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«Review»

Mechanisms underlying the Effects of Heat Stress on Intestinal Integrity, Inflammation, and Microbiota in Chickens

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Poultry meat and egg production benefits from a smaller carbon footprint, as well as feed and water consumption, per unit of product, than other protein sources. Therefore, maintaining a sustainable production of poultry meat is important to meet the increasing global demand for this staple. Heat stress experienced during the summer season or in tropical/subtropical areas negatively affects the productivity and health of chickens. Crucially, its impact is predicted to grow with the acceleration of global warming. Heat stress affects the physiology, metabolism, and immune response of chickens, causing electrolyte imbalance, oxidative stress, endocrine disorders, inflammation, and immunosuppression. These changes do not occur independently, pointing to a systemic mechanism. Recently, intestinal homeostasis has been identified as an important contributor to nutrient absorption and the progression of systemic inflammation. Its mechanism of action is thought to involve neuroendocrine signaling, antioxidant response, the presence of oxidants in the diet, and microbiota composition. The present review focuses on the effect of heat stress on intestinal dysfunction in chickens and the underlying causative factors. Understanding these mechanisms will direct the design of strategies to mitigate the negative effect of heat stress, while benefiting both animal health and sustainable poultry production.

Key words: broiler, corticosterone, intestinal microbiota, oxidants, polyphenols

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Introduction

The rapid increase in the world population has raised concerns about global food shortages, calling for the development of more efficient food production systems. The poultry sector contributes substantially to human nutrition and food security because of its short production cycle. Moreover, the use of agricultural/commercial food waste and byproducts in meat and egg production has transformed the poultry industry into a sustainable source of animal proteins. According to the United Nations Food and Agriculture Organization, global poultry meat production increased from approximately 68.6 to 133 million tons between 2000 and 2020, with output estimated to reach 181 million tons by 2050. Excluding fish, these values account for 32.5% of global meat production (Alexandratos and Bruinsma, 2012). Poultry meat and egg production systems are more efficient and sustainable than those developed for pork, beef, and milk, as they have a smaller carbon footprint, as well as feed and water consumption per unit of generated product (Gerbens-Leenes *et al*., 2013; Pawar *et al*., 2016).

To meet the increased consumption and widespread production of poultry meet and eggs, productivity must be maintained high. However, heat stress (HS) can have a negative impact on the productivity and health of chickens. HS affects the physiology of homeothermic animals, resulting in decreased livestock performance. HS occurs mainly in the summer season or in tropical/subtropical areas, as well as during transportation from farms to processing facilities (Mitchell and Kettlewell, 1998, Kpomasse *et al*., 2021). The negative consequences of HS include reduced body weight gain, feed intake, and use of nutrients, thereby contributing to increased mortality, and ultimately decreasing meat and egg yields. Moreover, HS negatively influences meat quality (pH, drip loss, and water-holding capacity), eggshell strength/thickness, and reproductive performance (fertility and semen characteristics) (Lara and Rostagno, 2013; Nawab *et al*., 2018; Zaboli *et al*., 2019; Kim *et al*., 2020). Overall, HS results in an estimated annual economic loss of $128 to $165 million for the poultry industry in the United States, a major producer of chicken

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meat (St-Pierre *et al*., 2003; Lara and Rostagno, 2013). However, this loss is likely underestimated as it does not take into account loss of product quality and any compensatory veterinary/nutritional costs. Moreover, the estimate was made two decades ago, prior to the recent uptick in global warming (Tollefson, 2022). Consequently, the economic impact of HS on livestock production will be more harmful than initially estimated.

HS negatively affects the physiology, metabolism, immune response, and behavior of chickens, causing electrolyte imbalance, endocrine disorders, oxidative stress, inflammation, and immunosuppression (Renaudeau *et al*., 2012; Nawab *et al*., 2018; Rostagno, 2020). Recently, intestinal homeostasis has been identified as an important factor in nutrient absorption, with its disruption accelerating systemic inflammation via the neuroendocrine system, antioxidant response, dietary oxidants, and microbiota. However, the specific effects of HS on intestinal homeostasis and inflammation, as well as the underlying mechanisms are only beginning to be elucidated. Therefore, this review summarizes recent progress on the effects of HS on intestinal dysfunction in chickens and their causative factors. Moreover, this overview highlights future research directions for developing sustainable poultry production systems that can mitigate the expected increase in HS.

HS and Intestinal Physiology

Animals have a specific thermoneutral zone, defined as the temperature range in which the activation of thermogenesis or heat dissipation mechanisms is not required to maintain body temperature. The normal body temperature of chickens is approximately 41–42 °C, and the thermoneutral zone is thought to be 18–25 °C. Ambient temperature above this zone causes an imbalance in thermoregulatory control due to excess metabolic heat generation compared to the body's heat dissipation capacity, leading to HS (Donkoh, 1989). Humidity functions as a cofactor, which can exacerbate the effects of HS owing to reduced surface water evaporation (Lin *et al*., 2005; Esnaola-Gonzalez *et al*., 2020; Kim *et al*., 2022). Chickens are more susceptible to high temperatures than other livestock animals because they lack sweat glands, and heat dissipation is limited to the face, legs, and combs, which are not covered with feathers. In addition, the relatively low ratio of body surface area to body weight in chickens is negatively associated with body temperature control under HS conditions, especially in broilers. Modern broiler genotypes have been developed to exhibit elevated metabolic activity, which favors rapid growth but also greater heat production, resulting in lower heat tolerance (Deeb and Cahaner, 2002; Pawar *et al*., 2016). In poultry, heat dissipation depends mainly on panting (short and quick breathing), wing spreading, and increased blood flow to the skin, which serves as a sink for heat from the body core. However, excessive panting induces respiratory alkalosis (Teeter *et al*., 1985), and increased skin blood flow induces hypoxia, energy deficiency, oxidative damage, and intestinal inflammation (Hall *et al*., 2001; Lambert, 2009; Varasteh *et al*., 2015).

Management of intestinal function has emerged as a research hotspot in poultry science. Globally accepted norms now regulate the use of antimicrobial growth promoters in feed to suppress the emergence and development of drug-resistant pathogens. The small intestine plays an important role in digestion and subsequent absorption of nutrients from ingested feed, as well as in local defense against pathogenic bacteria and their harmful constituents such as lipopolysaccharide (LPS). However, HS disrupts intestinal function through pathogenic, metabolic, and endocrine stimuli, along with excessive production of oxidants. This results in increased permeability to potentially toxic luminal substances. The intestine consists of a single layer of epithelial cells connected by tight junctions made of occludins, claudins, junctional adhesion molecule-A, and zonula occludens, as well as outer and inner mucus layers covering the cellular partition (Suzuki, 2020). These mechanical structures are responsible for defending against pathogen invasion through paracellular pores and leakage pathways (Usuda *et al*., 2021). HS has been reported to downregulate the expression of tight junction proteins (Song *et al*., 2014; Wu *et al*., 2018), leading to the entry of LPS into the blood stream (Abdelqader *et al*., 2017; Alhenaky *et al*., 2017; Nanto-Hara *et al*., 2020). HS-induced intestinal hyperpermeability and consequent loss of barrier function has been demonstrated also by an increased plasma concentration of orally administered fluorescein-4-isothiocyanate dextran (Song *et al*., 2014; Ruff *et al*., 2020; Kikusato *et al*., 2021a; Sarsour and Persia, 2022).

LPS transferred from the intestinal lumen into circulation stimulates innate immunity, leading to inflammation in several organs and tissues. Inflammation triggers metabolic alterations that support the immune system and promote degradation of skeletal muscle proteins (Frost and Lang, 2008). Endocrine changes, particularly in glucocorticoid secretion and inflammatory cytokines, are involved in muscle proteolysis (Klasing and Johnstone, 1991; Zhou *et al*., 2016; Qaid and Al-Garadi, 2021). Amino acids derived from muscle protein degradation and blocked muscle protein synthesis are thought to be used for acute-phase protein synthesis and gluconeogenesis, thereby providing energy to the liver to counteract inflammation (Gessner *et al*., 2017). The generation of these metabolites represents not only a metabolic cost (Niewold, 2007; Broom and Kogut, 2018a), but leads also to loss of skeletal muscle mass. Strategies that effectively suppress HS-induced intestinal hyperpermeability could reduce costs and improve meat production.

Reduced Feed Intake and Intestinal Integrity

Several factors are associated with formation of a "leaky" gut in chickens under HS. Intestinal epithelial cells exhibit rapid cell turnover depending on nutritional intake (Yamauchi *et al*., 1996). A reduction in feed intake is an adaptive response to decreased diet-induced thermogenesis under HS conditions; whereas feed restriction (fasting) favors intestinal permeability (Vicuña *et al*., 2015; Gilani *et al*., 2017). Therefore, poor appetite caused by HS may contribute to intestinal hyperpermeability. However, pair-fed treatment, whereby chickens under thermoneutral conditions were fed an equal amount of feed as HS-treated birds, demonstrated little effect on intestinal permeability (Nanto-Hara *et al*., 2020; Emami *et al*., 2021). This suggests that other internal factors, such as hormonal changes or inflammation, are likely responsible for intestinal permeability in chickens under HS conditions.

Glucocorticoid Secretion and Intestinal Integrity

Activation of the hypothalamus-pituitary-adrenal axis is a neural response to stressors that affect intestinal integrity. In this axis, corticosterone is the main glucocorticoid secreted by avian species and plays a role in modulating peripheral oxidative homeostasis, metabolism, and immunity to combat stress. However, large, acute, and prolonged secretion of corticosteroids may have harmful effects on the host. Treatment with corticosteroids or synthetic glucocorticoids (such as dexamethasone) induces oxidative stress, proteolysis, gluconeogenesis (Lin *et al*., 2004a; Gao *et al*., 2008), and intestinal permeability (Vicuña *et al*., 2015; Barekatain *et al*., 2020). Corticosteroid treatment has also been reported to promote the expression of inflammatory cytokines in isolated peripheral blood lymphocytes of chickens (Shini and Kaiser, 2009). Increased intestinal permeability in HS-exposed chickens is accompanied by higher plasma corticosteroid concentrations (Alhenaky *et al*., 2017; Alhotan *et al*., 2021; Kikusato *et al*., 2021a); whereas dietary treatment with plant extracts or betaine ameliorates corticosteroid secretion, intestinal barrier function, and cytokine levels in HS-exposed chickens (Alhotan *et al*., 2021; Kikusato *et al*., 2021a; Wang *et al*., 2022b). It has also been proposed that inflammatory cytokines disturb the intestinal tight junction barrier, leading to increased tissue penetration by luminal antigens (Al-Sadi *et al*., 2009). These lines of evidence suggest that corticosteroids and inflammatory cytokines induce intestinal hyperpermeability in chickens under HS. However, it remains unclear whether this phenomenon is caused primarily by corticosteroids or circulating cytokines, and whether LPS plays a role in it.

Chickens inoculated with LPS exhibit a rapid (within 1 h) increase in serum corticosteroids, followed by a rise in cytokine levels (3 h after LPS injection) (Nakamura *et al*., 1998). Moreover, mice subjected to HS exhibited concomitantly elevated plasma corticosteroids, intestinal lesions, and exfoliated enterocytes at peak body temperature during HS, followed by hypersecretion of cytokines 2 h post-HS (Leon *et al*., 2006). These findings suggest that corticosteroids are the initial trigger of HS-induced intestinal inflammation and hyperpermeability, with cytokines potentially playing an exacerbating role. However, the role of LPS in this scenario remains unclear, as there is no information on time-course changes in circulating LPS levels during HS. In one study, plasma LPS increased 1 h after corticosteroid injection in chickens, although there were no data on the time course of cytokines (Shini *et al*., 2008). Other studies have reported that the stimulatory effect of LPS on inflammatory responses is enhanced in the presence of corticosteroids (Kelly *et al*., 2018, Chae, 2021). These findings suggest that LPS transferred through the leaky intestine may reinforce the effect of cytokines during HS. However, further investigation is required to verify the complex roles of various inflammatory stimulants in chickens subjected to HS.

Oxidative Stress, Exogenous Oxidants, and Intestinal Integrity

Oxidative stress has been suggested to trigger intestinal permeability dysfunction under HS conditions (Lara and Rostagno, 2013). Reactive oxygen species (ROS), reactive nitrogen species, and their oxidative products stimulate nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs) (Moldogazieva *et al*., 2018; Calibasi-Kocal *et al*., 2021), each of which initiates an inflammatory process in the epithelial and immune cells present in the lamina propria (Huang and Lee, 2018; Lauridsen, 2019). NF-κB regulates the inflammatory response by stimulating the production of cytokines and other bioactive substances, thereby reinforcing and restoring intestinal barrier function. MAPKs activate another transcription factor, activator protein-1, which also induces the transcription of inflammatory genes (Wang *et al*., 2013). Activated immune cells located near epithelial cells secrete inflammatory cytokines, such as interleukin-6, interferon-γ, and tumor necrosis factor-α, along with inflammatory enzymes, such as inducible nitric oxide and cyclooxygenase, to protect epithelial cells from invading pathogens. However, an excessive protective response may cause local inflammation and disrupt the intestinal barrier (Awad *et al*., 2017). Overproduction of mitochondrial ROS is associated with HS-induced oxidative damage in the liver, spleen, and skeletal muscles (Kikusato and Toyomizu, 2013; Zhang *et al*., 2018; Kikusato and Toyomizu, 2019; Wang *et al*., 2019). HS stimulates mitochondrial ROS production and lowers total antioxidant capacity of intestinal tissues (He *et al*., 2019; Wang *et al*., 2019; Lan *et al*., 2020; Liu *et al*., 2022b). NF-κB and MAPK signaling have been associated with HS-induced intestinal injury in chickens (Liu *et al*., 2022c; Wang *et al*., 2022b) and mice (He *et al*., 2015). Moreover, a study using heat-incubated cultured cells showed that HS induced mitochondrial ROS generation (Yi *et al*., 2017), as well as expression of NF-κB and tight junction proteins (Huang *et al*., 2020). Hence, HS-induced oxidative damage might occur independently of any circulating stimulants.

The ingestion of dietary oxidants can also initiate an exogenous inflammatory response. Lipids obtained from the diet are susceptible to peroxidation during feed processing and storage under hot conditions. Soybean and corn oils, which contain high levels of unsaturated fatty acids that are easily oxidized to hydroperoxide products, are widely used lipid sources. Fish meal also contains large amounts of polyunsaturated fatty acids in its oil residue. Synthetic antioxidants, such as ethoxyquin, dibutyl hydroxytoluene, and butyl hydroxyanisole, are supplemented to a lipid source or diet to suppress oxidation. However, the supplemented amount is restricted to prevent health problems in humans, resulting in incomplete suppression of the oxidation reaction. Broilers fed a diet with oxidized oil exhibited impaired intestinal morphology, inflammatory cytokine induction (Zhang *et al*., 2022b), reduced total antioxidant capacity, increased NF-κB expression (Liang *et al*., 2015), and greater lipid peroxidation (Tan et al., 2018; Sun *et al*., 2020) in the intestine. Administration of 4-hydroxy-2-hexenal, an end-product of *n-3* polyunsaturated fatty acids, augments the levels of plasma inflammatory cytokines and NF-κB activation in the small intestine (Awada *et al*., 2012). Based on this evidence, a diet rich in oxidants is likely to induce an intestinal inflammatory response and oxidative damage, possibly owing to NF-κB activation and downregulation of nuclear factor-erythroid 2-related factor (Ringseis *et al*., 2016; Dong *et al*., 2020), an emerging regulator of cellular resistance to oxidants. A recent investigation demonstrated that lipid hydroperoxide was not absorbed but rather gave rise to other lipid hydroperoxides in the gastrointestinal tract (Takahashi *et al*., 2022). Moreover, lipid oxidation levels in chickens fed oxidized oil correlated negatively with α-tocopherol (Sheehy *et al*., 1994), lutein, β-carotene, and retinol levels (Engberg *et al*., 1996). These findings suggest that the ingestion of oxidants could stimulate several signaling cascades, as well as divert antioxidants from other important cell processes, thereby increasing the susceptibility to additional HS-induced oxidative damage. Therefore, the quality of feeds, especially their oxidative load, should be considered to prevent synergistic damage caused by the negative effects of environmental stressors and oxidized feed.

Lipid Fortification: Can Ketone Bodies Mitigate HS-induced Intestinal Dysfunction?

Although fasting or feed withdrawal potentiate intestinal barrier dysfunction, these nutritional treatments are effective in improving short-term survival during acute HS exposure (McCormick *et al*., 1979; Garlich and McCormick, 1981). Lipid fortification is a conventional method of alleviating acute HS-induced ‘thermal death’ (McCormick *et al*., 1979; Garlich and McCormick, 1981), possibly via a reduction in diet-induced thermogenesis. Feeding an isocaloric diet with fortified lipids suppressed HS-induced body weight loss in laying hens (Kim *et al*., 2019) and broilers (Ghazalah *et al*., 2008; Attia *et al*., 2021). Moreover, addition of 6.7% lipids to the diet suppressed acute HS-induced body weight loss, mitochondrial ROS generation, and oxidative damage in broiler chickens (Mujahid *et al*., 2009). Lipid fortification has been reported to lower feed retention in the gastrointestinal tract, contributing to fecal heat loss (Saeed *et al*., 2019) and preventing bacterial overgrowth (Pan and Yu, 2014). Meanwhile, greater lipid retention in peripheral tissues has been suggested to hinder the dissipation of cutaneous heat loss (Renaudeau *et al*., 2012, Brugaletta *et al*., 2022) and heavier broilers fed a high-fat diet exhibited increased mortality during HS (Zulkifli *et al*., 2007). To improve immunological parameters, supplemented lipid levels must be higher than those required for optimal performance in HS-exposed chickens (Attia *et al*., 2021), suggesting that lipid fortification can partially overcome the negative effects of HS.

Liver ketogenesis is a metabolic event induced by both fasting and lipid fortification. It yields acetone, acetoacetate, and β-hydroxybutyrate (BHB). Future studies on the physiological effects of ketone bodies on HS may clarify the mechanisms by which nutritional treatments counteract the effects of HS. Recent studies have demonstrated that BHB exhibits anti-inflammatory activity and suppresses inflammasome formation (Youm *et al*., 2015), as well as ameliorates intestinal inflammation in patients with colitis, in a dextran sodium sulfate-induced mouse model (Huang *et al*., 2022a) and in Caco2/HT29 cells treated with inflammatory cytokines (Kim *et al*., 2021). Given that plasma BHB concentrations are reduced in HS chickens (Han *et al*., 2018; Lu *et al*., 2018), the above findings suggest that HS-induced BHB hyposecretion is associated with intestinal dysfunction. In contrast, BHB hypersecretion may suppress HS-induced brain inflammation, which may alleviate poor appetite. BHB crosses the blood–brain barrier, thereby suppressing HS-induced neural inflammation in the mouse hippocampus (Huang *et al*., 2022b). However, the mechanisms underlying HS-induced anorexia and the related brain dysfunction in chickens remain unclear. Thus, further investigation is required to determine the role of BHB in HS, as well as to elucidate the drop in plasma BHB levels in HS chickens.

HS and Intestinal Microbiota

HS results in atrophy of lymphoid organs, such as the thymus, spleen, and bursa of Fabricius, while also increasing the ratio of heterophils to lymphocytes and, thus, indicating a state of immune suppression (Nawab *et al*., 2018). In chickens, chronic HS decreases plasma immunoglobulin (Ig) levels to a varying extent (Quinteiro-Filho *et al*., 2017; Awad *et al*., 2020; Hirakawa *et al*., 2020; Li *et al*., 2020), as well as secretory IgA (Chen *et al*., 2014; Hu *et al*., 2017; Wang *et al*., 2020; Alhotan *et al*., 2021; Wu *et al*., 2021). The latter is the predominant IgA on the mucosal surface, where it inhibits the adhesion of pathogenic bacteria and viruses (Kogut *et al*., 2020). Accordingly, HS may reduce the immunological robustness of chickens.

The role of intestinal microbiota in modulating both the enteric and systemic immune systems of chickens has been reviewed previously (Brisbin *et al*., 2008; Awad *et al*., 2017; Broom and Kogut, 2018b; Sun and Jia, 2018). HS increases the numbers of *Escherichia coli, Clostridium perfringens*, and *Coliforms*; while reducing the loads of *Lactobacillus* and *Bifidobacterium* (Song *et al*., 2014; Awad *et al*., 2018; Liu *et al*., 2018,). These results indicate that HS induces dysbiosis (or dysbacteriosis) in the intestine, whereby harmful bacteria proliferate at the expense of beneficial ones. Such imbalance leads to the malabsorption of nutrients, barrier dysfunction, and local inflammation (Awad *et al*., 2017). Gram-positive bacteria dominate in chickens with low body weight compared to those with high body weight, with the former exhibiting also higher serum LPS levels (Zhang *et al*., 2022). The immune and inflammatory responses evoked by LPS originate mainly from its recognition by Toll-like receptor-4, which activates a series of downstream cascades that upregulate NF-κB and trigger cytokine production. HS is also a predisposing factor for necrotic enteritis in broiler chickens, and *C. perfringens* has been suggested to play a significant role in this process (Tsiouris *et al*., 2018).

The gastrointestinal microbiota has emerged as a promising target for preventing inflammatory and metabolic disorders, especially obesity (Cheng *et al*., 2022). However, the identification of certain pathogenic bacteria alone cannot fully explain disease pathogenesis. Recently, the roles and behaviors of opportunistic pathogens have been investigated in detail. Normally, these commensal bacteria are harmless; however, they can cause infectious diseases under certain circumstances, such as in a state of reduced immunological robustness. Therefore, it is important to evaluate global shifts in microbial composition in response to pathophysiological stress. Metagenomic analysis of 16S rRNA-based microbiome data has been used to identify microbial signatures associated with disorders and to precisely evaluate intestinal microbial compositions at the phylum, class, order, family, genus, and species levels, including several bacteria that cannot be cultured *in vitro*. Microbial metagenomic data can also be used to evaluate correlations between the abundance of certain microbes and host parameters such as immune receptors (Li *et al*., 2022), thereby identifying the immune-stimulating or immune-suppressing mechanisms of each microbe.

Firmicutes and Bacteroidetes are the two dominant bacterial phyla in the intestines of mammals and chickens. The Firmicutes/Bacteroidetes ratio (F/B ratio) has emerged as a useful microbial indicator of a host's intestinal and nutritional/energetic status (Stojanov *et al.*, 2020). The phylum Firmicutes includes gram-positive bacteria that belong predominantly to the genera *Bacillus*, *Clostridium*, *Enterococcus*, *Lactobacillus*, and *Ruminicoccus*. Compared to other bacteria, members of Firmicutes have a superior capacity to ferment and metabolize carbohydrates and lipids. The phylum Bacteroidetes includes approximately 7,000 different species of gram-negative bacteria that belong mainly to the genera *Bacteroides*, *Alistipes*, *Parabacteroides*, and *Prevotella*. *Bacteroides* species produce succinate, acetate, and propionate. Moreover, several members of this phylum appear to be opportunistic pathogens. An increased F/B ratio has been observed in the intestinal tract of obese patients, whereas a decreased ratio has been found in patients with inflammatory bowel disease (Stojanov *et al*., 2020). In chickens, an increased F/B ratio has been reported in broilers fed *Saccharomyces cerevisiae* hydrolysate (Lin *et al*., 2023), fermented grape seed meal (Nan *et al*., 2022), sodium butyrate (Zhang *et al*., 2022a), or xylo-oligosaccharides and *Astragalus* polysaccharides (Wang *et al*., 2022a). In addition, it has been found in native chickens fed *Bacillus amyloliquefaciens* and *S. cerevisiae* (Lee *et al*., 2022), and in laying hens fed 25-hydroxyvitamin D under high stocking density (Wang *et al*., 2021) or receiving fecal microbial transplants from highly efficient broiler chickens (Elokil *et al*., 2022). In some cases, these treatments have resulted in improved growth performance, immunity, and intestinal health. Although the F/B ratio is a possible signature of metabolic disorders in humans, it may also reflect better growth or intestinal parameters in chickens. There is limited information on the F/B ratio in HS chickens and the results are conflicting, with some studies showing an increased ratio in broilers (Wang *et al*., 2018; Shi *et al*., 2019; Liu *et al*., 2020; Yang *et al*., 2021), and others reporting a decreased ratio in laying hens (Zhu *et al*., 2019), pullets (Wang *et al*., 2020), and native chickens (Liu *et al*., 2022c) under HS conditions. At present, the reason for these conflicting results remains unclear. One possibility is that the duration and intensity of HS, as well as the chicken type (egg or meat production) influence the F/B ratio (He *et al*., 2021). Nutritional status may also affect the F/B ratio, given that reduced feed intake is associated with altered gut microbiota (Xing *et al*., 2019; Xiong *et al*., 2020). F/B, gram-positive/gram-negative bacteria, *Prevotella*/*Bacteroides*, and *Fusobacterium nucleatum*/*Faecalibacterium prausnitzii* ratios have been associated with intestinal and metabolic diseases (Di Pierro, 2021). The changes in intestinal microbial composition observed in the current study are summarized in Table 1. Further investigation is required to identify a suitable microbial indicator of intestinal health status and the machinery that induces deleterious effects in HS chickens, from which a potential therapeutic target could be identified.

Microorganisms in chicken litter influence the intestinal microbiota because chickens may incorporate litter via ground pecking and severe footpad dermatitis (Thøfner *et al*., 2019). HS affects nutrient digestion and promotes water consumption (Renaudeau *et al*., 2012; Brugaletta *et al*., 2022,), which alters the characteristics of excreta. Enhanced fecal excretion contributes to transient heat loss (Saeed *et al*., 2019); however, excreta also reduce litter quality, result in a high-moisture environment, and compromise microbial composition. HS was found to reduce nitrogen efficiency and excretion, while increasing moisture, pH, and uric acid in excreta (Liu *et al*., 2022a). Higher litter moisture favors the proliferation of bacteria (Dumas *et al*., 2011) and induces footpad dermatitis in floor-reared chickens (Taira *et al*., 2014). Litter pH, moisture content, and water activity may affect the presence and multiplication of *Salmonella* (Carr *et al*., 1995; Payne *et al*., 2007). Litter conditions have a more profound effect on the ileal than the cecal microbiota (Cressman *et al*., 2010). However, there is no information on the influence of HS on litter microbiota. Thus, understanding HS-induced alterations to these microorganisms and the interplay between the environment and the host could provide useful information for improving intestinal conditions.

Conclusion and Perspective

HS causes complex intestinal disorders with systemic effects. Given current limitations on the installation and running costs of ventilation and air-conditioning systems in poultry houses, HS is unavoidable. However, growing evidence highlights HS as a relevant environmental factor that can substantially decrease profitability and compromise animal welfare. The main nutritional strategies aimed at mitigating the effects of HS investigated to date include fortification with dietary antioxidants (Azad *et al*., 2013; Kikusato *et al*., 2016; Sumanu *et al*., 2022), amino acids (see reviews by Alagawany *et al*., 2022; Teyssier *et*

Table 1. **Heat stress (HS)-induced changes in intestinal microbial composition identified by 16S rRNA-based metagenomic analysis.**

Strain; sample; sex; HS protocols; age	Taxonomic category	Increase vs. thermoneutral condition	Decrease vs. thermoneutral condition	References
Broiler; cecum; female; chronic, 34–38 °C, 28 days	Phylum	Firmicutes, Tenericutes, Anaeroplasma, Proteobacteria, Lactobacillus,	Bacteroidetes, Cyanobacteria	Shi *et al*., 2019
	Genus	(-)	*Bacteroides, Oscillospira, Dorea, Faecalibacterium*	
Broiler; cecum; (-); acute, 31 °C for 6 h, 37 d	Genus	*Parabacteroides, Shigella Anaerobutyricum*	*Bacteroides*	Goel *et al*., 2022
Broiler; cecum; (-); chronic, 33–35 °C	Phylum	(-)	(-)	Wang *et al*., 2022b
	Family	(-)	Ruminococcaceae, Lachnospiraceae	
	Genus	(-)	Faecalibacterium, Marvinbryantia	
Broiler; cecum; female; 32.5 °C, cyclic 8 h/day, 56 d	Phylum	(-)	(-)	Liu *et al*., 2022c
	Genus	*Anaerovorax*	(-)	
Broiler; ileum; male; chronic, 35 °C, 35 d	Family; Genera	Clostridiales vadinBB60 Erysipelatoclostridium	Porphyromonadaceae, Enterococcus Alcaligenaceae, *Enterococcaceae, Parabacteroides, Parasutterella*	Calik *et al*., 2022
Broiler; ileum; male; 36 °C, cyclic, 8 h/day, 29–42 d	Phylum	Proteobacteria	(-)	Emami *et al*., 2022
	Genus	*Blautia*	(-)	
Broiler; cecum; male; 28–35 °C, cyclic, 12 h/day 22–42 d	Phylum	Actinobacteria, Proteobacteria	Bacteroidetes	Li *et al*., 2022
	Genus	*Prevotella, Clostridium (mucosa)*	*Megamonas, Lactococcus*	
Broiler; ileum; female; 32.5 °C, cyclic, 8 h/day, 8–12 wk	Phylum	Firmicutes, Thermi	Proteobacteria, Actinobacteria, Bacteroidetes	Jin *et al*., 2022
	Class	Bacilli, Alphaproteobacter	Gammaproteobacteria, Clostridia, Alphaproteobacteria	
Broiler; cecum; male; chronic, 32 °C, 21–42 d	Phylum	Firmicutes	Bacteroidota	Yin *et al*., 2021
Pullets; cecum; female; acute, 38 °C, 4 h, 100 d	Genus	(-)	*Mucispirillum*	Chen *et al*., 2021
Pullets; cecum; female; cyclic, 30 °C, 8 h/day, 11 wk	Phylum	Bacteroidetes	(-)	Wang *et al*., 2020
	Order	Bacteroidales	Campylobacterales	

(−) indicates that the corresponding parameter was not reported in this study.

al., 2022), phytochemicals (Madkour *et al*., 2022), or changing dietary protein levels (Awad *et al*., 2019; Teyssier *et al*., 2022). Probiotic/prebiotic treatment and thermal manipulation of embryos, chicks, and lighting have also been investigated as possible strategies (Loyau *et al*., 2015; Abd El-Hack *et al*., 2020; Jiang *et al*., 2021; Madkour *et al*., 2022; Yalcin *et al*., 2022). Several manipulations have yielded successful results, with improved physiological parameters and performance of chickens subjected to HS. However, this may reflect a publication bias to some extent, as numerous other trials may have failed to produce positive outcomes. Phytochemicals have been widely used to ameliorate the negative effects of HS because of their strong antioxidant activity; however, their bioavailability is low owing to poor absorption (Martel *et al*., 2020; Kikusato, 2021). Therefore, these effects may be exerted mainly in the intestinal epithelium or by compounds produced via bacterial fermentation or catabolism (Marhuenda-Muñoz *et al*., 2019; Man *et al*., 2020). Thus, intestinal conditions may influence the efficacy of phytochemicals in chickens grown under HS.

Thermal treatment of *in vitro* cultured cells often results in symptoms similar to those observed *in vivo* (Furukawa *et al*., 2015; Kikusato *et al*., 2015b; Yang *et al*., 2019; Mackei *et al*., 2020; Furukawa *et al*., 2021; Lian *et al*., 2021; Siddiqui *et al*., 2021), offering a useful experimental tool for understanding the effect of HS on certain organs and tissues. However, the machinery governing enteric and systemic dysfunction caused by HS could not be determined from these investigations. Further investigations evaluating time-dependent changes, multi-organ/tissues, and cause-and-effect links in several types of HS are required to elucidate the crucial mechanisms underlying the observed effects of HS. They will then offer effective solutions for mitigation via appropriate manipulation.

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Manuscript design: MK and MT. Manuscript writing: MK. Manuscript supervision: MT.

Conflicts of Interest

The authors declare no conflict of interest.

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