

Review

Deleterious Effects of Heat Stress on Poultry Production: Unveiling the Benefits of Betaine and Polyphenols

Majid Shakeri ^{1,*}  and Hieu Huu Le ^{2,3} ¹ Department of Medicine, University of Washington, Seattle, WA 98195, USA² Faculty of Animal Sciences, Vietnam National University of Agriculture, Trau Quy, Gia Lam, Hanoi 131004, Vietnam; lhhieu.hua@gmail.com³ Faculty of Veterinary and Agricultural Sciences, University of Melbourne, Parkville, VIC 3010, Australia

* Correspondence: majidmarch@live.com.my

Abstract: Managing and controlling environmental temperature conditions using practical strategies is crucial to avoid the negative impacts of high environmental temperature, improving poultry production and welfare. High environmental temperature is one of the significant factors challenging poultry production during hot seasons or in tropical areas causing heat stress (HS). The detrimental effects of HS on broilers range from reduced growth performance to impaired poultry meat quality. HS impairs physiological responses caused by alteration in blood parameters, which could lead to impaired product quality by reducing moisture content and altering the production of antioxidant enzymes resulting in increased oxidative stress. There has been a focus on the use of nutritional supplements as a cost effective HS amelioration strategy, such as betaine and polyphenols. Supplementing broiler chicken's diets with polyphenols aims to enhance growth performance via reduced levels of oxidative stress in tissues under HS conditions. Furthermore, using betaine as an osmolyte aims to protect tissues during osmotic stress conditions. The current review reveals that betaine and polyphenols are essential under crucial conditions such as HS to protect tissues from oxidative damage.



Citation: Shakeri, M.; Le, H.H. Deleterious Effects of Heat Stress on Poultry Production: Unveiling the Benefits of Betaine and Polyphenols. *Poultry* **2022**, *1*, 147–156. <https://doi.org/10.3390/poultry1030013>

Academic Editor: Ilias Giannenas

Received: 1 June 2022

Accepted: 15 July 2022

Published: 20 July 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Keywords: broiler chickens; heat stress; betaine; polyphenols; osmolyte; antioxidants; oxidative stress; growth performance; meat quality

1. Advantages of Poultry Meat Production

Global production of poultry meat has increased rapidly over the past decades in response to the rise in global poultry meat consumption [1]. Market demand for poultry meat is expected to increase because of the higher feed efficiency leading to lower meat production costs. This is evidenced by the rapid improvements in feed conversion ratio, with efficiency gains equating to a reduction of ~1 kg feed per kg of growth. The production of ~1 kg of chicken's meat requires ~2–2.5 kg feed, while the feed needed for other meats would be ~7 kg [2]. This makes poultry meat comparatively inexpensive, costing approximately 40% the price of beef and 70% the price of pork. Short breeding intervals also make poultry more economical than other meats. The poultry cycle is normally at 5–7 weeks, and therefore can be repeated 6 times a year [3]. Moreover, poultry meat does not confront cultural and religious taboos. In addition to these advantages, poultry production needs a smaller space in comparison with other livestock, making it more achievable for small investors. The significant increase in demand for chicken meat production in most countries around the world has important implications for the global poultry trade.

In response to market demand, commercial broiler chickens have undergone intensive genetic selection to achieve a better growth rate, making them the fastest-growing farmed species. However, selections for rapid growth and heavy musculature have been associated with risks of behavioral, physiological and immunological problems caused by higher

environmental temperature [4]. Chickens seem to be more sensitive to environmental temperature changes compared to other farm animals [3].

2. High Stocking Density and Heat Stress

Stocking density for poultry is defined as the number of birds in a standard area such as birds per square meter. The ultimate goal of having more birds per unit of area is to maximize the production of chicken meat. In many cases, commercial farms settle for slightly reduced growth performance to achieve a satisfactory economic return. However, having more birds per unit of area is not without consequences. High stocking density impacts animal welfare by reducing the quality of the environment and increasing competition for available resources such as feed [5]. Generally, overcrowding has adverse effects on performance, livability, litter moisture, feed efficiency [6], etc., and may decrease the amount of production resulting in economic losses [5,7]. High stocking density is considered to directly or indirectly cause HS, for a variety of reasons such as increased litter moisture during warm seasons [5,8].

Heat stress is a response to high temperature and humidity. It happens when birds are outside of their comfort temperature zone and struggle to regulate their body temperature. When birds are unable to dissipate their body's heat, physiological and biological disorders appear following multi organ dysfunction and often result in death [9]. Furthermore, depressed feed intake and minimized activity lessen the heat burden [10]. Additionally, HS alters the functions of hypothalamo-pituitary axis and orthosympathic nervous system resulting in altered thyroid hormonal activity that is involved in metabolism [11]. Thyroid hormones are necessary for skeletal development, growth and body temperature regulation that help chickens adapt their body's temperature to cope with the environment [12]. Therefore, any disruption of thyroid activity can impair performance [10]. In fact, thyroid hormones are considered to have major roles in metabolic processes (catabolism and anabolism), thereby influencing nutritional efficiency, catabolism, anabolic synthesis, and thermogenesis [13].

Heat stress challenges management decision making in the poultry industry by causing significant reduction in meat production, and can become one of the most damaging factors in the industry. Therefore, it is necessary to review different thermoregulation mechanisms involved in regulating body temperature to reduce the negative effects of HS.

3. Impact of Global Warming

Global temperature has been rising by ~ 0.18 °C per decade since 1980, with the highest increase rate in the last decade. Based on data by the National Oceanic and Atmospheric Administration, 2020 was the second warmest year on record [14], demonstrating more frequent and intense droughts and heat waves. Global warming may have severe impacts on different aspects of human life [15], one being livestock production, especially poultry meat production, an important source of human food. Increased temperatures, paired with frequent and intense heat waves, results in heat stress (HS) that has adverse effects on poultry meat production.

Heat stress impacts the broiler chicken's health by causing metabolic disruptions and oxidative stress, leading to impaired growth performance, infections and death. However, the demand for livestock products, especially broiler meat, is estimated to increase by approximately 100% by 2050 [16]. As demand climbs, commercial farms try to increase meat production by raising more birds per growing period, despite knowing its negative impacts on growth rate and meat quality following the increased incidence of HS. In this regard, the challenge is to maintain the balance between productivity, household food security, and environmental preservation [17].

Broiler chickens can maintain stable body temperature only in a narrow temperature range. Changes in environmental temperature can cause HS, forcing them through a series of adjustment and readjustments, which impacts poultry production [18]. Therefore, it is important to understand the problem and develop heat-related strategies to

reduce the harmful effects of high environmental temperature on performance in the chicken-rearing industry.

4. Thermoregulatory Responses

Thermoregulation in broilers is mediated by the hypothalamus in conjunction with central and peripheral thermoreceptors. Thermoreceptors are found throughout the skin. They are specialized nerve cells located in the preoptic anterior hypothalamus that detect environmental temperature. Thermoreceptors allow sensory reception throughout the body to evoke adequate thermoregulatory responses via the control of physiological, endocrinological, and behavioral responses to adjust the rates of heat produced by metabolism, dissipated to and absorbed from the environment [12].

Chickens are homeothermic and capable of regulating their body heat balance and saving most of their energy obtained from feed for growth [19]. Broiler chickens can control and maintain their body's temperature when the environmental temperature is not higher than the upper limit of the critical temperature zone according to their thermoregulation mechanisms [9]. Thermoregulation is the ability to keep the body temperature within optimum temperature zones to ensure the function of all vital organs, even when the surrounding temperature is not optimal. However, when the environmental temperature is far different from the normal range, the energy cost of thermoregulation spikes. To minimize this energy cost, chickens use a variety of morphological, behavioral and biological responses to adjust their body's temperature by balancing the ratio of heat loss and heat gain [20].

4.1. Physiological and Behavioral Responses

Physiological responses are automatic reactions to a stimulus. In broiler chickens, physiological responses are the initial defensive actions against HS. Broiler chickens attempt to reduce their body temperature through different actions. Featherless parts of the body appear to act as "thermal windows" where heat dissipation is the most efficient, a means of thermoregulation at high temperatures in broilers [21]. Plumage related adaptive behaviors in the context of thermoregulation include: keeping the wings away from the body, ruffling feathers, and dustbathing. Furthermore, they limit feed intake and increase water drinking and resting [22], and move to a shaded area to avoid absorbing more heat from the environment. Although these initial responses help chickens regulate their body temperature, they may fall short in higher environmental temperatures, and the chicken's body temperature may still exceed the optimum zone. In that case, other biological mechanisms are required to reduce their body temperature.

4.2. Biological Responses

Though chickens cannot cool their bodies down by the evaporation of moisture from their skin due to a lack of sweat glands, they are equipped with air sacs in the lungs that help them dissipate heat from their body to the environment by improving air circulation on surfaces. When the environmental temperature increases, their principal metabolic option for cooling is to evaporate moisture from the lining of the throat and the air-sacs. The increase in air movement over the air-sacs leads to a significant increase in moisture evaporation, which in turn leads to the loss of body heat and therefore cooling. To further aid radiant heat loss, chickens redistribute blood flow to their skin while panting. Increased peripheral blood flow reduces excessive produced heat, and increased panting facilitates evaporative cooling [19]; both are biological responses that help chickens cope with excess body heat. This requires a commensurate reduction of blood flow from elsewhere and is principally derived from the body core. Both mechanisms help chickens to lower their body temperature when the environmental temperature is high. However, the responses are not without consequences, and they could negatively impact the quantity and quality of the final meat products [23,24].

5. Heat Stress Impairs Production

As we mentioned earlier, HS leads to reduced feed consumption, resulting in reduced weight gain. Under HS, the changes in the blood pH impair the immune system's functions and alter the body's hormonal activity responsible for metabolic activities [11], leading to impaired growth performance. Fast panting leads to respiratory alkalosis and hyperthermia [24,25] as well as higher oxidative stress for the increased production of reactive oxygen species (ROS). Higher levels of ROS increase excretion from the body [26,27] which alters vitamins and mineral concentrations which are important for the defense system. Reactive oxygen species are a major reason for oxidation resulting from cellular metabolism and external sources, including feed that contains oxidized fats and lipids in mitochondria [28], stimulating metabolic oxidation and increasing the activity of enzymes. Additionally, increased blood flow to the skin leads to a reduction in gastrointestinal, hepatic and renal blood flow, making these organs particularly sensitive to HS. Reduction of blood flow reduces oxygen supply to these organs with high metabolic activities leading to oxidative damage [23]. The negative impacts are not limited to the amount of production, but could have adverse impacts on organ functions, leading to lower meat quality. The reduction of blood flow causes mitochondria to malfunction and affects energy-substance aerobic metabolism, resulting in increased glycolysis and intramuscular fat deposition [29]; this leads to lower consumer acceptability [10] due to paler meat colour [30] with lower water holding capacity [31] and increased cook and drip losses [30].

Therefore, poultry farmers in hot regions or during hot seasons must apply management strategies to help chickens to endure HS. Among all available strategies, nutritional strategies have shown to be promising, easy to apply and low cost ways to help chickens to cope with high temperature.

6. Solutions to Cope with Heat Stress

Genetically modified broiler chickens have a higher growth rate in a shorter period of time compared to natural breeds. They consume more feed, their body produces more heat due to their greater metabolic activity, making them more susceptible to HS. The increasing demand for poultry production around the world calls for an re-evaluation of long-term strategies for modern genetically-modified commercial breeding programmers.

Many strategies have been introduced to the industry, such as improving the housing system to help broiler chickens cope with HS. However, such strategies are expensive to apply or have limited effects on broiler chicken health and performance, while potential supplementations such as betaine (osmolytes) and polyphenols (antioxidants) could help them to improve their health and the body's heat tolerance by protecting tissues or improving enzyme activities, thereby lowering oxidative stress. One of the major functions of the additives is improving gut health. A healthy digestive system plays an important role in the efficient conversion of feed into absorbable form for optimal nutrient utilization and stability of the microbiota, and what follows is better growth performance. When gut health is compromised, digestion, and nutrient absorption are affected, which in turn, may have a detrimental effect on feed efficiency and lead to economic loss. Therefore, supplementing a diet with potential additive such as osmolytes and antioxidants may help to improve gut health, reduce metabolic heat production and maintain nutrient intake under HS.

7. Nutritional Additives to Ameliorate Heat Stress

Nutritional solutions are among the most practical and cheapest ways to protect chickens against HS. These solutions involve selecting nutrients with a low heat increment, or providing bioactive nutrients that improve the physiological dysfunctions associated with HS, such as gut leakage and oxidative stress. Therefore, research is needed to identify the ideal nutrients and their ideal forms that improve the performance of chickens exposed to HS. Nutrients provided for broiler chickens can be divided into two categories: macronutrient and micronutrients, and both are important for broiler chicken growth.

7.1. *Macronutrients and Micronutrients*

Macronutrients are energy-providing nutrients that are required in larger quantities such as carbohydrates. Carbohydrates break down into smaller sugars like glucose, which will be used as an energy source. Macronutrients are thus essential for growth, developing and repairing tissues that help the body cope with HS by improving thermoregulation pathways without using the stored proteins in tissues. However, to maintain muscle, blood circulation and the immune system, the body requires a supply of different materials including vitamins and other micronutrients.

Micronutrients including minerals and vitamins do not provide energy for the body but they participate in metabolic pathways. They are required in small quantities. Polyphenols, for example, are essential for many pathways including the function of enzymes.

Animals under HS require higher levels of micronutrients, but this may be exacerbated by reduced levels of feed intake. Reduced levels of micronutrients will compromise growth performance [32], and therefore the replacement of micronutrients with increased utilisation during HS is one micronutrient amelioration strategy. We previously reviewed the importance of supplementing broiler chickens' diet with an antioxidant (selenium), and vitamins (E and C) to cope with HS [9]. In this review we attempt to introduce more potential additives with positive influence on broiler chickens' performance under HS. One example is increasing supplementation of antioxidants such as phytochemicals to combat oxidative stress in HS broiler chickens. Other strategies involve organic osmolytes such as betaine. Heat stress can increase cellular osmotic stress, and betaine was found accumulated in plants experiencing osmotic stress [33]. Betaine has since demonstrated multiple functions, including as a methyl donor and chaperone [34].

7.2. *Betaine*

Previous studies unveiled the critical roles of amino acids in the prevention of oxidative stress, sustaining the intestinal barrier against pathogens, enhancing the immune system and growth performance [5,23]. Among amino acids, betaine is found to alleviate stress symptoms in different farm animals.

Betaine (trimethylglycine) is extracted from various natural sources, including sugar beet, from which its name is derived. Betaine undertakes two major roles in an animal's body: as an osmolyte to protect cells against osmotic stress, or as the "methyl donor", being a catabolic source of methyl groups via transmethylation [35] to transform excess homocysteine into L-methionine.

As an osmolyte, betaine is a small, highly-soluble organic compound that accumulates in cells without disrupting their function. It affects the process of osmosis by maintaining the balance of fluid levels outside and inside of cells, protecting cells against osmotic inactivation [36], alleviates negative impacts of osmotic stress in the intestine [37], and maintains water and metabolic balance [38]. Imbalanced fluid levels can increase cellular shrinkage depending on the excess fluid on the inside or the outside of the cell. Hyperosmosis causes water efflux and concomitant reduction in cell volume, leading to more cell deaths [39].

Osmolarity effects of betaine can help gut tissues continue regular metabolic activities under stressful conditions. Damage to intestine cells during HS increases osmolarity in the intestine, which impairs cell metabolism and its enzyme activity. Any alterations in the cell's structure can reduce nutrient absorption, making it easier for external pathogens or toxins to enter the blood. Betaine can enhance intestinal integrity which helps the intestine work normally, resulting in optimized nutrient digestibility and reduced excretion [40]. Betaine is also effective in this regard in premature birds. The gut structure of a young chick is not developed sufficiently to absorb or digest nutrients well, leading to osmotic pressure across the tight junctions as the gut structure moves water into the lumen. With betaine accumulated in gut cells, osmolarity increases, and this protects epithelial cell morphology and stabilizes gut mucosa [41] as well as reducing movement of water from cells [37].

Betaine is an important methyl group donor present in diets. Methionine is metabolized in the liver and is required for protein synthesis and cellular function regulation [42]. The transmethylation reaction of betaine, which is a part of a one-carbon metabolism via the methionine cycle, occurs principally in the mitochondria of liver and kidney cells. One of the important cellular methylation processes is when betaine is involved in the remethylation of homocysteine to eliminate toxic metabolites [43]. Homocysteine is generated by deamination of methionine and is a toxic sulphur-containing intermediate product, and has various consequences for cells, such as oxidative stress, mitochondrial dysfunction, increased cytosolic calcium and protein damage [44], which all contribute to apoptosis [45]. Homocysteine generates ROS and inhibits the expression of antioxidant enzymes which might potentiate the toxic effects of ROS [45]. A high level of homocysteine appears to be toxic to the cell and slows its growth rate, and it requires a re-conversion of homocysteine to methionine through the remethylation process [46]. There are two major remethylation pathways that employ the methionine synthase enzyme and cofactors such as B12 and folic acid, while the minor pathway involves betaine-homocysteine methyltransferase and betaine as a cofactor [43]. Under stressful thermal conditions, the ROS may impair a major pathway (folate-dependent methionine synthesis), hence the minor betaine-homocysteine methyltransferase pathway regulates the homocysteine homeostasis [47]. Betaine enhances the methionine-homocysteine cycle and increases production of methionine in the cell, which may result in a reduction of methionine requirement in animals. Furthermore, betaine can improve carcass quality through the methionine pathway by the synthesis of carnitine. Carnitine is concentrated in skeletal muscle and functions as a source of energy, transporting fatty acids into the mitochondria and oxidizing them. It boosts protein metabolism and alters carcass composition by reducing protein turnover, resulting in higher nitrogen retention, creating a positive effect on the accretion of protein in muscle. Moreover, it improves lipid catabolism [48] through the carnitine pathway due to the low carcass fat disposition [40].

In addition, betaine is demonstrated to be an antioxidant agent for the prevention of oxidative stress, enhancing glutathione peroxidative activity, the activity of superoxide dismutase and catalase activity, which subsequently decreases the lipid peroxidation process [45]. The protective effects of betaine against oxidative damage is associated with the restoration of S-adenosyl methionine as betaine supplies the required substrate for the synthesis of the enzymes [45]. Glutathione peroxidative activity encompasses the peroxidase activity that protects the organism from oxidative damages by reducing lipid hydroperoxides and free hydrogen peroxide [49]. The superoxide dismutase is an enzyme that converts superoxide radicals to ordinary molecular oxygen or hydrogen peroxidase. Though hydrogen peroxidase itself is harmful to cells, it can be converted to nontoxic compounds through catalase activity. Catalase is an enzyme that protects cells against oxidative damages caused by ROS by converting hydrogen peroxidase to water and oxygen.

It can be concluded that betaine as an osmolyte helps maintain cellular water balance and reduces the energy required for this mechanism under normal or stressful conditions, resulting in lower heat production in the body, as evidenced by lower rectal temperature and respiratory rate during HS shown in a few studies [24,33]. It improves weight gain by saving the energy used in Na⁺/K⁺ pump during HS and allows this energy to be used for growth. It improves the dry matter, crude protein, crude fiber, ether extract and non-nitrogen fiber extract digestibility [50] as it helps in the expansion of intestinal mucosa, which improves absorption and utilization of nutrients. It reduces the heterophil number and increases the number of lymphocytes. The reduction of lymphocytes during HS is due to the increase of inflammatory cytokines which stimulate the hypothalamic production of corticotrophin releasing hormones under HS. All these effects are directly or indirectly related to methionine biosynthesis and the osmoregulatory action of betaine. It has been recommended that betaine at doses between 0.5 g/kg to 2 g/kg improves weight gain and feed intake of broilers under HS, while higher doses of betaine seem more effective [33,51].

7.3. Polyphenols

Polyphenols are important for their antioxidant properties and can be divided into many classes; the main classes are phenolic acids and flavonoids [48]. Polyphenols are identified by their phenol structure, and polyhydroxy substitution of the benzene ring. Polyphenols can be found in high amounts in fruits and vegetables and have antioxidant activity [48] and immunostimulatory properties [49,50].

Polyphenols have been investigated as food additives for livestock based on their important roles in oxidative stress, which have important implications for the quality of the final products [51,52]. Furthermore, as natural antioxidants, they are more acceptable by the market as they are considered safe for human health. Based on their special properties, they can have anti-inflammatory effects and they enhance feed intake and growth rate [53]. They are bioactive compounds, meaning they are not essential for life but have positive impacts on tissue health. They are broken down easily by intestinal enzymes and gut microbiota and can be absorbed into the bloodstream [54].

Polyphenols have a hydrogen group in their chemical structure that eliminates ROS. Phenolic groups accept unpaired electrons with short half-life to form stable phenoxyl radicals [54,55], with a short reaction distance and susceptibility to neighboring molecules [56]. Indeed, free radicals are capable of damaging every major category of biomacromolecule, causing oxidative modification of lipids as well as damaging proteins by carbonyl modification [57]. Furthermore, they have protein sparing effects that can stimulate the activity of antioxidants and increase the concentrations of some antioxidants such as α -tocopherol [58], a type of vitamin E that can act against ROS [9]. Fluorophenols decrease the catalytic activity of enzymes involved in ROS production due to reduced oxidative damage [59]. Reactive oxygen species increase free metal ions by the reduction of hydrogen peroxidase with the generation of the highly reactive hydroxyl radical. Polyphenols, with their lower redox potentials, are thermodynamically able to reduce highly oxidizing free radicals because of their capacity to chelate metal ions and free radicals [60].

Studies have indicated that antioxidant properties of polyphenols helped to improve body weight gain and meat quality of broiler chickens and ameliorate the adverse effects of HS [52,54] by reducing the production of ROS leading to the reduction of oxidative stress [61,62]. It also has been reported that polyphenols could maintain and improve meat quality against HS or under normal conditions by increasing the muscle antioxidant capacity and the activity of antioxidants such as glutathione peroxidase [63]. It has been reported that polyphenols can reduce DNA damage and protein degradation [64]. They could inhibit lipid peroxidation and improve enzyme activity in hepatocytes, thus relieving damages to tissues by HS. Moreover, they act as hormonal and growth regulators [65], and enzyme modulators [66], leading to improved growth rate. Therefore, the functions of polyphenols make them a promising additive in broiler chickens' diets especially under HS [52] where there is a need to reduce ROS production. It has been found that polyphenols at doses between 0.05 g/kg to 10 g/kg improve weight gain and feed intake of broilers under HS, and that higher doses of polyphenols seem more effective [52,67,68].

8. Conclusions

Average global temperatures have risen considerably, and this increase has direct impact on broiler chicken production by increasing the incidence of HS. When the biological cost of coping with the stressors diverts resources away from other biological functions, such as maintaining reproduction or growth, economic losses happen. Micronutrients such as betaine and polyphenols constitute potential low cost dietary supplements to ameliorate the adverse effects of HS. Osmolarity properties of betaine improve intestinal and breast muscle structure by increasing the distribution of water and solutes in tissues, and this reduces damage to tissues. Furthermore, betaine improves the villous structure of the gut, which can lead to healthier gut and better muscle development. Polyphenols can eliminate reactive oxygen species, which lowers lipid peroxidation and leads to improved growth rates, indicating that they may also be useful nutritional agents for the amelioration of HS.

Author Contributions: M.S. and H.H.L. prepared and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Mottet, A.; Tempio, G. Global poultry production: Current state and future outlook and challenges. *Worlds Poult. Sci. J.* **2017**, *73*, 245–256. [CrossRef]
2. Farrell, D. *The Role of Poultry in Human Nutrition. Poultry Development Review*; Food and Agriculture Organization: Rome, Italy, 2013; pp. 2–9.
3. Wahyono, N.D.; Utami, M.M.D. A Review of the Poultry Meat Production Industry for Food Safety in Indonesia. *J. Phys. Conf. Ser.* **2018**, *953*, 012125. [CrossRef]
4. Elijah, O.A.; Adedapo, A. The effect of climate on poultry productivity in Ilorin Kwara State, Nigeria. *Int. J. Poult.* **2006**, *5*, 1061–1068.
5. Shakeri, M.; Zulkifli, I.; Soleimani, A.; O'Reilly, E.; Eckersall, P.; Anna, A.; Kumari, S.; Abdullah, F. Response to dietary supplementation of L-glutamine and L-glutamate in broiler chickens reared at different stocking densities under hot, humid tropical conditions. *Poult. Sci.* **2014**, *93*, 2700–2708. [CrossRef] [PubMed]
6. Abudabos, A.M.; Samara, E.M.; Hussein, E.O.; Al-Ghadi, M.a.Q.; Al-Atiyat, R.M. Impacts of stocking density on the performance and welfare of broiler chickens. *Ital. J. Anim. Sci.* **2013**, *12*, e11. [CrossRef]
7. Shakeri, M.; Oskoueian, E.; Najafi, P.; Ebrahimi, M. Impact of glutamine in drinking water on performance and intestinal morphology of broiler chickens under high stocking density. *İstanbul Üniversitesi Veteriner Fakültesi Dergisi* **2015**, *42*, 51–56. [CrossRef]
8. Shakeri, M.; Shakeri, M.; Omid, A. Effect of Garlic Supplementation to Diet on Performance and Intestinal Morphology of Broiler Chickens under High Stocking Density. *İstanbul Üniversitesi Veteriner Fakültesi Dergisi* **2014**, *41*, 212–217.
9. Shakeri, M.; Oskoueian, E.; Le, H.H.; Shakeri, M. Strategies to combat heat stress in broiler chickens: Unveiling the roles of selenium, vitamin E and vitamin C. *Vet. Sci.* **2020**, *7*, 71. [CrossRef]
10. Lara, L.; Rostagno, M. Impact of heat stress on poultry production. *Animals* **2013**, *3*, 356–369. [CrossRef]
11. Mack, L.; Felver-Gant, J.; Dennis, R.; Cheng, H. Genetic variations alter production and behavioral responses following heat stress in 2 strains of laying hens. *Poult. Sci.* **2013**, *92*, 285–294. [CrossRef]
12. Darras, V.M.; Van der Geyten, S.; Kühn, E.R. Thyroid hormone metabolism in poultry. *Biotechnol. Agron. Soc. Environ.* **2000**, *4*, 13–20.
13. Bueno, J.P.R.; Gotardo, L.R.M.; Dos Santos, A.M.; Litz, F.H.; Olivieri, O.C.L.; Alves, R.L.O.R.; Moraes, C.A.; de Mattos Nascimento, M.R.B. Effect of cyclic heat stress on thyroidal hormones, thyroid histology, and performance of two broiler strains. *Int. J. Biometeorol.* **2020**, *64*, 1125–1132. [CrossRef] [PubMed]
14. Lindsey, R.; Dahlman, L. Climate Change: Global Temperature. Climate.gov. Available online: <https://www.climate.gov/news-features/understanding-climate/climate-change-global-temperature> (accessed on 22 March 2021).
15. Gregory, J.M.; White, N.J.; Church, J.A.; Bierkens, M.F.; Box, J.E.; Van den Broeke, M.R.; Cogley, J.G.; Fettweis, X.; Hanna, E.; Huybrechts, P. Twentieth-century global-mean sea level rise: Is the whole greater than the sum of the parts? *J. Clim.* **2013**, *26*, 4476–4499. [CrossRef]
16. Garnett, T. Livestock-related greenhouse gas emissions: Impacts and options for policy makers. *Environ. Sci. Policy* **2009**, *12*, 491–503. [CrossRef]
17. Wright, I.A.; Tarawali, S.; Blümmel, M.; Gerard, B.; Teufel, N.; Herrero, M. Integrating crops and livestock in subtropical agricultural systems. *J. Sci. Food Agric.* **2012**, *92*, 1010–1015. [CrossRef]
18. Škrbić, Z.; Pavlovski, Z.; Lukić, M.; Perić, L.; Milošević, N. The effect of stocking density on certain broiler welfare parameters. *Biotechnol. Anim. Husb.* **2009**, *25*, 11–21. [CrossRef]
19. Yahav, S.; Collin, A.; Shinder, D.; Picard, M. Thermal manipulations during broiler chick embryogenesis: Effects of timing and temperature. *Poult. Sci.* **2004**, *83*, 1959–1963. [CrossRef]
20. Yahav, S.; Shinder, D.; Tanny, J.; Cohen, S. Sensible heat loss: The broiler's paradox. *Worlds Poult. Sci. J.* **2005**, *61*, 419–434. [CrossRef]
21. Yalcin, S.; Testik, A.; Ozkan, S.; Settari, P.; Celen, F.; Cahaner, A. Performance of naked neck and normal broilers in hot, warm, and temperate climates. *Poult. Sci.* **1997**, *76*, 930–937. [CrossRef]
22. Suganya, T.; Senthilkumar, S.; Deepa, K.; Amutha, R. Nutritional management to alleviate heat stress in broilers. *Int. J. Sci. Environ. Technol.* **2015**, *4*, 661–666.

23. Shakeri, M.; Cottrell, J.J.; Wilkinson, S.; Zhao, W.; Le, H.H.; McQuade, R.; Furness, J.B.; Dunshea, F.R. Dietary betaine improves intestinal barrier function and ameliorates the impact of heat stress in multiple vital organs as measured by Evans blue dye in broiler chickens. *Animals* **2019**, *10*, 38. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Shakeri, M.; Cottrell, J.J.; Wilkinson, S.; Le, H.H.; Suleria, H.A.; Warner, R.D.; Dunshea, F.R. Dietary betaine reduces the negative effects of cyclic heat exposure on growth performance, blood gas status and meat quality in broiler chickens. *Agriculture* **2020**, *10*, 176. [\[CrossRef\]](#)
25. Shakeri, M.; Cottrell, J.J.; Wilkinson, S.; Ringuet, M.; Furness, J.B.; Dunshea, F.R. Betaine and antioxidants improve growth performance, breast muscle development and ameliorate thermoregulatory responses to cyclic heat exposure in broiler chickens. *Animals* **2018**, *8*, 162. [\[CrossRef\]](#)
26. Şahin, E.; Gümüslü, S. Immobilization stress in rat tissues: Alterations in protein oxidation, lipid peroxidation and antioxidant defense system. *Comp. Biochem. Phys. C* **2007**, *144*, 342–347. [\[CrossRef\]](#) [\[PubMed\]](#)
27. Song, D.; King, A. Effects of heat stress on broiler meat quality. *Worlds Poult. Sci. J.* **2015**, *71*, 701–709. [\[CrossRef\]](#)
28. Cadenas, E.; Davies, K.J. Mitochondrial free radical generation, oxidative stress, and aging. *Free. Radic. Biol. Med.* **2000**, *29*, 222–230. [\[CrossRef\]](#)
29. Lu, Z.; He, X.; Ma, B.; Zhang, L.; Li, J.; Jiang, Y.; Zhou, G.; Gao, F. Chronic heat stress impairs the quality of breast-muscle meat in broilers by affecting redox status and energy-substance metabolism. *J. Agric. Food Chem.* **2017**, *65*, 11251–11258. [\[CrossRef\]](#)
30. Wang, R.; Liang, R.; Lin, H.; Zhu, L.; Zhang, Y.; Mao, Y.; Dong, P.; Niu, L.; Zhang, M.; Luo, X. Effect of acute heat stress and slaughter processing on poultry meat quality and postmortem carbohydrate metabolism. *Poult. Sci.* **2017**, *96*, 738–746. [\[CrossRef\]](#)
31. Feng, J.; Zhang, M.; Zheng, S.; Xie, P.; Ma, A. Effects of high temperature on multiple parameters of broilers in vitro and in vivo. *Poult. Sci.* **2008**, *87*, 2133–2139. [\[CrossRef\]](#)
32. Swennen, Q.; Decuyper, E.; Buyse, J. Implications of dietary macronutrients for growth and metabolism in broiler chickens. *Worlds Poult. Sci. J.* **2007**, *63*, 541–556. [\[CrossRef\]](#)
33. Shakeri, M.; Cottrell, J.J.; Wilkinson, S.; Le, H.H.; Suleria, H.A.R.; Warner, R.D.; Dunshea, F.R. Growth Performance and Characterization of Meat Quality of Broiler Chickens Supplemented with Betaine and Antioxidants under Cyclic Heat Stress. *Antioxidants* **2019**, *8*, 336. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Lever, M.; Slow, S. The clinical significance of betaine, an osmolyte with a key role in methyl group metabolism. *Clin. Biochem.* **2010**, *43*, 732–744. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Zhao, G.; He, F.; Wu, C.; Li, P.; Li, N.; Deng, J.; Zhu, G.; Ren, W.; Peng, Y. Betaine in inflammation: Mechanistic aspects and applications. *Front. Immunol.* **2018**, *9*, 1070. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Virtanen, E. Piecing together the betaine puzzle. *Feed Mix* **1995**, *3*, 12–17.
37. Kettunen, H.; Peuranen, S.; Tiitonen, K. Betaine aids in the osmoregulation of duodenal epithelium of broiler chicks, and affects the movement of water across the small intestinal epithelium in vitro. *Comp. Biochem. Physiol. A* **2001**, *129*, 595–603. [\[CrossRef\]](#)
38. Ferket, P. Flushing Syndrome in Commercial Turkeys During the Grow-out Stage. In Proceedings of the Pacesetter Conference, National Turkey Federation Annual Meeting, Orlando, FL, USA, 10 January 1994; Smithkline Beecham Animal Health: Nutley, NJ, USA, 1995; pp. 5–14.
39. Neuhofer, W.; Beck, F.-X. Cell survival in the hostile environment of the renal medulla. *Annu. Rev. Physiol.* **2005**, *67*, 531–555. [\[CrossRef\]](#)
40. Panda, A.; Raju, M.; Rao, S.; Sunder, G. QPM improves performance, increases broiler meat yield. *Poult. Int.* **2010**, 20–22.
41. dos Santos, T.T.; Baal, S.C.S.; Lee, S.A.; e Silva, F.R.O.; Scheraiber, M.; da Silva, A.V.F. Influence of dietary fibre and betaine on mucus production and digesta and plasma osmolality of broiler chicks from hatch to 14 days of age. *Livest. Sci.* **2019**, *220*, 67–73. [\[CrossRef\]](#)
42. Pacana, T.; Cazanave, S.; Verdianelli, A.; Patel, V.; Min, H.-K.; Mirshahi, F.; Quinlivan, E.; Sanyal, A.J. Dysregulated hepatic methionine metabolism drives homocysteine elevation in diet-induced nonalcoholic fatty liver disease. *PLoS ONE* **2015**, *10*, e0136822. [\[CrossRef\]](#)
43. Craig, S.A. Betaine in human nutrition. *Am. J. Clin. Nutr.* **2004**, *80*, 539–549. [\[CrossRef\]](#)
44. Borowczyk, K.; Wróblewski, J.; Suliburska, J.; Akahoshi, N.; Ishii, I.; Jakubowski, H. Mutations in homocysteine metabolism genes increase keratin N-homocysteinylation and damage in mice. *Int. J. Genom.* **2018**, *2018*, 1–7. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Alirezai, M.; Khoshdel, Z.; Dezfoulian, O.; Rashidipour, M.; Taghadosi, V. Beneficial antioxidant properties of betaine against oxidative stress mediated by levodopa/benserazide in the brain of rats. *J. Physiol. Sci.* **2015**, *65*, 243–252. [\[CrossRef\]](#) [\[PubMed\]](#)
46. Xie, M.; Tang, J.; Wen, Z.; Huang, W.; Hou, S. Effects of pyridoxine on growth performance and plasma aminotransferases and homocysteine of white Pekin ducks. *Asian-Australas. J. Anim. Sci.* **2014**, *27*, 1744. [\[CrossRef\]](#) [\[PubMed\]](#)
47. Weisberg, I.S.; Park, E.; Ballman, K.V.; Berger, P.; Nunn, M.; Suh, D.S.; Breksa, A.P., III; Garrow, T.A.; Rozen, R. Investigations of a common genetic variant in betaine-homocysteine methyltransferase (BHMT) in coronary artery disease. *Atherosclerosis* **2003**, *167*, 205–214. [\[CrossRef\]](#)
48. Hanje, A.J.; Fortune, B.; Song, M.; Hill, D.; McClain, C. The use of selected nutrition supplements and complementary and alternative medicine in liver disease. *Nutr. Clin. Pract.* **2006**, *21*, 255–272. [\[CrossRef\]](#)
49. Muthukumar, K.; Rajakumar, S.; Sarkar, M.N.; Nachiappan, V. Glutathione peroxidase3 of *Saccharomyces cerevisiae* protects phospholipids during cadmium-induced oxidative stress. *Antonie Van Leeuwenhoek* **2011**, *99*, 761–771. [\[CrossRef\]](#)

50. Ratriyanto, A.; Mosenthin, R. Osmoregulatory function of betaine in alleviating heat stress in poultry. *J. Anim. Physiol. Anim. Nutr.* **2018**, *102*, 1634–1650. [[CrossRef](#)]
51. Liu, W.; Yuan, Y.; Sun, C.; Balasubramanian, B.; Zhao, Z.; An, L. Effects of dietary betaine on growth performance, digestive function, carcass traits, and meat quality in indigenous yellow-feathered broilers under long-term heat stress. *Animals* **2019**, *9*, 506. [[CrossRef](#)]
52. Shakeri, M.; Cottrell, J.J.; Wilkinson, S.; Le, H.H.; Suleria, H.A.R.; Warner, R.D.; Dunshea, F.R. A Dietary Sugarcane-Derived Polyphenol Mix Reduces the Negative Effects of Cyclic Heat Exposure on Growth Performance, Blood Gas Status, and Meat Quality in Broiler Chickens. *Animals* **2020**, *10*, 1158. [[CrossRef](#)]
53. Serra, V.; Salvatori, G.; Pastorelli, G. Dietary polyphenol supplementation in food producing animals: Effects on the quality of derived products. *Animals* **2021**, *11*, 401. [[CrossRef](#)]
54. Brenes, A.; Viveros, A.; Chamorro, S.; Arija, I. Use of polyphenol-rich grape by-products in monogastric nutrition. A review. *Anim. Feed Sci. Technol.* **2016**, *211*, 1–17. [[CrossRef](#)]
55. Landete, J. Dietary intake of natural antioxidants: Vitamins and polyphenols. *Crit. Rev. Food Sci. Nutr.* **2013**, *53*, 706–721. [[CrossRef](#)] [[PubMed](#)]
56. Sies, H. Strategies of antioxidant defense. *Eur. J. Biochem.* **1993**, *215*, 213–219. [[CrossRef](#)] [[PubMed](#)]
57. Smith, P. *Electronic Applications of the Smith Chart*; The Institution of Engineering and Technology Country: London, UK, 1995.
58. Masella, R.; Di Benedetto, R.; Vari, R.; Filesi, C.; Giovannini, C. Novel mechanisms of natural antioxidant compounds in biological systems: Involvement of glutathione and glutathione-related enzymes. *J. Nutr. Biochem.* **2005**, *16*, 577–586. [[CrossRef](#)] [[PubMed](#)]
59. Kumar, S.; Sharma, U.; Sharma, A.; Pandey, A. Protective efficacy of *Solanum xanthocarpum* root extracts against free radical damage: Phytochemical analysis and antioxidant effect. *Cell. Mol. Biol.* **2012**, *58*, 171–178.
60. Mishra, A.; Kumar, S.; Pandey, A.K. Scientific validation of the medicinal efficacy of *Tinospora cordifolia*. *Sci. World J.* **2013**, *2013*, 1–8.
61. Paszkiewicz, M.; Budzyńska, A.; Różalska, B.; Sadowska, B. Immunomodulatory role of plant polyphenols. *Postepy Hig. Med. Dosw.* **2012**, *66*, 637–646. [[CrossRef](#)]
62. Petti, S.; Scully, C. Polyphenols, oral health and disease: A review. *J. Dent.* **2009**, *37*, 413–423. [[CrossRef](#)]
63. Zhang, C.; Zhao, X.; Wang, L.; Yang, L.; Chen, X.; Geng, Z. Resveratrol beneficially affects meat quality of heat-stressed broilers which is associated with changes in muscle antioxidant status. *Animal Sci. J.* **2017**, *88*, 1569–1574. [[CrossRef](#)]
64. Hu, R.; He, Y.; Arowolo, M.A.; Wu, S.; He, J. Polyphenols as potential attenuators of heat stress in poultry production. *Antioxidants* **2019**, *8*, 67. [[CrossRef](#)]
65. Majewska, M.; Czeżot, H. Flawonoidy w profilaktyce i terapii. *Farmakol. Pol.* **2009**, *65*, 369–377.
66. Archivio, M.D.; Filesi, C.; Di Benedetto, R.; Gargiulo, R.; Giovannini, C.; Masella, R. Polyphenols, dietary sources and bioavailability. *Annali-Istituto Superiore di Sanita* **2007**, *43*, 348.
67. Gopi, M.; Dutta, N.; Pattanaik, A.K.; Jadhav, S.E.; Madhupriya, V.; Tyagi, P.K.; Mohan, J. Effect of polyphenol extract on performance, serum biochemistry, skin pigmentation and carcass characteristics in broiler chickens fed with different cereal sources under hot-humid conditions. *Saudi J. Biol. Sci.* **2020**, *27*, 2719–2726. [[CrossRef](#)] [[PubMed](#)]
68. Mazur-Kuśnerek, M.; Antoszkiewicz, Z.; Lipiński, K.; Kaliniewicz, J.; Kotlarczyk, S. The effect of polyphenols and vitamin E on the antioxidant status and meat quality of broiler chickens fed low-quality oil. *Arch. Anim. Breed.* **2019**, *62*, 287–296. [[CrossRef](#)] [[PubMed](#)]