Alternatives to antibiotics for organic poultry production: types, modes of action and impacts on bird's health and production

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ABSTRACT The poultry industry contributes significantly to bridging the nutritional gap in many countries because of its meat and eggs products rich in protein and valuable nutrients at a cost less than other animal meat sources. The natural antibiotics alternatives including probiotics, prebiotics, symbiotics, organic acids, essential oils, enzymes, immunostimulants, and phytogenic (phytobiotic) including herbs, botanicals, essential oils, and oleoresins are the most common feed additives that acquire popularity in poultry industry following the ban of antibiotic growth promoters (**AGPs**). They are commonly used worldwide because of their unique properties and positive impact on poultry production. They can be easily mixed with other feed ingredients, have no tissue residues, improve feed intake, feed gain, feed conversion rate, improve bird immunity, improve digestion, increase nutrients availability as well as absorbability, have antimicrobial effects, do not affect carcass characters, decrease the usage of antibiotics, acts as antioxidants, anti-inflammatory, compete for stress factors and provide healthy organic products for human consumption. Therefore, the current review focuses on a comprehensive description of different natural antibiotic growth promoters' alternatives, the mode of their action, and their impacts on poultry production.

Key words: antibiotics, organic additives, poultry, performance, health

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INTRODUCTION

Organic farming is one of the fastest expanding agricultural sectors in the United States. Since the 1990s, demand for organically farmed commodities, including animal products, has increased, with American customers driving the market. Organic food sales in the United States are predicted to have surpassed $35 billion in 2014, up from $28.4 billion in 2012. (USDA-ERS, 2009, 2014; Greene, 2013; Salim et al., 2018). Since the demand for organic foods out-grew supplies in the last

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few years, the U.S. retailers imported several billion dollars' worths of organic foods to the American market (Crandall et al., 2009). Among the organic animal products, avian meat and eggs are available widely across the country and are well-accepted by the consumers (Agricultural Marketing Resource, 2013; Ponnampalam et al., 2019). The latest NASS NASS 2010 survey indicated that the sale of organic poultry meat and eggs fetched ~$350 million in 2008 (NASS, NASS 2010). However, even with 9 million certified broilers, 5.5 million certified layer hens and 400,000 certified organic turkeys (NASS, NASS 2010; Agricultural Marketing Resource, 2013), the industry has not met the increasing demand for organic poultry. This underscores the tremendous opportunity for the growth of the organic poultry sector in the coming years, as predicted by the Organic Trade Association (Greene, 2013; Wan et al., 2019). Although there is significant scope for expanding organic poultry, concerns over the safety of organic meat and eggs potentially contaminated with foodborne pathogens could curtail the opportunity (Mogelonsky, 2008; El Jeni et al., 2021).

Raising broiler chickens is a significant part of Egyptian poultry production (El Nagar and Ibrahim, 2021; Salem and Attia, 2021). This situation warrants rapid response to identify alternative and applicable antimicrobial intervention methods of pathogen control in organic poultry (El-Shall et al., 2022). The National Organic Program (**NOP**) restricts antibiotics, hormones, herbicides, and pesticides from organic agricultural activities to safeguard the environment, people, and animals, thereby potentially improving the sector's sustainability (Fanatico, 2008; Zhang et al., 2021).

In addition, the consumers of organic feed generally tend to perceive the products as safer alternatives due to less/no added preservatives/chemicals and choose them for their families. In line with NOP compliance, naturally derived enzymes, antioxidants, and botanicals can be used in organic poultry farming to combat infections, improve growth and enhance the quality of the products. Vaccines are allowed against many different diseases as Marek's disease virus, Newcastle disease virus, infectious bronchitis virus, *Mycoplasma*, and coccidia (Setta et al., 2018; Marouf et al., 2020, 2021; El-Naggar et al., 2022).

Probiotics are the beneficial bacteria that can fight pathogens in the gastrointestinal tract of chickens and could also improve general health and disease prevention in birds.

In severe infections where antibiotics are used for treatment, birds cannot be marketed as organic (Fanatico, 2008; Yang et al., 2009). However, the lack of sufficient and reliable research data on the methods as mentioned earlier on improving the microbiological quality of organically raised poultry is a hindering agent. In addition, supporting the inadequacy of the current techniques, several studies have indicated the presence of similar levels of pathogen contamination in organic and commercial poultry products (Sato et al., 2004; Cui et al., 2005; Stone et al., 2013; Noormohamed and Fakhr, 2014). This situation presents a unique challenge for the organic sector to advise its beneficiaries, including producers and processors, on potential antimicrobials that can render their products safe from infectious agents. In addition, as per the NOP standards, poultry must have outdoor access, an environment that may have pathogenic organisms such as Salmonella, Clostridia, and Campylobacter (Abd El-Hack et al., 2021a; Salem et al., 2021). Similar factors that could pose a challenge to safe organic poultry production include the use of slow-growing breeds and minimal slaughtering facilities − both potentially increase the propensity for pathogen contamination in the products (Cui et al., 2005). This review article highlights the different types of organic alternatives for AGPs, their mode of action and their impact on the poultry industry.

Feed Additives

Different feed additives, including biologically synthesized nanoparticles, probiotics, prebiotics, synbiotics, herbal extract, essential oils, organic acids, enzymes, essential amino acids, etc., have been widely used to substitute the use of AGPs (Reda et al., 2020; Sheiha et al., 2020; Abd El-Ghany et al., 2021; El-Saadony et al., 2021a,b,c; Reda et al., 2021a). Common feed additives include antibiotics, probiotics, prebiotics, and enzymes (Wenk, 2000; Abd El-Hack et al., 2021b). Like all other feed additives, antibiotics are expected to increase host health and production performance (Dibner and Richards, 2005). Although the exact physiological mechanisms of feed additives are unclear, the health effects are focused on the gut (Dibner and Richards, 2005; Krysiak et al., 2021). Probiotics are valuable gut microbe species that can colonize the gut, and prebiotics is indigestible oligosaccharides that can be utilized by the useful gut microbes (Wenk, 2000; Kulshreshtha et al., 2014; Murate et al., 2015). Endogenous enzymes such as carbohydrases and proteases are used to increase the digestibility of feed in the gut (Wenk, 2000; Sharma et al., 2005).

Phytogenic feed additives (**PFAs**) are another promising type of alternative. This phytogenic class contains four main subgroups: herbs, botanicals, essential oils, and oleoresins (Abdelnour et al., 2020a,b; Ogbuewu et al., 2020). These herbal products (cinnamon, ginger, pepper, turmeric, etc.) positively affect bird performance and health due to their antimicrobial, antioxidant, immune-boosting, and gut manipulation properties (Yakhkeshi et al., 2011; Abd El−Hack et al., 2021c,d).

Antibiotic Additives

Many infectious diseases, viral, bacterial, parasitic, and fungal, threatenpoultry and animal production (Abd El Hamid et al., 2019; Salem et al., 2019; Morsy et al., 2020; Yousry et al., 2020; Attia and Salem, 2022). The use of an antibiotic as a growth promoter began in the 1940s with the discovery of growth responses from the presence of *Streptomyces* *aureofaciens* in a monogastric diet (Hashemi and Davoodi, 2010). When used as a feed additive in the diet, subtherapeutic antibiotic levels are present in the range of about 2.5 to 50 ppm (Hashemi and Davoodi, 2010). Due to antibiotic supplementation in the diet, broilers' growth rate and overall productiveness have increased in the last 50 yr (Tajodini et al., 2015).

As some antibiotic growth promoters (**AGPs**) are not absorbed, the mechanism of antibiotics is most likely in the gut with interactions with the microflora. Thinning of the intestinal wall villi and the total gut wall and reducing opportunistic pathogens by competitive exclusion have been associated with the use of AGPs (Dibner and Richards, 2005). In an antibiotic comparison study, male and female broilers fed Bacitracin methylene di-salicylate, Virginiamycin, and a control diet. Miles et al. (2006) found that antibiotic-fed birds were heavier at 7 wk than the control birds and their *muscularis interna* in the duodenum was thinner. At 3 and 7 wk, the antibiotic-fed birds had a lighter GIT weight than the control birds. Resistance and residue problems have increased the negative consumer perception of growth-promoting antibiotic use in animal diets. One study examining antibiotic resistance tested 58 *Salmonella enterica* serovar Heidelberg isolates and found that 72% were resistant to at least one antibiotic and 24% of the isolates were resistant to 8 or more antimicrobials (Hoffman-Pennesi and Wu 2010). In 1997, the World Health Organization (**WHO**) announced that antibiotic resistance was a global public health problem (Tajodini et al., 2015).

The WHO promotes a proactive approach to reduce the need and use of AGPs in animals, especially within the classes used in humans (Dibner and Richards 2005). There is accumulated evidence of a correlation between antibiotics used as a growth-promoting feed additive and antibiotic resistance in humans and animals. However, in 2009, the American Veterinary Medical Association (**AVMA**) cited no established direct link between antimicrobials used in animals and subsequent resistance in humans (Hoffman-Pennesi and Wu, 2010). Besides the potential for resistance, antibiotics also can leave a residue in the meat (Khan and Naz, 2013). In 1986, Sweden became the first country to ban the use of AGPs (Dibner and Richards, 2005; Wenk, 2000). On January 1, 2006, the European Union banned growth-promoting antibiotics (Kulshreshtha et al., 2014; Hafeez et al., 2016). Due to the potential and realized problems occurring with the use of growth-promoting antibiotics and consumer pressure, the need for an alternative is essential for the poultry industry.

Natural Alternatives for AGPs

The three main options for lowering our dependency on antibiotics in animals are creating antibiotic-free alternatives that stimulate growth by improving feed conversion efficiency. Promoting animal condition by proper rearing methods might be difficult to accomplish in most situations (Adams, 1999). Growth promoters have been demonstrated to work best under the most adverse settings, such as animals in poor health and living in filthy conditions. The need for growth stimulants may be eliminated if the environment is improved through reduced overcrowding and improved infection control procedures (Prescott et al., 2000; Chervonova, 2021). Antibiotic growth promoters and the emergence of antibiotic resistance are inextricably linked. Enzymes, probiotics, prebiotics, herbs, amino acids, immunostimulants, organic acids, bacteriocins, and phytotherapeutic plants have been investigated as antibiotics growth promotors' alternatives (Figure 1; Langout, 2000; Abou-Kassem et al., 2021a; Arif et al., 2021). There is growing concern about developing antibiotic-resistant bacteria strains because of exposure to these subtherapeutic antibiotic dosages.

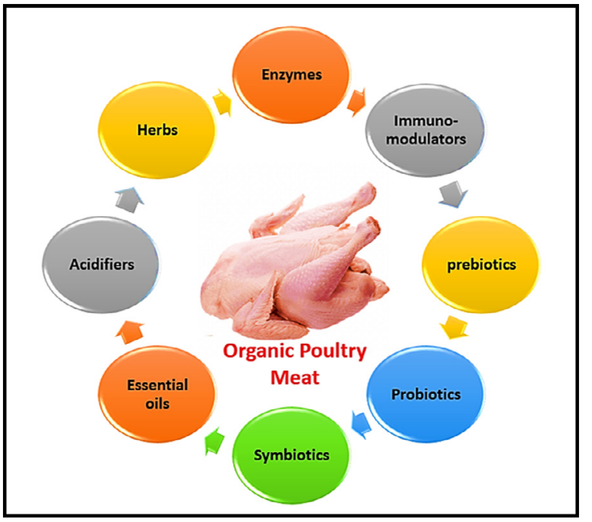

Figure 1. Most common natural alternatives used for production of organic poultry meat.

Prebiotic and Probiotic Additives

Prebiotics, probiotics and symbiotics (prebiotic and probiotic combination; Figure 2) are alternative feed additives used to control pathogens in the gut and increase bird performance (Murate et al., 2015; Peralta-Sánchez et al., 2019). Prebiotics are oligosaccharides

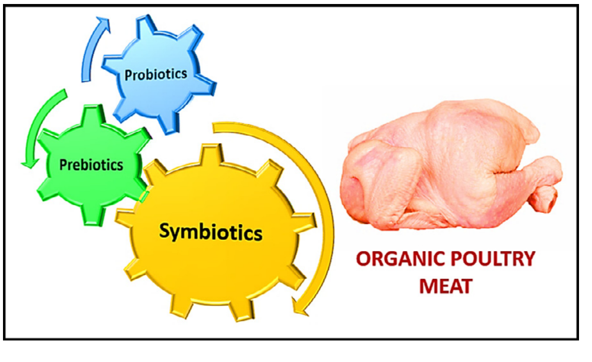

Figure 2. The use of probiotics, prebiotics and symbiotics for organic poultry meat production.

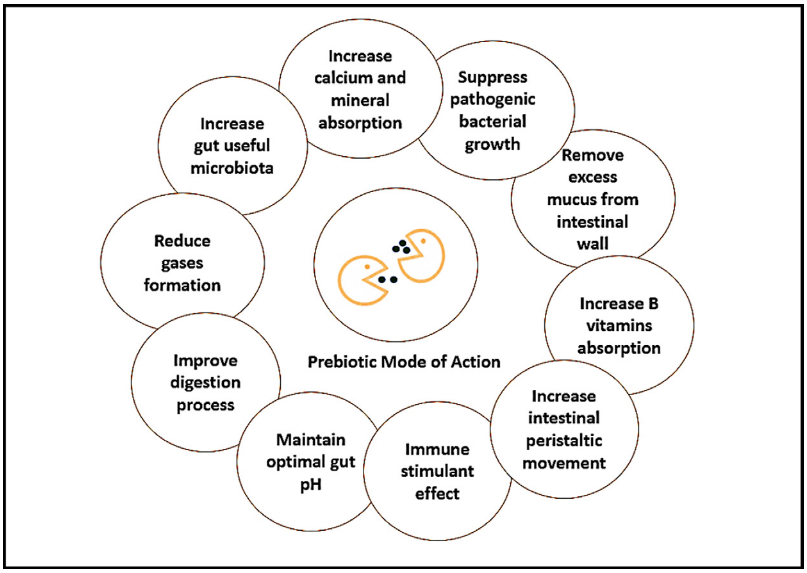

Figure 3. Prebiotics' mode of action.

indigestible by the host animal but are utilized by specific populations of gut microorganisms. Prebiotics enable already present microorganisms to increase their numbers, reduce pathogenic bacteria, increase digestibility, increase minerals and vitamins absorbability, maintain optimal intestinal pH, and maximize nutrients utilization (Figure 3; Wenk, 2000; Kulshreshtha et al., 2014; Murate et al., 2015; Mazanko et al., 2018).

Prebiotics can affect host health in several ways, such as the production of metabolites like lactic acid, modification of microbial metabolism, and increased cell integrity of the epithelium (Neupane et al., 2019; Abd El-Hack et al., 2021c,d; Yaqoob et al., 2021). Unlike prebiotics, probiotics are microorganisms that can alter the host health by colonizing the host GIT and providing a more balanced microbiota (Wenk, 2000; Khan and Naz, 2013; Murate et al., 2015). Probiotics can be yeast, bacteria, or fungi based and, unlike antibiotics, do not have the potential to leave a residue (Khan and Naz, 2013). Lactic acid bacteria, which produce antifungal metabolites, are common probiotic bacteria (Londero et al., 2014).

Probiotics, also known as direct-fed microbial (**DFMs**), are classified by FAO/WHO (2001) as "live microorganisms which when administered in adequate amounts confer a health benefit on the host." Probiotics specific to broilers include the genera *Lactobacillus, Streptococcus, Bacillus, Bifidobacterium, Enterococcus, Aspergillus, Candida*, and *Saccharomyces* (Kabir, 2009). The beneficial effects of probiotics include improved performance, modulating the intestinal microbiota, inhibiting pathogens, improved intestinal integrity, immunomodulation, and improving microbiological and sensory characteristics of broiler meat (Figures 4 and 5; Alagawany et al., 2021a; El-Saadony et al., 2021d).

Essential characteristics of a probiotic include being resistant to bile and acid, being strain-specific, having no side effects, reducing the number of pathogenic microorganisms and can withstand feed processing (Stęczny and Kokoszyński, 2020). The most common probiotic mode of action is by lowering the gut pH through the volatile fatty acids and organic acids produced during the probiotic product breakdown (Khan and Naz, 2013; Al-Fatah, 2020). Pathogenic bacteria such as *Salmonella* and *E. coli* strains cannot grow well below a certain pH (Wenk, 2000; Khan and Naz, 2013; Hidayat et al., 2019; Swelum et al., 2021).

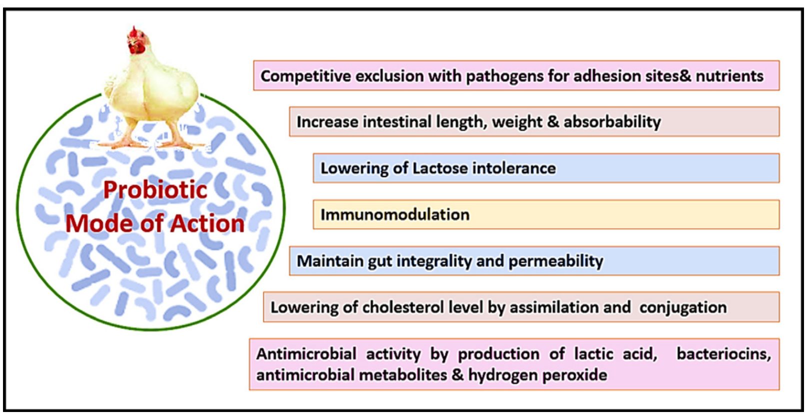

Figure 4. Probiotics' mode of action.

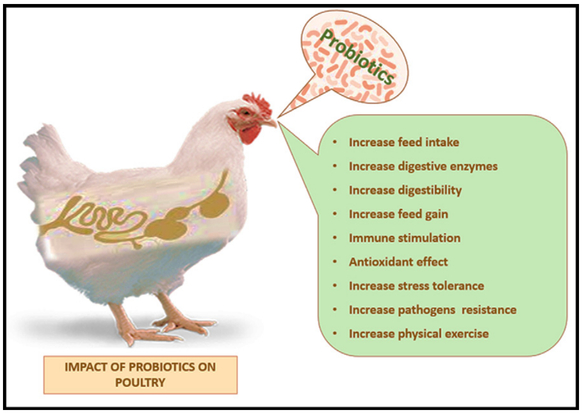

Figure 5. Impacts of probiotics on chickens.

Furthermore, probiotics effectively control pathogen levels in the gut is through the competitive exclusion of adhesion areas along the gut lining. Immune system stimulation, nutrient competition and reduced levels of toxin-producing β-glucosidase and β-glucuronidase in the intestines and feces are other mechanisms probiotics utilize for pathogen protection (Khan and Naz, 2013).

Research on polysaccharides in seaweed for use as a prebiotic supplement has seemed promising due to its indigestibility by the host digestive enzymes and its strain specificity for beneficial microbes. Supplementation with seaweed increased the acetic acid, propionic acid, *n*-butyric acid, and *i*-butyric acid in the cecum by significant levels while decreasing the prevalence of *Clostridium perfringens* (Kulshreshtha et al., 2014). In a study done by Murate et al. (2015) on probiotic, prebiotic, and symbiotic supplementation, broilers and layers were challenged with *Salmonella enterica serovar* Enteritidis. Significant decreases in infected birds were found in the layers with the prebiotic treatment but not the control treatments. There was no effect between the probiotic, prebiotic and symbiotic control treatments in the broiler birds concerning *Salmonella* infection.

At early postinfection, there was a significant reduction in *Salmonella* counts in the broiler and layer birds receiving the prebiotic compared to the control diet. However, by d 14 and 21, there were no significant differences in the *Salmonella* count (Murate et al., 2015; Michel et al., 2019). For decades, it has been custom to use anticoccidials in poultry feed to control coccidiosis (Dalloul and Ritzi, 2016). Consumer concerns over drug residues in their food products and concerns about multidrug-resistant parasites and bacteria have driven the modern research community to search for alternative methods. Vaccines have a positive outcome; however, they are expensive and must be carefully administered to be effective and not cause unwanted harm. Immunomodulators such as probiotics have been at the forefront of worldwide research (Dalloul and Ritzi, 2016).

Probiotic's Modes of Action

Probiotics help maintain a healthy balance in the gut to promote proper health, performance, and defense against enteric diseases (Dalloul, 2017; Abd El−Hack et al., 2020). Probiotics function through 3 main mechanisms: competitive exclusion, bacterial antagonism, and stimulation of the immune system (Ohimain and Ofongo, 2012). As soon as a chick hatches, gut microbiota begins to establish within hours, so early administration of probiotics has a better chance of improving gut microbial profiles (Timmerman et al., 2006).

A chick would typically establish a gut microbiota via contact with adult chickens' feces. However, probiotic supplementation is beneficial in a hatchery due to lack of contact with grown chickens (Kabir, 2009). Probiotics can competitively exclude pathogenic strains of bacteria by establishing in the gut, taking up the space and nutrients in the digestive tract that pathogens would otherwise use to colonize. Many probiotic species are antagonistic to bacterial pathogens by producing antimicrobial substances and secretions that lower pH in the gut, which inhibit pathogenic growth (Hume, 2011). Short-chain fatty acids (**SCFA**) produced by beneficial bacteria have been shown to increase host defense peptide gene expression (Sunkara et al., 2011, 2012), and in high concentrations, disrupt proton motive force and metabolic reactions in bacteria when small, nonionized acids cross bacterial membranes and then dissociate into protons and anions in the cytoplasm.

The protons lead to acidification of intracellular compartments where proton motive force occurs, disturbing metabolic reactions, and anions disrupt osmotic balance (Sun and O'Riordan, 2013). Bacteriocins, small peptides or proteins secreted by beneficial bacteria, kill closely related strains of bacteria by forming pores in the cell membrane and disrupting enzyme function. Beneficial *Lactobacillus* spp. is known for secreting lactic acid, which lowers intestinal pH and inhibits pathogenic growth (Figure 6; Travers et al., 2011). The vital functions of probiotics to stimulate the immune system are discussed below.

Probiotics, Performance, and Intestinal Development

A healthy gut is linked with the proper performance of poultry (Getachew, 2016; Hargis et al., 2021). Probiotics can boost performance by helping to establish a healthy gut environment. In chickens, body weight gain (**BWG**) and feed conversion ratio (**FCR**) have been improved with probiotic supplementation (Sen et al., 2012; Popova, 2017). A study by Mountzouris et al. (2007) demonstrated performance results at the same level as the AGPs avilamycin.

Other studies have shown no improvement in performance due to probiotic supplementation (Rahimi et al., 2011; Wolfenden et al., 2011; Getachew, 2016). This could be explained by the strain of probiotic bacteria not having an effect, the viability being compromised during feed preparation, or improper dosage levels. Other factors that can affect probiotic efficacy are diet, overall health and age of birds, interactions with other additives in the feed, or stress factors such as

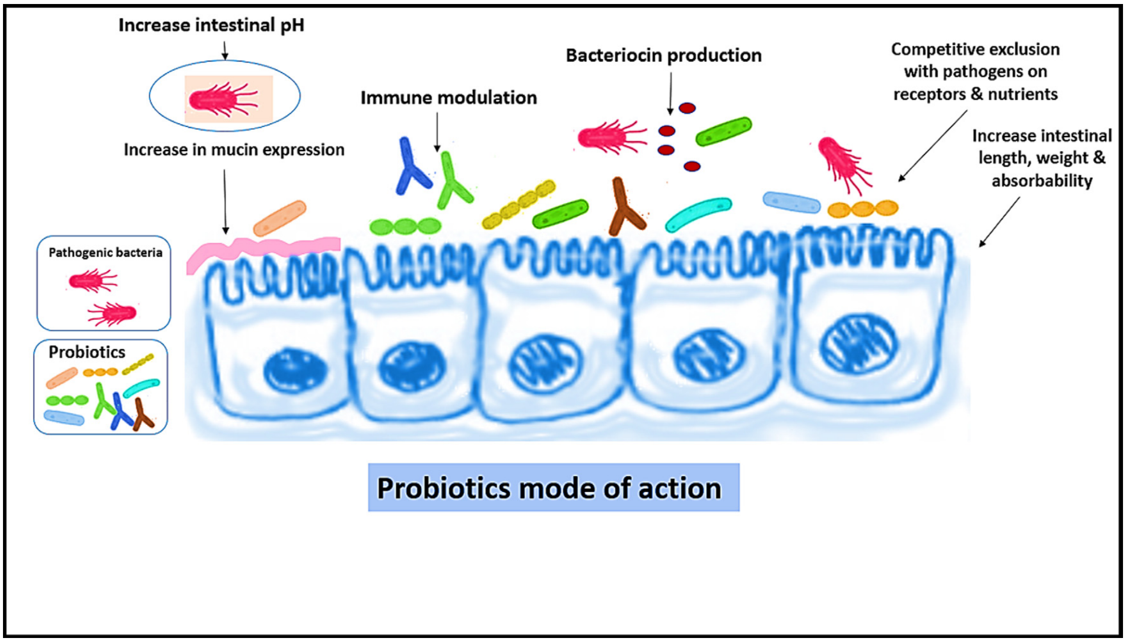

Figure 6. Probiotic effect on intestinal villi & their mode of action.

temperature and stocking density (Patterson and Burkholder, 2003; Mountzouris et al., 2007; Cox and Dalloul, 2015). Probiotics have also shown the potential to improve gut development and makeup. They have resulted in an increased length of intestinal villi and a decrease in crypt depth (Samanya and Yamauchi, 2002; Marković, 2009).

Longer villi length correlates to a larger surface area for absorbing nutrients. Crypt sites are the location of enterocyte proliferation, and shallow crypts indicate less need for epithelial cell turnover, taking energy that would go toward cell turnover and placing it toward animal growth (Marković, 2009). Another example of probiotics benefiting gut health was demonstrated when the mycotoxin deoxynivalenol (**DON**) was added to feed (Awad et al., 2006). DON usually damages the gut by reducing the villus height and width in the duodenum and jejunum, whereas probiotic treatment alleviated the deleterious effects of villus reduction (Awad et al., 2006).

Probiotics and Innate Immunity

Innate immune responses are non-specific defenses consisting of physical, chemical, and cellular barriers (Applegate et al., 2010). Physical barriers include epithelial cells (enterocytes), chemical barriers include secretions or mucus or antibacterial peptides (defensins, lysozymes), and cellular barriers include phagocytes and macrophages that engulf bacteria and present it to the adaptive immune system (Applegate et al., 2010). The avian heterophil is equivalent to the mammalian neutrophil.

These cells play an essential role in the first line of defense, phagocytosing pathogens, then using oxidative burst and degranulation to destroy them. Probiotics have been shown to enhance oxidative burst and degranulation, thus protecting against pathogens (Harmon, 1998; Duskaev et al., 2020). Heterophils isolated from probiotic-supplemented broilers displayed increased oxidative burst and degranulation (Farnell et al., 2006; Stringfellow et al., 2011). Macrophages phagocytose pathogens, process them intracellularly, and present antigens to the adaptive immune system cells, playing a role in lymphocyte differentiation. Broiler chicks fed a commercially available *Lactobacillus*-based product had increased macrophages in the ileum and cecum. Still, macrophage levels were reduced after exposure to the pathogen *Salmonella enteritidis* and supplementation with probiotics one hour after the challenge. Competitive exclusion by the probiotics could cause a decrease in macrophages after the challenge, reducing the pathogen load in the intestine (Higgins et al., 2007a; Price et al., 2020). Probiotics play a role in enhancing innate immune responses and the competitive exclusion of pathogens in the gut.

Probiotics and Adaptive Immunity

The adaptive immune system mounts a specific defense to foreign antigens, consisting of T cells and B cells that produce antigen-specific antibodies (Applegate et al., 2010; Xiang et al., 2019). It is the second line of defense and essential to protection against reinfection (Dalloul, 2017). Supplementation with probiotics increased antibody titers to sheep red blood cells and Newcastle disease virus and infectious bursal disease, both important avian viral diseases (Apata, 2008; Karimi Torshizi et al., 2010). A study involving oral gavage female broilers found that probiotic treated birds had increased natural antibody production and increased levels of IgA responsive to tetanus toxoid and increased IgG and IgM antibodies reactive to tetanus toxoid and alpha-toxin (Haghighi et al., 2006).

Mountzouris et al. (2009) compared probiotic treatments to the AGP avilamycin. They determined that both resulted in lower plasma IgA and IgG levels and decreased intestinal IgA against *Salmonella enteritidis* compared to a challenging control. Reduced antibody levels may indicate enhanced clearing and recovery of the disease. *Eimeria*-infected birds supplemented with probiotics produced more *Eimeria*-specific antibodies than controls (Lee et al., 2007a,b; Elkhouly et al., 2016). Probiotic supplementation has been shown to increase the number of intestinal intraepithelial lymphocytes expressing the cell surface markers CD^3, CD^4, and CD^8 (Dalloul et al., 2003; Noujaim et al., 2008).

A study by Karimi Torshizi et al. (2010) challenged birds with 1- chloro-2, 4-dinitrobenzene (**DNCB**) and birds supplemented with a water application of probiotics displayed enhanced immune response. Birds challenged with a PHA-M (phytohemagglutinin-M) injection were supplemented with feed or water applied probiotics and showed enhanced immune response as measured by increased skin thickness. Different strains of probiotics can have other effects on cytokine production, as indicated by studies using *Lactobacillus* and *Bacillus*-based probiotics that modulated the levels of proinflammatory cytokines (IL-1β, IL-6, IL-17a, IL-18), Th1 cytokines (IFN-γ, IL-2, IL-12), and Th2 cytokines (IL-4, IL-10, IL-13) (Dalloul et al., 2005; Brisbin et al., 2010; Lee et al., 2010). The strain of probiotics used can profoundly affect the immune response, as measured by lymphocyte and cytokine production.

Probiotics and Host Defense Against Pathogens

Pathogens such as *Eimeria* spp., *Clostridium perfringens, Campylobacter jejuni* and *Salmonella enteritidis* are making a comeback in modern poultry and rabbit production due to the ban on the prophylactic use of antibiotics (Khelfa et al., 2012, 2012a,b; Dalloul and Ritzi, 2016; Jiang et al., 2017). These diseases can have devastating effects on the intestines, leading to reduced performance and death. Probiotics can improve gut health and reduce the impacts of common enteric disorders. Reduced oocyst shedding has been observed in probiotic-fed chicks that were later infected with *E. acervulina* or *E. tenella* (Dalloul et al., 2003, 2005; Lee et al., 2007a,b). The severity of lesions from *E. maxima* infected broilers was reduced in probiotic supplemented treatments (Lee et al., 2010). Ritzi et al. (2014) conducted studies on feed vs. water application of probiotics in assessing anticoccidial effects.

It was found that a water-based probiotic led to lower duodenal and jejunal lesion scores and those birds intermittently given water-based probiotic treatment shed fewer oocysts. The subsequent study concluded that probiotics in conjunction with vaccination lead to additional benefits, as seen by improved performance and reduced lesion scores when challenged birds with *Eimeria* (Ritzi et al., 2016). Further, probiotics given to birds on embryonic d 18 had reduced disease severity after being challenged with *Eimeria* (Pender et al., 2016). Other pathogens, such as *Salmonella, Campylobacter jejuni,* and *Clostridium perfringens*, were reduced by probiotic supplementation as well (Saint-Cyr et al., 2016). A study by Revolledo et al. (2009) found that probiotic supplementation reduced colonization of *Salmonella* in the ceca, liver, and spleen of broiler chicks. Necrotic enteritis induced by *C. perfringens* was partially alleviated as indicated by reduced lesion scores, mortality, and levels of *C. perfringens* (McReynolds et al., 2009).

Intracellular pathogens such as *Salmonella enteritidis* and *Campylobacter jejuni* were reduced by probiotic supplementation (Higgins et al., 2007b; Ghareeb et al., 2012). Reducing pathogens in the gut can aid in protection against secondary infections that are often associated with the primary disease; for example, *Eimeria* infection often leads to necrotic enteritis by *C. perfringens* (Chapman et al., 2002).

Phytogenic Feed Additives and Poultry

Antibiotic-growth promoters have been used to improve poultry performance for decades; however, recent bans in the European Union (**EU**) on these products and concerns over microbial resistance and health effects in humans have led to increased interest in natural alternatives (Alcicek et al., 2004).

A broad category of feed additives commonly researched in poultry is phytogenic (PFAs), intended to improve gut health and function (Alcicek et al., 2004). PFAs are plant-derived compounds such as essential oils, spices, safe natural compounds, and herbs intended to provide a health benefit when added to feed (Puvača et al., 2013; Ashour et al., 2021). Typical examples are rosemary derivatives, oregano, thyme, sage, cinnamon, citrus, pepper, and anise (Mountzouris, 2016). The efficacy of phytogenics can depend on numerous factors, including composition, inclusion level in the feed, bird genetics, and feed composition (Ferdous et al., 2019).

According to Mountzouris (2016), optimal gut function, animal health, and performance are linked and can be achieved when healthy gut microbiota, dietary factors, gut mucosa, and immune responses are balanced and work together to eliminate pathogens, improve nutrient absorption, and modulate inflammation (Koutsos and Arias, 2006; Choct, 2009; Applegate et al., 2010; Mountzouris, 2016). The efficacy of plants depends on the type and amount of plant secondary metabolites or phytochemicals contained in the plant. These components act on the GIT of the host animal and help to improve the microbial community, which in turn helps resist colonization and take over from pathogenic microorganisms (El-Saadony et al., 2021e; El-Saadony et al., 2021f).

The antimicrobial property of phytogenic feed additives is due to the bioactive components such as tannic acid and saponins. Tannic acid can promote iron deprivation, and saponins can bind with sterols to cause microorganism damage and cell destruction (Hashemi and Davoodi, 2011). There are many examples of positive findings with PFA supplementation. The impact of nutrient density and PFA supplementation (quillaja, anise, and thyme) on the growth and performance of meat ducks was investigated by Gheisar et al. (2015). Authors found that it was possible to recover some growth performance, meat quality, and nutrient digestibility loss that resulted from the lower nutrient density diet by supplementing the diet with a PFA (Gheisar et al., 2015). This study highlights the positive effects of PFA's with reduced nutrient diets. A study with a phytogenic compound containing thyme and star anise was supplemented at 150, 750, and 1,500 mg/kg in the diet.

The PFA was not found to affect the body weight positively, body weight gain, or feed conversion intake compared to the non-supplemented control diet. Although there were no positive production findings, as supplementation increased, the apparent ileal digestibility of crude ash, crude protein, crude fat, and phosphorous and calcium absorption increased linearly. The birds fed the highest level of supplementation had the highest level of nutrient digestibility (Amad et al., 2011).

Modes of Action

PFAs may promote a healthy gut and improve performance through various mechanisms: antioxidative and antimicrobial properties, improved palatability, improved digestion, growth promotion, and improved gut health (Alcicek et al., 2004). Studies on palatability are inconclusive, but the PFAs may improve feed quality due to antioxidative properties and slow bacterial and fungal growth (Lambert et al., 2001; Soliman and Badeaa, 2002; Burt, 2004).

Phytogenic (Phytobiotic), Avian Performance, and Intestinal Effects

Phytogenic or phytobiotic feed additives have had varying effects on performance. Some studies demonstrated no differences in various performance parameters. One study used essential oregano oil at 50 or 100 mg/kg in a wheat-soybean meal diet with Cobb broilers, and there was a difference in body weight (**BW**) or FCR from controls (Botsoglou et al., 2002; Grashorn, 2010). Another study using female Cobb broilers found that supplementation with thymol, cinnamaldehyde, and commercial preparation had no effects on feed intake (**FI**), BWG, or FCR (Lee et al., 2003; Ren et al., 2019).

Other studies later demonstrated the benefits of various PFAs in poultry feed given to different breeds of broiler chickens. Two studies involving different diets, the first diet included carboxyl methyl cellulose to corn to increase intestinal viscosity. The adverse effects on BWG were partially offset (Lee et al., 2004a) while the second diet was rye-based to suppress weight gain, but the cinnamaldehyde partially offset the reduced weight gain over the first 2 wk (Lee et al., 2004b). *Eimeria*-infected Cobb birds fed wheat soybean meal with oregano supplementation at 300mg/kg had better BWG and FCR, although they were lower than the group provided a coccidiostat (Giannenas et al., 2003).

In another 6-wk study by Mountzouris et al. (2011), using different inclusion levels of PFA, no significant differences were seen during the starter and grower phases in BW, BWG, FI, or FCR; however, during the finisher phase, BWG increased linearly, FI decreased linearly, and FCR improved linearly with the PFA inclusion level. Cumulatively, the addition of PFA improved BWG, FI, and FCR (Mountzouris et al., 2011). Similarly, another study demonstrated no significant difference in performance parameters until the finisher phase. BWG increased linearly, FI was reduced quadratically, and overall FCR was improved quadratically with increasing PFA inclusion level (Paraskeuas et al., 2017). Soltan et al. (2008) demonstrated varying outcomes, depending on the PFA concentration, emphasizing the importance of composition in a feed additive. Anise seeds were included in a corn-soybean meal diet at 0.5 to 0.75 g/kg fed to Hubbard broilers for 6 wk.

Overall, these treatments improved BWG with no effect on FI or FCR. The highest inclusion rate of anise seed was 1.5 g/kg and reduced growth performance (Soltan et al., 2008). A proper balance of ingredients and concentrations of PFAs can lead to improved performance. The importance of concentration has been documented in several studies. Bolukbasi and Erhan (2007) added thyme to layer diets at 0, 0.1, 0.5, and 1% and observed improved FCR, egg production, and reduced fecal *E. coli* levels in the 0.1 and 0.5% concentrations. Another study evaluated three different levels of *Azadirachta indica* (Indian lilac) dried leaf meal at 0, 1.25, 2.5, and 5.0 g/kg of feed, resulting in better body weight, FCR, and dressing percent in the 2.5 g/kg diet, but no improvement in higher or lower amounts (Ansari et al., 2011). Jamroz et al. (2006) divided broilers into corn-fed or wheat and barley-fed diets, with or without carvacrol, cinnamaldehyde, and capsicum oleoresin plant extracts to investigate the effect of diet composition on the efficacy of PFAs. The diet's significant effect was observed by shorter jejunal villi height and shallower crypt depth in broilers fed corn and PFAs, while no difference was observed in the wheat and barley diet supplemented with PFAs. Both corn and wheat/barley diets that had PFAs had improved FCR. The range of efficacy varies depending on the type of plant used, type of basal diet, chicken breed, and age. Phytogenic feed additives may improve digestibility by increasing enzyme action and mucus production in the gut. Broilers had greater trypsin, lipase, and amylase activity (Lee et al., 2003; Jamroz et al., 2005).

Older broiler chickens began receiving PFAs at 41 d of age and exhibited a 38 to 46% increase in lipase activity (Jamroz et al., 2005). Another study reported increased thickness in the jejunum and stomach and increased mucus production, signifying a protective effect against pathogen colonization (Jamroz et al., 2006). The effects on gut microflora indicate PFAs have antimicrobial properties. Many phytogenic mixtures have shown antimicrobial activity against foodborne pathogens, including *Salmonella typhimurium, S. enteritidis, E. coli* 0157: H7, *Shigella dysenteria, Listeria monocytogenes, Bacillus cereus, Pseudomonas aeruginosa*, and *Staphylococcus aureus* (Lambert et al., 2001; Burt, 2004; Chorianopoulos et al., 2004; Penalver et al., 2005; Si et al., 2006).

Speculation as to the mechanism of these actions is credited toward PFAs phenolic structures (Burt, 2004; Penalver et al., 2005; Si et al., 2006). Phenolics can create disturbances in bacterial cytoplasmic membranes, disrupt the proton motive force, electron flow, active transport, and coagulate cell contents (Lambert et al., 2001; Burt, 2004). These studies above indicate that PFAs may be able to control the growth of pathogens in the gut; however, subsequent studies involving birds result in various outcomes. One commercial blend of essential oils could lower *E. coli* levels and increase beneficial *Lactobacillus* levels (Jamroz et al., 2005). Another study using a mixture of 5 herbs had no significant effect on cecal or excreta microbial populations (Cross et al., 2007). Mountzouris et al. (2011) demonstrated no difference in microbial populations by d 14 or d 28, but variations by d 42 when linear increases in cecal aerobes, *Clostridium, Lactobacillus, Bifidobacterium,* and Gram +ve cocci were observed in direct relation to PFA inclusion levels.

Phytogenics and Innate Immunity

The innate immune system acts as the first line of defense against disease. A critical barrier to pathogens in the gut is mucus production by goblet cells in the epithelial layer. Mucus coats the epithelial cells lining the length of the gut, protecting them from pathogenic colonization (Mountzouris, 2016). Mucins are glycoproteins that can be produced, stored, and secreted by goblet cells. A study by Tsirtsikos et al. (2012) isolated mucin from d 14 broilers fed a control diet, AGP (avilamycin) diet, or PFA treatments at increasing levels of 80, 125, and 150 mg/kg diet. In the mucin, increased mannose in the ileum and increased galactose in the duodenum of birds fed PFA compared to the negative control.

Mannose and galactose are oligosaccharides that have been associated with increased response to enteric disease (Mountzouris, 2016). A separate trial used a different mixture of PFA and found a trend for increased ileal MUC2 gene expression in PFA-treated birds at d 42. Those birds also exhibited a trend towards lower spleen iNOS levels, indicating an anti-inflammatory effect on the innate immune system (Paraskeuas et al., 2016). The same study substituted corn for wheat, and contrastingly, there were no observed differences in ileal MUC2 or spleen iNOS between treatments (Paraskeuas et al., 2016).

Phytogenics and Adaptive Immunity

The immune system strives to maintain homeostasis between immunostimulation and immunosuppression (Applegate et al., 2010). In human literature, phytogenics have been shown to have immunostimulatory activity, as is the case with ginseng stimulating lymphocyte activity and increased cytokine production of IL-1, IL-6, IL-12, IL-6, TNF-α, and interferon-γ (Tan and Vanitha, 2004). Anti-inflammatory properties of *Ginko biloba* have been noted in human studies, demonstrating how its flavonoids and terpenes mediate the production of proinflammatory cytokines (Li, 2000). The study by Paraskeuas et al. (2016) increased ileal IgA levels and a trend towards a decrease in spleen IL-18 of d 42 broilers fed a PFA mixture. The same study using wheat instead of corn observed no differences in ileal IgA or spleen IL-18.

Essential Oils

Essential oil is classified as the plant essence or benzene or terpene derivatives obtained through water and/or steam distillation (El-Tarabily et al., 2021; Abd El-Hack et al., 2022a,b,c). Essential oils are valuable due to their antimicrobial, antiviral, antioxidant and antiparasitic capabilities. Many plant sources of essential oils have been studied for feed additive efficacy. Tecnaroma Herbal Mix PL essential oil blend, containing herbs such as thyme, basil, and oregano, was supplemented in 100-g increments from 100 to 500 in broiler chickens in a study by Khattak et al. (2014). The addition of essential oil positively impacted avian performance and carcass characteristics (Khattak et al., 2014). Essential oils can reduce the levels of pathogens such as gram-negative *E. coli* and *Salmonella* bacteria in the gut.

To test the antioxidant capabilities of specific phytogenic products, the oxygen radical absorbance capacity is determined. In a study by Hoffman-Pennesi and Wu (2010), thyme oil was found to be a better antioxidant than cinnamon bark oil and caeffic acid was found to have the highest antioxidant capability. However, the feed conversion efficiency of broilers was not affected by the supplementation of thymol and thyme oil (Hoffman-Pennesi and Wu, 2010). With phenolic OH groups, certain PFAs have antioxidant qualities which promote a reduction in hydroxyl peroxide formation (Gheisar et al., 2015). The area of PFAs is still relatively new and debated. There have been many conflicting results from different studies. The quality and quantity of the herbs is an important component that can affect study outcomes/findings. The quality can be affected by plant age, when it was harvested, how it was extracted, and what other ingredients are combined to produce the additive (Hashemi and Davoodi, 2010).

Mode of Action

In broiler production, essential oils demonstrate the potential for curative treatment in various situations. Essential oils improve poultry production by increasing the activity of digestive enzymes, lowering the number of fermentation products, lowering the number of pathogens, improving nutrient digestion, enhancing intestinal accessibility of important nutrients, and enhancing antioxidant capacity and immune function (Brenes and Roura, 2010; Alagawany et al., 2021b; Abd El-Hack et al., 2022a).

The authors' research focused on applying the aforementioned essential oil, compounds, and other newly screened compounds to control pathogens in organic poultry. The feed conversion ratio measures how well feed mass is converted to body mass over a set period. Cinnamon powder, which includes cinnamaldehyde, has been demonstrated to help broilers enhance their FCR (Hernandez et al., 2004). These molecules have shown not only antibacterial effect against *Salmonella* and *Campylobacter*, but also on several other economically important and hazardous infectious agents such as *Clostridium jejuni, E. coli* O157: H7 and *Listeria monocytogenes* on several nonpoultry food matrices (Baskaran et al., 2013; Upadhyay et al., 2013; Mooyottu et al., 2014). Since these compounds are safe for animals and humans and are environment-friendly, we explore their potential in organic poultry production for pre-harvest and post-harvest applications. A part from salmonellosis and campylobacteriosis, the organic industry faces challenges with coccidiosis, clostridia infections, internal and external parasites, and high mortality from diseases for which the potential of essential oils and their compounds must be explored. Moreover, economic considerations for including these compounds in organic poultry feeds must be determined (Darre et al., 2014; Bortoluzzi et al., 2019).

Organic Acids

Organic acids are organic substances that have an acidic pH. Carboxylic acids such as lactic acid, propionic acid, acetic acid, formic acid, sorbic acid, citric acid, oxalic acid, uric acid, and butyric acid are the most prominent types (Dibner and Buttin, 2002). Organic acids are not antibiotics, but when used in conjunction with excellent nutrition, management, and biosecurity procedures, they can help poultry maintain intestinal health, improving livability, feed conversion ratios, weight gain, live weight, and immunological responses (Adil et al., 2011).

Organic Acids' Effects on Broiler Performance and Intestinal Health

Organic acids' antibacterial activity is linked to pH decrease and their tendency to dissociate, making them reluctant proton donors in aqueous solution, producing weak acids. A weak acid's dissociation is pH-dependent; therefore, the antibacterial activity improves with a lower pH value (Hajati, 2018; Jadhao et al., 2019). Organic acids are lipid-soluble in their undissociated form, easily transferring them into microbial cells via passive and carrier-mediated pathways.

In the alkaline condition, the organic acid releases the proton H^+, lowering intracellular pH that changes microbial metabolism by blocking the function of crucial microbial enzymes, forcing the bacterial cell to expend energy to export surplus protons H+, resulting in starving death. In bacteria, acid-sensitive proteins and DNA can be denatured by protons H^+ (Khan and Iqbal, 2016). Lactic acid bacteria may grow at a lower pH than other bacteria like *E. coli* and *Salmonella*, making them more resistant to organic acids. Gram-positive bacteria (such as Lactobacilli) have a high intracellular potassium content protecting them against acid anions (Russell and Diez-Gonzalez, 1998; Araujo et al., 2019).

Organic acids suppress pathogenic intestinal bacteria due to their antimicrobial activity, resulting in less bacterial competition for available nutrients, lower levels of harmful bacterial metabolites, improved protein and energy digestibility, and improved avian performance (Baurhoo et al., 2007). Supplementation of organic acids affects the histological structure of the gastrointestinal tract resulting in increased villus length, improving the absorptive ability of the intestinal mucosa; consequently, better nutrient absorption, maximizing nutrient utilization and improving growth performance were obtained. Lowered pH values in the gut encourage the growth of beneficial bacteria and suppress the growth of harmful bacteria, which thrive at a higher pH. Also, these acid anions join with calcium, phosphorus, magnesium, and zinc, thus enhancing their digestibility. Pepsin activity is increased because of the lower gastric pH. The peptides produced by pepsin proteolysis stimulate the release of hormones such as gastrin and cholecystokinin, which regulate protein digestion and absorption (Lan et al., 2005; Araujo et al., 2019). Acidomix FG, a microgranulated feed acidifier based on formic acid, lactic acid, fumaric acid, and ammonium format, is an example of commercially available organic acids and is considered as an unprotected organic acid mixture which is active in the foregut as it is neutralized by bile. Avimatrix consists of 3.0% calcium format and 49.0% benzoic acid. It is considered a protected organic acid mixture active in the midgut as it dissociates in the alkaline pH within the jejunum.

Activate WD is an unprotected organic acid that contains methionine hydroxyl analogue (HMTBa), formic acid, and propionic acid. It works as a water sanitizer and affects the upper intestine by reducing stomach pH, boosting pepsin activity, and improving protein digestion. Low pH promotes the growth of acid-tolerant beneficial bacteria and inhibits the growth of acid-labile harmful pathogens.

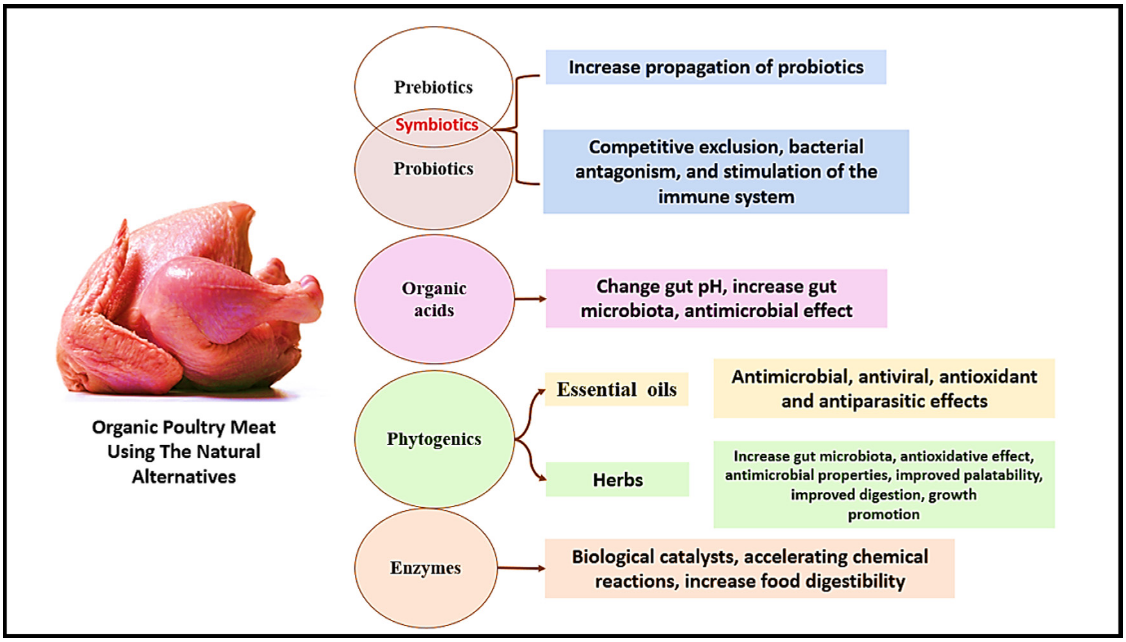

Figure 7. Types of the natural alternatives for antibiotics and their mode of action.

Application of Organic Acids in Poultry Production

Both prophylactic and therapeutic antibiotics have been used in the poultry industry to treat gastrointestinal diseases. Because of the difficulties associated with antibiotics in food animal production, efforts have been made to employ the commensal intestinal microbiota to manage pathogenic microorganisms. This includes stabilizing the microbiota at required levels or modifying those using natural alternatives (Lan et al., 2005).

Prebiotics, enzymes, acidifiers, herbs, essential oils, and immunomodulators (Figure 7). Organic acids have long been used to combat bacterial and fungal pollution in poultry feeds. Citric, propionic, fumaric, lactic, formic, and benzoic acids are the most prevalent organic acids in animal nutrition. They efficiently reduce pathogenic bacterial infections caused by *Salmonella, Campylobacter, Clostridium perfringens*, and others (Banupriya et al., 2016). Therefore, organic acids can alternate AGPs in chickens (Chaveerach et al., 2001; Montonya et al., 2011; Abdelrazek et al., 2016).

Herbal Alternatives

Herbal extracts and spices play a significant role in improving both productivity and health condition of avian species (El-Saadony et al., 2021g). Positive impacts of plant extracts or active substances in bird feed may involve the stimulation of appetite and increase feed intake, enhance the endogenous digestive enzyme production, stimulate immunity and have antiviral, antibacterial, anthelminthic and antioxidant activities. Isoprene derivatives, flavonoids, glucosinolates and other herbal metabolites may affect the physiological and chemical function of the birds gut. The stabilizing impact on the intestinal microbiome may be accompanied by intermediate nutrient metabolism (El-Saadony et al., 2021h; Reda et al., 2021b; Saad et al., 2021a,b,c).

Many different pathogens threaten poultry and animal production resulting in severe economic losses (Attia et al., 2021, 2021a; Hegazy et al., 2021; Salem et al., 2021a, 2022; Soliman et al., 2021). Due to the limitation on using some antibiotics, dangerous residual effects, and cost-effectiveness, the use of herbal feed additives is gaining traction in poultry production. Herbs, spices, and their extracts (botanicals) can be used for various purposes (Suganya et al., 2016; Abou-Kassem et al., 2021b). They have antibacterial, coccidiostats, anthelmintic properties, and promote feed intake, stimulate the immune response, and act as antioxidants. Nutmeg, Cinnamon, Cloves, Cardamom, Coriander, Cumin, Anise, Celery, Parsley, Fenugreek, Capsicum, Pepper, Horseradish, Mustard, Ginger, Garlic, Onion, Rosemary, Thyme, Mint, Shatavari, Jivanti, Shatavari, and turmeric are the most common herbal feed additives used in poultry feed (Muanda et al., 2011; Suganya et al., 2016).

Modes of Action

Herbs or botanicals have a great impact on poultry production. They improve bird feed intake, increase feed digestibility, and have antibacterial, antiviral, anthelmintic, coccidiostats, anti-inflammatory, antioxidant, etc., immunostimulant effects (El Tazi et al., 2014). Some herbs have Pro-oxidative action as Cardamom, Sage, Verbena, Coriander, Estragon, and Eucalyptus. While, Clove, Cinnamon, Laurel, Almond bitter, Rosemary Thyme, Peppermint, Pepper, Nutmeg, and Mint are considered effective antioxidative agents (Suganya et al., 2016).

Herbs or Botanicals as a Potent Immunostimulant

Some herbs feed additives are rich in vitamin C and carotenoids, which plays a severe role in bird immune response, and they stimulate the activity of lymphocytes, macrophages, interferons, and natural killer cells (**NK**) (Frankic et al., 2009; Suganya et al., 2016)

Enzymes

Purpose and History of Enzymes Enzymes are biological catalysts that can speed up chemical reactions. Enzymes are protein molecules with significant consequences for their stability during the production of high-temperature feeds (pelleting) and transit through the alimentary tract (Ravindran, 2013). All animals use enzymes to digest feed. Supplementing the feed with particular enzymes improves the nutritional value of feed ingredients, increasing digestion efficiency (Llamas-Moya et al., 2019). Ultimately, feed enzymes are used to improve feed efficiency, reduce feed cost, and create a better environment by reducing the volume of manure produced and phosphorus and nitrogen content excreted (Barletta, 2010).

Enzymes can be categorized into several classes. They can be categorized by the substrate they act upon and their origin. The enzymes classified by the substrates they act upon are phytases, phytate degrading enzymes; proteases, fiber, and starch degrading enzymes; and proteases, which consist of protein degrading enzymes. The second area of categorization of enzymes is the origin from which the enzymes are derived, including exogenous and endogenous sources. Research regarding enzymes in poultry diets has been ongoing since the 1920s. The first report of an enzyme product used in poultry diets was known as Protozyme, which derived from the fungus *Aspergillus oryzae* (Ravindran, 2013). Adding an enzyme cocktail containing xylanase and ß-glucanase to a un pelleted poultry diet containing rye and wheat at various inclusion levels resulted in a significant increase in body weight gain and feed intake (Pettersson and Aman, 1989).

Exogenous Enzymes The addition of exogenous enzymes has become the standard to improving digestibility and efficiency of nutrient utilization (Ravindran, 2013). According to Pariza and Cook (2010), to digest food, all animals need enzymes, which are either created by the animal or by bacteria in the digestive tract. The digestive system, on the other hand, isn't perfect. Therefore, supplementing the animal feed with appropriate enzymes improves digestive efficiency (Munir and Maqsood, 2013).

Enzyme supplementation helps to reduce the amount of nutrient excretion, which, if ignored, can result in extra cost to the farmer, feed supplier, and the environment (Sheppy, 2010; Ali and Abdelaziz, 2018). Exogenous enzymes are essential to the reduction of feed cost. Because feed accounts for most production costs, enzymes can reduce costs by poorly absorbing other nutrients. When the price of corn, wheat, fat, and inorganic P increases, the use of enzymes in feed becomes more economically attractive, providing a more significant return on investment (Barletta, 2010). Phytase is an enzyme that hydrolyzes phytate to inositol and inorganic phosphate (Bilal et al., 2015). On a more in-depth level, phytase is known as Myo-inositol hexakisphosphate phosphohydrolase. Poultry needs to have dietary phosphorus (**P**) for maintenance and growth. Therefore, an adequate amount must be included in the diet. Even with enough total P in the diet, a portion of the total P comes from cereal grains and this P exists in a form that poultry cannot digest.

The majority of P, about 60%, is not accessible to non-ruminants because it is associated with phytate. Phytate binds to many dietary cations as Cu, Zn, Ca, Fe, Mg, Mn protein, fat, and vitamins, resulting in serious reductions in nutrient availability (Bohn et al., 2008). In the current market, trends have shown that hydrolytic enzymes have emerged as feed supplements to improve the digestion and absorption of poorly available nutrients, such as dietary phytate (Barletta, 2010). Based on Iqbal et al. (1994), non-ruminant animals can only digest phytate due to the lack of significant endogenous phytase activity and low microbial population in the upper portion of the digestive tract.

The main sites of phytate degradation by phytases are the forestomach (crop, proventriculus, gizzard) in poultry, where there is little degradation in the distal gastrointestinal tract (Selle et al., 2010). Phytases can be divided into two classes, depending on the carbon site of hydrolysis of phytic acid. The 3-phytase begins hydrolysis at the three positions of the myo-inositol ring, while the 6-phytase begins hydrolysis at position 6 of the ring (Dersjant-Li et al., 2015). Furthermore, phytases have different origins of expression, pH optima and temperature optima. The most common origins of phytase used in poultry feeds include *Aspergillus niger, Escherichia coli,* and *Buttiauxella* spp. Optimal pH and temperature range are essential factors affecting the feed's phytase activity. Naves et al. (2012) examined three commercials microbial phytase products, and results show that *A. oryzae* exhibited optimal activity at pH 4.0 and temperature 40°C. The second expression, *A. niger* exhibited maximal activity at pH 5.0 and 45°C. Lastly, *S. cerevisae* presented its highest activity at pH 4.5 and temperature between 50 and 60°C. The researchers ultimately advised *A. niger* and *S. cerevisae* exhibited the highest in-vitro activities that correspond with the optimal physiological conditions of broiler chickens.

This finding would allow a higher rate of hydrolysis of phytate. Phytase is expressed as phytase units (**FTU**). Ballam et al. (1984) and Edwards and Veltmann (1983) reported that broiler chickens fed a corn-soybean meal (**SBM**) based diet had phytate-P utilization between 10 and 53% − adding exogenous phytase increased the P availability to 65%.

However, there have often been studies where the addition of phytase to diets has been inconsistent. The inconsistency in the relationship between microbial phytase and P digestibility can be linked to dietary phytate level, feed composition, or the Ca:P ratio in broilers of all ages. High levels of Ca in poultry diets (Scheideler and Sell, 1987) decrease the availability of P absorbed. Calcium can form insoluble complexes with phytate-P, ultimately obstructing the phytase activity (Angel et al., 2002).

Calcium-phytate complexes are mainly formed in the small intestine, where it adversely influences the efficacy of mucosal phytase. While these studies (Scheideler and Sell, 1987) reported Ca negatively impacted P digestibility, the influence of Ca on phytase tends to be positive. In essence, the use of exogenous phytase in non-ruminant animals' diets such as poultry is important because phytase can cleave the phosphate groups from phytate, complex cations, and proteins, which increases availability (Kies et al., 2006). Nelson et al. (1968) were the first to show that a phytase could hydrolyze phytate-P in diets. The use of phytase significantly increased after it was included in several publications after Nelson et al. (1968) and Rojas and Scott (1969) reported their results.

Since the Nelson et al. (1968) publication, phytase has been relied upon heavily to increase P availability and performance while reducing P excretion. To achieve success in poultry production, there must be a reduction of cost and waste output while increasing animal performance. Phosphorus excretion plays a vital role in poultry production because environmental pollution and waste of nutrients raise production costs (Martins et al., 2013). Still, it also reduces feed cost because P is one of the most important expensive nutrients in poultry diets. Assuena et al. (2009) reported that the highest phytase inclusion level resulted in the lowest P excreted. It was also stated that any phytase inclusion level over 250 FTU compromised live broiler performance. The results presented contradict other studies (Lan et al., 2002).

In the previously mentioned literature, phytase nutritional matrix results were not considered in the formulation of experimental diets, which Assuena et al. (2009) attribute the difference in results. Because of phytase, researchers and nutritionists have made phosphorus available to nonruminants in a once unavailable way. Carbohydrases are fiber and starch degrading enzymes. In poultry, carbohydrates are known as non-starch polysaccharides (**NSP**) degrading enzymes because they degrade the NSP in feed ingredients. Because of the degradation, xylanase and β-glucanase are common carbohydrates supplemented to the diet to improve performance and digestibility. Xylanase is an enzyme that originates from the hemicellulosic polysaccharide, xylan. Xylan, a polysaccharide, comprises units of D-xylose, a pentose sugar. Xylans make up 30 to 35% of the cell wall material of annual plants; therefore, it is considered an integral part of animal feed. Xylanase has been used as a feed additive for over 20 yr in poultry diets, primarily to improve feed conversion ratio and weight gain (Bedford and Partridge, 2001).

According to a study done by Conte et al. (2003), xylanase inclusion improved broilers' feed conversion ratio, but there was no influence on other performance parameters measured. Soluble NSPs cause highly viscous digesta and poor litter quality (Ward, 1996). The jejunal and ileal digesta viscosity could be affected by age and adaptation to the experimental diets (Petersen et al., 1999). Arabinoxylans and β-glucans are the essential antinutritive NSP in cereal grains. While arabinoxylans are more prevalent in wheat and rye diets and β-glucans in barley, β-glucans are more susceptible to bacterial degradation through the intestinal tract (Knudsen, 2014; Gonzalez-Ortiz et al., 2017). Because of the issues related to NSPs, xylanase supplementation has been added to diets to decrease litter issues, such as wet litter, and increase nutrient uptake.

Wu and Ravindran (2004) completed a study and reported that supplemented xylanase significantly lowered feed efficiency in whole wheat and ground wheat-based diets. Also, feed intake was significantly reduced ($P < 0.001$) in whole wheat-based diets with supplemented xylanase compared to the control and ground wheat-based diets with supplemented xylanase. Cowieson et al. (2010) reported an improvement in DE content (3.2%) when broiler corn-SBM-based diets were supplemented with xylanase. Additionally, Aftab (2012) reported a ME improvement, from 2.2 to 5.3%, in broiler corn-SBM diets supplemented with xylanase. While this study by Cowieson et al. (2010) showed a positive effect of xylanase, this enzyme does not always prove to have a positive effect on digestibility, growth, or performance. Ideally, xylanase is used to break down NSPs and reduce the viscosity of digesta to improve pre-cecal nutrient digestibility (Bedford, 2000).

However, nutrient digestibility improvement does not always explain the effects of enzyme supplementation on performance. β-glucanase is another common carbohydrase supplement in poultry diets. High levels of β-glucans have been reported to reduce the nutritional value of barley in non-ruminants by increasing the viscosity of the intestinal fluid (Burnett, 1966; Adeola and Cowieson, 2011).

White et al. (1983) states that the increase in viscosity likely interferes with the digestive process by blocking the enzyme-substrate association. Increased viscosity also reduces the rate at which the released nutrients approach the mucosal surface for absorption. When poultry diets are supplemented with β-glucanase, the nutritional value of barley can increase significantly. Campbell et al. (1989) fed broiler chickens barley-based diets with or without supplemented β-glucanase and the results show that chickens fed the diet with supplemented β-glucanase were 35% heavier and 15% more efficient in feed utilization.

When xylanase and glucanase are combined in poultry diets, it has also been reported to improve digestibility and performance. Mathlouthi (2002) conducted a study to determine if supplementation of xylanase and glucanase improved conjugated bile acid fraction in intestinal contents in broilers fed corn or rye-based diet. Adding these exogenous enzymes to the rye-based diet improved weight gain, feed intake, feed efficiency, and decreased water intake. The digestibility of nutrients and AME were also significantly increased.

CONCLUSIONS

The natural antibiotics growth promoter alternatives are recommended to use on a large scale as safe and healthy alternatives that have a positive immune-modulating effect, enhance productivity, enhance digestion, improve nutrients availability, increase absorbability, improve intestinal health, reduce the incidence of antibiotic resistance, and help obtain nutritious, useful, and safe organic chicken meat for human consumption.

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DISCLOSURES

The authors declare no conflict of interest.

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