Use of Phytogenic Compounds in Poultry for Improving the Functions of Intestinal Barriers

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Abstract

The ban on antibiotic growth promoters in European Union animal feed regulation has triggered intense research into innovative approaches to promote gut health, as the poultry industry tackles issues previously managed by antibiotics. Meanwhile, there is increasing public demand to reduce the use of antibiotics and replace them with other feed additives. Consumers view a safe range of available alternatives as safe, with phytogenic feed additives as a safe option. Phytogenic feed additives have been found to offer protection to poultry birds from environmental challenges that can disrupt the integrity of the intestinal epithelial barrier. Phytogenic feed additives can potentially optimise intestinal mucosa's structural integrity and fortify gut barrier function at the molecular level. A deeper knowledge of how phytogenic compounds influence the components of intestinal barriers can enable targeted selection of phytogenics to counteract the adverse effects of various pathological agents.

Keywords: Phytogenic feed additives, Intestinal barriers, Antibiotic growth promoters, Tight junctions, Gut health, Enterocytes

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Introduction

The poultry sector represents a significant portion of global livestock output. Poultry meat production worldwide experienced exponential growth, rising from 9 million tons in 1961 to 122 million tons in 2017, accounting for around 37% of total meat output in 2017, according to FAO (Food and Agriculture Organization). Researchers, veterinarians, nutritionists, and breeders face a massive task in streamlining eco-friendly and customer-centric production processes. Since it has been recognized as key contributor in influencing animal performance, the idea of "gut health" has drawn a lot of attention in recent years. The ban on antibiotic growth promoters in European Union (EU) animal feed regulation promoters sparked a surge in research into various gut health improvement strategies. The administration of coccidiostats has also been the subject of dispute because of concerns about environmental residues and parasite resistance (European Parliament and the Council of the European Union, 2003; Kadykalo et al., 2018). In a position paper on coccidiostats, often known as anticoccidials, the Federation of Veterinarians of Europe recommended stringent veterinary oversight of their usage throughout the European Union in 2016 (Federation of Veterinarians of Europe, 2021). Notably, there is rising consumer concerns driving demand for natural feed additives (Čapkovičová et al., 2014).

Feed additives are defined by EU law as materials, microorganisms, or preparations that are targeted feed or water supplements to meet the nutritional needs of animals, improve animal performance, welfare, or production (especially by influencing the microbes of gut or efficiency of nutrient utilization in feed material), refines the nutritional quality and safety of animal product attributes, or implement regenerative agriculture practices for animal production. Additionally, animal dietary supplements have histomonostatic or antiparasitic properties (European Parliament and the Council of the European Union, 2003).Numerous safe and well-liked alternative feed additives are available, including organic acids, pro-, pre-, and synbiotics, and phytogenics (Yadav et al., 2016). The majority of research on their effectiveness has focused on how they affect growth performance, absorbability, or antibacterial and antiparasitic action (Attia et al., 2017). The hunt for the best feed additives is still ongoing, even though a lot of study has already been done in this area. Gut health is influenced by a variety of circumstances, however maintaining an integrated and undamaged gut barrier is essential.

The processes behind the intestinal barrier's appropriate operation are rapidly evolving. Increased knowledge of the problem has revealed that many things were previously misrepresented (Kogut & Arsenault, 2016). Even though, scientific attention has been devoted to understand how dietary supplements affect the histological and morphological characteristics of the gastrointestinal tract (Attia et al., 2017). In addition to having additional beneficial benefits on gut health, phytogenics are an intriguing class of feed additives that may strengthens the gut's natural barrier against pathogens (Patra et al., 2019). Improving gut health is a complicated matter that calls for multifaceted approaches.

Plant extracts have the potential to act in multiple ways and are a prospective substitute for antibiotic growth promoters because of their diverse active ingredients and rich composition (Yang et al., 2015). Characterizing the physiological effects of dietary supplements and the factors that would support their inclusion in animal nutrition may be improved with the application of molecular technologies. Natural feed additives are becoming more and more popular among veterinarians and poultry farmers, but more scientific proof is still required to support their use, demonstrate their efficacy, and win over the public. Current understanding of the effects of plant based additives and their combinations, on the gut epithelial barrier in chickens is intended to be compiled in this chapter.

Gut Integrity and Role of Intestinal Barriers

The body's digestive system is an intricate and multifaceted mechanism. A well-functioning digestive system is essential for efficient nutrient absorption, enabling animals to grow and develop at the optimal rate. This, in turn, directly impacts the economic probability. An animal's total immunity depends on the gut immune system, and the intestinal barrier's integrity protects against infections and xenobiotics that enter the body through the digestive system (Latek et al., 2022).

The intestinal barrier comprises a complex layer of protection, consisting of mucous, gut-associated microbiota, components of the immune system and intimately associated intestinal epithelial cells (Turner, 2009). These components continue to interact dynamically with the environment and one another. The single layer of intact epithelial cells and the functional connections between them are crucial for preserving the intestinal barrier's structure and permeability. Desmosomes, adherent junctions, gap junctions, and tight junctions are among the various types of junctions that join enterocytes. The regulation of epithelial barrier function and control of paracellular transport depend heavily on tight junctions (Patra et al., 2019).

The apical end is opposite to the basolateral side of the epithelial cells is where tight connections are found. Transmembrane proteins assemble into multiprotein complexes, linking plaque proteins that connect to the perijunctional actomyosin ring, thereby creating distinct extracellular and intracellular domains. There are currently more than 50 tight junction proteins known to exist. Claduins, JAMs, tricellulin, and the Coxsackie and adenovirus-associated receptors are examples of transmembrane proteins. The cytoplasmic plaque, which is primarily made up of the zonula occludens protein, is connected to them (Awad et al., 2017).

The proteins that make up tight junctions are dynamic structures that can change based on the surroundings. For instance, in response to different stresses, the zonula occludens proteins might redistribute into the intracellular compartment and move cyclically between the membrane and cytosolic pools (John et al., 2011). OCLN can internalize in cytoplasmic vesicles, altering the epithelium's permeability (Steed et al., 2010). In contrast, claudin localization in tight junctions is comparatively stable (Shen et al., 2008), although their distribution and characteristics can vary greatly, as evidenced by the epithelia's fluctuating tightness (Suzuki, 2013). It is commonly known that preserving mucosal homeostasis requires the presence and appropriate operation of tight junctions. The proteins in tight junctions are crucial for signalling pathways in addition to tying epithelial cells together and controlling paracellular permeability (Awad et al., 2017).

Disruption of the Intestinal Barrier

Numerous substances have been identified that potentially endanger intestine health and, consequently, animal health (Alhenaky et al., 2017). Different tight junction proteins' expression, phosphorylation, and distribution have been linked to a variety of gastrointestinal and systemic disorders across the species including animals and humans (Zeissig et al., 2007). Exposure to various agents, including mycotoxins, pathogens, and heat stress, has been shown to cause significant molecular changes in the intestinal barrier's structure (Muza-Moons et al., 2004; Wan et al., 2018; Santos et al., 2019).

Pathogens

Awad et al. (2017) explained the function of tight junctions in controlling the intestinal barrier and how infections can interfere with it in chickens, hence it is not discussed more here. To put it briefly, certain enteric pathogens, such as *Salmonella* or enteropathogenic *Escherichia coli*, can alter tight junctions and impair the operation of the chicken's mucosal barrier. Certain tight junction components may be disrupted by pathogen-derived proteases, modifications to the proteins' phosphorylation status, or changes in protein synthesis (O'Hara & Buret, 2008).

Restriction of Antibiotic use in Animal Feed

Undoubtedly, the chicken business also faced some challenges as a result of the antibiotic growth boosters' withdrawal, which are linked to a decline in intestinal health, such as a rise in the (FCR) feed conversion ratio, the return of diseases that were under prior control, such as leaky gut syndrome, damp litter, or necrotic enteritis, and the development of diseases brought on by commensal microbiota that can pass through the intestinal barrier because of its compromised integrity (Van et al., 2016). Gaucher et al. (2015) described an experimental drug-free program in which some adverse consequences were observed. The findings highlighted important challenges that must be addressed when thinking about large-scale drug-free poultry production.

Higher rates of both clinical and subclinical necrotic enteritis as well as higher litter moisture content were linked to this program. Additionally, the (FCR) feed conversion ratio, the weight at the time of slaughter and daily growth rate were much lower in animals raised without treatment. In addition, the chicken business must contend with the new issues brought about by climate change, like heat stress and the rise in mycotoxin contamination of feed.

Heat Stress

Heat stress has been shown to enhance intestinal barrier permeability in broiler chickens, as evidenced by elevated blood endotoxin, inflammatory cytokine levels, and intestinal pathogen transmission (*Salmonella spp.*) (Shen et al., 2008). According to a different study, heat exposure in broiler also causes unfavorable alterations in the morphology of the jejunum, altered tight junction protein expression including decreased occluding and zonula occuldens protein-1, leading to increased paracellular permeability (Song et al., 2014).

Mycotoxins

It has been demonstrated that even subclinical exposure to deoxynivalenol can cause substantial molecular alterations and serve as a risk factor for necrotic enteritis, despite the fact that hens are generally indifferent to the toxic effects of this mycotoxin (Antonissen et al., 2014). Broiler chickens exposed to deoxynivalenol both in vivo and in vitro have shown impaired epithelial integrity, a sign of increased gut barrier permeability (Awad and Zentek, 2015). Exposure to deoxynivalenol has also been linked to decreased intestinal absorption of nutrients in chickens (Awad et al., 2008). Pekin ducks exposed in vivo to ochratoxin A showed decreased villous length, growth limitations, and downregulation of OCLD expression and the tight junction proteins zonula occludens protein-1 (Ruan et al., 2019). Aflatoxin B1 exposure also caused molecular alterations in hens, including decreased digestibility of amino acids, leaky gut syndrome contributing to reduced growth rates (Chen et al., 2016). All of the previously listed elements are known to contribute to the vicious cycle of illness, which has a detrimental effect on gut health and general avian performance.

Phytogenic Feed Additives for Enhancing Gut Barrier Function

Plant derivatives known as phytogenic feed additives can be incorporated into animal feed to promote better growth and production. Herbs, spices, essential oils, and oleoresins are among these substances (Windisch et al., 2008). The positive impacts of plant based supplements on poultry health have previously been seen by numerous investigators, and their application is known to have positive effects on animal output (Liu et al., 2018). Many products currently available on the market contain one or more phytogenic compounds, sometimes in combination with other additives like organic acids or pre- and probiotics.

Numerous phytogenics have a distinct, intricate makeup that gives them various beneficial qualities associated with plant-based goods, including antibacterial, anti-inflammatory, immunomodulatory, antioxidant, and antiparasitic actions, all of which improve animal health. The supplementation with phytogenic feed additives in poultry has been associated with additional advantages, including enhanced flavor, stimulated gut motility, improved gut integrity and superior quality of meat attributes. There has been a thorough analysis of these elements of using phytogenics in animal nutrition (Shao et al., 2013). The properties of phytogenic feed additives are given in the figure 1 which include reinforcement of intestinal structure, immune system modulation, increase the proliferation rate of beneficial bacteria and minimizing the nutrient accessibility to pathogenic microbes.

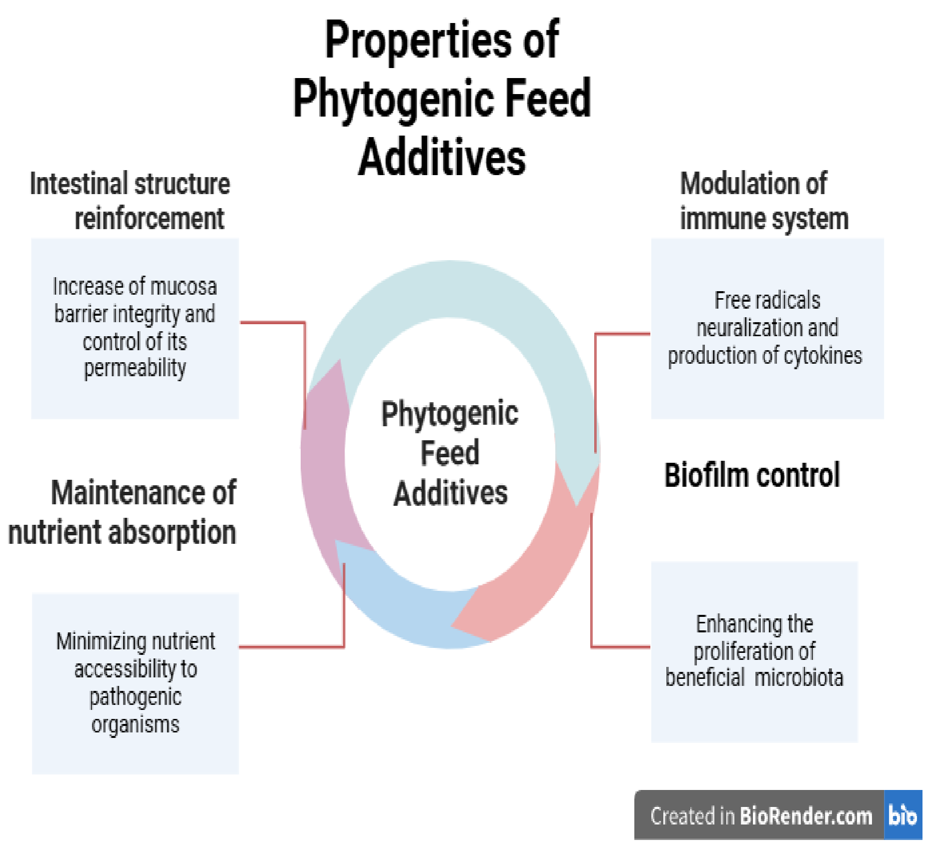

Fig. 1: Properties of Phytogenic Feed Additives

The physical barrier, which is mostly made up of closely knit intestinal epithelial cells, mucin producing cells, and precursor cells, is an essential component of the gut barrier (Liu et al., 2018). The mucosa's structure may be a key sign of gut barrier function and resilience (Paiva et al., 2014). Table 1 shows the alterations in intestinal mucosal structure brought on by phytogenic supplementation. The characteristics that are most frequently employed to assess the physical barrier condition are the number of mucin producing cells, crypt depth, villus height, and crypt depth to villus height. The balance between villus height and crypt depth is directly related to the villus height to crypt depth ratio (Paiva et al., 2014). The precise processes underlying the favorable impacts of plant based dietary supplements on gut morphology are yet unknown, however it is known that one of the reasons is their anti-inflammatory action. Another mechanism may be the regulation of cell development and apoptosis (Patra et al., 2019). The antioxidant qualities of phytogenics are another potential protective characteristic (Windisch et al., 2008). Since intestinal villi are the primary component in charge of absorbing nutrients, variations in their length may have an immediate effect on a bird health and productivity. The villi's surface area increases with height, suggesting there is a greater area available for efficient absorption (Petrolli et al., 2012). Supplementing poultry with different phytogenic feed additives has been shown to improve their villous height (Guo et al., 2018). Nevertheless, even though phytogenic supplementation had a number of beneficial impacts, in certain instances, growth performance did not significantly change as a result. Furthermore, supplementing with phytogenic feed additives was occasionally linked to a shortening of intestinal villus height in treated birds, in addition to having a good impact on intestinal morphology in certain areas (Jamroz et al., 2006). There was no discernible improvement in the birds' productivity, but feed additives of meat producing birds with coated cinnamon oil was linked to better gut health as evidenced by villus formation and modification of the molecular expression of tight junction proteins and mucin-2 (Guo et al., 2018).

Table 1: Effect of phytogenic feed additives on the morphology of intestine

No.	Feed Additives	Effects	References
1.	*Berberies vulgaris*	Increase villus height, villus surface, jejunal villus height and illeal villus surface area	(Yazdani et al., 2013)
2.	*Allium sativum* extract	Increase jejunal villus height	(Petrolli et al., 2012)
3.	*Lavandula angustifolia* powder	Decrease jejunal crypt depth and increase villus height to crypt depth	(Salajegheh et al., 2018)
4.	Blend of three active ingredients (curcuminoids, cinnamaldehyde and glycerol monolaurate)	Increase villus height , crypt depth and lower villus height to crypt depth	(Galli et al., 2021)
5.	Anta Phyta (contains hops, licorice and Arabic gum derivates)	Increase jejunal wall thickness , jejunal crypt depth and decrease villus width	(Ząbek et al., 2020)
6.	Coated cinnamon oil (37.5 % aldehyde)	Decrease jejunal crypt depth, increase villus height to crypt depth and increase duodenal crypt depth	(Guo et al., 2018)

Since the Lieberkühn crypts are the site of enterocyte creation, the depth of these crypts corresponds to the intensity of the synthesis of epithelial cells (Petrolli et al., 2012). Damaged cells must be extensively replaced with new ones to preserve the integrity of the epithelium, which leads to a high rate of cell turnover.

The presence of shallow crypts indicates that the bird is able to conserve energy for growth, despite the energy expenditure associated with cellular turnover (Ahsan et al., 2018). Increased villus height to crypt depth ratio is indicative of optimal intestinal health, characterized by differentiated intestinal cells, and balanced cellular dynamics, efficient nutrient absorption ultimately optimal growth (Paiva et al., 2014). Longer villi survival without the need for intensive cell formation is demonstrated by longer villi length without increased crypt depth (Kamboh et al., 2014). It is in line with the findings of observations made on animals that have been contested. The research carried out by Du et al. (2016). Mucosal erosion and noticeably deeper ileal crypts were linked to the Clostridium perfringens challenge. The intestinal lesions were linearly reduced by dietary essential oil supplementation (commercial product containing 25% thymol and 25% carvacrol); additionally, 60–240 mg/kg essential oil elevated villus height and decreased crypt depth, resulting in a markedly elevated villus height to crypt depth ratio. Similarly, the addition of plant based dietary supplements significantly mitigated the effects of the *Campylobacter jejuni* challenge, which caused a decrease in villous length and an increase in crypt depth (Gharib et al., 2012).

Mucus, produced by mucin producing cells scattered throughout the villi, form a protective layer over epithelial cells (Čapkovičová et al., 2014). Mucins are glycoproteins with polymeric, viscoelastic, and protective qualities that make up the majority of the mucus layer (Dharmani et al., 2009). The dual function of the mucus layer is to provide a defensive barrier against luminal pathogens and toxins and to facilitate selective exchange between the intestinal lumen and the brush border membrane (Uni et al., 2003). in addition to forming a physical barrier in chicken broiler (Chacher et al., 2017), LPS exposure was linked to downregulation of the mucin-2 gene, and supplementing with 1% (but not 5%) *Allium hooker* fermented root led to noticeably increased mucin-2 expression (Lee et al., 2017). On the other hand, neither the *C. perfringens* infection nor the use of essential oils (a commercial essential oil product that contains 25% thymol and 25% carvacrol) caused any appreciable alterations in mucin-2 expression, according to Du et al. (2016). Utilizing molecular technologies could increase our understanding of phytogenics' mode of action and help us choose the best ones to mitigate the adverse impacts of various causes. However, there aren't many studies that discuss how phytogenic compounds directly affect the distribution and presence of tight junction proteins in chickens.

It's also important to note that while there are many instances of successful phytogenic preparation supplementation, several studies also show no impact from this kind of dietary intervention. Notably, the addition of lemon or orange peel extract did not alter the intestinal morphology of birds exposed with heat stress (Akbarian et al., 2013). Furthermore, there is very little evidence on the safety and long-term toxicity of phytogenics, even though the majority of them are thought to be safe feed additives. In this context, Yu et al. investigated five phytogenic chemicals, including berberine, and found that it is safe to utilize them in broiler chicken starter, grower, and finisher feeds (Yu et al., 2017). The utilization of different phytogenic chemicals as poultry feed additives, however, requires more research of this type.

Conclusion

The incorporation of phytogenic feed additives has demonstrated to significantly enhance gastrointestinal integrity. Recent breakthroughs in molecular biology techniques, combined with great understanding of intestinal barrier physiology and regulation hold great promise for optimizing the formulation of alternative feed additives. Among phytogenic feed additives essential oils are particularly noteworthy, as they encapsulate the majority of plant's active ingredients. Essential oils may help to restore mucosal morphology and influence the dynamics of tight junction proteins, ultimately supporting gut integrity and gut physiology. Hence there is a greater chance that evidence-based data will form the basis of essential oils use in animal diets. However, there is still a need for more study into phytogenic substances in poultry nutrition. A comprehensive understanding of molecular mechanisms underlying the action of phytogenic feed additives is essential to unlock their full potential in poultry production. The complexity of animal health problems demands a comprehensive approach, incorporating the multiple feed additives to address aspects of health and break the cycle of disease in poultry production.

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