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Review article

Effects of chronic stress and intestinal inflammation on commercial poultry health and performance: A review

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Abstract

The gastrointestinal tract provides the biological environment for nutrient digestion and absorption. Its physical and chemical barriers are crucial to protect from invading pathogens and toxic substances. On this basis, the intactness of the gastrointestinal tract, with its multiple functions and impacts, is one of the key prerequisites for human and animal health. Undoubtedly, the functions of a healthy gut system also largely benefit the welfare and performance of animals in farming systems such as poultry industries. Broiler chickens grow rapidly, as a result of rigorous genetic programs, due to the high absorption capacity of intestinal epithelia for nutrients, the quick transport of nutrients to the muscle, and their efficient conversion into energy and biomass. Due to oxygen metabolism or enteric commensal bacteria, intestinal epithelial cells create reactive oxygen and nitrogen species physiologically. However, increased generation of these oxidants goes along with the formation of free radicals resulting in oxidative stress causing lipid peroxidation and dramatic molecular changes in the structure and function of the cell and mitochondrial membranes. These effects contribute to chronic oxidative stress and inflammation of the gastrointestinal tract and generally affect all chicken organs, tissues, and cells. Hence, all forms of chronic stress, regardless of the origin, negatively impact the chickens' overall performance, health, and welfare. This review article highlights some enteric inflammation models and biomarkers to evaluate gut integrity in chickens and discusses the repercussions that chronic stress and intestinal inflammation have on the health and performance of commercial poultry.

Keywords: Ceca, Chickens, Inflammation, Oxidative stress, Stress

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Introduction

Modern broiler chickens are most certainly the most visible manifestation of genetic advancements. At hatch, a Cobb500 broiler weighs 42 grams. This newborn chick grows 31 % (55 g/bird) in twenty-four hours. By day 35 of age, this chicken reaches a body weight of 2,521 grams, representing 5,902 % relative to hatching mass (Cobb-Vantress, 2022). Genetic selection, food, health, and management measures carried out intensively have resulted in these successes. However, it is essential for production to keep the gastrointestinal tract (GIT) in good condition. The GIT is the prin-

cipal organ responsible for digestion and nutrient absorption. The cost of subclinical coccidiosis or necrotic enteritis in broiler chickens is likely higher than that of clinically identified acute infections in poultry because feed conversion accounts for over 70% of the total cost of production (Aggrey et al., 2010). As the growing period of broilers shortens and feed efficiency improves, the need for improved health and nutrition programs becomes more apparent. Because the changes during intestinal growth are minute, they are often overlooked, yet gut health impacts general health and productivity.

Currently, animal production systems require a constant search to reduce the effects of stress and chronic inflammation to improve energy use by producing animals. Although there is no "silver bullet" to prevent multifactorial conditions associated with chronic stress, several studies show improvement in intestinal microbial balance, metabolism, and intestinal integrity through alternative products such as probiotics (Latorre et al., 2016; Tellez-Isaias et al., 2021), prebiotics (Torres-Rodriguez et al., 2007), organic acids (Hernandez-Patlan et al., 2019), plant extracts (Leyva-Diaz et al., 2021), essential oils (Coles et al., 2021; Ruff et al., 2021) and trace minerals (Baxter et al., 2020); this being an international scientific trend, due to the anti-inflammatory, antioxidant and immunomodulatory effects, as well such as improvement in intestinal integrity.

Substitution of antibiotics in production systems with alternative products, improved management practices, strict biosecurity, quality ingredients, absence of diseases (*Mycoplasma*/*Salmonella*), and effective immunization programs are effective strategies for health objectives and productivity. In this work, we focus on reviewing the significant repercussions of chronic stress and intestinal inflammation on the health and performance of commercial birds.

Chicken gastrointestinal tract architecture and players

In addition to absorbing and digesting water and food, the intestinal tract contains a diverse and complex microbial community (Celluzzi and Masotti, 2016), as well as an enteric nervous system (ENS) of metazoans considered the "second brain" of the organism (Schneider et al., 2019). This microbial population can be similar to the number of somatic cells in this tissue (Wallis et al., 2004; Zhu et al., 2010; Li et al., 2014; Sender et al., 2016). In addition to this complexity in the structure and microbial relationships, in chickens, the gut-associated lymphoid tissue (GALT) contains the highest concentration of immune cells in the organism, showing its relevance (Peralta et al., 2017; Casteleyn et al., 2010).

Furthermore, the digestive system has primary lymphoid organs such as the bursa of Fabricius, where B lymphocytes originate and multiply; this component of GALT in avian species is essential for protecting the digestive system (Bar-Shira et al., 2003). In mammals, GALT contains nearly 80% of plasma cells that produce secretory IgA, the most abundant immunoglobulin (Ig) (Vighi et al., 2008). Because the GALT harbors most immune cells, human chronic intestinal inflammation has been linked to various diseases and pathological states (Sekirov et al., 2010; Fasano, 2020; Feye et al., 2020). The intestinal microbiome can influence host biology, nutrition, immunity, and the neuroendocrine system (Dimitrov, 2011). GIT function appears to be mediated by short-chain fatty acids (SCFA) generated by bacterial fermentation (Wu et al., 2017), communication between the microbiota and neurons (Megur et al., 2020) , the endocrine system (Fukui et al., 2018), the immune system (Maslowski and Mackay, 2011) and modulation of the intestinal epithelial barrier (Sharma et al., 2010). The ENS and endocrine gut network control the GIT motility and disruption in functional GIT disorders (Fukui et al., 2018).

Enteroendocrine cells (EECs) are found throughout the GIT epithelium and produce several hormones (Gribble and Reimann, 2019). The first GIT hormones discovered were gastrin, secretin, cholecystokinin, insulin, and glucagon (Bloom, 1987). Over 50 hormones or bioactive peptides have been identified, making the GIT the primary organ displaying endocrine, neuroendocrine, autocrine, or paracrine activities (Rao and Wang, 2010; Gribble and Reimann, 2017). In metazoans, intestinal enterochromaffin cells, a subpopulation of numerous EECs, produce 90% of the neurotransmitter serotonin (5-hydroxytryptamine) (Lund et al., 2018).

Serotonin has multiple biological functions related to psychology and physiological activities in prokaryotes and eukaryotes, such as regurgitation, vasodilation, GIT motility, wound healing, reproduction, and vasoconstriction, among others (Negri et al., 2021; Berger et al., 2009). Additionally, the intestinal microbiota partially controls the secretion of serotonin, dopamine, oxytocin, and endorphins produced by EECs (Forsythe et al., 2010; Liang et al., 2014; Mayer et al., 2014). Hence, in humans, the microbiota is associated with neurological syndromes such as schizophrenia, autism, depression, Alzheimer's, and Parkinson's disease (Forsythe et al., 2010; Cryan and Dinan, 2012; Sherwin et al., 2016; Slavich and Irwin, 2014). There is great wisdom in the old saying "gut feelings". Gut health balance or homeostasis is affected by the microbiota-brain-gut axis, the immune system, oxidative stress, nutrition, the intestinal epithelial barrier, genetic factors, and feed additives, such as nutraceuticals (Figure 1).

The complex neuroendocrine network that connects the brain, the ENS, the intestinal microbiota, and the GALT (microbiota-brain-gut axis) substantially impacts the fragile intestinal epithelial barrier (Neuman et al., 2015; Megur et al., 2020), which also maintains tolerance and the immune response against foreign antigens and the balance of the microbiota (Maslowski and Mackay, 2011). Hence, prolonged stress and inflammation negatively impact the microbiota-brain-gut axis, causing dysbacteriosis and disrupting the

tight junction proteins with systemic translocation of bacteria and other antigens (Figure 2). During chronic stress and, as a result, chronic intestinal inflammation, energy for growth and reproduction is diverted away from these functions to sustain the inflammatory response. Poultry is no exception to this rule.

The hypothalamic–pituitary–adrenal axis (HPA axis) is a complex network of direct influences and feedback interactions between three components: the hypothalamus, the pituitary gland, and the adrenal glands on top of the kidneys (Lu et al., 2021). The HPA axis is a significant neuroendocrine system that controls stress reactions. It regulates numerous physiological systems, including digestion, the immune system, mood and emotions, sexuality, and energy storage and expenditure in response to environmental stimuli (Cohen et al., 2006). While vertebrates manufacture the majority of steroid hormones, the HPA axis and the physiological role of corticosteroids in stress response are crucial in eukaryotes (Lichtenthaler, 1998). Still, comparable systems can also be found in prokaryotes (Hentchel and Escalante-Semerena, 2015).

Pathogens and diseases

In general, constant damage or the presence of pathogenic agents induces a stress process in the GIT, increasing inflammation and, therefore, oxidative stress (Federico et al., 2007). Among the different possible pathogens in the GIT, we can include bacteria, and even protozoa, which infections can induce severe enteric damage, causing illness and high mortality rates. In chickens, *Eimeria tenella* is a primary cecal pathogen that negatively affects growth, feed utilization, and productivity due to necro-hemorrhagic typhlitis (Soutter et al., 2021). Conventional coccidiosis prevention relies heavily on chemoprophylaxis and life vaccines (Chapman, 2014), and on a global scale, economic costs in 2016 were estimated to be around USD 11.77 billion (Blake et al., 2020). As a result of growing consumer concerns about "superbugs" and the forthcoming rules prohibiting the use of growth-promoting or anticoccidial medications in chicken production, the industry has looked for alternative methods of control tactics to prevent coccidiosis (Chapman, 2008; Shivaramaiah et al., 2014; Hess et al., 2015). The emergence of multi-drug resistant *Eimeria* spp. in the field has limited the efficacious tools available for coccidiosis in commercial poultry operations (Chapman, 2014). The antigenic diversity of field strains and the high expense of manufacturing live vaccines for numerous *Eimeria* spp. hampers current vaccination efforts against coccidial infections relevant in the field (Blake et al., 2015; Clark et al., 2017).

Another protozoon that targets the ceca is *Histomonas meleagridis*, the cause of histomonosis in chickens and turkeys, which is traditionally controlled with arsenicals in the diet. Still, these compounds are considered prohibited (Sulejmanovic et al., 2013). Severe outbreaks and flock losses are becoming more common. Alternatives to control protozoa infections include feed additives and other immunomodulators, adjuvants, and recombinant vaccine development. However, there are no approved prophylactic or therapeutic compounds for histomonosis. To develop a chemotherapeutic treatment for the disease, novel compounds, including phytogenic compounds, can be tested *in-vitro*. Some phytogenic components evaluated include plant-derived essential oils, ethanol-water plant extracts, complex extracts, alkaloids, and sesquiterpene lactones (Liebhart et al., 2017). Alkaloids and sesquiterpene lactones showed an inhibiting effect of *Histomonas* in growth *in-vitro* but not in chickens or turkeys (Thøfner et al., 2012). Some commercial products claim to be effective against histomonosis with mixed results and claims unsupported by data (Hess et al., 2015).

Additionally, no commercial vaccines are available for *H. meleagridis* (Liebhart et al., 2017). The current understanding of parasite assault and host elimination is insufficient. The particularities of the host immunological response to *Histomonas* are becoming more apparent (Barros et al., 2020; Beer et al., 2020, 2022; Lagler et al., 2021; Mitra et al., 2021). Despite immunological research advancements, a histomonosis vaccine has no commercial application yet (Mitra et al., 2018); some experiments like oral or cloacal administration of clonal *in-vitro* attenuated histomonads provided adequate protection against virulent challenges in laboratory settings but not against heterologous, multi-isolate challenges in the field (Liebhart et al., 2013). Recently, research showed the application of attenuated isolates orally or locally to turkeys has no protective effect against wild-type challenge (Beer et al., 2022), contrary to previously reported success with oral vaccination at this age (Sulejmanovic et al., 2016). Unfortunately, using live histomonads in the industry would be problematic due to intra-cloacal administration requirements, attenuation stability, variable protective immunity (Hess et al., 2015), and the cost of cell culture (McAllister, 2014). There is an undeniable need to identify more effective solutions to lessen the impact of chicken coccidiosis and histomonosis. Yet, crucial resources still need to be included, making rapid progress difficult. New control strategies for protozoal infections are required, but only after a thorough molecular and cellular assessment of host-parasite interfaces is completed.

In particular, bacterial infections are considered one of the main GIT-associated infections, which due to their infection process and presence, are inducers of acute or even chronic inflammatory processes (Yamamoto et al., 2013). In murine models, *Salmonella* growth is aided, ironically, by acute inflammatory responses to pathogenic bacteria in the intestine, as there is increased migration of neutrophils and production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) as a result of the *Salmonella* infection disrupting the balance of the microbiota (Winter et al., 2010a). An increase in molecular oxygen in the lumen of the gut depletes important commensal anaerobes like *Bacteroidetes* and *Clostridiales*, which are essential butyric acid-producing bacteria (Rigottier-Gois, 2013). The thiosulfate oxidation to tetrathionate is also a ROS

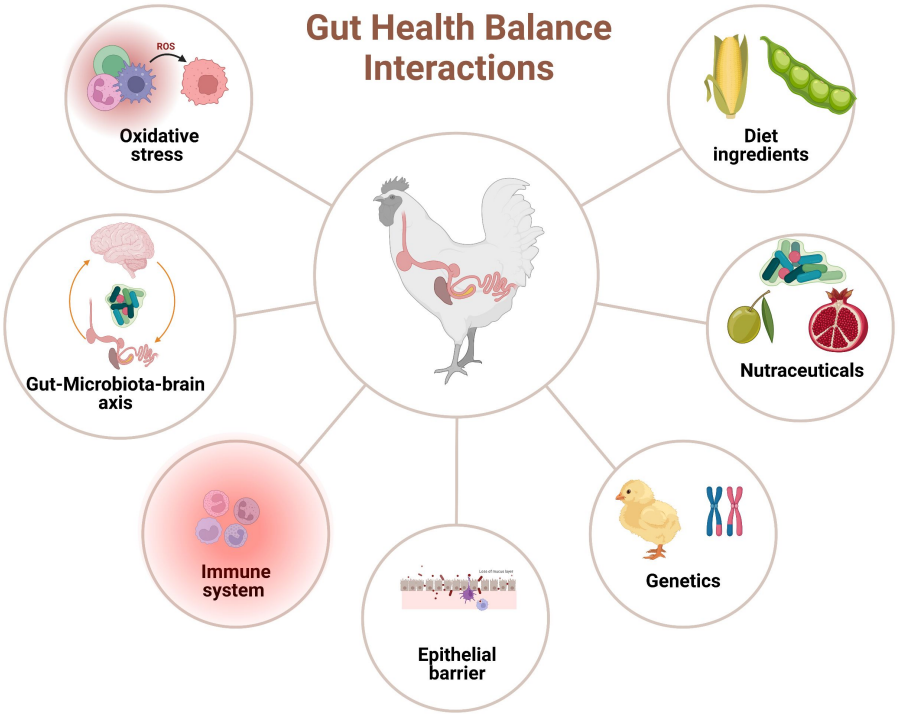

Figure 1: Interactions between the host (poultry species) and intrinsic or extrinsic factors that influence gut health (created with BioRender.com).

by-product (Winter et al., 2010b). In murine models, it has been shown that *Salmonella* uses tetrathionate to strengthen its development (Winter et al., 2010b); tetrathionate broth is a component of enriched media for the culture of *Salmonella* in diagnostic laboratories.

However, a recent study has found that this differs for chickens (Saraiva et al., 2021). In contrast to murine models, in poultry, the *ttr*A and *pdu*A genes do not appear to be significant virulence determinants in fecal excretion of invasiveness for *Salmonella* Enteritidis and *Salmonella* Typhimurium. Interestingly, the deletion of both genes does not attenuate the pathogen but slightly decreases the numbers of *Salmonella* Enteritidis and *Salmonella* Typhimurium in caecum in poultry, reducing inflammation and allowing the bacteria to more easily invade gut epithelial cells and disseminate systemically, leading to severe clinical signs and higher mortality rates (Saraiva et al., 2021). Similar results have been reported by Rimet et al. (2019). Therefore, the study of these interactions has shown their participation in the process of oxidative stress and inflammation.

In the case of physiological processes associated with the particular species, they can have an effect on triggers for stress processes and therefore induce chronic inflation. In most vertebrates, the renal system regulates body fluid and electrolytes. However, skin, salt glands, urine bladders, and digestive systems work together with the kidneys in non-mammalian vertebrates (Braun, 1999). Avian species are unique because they lack a urinary bladder, and renal discharge accesses the GIT directly. Both turkeys and chickens have a cloaca or common excretory pathway (Goldstein, 2006). Unlike mammals, where the kidney regulates the extracellular fluid composition independently, the urine flows into the cloaca in birds by a reverse peristaltic action to the ceca (Karasawa and Duke, 1995; Duke, 1999). Thus, the kidneys and lower GIT must regulate the extracellular fluid composition. Here, the avian ceca perform water reabsorption, fiber digestion (by bacterial fermentation), nitrogen recycling, microbial vitamin synthesis, and osmoregulation (Duke, 1982; Duke et al., 1983; Hall and Duke, 2000). SCFA are the primary bacterial fermentation metabolites absorbed in the ceca by two mechanisms: i) nonionic diffusion of protonated SCFA involving the consumption of luminal CO_2; this process accounts for about 60% of total SCFA absorption. ii) cellular uptake by ionic diffusion of the Na or K salt of the SCFA (Ruppin et al., 1980). Inflammation in the ceca (typhlitis) impairs the function of the ceca, decreasing the efficiency of water reabsorption (Awad et al., 2017).

Additionally, the dietary composition can affect the moisture in fecal droppings. The water content of the feces directly impacts the litter moisture in poultry production systems, with moisture levels ranging from 15% to 44%. Poultry litter contains high levels of proteins and nitrogen (Kelleher et al., 2002). A significant issue with poultry litter is the loss of nitrogen, such as ammonia, during microbial fermentation of urea and uric acid (Nahm, 2003). In chicken houses, ammonia volatilization is one of the most stressful gases to

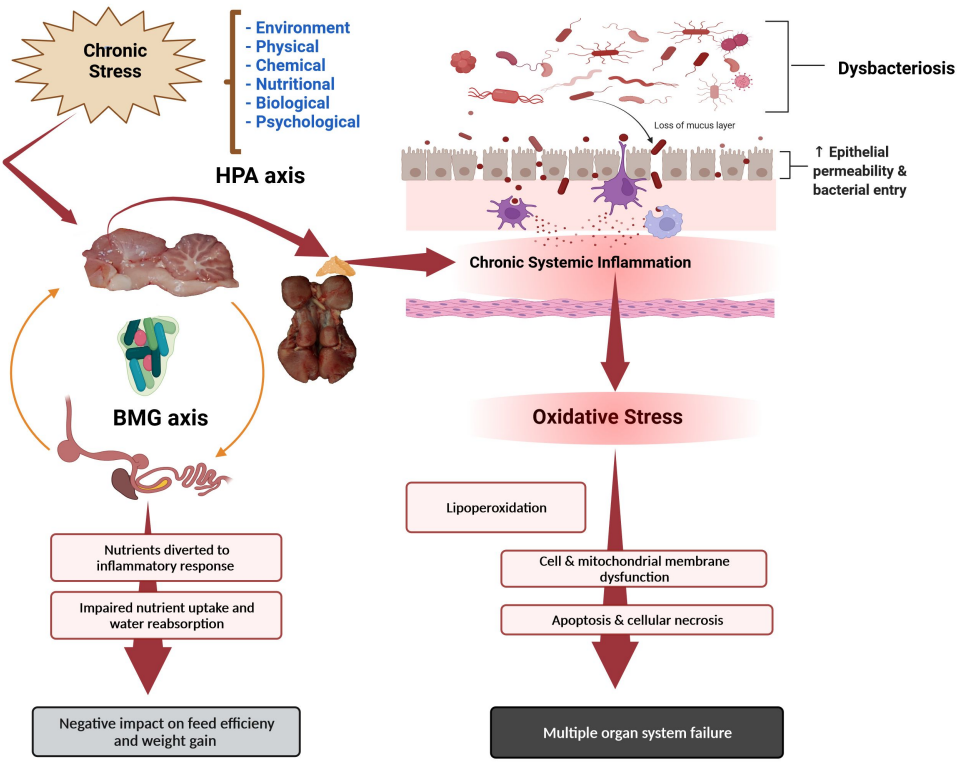

Figure 2: Chronic stress (regardless of its source) has a direct impact on the hypothalamic–pituitary–adrenal axis (HPA axis), the brain-microbiota-gut axis (BMG axis), and the endocrine and immunological systems. Intestinal and chronic systemic inflammations originate from disruptions in the delicate balance and environment of the intestinal microbiota (dysbacteriosis) and alterations in tight junction proteins among enterocytes causing leaky gut. Prolonged oxidative stress induced by the inflammatory process causes phospholipid peroxidation in cell and mitochondrial membranes, leading to apoptosis, cellular necrosis, and multiple organ failure (created with BioRender.com).

poultry that severely affects the birds' welfare, health, and performance (Moore et al., 2011; van der Hoeven-Hangoor et al., 2014).

Defense NF-κB TNFa Cytokines Cytokine storm

Pathogen-associated molecular patterns (PAMPs) are elements of pathogenic bacteria that metazoans recognize. PAMPs include lipopeptides, peptidoglycans, and teichoic acids (Salminen and Isolauri, 2006). The endotoxin lipopolysaccharide (LPS), found in Gram-negative bacteria outer membranes, is a classic example (Kallapura et al., 2014). As a main trigger, PAMPs activate the NF-κB axis (Jonkers and Stockbrügger, 2003). Inadequate NF-κB regulation has been associated with several immunological disorders (Elson and Cong, 2012).

Generally, infectious agents (bacterial, protozoal, viral, helminth) stimulate host pro-inflammatory responses. For instance, in domestic poultry, coccidiosis may cause necrosis and inflammation in the intestine, resulting in fever, depression, reduced performance, and death depending on the *Eimeria* spp. and infectious dose (Rose et al., 1975) (Figure 3). Infections with highly pathogenic strains of avian influenza (i.e., H5 or H7 subtypes) cause shock and mortality without clinical signs or lesions (Fernandez-Siurob et al., 2014; Smatti et al., 2019) (Figure 4). In both cases, the physiological consequences and death of the chicken are caused by the cascade of host-generated pro-inflammatory cytokines rather than by the protozoan or the virus.

ROS and RNS and their effects on a molecular level

Polymorphonuclear (PMN) leukocytes and macrophages fight pathogens as the first line of defense by producing reactive molecules capable of inducing oxidation or reduction reactions (Qureshi, 2003; Petrone-Garcia et al., 2021). These include ROS, such as superoxide, hydrogen peroxide, and hydroxyl radical. RNS comprise nitric oxide and peroxynitrite molecules. Both ROS and RNS are highly toxic to fight against invaders. They can penetrate the microbial cell wall easily, causing irreversible damage (Gostner et al., 2013). Immune signaling only initiates the production of these ROS and RNS molecules to intercept and kill pathogens (Sun et al., 2020). However, when ROS molecules overreact, they become immunotoxins capable of damaging the host cells and adjacent

tissues (Figure 5), leading to severe local and systemic inflammation and multiple organ failure (Chen and Kevil, 2020). Due to this, its control is key to avoiding the adverse effect due to its overproduction and its negative impact (Lian et al., 2020).

Chronic inflammation: Models and biomarkers

There is a delicate balance between pro-oxidant and antioxidant production during homeostasis, but chronic inflammation promotes an overabundance of ROS molecules, which can be severely damaging. ROS are associated with oxidative stress, including forming more RNS following the interaction of ROS with nitric oxide (NO). NO/RNS and ROS elicit immune responses and regulate immune function (Lee and Griendling, 2008; Wink et al., 2011). Extracellular pathogens that are too large for phagocytosis are targeted by ROS (Griffiths, 2005). When stimulated, RNS target intracellular/phagocytosed pathogens, extracellular pathogens, and tumor cells. Macrophages, the primary producers of ROS and RNS, detect and activate to eliminate bacterial infection via LPS recognition, a necessary and beneficial host mechanism (Lauridsen, 2019). However, prolonged exposure to high doses of LPS triggers inflammatory mediators (cytokine cascade), causing oxidative stress (Figure 4 & Figure 5). As a result, oxidative stress contributes to high mortality rates in metazoans (Rubartelli and Lotze, 2007). Organ failure and hypotension are common symptoms of septic shock (Jones and Sies, 2015). Nevertheless, it is essential to recognize that all forms of chronic stress (biological, nutritional, physical, chemical, or psychological) induce prolonged inflammation (Khansari et al., 2009).

In the GIT, chronic inflammation affects the integrity of the intestinal barrier by disrupting tight junction proteins leading to increased intestinal permeability ("leaky gut") (Fasano, 2020), causing bacterial translocation and systemic inflammation (Ilan, 2012). The inflammatory response can help the animal regain tissue homeostasis if adequately controlled. Nevertheless, tissues and organs are damaged if the stress and inflammation persist (Dal Pont et al., 2020, 2021). Researchers may use enteric inflammation models in a laboratory setting to examine alternative growth promoters and dietary supplements for poultry. Several intestinal inflammatory models have been developed, including high NSP diets (Tellez et al., 2014, 2015; Dal Pont et al., 2021), dexamethasone (Vicuña et al., 2015), dextran sodium sulfate (Menconi et al., 2015; Zou et al., 2018; Gilani et al., 2017a), feed restriction/fasting (Kuttappan et al., 2015), and heat stress (Ruff et al., 2020; Rostagno, 2020). Gut integrity is dependent on barrier function. Oxidative stress, antinutritional components in soy, indigestible protein or energy sources, heat stress, and histomonosis are all examples of stressors that might result in gut barrier breakdown (Williams, 2005; Sharma et al., 2007; Pastorelli et al., 2013; Tellez et al., 2014; Biswal et al., 2022). However, as a result of the elimination of antimicrobial growth boosters, novel multifactorial diseases causing enteritis and unknown gut disorders have evolved in broilers, resulting in significant health and performance consequences (Dahiya et al., 2006; Gholamiandehkordi et al., 2007; Yegani and Korver, 2008).

Dysbacteriosis, defined as an aberrant microbiota on a qualitative and quantitative level, triggers a cascade of events in the GIT, including decreased nutrient digestibility, inflammation, and leaky gut (Teirlynck et al., 2011). Furthermore, poor gut health has been linked to bacterial chondronecrosis, osteomyelitis lesions, and lameness in broiler chickens (Wideman and Prisby, 2012; Wideman et al., 2015). Proper gut barrier function is critical for overall health and homeostasis and serves as the first line of defense against environmental antigens (Jeon et al., 2013). The first layer of the gut barrier is the extrinsic mucus layer, which is composed of an outer layer of bacteria that is loosely attached to the epithelium and an inner layer of secretory IgA and mucin that is adherent to the second layer of the gut barrier, the intestinal epithelial cells (IECs), which is composed of a single layer of epithelial cells that separates the intestinal lumen from the underlying lamina propria (Sakamoto et al., 2000; Kim and Ho, 2010). These epithelial cells must have the ability to recover rapidly in the event of tissue damage (Audy et al., 2012). Enterocytes in the apical epithelium are responsible for nutrition absorption. Tight junctions close the paracellular space between adjacent epithelial cells on the apical surface, regulating the intestinal barrier's permeability by preventing bacteria and antigens from spreading paracellularly across the epithelium (Ulluwishewa et al., 2011). Because IECs are the predominant cell type in touch with the external environment, they serve as the first line of defense for the host.

Despite their non-hematopoietic origins, IECs are a critical component of innate immunity in the GALT, performing a broad range of immunological functions. Indeed, IECs are capable of recognizing pathogens via the expression of innate immune receptors, releasing antimicrobial molecules, and secreting a variety of hormones, neurotransmitters, enzymes, as well as cytokines and chemokines that mediate the interaction between innate and adaptive immune responses (Alverdy et al., 2005; Edelblum and Turner, 2009). Thus, any damage to IECs, whether direct or indirect, may result in a collapse of the gut barrier and subsequent disturbance of normal mucosal immune homeostasis, resulting in uncontrolled chronic intestinal and systemic inflammation (Schulzke et al., 2009; Ilan, 2012).

Numerous researchers have revealed the pathways behind the disruption of the protein networks that connect epithelial cells by inflammatory mediators (hormones, oxygen-free radical species, enzymes, and various pro-inflammatory cytokines) induced by infections, food elements, or any other stress (Steed et al., 2010; Hu et al., 2013). Other factors can also contribute to the breakdown of the intestinal barrier. Feeding oxidized/unpreserved fat in chicken and swine has increased intestinal epithelial turnover rates and apopto-

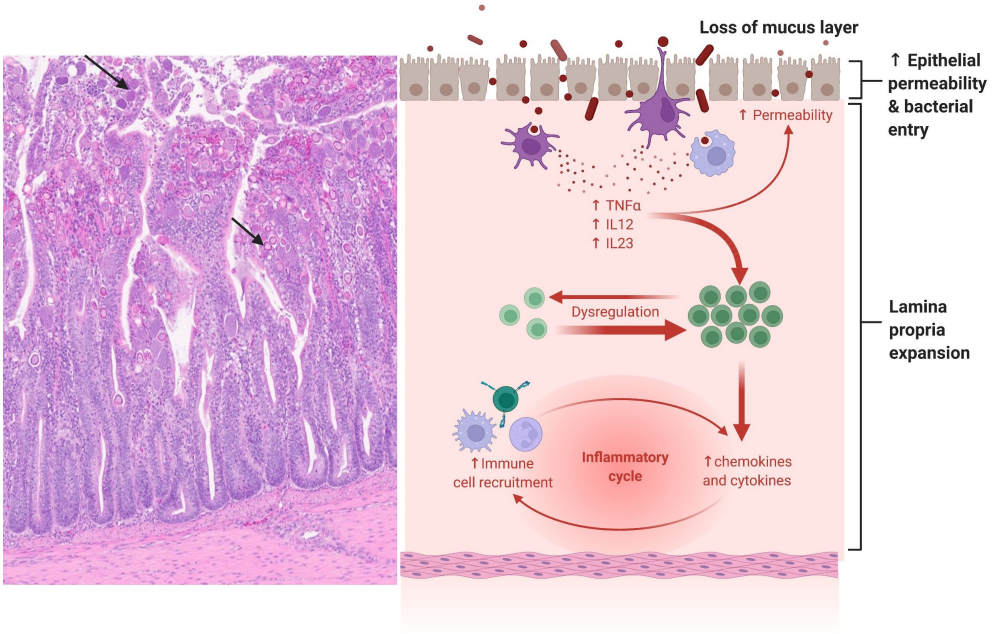

Figure 3: Gut barrier failure. Infectious agents (bacterial, protozoal, viral, helminth) in poultry stimulate host proinflammatory responses. Gut barrier failure caused by *Eimeria tenella*. Mucosa and submucosa of ceca with infiltration of inflammatory cells, ulceration, and necrosis. Arrows show the presence of the parasite. Hematoxylin and eosin staining (created with BioRender.com).

sis at villus tips (Dibner et al., 1996). Mineral nutrition also plays a role in the operation of the intestinal barrier, and metals are pro-oxidants, which may result in oxidative stress and barrier breakdown (Teirlynck et al., 2009). Simultaneously, zinc regulates several proteins essential for the formation of tight junctions between intestinal epithelial cells, and zinc deficiency has been found to impair barrier function (Debon and Tester, 2001; Ulluwishewa et al., 2011).

The ability of the GIT to work properly is critical in determining animal health, welfare, and performance. As previously noted, gut health encompasses a variety of elements such as oxidative stress, genetics, diet ingredients, the gut barrier, the interplay of the brain, gut microbiota, and the immune system. Each of these components is linked to each other via several complex mechanisms and pathways; however, identifying some critical elements of gastrointestinal functionality allows scientists to evaluate potential biomarkers that can enable them to measure the functionality of the GIT in poultry. Numerous and quickly expanding approaches are being used to create biomarkers, each with advantages and disadvantages. In most cases, several biomarkers to assess GIT functionality must be used due to the intricacy of the connections between the fundamental components of gastrointestinal performance. Using the keywords "biomarkers for intestinal integrity in poultry" in Google Scholar, the resulting survey yielded 1,730 articles. Having adequate models to induce gut inflammation in chickens and the tools to assess it are paramount to determining the impacts of nutraceutical feed additives or treatments as alternatives to antibiotic growth promoters. Table 1 summarizes some related and reliable biomarkers to evaluate intestinal integrity in chickens.

Damages in poultry farming

Hans Selye's 1975 Journal of Human Stress article "Confusion and controversy in the stress field" discusses stress research's confusion and controversies. Stress pioneer Hans Selye claims that the lack of a clear definition and the use of various terms have confused and slowed research. He proposes defining stress as "the body's nonspecific response to any demand." Selye also addresses the debate over "good stress" or eustress, which some researchers believe can improve performance and well-being. Selye believes that all stress, good or negative, can harm and that the key to managing stress is finding the optimal level that can be tolerated without harm. Selye suggests interdisciplinary stress research because the stress response is complex and needs input from psychology, physiology, and endocrinology. He stresses the need for researchers to consider both biological and psychological aspects of stress and to view stress as a whole-person phenomenon.

In humans, stress is described as a state of homeostasis being tested, manifesting as systemic and local stress (Juruena et al., 2021). Sometimes, a specific stressor may be associated with unique local stress. However, the stress level above a certain threshold may commonly activate the HPA axis and result in a systemic stress response. According to the system-stress conceptual framework, stress can be classified into three types. These are stress (inadequate stress), eustress (good stress), and distress (poor stress) (Selye, 1975). Both stress and distress can impede nor-

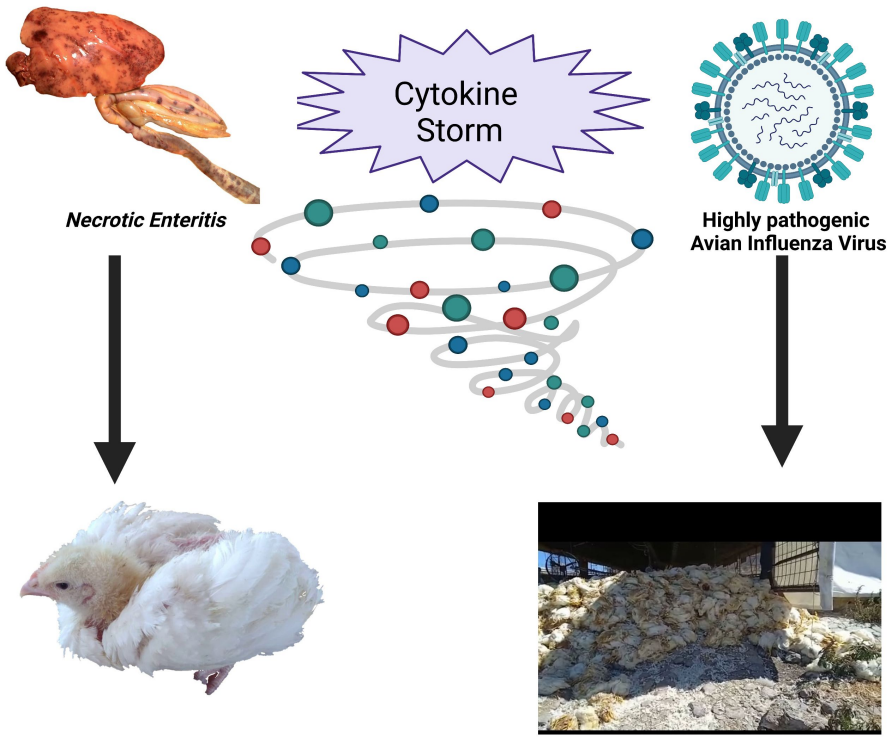

Figure 4: Necrotic enteritis may cause necrosis and severe inflammation in the intestine and bacterial liver translocation, resulting in fever, depression, and reduced performance. Infections with highly pathogenic strains of avian influenza (i.e., H5 or H7 subtypes) cause 100% mortality without clinical signs or lesions. In both examples, the excess proinflammatory cytokines or "cytokine storm" is responsible for those impressive effects. Image shows extensive mortality related to H7N7 (A/chicken/Jalisco/CPA1/2012) in a commercial flock in Mexico "Courtesy of Dr. Victor Petrone" (created with BioRender.com).

mal physiological functioning and even result in pathological situations, whereas eustress has the potential to promote health by promoting equilibrium through hormesis-induced optimization. As a result, maintaining an adequate stress level is critical for developing biological shields that ensure normal life processes (Lu et al., 2021). Although the impacts of stress have been linked to the development of most chronic illnesses, few physicians know how malfunctioning within the stress management system (HPA axis) alters pathophysiology (Karaca et al., 2021). A century of research on stress and the physiologic and metabolic consequences of stress has provided essential insight and enhanced our understanding of the subject. The clinical repercussions of stress in managing chronic diseases, on the other hand, continue to be a significant challenge (Guilliams and Edwards, 2010).

On the other hand, in poultry, infections, decreased feed intake, impaired feed conversion, and carcass condemnation are some of the repercussions that chronic neuroendocrine-immune interaction causes chicken (Calefi et al., 2017). Understanding and regulating environmental variables is critical to the success and welfare of chicken farming. Heat stress is one of the most significant ecological stressors threatening chicken production worldwide. It harms broiler chickens, ranging from lower performance to poor immunological response and food safety (Lara and Rostagno, 2013). Heat stress causes changes in protein, membrane lipid, and metabolic rate, all associated with the body's response and the production of heat shock proteins as a defense mechanism for cells and tissues. When it comes to maintaining homeostasis in an animal, the hypothalamus, in conjunction with all cells, tissues, and organs, plays a critical role. In experiencing stress, the HPA axis is activated through many sensory organs (Kuenzel and Jurkevich, 2010), releasing steroid hormones from the adrenal gland. The activation of the pituitary component of the HPA axis can be mediated by neuroendocrine hormones, including corticotropin-releasing hormone and adrenocorticotrophic hormone (Cao et al., 2021). Secretion of steroids from the adrenal cortex is induced by ACTH, which is released by the anterior pituitary gland. Adrenal corticoid production is mediated by the actions of the endocrine hormones ACTH, CRH, and Vasopressin (VP). The HPA axis is critical in directing the neuroendocrine systems that regulate the complex adaptive responses of animals to environmental stresses to maintain a healthy chicken (Binsiya et al., 2017). Activating glucocorticoids is critical in the induction of hepatic gluconeogenesis, which is necessary to promote the adaption process. Glucocorticoids also increase the production of epinephrine in the adrenal medulla, which is another crucial hormone (Wickramasuriya et al., 2022).

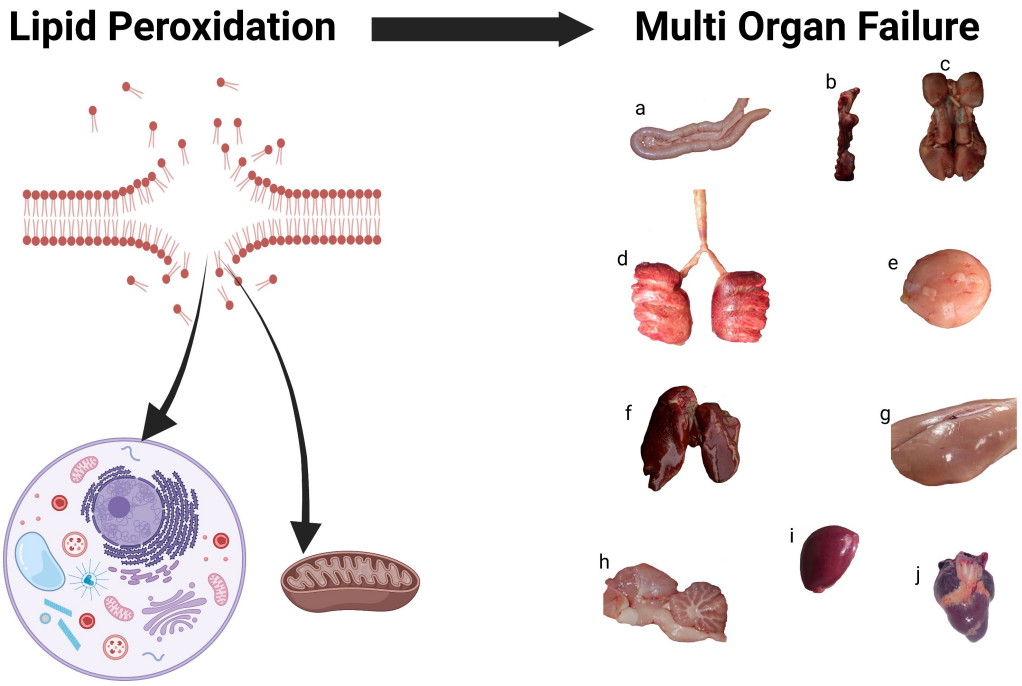

Figure 5: Excessive and chronic oxidative stress causes damage and lipid peroxidation of the mitochondrial and cell membranes. Alteration of these vital organelles affects all cells and tissues, causing apoptosis, necrosis, and multiple organ failure [a) intestine; b) thymus; c) kidneys; d) lungs; e) bursa of Fabricius; f) liver; g) muscle; h) brain/cerebellum; i) spleen; j) heart] (created with BioRender.com).

Flock density, or the number of chickens housed in a given area, can significantly affect the social dynamics of a chicken flock. As the density of a flock increases, so does the potential for social stress among individual birds. This is because chickens are social animals that establish hierarchies and interact with one another in complex ways. When too many birds are in a given space, competition for resources such as food, water, and space can lead to increased aggression and social tension (Naga Raja Kumari and Narendra Nath, 2018). Social stress can have a range of negative effects on chickens, including reduced immune function and increased susceptibility to disease. For example, chickens experiencing social stress may have higher levels of the stress hormone cortisol, which can suppress the immune system and make them more vulnerable to infections such as enteritis (Collins and Siegel, 1987). In addition, social stress can lead to increased levels of feather pecking and cannibalism, which can create wounds that provide entry points for bacterial infections. High flock density can also exacerbate the effects of heat stress on chickens. When temperatures rise, chickens may experience heat stress, leading to reduced feed intake, reduced egg production, and increased mortality. In addition, heat stress can exacerbate social stress by increasing competition for resources and creating a more hostile environment within the flock (Nicol et al., 2006). In this way, high flock density can make chickens more vulnerable to the negative effects of social and heat stresses. It is important to carefully manage flock density to minimize the potential for social stress and its negative effects on chicken health and well-being. This can include providing adequate space, ensuring access to resources such as food and water, and monitoring the flock for signs of stress or disease (Heckert et al., 2002). In a recent study, breeder age, chick gender, and breed were the internal factors significantly related to chick mortality associated with housing factors and management routines (Yerpes et al., 2020). Moreover, important characteristics linked with stress in broiler chickens during transport to the processing plant required immediate attention (Yerpes et al., 2021).

In response to cellular harm, inflammation is the final stage of the stress response, regardless of the source that triggered the stress. Stress and inflammation are innately regulated by immune and endocrine mechanisms (Stecher, 2015). When stressed, the autonomic nervous system and endocrine hormones (adrenaline and glucocorticoids) prepare every cell in the body for "fight-or-flight". As long as the stressful signal persists, the animal remains in survival mode, a biological process intended to be short and acute (Winter et al., 2010a). If the stress continues, stress hormones and other pro-inflammatory molecules persist in circulation, causing oxidative stress and chronic systemic inflammation (Fasano, 2011; Bickler et al., 2020), severely damaging the cell and mitochondrial membranes (lipid peroxidation), as described below.

The cell and mitochondrial membranes contain a phospholipid bilayer containing proteins and transport channels. The cell membrane regulates cell adhesion,

Table 1: Biomarkers to evaluate intestinal integrity in chickens.

Assessment	Biomarker	Reference
Serum intestinal permeability	Fluorescein isothiocyanate dextran	Baxter et al. (2017); Gilani et al. (2017a); Vuong et al. (2021)
	Mannitol and rhamnose sugars	Gilani et al. (2017b)
	d(-)-Lactate	Zou et al. (2018)
	Fibronectin, intestinal alkaline phosphatase, and lipocalin-2	Barekatain et al. (2020)
Intestinal permeability	Faecal ovotransferrin	Goossens et al. (2018)
	Liver bacterial translocation	Latorre et al. (2014, 2015)
Serum intestinal anti-oxidant activity	Griess, superoxide dismutase, thiobarbituric acid reactive substances, total antioxidant capacity	Baxter et al. (2019)
Serum and tissue inflammation	Isoprostane 8-iso-PGF2α	Petrone-Garcia et al. (2021)
	Prostaglandin GF2α	
	Endotoxin and α1-acid glycoprotein	Chen et al. (2015)
	Interleukin (IL)-1β, tumour necrosis factor-α and IL-10	Zou et al. (2018)
Cellular and immunological intestinal inflammation (mRNA)	IL-8, IL-1β, transforming growth factor (TGF)-β4, and fatty acid-binding protein	Chen et al. (2015)
Serum enterocyte biomarkers	Extracellular signal-regulated kinase	Baxter et al. (2019)
	Citrulline	
Serum immune biomarkers	IFN-γ	
	Secretory IgA	
Circulating inflammatory and redox markers	IL-3, IL-6, IL-4, IL-18, and tumor necrosis factor-α, chemokines (CCL-20), and NOD-like receptor family pyrin domain containing three inflammasomes	Mullenix et al. (2021)
Indirect way to evaluate short-chain fatty acids	Peptide YY	Tellez et al. (2020)
Serum and feces intestinal inflammation	Calprotectin	Dal Pont et al. (2021)

ion conductivity, and cellular signaling (Sharma et al., 2010). Prokaryotes, the most primitive organisms on the planet, have taught cell scientists about the extraordinary properties of the cell membrane. This organelle represents not only the protective permeable exterior barrier of the cell but also the brain of the cell ("mem-brain") (Lipton, 2016). Like eukaryotes, prokaryotes, including bacteria and other microorganisms, have membranes surrounding a droplet of cytoplasm. Prokaryotes acquire nutrients, communicate, excrete, and even process information in a "neurological" way (Desvaux et al., 2009; Lazcano and Peretó, 2021). They can detect the presence of nutrients, toxins, and predators adopting powerful escape techniques to preserve their viability (Liversidge, 1993). However, the nucleus and mitochondria in more evolved eukaryotic cells are absent in the prokaryotic cytoplasm. Thus, only the cell membrane can be considered a contender for the "prokaryote's brain" (Lipton, 2016). Any damage to this organelle compromises the biology of the prokaryotic cell or the eukaryotic cell.

On the other hand, according to endosymbiotic theory, several essential eukaryotic organelles evolved from symbiotic relationships between prokaryotes. Two billion years ago, an endosymbiont, a free-living bacterium, was incorporated into a host cell (Sagan, 1967). According to available evidence, both mitochondria and chloroplasts descended from proteobacteria and cyanobacteria, respectively, during the evolution of life (Gray, 2017). On our planet, that symbiotic association changed the course of evolution indefinitely. Mitochondria, commonly known as the "powerhouse of eukaryotic cells," have a membrane structure comparable to the cell membrane. Nevertheless, in addition to providing energy to the cell, mitochondria are crucial for several cellular metabolic processes, including signal transduction and apoptosis (Osellame et al., 2012). Because mitochondrial injury and dysfunction affect cell metabolism, they are implicated in many animal and plant illnesses (Frye et al., 2016). As biologist Nick Lane colorfully puts it, "mitochondria rule the world" (Lane, 2013). Avian species are not the exception (Kimball et al., 2021). Oxidation of lipids in membranes occurs because persistent inflammation produces reactive oxygen species. Hence, oxidative stress has profound implications during this reactive oxygen species misbalance (Niki et al., 1991; Itri et al., 2014). The disruption of cell and mitochondrial membranes is detrimental to cell function (Collett, 2012; López-González et al., 2015). Not surprisingly, in humans, chronic stress and inflammation have been identified as the "secret killers" for these reasons (Korniluk

et al., 2017). However, the concept also applies to poultry (Mishra and Jha, 2019).

All biological and physiological processes are balanced for the various microbiomes found on mucosal surfaces (Tlaskalová-Hogenová et al., 2004). Loss of balance of the microbiota (dysbiosis) in the GIT is associated with intestinal inflammation leading to loss of intestinal integrity (Weiss and Hennet, 2017). The composition of feed and the viscosity of intestinal contents influence the development of the microbial population in the GIT, especially in the small intestine (Tellez et al., 2014). Exogenous enzymes must be added to high non-starch polysaccharides (NSP)-monogastric diets to avoid anti-nutritional effects associated with excessive viscosity, intestinal irritation, and decreased performance (Bedford and Classen, 1993; Choct et al., 1995; Kiarie et al., 2013); Furthermore, researching in chickens and turkeys revealed that rye fed as an energy source enhanced digesta viscosity, bacterial translocation, and leakage of fluorescein isothiocyanate-dextran (FITC-d), affecting the microbiota composition as well as bone mineralization (Tellez et al., 2014, 2015). The grain's nutritional value will determine the usage of energy sources in chicken diets.

Low-grade intestinal tract damage and inflammation may cause poor feed efficiency, which is extremely costly to the poultry industry (Porter, 1998). Endogenous and exogenous factors influence the homeostatic balance of the host GIT (Figure 1). These factors may benefit or negatively impact the host (Dal Pont et al., 2020, 2021). Any cause of stress, regardless of its origin, will promote an inflammatory response. The effects of stressors, including biological factors, nutritional factors (Solis-Cruz et al., 2019; Morales-Mena et al., 2020; Hernández-Ramírez et al., 2021), environmental factors (Kim and Patterson, 2003), and chemicals (Morales-Barrera et al., 2016) on oxidative stress and inflammation in poultry is shown in Figure 2. All of the factors represent different types of stress capable of inducing inflammation and disrupting the microflora, causing dysbacteriosis (Iebba et al., 2016). Additionally, chronic stress and inflammation cause malabsorption by severely impairing nutrient acquisition and water reabsorption (Mishra and Jha, 2019).

Determining the best microbiome for chickens is an ongoing area of research for poultry scientists, nutritionists, and flock managers. A healthy and diverse microbiome can improve chickens' overall health, growth, and productivity. To determine the best microbiome for chickens, researchers and flock managers usually follow these steps: i) Literature review: Researchers consult existing literature and studies to gather information on the composition of a healthy chicken microbiome. This includes beneficial microbes known to have positive effects on chicken health, growth, and productivity (Oakley et al., 2014). ii) Analyzing samples: Researchers and flock managers collect samples from healthy chickens, such as fecal or intestinal samples, to identify the types and proportions of microbes present. This information can serve as a benchmark for a healthy microbiome (Yeoman et al., 2012), iii) Experimental trials: Researchers conduct controlled experiments with various diets, supplements, or probiotics to determine their effects on the chicken microbiome. They also monitor chickens' health, growth, and productivity to identify positive correlations between specific microbial populations and desired outcomes (Shehata et al., 2022b). iv) Metagenomic sequencing: Advances in technology, such as metagenomic sequencing, have made it possible to analyze the entire genetic material of the microbial communities within a sample. This provides a more comprehensive understanding of the microbiome's diversity and function (Feye et al., 2020). v) Data analysis and modeling: Researchers analyze and model the collected data to identify patterns and relationships between the microbiome's composition and chicken health, growth, and productivity. This helps them determine the optimal microbiome (Diaz Carrasco et al., 2019).

Intestinal homeostasis is defined as the absence of inflammation and the absence of excessive secretions (water or mucus) within the intestinal tract (Gabriel et al., 2006). Physiological inflammation is ongoing during intestinal homeostasis as a controlled response to maintain tolerance to dietary antigens and the commensal microbiota and to prevent damage to the epithelium (Kogut et al., 2018). However, when induced, a pro-inflammatory cascade promotes an influx of immune cells and plasma proteins to the affected area, which can cause excessive fluid secretion, especially during chronic inflammation (Noguchi et al., 1998). The inflammatory response is an energetically expensive process, and rather than being partitioned for growth or protein accretion, nutrients are diverted to the host inflammatory response (Korver, 2012). It has been reported that inflammation, fever, and altered organ metabolism result in muscle catabolism and anorexia during the acute phase responses in chickens challenged with LPS, reducing body weight growth by 22%, but only 59% of this reduction was due to a decrease in caloric intake during the challenge with LPS. Thus, additional mechanisms such as the immunological response were responsible for 41% of the body weight gain depression (Jiang et al., 2010). Damage to the intestinal epithelial barrier increases permeability, promotes inflammation, and reduces the surface area available for nutrient absorption (Dunaway and Adedokun, 2021). Additionally, factors that slow gut transit time and increase the viscosity of digesta, such as diets high in NSP without the addition of exogenous enzymes, are associated with dysbacteriosis and intestinal inflammation that negatively impact performance (Tellez et al., 2014). Undigested feed in the fecal droppings indicates digestive malfunction (Yegani and Korver, 2008).

Because urine and feces are ejected concurrently through the cloaca, it is difficult to separate increased urine output or polyuria from increased fecal water loss or diarrhea in poultry. This increase in water excretion is frequently caused by physiological diuresis or diarrhea. However, pathological changes caused by nutrition can exacerbate polyuria by hindering water recov-

ery or diarrhea by inducing enteritis (Collett, 2012). On the other hand, watery intestinal contents may occur due to excessive digestive secretions or an osmotic effect of the diet due to composition or electrolyte imbalances (Francesch and Brufau, 2004). Inflammation of the renal or gastrointestinal lining compromises water and nutrient transfer, which increases the amount of water, mucus, and non-digested nutrients in the excreta (Dunaway and Adedokun, 2021). Besides loading the litter with water, the mucus and non-digested lipids reduce the litter's water-buffering capacity and exacerbate the consequences of flushing (Collett, 2012). Infections or toxins can also cause excessive secretion by the intestinal cells (Sears and Kaper, 1996).

Enteric inflammation in poultry is often related to the passage of undigested feed and increased intestinal permeability. Heat stress, enteropathogens, or disturbances in nutrition may cause chronic intestinal inflammation. Enteric inflammation, epithelial cell death, and leaky gut affect feed efficiency, litter moisture, and water consumption. Several manuscripts have described the economic implications of heat stress, coccidiosis, or necrotic enteritis, causing billions of dollars to the poultry industry. Nevertheless, while this review is focused on broiler chickens, the biological and pathological consequences of chronic stress and chronic intestinal or systemic inflammation apply to all eukaryote or prokaryote organisms. The ability to induce gut inflammation *in-vivo* and the tools (biomarkers) to evaluate such physiological changes in poultry are of supreme importance to consider nutraceuticals as feed additives with promising antioxidant, anti-inflammatory, and immune modulator capabilities to help scavenge redox molecules. They are, therefore, potentially effective in reducing chronic oxidative stress and inflammation in the gastrointestinal system of modern poultry operations.

Countermeasures

Since the origin of intestinal inflammation and oxidative stress is multifactorial, it is important to mention that its prevention must include various approaches. Using probiotics, prebiotics, and phytogenic substances is one of the main strategies for improving nutrient utilization (Shehata et al., 2022a). This strategy is focused on reducing the colonization of various pathogens associated with the induction of inflammatory processes in GIT. The complex interaction of these microorganisms in relation to the intestinal microflora plays a decisive role in their use and the correct effect in modulating the natural microflora of the host. Coupled with the use of dietary components such as essential oils (Zou et al., 2016) and trace minerals (Chen et al., 2022), turn out to be possibly successful strategies for reducing these negative effects of chronic inflammatory and stress oxidative on the GIT.

Outlook

The study and understanding of the complex relationship between microflora, diet, environment, genetic factors, as well as the components of the diet of production animals, particularly production birds, make this multidisciplinary approach one of the branches of nutrition with a greater impact in the future before the current remains of food production worldwide.

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References

Aggrey, S.E., Karnuah, A.B., Sebastian, B., Anthony, N.B., 2010. Genetic properties of feed efficiency parameters in meat-type chickens. Genetics, Selection, Evolution 42, 25. 10.1186/1297-9686-42-25.

Alverdy, J., Zaborina, O., Wu, L., 2005. The impact of stress and nutrition on bacterial-host interactions at the intestinal epithelial surface. Current Opinion in Clinical Nutrition and Metabolic Care 8, 205–209. 10.1097/00075197-200503000-00016.

Audy, J., Mathieu, O., Belvis, J., Tompkins, T.A., 2012. Transcriptomic response of immune signalling pathways in intestinal epithelial cells exposed to lipopolysaccharides, gram-negative bacteria or potentially probiotic microbes. Beneficial Microbes 3, 273–286. 10.3920/BM2012.0027.

Awad, W.A., Hess, C., Hess, M., 2017. Enteric pathogens and their toxin-induced disruption of the intestinal barrier through alteration of tight junctions in chickens. Toxins 9. 10.3390/toxins9020060.

Bar-Shira, E., Sklan, D., Friedman, A., 2003. Establishment of immune competence in the avian GALT during the immediate post-hatch period. Developmental and Comparative Immunology 27, 147–157. 10.1016/s0145-305x(02)00076-9.

Barekatain, R., Howarth, G.S., Willson, N.L., Cadogan, D., Wilkinson, S., 2020. Excreta biomarkers in response to different gut barrier dysfunction models and probiotic supplementation in broiler chickens. Plos One 15, e0237505. 10.1371/journal.pone.0237505.

Barros, T.L., Beer, L.C., Tellez, G., Fuller, A.L., Hargis, B.M., Vuong, C.N., 2020. Research note: Evaluation of dietary administration of sodium chlorate and sodium nitrate for histomonas meleagridis prophylaxis in turkeys. Poultry Science 99, 1983–1987. 10.1016/j.psj.2019.11.055.

Baxter, M.F.A., Greene, E.S., Kidd, M.T., Tellez-Isaias, G., Orlowski, S., Dridi, S., 2020. Water amino acid-chelated trace mineral supplementation decreases circulating and intestinal HSP70 and proinflammatory cytokine gene expression in heat-stressed broiler chickens. Journal of Animal Science 98. 10.1093/jas/skaa049.

Baxter, M.F.A., Latorre, J.D., Dridi, S., Merino-Guzman, R., Hernandez-Velasco, X., Hargis, B.M., Tellez-Isaias, G., 2019. Identification of serum biomarkers for intestinal integrity in a broiler chicken malabsorption model. Frontiers in Veterinary Science 6, 144. 10.3389/fvets.2019.00144.

Baxter, M.F.A., Merino-Guzman, R., Latorre, J.D., Mahaffey, B.D., Yang, Y., Teague, K.D., Graham, L.E., Wolfenden, A.D., Hernandez-Velasco, X., Bielke, L.R., Hargis, B.M., Tellez, G., 2017. Optimizing fluorescein isothiocyanate dextran measurement as a biomarker in a 24-h feed restriction model to induce gut permeability in broiler chickens. Frontiers in Veterinary Science 4, 56. 10.3389/fvets.2017.00056.

Bedford, M.R., Classen, H.L., 1993. An *in-vitro* assay for prediction of broiler intestinal viscosity and growth when fed rye-based diets in the presence of exogenous enzymes. Poultry Science 72, 137–143. 10.3382/ps.0720137.

Beer, L.C., Graham, B.D.M., Barros, T.L., Latorre, J.D., Tellez-Isaias, G., Fuller, A.L., Hargis, B.M., Vuong, C.N., 2022. Evaluation of live-attenuated *Histomonas meleagridis* isolates as vaccine candidates against wild-type challenge. Poultry Science 101, 101656. 10.1016/j.psj.2021.101656.

Beer, L.C., Latorre, J.D., Rochell, S.J., Sun, X., Tellez, G., Fuller, A.L., Hargis, B.M., Vuong, C.N., 2020. Research note: Evaluation of deoxycholic acid for antihistomonal activity. Poultry Science 99, 3481–3486. 10.1016/j.psj.2020.03.049.

Berger, M., Gray, J.A., Roth, B.L., 2009. The expanded biology of serotonin. Annual Review of Medicine 60, s. 355–366. 10.1146/annurev.med.60.042307.110802.

Bickler, S.W., Prieto, J.M., Cauvi, D.M., De Cos, V., Nasamran, C., Ameh, E., Amin, S., Nicholson, S., Din, H., Mocumbi, A.O., Noormahomed, E.V., Tellez-Isaias, G., Fisch, K.M., De Maio, A., 2020. Differential expression of nuclear genes encoding mitochondrial proteins from urban and rural populations in morocco. Cell Stress & Chaperones 25, 847–856. 10.1007/s12192-020-01108-x.

Binsiya, T.K., Sejian, V., Madiajagan, B., Krishnan, G., Hyder, I., Ayyasamy, M., Lees, A., Gaughan, J., Bhatta, R., 2017. Significance of hypothalamic-pituitary-adrenal axis to adapt to climate change in livestock. International Research Journal of Agricultural and Food Sciences 2, 1–20.

Biswal, J., Vijayalakshmy, K., T. K, B., Rahman, H., 2022. Impact of heat stress on poultry production. World's Poultry Science Journal 78, 179–196. 10.1080/00439339.2022.2003168.

Blake, D.P., Clark, E.L., Macdonald, S.E., Thenmozhi, V., Kundu, K., Garg, R., Jatau, I.D., Ayoade, S., Kawahara, F., Moftah, A., Reid, A.J., Adebambo, A.O., Álvarez Zapata, R., Srinivasa Rao, A.S.R., Thangaraj, K., Banerjee, P.S., Dhinakar-Raj, G., Raman, M., Tomley, F.M., 2015. Population, genetic, and antigenic diversity of the apicomplexan *Eimeria tenella* and their relevance to vaccine development. Proceedings of the National Academy of Sciences of the United States of America 112, E5343–50. 10.1073/pnas.1506468112.

Blake, D.P., Knox, J., Dehaeck, B., Huntington, B., Rathinam, T., Ravipati, V., Ayoade, S., Gilbert, W., Adebambo, A.O., Jatau, I.D., Raman, M., Parker, D., Rushton, J., Tomley, F.M., 2020. Re-calculating the cost of coccidiosis in chickens. Veterinary Research 51, 115. 10.1186/s13567-020-00837-2.

Bloom, S.R., 1987. Gut hormones in adaptation. Gut 28 Suppl, 31–35. 10.1136/gut.28.suppl.31.

Braun, E.J., 1999. Integration of renal and gastrointestinal function. Journal of Experimental Zoology 283, 495–499. URL: https://pubmed.ncbi.nlm.nih.gov/10069044/.

Calefi, A., Quinteiro-Filho, W., Ferreira, A., Palermo-Neto, J., 2017. Neuroimmunomodulation and heat stress in poultry. World's Poultry Science Journal 73, 493–504. 10.1017/S0043933917000472.

Cao, C., Chowdhury, V.S., Cline, M.A., Gilbert, E.R., 2021. The microbiota-gut-brain axis during heat stress in chickens: A review. Frontiers in Physiology 12, 752265. 10.3389/fphys.2021.752265.

Casteleyn, C., Doom, M., Lambrechts, E., Van den Broeck, W., Simoens, P., Cornillie, P., 2010. Locations of gut-associated lymphoid tissue in the 3-month-old chicken: A review. Avian Pathology 39, 143–150. 10.1080/03079451003786105.

Celluzzi, A., Masotti, A., 2016. How our other genome controls our epi-genome. Trends in Microbiology 24, 777–787. 10.1016/j.tim.2016.05.005.

Chapman, H.D., 2008. Coccidiosis in the turkey. Avian Pathology 37, 205–223. 10.1080/03079450802050689.

Chapman, H.D., 2014. Milestones in avian coccidiosis research: A review. Poultry Science 93, 501–511. 10.3382/ps.2013-03634.

Chen, J., Tellez, G., Richards, J.D., Escobar, J., 2015. Identification of potential biomarkers for gut barrier failure in broiler chickens. Frontiers in Veterinary Science 2, 14. 10.3389/fvets.2015.00014.

Chen, J., Yan, F., Kuttappan, V.A., Wedekind, K., Vázquez-Añón, M., Hancock, D., 2022. Effects of bis-chelated copper in growth performance and gut health in broiler chickens subject to coccidiosis vaccination or coccidia challenge. Frontiers in Physiology 13, 991318. 10.3389/fphys.2022.991318.

Chen, Y., Kevil, C.G., 2020. Redox signaling and cardiovascular disease: New paradigms and discoveries. Redox Biology 37, 101743. 10.1016/j.redox.2020.101743.

Choct, M., Hughes, R.J., Trimble, R.P., Angkanaporn, K., Annison, G., 1995. Non-starch polysaccharide-degrading enzymes increase the performance of broiler chickens fed wheat of low apparent metabolizable energy. The Journal of Nutrition 125, 485–492. 10.1093/jn/125.3.485.

Clark, E.L., Tomley, F.M., Blake, D.P., 2017. Are eimeria genetically diverse, and does it matter? Trends in Parasitology 33, 231–241. 10.1016/j.pt.2016.08.007.

Cobb-Vantress, 2022. Cobb500 broiler performance & nutrition supplement (2022). URL: https://www.cobb-vantress.com/assets/Cobb-Files/product-guides/5502e86566/2022-Cobb500-Broiler-Performance-Nutrition-Supplement.pdf.

Cohen, H., Zohar, J., Gidron, Y., Matar, M.A., Belkind, D., Loewenthal, U., Kozlovsky, N., Kaplan, Z., 2006. Blunted HPA axis response to stress influences susceptibility to post-traumatic stress response in rats. Biological Psychiatry 59, 1208–1218. 10.1016/j.biopsych.2005.12.003.

Coles, M.E., Forga, A.J., Señas-Cuesta, R., Graham, B.D., Selby, C.M., Uribe, J., Martínez, B.C., Angel-Isaza, J.A., Vuong, C.N., Hernandez-Velasco, X., Hargis, B.M., Tellez-Isaias, G., 2021. Assessment of lippia origanoides essential oils in a *Salmonella* Typhimurium, *Eimeria maxima*, and *Clostridium perfringens* challenge model to induce necrotic enteritis in broiler chickens. Animals 11. 10.3390/ani11041111.

Collett, S.R., 2012. Nutrition and wet litter problems in poultry. Animal Feed Science and Technology 173, 65–75. 10.1016/j.anifeedsci.2011.12.013.

Collins, J., Siegel, P., 1987. Human handling, flock size and responses to an *E. coli* challenge in young chickens. Applied Animal Behaviour Science 19, 183–188. 10.1016/0168-1591(87)90215-2.

Cryan, J.F., Dinan, T.G., 2012. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. Nature Reviews. Neuroscience 13, 701–712. 10.1038/nrn3346.

Dahiya, J., Wilkie, D., Van Kessel, A., Drew, M., 2006. Potential strategies for controlling necrotic enteritis in broiler chickens in post-antibiotic era. Animal Feed Science and Technology 129, 60–88. 10.1016/j.anifeedsci.2005.12.003.

Dal Pont, G.C., Belote, B.L., Lee, A., Bortoluzzi, C., Eyng, C., Sevastiyanova, M., Khadem, A., Santin, E., Farnell, Y.Z., Gougoulias, C., Kogut, M.H., 2021. Novel models for chronic intestinal inflammation in chickens: Intestinal inflammation pattern and biomarkers. Frontiers in Immunology 12, 676628. 10.3389/fimmu.2021.676628.

Dal Pont, G.C., Farnell, M., Farnell, Y., Kogut, M.H., 2020. Dietary factors as triggers of low-grade chronic intestinal inflammation in poultry. Microorganisms 8. 10.3390/microorganisms8010139.

Debon, S.J., Tester, R.F., 2001. *in-vitro* binding of calcium, iron and zinc by non-starch polysaccharides. Food Chemistry 73, 401–410. 10.1016/S0308-8146(00)00312-5.

Desvaux, M., Hébraud, M., Talon, R., Henderson, I.R., 2009. Secretion and subcellular localizations of bacterial proteins: A semantic awareness issue. Trends in Microbiology 17, 139–145. 10.1016/j.tim.2009.01.004.

Diaz Carrasco, J.M., Casanova, N.A., Fernández Miyakawa, M.E., 2019. Microbiota, gut health and chicken productivity: What is the connection? Microorganisms 7. 10.3390/microorganisms7100374.

Dibner, J., Atwell, C., Kitchell, M., Shermer, W., Ivey, F., 1996. Feeding of oxidized fats to broilers and swine: Effects on enterocyte turnover, hepatocyte proliferation and the gut associated lymphoid tissue. Animal Feed Science and Technology 62, 1–13. 10.1016/S0377-8401(96)01000-0.

Dimitrov, D.V., 2011. The human gutome: Nutrigenomics of the host-microbiome interactions. Omics: Journal of Integrative Biology 15, 419–430. 10.1089/omi.2010.0109.

Duke, G.E., 1982. Gastrointestinal motility and its regulation. Poultry Science 61, 1245–1256. 10.3382/ps.0611245.

Duke, G.E., 1999. Mechanisms of excreta formation and elimination in turkeys and ostriches. The Journal of Experimental Zoology 283, 478–479. 10.1002/(sici)1097-010x(19990301/01)283:4/5<478::aid-jez18>3.0.co;2-e.

Duke, G.E., Evanson, O.A., Epstein, D.R., 1983. Coordination of cecal motility during cecal evacuation. Poultry Science 62, 545–550. 10.3382/ps.0620545.

Dunaway, A., Adedokun, S.A., 2021. Coccidia vaccine challenge and exogenous enzyme supplementation in broiler chicken 1. Effect on digesta viscosity, diet energy utilization, and apparent metabolizable energy value of wheat. Animals 11. 10.3390/ani11030641.

Edelblum, K.L., Turner, J.R., 2009. The tight junction in inflammatory disease: Communication breakdown. Current Opinion in Pharmacology 9, 715–720. 10.1016/j.coph.2009.06.022.

Elson, C.O., Cong, Y., 2012. Host-microbiota interactions in inflammatory bowel disease. Gut Microbes 3, 332–344. 10.4161/gmic.20228.

Fasano, A., 2011. Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer. Physiological Reviews 91, 151–175. 10.1152/physrev.00003.2008.

Fasano, A., 2020. All disease begins in the (leaky) gut: Role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases. F1000Research 9. 10.12688/f1000research.20510.1.

Federico, A., Morgillo, F., Tuccillo, C., Ciardiello, F., Loguercio, C., 2007. Chronic inflammation and oxidative stress in human carcinogenesis. International Journal of Cancer 121, 2381–2386. 10.1002/ijc.23192.

Fernandez-Siurob, I., Retana, M.A., Tellez, G., Arroyo-Navarro, L., Bañuelos-Hernandez, B., Castellanos-Huerta, I., 2014. Assessment of viral interference using a chemical receptor blocker against avian influenza and establishment of protection levels in field outbreaks. Vaccine 32, 1318–1322. 10.1016/j.vaccine.2014.01.006.

Feye, K.M., Baxter, M.F.A., Tellez-Isaias, G., Kogut, M.H., Ricke, S.C., 2020. Influential factors on the composition of the conventionally raised broiler gastrointestinal microbiomes. Poultry Science 99, 653–659. 10.1016/j.psj.2019.12.013.

Forsythe, P., Sudo, N., Dinan, T., Taylor, V.H., Bienenstock, J., 2010. Mood and gut feelings. Brain, Behavior, and Immunity 24, 9–16. 10.1016/j.bbi.2009.05.058.

Francesch, M., Brufau, J., 2004. Nutritional factors affecting excreta/litter moisture and quality. World's Poultry Science Journal 60, 64–75. 10.1079/WPS20035.

Frye, R.E., Rose, S., Chacko, J., Wynne, R., Bennuri, S.C., Slattery, J.C., Tippett, M., Delhey, L., Melnyk, S., Kahler, S.G., MacFabe, D.F., 2016. Modulation of mitochondrial function by the microbiome metabolite propionic acid in autism and control cell lines. Translational Psychiatry 6, e927. 10.1038/tp.2016.189.

Fukui, H., Xu, X., Miwa, H., 2018. Role of gut microbiota-gut hormone axis in the pathophysiology of functional gastrointestinal disorders. Journal of Neurogastroenterology and Motility 24, 367–386. 10.5056/jnm18071.

Gabriel, I., Lessire, M., Mallet, S., Guillot, J., 2006. Microflora of the digestive tract: critical factors and consequences for poultry. World's Poultry Science Journal 62, 499–511. 10.1017/S0043933906001115.

Gholamiandehkordi, A.R., Timbermont, L., Lanckriet, A., Van Den Broeck, W., Pedersen, K., Dewulf, J., Pasmans, F., Haesebrouck, F., Ducatelle, R., Van Immerseel, F., 2007. Quantification of gut lesions in a subclinical necrotic enteritis model. Avian Pathology 36, 375–382. 10.1080/03079450701589118.

Gilani, S., Howarth, G.S., Kitessa, S.M., Tran, C.D., Forder, R.E.A., Hughes, R.J., 2017a. Intestinal permeability induced by lipopolysaccharide and measured by lactulose, rhamnose and mannitol sugars in chickens. Animal 11, 1174–1179. 10.1017/S1751731116002470.

Gilani, S., Howarth, G.S., Kitessa, S.M., Tran, C.D., Forder, R.E.A., Hughes, R.J., 2017b. New biomarkers for increased intestinal permeability induced by dextran sodium sulphate and fasting in chickens. Journal of Animal Physiology and Animal Nutrition 101, e237–e245. 10.1111/jpn.12596.

Goldstein, D.L., 2006. Regulation of the avian kidney by arginine vasotocin. General and Comparative Endocrinology 147, 78–84. 10.1016/j.ygcen.2005.09.018.

Goossens, E., Debyser, G., Callens, C., De Gussem, M., Dedeurwaerder, A., Devreese, B., Haesebrouck, F., Flügel, M., Pelzer, S., Thiemann, F., Ducatelle, R., Van Immerseel, F., 2018. Elevated faecal ovotransferrin concentrations are indicative for intestinal barrier failure in broiler chickens. Veterinary Research 49, 51. 10.1186/s13567-018-0548-4.

Gostner, J.M., Becker, K., Fuchs, D., Sucher, R., 2013. Redox regulation of the immune response. Redox Report: Communications in Free Radical Research 18, 88–94. 10.1179/1351000213Y.0000000044.

Gray, M.W., 2017. Lynn margulis and the endosymbiont hypothesis: 50 years later. Molecular Biology of the Cell 28, 1285–1287. 10.1091/mbc.E16-07-0509.

Gribble, F.M., Reimann, F., 2017. Signalling in the gut endocrine axis. Physiology & Behavior 176, 183–188. 10.1016/j.physbeh.2017.02.039.

Gribble, F.M., Reimann, F., 2019. Function and mechanisms of enteroendocrine cells and gut hormones in metabolism. Nature Reviews. Endocrinology 15, 226–237. 10.1038/s41574-019-0168-8.

Griffiths, H.R., 2005. ROS as signalling molecules in t cells–evidence for abnormal redox signalling in the autoimmune disease, rheumatoid arthritis. Redox Report: Communications in Free Radical Research 10, 273–280. 10.1179/135100005X83680.

Guilliams, T., Edwards, L., 2010. Chronic stress and the HPA axis: Clinical assessment and therapeutic considerations. The Standard 9, 1–12. URL: http://www.pointinstitute.org/wp-content/uploads/2012/10/standard_v_9.2_hpa_axis.pdf.

Hall, A.J., Duke, G.E., 2000. Effect of selective gastric intrinsic denervation on gastric motility in turkeys. Poultry Science 79, 240–244. 10.1093/ps/79.2.240.

Heckert, R.A., Estevez, I., Russek-Cohen, E., Pettit-Riley, R., 2002. Effects of density and perch availability on the immune status of broilers. Poultry Science 81, 451–457. 10.1093/ps/81.4.451.

Hentchel, K.L., Escalante-Semerena, J.C., 2015. Acylation of biomolecules in prokaryotes: A widespread strategy for the control of biological function and metabolic stress. Microbiology and Molecular Biology Reviews 79, 321–346. 10.1128/MMBR.00020-15.

Hernandez-Patlan, D., Solís-Cruz, B., Patrin Pontin, K., Latorre, J.D., Baxter, M.F.A., Hernandez-Velasco, X., Merino-Guzman, R., Méndez-Albores, A., Hargis, B.M., Lopez-Arellano, R., Tellez-Isaias, G., 2019. Evaluation of the dietary supplementation of a formulation containing ascorbic acid and a solid dispersion of Curcumin with boric acid against *Salmonella* Enteritidis and necrotic enteritis in broiler chickens. Animals 9. 10.3390/ani9040184.

Hernández-Ramírez, J.O., Merino-Guzmán, R., Téllez-Isaías, G., Vázquez-Durán, A., Méndez-Albores, A., 2021. Mitigation of AFB1-related toxic damage to the intestinal epithelium in broiler chickens consumed a yeast cell wall fraction. Frontiers in Veterinary Science 8, 677965. 10.3389/fvets.2021.677965.

Hess, M., Liebhart, D., Bilic, I., Ganas, P., 2015. *Histomonas meleagridis*- New insights into an old pathogen. Veterinary Parasitology 208, 67–76. 10.1016/j.vetpar.2014.12.018.

van der Hoeven-Hangoor, E., Rademaker, C.J., Paton, N.D., Verstegen, M.W.A., Hendriks, W.H., 2014. Evaluation of free water and water activity measurements as functional alternatives to total moisture content in broiler excreta and litter samples. Poultry Science 93, 1782–1792. 10.3382/ps.2013-03776.

Hu, Y.J., Wang, Y.D., Tan, F.Q., Yang, W.X., 2013. Regulation of paracellular permeability: Factors and mechanisms. Molecular Biology Reports 40, 6123–6142. 10.1007/s11033-013-2724-y.

Iebba, V., Totino, V., Gagliardi, A., Santangelo, F., Cacciotti, F., Trancassini, M., Mancini, C., Cicerone, C., Corazziari, E., Pantanella, F., Schippa, S., 2016. Eubiosis and dysbiosis: The two sides of the microbiota. The New Microbiologica 39, 1–12. URL: https://www.ncbi.nlm.nih.gov/pubmed/26922981.

Ilan, Y., 2012. Leaky gut and the liver: A role for bacterial translocation in nonalcoholic steatohepatitis. World Journal of Gastroenterology 18, 2609–2618. 10.3748/wjg.v18.i21.2609.

Itri, R., Junqueira, H.C., Mertins, O., Baptista, M.S., 2014. Membrane changes under oxidative stress: The impact of oxidized lipids. Biophysical Reviews 6, 47–61. 10.1007/s12551-013-0128-9.

Jeon, M.K., Klaus, C., Kaemmerer, E., Gassler, N., 2013. Intestinal barrier: Molecular pathways and modifiers. World Journal of Gastrointestinal Pathophysiology 4, 94–99. 10.4291/wjgp.v4.i4.94.

Jiang, Z., Schatzmayr, G., Mohnl, M., Applegate, T.J., 2010. Net effect of an acute phase response-partial alleviation with probiotic supplementation. Poultry Science 89, 28–33. 10.3382/ps.2009-00464.

Jones, D.P., Sies, H., 2015. The redox code. Antioxidants & Redox Signaling 23, 734–746. 10.1089/ars.2015.6247.

Jonkers, D., Stockbrügger, R., 2003. Probiotics and inflammatory bowel disease. Journal of the Royal Society of Medicine 96, 167–171. URL: https://www.ncbi.nlm.nih.gov/pubmed/12668702.

Juruena, M.F., Bourne, M., Young, A.H., Cleare, A.J., 2021. Hypothalamic-pituitary-adrenal axis dysfunction by early life stress. Neuroscience Letters 759, 136037. 10.1016/j.neulet.2021.136037.

Kallapura, G., Pumford, N.R., Hernandez-Velasco, X., Hargis, B.M., Tellez, G., 2014. Mechanisms involved in lipopolysaccharide derived ROS and RNS oxidative stress and septic shock. Journal of Microbiology Research and Reviews 2, 6–11.

Karaca, Z., Grossman, A., Kelestimur, F., 2021. Investigation of the hypothalamo-pituitary-adrenal (HPA) axis: A contemporary synthesis. Reviews in Endocrine & Metabolic Disorders 22, 179–204. 10.1007/s11154-020-09611-3.

Karasawa, Y., Duke, G.E., 1995. Effects of cecal ligation and colostomy on motility of the rectum, ileum, and cecum in turkeys. Poultry Science 74, 2029–2034. 10.3382/ps.0742029.

Kelleher, B.P., Leahy, J.J., Henihan, A.M., O'Dwyer, T.F., Sutton, D., Leahy, M.J., 2002. Advances in poultry litter disposal technology- A review. Bioresource Technology 83, 27–36. 10.1016/s0960-8524(01)00133-x.

Khansari, N., Shakiba, Y., Mahmoudi, M., 2009. Chronic inflammation and oxidative stress as a major cause of age-related diseases and cancer. Recent Patents on Inflammation & Allergy Drug Discovery 3, 73–80. 10.2174/187221309787158371.

Kiarie, E., Romero, L.F., Nyachoti, C.M., 2013. The role of added feed enzymes in promoting gut health in swine and poultry. Nutrition Research Reviews 26, 71–88. 10.1017/S0954422413000048.

Kim, W.K., Patterson, P.H., 2003. Effect of minerals on activity of microbial uricase to reduce ammonia volatilization in poultry manure. Poultry Science 82, 223–231. 10.1093/ps/82.2.223.

Kim, Y.S., Ho, S.B., 2010. Intestinal goblet cells and mucins in health and disease: recent insights and progress. Current Gastroenterology Reports 12, 319–330. 10.1007/s11894-010-0131-2.

Kimball, R.T., Guido, M., Hosner, P.A., Braun, E.L., 2021. When good mitochondria go bad: Cyto-nuclear discordance in landfowl (Aves: Galliformes). Gene 801, 145841. 10.1016/j.gene.2021.145841.

Kogut, M.H., Genovese, K.J., Swaggerty, C.L., He, H., Broom, L., 2018. Inflammatory phenotypes in the intestine of poultry: Not all inflammation is created equal. Poultry Science 97, 2339–2346. 10.3382/ps/pey087.

Korniluk, A., Koper, O., Kemona, H., Dymicka-Piekarska, V., 2017. From inflammation to cancer. Irish Journal of Medical Science 186, 57–62. 10.1007/s11845-016-1464-0.

Korver, D., 2012. Implications of changing immune function through nutrition in poultry. Animal Feed Science and Technology 173, 54–64. 10.1016/j.anifeedsci.2011.12.019.

Kuenzel, W.J., Jurkevich, A., 2010. Molecular neuroendocrine events during stress in poultry. Poultry Science 89, 832–840. 10.3382/ps.2009-00376.

Kuttappan, V.A., Berghman, L.R., Vicuña, E.A., Latorre, J.D., Menconi, A., Wolchok, J.D., Wolfenden, A.D., Faulkner, O.B., Tellez, G.I., Hargis, B.M., Bielke, L.R., 2015. Poultry enteric inflammation model with dextran sodium sulfate mediated chemical induction and feed restriction in broilers. Poultry Science 94, 1220–1226. 10.3382/ps/pev114.

Lagler, J., Schmidt, S., Mitra, T., Stadler, M., Patricia, W., Grafl, B., Hatfaludi, T., Hess, M., Gerner, W., Liebhart, D., 2021. Comparative investigation of IFN-γ-producing t cells in chickens and turkeys following vaccination and infection with the extracellular parasite histomonas meleagridis. Developmental and Comparative Immunology 116, 103949. 10.1016/j.dci.2020.103949.

Lane, N., 2013. Power, Sex, Suicide: Mitochondria and the Meaning of life . Oxford University Press., New York.

Lara, L.J., Rostagno, M.H., 2013. Impact of heat stress on poultry production. Animals 3, 356–369. 10.3390/ani3020356.

Latorre, J.D., Hernandez-Velasco, X., Bielke, L.R., Vicente, J.L., Wolfenden, R., Menconi, A., Hargis, B.M., Tellez, G., 2015. Evaluation of a *Bacillus* direct-fed microbial candidate on digesta viscosity, bacterial translocation, microbiota composition and bone mineralisation in broiler chickens fed on a rye-based diet. British Poultry Science 56, 723–732. 10.1080/00071668.2015.1101053.

Latorre, J.D., Hernandez-Velasco, X., Kogut, M.H., Vicente, J.L., Wolfenden, R., Wolfenden, A., Hargis, B.M., Kuttappan, V.A., Tellez, G., 2014. Role of a *Bacillus subtilis* direct-fed microbial on digesta viscosity, bacterial translocation, and bone mineralization in turkey poults fed with a rye-based diet. Frontiers in Veterinary Science 1, 26. 10.3389/fvets.2014.00026.

Latorre, J.D., Hernandez-Velasco, X., Wolfenden, R.E., Vicente, J.L., Wolfenden, A.D., Menconi, A., Bielke, L.R., Hargis, B.M., Tellez, G., 2016. Evaluation and selection of *Bacillus* species based on enzyme production, antimicrobial activity, and biofilm synthesis as direct-fed microbial candidates for poultry. Frontiers in Veterinary Science 3, 95. 10.3389/fvets.2016.00095.

Lazcano, A., Peretó, J., 2021. Prokaryotic symbiotic consortia and the origin of nucleated cells: A critical review of Lynn Margulis hypothesis. Bio Systems 204, 104408. 10.1016/j.biosystems.2021.104408.

Lee, M.Y., Griendling, K.K., 2008. Redox signaling, vascular function, and hypertension. Antioxidants & Redox Signaling 10, 1045–1059. 10.1089/ars.2007.1986.

Leyva-Diaz, A.A., Hernandez-Patlan, D., Solis-Cruz, B., Adhikari, B., Kwon, Y.M., Latorre, J.D., Hernandez-Velasco, X., Fuente-Martinez, B., Hargis, B.M., Lopez-Arellano, R., Tellez-Isaias, G., 2021. Evaluation of curcumin and copper acetate against *Salmonella* Typhimurium infection, intestinal permeability, and cecal microbiota composition in broiler chickens. Journal of Animal Science and Biotechnology 12, 23. 10.1186/s40104-021-00545-7.

Li, J., Jia, H., Cai, X., Zhong, H., Feng, Q., Sunagawa, S., Arumugam, M., Kultima, J.R., Prifti, E., Nielsen, T., Juncker, A.S., Manichanh, C., Chen, B., Zhang, W., Levenez, F., Wang, J., Xu, X., Xiao, L., Liang, S., Zhang, D., Zhang, Z., Chen, W., Zhao, H., Al-Aama, J.Y., Edris, S., Yang, H., Wang, J., Hansen, T., Nielsen, H.B., Brunak, S., Kristiansen, K., Guarner, F., Pedersen, O., Doré, J., Ehrlich, S.D., Consortium, M., Bork, P., Wang, J., Consortium, M., 2014. An integrated catalog of reference genes in the human gut microbiome. Nature Biotechnology 32, 834–841. 10.1038/nbt.2942.

Lian, P., Braber, S., Garssen, J., Wichers, H.J., Folkerts, G., Fink-Gremmels, J., Varasteh, S., 2020. Beyond heat stress: Intestinal integrity disruption and mechanism-based intervention strategies. Nutrients 12. 10.3390/nu12030734.

Liang, X., Bushman, F.D., FitzGerald, G.A., 2014. Time in motion: The molecular clock meets the microbiome. Cell 159, 469–470. 10.1016/j.cell.2014.10.020.

Lichtenthaler, H.K., 1998. The stress concept in plants: An introduction. Annals of the New York Academy of Sciences 851, 187–198. 10.1111/j.1749-6632.1998.tb08993.x.

Liebhart, D., Ganas, P., Sulejmanovic, T., Hess, M., 2017. Histomonosis in poultry: Previous and current strategies for prevention and therapy. Avian Pathology 46, 1–18. 10.1080/03079457.2016.1229458.

Liebhart, D., Sulejmanovic, T., Grafl, B., Tichy, A., Hess, M., 2013. Vaccination against histomonosis prevents a drop in egg

production in layers following challenge. Avian Pathology 42, 79–84. 10.1080/03079457.2012.760841.

Lipton, B., 2016. The Biology of Belief: Unleashing the Power of Consciousness, Matter & Miracles. Hay House Inc., USA. URL: https://psycnet.apa.org/record/2005-09741-000.

Liversidge, A., 1993. Bacterial consciousness: Why spirochetes think as we do. Omni 16, 10–11.

Lu, S., Wei, F., Li, G., 2021. The evolution of the concept of stress and the framework of the stress system. Cell Stress 5, 76–85. 10.15698/cst2021.06.250.

Lund, M.L., Egerod, K.L., Engelstoft, M.S., Dmytriyeva, O., Theodorsson, E., Patel, B.A., Schwartz, T.W., 2018. Enterochromaffin 5-HT cells - A major target for GLP-1 and gut microbial metabolites. Molecular Metabolism 11, 70–83. 10.1016/j.molmet.2018.03.004.

López-González, I., Aso, E., Carmona, M., Armand-Ugon, M., Blanco, R., Naudí, A., Cabré, R., Portero-Otin, M., Pamplona, R., Ferrer, I., 2015. Neuroinflammatory gene regulation, mitochondrial function, oxidative stress, and brain lipid modifications with disease progression in tau P301S transgenic mice as a model of frontotemporal lobar degeneration-tau. Journal of Neuropathology and Experimental Neurology 74, 975–999. 10.1097/NEN.0000000000000241.

Maslowski, K.M., Mackay, C.R., 2011. Diet, gut microbiota and immune responses. Nature Immunology 12, 5–9. 10.1038/ni0111-5.

Mayer, E.A., Knight, R., Mazmanian, S.K., Cryan, J.F., Tillisch, K., 2014. Gut microbes and the brain: Paradigm shift in neuroscience. The Journal of Neuroscience 34, 15490–15496. 10.1523/JNEUROSCI.3299-14.2014.

McAllister, M.M., 2014. Successful vaccines for naturally occurring protozoal diseases of animals should guide human vaccine research. A review of protozoal vaccines and their designs. Parasitology 141, 624–640. 10.1017/S0031182013002060.

Megur, A., Baltriukienė, D., Bukelskienė, V., Burokas, A., 2020. The microbiota-gut-brain axis and Alzheimer's disease: Neuroinflammation is to blame? Nutrients 13. 10.3390/nu13010037.

Menconi, A., Hernandez-Velasco, X., Vicuña, E.A., Kuttappan, V.A., Faulkner, O.B., Tellez, G., Hargis, B.M., Bielke, L.R., 2015. Histopathological and morphometric changes induced by a dextran sodium sulfate (DSS) model in broilers. Poultry Science 94, 906–911. 10.3382/ps/pev054.

Mishra, B., Jha, R., 2019. Oxidative stress in the poultry gut: Potential challenges and interventions. Frontiers in Veterinary Science 6, 60. 10.3389/fvets.2019.00060.

Mitra, T., Bramberger, B., Bilic, I., Hess, M., Liebhart, D., 2021. Vaccination against the protozoan parasite *Histomonas meleagridis* primes the activation of toll-like receptors in turkeys and chickens determined by a set of newly developed multiplex RT-qPCRs. Vaccines 9. 10.3390/vaccines9090960.

Mitra, T., Kidane, F.A., Hess, M., Liebhart, D., 2018. Unravelling the immunity of poultry against the extracellular protozoan parasite histomonas meleagridis is a cornerstone for vaccine development: A review. Frontiers in Immunology 9, 2518. 10.3389/fimmu.2018.02518.

Moore, P.A., Miles, D., Burns, R., Pote, D., Berg, K., Choi, I.H., 2011. Ammonia emission factors from broiler litter in barns, in storage, and after land application. Journal of Environmental Quality 40, 1395–1404. 10.2134/jeq2009.0383.

Morales-Barrera, E., Calhoun, N., Lobato-Tapia, J.L., Lucca, V., Prado-Rebolledo, O., Hernandez-Velasco, X., Merino-Guzman, R., Petrone-García, V.M., Latorre, J.D., Mahaffey, B.D., Teague, K.D., Graham, L.E., Wolfenden, A.D., Baxter, M.F.A., Hargis, B.M., Tellez, G., 2016. Risks involved in the use of enrofloxacin for *Salmonella* Enteritidis or *Salmonella* Heidelberg in commercial poultry. Frontiers in Veterinary Science 3, 72. 10.3389/fvets.2016.00072.

Morales-Mena, A., Martínez-González, S., Teague, K.D., Graham, L.E., Señas-Cuesta, R., Vuong, C.N., Lester, H., Hernandez-Patlan, D., Solis-Cruz, B., Fuente-Martinez, B., Hernandez-Velasco, X., Hargis, B.M., Tellez-Isaias, G., 2020. Assessment of fermented soybean meal on *Salmonella* Typhimurium infection in neonatal turkey poults. Animals 10. 10.3390/ani10101849.

Mullenix, G.J., Greene, E.S., Emami, N.K., Tellez-Isaias, G., Bottje, W.G., Erf, G.F., Kidd, M.T., Dridi, S., 2021. *Spirulina platensis* inclusion reverses circulating pro-inflammatory (chemo)cytokine profiles in broilers fed low-protein diets. Frontiers in Veterinary Science 8, 640968. 10.3389/fvets.2021.640968.

Naga Raja Kumari, K., Narendra Nath, D., 2018. Ameliorative measures to counter heat stress in poultry. World's Poultry Science Journal 74, 117–130. 10.1017/S0043933917001003.

Nahm, K., 2003. Evaluation of the nitrogen content in poultry manure. World's Poultry Science Journal 59, 77–88. 10.1079/WPS20030004.

Negri, S., Commisso, M., Avesani, L., Guzzo, F., 2021. The case of tryptamine and serotonin in plants: A mysterious precursor for an illustrious metabolite. Journal of Experimental Botany 72, 5336–5355. 10.1093/jxb/erab220.

Neuman, H., Debelius, J.W., Knight, R., Koren, O., 2015. Microbial endocrinology: the interplay between the microbiota and the endocrine system. FEMS Microbiology Reviews 39, 509–521. 10.1093/femsre/fuu010.

Nicol, C.J., Brown, S.N., Glen, E., Pope, S.J., Short, F.J., Warriss, P.D., Zimmerman, P.H., Wilkins, L.J., 2006. Effects of stocking density, flock size and management on the welfare of laying hens in single-tier aviaries. British Poultry Science 47, 135–146. 10.1080/00071660600610609.

Niki, E., Yamamoto, Y., Komuro, E., Sato, K., 1991. Membrane damage due to lipid oxidation. The American Journal of Clinical Nutrition 53, 201S–205S. 10.1093/ajcn/53.1.{201S}.

Noguchi, M., Hiwatashi, N., Liu, Z., Toyota, T., 1998. Secretion imbalance between tumour necrosis factor and its inhibitor in inflammatory bowel disease. Gut 43, 203–209. 10.1136/gut.43.2.203.

Oakley, B.B., Lillehoj, H.S., Kogut, M.H., Kim, W.K., Maurer, J.J., Pedroso, A., Lee, M.D., Collett, S.R., Johnson, T.J., Cox, N.A., 2014. The chicken gastrointestinal microbiome. FEMS Microbiology Letters 360, 100–112. 10.1111/1574-6968.12608.

Osellame, L.D., Blacker, T.S., Duchen, M.R., 2012. Cellular and molecular mechanisms of mitochondrial function. Best Practice & Research. Clinical Endocrinology & Metabolism 26, 711–723. 10.1016/j.beem.2012.05.003.

Pastorelli, L., De Salvo, C., Mercado, J.R., Vecchi, M., Pizarro, T.T., 2013. Central role of the gut epithelial barrier in the pathogenesis of chronic intestinal inflammation: Lessons

learned from animal models and human genetics. Frontiers in Immunology 4, 280. 10.3389/fimmu.2013.00280.

Peralta, M.F., Magnoli, A., Alustiza, F., Nilson, A., Miazzo, R., Vivas, A., 2017. Gut-associated lymphoid tissue: A key tissue inside the mucosal immune system of hens immunized with *Escherichia coli* f4. Frontiers in Immunology 8, 568. 10.3389/fimmu.2017.00568.

Petrone-Garcia, V.M., Lopez-Arellano, R., Patiño, G.R., Rodríguez, M.A.C., Hernandez-Patlan, D., Solis-Cruz, B., Hernandez-Velasco, X., Alba-Hurtado, F., Vuong, C.N., Castellanos-Huerta, I., Tellez-Isaias, G., 2021. Curcumin reduces enteric isoprostane 8-iso-PGF2α and prostaglandin GF2α in specific pathogen-free leghorn chickens challenged with *Eimeria maxima*. Scientific Reports 11, 11609. 10.1038/s41598-021-90679-5.

Porter, R.E., 1998. Bacterial enteritides of poultry. Poultry Science 77, 1159–1165. 10.1093/ps/77.8.1159.

Qureshi, M., 2003. Avian macrophage and immune response: An overview. Poultry Science 82, 691–698. 10.1093/ps/82.5.691.

Rao, J.N., Wang, J.Y., 2010. Role of GI hormones on gut mucosal growth, in: Regulation of Gastrointestinal Mucosal Growth. Morgan & Claypool Life Sciences, San Rafael, CA, pp. 21–33. URL: https://www.ncbi.nlm.nih.gov/books/NBK54093/.

Rigottier-Gois, L., 2013. Dysbiosis in inflammatory bowel diseases: the oxygen hypothesis. The ISME Journal 7, 1256–1261. 10.1038/ismej.2013.80.

Rimet, C.S., Maurer, J.J., Berghaus, R.D., Jordan, B.J., Antoniassi da Silva, L.H., Stabler, L.J., Johnson, K.K., Tensa, L.R., Segovia, K.M., França, M.S., 2019. The contribution of *Eimeria* coinfection and intestinal inflammation to cecal colonization and systemic spread of *Salmonella* Typhimurium deficient in tetrathionate reductase or type III secretion systems *Salmonella* pathogenicity island 1 or 2. Avian Diseases 63, 559–567. 10.1637/aviandiseases-D-19-00082.

Rose, M.E., Long, P.L., Bradley, J.W., 1975. Immune responses to infections with coccidia in chickens: Gut hypersensitivity. Parasitology 71, 357–368. 10.1017/s0031182000047132.

Rostagno, M.H., 2020. Effects of heat stress on the gut health of poultry. Journal of Animal Science 98. 10.1093/jas/skaa090.

Rubartelli, A., Lotze, M.T., 2007. Inside, outside, upside down: Damage-associated molecular-pattern molecules (DAMPs) and redox. Trends in Immunology 28, 429–436. 10.1016/j.it.2007.08.004.

Ruff, J., Barros, T.L., Tellez, G., Blankenship, J., Lester, H., Graham, B.D., Selby, C.A.M., Vuong, C.N., Dridi, S., Greene, E.S., Hernandez-Velasco, X., Hargis, B.M., Tellez-Isaias, G., 2020. Research note: Evaluation of a heat stress model to induce gastrointestinal leakage in broiler chickens. Poultry Science 99, 1687–1692. 10.1016/j.psj.2019.10.075.

Ruff, J., Tellez, G., Forga, A.J., Señas-Cuesta, R., Vuong, C.N., Greene, E.S., Hernandez-Velasco, X., Uribe, J., Martínez, B.C., Angel-Isaza, J.A., Dridi, S., Maynard, C.J., Owens, C.M., Hargis, B.M., Tellez-Isaias, G., 2021. Evaluation of three formulations of essential oils in broiler chickens under cyclic heat stress. Animals 11. 10.3390/ani11041084.

Ruppin, H., Bar-Meir, S., Soergel, K.H., Wood, C.M., Schmitt, M.G., 1980. Absorption of short-chain fatty acids by the colon. Gastroenterology 78, 1500–1507. 10.1016/S0016-5085(19)30508-6.

Sagan, L., 1967. On the origin of mitosing cells. Journal of Theoretical Biology 14, 255–274. 10.1016/0022-5193(67)90079-3.

Sakamoto, K., Hirose, H., Onizuka, A., Hayashi, M., Futamura, N., Kawamura, Y., Ezaki, T., 2000. Quantitative study of changes in intestinal morphology and mucus gel on total parenteral nutrition in rats. The Journal of Surgical Research 94, 99–106. 10.1006/jsre.2000.5937.

Salminen, S., Isolauri, E., 2006. Intestinal colonization, microbiota, and probiotics. The Journal of Pediatrics 149, S115–S120. 10.1016/j.jpeds.2006.06.062.

Saraiva, M.M.S., Rodrigues Alves, L.B., Monte, D.F.M., Ferreira, T.S., Benevides, V.P., Barbosa, F.O., Freitas Neto, O.C., Almeida, A.M., Barrow, P.A., Berchieri Junior, A., 2021. Deciphering the role of ttrA and pduA genes for *Salmonella enterica* serovars in a chicken infection model. Avian Pathology , 1–1210.1080/03079457.2021.1909703.

Schneider, S., Wright, C.M., Heuckeroth, R.O., 2019. Unexpected roles for the second brain: Enteric nervous system as master regulator of bowel function. Annual Review of Physiology 81, 235–259. 10.1146/annurev-physiol-021317-121515.

Schulzke, J.D., Ploeger, S., Amasheh, M., Fromm, A., Zeissig, S., Troeger, H., Richter, J., Bojarski, C., Schumann, M., Fromm, M., 2009. Epithelial tight junctions in intestinal inflammation. Annals of the New York Academy of Sciences 1165, 294–300. 10.1111/j.1749-6632.2009.04062.x.

Sears, C.L., Kaper, J.B., 1996. Enteric bacterial toxins: Mechanisms of action and linkage to intestinal secretion. Microbiological Reviews 60, 167–215. URL: https://www.ncbi.nlm.nih.gov/pubmed/8852900.

Sekirov, I., Russell, S.L., Antunes, L.C.M., Finlay, B.B., 2010. Gut microbiota in health and disease. Physiological Reviews 90, 859–904. 10.1152/physrev.00045.2009.

Selye, H., 1975. Confusion and controversy in the stress field. Journal of human stress 1, 37–44. 10.1080/0097840X.1975.9940406.

Sender, R., Fuchs, S., Milo, R., 2016. Revised estimates for the number of human and bacteria cells in the body. PLoS Biology 14, e1002533. 10.1371/journal.pbio.1002533.

Sharma, R., Tepas, J.J., Hudak, M.L., Mollitt, D.L., Wludyka, P.S., Teng, R.J., Premachandra, B.R., 2007. Neonatal gut barrier and multiple organ failure: Role of endotoxin and proinflammatory cytokines in sepsis and necrotizing enterocolitis. Journal of Pediatric Surgery 42, 454–461. 10.1016/j.jpedsurg.2006.10.038.

Sharma, R., Young, C., Neu, J., 2010. Molecular modulation of intestinal epithelial barrier: contribution of microbiota. Journal of Biomedicine & Biotechnology 2010, 305879. 10.1155/2010/305879.

Shehata, A.A., Attia, Y., Khafaga, A.F., Farooq, M.Z., El-Seedi, H.R., Eisenreich, W., Tellez-Isaias, G., 2022a. Restoring healthy gut microbiome in poultry using alternative feed additives with particular attention to phytogenic substances: Challenges and prospects. German Journal of Veterinary Research 2, 32–42. 10.51585/gjvr.2022.3.0047.

Shehata, A.A., Yalçın, S., Latorre, J.D., Basiouni, S., Attia, Y.A., Abd El-Wahab, A., Visscher, C., El-Seedi, H.R., Huber, C., Hafez, H.M., Eisenreich, W., Tellez-Isaias, G., 2022b. Probiotics, prebiotics, and phytogenic substances for optimizing gut health in poultry. Microorganisms 10. 10.3390/microorganisms10020395.

Sherwin, E., Rea, K., Dinan, T.G., Cryan, J.F., 2016. A gut (microbiome) feeling about the brain. Current Opinion in Gastroenterology 32, 96–102. 10.1097/MOG.0000000000000244.

Shivaramaiah, C., Barta, J.R., Hernandez-Velasco, X., Téllez, G., Hargis, B.M., 2014. Coccidiosis: Recent advancements in the immunobiology of *Eimeria* species, preventive measures, and the importance of vaccination as a control tool against these apicomplexan parasites. Veterinary medicine (Auckland, N.Z.) 5, 23–34. 10.2147/VMRR.S57839.

Slavich, G.M., Irwin, M.R., 2014. From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. Psychological Bulletin 140, 774–815. 10.1037/a0035302.

Smatti, M.K., Cyprian, F.S., Nasrallah, G.K., Al Thani, A.A., Almishal, R.O., Yassine, H.M., 2019. Viruses and autoimmunity: A review on the potential interaction and molecular mechanisms. Viruses 11. 10.3390/v11080762.

Solis-Cruz, B., Hernandez-Patlan, D., Petrone, V.M., Pontin, K.P., Latorre, J.D., Beyssac, E., Hernandez-Velasco, X., Merino-Guzman, R., Arreguin, M.A., Hargis, B.M., Lopez-Arellano, R., Tellez-Isaias, G., 2019. Evaluation of a *Bacillus*-based direct-fed microbial on aflatoxin B1 toxic effects, performance, immunologic status, and serum biochemical parameters in broiler chickens. Avian Diseases 63, 659–669. 10.1637/aviandiseases-D-19-00100.

Soutter, F., Werling, D., Kim, S., Pastor-Fernández, I., Marugán-Hernández, V., Tomley, F.M., Blake, D.P., 2021. Impact of *Eimeria tenella* oocyst dose on parasite replication, lesion score and cytokine transcription in the caeca in three breeds of commercial layer chickens. Frontiers in Veterinary Science 8, 640041. 10.3389/fvets.2021.640041.

Stecher, B., 2015. The roles of inflammation, nutrient availability and the commensal microbiota in enteric pathogen infection. Microbiology Spectrum 3. 10.1128/microbiolspec.MBP-0008-2014.

Steed, E., Balda, M.S., Matter, K., 2010. Dynamics and functions of tight junctions. Trends in Cell Biology 20, 142–149. 10.1016/j.tcb.2009.12.002.

Sulejmanovic, T., Bilic, I., Hess, M., Liebhart, D., 2016. An *in-vitro* attenuated strain of histomonas meleagridis provides cross-protective immunity in turkeys against heterologous virulent isolates. Avian Pathology 45, 46–53. 10.1080/03079457.2015.1117057.

Sulejmanovic, T., Liebhart, D., Hess, M., 2013. *In-vitro* attenuated *Histomonas meleagridis* does not revert to virulence, following serial *in-vivo* passages in turkeys or chickens. Vaccine 31, 5443–5450. 10.1016/j.vaccine.2013.08.098.

Sun, L., Wang, X., Saredy, J., Yuan, Z., Yang, X., Wang, H., 2020. Innate-adaptive immunity interplay and redox regulation in immune response. Redox Biology 37, 101759. 10.1016/j.redox.2020.101759.

Teirlynck, E., Bjerrum, L., Eeckhaut, V., Huygebaert, G., Pasmans, F., Haesebrouck, F., Dewulf, J., Ducatelle, R., Van Immerseel, F., 2009. The cereal type in feed influences gut wall morphology and intestinal immune cell infiltration in broiler chickens. The British Journal of Nutrition 102, 1453–1461. 10.1017/S0007114509990407.

Teirlynck, E., Gussem, M.D.E., Dewulf, J., Haesebrouck, F., Ducatelle, R., Van Immerseel, F., 2011. Morphometric evaluation of "dysbacteriosis" in broilers. Avian Pathology 40, 139–144. 10.1080/03079457.2010.543414.

Tellez, G., Arreguin-Nava, M.A., Maguey, J.A., Michel, M.A., Latorre, J.D., Merino-Guzman, R., Hernandez-Velasco, X., Moore, P.A., Hargis, B.M., Tellez-Isaias, G., 2020. Effect of *Bacillus*-direct-fed microbial on leaky gut, serum peptide YY concentration, bone mineralization, and ammonia excretion in neonatal female turkey poults fed with a rye-based diet. Poultry Science 99, 4514–4520. 10.1016/j.psj.2020.06.018.

Tellez, G., Latorre, J.D., Kuttappan, V.A., Hargis, B.M., Hernandez-Velasco, X., 2015. Rye affects bacterial translocation, intestinal viscosity, microbiota composition and bone mineralization in turkey poults. Plos One 10, e0122390. 10.1371/journal.pone.0122390.

Tellez, G., Latorre, J.D., Kuttappan, V.A., Kogut, M.H., Wolfenden, A., Hernandez-Velasco, X., Hargis, B.M., Bottje, W.G., Bielke, L.R., Faulkner, O.B., 2014. Utilization of rye as energy source affects bacterial translocation, intestinal viscosity, microbiota composition, and bone mineralization in broiler chickens. Frontiers in Genetics 5, 339. 10.3389/fgene.2014.00339.

Tellez-Isaias, G., Vuong, C.N., Graham, B.D., Selby, C.M., Graham, L.E., Señas-Cuesta, R., Barros, T.L., Beer, L.C., Coles, M.E., Forga, A.J., Ruff, J., Hernandez-Velasco, X., Hargis, B.M., 2021. Developing probiotics, prebiotics, and organic acids to control *Salmonella* spp. in commercial turkeys at the University of Arkansas, USA. German Journal of Veterinary Research 1, 7–12. 10.51585/gjvr.2021.3.0014.

Thøfner, I.C.N., Liebhart, D., Hess, M., Schou, T.W., Hess, C., Ivarsen, E., Fretté, X.C., Christensen, L.P., Grevsen, K., Engberg, R.M., Christensen, J.P., 2012. Antihistomonal effects of artemisinin and *Artemisia annua* extracts *in-vitro* could not be confirmed by in-vivo experiments in turkeys and chickens. Avian Pathology 41, 487–496. 10.1080/03079457.2012.714459.

Tlaskalová-Hogenová, H., Stepánková, R., Hudcovic, T., Tucková, L., Cukrowska, B., Lodinová-Zádníková, R., Kozáková, H., Rossmann, P., Bártová, J., Sokol, D., Funda, D.P., Borovská, D., Reháková, Z., Sinkora, J., Hofman, J., Drastich, P., Kokesová, A., 2004. Commensal bacteria (normal microflora), mucosal immunity and chronic inflammatory and autoimmune diseases. Immunology Letters 93, 97–108. 10.1016/j.imlet.2004.02.005.

Torres-Rodriguez, A., Higgins, S., Vicente, J., Wolfenden, A., Gaona-Ramirez, G., Barton, J., Tellez, G., Donoghue, A., Hargis, B., 2007. Effect of lactose as a prebiotic on turkey body weight under commercial conditions. Journal of Applied Poultry Research 16, 635–641. 10.3382/japr.2006-00127.

Ulluwishewa, D., Anderson, R.C., McNabb, W.C., Moughan, P.J., Wells, J.M., Roy, N.C., 2011. Regulation of tight junction permeability by intestinal bacteria and dietary components. The Journal of Nutrition 141, 769–776. 10.3945/jn.110.135657.

Vicuña, E.A., Kuttappan, V.A., Galarza-Seeber, R., Latorre, J.D., Faulkner, O.B., Hargis, B.M., Tellez, G., Bielke, L.R., 2015. Effect of dexamethasone in feed on intestinal permeability, differential white blood cell counts, and immune

organs in broiler chicks. Poultry Science 94, 2075–2080. 10.3382/ps/pev211.

Vighi, G., Marcucci, F., Sensi, L., Di Cara, G., Frati, F., 2008. Allergy and the gastrointestinal system. Clinical and Experimental Immunology 153 Suppl 1, 3–6. 10.1111/j.1365-2249.2008.03713.x.

Vuong, C.N., Mullenix, G.J., Kidd, M.T., Bottje, W.G., Hargis, B.M., Tellez-Isaias, G., 2021. Research note: Modified serum fluorescein isothiocyanate dextran (FITC-d) assay procedure to determine intestinal permeability in poultry fed diets high in natural or synthetic pigments. Poultry Science 100, 101138. 10.1016/j.psj.2021.101138.

Wallis, J.W., Aerts, J., Groenen, M.A.M., Crooijmans, R.P.M.A., Layman, D., Graves, T.A., Scheer, D.E., Kremitzki, C., Fedele, M.J., Mudd, N.K., Cardenas, M., Higginbotham, J., Carter, J., McGrane, R., Gaige, T., Mead, K., Walker, J., Albracht, D., Davito, J., Yang, S.P., Leong, S., Chinwalla, A., Sekhon, M., Wylie, K., Dodgson, J., Romanov, M.N., Cheng, H., de Jong, P.J., Osoegawa, K., Nefedov, M., Zhang, H., McPherson, J.D., Krzywinski, M., Schein, J., Hillier, L., Mardis, E.R., Wilson, R.K., Warren, W.C., 2004. A physical map of the chicken genome. Nature 432, 761–764. 10.1038/nature03030.

Weiss, G.A., Hennet, T., 2017. Mechanisms and consequences of intestinal dysbiosis. Cellular and Molecular Life Sciences 74, 2959–2977. 10.1007/s00018-017-2509-x.

Wickramasuriya, S.S., Park, I., Lee, K., Lee, Y., Kim, W.H., Nam, H., Lillehoj, H.S., 2022. Role of physiology, immunity, microbiota, and infectious diseases in the gut health of poultry. Vaccines 10. 10.3390/vaccines10020172.

Wideman, R.F., Al-Rubaye, A., Kwon, Y.M., Blankenship, J., Lester, H., Mitchell, K.N., Pevzner, I.Y., Lohrmann, T., Schleifer, J., 2015. Prophylactic administration of a combined prebiotic and probiotic, or therapeutic administration of enrofloxacin, to reduce the incidence of bacterial chondronecrosis with osteomyelitis in broilers. Poultry Science 94, 25–36. 10.3382/ps/peu025.

Wideman, R.F., Prisby, R.D., 2012. Bone circulatory disturbances in the development of spontaneous bacterial chondronecrosis with osteomyelitis: A translational model for the pathogenesis of femoral head necrosis. Frontiers in Endocrinology 3, 183. 10.3389/fendo.2012.00183.

Williams, R.B., 2005. Intercurrent coccidiosis and necrotic enteritis of chickens: Rational, integrated disease management by maintenance of gut integrity. Avian Pathology 34, 159–180. 10.1080/03079450500112195.

Wink, D.A., Hines, H.B., Cheng, R.Y.S., Switzer, C.H., Flores-Santana, W., Vitek, M.P., Ridnour, L.A., Colton, C.A., 2011. Nitric oxide and redox mechanisms in the immune response. Journal of Leukocyte Biology 89, 873–891. 10.1189/jlb.1010550.

Winter, S.E., Keestra, A.M., Tsolis, R.M., Bäumler, A.J., 2010a. The blessings and curses of intestinal inflammation. Cell Host & Microbe 8, 36–43. 10.1016/j.chom.2010.06.003.

Winter, S.E., Thiennimitr, P., Winter, M.G., Butler, B.P., Huseby, D.L., Crawford, R.W., Russell, J.M., Bevins, C.L., Adams, L.G., Tsolis, R.M., Roth, J.R., Bäumler, A.J., 2010b. Gut inflammation provides a respiratory electron acceptor for *Salmonella*. Nature 467, 426–429. 10.1038/nature09415.

Wu, R.Y., Määttänen, P., Napper, S., Scruten, E., Li, B., Koike, Y., Johnson-Henry, K.C., Pierro, A., Rossi, L., Botts, S.R., Surette, M.G., Sherman, P.M., 2017. Non-digestible oligosaccharides directly regulate host kinome to modulate host inflammatory responses without alterations in the gut microbiota. Microbiome 5, 135. 10.1186/s40168-017-0357-4.

Yamamoto, M.L., Maier, I., Dang, A.T., Berry, D., Liu, J., Ruegger, P.M., Yang, J.I., Soto, P.A., Presley, L.L., Reliene, R., Westbrook, A.M., Wei, B., Loy, A., Chang, C., Braun, J., Borneman, J., Schiestl, R.H., 2013. Intestinal bacteria modify lymphoma incidence and latency by affecting systemic inflammatory state, oxidative stress, and leukocyte genotoxicity. Cancer Research 73, 4222–4232. 10.1158/0008-5472.CAN-13-0022.

Yegani, M., Korver, D.R., 2008. Factors affecting intestinal health in poultry. Poultry Science 87, 2052–2063. 10.3382/ps.2008-00091.

Yeoman, C.J., Chia, N., Jeraldo, P., Sipos, M., Goldenfeld, N.D., White, B.A., 2012. The microbiome of the chicken gastrointestinal tract. Animal Health Research Reviews / Conference of Research Workers in Animal Diseases 13, 89–99. 10.1017/S1466252312000138.

Yerpes, M., Llonch, P., Manteca, X., 2020. Factors associated with cumulative first-week mortality in broiler chicks. Animals 10. 10.3390/ani10020310.

Yerpes, M., Llonch, P., Manteca, X., 2021. Effect of environmental conditions during transport on chick weight loss and mortality. Poultry Science 100, 129–137. 10.1016/j.psj.2020.10.003.

Zhu, B., Wang, X., Li, L., 2010. Human gut microbiome: The second genome of human body. Protein & cell 1, 718–725. 10.1007/s13238-010-0093-z.

Zou, X., Ji, J., Wang, J., Qu, H., Shu, D.M., Guo, F.Y., Luo, C.L., 2018. Dextran sulphate sodium (DSS) causes intestinal histopathology and inflammatory changes consistent with increased gut leakiness in chickens. British Poultry Science 59, 166–172. 10.1080/00071668.2017.1418498.

Zou, Y., Xiang, Q., Wang, J., Peng, J., Wei, H., 2016. Oregano essential oil improves intestinal morphology and expression of tight junction proteins associated with modulation of selected intestinal bacteria and immune status in a pig model. BioMed Research International 2016, 5436738. 10.1155/2016/5436738.