing infections (Pew Charitable Trusts, 2017). To limit or eliminate the use of growth-promoting antimicrobials in agriculture, several countries have adopted action plans with a focus on antimicrobials that are significant in human medicine (Table 1) (Rahman et al., 2022).

Table 1. Regulations regarding use of antibiotics as growth promoters in different countries.

Country	Year	Action Taken
Australia	2017	Antibiotics used in human medicine are no longer licensed as growth promoters (Australian Government, 2018).
Canada	2020	Growth promotion claims on medically important antimicrobials no longer permitted (Government of Canada, 2018; Bosman et al., 2022).
China	2020	All antibiotic growth promoters except herbal medicine are banned (MARAPRC, 2019).
European Union	2006 2022	Illegal across the EU. EU will ban importation of meat/dairy produced using antibiotic growth promoters (Van Boeckel et al., 2017).

New Zealand	2017	No banning claim found (Ministry for Primary Industries, 2017).
Sweden	1986	First country to ban the use of antibiotics as growth promoters (Bengtsson and Wierup, 2006).
United States	2017	Medically important antimicrobials are banned.

Source: Adapted from Rahman et al., 2022.

The major concerns for the use of antibiotics as growth promoters in poultry are:

- 1) Sub-therapeutic levels of antibiotics could promote development of antibiotic-resistant strains through selection pressure
- 2) Release of antibiotic-resistant bacteria into the environment
- 3) Transfer of antibiotic-resistant genes to non-resistant bacteria in the environment or human flora by horizontal or vertical transfer
- 4) Release of small amounts of antibiotics and their metabolites in the environment could promote mutations or evolution of sensible bacteria, leading to antibiotic resistance (Rahman et al., 2022)

The ban on antibiotic use by multiple countries and changing consumer preferences and demands have hastened the search for antibiotic alternatives (Diarra and Malouin, 2014).

As a result, various feed additives have attracted attention from the poultry industry as antibiotic alternatives, with the greatest interest being in possibly improving feed conversion ratio and growth rate, maintaining healthy intestinal microbial populations and improving overall flock health (Mehdi et al., 2018). The most used and studied alternatives to date are the phytogetic feed additives, probiotics, prebiotics, synbiotics, acidifiers, enzymes, bacteriophages and antimicrobial peptides. Each of these have shown promising results at times, but all appear to have issues with consistency and repeating promising results time after time. We are searching for a product that can consistently do what antibiotics can do and do it just as well.

Unfortunately, that product may not exist.

Phytogetic feed additives

Phytogetic feed additives (PFAs) are compounds extracted from plants that include a wide range of substances such as essential oils, botanicals, herbs, spices and oleoresins used in poultry diets. The modes of action are not fully understood for most phytogetic feed additives (Rahman et al., 2022). However, it is believed that their antimicrobial activity relies on their lipophilic properties and their ability to damage membranes or inhibit DNA synthesis. Essential oils are any class of volatile oil obtained from plants; they possess the aroma and other characteristic properties of plants and are used mainly to manufacture perfumes, flavors and pharmaceuticals. Botanicals are parts of a plant like barks, leaves or roots that are used to make drugs for medical use. Herbs are flowering plants whose stem does not become woody and are valued for their medical properties, flavor and scent, while spices are pungent or aromatic substances of vegetable origin that are used as seasonings and preservatives (Suganya et al., 2016). The most widely used herbs and spices for PFAs in poultry production are thyme, oregano, garlic, horseradish, chili, cayenne, pepper, peppermint, cinnamon, anise, clove, rosemary derivatives, citrus and sage (Mountzouris, 2016; Madhupriya et al., 2018).

PFAs improve the palatability, digestibility, absorption of feed nutrients, control animal intestinal microbiome structure, improve performance and feed quality, and slow microbial

growth in poultry (Lambert et al., 2001; Yang et al., 2015; Zeng et al., 2015). In addition, they have been shown to enhance gut health by reducing bacterial colony populations, lessening fermentation products including ammonia and biogenic amines, decreasing the activity of gut-associated lymphatic system and increasing pre-cecal nutrient digestion (Ayalew et al., 2022). Despite the potential of PFAs as animal growth promoters, additional research is needed to assess the timely introduction (phase of production to introduce), composition (blends or individual compounds), and the type of active compound best suited for each animal species (Rahman et al., 2022).

Probiotics

Probiotics are beneficial bacteria that can fight pathogens in the gastrointestinal tract of chickens, stimulate growth and improve immunity in the host. They are defined as “live microorganisms which are administered in adequate amounts to confer a health benefit on the host.” Probiotics can be bacterial (*Bacillus*, *Lactobacillus*, *Enterococcus* and *Bifidobacterium*) or non-bacterial (yeast or fungus). Choosing to use probiotics, specifically the correct probiotic, can be challenging. It’s important to consider their handling procedures, risks and adaptability to the environment. Their use in animal feed has raised several questions and concerns about the risks of emergence of acquired antibiotic resistance in bacteria present in the intestinal microflora. Probiotic strains contain genes for immunity to some antimicrobials and antibiotic resistance and could potentially transmit antibiotic resistance genes to pathogenic bacteria through horizontal gene transfer (Alayande et al., 2020). To minimize this risk, it is important to verify if a prospective probiotic strain contains potentially transferable resistance genes.

Probiotics compete with pathogenic bacteria for locations in the intestinal mucous membrane to adhere for nutrients and secrete products that inhibit development such as organic acids and hydrogen peroxide. Lowering the gut pH through volatile fatty acid and organic acid production during probiotic product breakdown is the most common probiotic mode of action (Khan and Naz, 2013; AlFatah, 2020). The low pH in the intestine suppresses the colonization of pathogens in the digestive tract, thereby competitively inhibiting the effects of pathogens (Sandvang et al., 2021).

Prebiotics

Prebiotics are indigestible carbohydrates that act as a food source for beneficial microorganisms in the gut by stimulating their growth. They are found in a variety of food sources such as barley, flax seeds, chia seeds, chicory, dandelion greens, almonds, artichoke, onions and garlic. Green algae are also considered a prebiotic, and much work is underway looking at various strains of green algae. Several potential prebiotics that have been tried in broiler diets include fructooligosaccharides, galactooligosaccharides, xylooligosaccharides, milk oligosaccharides, pectin, galactan, inulin, oligofructose, fructan and various fiber components. Various carbohydrates derived from the cell wall of *Saccharomyces cerevisiae* are also a readily available source of prebiotics for animal use. The most common of these used in commercial poultry feed production are the mannan-oligosaccharides and fructooligosaccharides (Sun et al., 2019).

Prebiotics serve as food for beneficial bacteria found in the lower intestines and are not digested or absorbed in the upper intestines. Animal enzymes cannot degrade prebiotics in the intestines (El-Hack et al., 2021). Prebiotics are considered eco-friendly, but their use and regulation are not well-established. Most reported prebiotic-based products in animal feed have not shown

antimicrobial activity by themselves, but their use has promoted beneficial bacterial strains in the gut and inhibited the growth of some pathogenic strains (Scott et al., 2020).

Synbiotics

Synbiotics are combinations of probiotics and prebiotics developed to circumvent challenges associated with probiotic survival in the intestines. Synbiotics have been shown to have a greater effect on the gut microbiota than probiotics or prebiotics used separately. Their benefits go beyond the improved growth and microbiota health; they also include the limitation of antibiotic resistance development. Because synbiotics are a mixture of prebiotics and probiotics, they have the same strengths and weaknesses as prebiotics and probiotics, as well as the same potential risks for bacterial resistance development (Rahman et al, 2022). Like prebiotics and probiotics, synbiotics reduce diarrhea, increase digestibility and daily weight gain, and promote beneficial bacterial strains, such as *Lactobacillus* and *Bifidobacterium* strains, leading to a more balanced gut microbiota (Rahman et al. 2022).

Acidifiers

Acidifiers are organic acids such as acetic, benzoic, butyric, lactic, propionic, citric, formic and fumaric acid or their salt counterparts. Organic acids have been used as feed preservatives for protecting feed from microbial and fungal deterioration by means of acidification and serve as a powerful tool in maintaining the health of the gastrointestinal tract of poultry, resulting in improvement in the birds' production performance (Ayalew et al., 2022). Acidifiers have had GRAS (generally recognized as safe) status since 1972 and have long been used in poultry diets and drinking water for decades with positive responses on growth performance (Markets and Markets, 2020; Guo et al., 2022). Organic acids are weak acids that have some level of antibacterial effect in animal feed. Organic acids and their salts are used to reduce the load of pathogenic microorganisms in the intestine, activate digestive enzymes, improve digestibility and increase the absorption of nutrients, gut microflora function and performance of chickens (Ayalew et al., 2022).

Enzymes

Enzymes are biologically active proteins which enable the breakdown of specific chemical bonds of nutrients into smaller compounds for further digestion and absorption (Rahman et al., 2022). Enzymes are the most important and useful additives in the animal feed industry (Ojha et al., 2019). Phytase, carbohydrases, lipases, proteases, pectinase, xylanase, α -galactosidase, β -mannanase, α -amylase and β -glucanase are some of the most used feed enzymes. Enzymes are produced by fermentation of fungi and bacteria and are used for maximization of feed conversion efficiency (Letlhogonolo et al., 2020). Animals produce endogenous enzymes that are involved in digestion; however, they do not efficiently degrade feedstuffs and take advantage of all their nutritional components; therefore, exogenous enzymes are supplemented to increase animal performance (Ravindran, 2013; Ojha et al., 2019). Their greatest advantage is their ability to increase digestibility and nutrient availability while degrading antinutritional factors (Torres-Pitarch et al., 2017). However, enzyme-based products often suffer from poor quality control and lack of information about their concentration and optimal use conditions (Jang et al., 2020). Enzymes must be active under physiological conditions prevailing in the animal's digestive tract and must complement the characteristics of dietary ingredients and additives to realize their functions (Doskovic, et al., 2012).

Bacteriophages

Bacteriophages are viruses that can infect only bacterial cells. They were discovered in the 19th century but have attracted much attention in recent years due to their unique specificity, non-toxicity and natural abundance. Outside of Eastern Europe, they are not well accepted; this includes the United States. However, several studies on the use of bacteriophages to prevent infections in animals and humans to pathogens have yielded promising results. It has been reported that bacteriophage biocontrol can reduce *Campylobacter jejuni* in chickens without negative effects on gut microbiota and help prevent human exposure and food-borne illness from contaminated poultry products (Zheng et al., 2020). Van Belleghem et al. (2018) reported that *Salmonella gallinarum* could be a promising alternative to antibiotics for the control of fowl typhoid in chickens.

Antimicrobial peptides

Antimicrobial peptides (AMPs) are part of the innate immune defense system that exists in nearly all classes of organisms. AMPs are a family of short (less than 100 amino acids), mostly positively charged proteins that are often broad-spectrum inhibitors of Gram-positive or Gram-negative bacteria. AMPs have been widely studied and are considered strong candidates to replace antibiotics in the animal feed production industry (Rima et al., 2021). Their antimicrobial activity is based primarily on the interaction of positively charged peptides with negatively charged components of the bacterial membrane, leading to pore formation, membrane permeabilization and, eventually, cell death (Rahman et al., 2022). The ability of AMPs to improve growth performance and gut health, positively influence the intestinal microbiota, decrease the occurrence and severity of diarrhea and inhibit the expression of pro-inflammatory factors have been documented (Kurt et al., 2019). Degradation of AMPs in the intestines prevents their release into the environment and reduces the risk of exposure that can lead to resistance development; however, this decreases the half-life of the peptides in the intestines (Rahman et al., 2022). Despite the beneficial characteristics, the use of AMPs has been limited by problems associated with their large-scale production, their stability during feed manufacturing, pelleting and storage, and their interactions with feed matrices (Ioannou et al., 2018).

Summary

The shift to “No Antibiotics Ever” and antibiotic-free poultry production programs has promoted the use of numerous antibiotic alternatives in broiler production. Bringing a new alternative to antibiotics to market is no easy task. It involves assessing its safety for the animal, consumer, user, and the environment as well as its efficacy, acceptability, and feasibility. Overall costs and benefits, regulatory approval, and the target animal are all important factors to consider. There does not appear to be a single alternative that can claim to fully replace antibiotics in animal feed on a consistent basis; however, several do show value and will likely play a role in overall antibiotic-free programs. Antibiotic alternatives have comparable advantages to antibiotics to enhance production performance and well-being of broilers without the human health challenges associated with antibiotics. In addition, these alternatives can increase body weight, average daily gain, carcass weight, improve feed conversion and the nutritive value of feed ingredients, and enhance gut health of broilers.

Nevertheless, there are several challenges to evaluating whether alternative products might substitute for antibiotic growth promoters. First, the mechanism of action by which antibiotics promote growth is not well understood. In addition, the cost-effectiveness of antibiotic growth promoters may be negatively correlated with the level of farm management and animal care. In other words, antibiotics may be less beneficial to good managers. As a result, the minimum effectiveness and cost-effectiveness needed to make alternative products viable substitutes to antibiotics is often unknown and could vary as management practices improve or decline. The main issues with most antibiotic alternatives are their reliability and consistency flock after flock, how different they are between various species, their cost, and how difficult they are to produce and bring to market. While a combination of antibiotic alternatives may be the best approach for now, even that route is not without serious concerns. Going forward, special attention must be directed to sustainable manufacturing practices, potential environmental impacts, and the possibility of resistance development during creation and regulation of antibiotic alternatives in poultry feed.

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