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Revisión de literatura

Organic acids, microbiota, gut health and productive response in broilers chickens

Ácidos orgánicos, microbiota, salud intestinal y respuesta productiva en pollos de engorde

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ABSTRACT

Since the middle of the last century, the use of antibiotic growth promoters in feed has improved the performance of several food-producing animal species. However, bacterial resistance to these drugs threatens public health and has led to their prohibition in animal feed. This has increased enteric problems in broilers and consequently the use of antibiotics for therapeutic purposes. In this context, several alternatives to antibiotic growth promoters have been proposed, among them organic acids, which, according to their physical and chemical properties, modify the composition of the intestinal microbiota, whose metabolites, such as short-chain fatty acids, favor the intestinal morphology, physiology, integrity, and immunity, aspects that contribute to maintain the health of this organ and increase the bioavailability of nutrients and, ultimately, to improve the productive response of birds. This review describes the main characteristics of the organic acids commonly used in the poultry industry, their mechanism of action, and their effects, individually and in combinations of organic acids, on the microbiota. It also analyzes how these changes affect the gut health and productive performance of broilers under different sanitary and environmental conditions. In addition, factors that may interfere with the activity of organic acids are explored.

Keywords: Animal feed; anti-bacterial agents; digestion; dysbiosis; intestinal mucosa; public health (*DeCS*).

RESUMEN

Desde mediados del siglo pasado, el uso de antibióticos promotores de crecimiento en los piensos ha mejorado el rendimiento de varias especies animales productoras de alimentos. Sin embargo, la resistencia bacteriana a estos fármacos amenaza a la salud pública y ha conducido a su prohibición en la alimentación animal. Esto ha incrementado los problemas entéricos en pollos de engorde y, en consecuencia, el uso de antibióticos con fines terapéuticos. En este contexto, se han propuesto varias alternativas a los antibióticos promotores de crecimiento, entre estas, los ácidos orgánicos que, de acuerdo con sus propiedades físicas y químicas, modifican la composición de la microbiota intestinal, cuyos metabolitos, como los ácidos grasos de cadena corta, favorecen la morfología, fisiología, integridad e inmunidad intestinal, aspectos que contribuyen a preservar la salud de este órgano y a incrementar la biodisponibilidad de nutrientes y, en última instancia, a mejorar la respuesta productiva de las aves. Esta revisión describe las principales características de los ácidos orgánicos comúnmente utilizados en la industria avícola, sus mecanismos de acción y sus efectos, individualmente y en

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combinaciones de ácidos orgánicos, sobre la microbiota. También analiza cómo estos cambios afectan la salud intestinal y al rendimiento productivo de pollos de engorde en diferentes condiciones sanitarias y ambientales. Además, se exploran los factores que pueden interferir con la actividad de los ácidos orgánicos.

Palabras clave: Alimentación animal; agentes antibacterianos; digestión; disbiosis; mucosa intestinal; salud pública (*DeCS*).

INTRODUCTION

Current demographic and social conditions have increased the global demand for animal nutrients (1). In this regard, the poultry industry often uses intensive production, which increases the probability of infectious outbreaks in the flock (2). In this sense, the use of antimicrobials in broilers is aimed at controlling enteric diseases (1) and optimizing their performance, reducing subclinical infections and the synthesis of growth-suppressing metabolites, increasing nutrient availability and digestibility, animal performance, and reducing the production costs in the poultry industry. However, the use of antibiotic growth promoters (AGPs) has been associated with bacterial resistance to these drugs, posing a global health challenge (3). On this basis, the European Union vetoed their use in 2006 (4), the Food and Drug Administration (FDA) banned the use of fluoroquinolones in poultry (5), and there is a growing demand for meat products free of antibiotic residues (6).

On the other hand, the suppression of AGPs from broiler diets has increased the incidence of enteric diseases, thus increasing the use of antibiotics for therapeutic purposes (1,5). In light of this, several alternatives have been proposed to replace AGPs, including organic acids (OA), which promote gastrointestinal tract (GIT) health, improve nutrient bioavailability, health, and productive performance of poultry, reducing the environmental impact of poultry farms (7). Therefore, this review will focus on the key characteristics of OAs, their interactions with microbiota and gut health, and how these factors influence broiler production performance.

Review methodology

This review proposes to discuss the most recent data on the effects of OA as an alternative in broiler feed, their effects, and their influence on intestinal health and broiler performance. We have consulted papers recently published in specialized databases such as PubMed, ResearchGate, Scopus, and Google Scholar using the following or their combination terms for searching: “broiler/chickens”, “poultry”, “animal feed”, “organic acid”, “antibiotic growth promoters”, “gastrointestinal tract”, “digestion”, “dysbiosis”, “microbiota”, “intestinal health”, “junction proteins”. The effects of OA on intestinal health and the most recurrent OA have been summarized in a figure and table, respectively.

Organic Acids. Organic acids are composed of organic carboxylic acid and fatty acids with an R-COOH structure. They are grouped into monocarboxylic OAs (formic, acetic, propionic, and butyric acids), carboxylic acids with hydroxyl groups (lactic, malic, tartaric, and citric acids), or short-chain carboxylic acids with double bonds (fumaric and sorbic acids). They are weakly acidic, soluble in water, and partially dissociate in water (8,9). Their efficacy is related to, among other factors, a pKa between 3 and 5, their inclusion rate, the composition and buffering capacity of the diet, the structure and physiology of the target bacterial species, and aspects inherent to the bird such as its age, intestinal pH, the presence and colonization capacity of lactic acid-producing bacteria in the GIT (9,10,11)(Table 1).

Table 1. Description of organic acids commonly used in poultry farming.

Acid	Chemical name	Form	Type of acid	pKa
Formic	Formic Acid	HCOOH	Short Chain	3,75
Acetic	Acetic Acid	CH_3COOH	Short Chain	4,76
Propionic	2-Propanoic Acid	CH3CH2COOH	Short Chain	4,88
Butyric	Butyric acid	$CH_3CH_2CH_2COOH$	Short Chain	4,82
Lactic	2-Hydroxypropanoic acid	$CH_3CH(OH)COOH$	Short Chain	3,83
Fumaric	2-butenodioic acid	COOHCH:CHCOOH	Dicarboxylic acid	3,02
Malic	Hydroxybutanedioic acid	$COOHCH_2CH(OH)COOH$	Dicarboxylic acid	3,40
Tartaric	2,3-dihydroxybutanedioic acid	COOHCH(OH)CH(OH) COOH	Dicarboxylic acid	2,93
Citrus	2-hydroxy-1,2,3-acid propanetricarboxylic acid	$COOHCH_2C(OH)(COO)\ CH_2COOH$	Monocarboxylic	3,13
Sorbic	2,4-hexadienoic acid	$CH_3CH{:}CHCH{:}CHCOOH$	Monocarboxylic	4,76

Taken from (9,11).

Microbiota in broilers. The GIT of broilers is colonized by a complex microbiota, defined as a community of symbiotic and pathogenic commensal microorganisms (12). The colonization of the GIT occurs during hatching and from the first day of life by consuming small portions of the litter, and is an aspect of vital importance for the absorption of nutrients, health, and productivity of the birds, as less development of the intestine, its villi and crypts have been shown in chickens free of germs or with a low bacterial load than in conventionally reared birds (2,12,13).

In broilers, the gut microbiota generally refers to the bacterial population (14). Of the 13 phyla that comprise it, more than 90% of the microorganisms belong to Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria, while the predominant genera are *Clostridium*, *Ruminococcus*, *Lactobacillus*, and *Bacteroides* (15).

Several factors influence the composition of the gut microbiota. For example, its complexity and stability are positively related to the age of the birds; stress and welfare animal, diet, infectious processes, litter management, or antibiotic supply also affect its composition (2,12), which on the other hand varies in each section of the GIT.

The small intestine, where the rapid passage of food and the digestion and absorption of nutrients occurs, is usually colonized by facultative anaerobic and acid-tolerant bacteria, such as *Lactobacillus*, *Enterococcus,* and *Streptococcus* (16). In contrast, cecum, with a slower transit, are colonized by a more diverse and abundant microbiota, mainly obligate anaerobic microorganisms of the genera *Clostridium, Bacteroides,* and *Ruminococcus* (17,18).

The microbiota of the cecum is involved in the fermentation processes of nondigestible carbohydrates and the production of short-chain fatty acids (SCFA) such as acetate, propionate, and butyrate, which are useful as energy and carbon sources for the host (12), and that regulate intestinal blood flow, production, composition, and establishment of the mucin layer, a component of intestinal mucus secreted by goblet cells, with important implications for avian intestinal health by coating the intestine and acting as a protective barrier of the intestinal epithelium against pathogenic microorganisms in the small intestine (16,17,19).

Additionally, the gut microbiota reduces and prevents pathogen colonization by inhibiting the adhesion and colonization of pathogenic microorganisms through competitive exclusion and the production of bacteriostatic and bactericidal agents (12). However, the microbiota also competes with the host for nutrients and is a potential source of pathogenic bacteria and toxic metabolites (20,21). Thus, in the absence of a defined and stable boundary between symbiosis and pathogenicity, the host is susceptible to dysbiosis, defined as altered gut microbiota composition accompanied by inflammation and interference with intestinal functions (21,22). Although there is limited information on the factors that cause dysbiosis, it occurs mainly in farms where greater biosecurity and hygiene measures have been implemented, probably due to a lower degree of maturation of the immune system in young individuals; it also occurs in birds of higher productivity and age, mainly females, in the presence of *E. tenella* and is associated with the use of antimicrobials, that cause an imbalance between commensal and opportunistic pathogenic bacteria (1).

How Organic Acids Work. OA reduces the pH of the feed and, after ingestion, of the GIT (23). Depending on their chain length, they exert a specific effect on gram-positive and gram-negative bacteria, reducing their viability (11,24). Thus, the undissociated form and lipophilic nature of OA favor their entry into the bacterium, whose highest cytoplasmic alkalinity promotes the dissociation of OA, releasing a hydrogen proton (H^+), which reduces the intracellular pH and affects the structure and function of proteins, enzymes, nucleic acids, phospholipids, and bacterial metabolism, which, as a defense mechanism, expels excess protons. This process depletes cellular adenosine triphosphate (ATP). In addition, the bacteriostatic and bactericidal effects of OA are attributed to the ability of their anions to inhibit DNA and protein synthesis (15). Thus, dietary OA affects the gut microbiota composition (11,25).

On the other hand, the decrease in pH in the proximal parts of the GIT associated with OA supplementation, inhibits the growth of acid-sensitive microorganisms such as *Clostridium perfringens*, *Escherichia coli,* or *Salmonella spp*. and *Bacteroidetes*, increasing the population of *Firmicutes* and *Lactobacillus* in the ileum of birds, with increased production of SCFA (9,24,25), which, due to their antimicrobial effects, reduce the population of pathogenic microorganisms and their metabolites inhibiting the infectious and inflammatory processes of the intestinal mucosa and preventing changes in its morphology (16,17,24) by upregulating gene expression of small intestinal junction proteins such as claudins and zonula occludens-1 (ZO-1) and stimulating goblet cell proliferation (24,25,26), increased length and villus length: depth ratio in ileal villi (2,27).

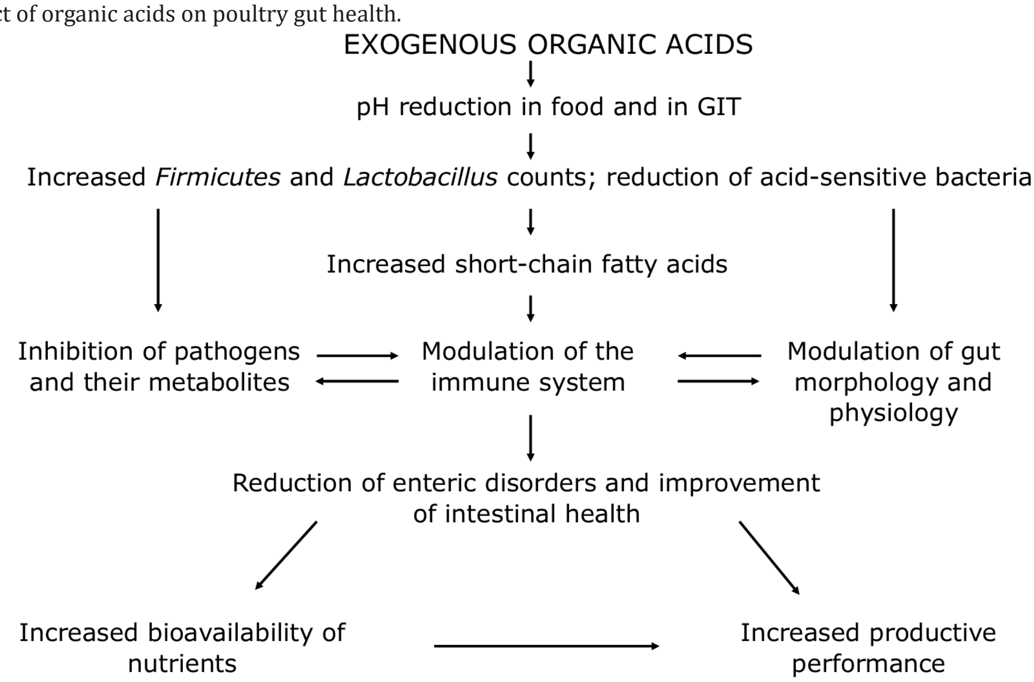
Gut and microbiota composition. The length of the villi and the depth of the crypts of the small intestine are indicators of its capacity to digest and absorb nutrients and of the health of this organ. In contrast, shorter villus length is associated with intestinal disorders and lower nutrient bioavailability, while greater intestinal crypt depth suggests a higher rate of enterocyte cell turnover and, consequently, increased nutrient requirements (7,22,28).

In addition, the microbiota stimulates the development of the intestinal immune system (29,30). Thus, fermentation products of commensal bacteria, such as SCFA, in particular butyrate, promote mucin production (19,27), which due to its antibacterial properties and by acting as a physical barrier, protects the epithelium from pathogenic microorganisms and contributes to the colonization of commensal bacteria, which together with antimicrobial peptides, lysozyme and the intestinal microbiota itself, constitute the first line of immunity of the GIT (19).

SCFA also contribute to the regulation of the immune response by acting on colonocytes and neutrophils and promoting the differentiation of regulatory T cells and their production of interleukin 17 (31,32). In turn, elements of the immune system such as mucin, IgA, and defensin, by regulating the composition of the microbiota (32), determine that this, through its metabolites such as SCFA, favorably affects the components of the intestinal epithelial barrier, preventing inflammatory processes, tissue damage, and permeability of intestinal epithelium against pathogenic microorganisms and antigens (25).

Organic Acids Function in Gut. Supplementation with OA or in combination with essential oils has also been associated with higher digestive enzyme activity (9,26,33), the resulting increase in digestibility would reduce the likelihood of dysbiosis (7). Similarly, a higher concentration of catalase and superoxide dismutase in the duodenum has been reported in birds supplemented with OA than in non-supplemented birds, demonstrating the potential to reduce the deleterious effects of oxidative stress in this part of the GIT (26). Thus, OA and their close relationship with immunity and microbiota influence gut health and the productive response of birds (9,10,11,32). Figure 1 summarizes the effects of OA on the intestinal health of poultry, the underlying mechanisms, and the interactions that affect the productive performance of poultry.

Figure 1. Effect of organic acids on poultry gut health.



Organic acids and productive response in broilers chickens. By decreasing the pH of the feed and the proximal portion of the GIT and altering the composition of the microbiota, OA affects the structure and physiology of the intestinal mucosa, nutrient digestion, absorption, and consequently bird performance (23,34). In this regard, the supply of formic, lactic, propionic, and citric OA or their combinations in the drinking water improves the intestinal villus characteristics, final weight, and feed conversion ratio (FCR) in broilers (35). The inclusion of sodium butyrate in the diet also favored the intestinal morphology, lymphoid organs, and humoral immune response, affecting their productive performance.

Similarly, the inclusion of formic acid and potassium diformate in the diets of broilers decreased the pH of the proventriculus, ventriculus, and small intestine, which was associated with improvements in intestinal mucosal microarchitecture, inhibition of growth and colonization of total *Clostridia spp*., and *Salmonella spp*. cecal, and increased spleen lymphocytes, crude protein digestibility, and immune response of these birds (24). Supplementation with OAs also improved intestinal health, digestibility, and immune status of broilers challenged with Coccidia, *E. coli,* or induced subclinical necrotic enteritis, reduced FCR, and improved their production parameters compared to birds challenged and not supplemented with OAs (34,36). Likewise, fumaric acid supplementation increased the productive response of heat-stressed chicks compared to unsupplemented chicks, which was associated with improved hematological and biochemical parameters (37). Thus, supplementation with OAs would improve performance in healthy birds or under adverse sanitary and environmental conditions.

Also, Zhang et al (38) found no evidence that acidification of drinking water with a mixture of 2-hydroxy-4-methylthiobutyric, lactic, and phosphoric acids affected final weight and feed intake in broilers. However, they reported changes in intestinal morphology and microbiota, with consequent improvement in its barrier function, inhibition of intestinal dysbiosis, and release of ileal and serum inflammatory factors that promote osteoclastogenesis and bone resorption. In addition, the reduction of the GIT pH of birds after supplementation with OA increases the solubility and absorption of minerals, and therefore the mineralization of bone tissue (38). This reduces the mobility problems of birds caused by leg weakness or lameness, which negatively affect animal welfare and production, causing economic damage to the poultry industry (38).

On the other hand, Hernández et al (39) showed inconclusive results on the intestinal histomorphometry and productive performance of broilers reared under appropriate sanitary conditions after the inclusion of formic acids in the diet, similar results were reported in turkeys supplemented with a mixture of AOs (40). Similarly, acidification of water with formic or butyric acid, or a combination of these, did not affect animal response and lymphoid organ weights compared to the control treatment. However, it did improve carcass yield (41).

Differences in digestibility and performance reported in broilers after the inclusion of AOs have been attributed to diet composition, type, doses, combinations and symbiotic effects of AO used, environmental conditions, bird health status, challenges, and management conditions (34,41). In addition, AO is metabolized in the upper gastrointestinal tract, therefore their effects are mainly observed in the crop and the proximal portion of the small intestine (33), microencapsulation has been proposed to maximize their action in the distal portions of the GIT (26). Table 2 summarizes the effect of individual OAs or in combinations with different products on the health and productive response of broiler chickens.

Future Perspectives. In the context of AGP bans and climate change, OA has shown positive effects on broiler health and productivity. Microencapsulation and combinations with essential oils, polyphenols, and fibers enhance their effects. However, inconsistencies between studies require the evaluation of specific compounds, doses, application times, and underlying mechanisms of action. Molecular techniques are needed to identify changes in the microbiota and its metabolites, their occurrence in the morphology of the structures of the intestinal mucosa, the colonization of microorganisms, the gene expression of various proteins related to the integrity and immunity of the GIT, as well as the influence of OAs on the bioavailability of nutrients. This optimization of broiler performance and health is critical in challenging scenarios.

In conclusions OAs modulate gut microbiota, enhancing GIT morphology and physiology, and improving nutrient utilization and bird performance. However, reports on OA's benefits vary due to environmental conditions and OAs characteristics. To maximize their potential as AGP alternatives, conditions optimizing OAs effects in poultry farming must be evaluated.

Table 2. Current use and prospects of OAs.

Experiment	Results
Comparative effect of enrofloxacin (ENR) and microencapsulated essential oils and organic acids (EO+OA) on *S. enteritidis*-challenged White Leghorn chickens (38).	EO+OAs showed a bacteriostatic effect on *S. enteritidis*, anti-inflammatory activity, and improved intestinal health compared to ENR-treated, *S. Enteritidis*-challenged birds.
Evaluation of microencapsulated OAs (sorbic, fumaric acids) + EO combinations vs. enramycin (ERM) on epithelial restitution, microflora, and SCFA production in Cobb 500 chickens (33).	OA+EO and ERM have antimicrobial action, reduce pH, increase disaccharidase activity, SCFA production, improve microbiota, immunity, and intestinal integrity. Microencapsulation enhances OA+EO effectiveness.
Evaluation of microencapsulated OAs (fumaric, citric, malic acids) and MCFA (capric, caprylic acids) as growth promoter alternatives in Ross 308 chickens (42).	OAs+MCFA improved weight gain, FCR, digestibility, reduced *E. coli*, increased Lactobacillus, and enhanced bursa of Fabricius development and IgG concentration.
Effect of MCFA, OAs, and polyphenol (PF) mixture on performance, intestinal integrity, and morphology in HS-exposed Ross chickens (43).	HS-induced inflammation, impaired intestinal integrity, nutrient transport (jejunum), weight, and feed intake. OAs+MCFA+PF supplementation attenuated these effects.
Comparative digestibility and performance of Ross 308 broilers challenged (Ch) or not challenged (NCh) by *E. coli*, supplemented with Novacid (organic acids, glucomannans, phytochemicals) or AGPs (BMD) (36).	Digestibility and performance improved similarly with Novacid or BMD compared to control in NCh birds, but not in Ch birds. Novacid and BMD showed stronger antimicrobial activity in NCh birds than in Ch birds. Mortality rates were similar in Ch and NCh birds.
Effect of OAs (lactic, citric, acetic, formic, propionic, phosphoric acids) with SF (beet pulp) and IF (rice husk) on performance, immunity, morphology, and microbiota in Ross 308 broilers (44).	OAs + IF increase jejunal villi length, humoral immune response. OAs+SF reduce abdominal fat, and OAs increase Lactobacillus count and improve productivity.
Comparison of OAs (ammonium/calcium formate, propionate) and enramycin on cecal microbiota, intestinal morphology, blood biochemistry, performance, and carcass in Cobb-500 broilers (45).	OAs improved weight gain, FCR, carcass characteristics, reduced ileal bacterial count, and increased villus length. No effects on protein, globulin, c-HDL, and c-LDL.
Effect of a blend of fatty acids whit additives (phytochemicals, fatty acids, organic acids) on villus morphology, intestinal integrity markers, and inflammatory response in coccidiosis-vaccinated Ross 708 chickens (46).	Additives reduced villus length: crypt depth ratio, improved barrier function, attenuated inflammation compared to BMD, without affecting growth.
Effect of EO+OAs (sorbic acid, fumaric acid, thymol) on productivity, morphology, and intestinal function in laying hens (47).	Increased laying rate, egg quality; improved digestion, absorption, barrier functions reported. Bifidobacterium counts in cecal digesta tended to increase.
Effects of dietary supplementation with EO+OAs on chickens with induced necrotic enteritis (NE) evaluated (48).	EO+EOAs improved performance, intestinal health in NE-infected broilers by enhancing integrity and microbiota composition.
Comparison of encapsulated OAs+EOs and AGPs on broiler performance challenged with *Eimeria spp* (49).	EO+OAs supplementation in broilers improved intestinal integrity by increasing Mucin 2, Claudin 1, occludin gene expression in the jejunum. Encapsulation modulated microbiota in the GIT.

Abbreviation: essential oils EO; organic acids OA; enrofloxacin ENR; Short-Chain Fatty Acid SCFA; Medium-Chain Fatty Acid MCFA; feed conversion ratio FCR; heat stress HS; polyphenol PF; challenged Ch; not challenged NCh; antibiotic growth promoters AGP; bacitracin methylene disalicylate BMD; soluble fiber SF; insoluble fiber IF.

Conflicts of interest

The authors declare no conflicts of interest

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