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Insights on the use of butyric acid, and nucleotides as feed additives in poultry: A review

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ABSTRACT

Despite rising demand for chicken, laws and public uproar forced the industry to find alternatives to maintain flock health by outlawing antibiotic growth boosters. Incorporating a program that naturally improves or modifies the bird's immune response is one strategy. A tailored dietary supplement and/or feed additive can be used to modify immune function and achieve immunomodulation of the immune system. The best alternatives to antibiotic growth promoters (AGPs) may be the use of probiotics and organic acids. Probiotics provide advantages such as altering the host's metabolism, stimulating the immune system, excluding pathogens, enhancing nutrient absorption, and ultimately lowering the danger to human health. Nucleotide supplementation in the feed may enhance gut shape, digestive enzyme activity, and growth performance in broilers. In the current review, we threw light on the use of butyric acid as ecofriendly animal feed additives.

Introduction

Despite increasing demand for poultry, regulations and public outcry resulted in the ban of antibiotic growth promoters, pressuring the industry to find alternatives to manage flock health. One approach is to incorporate a program that naturally enhances/modulates the bird's immune response. Immunomodulation of the immune system can be achieved using a targeted dietary supplementation and/or feed additive to alter immune function. Science-based modulation of the immune system targets ways to reduce inflammation, boost a weakened response, manage gut health, and provide an alternative approach to prevent disease and control foodborne pathogens when conventional methods are not efficacious or not available. The role of immunomodulation is just one aspect of an integrated, coordinated approach to produce healthy birds that are also safe and wholesome products for consumers. Some examples of phytogenic feed additives (PFAs) that include essential oils, oleoresins, flavonoids, and bioactive molecules such as carvacrol, thymol, capsaicin, and cineole could be used for immunomodulatory purposes (Swaggerty *et al*., 2019).

The usage of probiotic and organic acids could offer the best alternatives for antibiotic growth promoters (AGPs). Probiotic has benefits of modification of host metabolism, immunostimulant, exclusion inhibition of pathogens, enhance nutrients absorption and finally resulting in decreasing the human health risk. Probiotic and prebiotic could improve the poultry production as they can produce short chain fatty acids inside the gastrointestinal tract (GIT), so revealing an additional mechanism of action. Organic acids, vitamins, minerals, herbs could be more beneficial than AGPs to decrease the load of pathogens and to combat the heat stress. Betaine, carnitine, ractopamine and nucleotides could be used for a better meat quality production (Kuldeep *et al*., 2014).

A frequently used oligosaccharide, mannooligosaccharide (MOS), has been shown to inhibit pathogens such as *E. coli*, *Salmonella*, and coccidiosis while fructooligosaccharides (FOS) has been shown to improve chicken performance, induce beneficial bacteria, increase villus height and aid digestion. MOS or FOS supplementation did changes in the caecal microbiota (Stanley *et al*., 2014).

In consequence of the withdrawal of antimicrobial growth promoters, once-controlled enteric diseases have returned and new multifactorial diseases causing gut disorders of unknown origin have emerged in broilers. One of these widespread syndromes causing intestinal health problems in broilers is in the field referred to as ''dysbacteriosis'. An increase in the macroscopic dysbacteriosis score coincided with increased villus atrophy, a decrease in the thickness of the tunica muscularis and an increase in T-lymphocyte infiltration in the gut mucosa. Also more and larger goblet cells were observed in the animals with high macroscopic dysbacteriosis scores. Although the exact etiology remains to be identified, dysbacteriosis in broiler chickens thus coincides with an inflammatory reaction in the gut mucosa. Some characteristic changes, which aid in confirming dysbacteriosis, are malabsorption syndrome (MAS) and runting-stunting syndrome (RSS) (Teirlynck *et al*., 2011). This review threw light on some alternatives to the use of antimicrobials as animal feed additives.

Butyric acid

Feeding a microencapsulated sorbic acid blend proved effective at reducing the load of *Salmonella* Enteritidis by two log_{10} in market-age broilers following experimental challenge. A different encapsulated product comprised of a blend of organic acids and botanicals similarly reduced the load of *Campylobacter jejuni* in slaughter-age broilers (Swaggerty *et al*., 2019).

Butyrate glycerides, 3,000-ppm butyrate, can modulate the immune response and energy expenditure of animals and enhance intestinal health. The dietary treatment did not affect the alpha diversity of intestinal microbiota but altered its composition. *Bifidobacterium* was affected by the dietary treatment significantly, showing an increase in not only the abundance but also the species diversity. The nuclear magnetic resonance (NMR)-based analysis revealed an increase in serum concentrations of alanine, low-density and very low-density lipoproteins, and lipids in case of butyrate glycerides supplementation. More interestingly, it boosted serum concentrations of bacterial metabolites, including choline, glycerol-phosphoryl-choline, dimethylamine, trimethylamine, trimethylamine-N-oxide, lactate, and succinate. It can modulate the intestinal microbiota and serum metabolites and potential contribution of intestinal bacteria to lipid metabolism/energy homeostasis in broilers (Yang *et al*., 2018).

Organic acids are used in poultry to lower the pH of intestinal tract, which favors good microbes, which in turn suppress pathogenic microbes thus evicting the use of antibiotics. They are used in poultry diets and drinking water to elicit a positive growth response, improving nutrient digestibility, performance and immunity in poultry. Organic acids have pronounced antimicrobial activity, depending on both the concentration of the acid and the bacterial species that is exposed to the acid. The beneficial effects of organic acids are seen as significantly increased the villus width, height and area of the duodenum, jejunum and ileum of broilers thus boosting the performance of broilers. They also improved nutrient digestibility by reducing microbial competition with the host for nutrients and endogenous nitrogen losses. They lower the incidence of subclinical infections by secretion of immune mediators, reducing production of ammonia and other growth-depressing microbial metabolites. They have proved to be a promising alternative to growth promoting antibiotics, as their supplementation does not lead to antibiotic resistance besides protecting environment as well by less fecal nitrogen losses (Haq *et al*., 2018).

In poultry production, short chain fatty acids (formic acid, acetic acid, butyric acid) are preferred acidifiers. Among which, butyric acid is considered as the prime enterocyte energy source, necessary for development of Gut Associated Lymphoid Tissue (GALT) and has the highest bactericidal efficacy against the acid-intolerant species such as *Escherichia coli* and *Salmonella* sp. with selective stimulation of beneficial gut bacteria (Deepa *et al*., 2018).

Gamma amino butyric acid supplementation during heat stress significantly reduced the birds' increased body temperature and increased their body weight gain). This effect was associated with increases in the heat stress-induced reductions in jejunal villus length, crypt depth and mucous membrane thickness, and decreases in the vascular changes occurred due to heat stress. Additionally, it significantly modulated heat stress-induced changes in glucose facilitated transporter 2 (GLUT2), peptide transporter 1 (PEPT1) and heat shock protein 70 (HSP70) mRNA expression in the jejunal mucosa. It significantly elevated the triiodothyronine (T3) hormone level and hemoglobin levels and decreased the heterophil lymphocyte ratio (H/L ratio). Furthermore, it induced higher hepatic glutathione peroxidase enzyme activities and decreased the malondialdehyde dehydrogenase content (Al Wakeel *et al*., 2017).

Body weight gain increased by the feeding of diets containing different levels of butyric acid, but feed intake, feed conversion ratio (FCR) and mortality did not differ significantly. A significant reduction was observed in coliforms and *Lactobacillus* counts in cecal contents and excreta whereas, total plate counts (TPC) at 42 d were significantly reduced in butyrate supplemented groups as compared to others. Therefore, butyric acid could be a good alternative to AGP for growth performance and improving gut microbial status in broiler chickens (Raza *et al*., 2017).

Organic acid supplementation had a beneficial effect on the performance of broiler and layer chicken. Some organic acids are more effective against acid intolerant species such as *E. coli*, *Salmonella* and *Campylobacter*. They significantly increased the villus width, height and area of the duodenum, jejunum and ileum of broilers. They improved nutrient digestibility by reducing microbial competition with the host for nutrients and endogenous nitrogen losses, by lowering the incidence of subclinical infections and secretion of immune mediators, and by reducing production of ammonia and other growth-depressing microbial metabolites. Short-chain fatty acids, medium-chain fatty acids and other organic acids have more or less pronounced antimicrobial activity, depending on both the concentration of the acid and the bacterial species that is exposed to the acid. Lack of consistency in demonstrating an organic acid benefit is related to uncontrolled variables such as buffering capacity of dietary ingredients, presence of other antimicrobial compounds, cleanliness of the production environment and heterogeneity of gut microbiota (Khan and Iqbal, 2016).

The distal gut of chickens has an abundance of bacteria from the Firmicutes *Clostridium* clusters IV and XIVa that produce butyric acid, which is one of the metabolites that are sensed by the host as a signal. The host responds by strengthening the epithelial barrier, reducing inflammation, and increasing the production of mucins and antimicrobial peptides. Stimulating the colonization and growth of butyrate-producing bacteria thus may help optimizing gut health (Onrust *et al*., 2015).

The use of protected calcium butyrate improved feed conversion ratio irrespective of the dose. Apparent total tract crude fat digestibility and apparent metabolizable energy corrected for nitrogen (AMEN) were improved. Avilamycin alone or with butyrate improved body weight gain compared to the control treatment. Avilamycin, butyrate or combination of both improved feed conversion ratio compared to the control treatment. Birds from the treatment diet had the thickest mucosa. Avilamycin and butyrate combination improved AMEN content compared to the control treatment. The apparent ileal digestibility of amino acid data showed that Avilamycin alone or in combination with butyrate had higher Aspartate, Glutamate, Cysteine, Glycine, and Alanine ileal digestibility than the control animals. Avilamycin, butyrate or combination of both increased ileal digestibility of Threonine, Serine, and Proline. There is an indication that butyrate, alone or in combination with avilamycin, improve the digestion and absorptive processes and consequently birds performance results (Kaczmarek *et al*., 2015).

The effect of butyric acid injection on jejunum and ileum pH on hatch day was significant. Jejunum villi height increased on the 7th day compared with the control. The increased villus height suggests an increased surface area capable of greater absorption of nutrients. The highest ileum villi were observed following the butyric acid injection. By that, butyric acid injection affects small intestine morphology and increases body weight of chicks (Salahi and Salahi, 2015).

The minimal inhibitory concentrations of lauric acid, thymol, and cinnamaldehyde were determined *in vitro*, and showed good results in inhibiting the growth of *C. perfringens*. *In vivo*, butyric acid, medium chain fatty acids (mainly lauric acid) and essential oils (thymol, cinnamaldehyde and essential oil of eucalyptus eucalyptus), or combinations of these additives, can be used to control necrotic enteritis in broiler chickens. They showed a significant decrease in the number of birds with necrotic lesions was found compared with the infected, untreated control birds (Timbermont *et al*., 2010).

Broiler chicken fed diets supplemented with organic acids had significantly improved body weight gains and feed conversion ratio. The addition of organic acids increased villus height in the small intestines, but the differences were not significant in case of the ileum. Serum calcium and phosphorus concentrations were increased but no effect on the concentration of serum glucose and cholesterol, serum glutamic pyruvic transaminase (SGPT), and serum glutamic oxaloacetate transaminase (SGOT) was observed. Therefore organic acid supplementation, irrespective of type and level of acid used, had a beneficial effect on the performance of broiler chicken (Adil *et al*., 2010).

Both butyrate-based additives showed a significant reduction of *Salmonella* Enteritidis infection in birds. Partially protected butyrate additive was more effective at the late phase of infection. It successfully decreased infection not only in the crop and cecum but also in the liver. There were no differences in the spleen. Sodium butyrate partially protected with vegetable fats offers a unique balance of free and protected active substances effective all along the gastrointestinal tract because it is slowly released during digestion (Fernández-Rubio *et al*., 2009).

Butyrate at 0.4% inclusion in the diet was like antibiotic in maintaining body weight gain and reducing *E. coli* numbers but superior for feed conversion ratio in broilers. A reduction in pH of the upper GI tract (crop, proventiculus and gizzard) was observed by inclusion of butyrate in the diets of broilers compared to either control or antibiotic-fed group. Butyrate at 0.4% was more effective in reducing the pH than 0.2% butyrate. Within the lower GIT, 0.4 and 0.6% butyrate was effective in lowering pH in the duodenum, but no effect was found in either the jejunum or ileum (Panda *et al*., 2009).

Blend of butyrate glycerides showed a higher live weight at slaughtering with a better feed conversion rate. The carcass characteristics were not influenced, but the small intestine wall resulted slightly modified with shorter villi, longer microvilli, and larger crypts depth in jejunum, only with lowest concentration of the supplement (0.2%). Butyric acid glycerides are an efficient supplement to broilers' diets, deserving particular attention as a possible alternative to antimicrobial drugs, which have been banned in Europe (Leeson *et al*., 2005).

Organic acids in drinking water were able to keep the water free from *Campylobacter*, consumption of acidified drinking water had limited effect on the microflora in the chicken intestinal tract, and chicken digestive epithelial cells were not damaged by drinking acidified drinking water. Acidified drinking water could play a crucial role in a biosecurity strategy of preventing *Campylobacter* spread via drinking water in broiler flocks (Chaveerach *et al*., 2004).

Nucleotides

Dietary inclusion of nucleotides increased the body weight gain, reduced feed intake, improved feed conversion ratio (FCR) and performance index significantly in broilers, with best performance during all the periods was noted in case of 0.03 % of nucleotides dietary supplementation so it may be recommended to improve growth performance of broiler chickens (Fonia *et al*., 2018).

Supplementation of the diet with adenosine could improve growth performance, gut morphology, and digestive enzyme activity in broilers' intestinal lumen. Chickens receiving adenosine showed improved lipid profile and lower concentration of uric acid in serum samples. Adenosine increased immunoglobulin A (IgA) production and enhanced immune function in birds. Therefore, supplementing broiler diets with individual purine nucleosides, particularly adenosine, improved various parameters such as growth performance, intestinal morphology, and immune enhancement of broilers. The combination of cytidine plus uridine increased body weight and average daily gain of broilers. Supplementing cytidine plus uridine increased villus height and width along with activities of alkaline phosphatase and aminopeptidase; however, maltase was not affected by the experimental diets. The combination of cytidine and uridine increased the relative weight of the bursa of Fabricius and IgA activity in the jejunum, but there was no significant difference among treatments regarding the relative weight of the spleen. Therefore, combination of cytidine and uridine could improve health status and performance of broilers. Adenosine, Uridine and Cytidine nucleotides combination significantly increased body weight and average daily gain, intestinal villus height and width, activity of brush border enzymes (alkaline phosphatase and aminopeptidase). Adenosine, uridine and cytidine combination or adenosine, guanosine, uridine and cytidine combination significantly increased high-density lipoprotein and uric acid, respectively, while dietary nucleosides did not affect cholesterol and triglyceride concentrations in serum samples. Adenosine, uridine and cytidine combination significantly improved immune indices such as the relative weight of the bursa of fabricius and the concentration of Ig A. Accordingly, combination of adenosine, uridine and cytidine could be useful feed additive for improving economically important traits in broilers (Daneshmand *et al*., 2017).

Decreased serum glucose, serum cholesterol and low density lipoprotein (LDL) cholesterol and increased high density lipoprotein (HDL) cholesterol was noticed in nucleotide supplemented to Japanese quails feed at higher levels. Protein profile showed significant improvement in total protein, albumin and globulin while albumin / globulin ration (A/G ratio) revealed no effect of supplementation. Serum creatinine and SGPT contents showed non-significance whereas, serum uric acid and SGOT contents were significantly reduced in nucleotide supplemented. It is concluded that nucleotide supplementation improves serum biochemical parameters without affecting liver and kidney functions (Prakash *et al*., 2017).

The feed intake, body weight gain, feed conversion ratio of broilers were not affected by nucleotides treatments. Ascites-related mortality, plasma T3 concentrations were significantly decreased in treatment with 1 g/Kg nucleotide in diets. Right ventricle weight was significantly heavier and right ventricle / total ventricle ratios was significantly higher in treatment at no nucleotide diets and decreased in treatment with 1 g/Kg nucleotide in diets. Nucleotide in pulmonary hypertension syndrome broiler chicken had a systemic anti-hypertensive effect and could decrease ascites incidence (Safaei *et al*., 2017).

Dietary nucleotide supplementation to the diets did not affect physical development of the gastrointestinal tract and performance when birds were not exposed to obvious stress conditions. Thus, nucleotides are not considered an essential nutrient for use in poultry feed. However, dietary nucleotide supplementation may be an important factor for birds to maintain maximum performance under certain stress conditions, such as high stocking density combined with dirty litter. There is a relationship between dietary nucleotides and the morphological development of the gastrointestinal tract, as well as growth performance, when birds are exposed to stress conditions (Jung and Batal, 2012).

The meat of the nucleotides group showed significantly higher redness and Hue values, lower shear force values, higher lipid and ash percentages and iron content. Moreover, nucleotides significantly increased monounsaturated acids and linolenic acid and decreased eicosatetraenoic and docosahexaenoic acids. The unsaturation degree was higher in the Nucleotides group and the atherogenic index was positively influenced by the nucleotide supplementation. Nucleotide dietary supplementation improved the physical and nutritional characteristics of the Pectoralis major muscle of broiler chickens (Chiofalo *et al*., 2011).

Diets supplemented with nucleotides did not influence broiler performance or carcass yield at 42 days of age, and were not different from the feeds not containing any additive or with AGP (Pelícia *et al*., 2010)

Nucleotides preparation at 500 mg/kg feed significantly improve the broiler weight by 1% and feed conversion ratio by 1.9% especially at the first 3 weeks. That indicates the greater need of nucleotides at the period of fast cell proliferation. Therefore, it limits the performance during this period. At a level of 1000 mg/kg, feed has no significant effect as the cost of disposal of excess nucleotides may compensate the performance improvement (Esteve-Garcia *et al*., 2007).

The nucleotides significantly increase the lipid content of broiler meat, probably in relation to the physiological effect of nucleotides to stimulate the alfa-lipoprotein synthesis during the neonatal period. No significant differences were observed for the total polyunsaturated fatty acids (PUFA), linoleic, and arachidonic acids, whereas the nucleotides have significantly influenced the linolenic, eicosatetraenoic and docosahexaenoic acids. As regard the quality indices, the nucleotide supplementation influenced the atherogenic index but not the thrombogenic index

(Chiofalo *et al*., 2006).

In comparison to control group, values of total antioxidant status (TAS) and AST decreased significantly in the groups fed T-2 toxin with or without nucleotide supplementation. Dietary nucleotides did not affect MDA formation when added to the diets with mycotoxins. It has the potency to reduce the extent of DNA damage induced by the action of T-2 toxin in immune cells. This underlines their possible beneficial effect on the immune system in mycotoxin intoxication (Frankič *et al*., 2006).

Combinations of AGPs alternatives

The ban of antibiotic growth promoters in many countries necessitates finding an alternative to suppress microbial load particularly the gut. Probiotics, prebiotics or organic acids have been included to replace antibiotics. Of which, prebiotics are costlier affecting economics in poultry production, while probiotics have different degrees of survivability in feed and in the gut environment. Organic acids could be the possible alternative to antibiotics. The *Pediococcus acidilactici* probiotic, mannan-oligosaccharide prebiotic and butyric acid supplements were, to some extent, efficacious at combatting the negative effects of the *S. Typhimurium* challenge on broiler performance and gut health. However, a complete recovery from the challenge effects was observed only when a mixture of the additives was administered, suggesting a synergistic effect between the additives. Dietary supplementation with a combination of probiotic, prebiotic and butyric acid can be considered as a practical and effective strategy for controlling the incidence of *Salmonella* in broiler chickens in a post-antibiotic era. Moreover, birds fed diets supplemented with the three additives or probiotic had greater jejunum villus height and villus height to crypt depth ratio than birds on the challenged treatment (Jazi *et al*., 2018).

Various strategies are available to stimulate butyrate production in the distal gut. These include delivery of prebiotic substrates that are broken down by bacteria into smaller molecules, which are then used by butyrate producers, a concept called cross feeding. Xylo-oligosaccharides (XOS) are compounds as they can be converted to lactate, which is further metabolized to butyrate. Probiotic lactic acid producers can be supplied to support cross-feeding reactions. Direct feeding of butyrate-producing *Clostridium* cluster IV and XIVa strains are a future tool provided that large scale production of strictly anaerobic bacteria can be optimized. Current results of strategies that promote butyrate production in the gut are promising (Onrust *et al*., 2015).

Broilers infected with *C. perfringens* and treated with essential oils or the combination of sodium butyrate and essential oils showed significantly better body weight gain, increased villus length and villus length: crypt depth ratio, and decreased gross pathological and histopathological lesion scores. Sodium butyrate alone and *Bacillus Amyloliquefaciens* (*B. amyloliquefaciens*) probiotic had no beneficial effects on the course of the disease except a significant increase in villus length. Therefore, the protected combination of sodium butyrate and essential oils (synergistic effect), as well as the protected essential oils, can be potential candidates for the prevention and treatment of necrotic enteritis in broiler chickens (Jerzsele *et al*., 2012).

Conclusion

From the cited literatures in the current review, there are several alternatives to the antimicrobials that can be used as friendly feed additives such as prebiotic and butyric acid, probiotics, and nucleotides.

Conflict of interest

The authors declare that they have no conflict of interest.

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