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Review

Alternatives to antibiotics for maximizing growth performance and feed efficiency in poultry: a review

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Abstract

With the increase in regulations regarding the use of antibiotic growth promoters and the rise in consumer demand for poultry products from 'Raised Without Antibiotics' or 'No Antibiotics Ever' flocks, the quest for alternative products or approaches has intensified in recent years. A great deal of research has focused on the development of antibiotic alternatives to maintain or improve poultry health and performance. This review describes the potential for the various alternatives available to increase animal productivity and help poultry perform to their genetic potential under existing commercial conditions. The classes of alternatives described include probiotics, prebiotics, synbiotics, organic acids, enzymes, phytogenics, antimicrobial peptides, hyperimmune egg antibodies, bacteriophages, clay, and metals. A brief description of the mechanism of action, efficacy, and advantages and disadvantages of their uses are also presented. Though the beneficial effects of many of the alternatives developed have been well demonstrated, the general consensus is that these products lack consistency and the results vary greatly from farm to farm. Furthermore, their mode of action needs to be better defined. Optimal combinations of various alternatives coupled with good management and husbandry practices will be the key to maximize performance and maintain animal productivity, while we move forward with the ultimate goal of reducing antibiotic use in the animal industry.

Keywords: poultry, antibiotic alternatives, performance.

Introduction

Since the discovery of antibiotics in the 1920s, they have played a substantial role in the advancement and prosperity of the poultry industry. Antibiotics have been supplemented in animal feed at sub-therapeutic doses to improve growth and feed conversion efficiency and to prevent infections for more than 60 years (Castanon, 2007). The effect of antibiotics on improving performance was first reported by Moore *et al.* (1946) when they observed that birds fed streptomycin exhibited increased growth responses. Many experiments conducted later in the early 1950s in chickens (Groschke and Evans, 1950; McGinnis, 1950; Whitehill *et al.*, 1950), pigs (Jukes *et al.*, 1950; Luecke *et al.*, 1950a, b), and calves (Rusoff *et al.*, 1951) corroborated these results. In-feed antibiotic (IFA) use soon became a common and well-established practice in the animal industry and rose with the intensification of livestock production. In a review conducted by Rosen (1995), it was concluded that inclusion of antibiotics in the diets gave a positive response 72% of the time. It was also proposed that the net effect of using IFA in the poultry industry was a 3–5% increase in growth and feed conversion efficiency (Choct, 2001; Dahiya *et al.*, 2006). Thus, it can be noted that IFA played a crucial role in contributing to the economic

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effectiveness of the livestock production (Wierup, 2000). Despite the well-demonstrated beneficial effects of IFA in improving the growth rate, reducing the mortality and increasing resistance to disease challenge, their use was also known to be associated with some disadvantages and challenges. Concerns exist that the use of IFA leads to development of antimicrobial resistance, posing a potential threat to human health (WHO, 2012). However, mixed opinions still exist on the transfer of antibiotic resistance genes from animal to human pathogens. Several studies showed that there might be a link between the practice of using subtherapeutic antibiotics and the development of antimicrobial resistance among the microflora (Endtz *et al.*, 1990; Witte, 1998; Wegener *et al.*, 1999; Greko, 2001; M'ikanatha *et al.*, 2010; Medeiros *et al.*, 2011; Cosby *et al.*, 2015).

Despite these debates on the role of IFA use in conferring antimicrobial resistance to human pathogens, the European Union issued a ban on the approval for antibiotics as growth promoters since 1 January 2006 on precautionary grounds (Dibner and Richards, 2005; Castanon, 2007). In the USA, antibiotic use in livestock and poultry feeds is under great scrutiny as a result of increasing consumer awareness and the demand for livestock products from antibiotic-free production systems. In 2013, the US Food and Drug Administration (FDA) called for major manufacturers of medically important animal drugs to voluntarily stop labeling them for growth promotion in animals and revise the labels such that veterinary supervision is required for therapeutic uses (GFI#213; FDA, 2013). FDA continued to strengthen its agenda on promoting judicious use of antimicrobials in food-producing animals and published its final rule of the VFD (Veterinary Feed Directive) in early 2015, bringing the use of medically important antimicrobials in feed under veterinary supervision, so that they are used only when necessary to ensure the health of the animals. In late 2015, the state of California passed a bill (Senate Bill 27) enforcing a strict ban on using medically important antimicrobials in animal feeds for both growth promotion and disease prevention.

The decline in the use of antibiotic growth promoters (AGPs) in the future seems inevitable, and the practice of using antimicrobials may prove economically impractical because of market limitations and export restrictions (Dibner and Richards, 2005). In view of the increasing concerns over AGP use, the quest for novel alternate replacements to mitigate antibiotic use in animal agriculture has grown over the years. In the past two decades, a great deal of research has focused on the development of antibiotic alternatives to maintain or improve poultry health and performance. This review, therefore, is focused on current knowledge pertaining to several of the strategies that are being employed to improve poultry growth performance and provides a brief overview of such alternatives along with a description of their efficacy and modes of action.

Mechanism of action of AGPs

The successful development of antibiotic alternatives, at least to some extent, relies on understanding the mechanism of action of AGPs. Several ideas have been proposed to elucidate the rationale behind antibiotic-mediated growth enhancement, but to date there is no clear-cut explanation. Preliminary theories have linked their efficacy to their antibacterial action, which was thought to be mediated by a reduction in the overall numbers or diversity of the gut microbiota (Francois, 1961; Visek, 1978), resulting in decreased competition for nutrients and reduced microbial metabolites that affect growth (amino acid and bile catabolism) (Feighner and Dashkevicz, 1987; Gaskins *et al.*, 2002; Knarreborg *et al.*, 2004). This theory was contradicted by Niewold (2007), who proposed that the beneficial effects of antibiotics are due to their interaction with host immune cells rather than the growth inhibitory effects on microbiota. He hypothesized that antibiotics lower the inflammatory response and thus the production of proinflammatory cytokines, which reduce the appetite and promote muscle catabolism. The anti-inflammatory role of AGP reduces wasted energy and directs it toward production (Niewold, 2007).

Though a clear consensus on how AGP acts still does not exist in the scientific community, it is now clear – with the advent of novel molecular biology and bioinformatics techniques – that shifts in microbiota composition (structure and diversity) do occur when antibiotics are included in animal diets (Dumonceaux *et al.*, 2006; Pedroso *et al.*, 2006; Wise and Siragusa, 2007; Lin *et al.*, 2013). These shifts may ultimately result in an optimal and balanced microbiota that is less capable of evoking an inflammatory response, increases energy harvest from nutrients, and helps animals perform to their genetic potential (Huyghebaert *et al.*, 2011; Lin, 2011). However, it still remains challenging to definitively link-specific bacterial populations to enhanced growth and pinpoint ways/tools to modify microbiota to a desired one (Lin, 2014). A few research trials were conducted to associate bacterial products or enzymes to enhanced performance, and have shown a decrease in bile salt hydrolase (BSH) enzyme activity in the gut. It was proposed that BSH produced by gut bacteria catalyzes deconjugation of bile acids and alters host lipid metabolism, and AGPs acts by reducing the number of bacteria that are producing BSH (Feighner and Dashkevicz, 1987; Knarreborg *et al.*, 2004; Guban *et al.*, 2006; Lin, 2014). Recent studies conducted in mice revealed that exposure to sub-therapeutic antibiotic levels not only altered the composition of gut microbiota, but also their metabolic capability by selecting for microbial species that were capable of extracting a high proportion of calories from complex carbohydrates (increase in copies of genes involved in metabolism of carbohydrates to short-chain fatty acids (SCFA)) (Cho *et al.*, 2012). The growth-promotion phenotype was shown to be transferrable to germ-free hosts by low-dose antibiotic-selected microbiota, indicating that the altered microbiota and not the antibiotics played a causal role (Cho *et al.*, 2012). It was also shown from the studies in mice that exposure to low-dose antibiotics early in life induces long-term host metabolic effects by accelerating normal age-related microbiota development and altering ileal expression of the genes involved in immunity (Cox *et al.*, 2014). Though the effects observed in mice cannot be directly extrapolated to farm animals, they might provide an insight into a possible mechanism of action.

Classes of alternatives

An ideal alternative should have the same beneficial effects of AGP, ensure optimum animal performance, and increase nutrient availability (Huyghebaert *et al.*, 2011). Considering the proposed mechanism of action of AGPs (microbiome and immune-modulating activities), a practical alternative should possess both of these properties in addition to having a positive impact on feed conversion and/or growth (Huyghebaert *et al.*, 2011; Seal *et al.*, 2013). Several classes of alternatives have been proposed and tested in poultry production, including probiotics, prebiotics, synbiotics, organic acids, enzymes, phytogenics and metals. Novel alternatives such as hyperimmune egg yolk IgY, antimicrobial peptides (AMP), bacteriophages, and clay have come into existence in recent years.

Probiotics

Probiotics, sometimes used interchangeably with the term direct fed microbials (DFMs), are gaining acceptance as potential alternatives to antibiotics to improve production efficiency (Lee *et al.*, 2010c). They are defined as "*live microbial feed supplements which beneficially affect the host animal by improving its intestinal microbial balance*" (Fuller, 1989). A recent definition adopted by FAO/WHO (2001) states that "*Probiotics are mono or mixed cultures of live organisms which when administered in adequate amounts confer a health benefit to the host.*" Probiotics may contain one or more strains of microorganisms and may be given either alone or in combination with other additives in feed or water (Thomke and Elwinger, 1998). Novel application strategies such as spraying on chicks or embryonated eggs are also practiced and potential methods such as *in-ovo* application are being explored (Wolfenden *et al.*, 2007; Cox and Dalloul, 2015).

A variety of bacteria (*Bacillus, Bifidobacterium, Enterococcus, Lactobacillus, Streptococcus*, and *Lactococcus* spp.) and in some cases yeast (*Saccharomyces* spp.) have been tested as probiotics in poultry (Simon *et al.*, 2001; Patterson and Burkholder, 2003; Griggs and Jacob, 2005; Kabir, 2009). The majority of the conducted research was specifically aimed at investigating the effects of probiotics in reducing the numbers of pathogenic microorganisms in the gastrointestinal tract. However, a considerable amount of research also examined the effects of probiotics on improving growth and performance in poultry without apparent disease. Supplementation of diets with a single strain of *Lactobacillus* sp. (*L. casei, L. fermentum, L. bulgaricus, L. reuteri*) was shown to improve the body weight and feed efficiency in broilers (Yeo and Kim, 1997; Khan *et al.*, 2007; Apata, 2008; Nakphaichit *et al.*, 2011; Salim *et al.*, 2013). Similar results were shown when broilers were given multiple strains of *Lactobacillus* sp. (Jin *et al.*, 1998; Kalavathy *et al.*, 2003; Mookiah *et al.*, 2014). *Bacillus* sp.-based probiotics (*B. coagulans, B. subtilis, B. licheniformis*, and *B. amyloliquefaciens*) were also successfully employed in poultry diets and were shown to have growth-promoting effects (Cavazzoni *et al.*, 1998; Lee *et al.*, 2010a, 2011a; Wang and Gu, 2010; Liu *et al.*, 2012; Sen *et al.*, 2012; Ahmed *et al.*, 2014; Jeong and Kim, 2014; Park and Kim, 2014). The application of several other probiotic bacteria such as *Enterococcus faecium* (Samli *et al.*, 2007; Kabir *et al.*, 2004), *Clostridium butyricum* (Yang *et al.*, 2012; Zhao *et al.*, 2013a; Liao *et al.*, 2015), *Rhodopseudomonas palustris* (Xu *et al.*, 2014) also significantly increased the daily weight gains with decreased feed conversion ratio (FCR). Research trials have also been conducted with multi-microbe probiotic mixtures composed of combinations of different beneficial bacteria and/or yeast and were shown to exhibit a growth-promoting effect (Chiang and Hsieh, 1995; Huang *et al.*, 2004; Mountzouris *et al.*, 2007, 2010; Nayebpor *et al.*, 2007; Talebi *et al.*, 2008; Torshizi *et al.*, 2010; Kim *et al.*, 2012; Bai *et al.*, 2013; Alimohamadi *et al.*, 2014; Zhang and Kim, 2014). Faria Filho *et al.* (2006) performed a meta-analysis of 27 studies involving 30,146 broiler chickens that were conducted in Brazil during 1995–2005 to investigate the performance effects of 12 different probiotics. The results of their analysis showed that overall the probiotic supplementation improved the body weight gain by 0.14 and reduced FCR by 0.10 points compared with non-supplemented controls. A similar meta-analysis of several randomized controlled research trials that were carried out from 1980 to 2012 was conducted by Blajman *et al.* (2014) to investigate the effects of probiotics on body weight gain and feed efficiency in broilers. They concluded that probiotics inclusion increased body weight gain and improved feed efficiency, and also showed that probiotics application via water was more efficacious than through feed. The analysis also showed that there were no differences between the use of mono- or multi-strain probiotics and the effects observed may vary with the type of strain used.

In addition to the improved growth performance, probiotics supplementation was also shown to enhance the general immune function of broilers, as evidenced by the augmented serum/plasma immunoglobulin levels, increased antibody titers to pathogens, and changes in immune cell numbers (Nayebpor *et al.*, 2007; Apata, 2008; Lee *et al.*, 2011a; Bai *et al.*, 2013; Salim *et al.*, 2013; Ahmed *et al.*, 2014). The intestines of broilers that were given probiotics showed better development and an increase in villus height and crypt depth compared with controls (Samli *et al.*, 2007; Lee *et al.*, 2010a, 2011a; Kim *et al.*, 2012; Sen *et al.*, 2012). Probiotics supplementation also positively modulated the intestinal microbiota and increased numbers of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* spp. (Mountzouris *et al.*, 2007, 2010; Samli *et al.*, 2007; Nakphaichit *et al.*, 2011; Yang *et al.*, 2012; Jeong and Kim, 2014; Mookiah *et al.*, 2014; Zhang and Kim, 2014).

The beneficial effects of probiotics supplementation were also reported in laying hens. Kurtoglu *et al.* (2004) showed that hens fed diets supplemented with probiotics showed increased egg production compared with controls. Lei *et al.* (2013) reported that dietary inclusion of *B. licheniformis* improved laying performance and egg mass. Consistent with these findings, various DFM product supplementation was also shown to improve body weight and performance in turkeys (Russell and Grimes, 2009; Wolfenden *et al.*, 2011). *Lactobacillus*-based probiotics significantly improved market body weight and average daily gain of commercial turkeys (Torres-Rodriguez *et al.*, 2007). Albeit numerous publications show the performance improvement in broilers, layers, and turkeys, reports also exist that probiotics show limited and variable growth-promoting effect and in some instances none (Karaoglu and Durdag, 2005; O'Dea *et al.*, 2006; Lee *et al.*, 2010a; Waititu *et al.*, 2014). This inconsistency in the results can be attributed to the differences in the type and dose of strain used, processing variations, administration time and period, diet, and environment.

Although the modes of action by which probiotics improve performance and promote gut health are not completely understood, a few have been proposed and reviewed (Edens, 2003; Parvez *et al.*, 2006; Kabir, 2009; Ng *et al.*, 2009; Vilà *et al.*, 2010; Lee *et al.*, 2010a). The two most important mechanisms through which probiotics exert beneficial effects include balancing the gut microflora and immune regulation. Probiotics help establish a microenvironment in the gut that favors beneficial microorganisms and reduces the colonization of pathogenic bacteria (competitive exclusion) by: (1) creating a hostile environment for harmful bacterial species (through production of lactic acid, SCFA, and reduction in pH); (2) competing for nutrients with undesired bacteria; (3) production and secretion of antibacterial substances (e.g. bacteriocins by *Lactobacillus, Bacillus* spp.); and (4) inhibition of bacterial adherence and translocation (Nurmi and Rantala, 1973; Fuller, 1989; Netherwood *et al.*, 1999; Schneitz, 2005; Ng *et al.*, 2009; Brown, 2011). Probiotics are also known to improve intestinal function by maintaining epithelial cell homoeostasis, promoting cytoprotective responses and cell survival (through production of cytokines that enhance epithelial cell regeneration and inhibit apoptosis), improving barrier function (modulation of cytoskeletal and epithelial tight junctions), and increasing mucin synthesis (Chichlowski *et al.*, 2007; Ng *et al.*, 2009; Brown, 2011). They also play an important role in digestion and nutrient retention by increasing digestive enzyme activity and improving the breakdown of indigestible nutrients (Jin *et al.*, 2000; Ciorba, 2012; Ng *et al.*, 2009; Wang and Gu, 2010). Probiotics also exert their action by reducing toxic amine production and ammonia levels in the gut (Chiang and Hsieh, 1995). Another important mechanism of probiotics action includes modulating and regulating intestinal immune responses by reducing pro-inflammatory cytokines, increasing secretory IgA production, and promoting specific and non-specific immune responses against pathogens (activation of macrophages, increase cytokine production by intraepithelial lymphocytes) (Ng *et al.*, 2009; Lee *et al.*, 2010a, 2011a).

Thus, an ideal probiotic organism should be able to withstand processing and storage, survive in the gastric acidic environment, adhere to epithelium or mucus in the intestines, produce antimicrobial compounds, and modulate immune responses (Edens, 2003; Patterson and Burkholder, 2003; Cheng *et al.*, 2014). However, not all strains exhibit all of the above properties and care must be taken to select the strains or their combinations that will achieve maximum beneficial effect *in vivo*. Measures to protect the organisms during their passage through the upper alimentary tract such as a microencapsulation should be considered to ensure viability and colonization in the intestine (Han *et al.*, 2013). Overall, it can be said that probiotics can serve as potential alternatives to antibiotics for increasing poultry performance.

Prebiotics

Prebiotics are defined as 'non-digestible feed ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the gut' (Gibson and Roberfroid, 1995; Patterson and Burkholder, 2003). A recent definition (FAO, 2007) describes prebiotics as 'non-viable feed components that confer a health benefit on the host associated with modulation of the microbiota.' A variety of non-starch polysaccharides (NSP) or oligosaccharides have been considered as prebiotics, including mannan oligosaccharide (MOS), fructooligosaccharide (FOS), inulin, oligofructose, galactooligosaccharide, maltooligosaccharide, lactulose, lactitol, glucooligosaccharide, xylooligosaccharide, soya-oligosaccharide, isomaltooligosaccharide (IOS), and pyrodextrins (Patterson and Burkholder, 2003; Steiner, 2006).

Prebiotics are macromolecules that are either derived from plants or synthesized by microorganisms. MOS, derived from the outer cell-wall layer of *Saccharomyces cerevisiae*, has been studied extensively as a prebiotic supplement in poultry diets. The addition of various levels of MOS to the broiler diets significantly increased their body weight and improved feed conversion efficiency (Benites *et al.*, 2008; Bozkurt *et al.*, 2008; Hooge *et al.*, 2003; Yang *et al.*, 2007; Mohamed *et al.*, 2008) with increased intestinal villi height (Baurhoo *et al.*, 2007; Yang *et al.*, 2007), improved immune-competence in the intestine (Janardhana *et al.*, 2009; Shanmugasundaram and Selvaraj, 2012), altered jejunal gene expression (Xiao *et al.*, 2012; Brennan *et al.*, 2013), and influenced intestinal microbiota (Geier *et al.*, 2009; Corrigan *et al.*, 2011; Kim *et al.*, 2011; Pourabedin *et al.*, 2014). FOS, which is derived from plants, has also been shown to possess significant prebiotic effect and improve performance in broiler chickens (Xu *et al.*, 2003; Kim *et al.*, 2011). Another class of prebiotics includes IOS showing promise as an antibiotic alternative owing to their efficacy in improving weight gain and FCR when fed to broilers (Mookiah *et al.*, 2014).

Lactulose is a non-digestible, synthetic disaccharide that was also proven to show prebiotic effect in humans and pigs. Calik and Ergün (2015) showed that lactulose supplementation in broiler diets not only improved body weight and FCR, but also increased villi height, goblet cell numbers, total SCFA concentrations, and *Lactobacillus* counts. Similar results of improvement in FCR and *Lactobacillus* counts with lactulose supplementation were shown by Cho and Kim (2014). Various other prebiotics that were tested and found to be beneficial in poultry include lignin (Baurhoo *et al.*, 2007), inulin (Alzueta *et al.*, 2010; Rebolé *et al.*, 2010), and palm kernel extract (Rezaei *et al.*, 2015). In contrast to the previous results, several authors reported that prebiotic supplementation had no effect on performance (Baurhoo *et al.*, 2007; Józefiak *et al.*, 2008; Geier *et al.*, 2009; Corrigan *et al.*, 2011; Houshmand *et al.*, 2012). However, statistical analysis of numerous trials conducted with prebiotic supplementation in the diets of broiler chickens was shown to beneficially influence their growth and performance. Holo- and meta-analysis of several research trials conducted over the years using prebiotics in feed have confirmed these effects (Hooge, 2004; Rosen, 2007; Hooge and Connolly, 2011). It was shown that adding a yeast cell-wall product to the diets significantly improved body weight by 1.61% and reduced FCR by 1.99%, respectively (Hooge, 2004). Hooge and Connolly (2011) reported that prebiotics improved body weight by 5.41%, decreased FCR by 2.54%, and reduced mortality by 10.5%.

A number of characteristics should be taken into consideration when selecting prebiotics, including resistance to gastric acidic environment, intestinal/pancreatic enzyme hydrolysis, and absorption across intestinal epithelium (Hume, 2011; Heo *et al*., 2013; Ricke, 2015). The most important characteristic of an ideal prebiotic is the ability to selectively enrich beneficial microorganisms associated with health and well-being (Simmering and Blaut, 2001; Patterson and Burkholder, 2003; Heo *et al*., 2013; Samantha *et al*., 2013). Thus, the majority of the beneficial effects of prebiotics are thought to be mediated predominantly through altering the intestinal microbiota (Pourabedin and Zhao, 2015). Prebiotics also prevent pathogen colonization either by binding directly or by competitive exclusion by promoting the growth of beneficial microbes or by stimulating them to produce bacteriocins and lactic acid (Spring *et al*., 2000). In particular, MOS acts by binding to type 1 fimbriae of enteric pathogens and prevents their adhesion to intestinal epithelial cells (Spring *et al*., 2000). The fermentation of prebiotics by microflora also leads to the production of SCFA that act as energy sources for intestinal epithelial cells and thus maintain the integrity of the gut lining (Ferket *et al*., 2005). Prebiotics also act by beneficially altering luminal or systemic aspects of the host immune system. MOS is recognized by receptors of the innate immune system, act as adjuvants, and help boost the host immune responses (Ferket *et al*., 2005).

Synbiotics

Synbiotics are additives that combine the use of probiotics and prebiotics such that they act synergistically (Alloui *et al*., 2013). The use of synbiotics was based on the concept that a mixture of probiotics and prebiotics beneficially affect the host by improving the survival and implantation of probiotic organisms and by selectively promoting the growth or metabolism of beneficial bacteria in the intestinal tract (Gibson and Roberfroid, 1995). Few research trials have been conducted to demonstrate the effects of synbiotics on broiler performance. Supplementation of diets with a synbiotic product was shown to significantly improve body weight, average daily gain, feed efficiency, and carcass yield percentage compared with controls or probiotic-fed broilers (Awad *et al*., 2009). Ashayerizadeh *et al.* (2009) reported similar improvement in growth indices and Mohnl *et al.* (2007) showed that synbiotics increased body weight by 2.04% and reduced mortality by 0.9% compared with controls. Mookiah *et al.* (2014) reported a significant increase in weight gain and a decrease in the FCR when birds were fed diets with a combination of IOS and probiotic mixture (11 strains of *Lactobacillus* spp.). However, the synbiotic did not show a 2-fold synergistic effect compared with those of prebiotics or probiotics alone. A combination of yeast-derived carbohydrates and probiotics was shown to increase body weight gain compared with controls or prebiotic-supplemented pullets (Yitbarek *et al*., 2015). In contrast, some of the trials conducted with in-feed inclusion of synbiotics did not show that performance was affected (Willis *et al*., 2007; Jung *et al*., 2008). Synbiotics were also shown to beneficially alter the intestinal microbiota composition and increase villi height and crypt depth in the intestinal mucosa (Jung *et al*., 2008; Awad *et al*., 2009; Sohail *et al*., 2012). There is a great potential for synbiotics to be used as antibiotic alternatives for improving performance and reducing pathogenic load in the intestines of poultry. Careful consideration must be given when selecting the combinations of various prebiotics and probiotics to be used as synbiotics, and research trials should be conducted to demonstrate their synergistic effect compared with the use of either product alone (Fig. 1).

Organic acids

Dietary organic acids have been considered as potential alternatives to AGPs, owing to their antibacterial nature. Chemically, organic acids used in food animal production can be described as either simple monocarboxylic acids (e.g., formic, acetic, propionic, and butyric acids) or carboxylic acids bearing hydroxyl group (e.g., lactic, malic, tartaric, and citric acids) (Dibner and Buttin, 2002). They are widely distributed in nature as normal constituents of animal or plant tissues and some of them (specifically SCFA) are produced in the hind gut of food animals and humans through microbial fermentation of carbohydrates (Van Der Wielen *et al*., 2000; Ricke, 2003; Huyghebaert *et al*., 2011). They can be administered in the feed or drinking water and can be used either individually as organic acids or their salts (sodium, potassium, or calcium) or as blends of multiple acids or their salts (Huyghebaert *et al*., 2011).

Organic acid use has been shown to have significant benefits in swine and poultry production over the years. Dietary supplementation of fumaric acid in broiler chickens was shown to improve weight gain and feed efficiency (Patten and Waldroup, 1988; Skinner *et al*., 1991; Biggs and Parsons, 2008; Adil *et al*., 2010, 2011; Banday *et al*., 2015). Similar effects of growth performance improvement were seen when butyric acid was included in the broiler feed (Panda *et al*., 2009; Adil *et al*., 2010, 2011). Several other organic acids that were tested and shown to improve performance in poultry include lactic (Adil *et al*., 2010, 2011), citric (Chowdhury *et al*., 2009; Haque *et al*., 2010; Salgado-Tránsito *et al*., 2011), formic (Patten and Waldroup, 1988; Hernández *et al*., 2006; Panda *et al*., 2009), malic, sorbic, and tartaric acids. Research has shown that the beneficial effects of organic acids can be enhanced by using them as blends rather than a single acid. Various organic acid blends were tested and shown to improve the FCR in broiler chickens (Samanta *et al*., 2008, 2010).

Though the mechanism of action of organic acids is not clearly understood, it can be attributed to their antibacterial activity. Several possible mechanisms include the following: (1) reducing the pH level of the upper gastrointestinal tract (crop,

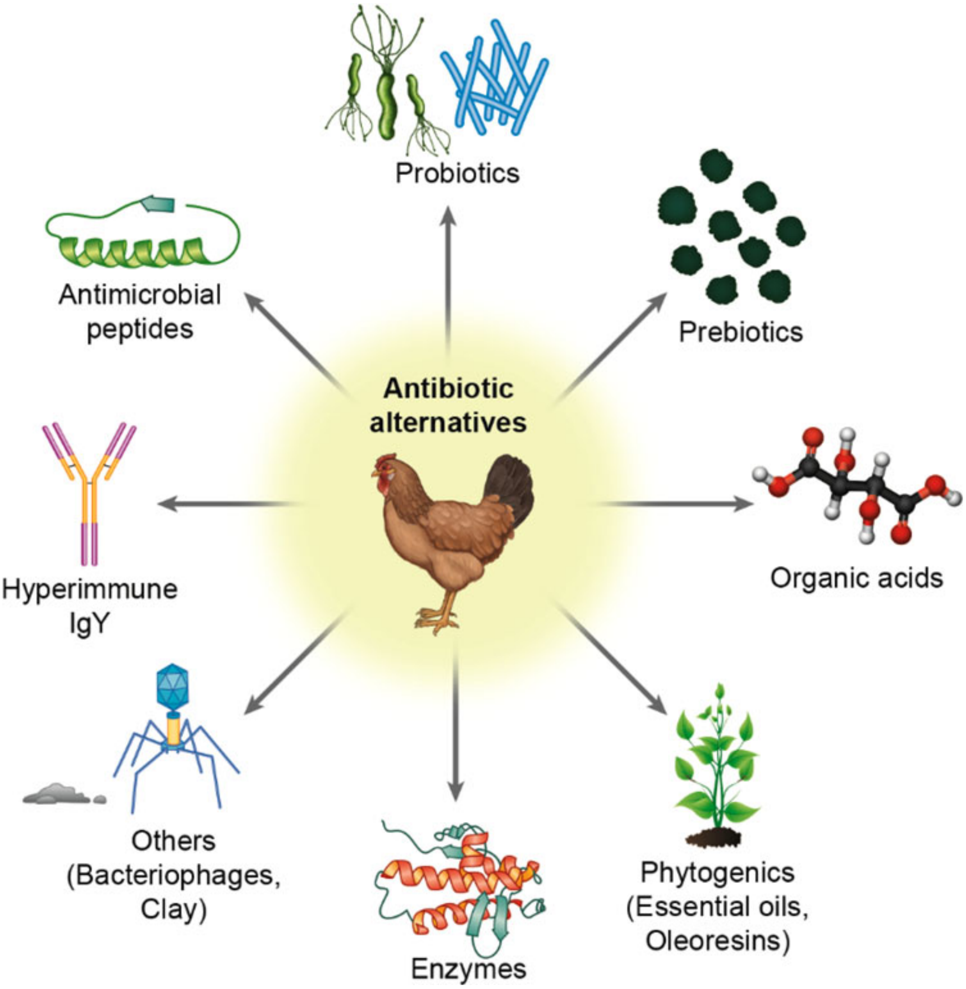

Fig. 1. Various classes of antibiotic alternatives that are available for use in poultry production.

proventriculus, gizzard) and associated physiological changes in the gut mucosa (Samanta *et al.*, 2008; Panda *et al.*, 2009); (2) altering the gut microflora either by directly killing through cell-wall penetration or by indirectly modifying pH and reducing the numbers of pathogenic bacteria, increasing acid-tolerant beneficial species such as *Lactobacilllus* spp. and reducing competition for nutrients by the altered microbes (Biggs and Parsons, 2008; Nava *et al.*, 2009; Czerwiński *et al.*, 2010; Boroojeni *et al.*, 2014); (3) increasing nutrient digestibility by elevating protein and dry matter retention, improving mineral absorption and phosphorous utilization (Rafacz-Livingston *et al.*, 2005; Nezhad *et al.*, 2011); and (4) improving gut health through direct effects on epithelial cells (e.g. SCFA are a direct energy source for the growth of epithelial cells). In spite of the demonstrated beneficial effects, using organic acids to improve performance lacks consistency. This can be attributed to various factors such as inclusion rates, the source of the organic acids, and the buffering capacity of other dietary ingredients (Dibner and Buttin, 2002; Kim *et al.*, 2015). Further research should address inconsistency issues and understand their mechanism of action to develop organic acids as effective antibiotic replacements.

Enzymes

Dietary enzymes are biologically active proteins that facilitate chemical breakdown of nutrients to smaller compounds for further digestion and absorption (Thacker, 2013). Various enzymes, derived from microbes (bacteria and fungi) through fermentation, have been used in swine and poultry feeds for the past several years, and their value in enhancing growth and feed efficiency is well noted. The different classes of enzymes commonly employed include phytase, carbohydrases (xylanase, cellulase, α-galactosidase, β-mannanase, α-amylase, and pectinase), and proteases. The effect of various in-feed enzymes in improving the growth and feed efficiency in poultry is well documented and reviewed (Bedford and Schulze, 1998; Choct, 2006; Selle and Ravindran, 2007; Adeola and Cowieson, 2011; Slominski, 2011; Woyengo and Nyachoti, 2011).

It is now well accepted that exogenous enzymes act on anti-nutritional factors that are present in plant-based feedstuffs such as phytic acid, NSP, and cell-wall complex carbohydrates. The improved performance that is a result of enzyme supplementation thus has been linked to an increase in the overall digestibility and availability of nutrients for absorption (Bedford, 2000; Verstegen and Williams, 2002; Rebolé *et al.*, 2010). The possible mechanisms of action of in-feed enzymes include the following: (1) increase in the digestibility of nutrients that are otherwise not degraded by host enzymes (e.g. phytic acid); (2) elimination of the nutrient-encapsulating effect of cell-wall polysaccharides and an increase in the availability of starches, amino acids, and minerals; (3) inactivation of anti-nutritional factors (e.g., phytic acid or soluble NSP) and reduced intestinal viscosity; (4) an increase in the solubility of non-soluble NSP and promotion of cecal fermentation; and (5) supplementation of endogenous enzymes that may be in insufficient amounts, especially in young animals in which the digestive system is not fully developed (Choct, 2009; Kiarie *et al.*, 2013). In addition to the effects enzymes have on nutrient digestibility, they are also thought to influence the composition of the gut microbiota. The enzyme-induced microbiota changes are mostly indirect and are thought to be mediated by two main mechanisms: (1) reducing the undigested substrates and (2) generating short-chain oligosaccharides from cell-wall NSP with potential prebiotic effects (Bedford, 2000; Bedford and Cowieson, 2012; Kiarie *et al.*, 2013). These mechanisms influence the nutrient supply and intestinal environment thus altering selection pressures on bacterial species (Bedford and Cowieson, 2012; Cheng *et al.*, 2014).

The potential for use of in-feed enzymes, as antibiotic alternatives, to improve performance in poultry is significant. Various meta-analyses conducted corroborate these beneficial effects in broilers upon enzyme supplementation. A meta-analysis performed by Hooge *et al.* (2010) showed that supplementation of a dietary multi-enzyme complex involving phytase and NSP enzymes improved final body weight by 3.73% and lowered FCR by 2.64%. Jackson and Hanford (2014) conducted a meta-analysis of seven pen trials investigating the effects of β-mannanase supplementation in male broilers raised to market age. They reported that the weight gain and FCR, analyzed across trials, were improved by 4.2% and 4.8 points, respectively, and concluded that β-mannanase supplementation is effective in broilers. A similar meta-analysis conducted by Swann and Romero (2014) investigated the beneficial effects of a xylanase, amylase, and protease combination. Their results, based on ten broiler studies, showed that the particular enzyme combination increased the apparent digestibility of undigested crude protein, starch and fat by 22.7, 88.9, and 33.4%, respectively. However, it should be noted that the beneficial effects of enzyme supplementation are sometimes inconsistent owing to the differences in the enzyme type, source, amount of enzyme used, presence of enzyme side effects, diet composition, and genetic variations among animals (Ravindran and Son, 2011; Cheng *et al.*, 2014).

Phytogenics

Phytogenic feed additives (PFAs), also referred as phytobiotics or botanicals, are natural bioactive compounds that are derived from plants and incorporated into animal feed to enhance productivity (Windisch *et al.*, 2008). A wide range of plants and their products fall under this category and, based on their origin (part of the plant), they can be broadly classified as herbs (flowering, non-woody, non-persistent plants from which leaves and flowers are used) or spices (non-leaf parts of plants, including seeds, fruits, bark or root with intensive taste or smell) (Windisch *et al.*, 2008; Van Der Klis and Vinyeta-Punti, 2014). They can be used in solid, dried, and ground form or as extracts (crude or concentrated). Depending on the process used to derive the active ingredients, PFA can also be classified as essential oils (EOs; volatile lipophilic substances obtained by cold extraction or by steam or alcohol distillation) and oleoresins (extracts derived by non-aqueous solvents) (Windisch *et al.*, 2008; Van Der Klis and Vinyeta-Punti, 2014). The main bioactive compounds of the PFAs are polyphenols and their composition and concentration vary according to the plant, parts of the plant, geographical origin, harvesting season, environmental factors, storage conditions, and processing techniques (Windisch *et al.*, 2008; Applegate *et al.*, 2010).

In recent years, PFAs have been used as natural growth promoters in the pig and poultry industries (Windisch *et al.*, 2008; Franz *et al.*, 2010). A wide variety of herbs and spices (e.g., thyme, oregano, rosemary, marjoram, yarrow, garlic, ginger, green tea, black cumin, coriander, and cinnamon) have been used in poultry for their potential application as AGP alternatives. Guo *et al.* (2004) showed a significant increase in body weight gain and improvement in feed efficiency when broilers were given diets supplemented with a mixture of 14 herbs. Similar results were shown with the addition of oregano (Florou-Paneri *et al.*, 2006), dried ground leaves of stevia (Atteh *et al.*, 2008), black cumin seeds (Khalaji *et al.*, 2011), fermented *Ginkgo biloba* leaves (Cao *et al.*, 2012), and dried and ground *Scrophularia striata* and *Ferulago angulata* (Rostami *et al.*, 2015) to poultry feed. Various plant extracts used as PFAs were also shown to improve the performance of broilers. Research trials conducted with the inclusion of sugar cane extract (El-Abasy *et al.*, 2002), aniseed extract (Durrani *et al.*, 2007), chestnut wood extract (Schiavone *et al.*, 2008), *Forsythia suspensa* extract (Wang *et al.*, 2008), and *Portulaca oleracea* extract (Zhao *et al.*, 2013b) showed a significant increase in body weight gain and a lower FCR. In contrast, several other PFAs such as grape pomace, cranberry fruit extract, *Macleaya cordata* extract, garlic powder, grape seed extract, and yucca extract tested as growth promoters did not show any effects on performance parameters (Goñi *et al.*, 2007; Brenes *et al.*, 2008; Leusink *et al.*, 2010; Juskiewicz *et al.*, 2011; Viveros *et al.*, 2011; Issa and Omar, 2012; Chamorro *et al.*, 2013).

In addition to herbs and spices, various EOs (thymol; carvacrol; cinnamaldehyde; EOs from clove, coriander, star anise, ginger, garlic, rosemary, turmeric, basil, caraway, lemon, and sage) have been used either individually or as blends to improve animal health and performance. Variable results have been reported with the use of EOs in poultry diets. Including a blend of thymol and cinnamaldehyde in feed which was shown to improve body weight gain in broilers (Tiihonen *et al.*, 2010; Amerah *et al.*, 2011). Similar results were shown when supplementing diets with EO from oregano (Malayoğlu *et al.*, 2010; Hashemipour *et al.*, 2013, 2014) and coriander (Ghazanfari *et al.*, 2015), blends of clove and cinnamaldehyde

(Chalghoumi *et al.*, 2013), thymol and EO from star anise (Kim *et al.*, 2016a), and an herbal EO mix (Alçiçek *et al.*, 2004; Khattak *et al.*, 2014). EO supplementation was also shown to improve feed efficiency as seen by reduced FCRs (Çabuk *et al.*, 2006; Isabel and Santos, 2009; Amad *et al.*, 2011; Kim *et al.*, 2016a). In contrast, several other trials did not show any beneficial effects of including EO on performance (Lee *et al.*, 2003; Basmacioğlu *et al.*, 2004; Hernández *et al.*, 2004; Zhang *et al.*, 2005; Jang *et al.*, 2007). The variations in the results could be attributed to the differences in the composition, type, and origin of the EO that were used, inclusion level, and the environmental conditions of the trials (Franz *et al.*, 2010). Nevertheless, one commercial blend of phytonutrients (containing carvacrol, cinnamaldehyde, and capsicum oleoresin) was approved in the EU as the first botanical feed additive for improving performance in broilers. Several research trials performed with this commercial blend demonstrated consistent improvement in growth and feed efficiency (Bravo *et al.*, 2014; Karadas *et al.*, 2014; Pirgozliev *et al.*, 2015). A meta-analysis of 13 broiler studies involving the use of this commercial blend showed that its inclusion in diets increased body weight gain and decreased FCR and mortality (Bravo and Ionescu, 2008).

The mechanism of action of PFAs is not clearly understood and depends greatly upon the composition of the active ingredients in the product being used. In general, the beneficial effects of PFAs are attributed to their antimicrobial and antioxidant properties. The inclusion of PFAs in the diets was shown to alter and stabilize intestinal microflora and reduce microbial toxic metabolites in the gut owing to their direct antimicrobial properties on various pathogenic bacteria, which results in relief from intestinal challenge and immune stress, thus improving performance (Tiihonen *et al.*, 2010; Viveros *et al.*, 2011; Zhang *et al.*, 2013; Zhao *et al.*, 2013b; Liu *et al.*, 2014). Another important beneficial effect of dietary inclusion of PFAs is reduction in oxidative stress and increase in antioxidant activity in various tissues and thus improved health (Basmacioğlu *et al.*, 2004; Brenes *et al.*, 2008; Wang *et al.*, 2008; Cao *et al.*, 2012; Mueller *et al.*, 2012; Zhang *et al.*, 2013; Liu *et al.*, 2014; Settle *et al.*, 2014). PFAs also exert their action through immunomodulatory effects such as increased proliferation of immune cells, elevated expression of cytokines, and increased antibody titers (Kim *et al.*, 2010; Lee *et al.*, 2010b; Park *et al.*, 2011; Pourhossein *et al.*, 2015). The addition of PFAs to the diet was also shown to increase intestinal and pancreatic enzyme production and activity and increase bile flow (Lee *et al.*, 2003; Jang *et al.*, 2007; Malayoğlu *et al.*, 2010; Hashemipour *et al.*, 2013, 2014). PFAs also help maintain and improve gut histology, increase villi height and thus expand absorptive surface of the intestine (Ghazanfari *et al.*, 2015; Murugesan *et al.*, 2015). Increase in digestive enzyme secretion and absorption results in improved apparent nutrient digestibility and thus improves performance (Jamroz *et al.*, 2003; Hernández *et al.*, 2004; Jørgensen *et al.*, 2008; Wang *et al.*, 2008; Amad *et al.*, 2011; Amerah *et al.*, 2011; Issa and Omar, 2012). They also might play a role in maintaining the intestinal barrier function as evidenced by the increase in the trans-epithelial electrical resistance of duodenal mucosa of broilers that included thymol in their diets (Placha *et al.*, 2014).

A growing body of scientific evidence has demonstrated that many of the health-promoting activities of phytochemicals are also mediated through their ability to enhance the host's defense against microbial infections and tumors (Lillehoj *et al.*, 2011). The immune-activating properties of medicinal plants such as dandelion (*Taraxacum officinale*), mustard (*Brassica juncea*), and safflower (*Carthamus tinctorius*) have been evaluated *in vitro* using avian lymphocytes and macrophages (Lee *et al.*, 2007). All three extracts inhibited tumor cell growth and exhibited antioxidant effects. Further, the safflower extract stimulated chicken lymphocyte proliferation, whereas the mustard extract induced nitric oxide production by macrophages. In a separate study, organic phase extracts from milk thistle (*Silybum marianum*), turmeric (*Curcuma longa*), reishi mushroom (*Ganoderma lucidum*), and shiitake mushroom (*Lentinus edodes*) were tested for their effects on chicken innate immunity and tumor cell cytotoxicity (Lee *et al.*, 2010a). In chicken macrophages treated with extracts of turmeric (*Curcuma longa*) or shiitake mushroom (*Lentinus edodes*) *in vitro* (Lee *et al.*, 2010b), the levels of gene transcripts for IL-1β, IL-6, IL-12, IL-18, and TNFSF15 were increased. The phagocytic activity of chicken heterophils was shown to be significantly improved with the addition of non-dialyzable materials of cranberry extract at 4 mg ml^{-1} concentration (Islam *et al.*, 2016). Cinnamaldehyde ((2E)-3-phenylprop-2-enal) is a constituent of cinnamon (*Cinnamomum cassia*), a widely used flavoring compound that has been traditionally used to treat human diseases, including dyspepsia, gastritis, and inflammation. Chicken spleen lymphocytes that were stimulated *in vitro* with cinnamaldehyde showed good cell proliferation, and cinnamaldehyde activated cultured macrophages to produce higher nitric oxide levels (Lee *et al.*, 2011b). The effects of carvacrol, cinnamaldehyde, and *Capsicum* oleoresin on the regulation of the expression of genes associated with immunology, physiology, and metabolism were investigated in chickens using high-throughput microarray analysis (Lillehoj *et al.*, 2011). These studies revealed that *Capsicum* oleoresin stimulated a great number of gene changes when compared with unsupplemented controls, and many of the altered genes were associated with metabolism and immunity. The most reliable genetic network induced by dietary cinnamaldehyde treatment was related to the functions of antigen presentation, humoral immunity, and inflammatory disease. Further studies to delineate the intestinal immune pathways affected by phytochemical feeding were conducted by mRNA microarray hybridization (Kim *et al.*, 2010). When compared with chickens fed an unsupplemented diet, carvacrol-fed chickens showed altered levels of 74 gene transcripts in gut lymphocytes (26 increased, 48 decreased), cinnamaldehyde supplementation was associated with altered levels of 62 mRNAs (31 increased, 31 decreased), and *Capsicum* oleoresin-fed chickens had altered levels of 254 mRNAs (98 increased, 156 decreased), compared with unsupplemented controls. Among the transcripts that showed greater than twofold altered expression levels, most were encoded by genes associated with metabolic pathways. In the case of *Capsicum* oleoresin, the transcripts included pathways for lipid metabolism, small molecule biochemistry, and cancer. In another investigation, global gene expression analysis by microarray hybridization identified

1810 transcripts (677 increased, 1133 decreased) whose levels were significantly altered in intestinal lymphocytes of anethole-fed birds when compared with unsupplemented controls (Kim *et al.*, 2013a). From these, 576 corresponding genes were identified that were related to the inflammatory response. A similar analysis was reported for the garlic metabolites, propyl thiosulphinate PTS) and PTS oxide (PTSO) (Kim *et al.*, 2013b). In that study, 1227 transcripts (552 increased, 675 decreased) were identified in intestinal lymphocytes whose levels were significantly altered in PTS/PTSO-fed birds when compared with unsupplemented controls. Many of these transcripts were encoded by genes related to innate immunity, including Toll-like receptor 3 (TLR3), TLR5, and nuclear factor (NF)-κB.

Hyperimmune egg yolk antibodies

Hyperimmune egg yolk antibodies (IgY), produced by repeated immunization of hens with specific antigens and collection of antibodies thereafter from their egg yolks, have been commonly employed in the prevention and treatment of various enteric diseases in humans and animals (Gadde *et al.*, 2015). Limited research exists on the use of egg yolk antibodies as viable alternatives to AGP in improving growth and feed efficiency in poultry (Cook, 2004). Earlier studies were focused on generation of egg antibodies in breeding hens that could be passively transferred to the progeny and improve their productivity. Pimentel and Cook (1988) and Pimentel *et al.* (1991) showed that progeny from hens injected with jack bean urease had improved body weight at 3 weeks of age. It 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. As IgY technology evolved, research trials conducted later on involved the use of antibodies in feed to improve performance or enhance host immunity (Lee *et al.*, 2009a, b). The majority of these studies encompassed the use of antibodies that were raised against components involved in the immune regulation of growth. The growth suppression associated with immune stimulation is well established, and it is hypothesized that interleukin 1 (IL-1) released during inflammation causes anorexia (through the release of neuropeptides like cholecystokinin (CCK), neuropeptide Y into gut lumen) and muscle wasting (Goldberg *et al.*, 1984; Klasing *et al.*, 1987). Cook (2004) reported that hyperimmune egg yolk antibodies raised against various neuropeptides (CCK, neuropeptide Y) improved body weight and feed efficiency when fed to broiler chickens up to 3 weeks of age. They showed that supplementing diets with egg powder containing CCK antibodies at 0.25 g kg^{-1} dose improved the feed conversion efficiency by 13 points compared with that of birds fed egg powder from unimmunized hens. Similar results were shown in a series of trials in which chicks were fed dried egg yolk powder from hens vaccinated with neuropeptide Y or from control unimmunized hens. The average improvement in weight gain and FCR at 3 weeks of age was shown to be 9% and 8 points, respectively, compared with controls (Cook, 2004). Eicosanoids are also believed to play a proinflammatory role in immune stimulation, and supplementing feed with egg antibodies (BIG™) developed against phospholipase A2 (an enzyme involved in eicosanoid synthesis) for 3 weeks improved the mean weight gain of broilers by 5.4% and the FCR by 6.2 points (Cook, 2001, 2002).

The use of egg yolk antibodies offers several advantages. Large quantities of antibodies can be produced in laying hens and non-invasively collected. Their use is environmentally friendly, less toxic and does not select for resistance. Although the existing results seemed encouraging, much more research is needed on using egg antibodies for growth promotion in poultry.

Antimicrobial peptides

AMPs are widely distributed, small, gene-encoded peptides that have germicidal properties. They have been seen in all kingdoms of life and have shown activity against a wide range of pathogens such as Gram-negative and Gram-positive bacteria, fungi, enveloped viruses, and parasites (Koczulla and Bals, 2003; Li *et al.*, 2012; Kim *et al.*, 2016b). Mature AMPs generally contain 12–100 amino acids, are rich in hydrophobic cationic residues, and have an amphipathic structure that facilitates interaction with negatively charged membranes of microbials as well as other cellular targets (Yeaman and Yount, 2007; Linde *et al.*, 2008; Wang *et al.*, 2014). To date, over 2600 endogenous AMPs have been isolated and many more synthetic analogues were reported in various publications (http://aps.unmc.edu/AP/main.php; Fosgerau and Hoffmann, 2015). The studies that have been done on AMPs and their applications in poultry have been mostly focused on their protective potential against diverse pathogens causing infectious diseases rather than growth-promoting activities. However, a few research trials investigating the effect of AMPs on poultry growth performance, intestinal morphology, and gut microbiology as potential AGP alternatives have been explored. One such trial demonstrated that supplementing with yeast-expressed cecropin A (1-11)-D(12-37)-Asn (CADN), a chimeric peptide derived from insects, in poultry diets increased weight gain, feed intake, feed:gain ratio, and intestinal villus height while decreasing aerobic bacterial counts in both jejunal and cecal digests (Wen and He, 2012). In consistency with the previous result, Choi *et al.* (2013) reported the beneficial effects of diets supplemented with a chemically synthesized AMP-P5, analog of hybrid AMP cecropin A (1-8)-magainin 2(1-12) (CAMA), on chicken performance, nutrient retention, intestinal morphology, as well as excreta and intestinal microflora. One Chinese research group investigated the effects of naturally synthesized AMPs obtained from swine and rabbit. The AMPs were extracted from swine gut and rabbit sacculus rotundus, respectively, and were orally inoculated or supplemented in water or diets. They reported that the birds that were given naturally synthesized AMPs showed improvement in growth performance, intestinal ability to absorb nutrients and mucosal immune parameters such as intraepithelial lymphocytes or mast cell counts, and in secretory IgA levels when compared with unsupplemented or non-inoculated birds (Liu *et al.*, 2008; Bao *et al.*, 2009; Wang *et al.*, 2009).

Based on the origins of AMPs, there is a particular group of AMPs called bacteriocins. Bacteriocins are defined as ribosomally synthesized peptides that are secreted by various bacteria that have antibacterial activity against other similar or closely related bacteria. In the past, bacteriocins were mostly used as food preservatives and were believed to be produced only by specific bacterial strains (Cleveland *et al*., 2001). Thus, its production had been considered an important feature in the selection of probiotic strains, but now one or more bacteriocins have been identified and believed to exist in all species of bacteria and archaea (Cotter *et al*., 2005; Willey and van der Donk, 2007). Currently, 177 bacteriocins have been identified in 31 genera, including Gram-positive and Gram-negative bacteria as well as archaea (http://bactibase.pfba-lab-tun.org/main.php). They are mainly cationic, hydrophobic, or amphiphilic like other AMPs (Riley and Wertz, 2002). Generally, they have been shown to possess a relatively narrow spectrum of antimicrobial activity when compared with AMPs produced by non-bacterial origin. One of the most reported bacteriocins as a dietary supplement in poultry is divercin AS7, which is produced by *Carnobacterium divergens* AS7, a lactic acid-producing bacterium isolated from fish, which has been extensively studied by Józefiak and colleagues. The authors have focused on the application of divercin AS7 to improve growth performance, nutrient retention, intestinal histomorphology, and balance of gastrointestinal microbiota. They demonstrated that supplementing broiler diets with divercin AS7 has an *in vivo* growth-promoting effect, increasing digestibility as well as a modulatory effect on intestinal microbiota (Józefiak *et al*., 2010, 2011a, b, 2012). Supplementation of divercin AS7 reduced intestinal digesta pH in a series of their studies, which reflected the activity of the gastrointestinal microbiota and digestion physiology (Engberg *et al*., 2002). In addition, dietary nisin, which is produced by *Lactococcus lactis* and is the sole bacteriocin approved for use as a food additive by the FDA, exerted a modulatory effect on the microbial ecology of the gastrointestinal tract with decreased counts of *Bacteroides* and *Enterobacteriacae*, but unchanged counts of *Clostridium perfringens, Lactobacillus* spp., *Enterococcus* spp., and total bacteria (Józefiak *et al*., 2013). Albusin B, which is another bacteriocin that is produced by *Ruminococcus albus* 7, was added to poultry feed and also showed improved growth performance, increased intestinal absorption and *Lactobacillus* counts, modulated lipid metabolism, and activated systemic antioxidant defense (Wang *et al*., 2011, 2013a).

Despite the fact that limited research exists on the use of AMPs as alternatives to AGP, collectively dietary supplementation of AMPs in poultry seems to affect the birds in a positive way by improving their intestinal balance and creating gut microecological conditions that suppress harmful microorganisms like *Clostridium* spp. and coliforms while favoring beneficial microorganisms like *Lactobacillus* spp. (Ohh *et al*., 2009). In conclusion, the AMPs including bacteriocins have the potential to considerably enhance poultry health as alternatives to AGP and their potential might be improved when a number of obstacles such as high production cost, resistance development, and instability of the AMPs are addressed in the future.

Bacteriophages

Bacteriophages, which were discovered in the early 1900s (Twort, 1915; d'Herelle, 1917), are highly species-specific viruses that kill bacteria through the production of endolysins and the subsequent lysis of the bacterial cells (Joerger, 2003; Huff *et al*., 2005). Bacteriophages can be considered safe antibiotic alternatives as they exhibit no activity against animal and plant cells. They have been used to prevent and treat various bacterial diseases in humans and animals (Huff *et al*., 2003; Miller *et al*., 2010). A significant amount of research was also done on their use in control of food-borne pathogens on agricultural and poultry products (Goode *et al*., 2003; Huff *et al*., 2004). Very few studies demonstrated the effects of supplementing diets with bacteriophages on growth performance. Zhao *et al*. (2012) evaluated the effects in laying hens and reported that incorporating 0.035 or 0.05% of bacteriophages in their diet significantly improved egg production. Increased body weight gain and reduced FCR were reported in broilers given diets supplemented with 0.10 and 0.15% (Kim *et al*., 2013c) or 0.5 g kg^{-1} of bacteriophages, respectively (Wang *et al*., 2013b). However, further research is needed to establish the performance effects of bacteriophages and make their use practical in poultry production systems.

Clay

Clay minerals (also designated as phyllosilicates) are formed by a net of stratified tetrahedral and octahedral layers containing molecules of silicon, aluminum, and oxygen, and interconnected by hydrogen bonds or a group of cations (Vondruskova *et al*., 2010). The natural extracted clays (bentonite, zeolite, kaolin, etc.) are a mixture of various clay minerals that differ in chemical composition (Vondruskova *et al*., 2010). Clay minerals, because of their stratified structure, have great adsorption capacity and can bind aflatoxins, plant metabolites, heavy metals, enterotoxins, and pathogens. The factors affecting the extent of adsorption include the chemistry of the clay minerals, the fine structure of the clay particles, and their surface properties, pH, dosage, and exposure time (Thacker, 2013). Many research trials were conducted to show the antibacterial and detoxifying effects of clay in poultry (Kubena *et al*., 1998; Phillips, 1999; Fowler *et al*., 2015), but very few trials investigated their growth-promoting effects. Xia *et al*. (2004) reported that including copper-bearing montmorillonite in broiler diets significantly improved growth performance, reduced *Escherichia coli* and *Clostridium* spp. counts in the intestine, and increased intestinal digestive enzyme activity. Dietary inclusion of hydrated aluminosilicate (5 g kg^{-1}) significantly increased body weight gain of broilers at 1 and 3 weeks of age and increased serum amylase and lactate dehydrogenase activity (Prvulović *et al*., 2008). Similar improvement results in performance were shown upon supplementing diets with kaolin, bentonite, zeolite (Katouli *et al*., 2010), clay (Ani *et al*., 2014), and kaolin (Jorge de Lemos *et al*., 2015). Wu *et al*. (2013) showed that adding clinoptilolite to diets improved antioxidant capacity in broilers as evidenced by increased glutathione peroxidase, catalase, and total superoxide dismutase activities and decreased malondialdehyde content of liver. However, results of including clay minerals appeared to be inconsistent, as some research trials showed no effect on performance (Wu *et al.*, 2013).

The mechanism by which clays and clay minerals influence growth is unclear, but it depends largely on their ability to physically bind and remove toxins, anti-nutritional components, and pathogenic organisms. This results in reducing microbial metabolites, toxins, and enzymes in the intestine and thus preventing irritation and damage and improving morphological characteristics of the intestinal mucosa (Xia *et al.*, 2004; Jorge de Lemos *et al.*, 2015) and thus performance. The inclusion of clay was also shown to improve nutrient digestibility by reducing digest transit time and also decreasing litter moisture (Olver, 1997; Jorge de Lemos *et al.*, 2015). Further research should be done on the role of clay as a potential alternative to AGP and its effects when combined with other products.

Metals

Heavy metals such as copper, zinc, iron, selenium and manganese, often referred to as trace minerals in animal nutrition, are extensively used in food animal production to maintain general health and normal physiology (Scott, 2012). They play a vital role in growth and metabolism as they are critical for many digestive, physiological, and biosynthetic processes (Richards *et al.*, 2010; Attia *et al.*, 2012). Traditionally, heavy metals have been supplemented in animal diets in the form of inorganic salts such as carbonates, chlorides, oxides, and sulfates (Pierce *et al.*, 2009; Attia *et al.*, 2012), but chelated or organic forms have also been used lately. The use of trace minerals to increase animal productivity and performance has been gaining importance in the recent years and they are being substituted in levels beyond the recommended nutritional requirements. Copper, an essential trace mineral, plays a significant role in hemoglobin synthesis, angiogenesis, connective tissue, bone development, and more importantly serves as a cofactor for many metabolic enzymes (Brainer *et al.*, 2003; Richards *et al.*, 2010; Vasanth *et al.*, 2015). The use of copper as growth promotant in poultry diets has been well demonstrated. Supplementation of diets with copper sulfate, citrate, or carbonate at levels ranging from 125 to 250 mg Cu kg^{-1} showed improvement in body weight and feed efficiency (Hoda and Maha, 1995; Pesti and Bakalli, 1996). Ewing *et al.* (1998) demonstrated that addition of cupric sulfate pentahydrate and copper oxychloride to the broiler diets increased weight gain by 4.9% and cupric citrate increased weight gain by 9.1% compared with non-supplemented controls. In-feed supplementation of tribasic copper chloride or copper sulfate was also shown to significantly increase average daily gain and carcass weight in broilers (Arias and Koutsos, 2006; Lu *et al.*, 2010). Zinc is another important essential trace mineral that has been used to improve performance in poultry. Zinc serves as a cofactor for several cellular enzymes and transcription factors and plays an essential role in cell proliferation, immune response, reproduction, gene regulation, and defense against oxidative stress and damage (Richards *et al.*, 2010). Supplementation of zinc sulfate up to 80 mg kg^{-1} in the basal diets was shown to significantly improve body weight gain of broilers but no differences in mortality and feed efficiency were observed (Burrell *et al.*, 2004). Similar improvements in performance were shown when broilers were given diets with zinc oxide along with sodium selenite for 4 weeks (Fawzy *et al.*, 2016). In contrast to these studies, several other research trials investigating the beneficial effects of zinc supplementation did not show any performance effects, but in general observed improved immune status of the birds (Sunder *et al.*, 2008; Yogesh *et al.*, 2013). The growth promotant effect seen following in-feed supplementation of some of the metals such as zinc, copper can be attributed to their antimicrobial properties (Cromwell, 1991; Brainer *et al.*, 2003; Yazdankhah *et al.*, 2014). From studies conducted in pigs, it was proposed that zinc and copper alter the intestinal microbiota by reducing the levels of both commensal and pathogenic bacteria, and also by reducing fermentation loss of nutrients (Højberg *et al.*, 2005; Yazdankhah *et al.*, 2014). Use of metals as growth promotants should be adapted with caution as they may come with some disadvantages. Inclusion of metals in excess amounts raises environmental concerns in terms of their accumulation in soil and surface water (Burrell *et al.*, 2004). Also, excess use of metals has been shown to develop metal resistance with concomitant cross-resistance to antibiotics among enteric bacteria in farm animals (Yazdankhah *et al.*, 2014).

Conclusions

Owing to the rise in consumer demand for livestock products from antibiotic-free production systems, there exists a great need for the development of antibiotic alternatives that can help improve performance and maintain optimal health of food animals. Several products have been evaluated in poultry over the past several years for their potential to replace antibiotics. Though the beneficial effects of many of the alternatives tested have been well demonstrated, there is the general consensus that these products lack consistency, as results vary greatly from farm to farm. Care must be taken in the choice of alternatives, such that they fit the needs of the individual production program. Further research is needed regarding understanding their mechanism of action, identifying means to standardize the effects, improving delivery methods (e.g. microencapsulation) for site-targeted delivery, and increasing their *in vivo* efficacy. Combinations of products may prove more beneficial than using them alone to achieve an effect similar to that of antibiotics. Using optimal combinations of various alternatives coupled with good management and husbandry practices will be the key to maximizing performance and maintaining animal productivity, while we move forward with the ultimate goal of reducing antibiotic use in the animal industry.

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