Regulation of Poultry Intestinal Health by Plant Extracts and Their Mechanisms of Action: Postprint

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Abstract

Active substances in plant extracts include flavonoids, plant essential oils, alkaloids, tea polyphenols, saponins, and polysaccharides. These active compounds exhibit multiple physiological functions in animal organisms, including antibacterial, antioxidant, intestinal immunity enhancement, promotion of digestive enzyme secretion, and improvement of intestinal health. Moreover, they are characterized by the absence of residues and drug resistance, making them one of the ideal alternatives to antibiotics. This article draws upon recent research findings from domestic and international scholars regarding the regulation of poultry intestinal health by plant extracts, summarizing and elaborating on the antibacterial active components and mechanisms of plant extracts. It focuses on reviewing the effects of plant extracts on poultry intestinal digestive physiology, intestinal development and mucosal morphology, intestinal microbiota, intestinal immunity, and intestinal harmful metabolites, as well as their underlying mechanisms, aiming to provide a scientific basis for the rational application of plant extracts in poultry production.

Full Text

Regulation of Poultry Gut Health and Its Mechanisms by Plant Extracts

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Abstract: Plant extracts contain bioactive substances such as flavonoids, essential oils, alkaloids, tea polyphenols, saponins, and polysaccharides. These active compounds exhibit multiple physiological functions in animals, including antibacterial, antioxidant, and gut immunity-enhancing effects, as well as promoting digestive enzyme secretion and improving gut health. Characterized by their lack of residues and absence of drug resistance, plant extracts represent ideal antibiotic alternatives. This paper reviews recent domestic and international research on the regulation of poultry gut health by plant extracts, summarizing the antibacterial active ingredients and their mechanisms. It focuses on the effects of plant extracts on poultry intestinal digestive physiology, intestinal development and mucosal morphology, intestinal microflora, intestinal immunity, and harmful intestinal metabolic products, along with their underlying mechanisms, to provide a scientific basis for the rational use of plant extracts in poultry production.

Keywords: plant extracts; poultry; gut health; mechanisms

The long-term addition of antibiotics to livestock feed has caused serious negative impacts on human health and environmental safety. Antibiotic abuse disrupts the microecological balance in livestock intestines, induces bacterial resistance, and threatens human health through antibiotic residues in animal products [1]. Consequently, many countries have banned or strictly restricted antibiotic use in livestock feed through legislation, mandating withdrawal periods [2]. Therefore, using low-dose antibiotics as intestinal microecological regulators in poultry feed is no longer acceptable, and identifying new antibiotic alternatives to regulate poultry intestinal microbiota and maintain gut health has become an urgent task in the post-antibiotic era. Plant extracts (PE) have emerged as a research hotspot in poultry nutrition under this background, primarily because their active substances can maintain the microecological balance of digestive tract flora through antibacterial action and selective bacterial inhibition. Additionally, plant extracts can ensure poultry gut health by improving intestinal immunity, promoting intestinal mucosal development, and stimulating digestive enzyme secretion [3]. Given heightened public concern over food safety and the need for sustainable livestock development, plant extracts have become a novel antibiotic alternative due to their safety, efficacy, lack of residues, and non-induction of drug resistance [4-6]. This review summarizes the antibacterial mechanisms of plant extracts and their effects on poultry intestinal digestive physiology, intestinal development and mucosal morphology, intestinal microflora, intestinal immunity, and harmful intestinal metabolic products, providing a theoretical foundation for future poultry production.

1 Overview of Plant Extracts

Plant extracts are substances derived from plants with one or more biological functions. When added to feed, they can improve livestock performance, enhance product quality, boost immunity, prevent certain diseases, and ensure gut health [7-9]. Plant extracts contain rich and complex organic constituents, including over 60 chemical components [5]. Bioactive substances identified thus far include flavonoids, essential oils, alkaloids, tea polyphenols, saponins, and polysaccharides. Flavonoids are compounds with a 2-phenylchromone structure found in plants. Their molecules contain a ketone carbonyl group, and the oxygen atom at position 1 has basic properties, enabling salt formation with strong acids. Their hydroxyl derivatives appear yellow, hence the name flavonoids or flavine. Flavonoids have been confirmed to possess antioxidant and antibacterial properties, with their antibacterial biological activity remaining a research focus. Alkaloids are important nitrogen-containing organic compounds in natural plants that are alkaline and can combine with acids to form salts. Natural plant alkaloids have been proven to exhibit antibacterial activity. Essential oils (EOs), widely present in natural plants, have attracted extensive attention for their antibacterial, antioxidant, and lipid-lowering properties. Numerous studies have investigated the antibacterial activity of different plant oils, and the antibacterial mechanisms of EOs are actively being explored [10-11].

2.1 Enhancing Intestinal Epithelial Defense Function

Some plant extracts have been confirmed not to directly inhibit or kill pathogenic bacteria in vitro, yet they can resist diarrhea caused by pathogenic microorganisms after ingestion by livestock, likely by enhancing the intestinal epithelium' s intrinsic defense function. For example, allicin cannot directly inhibit or kill *Escherichia coli*, but it can enhance intestinal epithelial cell resistance against K88 *E. coli* invasion and reduce the increased intestinal epithelial permeability caused by *E. coli* [12].

2.2 Enhancing Bacterial Cell Membrane Permeability

A key characteristic of plant extracts is hydrophobicity, which enables them to separate phospholipid structures on bacterial cell membranes and mitochondria, disrupt cell structure, and enhance cell membrane permeability [13-14], leading to leakage of intracellular ions and other substances [15-17]. Massive leakage of cellular contents or important ions and molecules may cause bacterial cell death [18]. Lambert et al. [19] confirmed that carvacrol from oregano (*Origanum vulgare* L.) caused phosphate molecule leakage in *Staphylococcus aureus* and *Pseudomonas aeruginosa* cells. The antimicrobial properties of carvacrol are related to its lipophilic nature and aromatic chemical structure [20].

2.3 Inhibiting Bacterial Peptidoglycan Synthesis

Some in vitro studies have shown that plant extracts can inhibit bacterial peptidoglycan synthesis, thereby damaging bacterial morphology. The antibacterial mechanism of *Stephania suberosa* plant extract primarily involves inhibiting bacterial peptidoglycan synthesis and damaging bacterial morphology [21]. Due to the complex composition of plant extracts, their specific antibacterial mechanisms remain unclear. In addition to the three mechanisms mentioned above, plant extracts can also destroy or degrade bacterial cell walls, disrupt cytoplasmic membranes, damage membrane protein structures, cause bacterial cytoplasm coagulation, and weaken bacterial proton motive force (PMF) [22-25]. These antibacterial mechanisms are not isolated and can influence each other, with reactions in one mechanism potentially being affected by reactants or products in another. Moreover, studies have confirmed that complete plant extracts are far more effective than their main components alone, indicating that non-primary active ingredients also play important roles, with synergistic effects between primary and non-primary components. Future research should strengthen investigations in this area.

3.1 Effects on Intestinal Digestive Physiology

Studies have shown that plant extracts stimulate the secretion of digestive enzymes in poultry intestines and enhance enzyme activity, thereby improving intestinal digestive function [26-28]. Capsaicin and piperine primarily promote digestion by stimulating digestive enzyme activity [29], mainly because active substances in some spice extracts stimulate bile salt secretion [30]. William et al. [31] demonstrated that essential oils increase endogenous enzyme secretion (such as amylase) in broiler intestines, improve digestive enzyme activity, alter feed morphology in the intestine, reduce intestinal chyme viscosity, and consequently enhance nutrient digestibility and absorption, improving poultry performance. Hawthorn extract can increase duodenal protease activity and pancreatic protease and lipase activity in broilers, improving nutrient digestibility [32]. Adding 200 mg/kg yucca extract (YSE) to broiler diets significantly increased ileal trypsin and lipase activities and duodenal lipase activity in 42-day-old broilers, as well as the apparent metabolic rate of crude protein [33]. Additionally, black cumin (*Nigella sativa* L.) seed extract significantly increased gizzard pH in chickens but had no significant effect on pH in the proventriculus, duodenum, ileum, or jejunum. Adding a mixture of *Artemisia sieberi* and black cumin seed extract to broiler diets significantly increased jejunal pH but had no significant effect on gizzard, duodenum, or ileum pH [34]. In summary, plant extracts may stimulate gastrointestinal mucus secretion (including some digestive enzymes), disrupt pathogen adhesion in the intestine, reduce pathogen damage to the intestine, improve nutrient digestion and absorption, and maintain gut health. However, some reports indicate that plant extracts have no significant effect on digestive enzyme secretion in poultry. For example, Lee et al. [35] reported that adding 100 mg/kg thymol and cinnamaldehyde to diets had no significant effect on the activity of amylase, lipase, trypsin, or chymotrypsin secreted by the pancreas and small intestine in chickens. These discrepancies may be related to the type and inclusion level of plant extracts, and further research should strengthen investigations in this area.

3.2 Effects on Intestinal Development and Mucosal Morphology

As the primary site for nutrient absorption and the first line of immune defense, the integrity of intestinal mucosal structure and function is crucial for maintaining poultry gut health and production. Feeding broilers with 0.1%, 0.2%, and 0.3% pine wood (*Pinus brutia*) extract containing galactoglucomannan oligosaccharides showed that 0.2% galactoglucomannan oligosaccharides increased small intestinal villus height and surface area while reducing the risk of *Salmonella typhimurium* infection [36]. Plant extracts affect pathogen adhesion in the intestine, maintain poultry intestinal microecological balance, and improve jejunal and colonic mucosal morphology by increasing villus height and crypt depth [37]. Khalaji et al. [34] found that dietary *Camellia* L. extract significantly increased villus height and crypt depth in broilers. Wang Mianchao [38] added 125 mg/kg yucca extract to broiler diets, and results showed that duodenal and jejunal villus lengths in the treatment group were significantly higher than in the control group, with no significant difference compared to the antibiotic group. Yucca extract maintained complete small intestinal mucosal structure with neatly arranged villi and obvious mucosal epithelial renewal. Alkaloids can promote the proliferation of beneficial bacteria, inhibit harmful bacteria growth, promote chicken small intestinal villus structure development, improve small intestinal absorption function, and consequently enhance chicken performance [39]. Dietary plant extract supplementation increased ileal and cecal villus height and villus height/crypt depth ratio, improved intestinal mucosal digestion and absorption function, and promoted broiler growth and development [40], consistent with results reported by Su et al. [33]. Dietary plant extracts can increase villus height in all small intestinal segments and crypt depth in the ileum and jejunum of broilers [41]. Adding yucca extract to Beijing duck diets increased villus height, villus depth, villus height/crypt depth ratio, and villus area in the duodenum, jejunum, and ileum, improving small intestinal nutrient absorption [42]. Additionally, plant extracts can repair damaged intestinal mucosa and regulate mucosal cytokine expression. Intestinal repair after mucosal damage is regulated by various active growth factors, including epidermal growth factor (EGF), transforming growth factor α (TGFα), transforming growth factor β (TGFβ), and proliferating cell nuclear antigen (PCNA). The Si Jun Zi decoction significantly enhanced the expression of intestinal mucosal repair factors PCNA, EGFR, and TGF$ $1 in diarrheal mice, regulated mucosal repair factor expression, and accelerated intestinal mucosal damage repair [43]. Plant extracts may affect intestinal mucosal morphology by influencing intestinal epithelial cell proliferation and differentiation and the expression of intestinal epithelium-related genes. Studies in piglets confirmed that essential oils downregulated the mRNA expression of cyclin D1 (related to cell proliferation) in the jejunum and ileum, reducing villus height. Considering the different reports on essential oils' effects on intestinal morphology, it can be hypothesized that one potential effect of essential oils is to stimulate intestinal tissue, causing surface damage, while other beneficial effects such as reducing pathogenic microorganisms may increase villus height and improve intestinal morphology. Therefore, the effect of essential oils on intestinal morphology depends on the balance between intestinal tissue stimulation and beneficial effects on the intestinal environment [44]. The specific mechanisms remain unclear, and future research should strengthen molecular-level investigations on plant extracts' effects on poultry intestinal mucosal-related cytokines.

3.3 Effects on Intestinal Microflora

Intestinal microflora is an important component of the intestinal mucosal barrier, also known as the biological barrier. Dysbiosis can cause poultry diarrhea, immunosuppression, and even systemic inflammatory response syndrome (SIRS). Adding 60, 120, and 180 mg/kg yucca extract to broiler diets showed that 60 mg/kg increased Firmicutes abundance while 120 and 180 mg/kg decreased it; 60 mg/kg decreased Bacillus abundance while 120 and 180 mg/kg increased it; 60 and 180 mg/kg decreased Proteobacteria abundance while 120 mg/kg increased it. Harmful bacteria such as *Bacteroides* and *Eubacterium* decreased with increasing yucca extract levels, while *Helicobacter* increased. Beneficial bacteria such as *Ruminococcus*, *Clostridium leptum*, and *Atopobium* increased with increasing yucca extract levels [45]. *Aloe secundiflora* extract reduced mortality from *Salmonella* infection in broilers, improved antibody levels, and decreased intestinal *Salmonella* counts [46]. Zhao et al. [47] added *Portulaca oleracea* extract to broiler diets and found that at 42 days, the 2 g/kg extract group had significantly higher cecal *Lactobacillus* and *Bifidobacterium* counts and significantly lower *Escherichia coli* counts compared to the control group, with no significant effect on intestinal pH. Wei [41] found that dietary plant extracts and enramycin both reduced harmful bacteria such as total non-anaerobes and *E. coli* while increasing beneficial bacteria such as *Lactobacillus* in the cecum, demonstrating that plant extracts can regulate chicken intestinal microecology. Ileal pH significantly decreased with increasing plant extract levels in broiler diets during the late rearing period. Additionally, dietary essential oils improved intestinal microbial flora, reduced *Clostridium perfringens* counts, and promoted colonization of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* [31]. Kavoosi et al. [48] studied the antibacterial effects of Indian ajowan (*Carum copticum*) seed essential oil and *Ferula assafoetida* essential oil, finding that ajowan oil significantly inhibited both Gram-positive and Gram-negative bacteria, while *F. assafoetida* oil only significantly inhibited Gram-positive bacteria, with both oils showing antifungal activity. Adding 2 g/kg oregano aqueous extract significantly reduced *E. coli* counts in the ileum and cecum, with no significant differences in cecal *Enterococcus*, *Lactobacillus*, or *Staphylococcus* counts among groups, and no significant decrease in ileal *Lactobacillus* counts [49]. In Japanese quail, thyme essential oil significantly increased ileal *Lactobacillus* counts while decreasing *E. coli* counts [50]. However, dietary essential oils had no significant effect on small intestinal flora in 7- to 28-day-old chickens [51]. These studies indicate that different plant extracts regulate intestinal flora differently—some directly inhibit or kill harmful bacteria through various pathways, while others indirectly suppress harmful bacteria by promoting beneficial bacteria growth. Some plant extract components, such as oligosaccharides, exhibit clear prebiotic effects by promoting the growth of beneficial bacteria like *Bifidobacterium* and *Lactobacillus* both in vivo and in vitro [52], as these anaerobic bacteria can utilize oligosaccharides for anabolic metabolism while aerobic pathogenic bacteria cannot. The mechanisms by which different plant extracts affect intestinal microecology in vivo vary, and combinations of multiple plant extracts may demonstrate stronger or broader-spectrum antibacterial effects. Future research should intensify screening and effective combination studies to comprehensively explain the effects of plant extracts on poultry intestinal microflora.

3.4 Effects on Intestinal Immunity

The intestine serves dual functions as both a vital organ for nutrient digestion and absorption and a congenital immune barrier maintaining internal environmental stability, representing the most complex immune system in the body. When the intestinal immune barrier is compromised, microorganisms and toxins can enter the bloodstream, causing bacterial and toxin translocation, which may lead to intestinal infections and even systemic inflammatory responses or organ failure. Plant extracts can bind to specific receptors on immune cell membranes, mediate immune cell activation signaling pathways, and regulate cytokine secretion by macrophages, T/B lymphocytes, and dendritic cells [3,53], thereby maintaining animal gut health by enhancing immunity and eliminating inflammation (Fig. 1 [Figure 1: see original paper]). Key cytokines maintaining intestinal health include interleukin-6 (IL-6), interferon-γ (IFN-γ), and TNF-α, which play crucial roles in inflammatory responses and immune reactions against various pathogens [54]. Studies show that *Zataria multiflora* Boiss extract significantly increased IFN-γ expression while decreasing interleukin-4 (IL-4) expression, improving the IFN-γ/IL-4 ratio and Th1/Th2 balance, suggesting its potential as an immunomodulator in inflammatory processes such as allergic reactions [55]. The Qi Wei Bai Zhu San formula increased IL-2, IL-10, and IFN-γ mRNA expression in intestinal mucosal epithelium of suckling mice, inhibited rotavirus-induced diarrhea, possibly by regulating T-cell subsets [56]. Romier-Crouzet et al. [57] investigated the effects of grape seed, cocoa, sugarcane, oak, mangosteen, and pomegranate extracts on inflammatory mediators in human intestinal Caco-2 cells, finding that sugarcane, oak, and pomegranate extracts inhibited NF- B activity, pomegranate extract inhibited extracellular signal-regulated kinase (Erk) 1/2 activation, oak and pomegranate extracts reduced nitric oxide (NO) and IL-8 synthesis, and pomegranate and cocoa extracts reduced prostaglandin E2 (PGE2) synthesis. Mouse studies demonstrated that plant extracts downregulated NF- B1 and NF- B2 gene expression, increased NF- B1 inhibitor expression, enhanced NF- B1 binding, translocated

NF- B1 from nucleus to cytoplasm, and reduced nitric oxide synthase (NOS) and cyclooxygenase-2 (COX-2) gene expression, consequently decreasing inflammatory factors NO and PGE2 and alleviating inflammatory responses [58]. This dual effect of enhancing immunity in infected animals while preventing excessive sensitivity-induced inflammation demonstrates the bidirectional regulatory advantage of plant extracts. However, the exact mechanisms of plant extracts on poultry intestinal immunity or inflammation reduction remain unclear and require further investigation.

3.5 Effects on Harmful Intestinal Metabolic Products

Plant extracts can also maintain gut health and improve farm environmental quality by reducing harmful metabolic products in the digestive tract and feces. Adding 150, 250, and 350 mg/kg of Lauraceae plant extract to broiler diets reduced uric acid (UA) and urea nitrogen (UN) contents in intestinal contents compared to the control group, with UA contents decreasing by 0.25%, 23.9%, and 41.3%, respectively, and reducing ammonia (NH_3) emissions [59]. Adding extracts of *Salvia splendens*, osmanthus, cinnamon, and yucca to broiler diets significantly reduced UA, UN, and ammonia nitrogen (AN) contents in the intestine and excreta, effectively improving air quality in chicken houses and enhancing broiler performance [47]. Chen [60] investigated the effects of Lauraceae, Allium, and yucca extracts on ammonia volatilization in broiler excreta, finding that at 42 days, UN contents in intestinal contents decreased by 31.08%, 28.34%, and 28.52%, respectively, while UA contents decreased by 22.48%, 22.13%, and 38.85% compared to the control group. Studies show that adding 0.1% fenugreek seed extract (FSE) to broiler diets improved nitrogen (N) and dry matter (DM) digestibility while reducing NH_3 release in excreta [61], consistent with results reported by Su et al. [33]. Plant extracts reduce harmful intestinal metabolic products by inhibiting xanthine oxidase (XO) activity and reducing UA production, and by inhibiting urease and uricase activities in the poultry intestine [62], thereby reducing UA, UN, and AN contents in both intestinal contents and excreta. Additionally, some plant extracts can stimulate protease secretion in the digestive tract, improve protein utilization efficiency, reduce nitrogen excretion, and enhance environmental quality.

Maintaining poultry gut health is a critical mission in post-antibiotic era poultry farming. Plant extracts possess dual nutritional and health benefits, making them ideal antibiotic substitutes. While researchers have conducted extensive work on the effects of plant extracts on poultry digestive physiology, intestinal development, intestinal microflora, and harmful metabolic products, the regulatory mechanisms of extracts from different sources, extraction methods, and plant growth stages on poultry gut health remain unclear. Future research should intensify screening and effective combination studies, elucidate their in vivo actions and molecular pathways affecting intestinal mucosal gene expression at the cellular and molecular levels, and provide theoretical foundations for plant extract application in poultry production.

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