Factors for Oxidative Stress and Inflammation in Poultry

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Chronic stress is recognized as a secret killer in poultry. It is associated with systemic inflammation due to cytokine release, dysbiosis, and the so-called leaky gut syndrome, which mainly results from oxidative stress reactions that damage the barrier function of the cells lining the gut wall. Poultry, especially the genetically selected broiler breeds, frequently suffer from these chronic stress symptoms when exposed to multiple stressors in their growing environments.

poultry inflammation oxidative stress stressors phytogenic substances

1. Introduction

Mitochondria, commonly referred as the “powerhouse of eukaryotic cells”, are responsible for the production of cellular energy [1]. However, mitochondria are also involved in numerous additional metabolic processes, such as signaling through mitochondrial reactive oxygen species (ROS), hormonal signaling, heme synthesis reactions, steroid synthesis, regulation of membrane permeability, apoptosis-induced cell death, calcium trafficking, and control of cellular metabolism [2][3]. As a result, mitochondrial damage and subsequent malfunction are significant contributing factors to a variety of animal diseases, owing to their influence on cellular metabolism [4][5]. Additionally, ROS can be generated in the cytosol and other cellular compartments, including the plasma membrane, but also the nucleus, peroxisome, endoplasmic reticulum (ER), and Golgi apparatus [6][7][8]. Due to the high contents of polyunsaturated fatty acids (PUFAs) in these membranes [9], lipid peroxidation can occur and, as a result, phospholipids become directly damaged and may also act as a signal for death [10].

Stress, regardless of its source or type (biological, environmental, nutritional, physical, chemical, or psychological), can lead to inflammation and further malicious downstream reactions [11][12][13]. Several synthetic compounds have been developed to significantly lower inflammation, but most of these drugs are accompanied by unwanted side effects, especially when used at higher doses and during long-term therapies. Natural compounds appear to be less compromised by these side effects [14] and, especially in poultry farming, phytogenic feed additives (PFAs) have attracted considerable interest [15]. Generally, the utilization of natural feed additives that contain anti-inflammatory phytochemicals has become very common for the enhancement of productivity, digestive enzymes, nutrient utilization and as an alternative to antibiotics in livestock species and poultry in particular. The phytochemical compounds of interest are diverse in their structures and include polyphenols, flavonoids,

terpenoids, alkaloids and plant sterols [16]. In addition to their anti-inflammatory and antioxidant properties, they may also have a number of other effects, including anticancer, antimicrobials, anti-diarrheal, and analgesic actions [17], which in turn enhance the profitability of poultry.

2. Factors for Oxidative Stress and Inflammation in Poultry: Secret Killers

In animal farming, a variety of environmental, nutritional, microbiological, and management factors contribute to oxidative stress. These stressors can be termed as “secret killers”, since they multiply in malignant states in animals [18]. This section focus on the most important factors that are relevant to poultry farming, such as heat stress, dysbiosis and mycotoxins.

During chronic inflammation, an increase in the generation of ROS causes the peroxidation of lipids in cell membranes, as well as mitochondrial and other endomembranes, finally leading to cell death [19]. When these membranes are damaged over time, it is not surprising that multiple cells and organs of an organism are affected [20]. Animal studies [21][22] have established that the complex interactions among diet ingredients, the gut microbiome, the nervous system, the immune system, and the endocrine system are crucial for metabolic and gastrointestinal health. Any disturbances in this delicate equilibrium, such as chronic oxidative stress, result in mitochondrial dysfunction, with its severe impacts upon the immune system and microbiota (see below).

Ninety percent of pathological problems are linked to intestinal chronic inflammation [23]. Disbalance of the gut microbiota has negative effects on the health and biology of metazoans because the gut integrity, biology, metabolism, nutrition, immunity, and neuroendocrine system are all dependent on a healthy microbiota [24][25][26][27][28][29], which is in constant interaction with the microbiota–brain–gut axis. In conclusion, it is justified to qualify oxidative stress and intestinal inflammation as the “secret killers” in animal farming, especially in poultry farming [18][24][30].

2.1. Heat Stress

High temperature is one of the most challenging stressors associated with poultry production [31][32]. It is a serious problem for poultry reared in tropical and subtropical regions, as well as in temperate climate zones, including central and eastern Europe [33]. Heat stress occurs when the ambient temperature exceeds the animal’s thermoneutral zone, and the animal’s physiological capacity to disperse heat through sweating, breathing, or panting fails to prevent a rise in body temperature [34]. Chickens are susceptible to high ambient temperatures due to their feathers, lack of skin sweat glands, and high production of heat, unlike mammals. Chickens lose excess heat by panting to prevent the increase in their body temperature [35]. Heat stress causes several adverse effects on the intestinal mucus layer, tight junctions, enteric immune system, and the antioxidant system [36], which are as follows: (i) a decrease in the size of mucin layers. Heat stress reduces the amount of goblet cells, as well as the expression and secretion of mucins, leading to the thinning of mucin protective layers [37]. As a result, their resistance to opportunistic bacteria decreases and these come in more contact with the intestinal epithelial cells.

The following effects are also caused by heat stress: (ii) disruption of tight junctions, as heat stress alters the expression of tight junction protein constituents, such as occludin (OCLN), various claudins (CLDN) and zonula occludens (ZO)-1, -2 and -3 [37][38]; (iii) intestinal barrier dysfunction, as the intestinal hyperpermeability is increased [39][40][41][42]; (iv) endotoxemia and systemic inflammation, which results from the translocation of opportunistic bacteria, endotoxins and lipopolysaccharides (LPS), leading to an increase in pro-inflammatory mediators, such as interleukins (IL-1β, IL-6) and tumor necrosis factor-α (TNF-α) [43]; v) hepatic and hypothalamic inflammation, which mainly results from the translocation of microbial-associated molecular patterns, such as LPS [44]; (vi) redox imbalance between the pro- and antioxidants in favor of pro-oxidants. Heat stress is a key contributor to systemic oxidative stress by increasing the levels of pro-oxidants (e.g., ROS). Several studies have revealed that heat stress leads to higher cellular energy demand, promoting the generation of ROS in the mitochondria [45][46]. Consequently, oxidative stress occurs in multiple tissues, leading to cell apoptosis or necrosis [47].

In summary, heat-induced oxidative stress disrupts the intestinal barrier and alters many cellular processes. Thus, the presence of ROS increases the intestinal permeability, which facilitates the translocation of bacteria and their molecular patterns (e.g., LPS) from the gut (leaky gut syndrome) [48] (see also **Figure 1**).

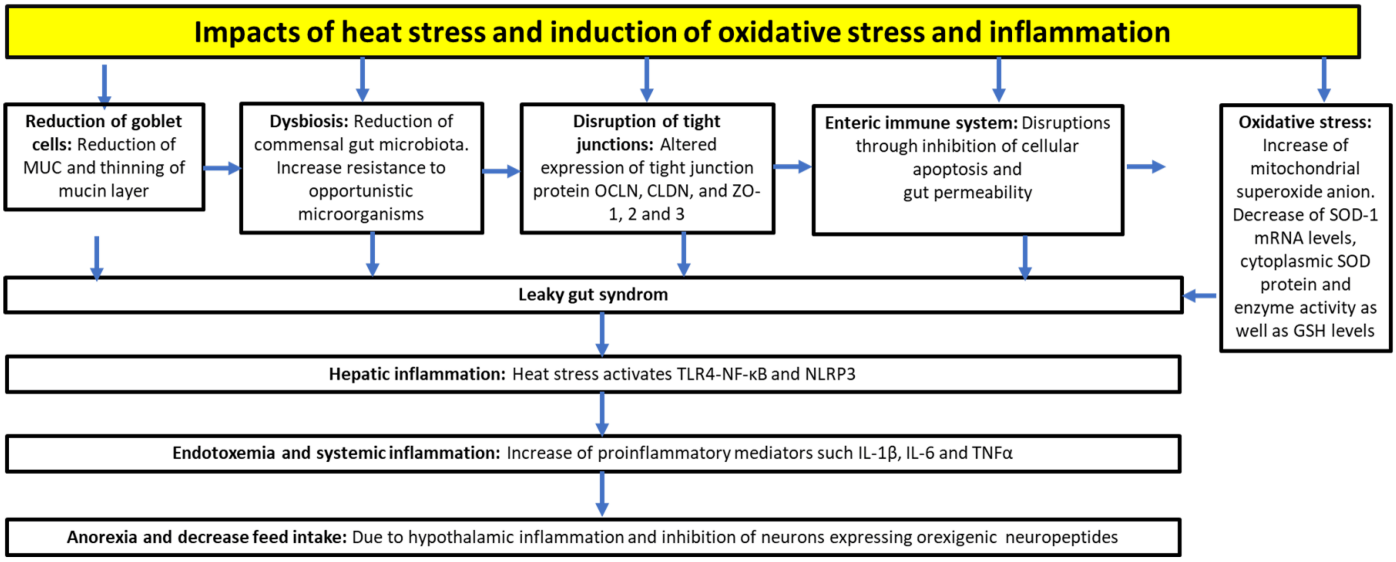

Figure 1. Impacts of heat stress on physiological functions, and induction of inflammation and oxidative stress. OCLN, occludin; CLDN, claudins; ZO, zonula occludens; TLR4, toll-like receptor 4; NF-κB, nuclear factor-kappa B; IL, interleukin; TNFα, tumor necrosis factor α; SOD, superoxide dismutase 1; GSH, glutathione.

2.2. Dysbiosis

Poultry production relies heavily on the animals' intestinal health and intestinal function to maximize nutrient uptake and growth, which in turn are associated with animal performance. Their gut microbiota mainly consists of bacteria, fungi, and protozoa. As a result of commensal bacteria, intestinal epithelial cells create ROS, which serve as second messengers in cellular signaling. Tight junctions between intestinal epithelial cells form a barrier and prevent the invasion of microorganisms into the host organism [49]. Dysbiosis refers to the alteration in the

composition of the gut microbiota with an imbalanced host–microbe relationship [50][51]. As a result, this can lead to increasing amounts of microbial metabolites (see below) that mediate oxidative stress and inflammation (**Figure 2**).

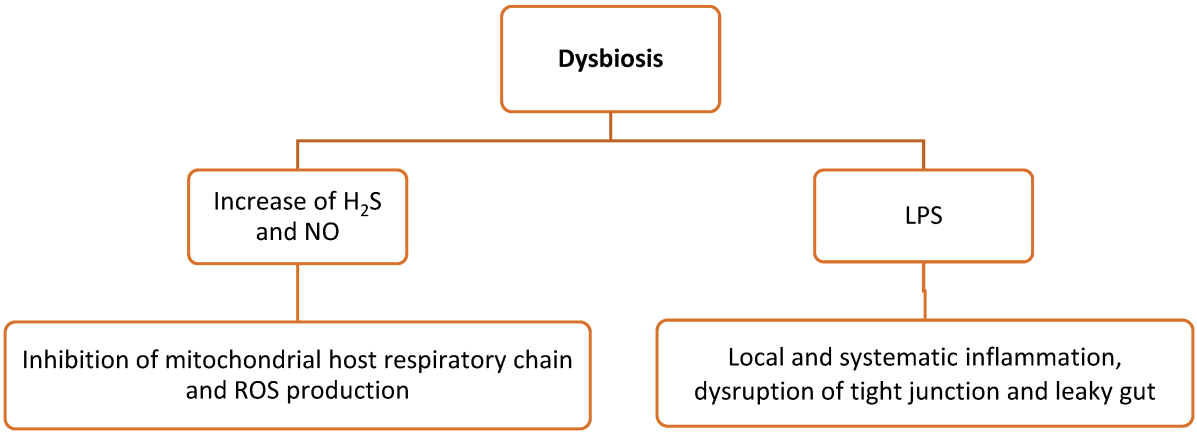

Figure 2. Microbial metabolites during dysbiosis-mediated oxidative stress and inflammation. H_2S, hydrogen sulfide; ROS, reactive oxygen species; IL, interleukins; LPS, lipopolysaccharides.

More specifically, ROS are generated in the gut epithelial cells by several ROS stressors that disrupt the redox balance and cause inflammation, which are as follows [21]: (i) NO is produced by the gut microbiota in the intestinal tissues via the conversion of nitrite and nitrate [52]. Excessive production of NO due to dysbiosis generates ROS associated with cellular damages, e.g., due to the inhibition of the host mitochondrial respiratory chain [53]. (ii) Some intestinal bacteria such as *E. coli* produce hydrogen sulfide (H_2S) in high amounts by the degradation of sulfur-containing peptides and amino acids in the gut. In the case of dysbiosis, the elevated H_2S concentration inhibits cytochrome oxidase, which in turn inhibits the host mitochondrial respiratory chain and leads to the overexpression of pro-inflammatory factors [54]. However, H_2S can also be detoxified by the cecal mucosa by converting it into thiosulfate, which is subsequently converted by ROS into tetrathionate, serving as an electron acceptor for salmonellae, as an example. As a result, a new nutrient niche in the gut is shaped by supporting the growth of more pathogenic bacteria and, thus, increasing dysbiosis and gut inflammation [55][56]. (iii) The TCA cycle can be stimulated by short-chain fatty acids (SCFAs), particularly butyrate. In addition, SCFAs can promote the production of the signaling hormone GLP-1 and the anti-inflammatory IL-10 cytokines to decrease energy intake [54]. (iv) During dysbiosis, LPS production by Gram-negative bacteria is increased and induces local and systematic inflammation by the stimulation of the intestinal epithelial cells and macrophages. As a result, tight junctions are damaged, leading to leaky gut syndrome [57][58][59][60][61][62].

2.3. Mycotoxins

Foods, grains, and animal diets are suitable substrates for a wide array of fungi and molds. In particular, molds such as *Aspergillus*, *Fusarium*, and *Penicillium* species produce their own strain-specific mycotoxins as secondary metabolites and the mycotoxin-contaminated diets have to be discarded [63]. Due to significant economic losses, mycotoxins are a global issue. Aflatoxin B1 (AFB1), deoxynivalenol (DON), nivalenol (NIV), fumonisin B1 (FB1), ochratoxin A (OTA), and zearalenone (ZEN) are the main mycotoxins [64][65][66] (**Figure 3**).

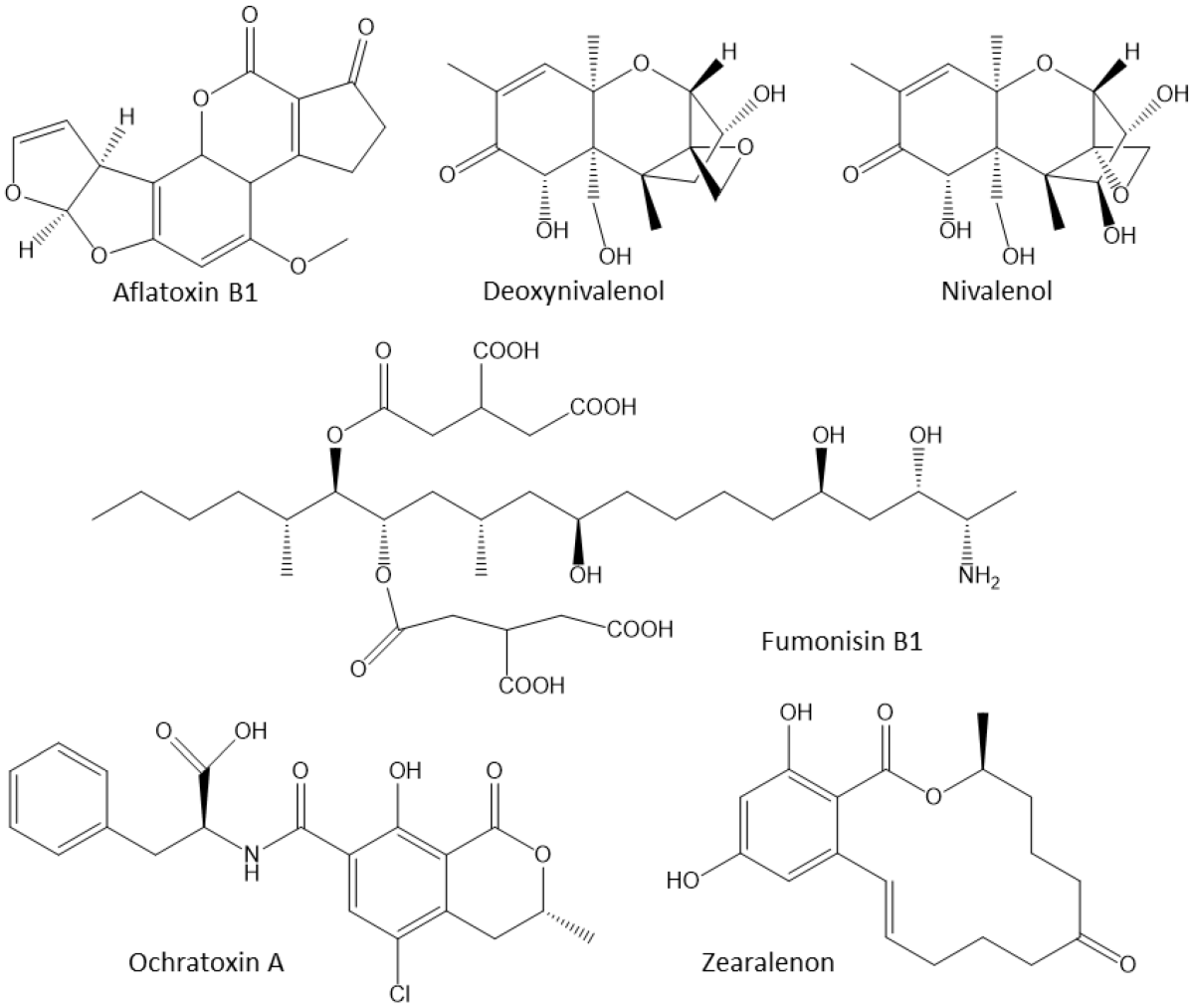

Figure 3. The most common mycotoxins that affect poultry. Aflatoxin B1 (AFB1) and fumonisin B1 (FB1) are polar mycotoxins that are more easily adsorbed by adsorbents than non-polar mycotoxins. Ochratoxin A, T-2 toxin, deoxynivalenol (DON) and zearalenone (ZEN) are non-polar.

In poultry farming, mycotoxins reduce feed intake, feed efficiency, growth performance, immunity, and hatchability [67][68]. The toxins increase mortality, organ damage, carcinogenicity, teratogenicity, and decrease egg production. On a molecular level, mycotoxins induce the generation of ROS, and thereby contribute to lipid peroxidation [69]. They also alter cellular redox signaling, antioxidant status, and membrane integrity [70]. Mycotoxins, particularly aflatoxin, suppress the intracellular levels of antioxidants Nrf2, SOD, GPx and CAT [71][72], and, thus, increase lipid peroxidation and reduce GSH levels [73][74]. The main intracellular endogenous antioxidants and pro-inflammatory cytokines that are associated with oxidative stress mediated by the different mycotoxins (adapted from [75]) are summarized in **Table 1**.

Table 1. Modulatory effect of mycotoxins on intracellular antioxidants and pro-inflammatory cytokines.

Mycotoxin	Downregulation of Intracellular Antioxidants	Upregulation of Pro-Inflammatory Cytokines
AFB1	Nrf2, CAT, GPx; SOD	Cytokines, NO; NO_2

Mycotoxin	Downregulation of Intracellular Antioxidants	Upregulation of Pro-Inflammatory Cytokines
DON	CAT, GPx; SOD	AP-1; ERK-MAPK
OTA	Nrf2, CAT, GPx; SOD	Fenton reaction
ZEN	CAT, GPx; SOD	CoX-2, cytokines; iNOS
T-2	Nrf2, CAT, GPx, GPx; SOD	Cytokines, iNOS; NO

AFB1, aflatoxin B1; DON, deoxynivalenol; NIV, nivalenol; FB1, fumonisin B1; OTA, ochratoxin A; ZEN, zearalenon. Nrf2, erythroid 2-related factor 2; CAT, catalase; GPx, glutathione peroxidase; SOD, superoxide dismutase; NO, nitric oxide; NO_2, nitrogen dioxide; AP-1, activator protein 1; ERK-MAPK, extracellular signal-regulated kinase-mitogen-activated protein kinase; CoX-2, cyclooygenase-2; iNOS, inducible nitric oxide synthetase.

2.4. Diet-Mediated Oxidative Stress

The supplementation of poultry diets with oils that are high in PUFAs is common as an efficient source of energy and as a means to increase palatability, to improve pellet quality, and to enhance the absorption of fat-soluble vitamins [76][77]. As mentioned earlier, PUFAs have a faster oxidation rate than saturated fats, meaning that they will become rancid more quickly. This is due to the oxidation of the reactive double bonds, which allows molecular oxygen to react with these moieties [78]. A number of additional factors, such as light exposure, the presence of catalytic transition metal ions, and high temperature during feed pelleting and storage, can lead to the production of free radicals, which in turn lead to lipid autoxidation [79][80]. The oxidation of lipids results in the production of more reactive substances, which exhibit potentially biological harmful effects and give the product an undesirable odor [81][82][83][84]. Notably, even mild oxidation can produce biologically reactive and toxic oxidation products. Lipid peroxidation results in a variety of degradation products, such as peroxides, aldehydes, and polar compounds that are differentially absorbed and metabolized. Peroxidation varies depending on the temperature, the duration of the thermal processing steps, and the composition of the oil. In this regard, feeding poultry with peroxidized oils that contain inadequate supplies of endogenous antioxidants may lead to in vivo metabolic oxidative stress [85][86][87][88]. As a result of this oxidative stress, ROS and free radical products cannot be converted into less reactive species by antioxidants and antioxidant enzymes, resulting in tissue-damaging free radicals that bind to lipids, proteins, and DNA [89] (see above). Indeed, it was demonstrated that, during the consumption of oxidized oils, reactive aldehydes accumulate in the stomach, which are adsorbed into the small intestine, where they are concentrated and metabolized in the liver [90]. Broilers that received oxidized oils had a slower growth rate, and the animals' plasma and tissues had higher thiobarbituric acid reactive substances (TBARS) as a marker of lipid damage and a low quantity of antioxidants [91].

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