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Green tea polyphenol epigallocatechin-3-gallate mediates an antioxidant response via Nrf2 pathway in heat-stressed poultry: A review

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ABSTRACT

Heat stress is a critical challenge in the poultry industry. It arises when birds are exposed to elevated ambient temperatures beyond their thermoneutral zone, often exacerbated by high humidity and inadequate ventilation. This condition disrupts the birds' ability to maintain thermal homeostasis, leading to physiological and behavioral changes such as increased panting, reduced feed intake, and elevated water consumption. These responses aim to dissipate heat but often result in energy imbalances, oxidative stress, and impaired immune function. Green tea polyphenols (**GTPs**) mitigate heat stress in poultry birds by modulating oxidative stress pathways, primarily by scavenging reactive oxygen species (**ROS**) and enhancing antioxidant defense mechanisms. These pathways play a pivotal role in neutralizing **ROS** generated during oxidative stress, inflammation, and exposure to electrophilic compounds. This action helps restore cellular balance and enhances overall antioxidant defense mechanisms by converting harmful free radicals into less reactive molecules, such as water and oxygen. Nuclear factor (erythroid-derived 2)-like 2 (**Nrf2)** plays a significant character in the activation of the enzymatic antioxidants network. It translocates to the nucleus upon activation, binds to antioxidant response elements (**AREs**) in the promoter regions of target genes, and upregulates the expression of key antioxidant enzymes. Therefore, the regulation of **Nrf2** is considered a critical molecular marker in mitigating the effects of heat stress, as its activation enhances the expression of antioxidant and detoxification enzymes, protecting against oxidative damage and inflammation induced by elevated temperatures. This exploratory review summarizes the antioxidant mechanisms and anti-oxidative stress effects of **GTPs** in mitigating heat stress in poultry. It highlights the cytoprotective molecular basis of epigallocatechin-3-gallate (**EGCG**), particularly its role in modulating Nrf2-mediated cellular pathways, which enhance antioxidant defense systems and protect against oxidative damage.

Introduction

Green tea is the most widely consumed beverage in the world, with approximately 14,380,000 tons produced annually in China. The most significant ingredients in green tea are polyphenols, containing catechins (which constitute almost 30% of its dry weight), polysaccharides, and alkaloids (Ahmed and Stepp, 2013). In green tea, **EGCG** is a natural antioxidant that modulates cellular signaling pathways, thereby preventing cellular damage and scavenging oxidative radicals. It has numerous biological benefits, such as antimicrobial,

Abbreviations: (EGCG), Epigallocatechin-3-gallate; (GTPs), Green tea polyphenols; (Keap1), Kelch-like-ECH-associated protein 1; (Nrf2), nuclear factor-erythroid-2- (NF-E2-) and related factor 2; (NF-κB), Nuclear factor kappa-light-chain-enhancer of activated B cells; (PI3K), phosphatidylinositol 3-kinase; (PKC), protein kinase C; (JNK), c-Jun NH 2 -terminal kinase; (ERK), Extracellular signal-regulated kinase; (MAPK), Mitogen-activated protein kinase; (Maf), MusculoAponeurotic-Fibrosarcoma; (ARE), Antioxidant-response element; (EpRE), Electrophile-responsive element; (GSH), Reduced glutathione; (ROS), Reactive oxygen species; (RNS), Reactive nitrogen species; (GPx), Glutathione peroxidase; (GSTs), Glutathione S-transferases; (Trx), Thioredoxin; (SOD), Superoxide dismutase; (CAT), Catalase; (MDA), Malondialdehyde; (H_2O_2), Hydrogen peroxide; (MAPKs), Mitogen-activated protein kinases; (UCPs), Uncoupling proteins.

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anti-inflammatory, antioxidant, and anti-proliferative properties, which are relevant to both human and animal medicine (Mukhtar and Ahmad, 2000; Trevisanato and Kim, 2000). The antioxidant effect of **EGCG** is ascribed to its ability to enhance reducing capacity, thereby mitigating the presence of singlet oxygen molecules and peroxyl radicals (Vladu, et al., 2022).

Heat stress in commercial poultry production is closely associated with a range of external and internal stressors, such as environmental, nutritional, technological, and biological factors. These stressors collectively lead to reduced growth performance, impaired reproductive efficiency, and compromised physiological functions (Surai, et al., 2019b; Vladu, Ficai, Ene and Ficai, 2022). On a global scale, heat stress has been associated with reduced feed efficiency and diminished egg quality, with certain regions reporting production losses of up to 30% during peak summer months (Onagbesan, et al., 2023). The economic consequences are particularly severe in regions with warmer climates, where poultry farmers face the dual challenge of rising temperatures and limited resources for mitigation strategies (Attia, et al., 2024). Furthermore, heat stress exacerbates disease susceptibility, making poultry more prone to infections, which further contributes to economic strain. A report by the Food and Agriculture Organization (FAO) in 2023 highlights that in the U.S., heat stress costs the poultry industry approximately $1.5 billion annually, while losses in other major poultry-producing countries like Brazil and China have been similarly high (Abbas, et al., 2025).

Additionally, these stresses can adversely affect the color and pH of the meat, making them key factors influencing overall meat quality (McKee and Sams, 1997; Wang, et al., 2017; Zhang, et al., 2012). Heat stress impairs growth performance by reducing nutrient intake and promoting free radical formation, which disrupts the antioxidant defense network and negatively affects feed consumption, metabolism, and nutrient absorption (Quinteiro-Filho, et al., 2012; Yang, et al., 2010). These free radicals are atoms or molecules that have an odd number of electrons (i.e., one or more unpaired electrons) in the outermost shell, making these species unstable and very reactive (Kannan and Jain, 2000). Free radicals are typically involved in numerous catabolic reactions. While the production of these radicals often exceeds baseline levels, living tissues and cells must carefully balance their generation and detoxification to maintain homeostasis. Cells are capable of withstanding mild oxidative stress and restoring the antioxidant/oxidant balance by synthesizing and supplementing various antioxidants, such as glutathione (GSH), thioredoxin (Trx), antioxidant enzymes, and coenzyme Q (CoQ) (Jaganjac, et al., 2020). Since excessive ROS can damage a wide range of biological molecules, the antioxidant defense network plays a crucial role in protecting cells and reducing oxidative damage. However, such physiological mechanisms in the living body have a limited capacity. When free radical production increases, the antioxidant defense network's capacity to counteract them becomes overwhelmed, leading to physiological stress. Thus, the antioxidant defense system in the organism functions collaboratively, through multiple mechanisms. First, it reduces the activation of enzymes responsible for ROS/RNS production (e.g., xanthine oxidase, NADPH oxidase) by limiting free radical production through decreased oxygen availability. Second, it maintains mitochondrial integrity, the primary source of ROS in living systems. Third, it scavenges ROS (e.g., GSH, coenzyme Q, *vitamins E*, and *C*) and neutralizes free radicals and other harmful products through enzymes like SOD, GPx, and CAT. Lastly, redox-signaling transcription factors, such as Nrf2, are potent antioxidant molecules and key components of the body's anti-stress strategy (Surai, 2015a; Surai, 2015b; Surai, 2018).

Transcription factors are proteins that regulate the rate of transcription of genetic information from DNA to messenger RNA by controlling downstream signaling cascades in response to both external and internal stimuli (He, et al., 2023). The Nrf2 pathway plays a critical role in cellular defense mechanisms against oxidative stress. In chickens, heat stress induces the upregulation of Nrf2, leading to the activation of antioxidant genes that help mitigate oxidative damage caused by elevated temperatures (Oke, et al., 2024). Similarly, studies in other *avian species* such as turkeys (*Meleagris gallopavo*), ducks (*Anas platyrhynchos*), and quail (*Coturnix coturnix*) have demonstrated that Nrf2 activation plays a protective role during heat stress (Chen, et al., 2021; Nazar, et al., 2018). In turkeys, for instance, heat stress also leads to Nrf2 upregulation, with enhanced expression of key antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT), suggesting a conserved stress response pathway (Surai et al., 2019). However, the effectiveness of the Nrf2 response varies across species, likely due to differences in baseline antioxidant levels and the efficiency of Nrf2 signaling. While ducks exhibit a more robust Nrf2 response to heat stress, likely due to their evolutionary adaptation to varying environmental temperatures, quail show a more moderate activation of the pathway, indicating potential species-specific variations in heat stress tolerance mechanisms (Castiglione, et al., 2020). In addition, recent studies highlight the role of co-regulators and upstream signaling molecules that interact with Nrf2, such as the MAPK (mitogen-activated protein kinase) pathway, which appears to be more pronounced in species like quail and ducks compared to chickens (Surai, Kochish, Fisinin and Kidd, 2019b).

Therefore, this review aims to provide a simplified molecular evaluation of EGCG's role in cytoprotection, performance enhancement, and oxidative stress mitigation, with a particular focus on its Nrf2-mediated activation of cellular defense mechanisms in poultry.

Data collection and selection criteria

The present study involved a review that encompassed numerous studies to showcase the in-depth exploration of how EGCG mediates antioxidant responses in poultry via the Nrf2 pathway, particularly under heat-stress conditions. EGCG is believed to exert its effects through several molecular mechanisms, including the inhibition of Keap1, the stabilization of Nrf2, and the induction of antioxidant gene expression. Potential studies eligible for inclusion in this review manuscript were identified through peer-reviewed journals indexed in the Science Citation Index (SCI) and a comprehensive search of databases, including Google Scholar, ScienceDirect, Scopus, PubMed, and ResearchGate. The search employed a combination of indexed terms, appropriate truncations, and variations, including Heat Stress; Nrf2; Green Tea Polyphenol EGCG; Oxidative Stress; Nutraceuticals; Heat-Stressed Poultry Production; Natural Antioxidants; Gene Expression; Transcription Factors; NF-κB; Lipid Metabolism; Redox Status; and Antioxidant Status; along with their respective plurals. The analysis included published studies in English, up to and including those published in 2024. Experiments were carried out on Avian species including (broilers, ducks, quails, and turkey) receiving daily dietary supplementation with a tea polyphenol as an antioxidant for the experimental period. Eligible experimental designs included controlled, randomized feeding trials involving multiple groups of poultry birds receiving different doses of tea polyphenol. To maintain the credibility and relevance of the sourced information, only articles published in English and SCI journals were included in this review. Book chapters and articles published in non-English languages were excluded to ensure a focused and high-quality dataset for analysis.

Heat stress and oxidative stress concepts in poultry

Under normal conditions, the external and internal systems of birds maintain a dynamic thermodynamic equilibrium, ensuring homeostasis and optimal physiological function. Under mild stress conditions, homeostasis can be restored through the coordinated regulation of the autonomic nervous system, the immune system, and the hypothalamic-pituitary-adrenal (HPA) axis, ensuring adaptive physiological responses. In addition, stress reactions involve the cascading of complex regulatory mechanisms, leading to metabolic changes (increased energy mobilization and metabolic changes) that lead to decreased live performance in

poultry (Bureau, et al., 2009). Mitochondrial integrity disruption is the root of oxidative distress induced by heat stress. The mitochondrial substrate oxidation and electron transport chain regulation enhanced in the early stage of acute heat stress, lead to ROS increase. In the late phase of acute stress, excessive ROS production damages DNA, proteins, amino acids, and lipids. This process also downregulates uncoupling proteins (UCPs), reduces mitochondrial energy production, causes mitochondrial dysfunction, and increases oxidative damage in the cells. Nevertheless, prolonged stress conditions can diminish the mitochondrial metabolic ability as it increases the **UCPs**, declines the natural defense network, and reduces the antioxidant reserve of the body which induces the accretion of ROS, causes damage to the oxidative homeostasis and induces oxidative stress (Akbarian, et al., 2016).

Poultry development is typically influenced by four main types of stress: internal, nutritional, technical, and environmental. These stresses can lead to harmful alterations at the cellular, molecular, and pathophysiological levels, ultimately reducing the reproductive and propagative capabilities of birds (Surai and Fisinin, 2016; Surai, 2018). Oxidative stress is defined as an imbalance between oxidants and antioxidants. There are two types of oxidative stress: first, low-level physiological stress, known as "oxidative eustress," which plays a beneficial role in cellular signaling, and second, high-level physiological stress, referred to as "oxidative distress," which leads to harmful effects and cellular damage and summarized in (Fig. 1) (Sies, 2019). ROS as a by-product is produced as mitochondrial energy under physiological conditions and as an essential phagocyte weapon. The antioxidant system is accountable for scavenging free radicals and changing them into harmless products to sustain a normal level of ROS. Low levels of ROS play vital roles in redox signaling by interacting with specific targets (i.e., oxidative eustress). Excessive exposure to ROS leads to impaired antioxidant defense or excessive ROS production due to high-stress conditions that can affect non-specific targets (impaired DNA, proteins, amino acids, PUFAs,) and induced oxidative distress response to disturbance of oxidation-reduction signaling. A stress response is a very complicated process, to meet the oxidative challenges because these stresses are associated with various essential physiological and biochemical pathways such as the unfolded protein and heat shock response pathways, the hypoxia-regulated, and numerous repair mechanism responses. Moreover, Nrf2/Keap1 and (NF-κB/IkB) system so-called NF-E2-related factor 2/Kelch-like ECH-associated protein and

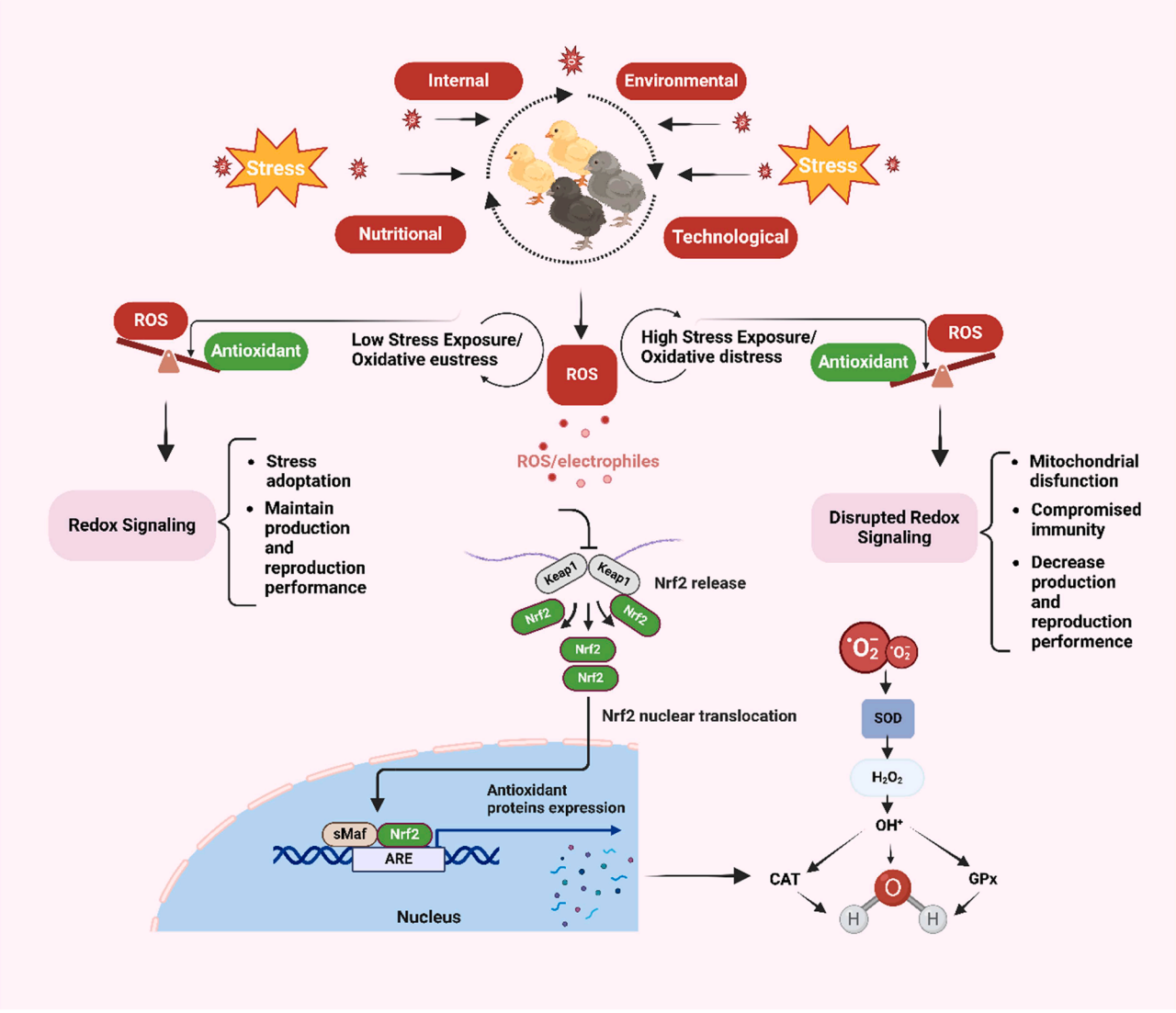

Fig. 1. Stresses initiate oxidative stress that disrupts redox signaling-induced ROS. Excessive amount of ROS instigates impairment of DNA, Protein, and lipids, decline mitochondrial energy, and disrupt the antioxidant reserve of the body. These stresses are associated with various biochemical pathways such as Nrf2/keep1. These pathways recognize the mechanism for the ARE-regulated antioxidants gene transcription, and thus stimulates antioxidant enzymes, including SOD, CAT, and GPx. The figure is created with BioRender.com.

nuclear factor kappa-light-chain-enhancer of activated B cells/inhibitory κB protein respectively are regarded the two main regulators for the oxidation-reduction response and are deeply involved in balancing of the stress maintenance (Sies, 2019). It is worth indicating that the signaling effect of ROS has achieved great attention, (Reczek and Chandel, 2015) and it has been proposed that gene expression and adaptive balance regulation based on oxidation-reduction (redox) are the basic regulatory mechanism of molecular biology. It is recommended to implement strict regulation and reliance on various defense mechanisms to manage oxidative stress in birds, as stress responses can develop over varying time scales, ranging from minutes to hours, days to weeks, or even months to years (Pomatto and Davies, 2018). Signal transduction pathways, such as the Nrf2-Keap1 system, play a crucial role in stimulating the antioxidant defense system. The Nrf2-Keap1 pathway is one of the key signaling response mechanisms that can rapidly adapt to environmental changes within minutes, activating antioxidant responses to protect cells from oxidative stress (Pomatto and Davies, 2018). During stressful conditions, disruptions in redox signaling may occur, potentially increasing susceptibility to infections, weakening immune function, (Forman, 2016), and reducing productivity performance in poultry (Surai, 2018). Nevertheless, oxidative stress at a low level is significant for generating adaptation response with the enhanced adaptive capability to stressful conditions for cell resistance, adaptation, and survival (Yan, 2014). Current studies suggest that the usage of free radicals as signaling molecules in redox-signaling pathways regulates the transcription of genes responsible for the stimulation of numerous biological purposes comprising growth development, cell differentiation, and proliferation, apoptosis, and regulation adaptability to stress in poultry (Surai, et al., 2019a). Adaptive redox balance is a mechanism that explains how changes in stress exposure such as the type, duration, and intensity of stress are managed through the coordinated action of various protective and preventive systems. This balance helps the body respond to and mitigate the effects of stress (Pomatto and Davies, 2018).

Green tea polyphenols (GTPs)

The various benefits of green tea, such as bacteriostatic, antioxidant, anti-cancer, and lipid metabolism regulation activity have been demonstrated in numerous studies. Typically, there are three main types of tea, classified based on their level of fermentation: black tea, oolong tea, and green tea (Chan, et al., 2011). The thermos-labile enzyme is polyphenol oxidase found in tea. It has been reported that the antioxidant capability of green tea is stronger than black tea because the activity of polyphenol oxidase is decreased by steam heating during fermentation, thus producing more polyphenol compounds (Anandh Babu and Liu, 2008). It has been found that numerous clinical and sub-clinical infections are related to oxidative injury. GTPs are biologically active compounds that play a significant role in modulating cellular redox balance and mitigating oxidative stress. Their antioxidant properties are primarily attributed to the presence of phenolic hydroxyl groups, which facilitate electron delocalization and enhance their capacity to donate hydrogen atoms. This structural feature weakens the binding affinity of hydrogen ions, making them more readily available to neutralize ROS (Zuo, et al., 2018). In poultry and livestock production, tea polyphenols are increasingly being used for their potential health benefits. However, their application faces several challenges, including lower bioavailability compared to synthetic antioxidants like vitamins, higher production costs, and reduced palatability due to the presence of tannins (Yan, et al., 2020). Importantly, while in vitro studies demonstrate strong free radical scavenging activities of polyphenols, these effects may not directly translate to *in vivo* systems due to the inability to achieve effective concentrations in target tissues (Brglez Mojzer, et al., 2016). Instead, polyphenols are more likely to exert their effects in the gut, where they are present in higher concentrations and can interact directly with the local environment (Wang, et al., 2022a). In poultry and livestock production, tea polyphenols are increasingly being utilized due to their beneficial properties, such as antioxidant and anti-inflammatory effects. However, their application faces several challenges, including lower bioavailability compared to synthetic antioxidants like vitamins, and reduced palatability caused by the astringency of polyphenolic tannins (Bié, et al., 2023; Formato, et al., 2022).

Bioavailability and bioactivity of tea polyphenol

Bioavailability refers to the extent and rate at which the active ingredients in a substance (in this case, tea polyphenols) are absorbed into the bloodstream and made available for biological activity. For tea polyphenols, several factors influence their bioavailability, including their chemical structure, solubility, the gut environment, and interactions with food components (Liu, et al., 2024). Tea polyphenols, particularly catechins such as EGCG, have gathered attention in the poultry industry due to their potential health benefits and performance-enhancing properties. Understanding the bioavailability of these compounds is crucial for optimizing their use in poultry diets (da Silva-Júnior and Silva, 2022). However, their bioavailability is limited by factors such as poor absorption in the gastrointestinal tract, metabolism in the liver and intestines, and interactions with food components (Lippolis, et al., 2023). Recent studies suggest that bioavailability can be enhanced through dietary modifications or nanoencapsulation, which may improve their effectiveness in poultry and the detail are shown in (Fig. 2) (Pugazhendhi, et al., 2025). Research has shown that co-administering tea polyphenols with dietary fats or proteins can enhance their absorption. Lipid digestion increases the solubility of polyphenols, allowing them to be absorbed more efficiently (Aatif, 2023). Derivatives of tea polyphenols with altered chemical structures (such as esterified, methylated, or glucuronidated forms) have been developed to improve their solubility, stability, and bioavailability (Landis-Piwowar, et al., 2013). Tea polyphenols are poorly absorbed in their native forms in the gastrointestinal (GI) tract due to their low water solubility. After ingestion, they undergo enzymatic and non-enzymatic transformations in the stomach and intestines. While small amounts of tea polyphenols may be absorbed directly in the stomach, most are absorbed in the small intestine, particularly in the jejunum and ileum, where they can undergo enzymatic breakdown by gut microbiota (Annunziata, et al., 2018; Yin, et al., 2022). One of the most significant factors influencing the metabolism of tea polyphenols is the gut microbiota. Microbial enzymes play a critical role in the hydrolysis and transformation of polyphenolic compounds. Once absorbed into the bloodstream, tea polyphenols undergo phase I (oxidation, reduction, hydrolysis) and phase II (conjugation with sulfate, glucuronide, or methyl groups) metabolism in the liver and intestines. This biotransformation process can modify the polyphenols' chemical structure, making them more water-soluble, but potentially reducing their biological activity (Sahraeian, et al., 2024). Their inclusion in poultry diets has also been linked to improved growth performance, better feed conversion, and enhanced meat quality, including extended shelf life due to their antioxidant and antimicrobial properties. Despite these benefits, challenges remain, including the low bioavailability of tea polyphenols in poultry, the need for optimized dosage formulations, and regulatory approval for their use in commercial systems (Abd El-Hack, et al., 2023). However, ongoing research aims to overcome these limitations, making tea polyphenols a promising alternative to synthetic growth promoters and preservatives in the poultry industry.

EGCG is the most enriched polyphenol

In general, polyphenolic compounds in green tea are mostly comprised of phenolic acids, flavonoids, and flavanols. Tea polyphenols are flavonoid compounds, usually recognized as catechins, with a fundamental arrangement of a -phenyl-benzopyran, the dry weight of tea leaves are round about 18 to 36 percent (Khan and Mukhtar, 2007).

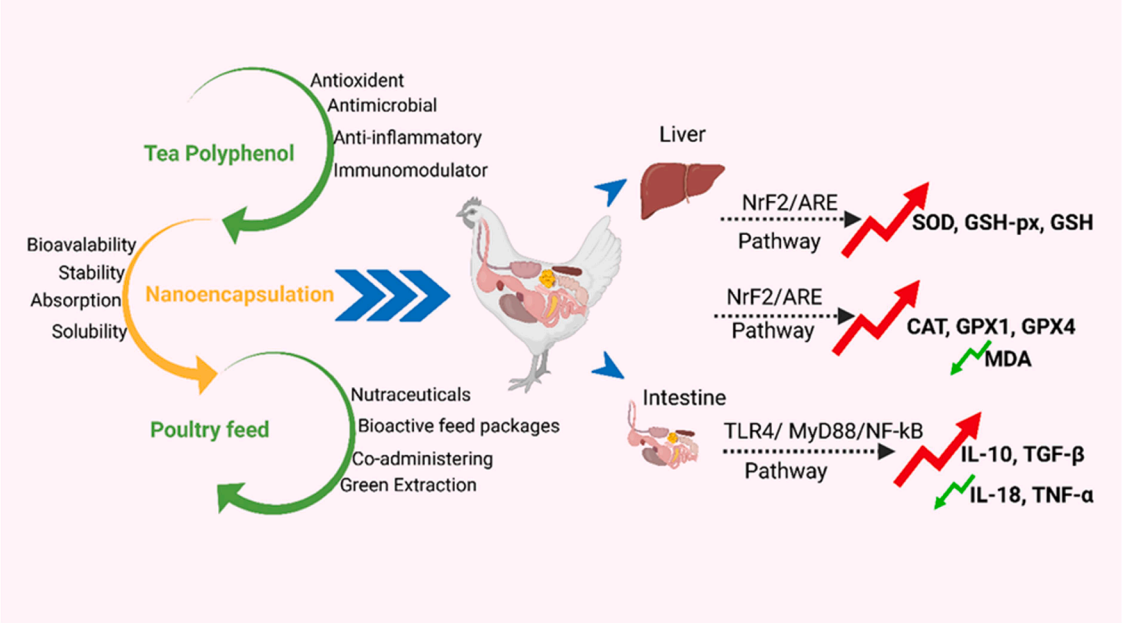

Fig. 2. The sketch represents the impact of nano-encapsulated tea polyphenols impact poultry health. Nanoencapsulation boosts the bioavailability, stability, absorption, and solubility of tea polyphenols, making them more effective when administered through feed. In the liver, these polyphenols activate the NrF2/ARE pathway, upregulating key antioxidant enzymes like SOD, GSH-px, GSH, CAT, GPX1, and GPX4, while lowering MDA levels. In the intestines, tea polyphenols affect the TLR4/MyD88/NF-κB pathway, enhancing the production of IL-18 and TNF-α, which play a role in immune response regulation. Advantages of these bioactive compounds are further amplified by their incorporation into nutraceuticals and bioactive feed packages, thus potentially boosting overall health and resistance to oxidative stress.

There are four major types of tea polyphenols, which include Epigallocatechin-3-gallate (EGCG), Epicatechin-3-gallate (ECG), Epigallocatechin (EGC), and Epicatechin (EC) (Yang, et al., 1999). There are 3 hydrocarbon rings in catechins, which are structurally categorized into catechins of ester and non-ester. The primary polyphenolic compounds in green tea include ester catechins, such as EGCG and ECG, and non-ester catechins, such as EGC and EC, with their chemical structure illustrated in (Fig. 3). EGCG constitutes approximately 59% of the total catechins, while EGC, ECG, and EC account for about 19%, 13.6%, and 6.4%, respectively (Ciraj, et al., 2001). EGCG is the most abundant and

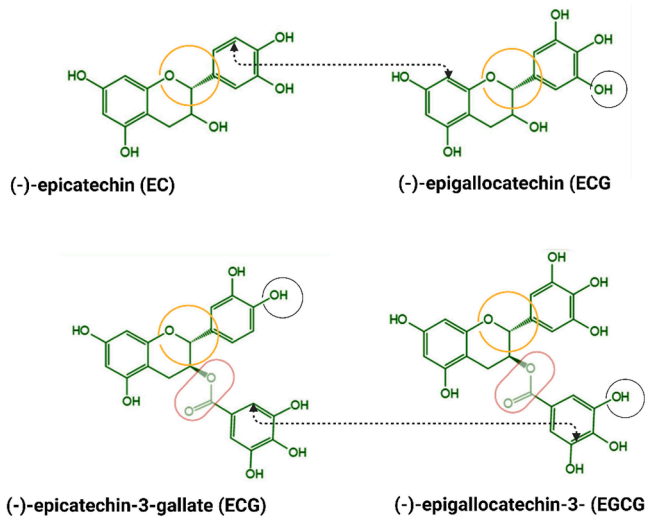

Fig. 3. Structural correlation of Epigallocatechin-3-gallate (EGCG) and its analogs Epicatechin-3-gallate (ECG), Epigallocatechin (EGC), Epicatechin (EC). It shows that ECG and EGC are esterified to form EGCG. The primary structural distinction across these compounds is indicated by dotted lines and red circles. The figure is created with BioRender.com.

biologically active polyphenol among the aforementioned components, exhibiting potent antioxidant properties, heat resistance, and chemo-preventive effects. It has been investigated widely in animal models and many sorts of tumor cells in the laboratory (Chen, et al., 2000; Katiyar, et al., 2007; Stuart, et al., 2006; Yang, et al., 2006). Recent studies demonstrated that EGCG alleviates the oxidant impairment, and improves bird's performance, reducing lipid peroxidation under heat stress through regulating the antioxidant defense network (Luo, et al., 2018; Xue, et al., 2017). It has been shown that eggs from laying hens fed EGCG had increased total antioxidant capacity (T-AOC), and reduced albumen and yolk MDA concentration in eggs (Wang, et al., 2020). Furthermore, EGCG has upregulated P-38MAPK, Nrf2, and hemeoxygenase 1 (HO-1) protein and gene expression in the liver of laying hens (Wang, Jia, Celi, Ding, Bai, Zeng, Mao, Xu and Zhang, 2020). Likewise, the antioxidant role of these polyphenols is associated with their chemical compositions, temperature profile, and biosynthetic pathways in the reaction medium (Dai, et al., 2008; Zhou, et al., 2005). Furthermore, besides tea flavonoids, green tea also contains a variety of phenol and polyphenol precursor-like kaempferol, quercetin, and myricetin. Subsequently, these elements have a 4-oxo 3-hydroxy C functional group, which they show resistance to oxidation (Xing, et al., 2019).

Antioxidant mechanism of tea polyphenols

Extensive research has shown that GTPs exert antioxidant effects through multiple pathways, which boosting antioxidant enzyme activity, reducing lipid peroxidation, neutralizing ROS in collaboration with other nutrients, and preventing degradation through metal ion chelation (Nakagawa and Yokozawa, 2002; Yiannakopoulou, 2013). To illustrate the impact of an antioxidants, these processes work in synergy. The antioxidant mechanisms in phenolic compounds can be classified as either hydrogen atom transfer or single electron-proton transfer (Tsao Rong and Li HongYan, 2012).

Tea polyphenols enzyme modulation and oxidative stress reduction

Tea polyphenolic compounds play a crucial role in protecting the body from free radicals by stimulating various oxidase and antioxidant pathways. The compounds, such as catechins (e.g., EGCG), have been shown to inhibit key enzymes involved in oxidative stress, including nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, cyclic oxidase, and lipoxidase, thereby reducing the generation of ROS (Obeme-Nmom, et al., 2024). Recent studies have demonstrated that EGCG, can achieve biologically active concentrations in target tissues such as the liver, brain, and cardiovascular system (Fung ST, 2013; KH, 2018; Mehmood, et al., 2022). These concentrations are effective in modulating oxidative stress pathways and enhancing cellular defense mechanisms. Furthermore, advanced pharmacokinetic studies have shown that nano-formulations and encapsulation techniques can enhance the bioavailability of polyphenols, allowing them to achieve even higher concentrations in target tissues (Aatif, 2023). Moreover, tea polyphenols regulate the transcription of specific antioxidant enzymes, such as glutathione peroxidase (GSH-Px), glutathione S-transferase (GST), and superoxide dismutase (SOD), which are critical for mitigating morphological and chemical damage induced by mitochondrial oxidative injury (Aatif, 2023). For instance, EGCG has been shown to upregulate the expression of SOD and GSH-Px in neuronal tissues at concentrations as low as 1 μM, providing neuroprotection against oxidative stress (Chen, et al., 2025). In addition to their enzymatic effects, tea polyphenols exert their antioxidant action by modulating cellular signaling pathways and enhancing the endogenous antioxidant defense system. It is upregulating the antioxidant enzymes such as **SOD, CAT**, and **GPx**, which play a crucial role in neutralizing ROS. Furthermore, tea polyphenols chelate metal ions, preventing the formation of highly reactive hydroxyl radicals via Fenton reactions. Hence, through the modulation of these mechanisms, tea polyphenols help mitigate oxidative damage and offer a multifaceted protective effect against diseases associated with oxidative stress (Truong and Jeong, 2021).

The role of tea polyphenols in reducing oxidative stress induced by transition metals

Oxidative stress, driven by the overproduction of ROS, is a major challenge in poultry production, particularly under conditions of metabolic stress or environmental heat stress. In poultry, metals play a significant role in oxidative processes, particularly in muscle tissues and during metabolic stress. As it is known, that Ca^{2+} stimulates the generation of xanthine oxidase, an enzyme that contributes to ROS production (Görlach, et al., 2015). Tea polyphenols, such as EGCG, have been shown to inhibit these processes by chelating Ca^{2+}, thereby reducing oxidative damage (Chi, et al., 2020b). Recent studies in poultry have demonstrated that dietary supplementation with GTPs significantly reduces xanthine oxidase activity and lipid peroxidation in muscle tissues, improving meat quality and shelf life (Nikoo, et al., 2018). Iron (Fe) is another pro-oxidant metal that can induce oxidative stress in biological systems. In poultry bird, iron overload can lead to oxidative damage in tissues, particularly in the liver and muscles, due to its role in Fenton reactions, which generate hydroxyl radicals (•OH). GTPs have a strong iron-chelating capacity, which prevents iron-induced oxidative damage. Another studies have shown that tea polyphenols protect against iron-induced lipid peroxidation in poultry synaptosomes by stabilizing semiquinone radicals and inhibiting the degradation of polyunsaturated fatty acids (PUFAs) (Dangles, 2012). The ability of polyphenols to chelate iron and stabilize free radicals is a key factor in their antioxidant efficacy. Moreover, the antioxidant activity of tea polyphenols in poultry is influenced by the stability of semiquinone molecules produced during the dehydrogenation of catechins. These semiquinone intermediates act as radical scavengers, further enhancing the antioxidant defense system (Bešlo, et al., 2023). Recent research has highlighted the role of GTPs in modulating antioxidant enzymes such as SOD, CAT, and GSH-Px in poultry, thereby improving oxidative stress resilience and overall health (Saeed, et al., 2018). Tea polyphenols play a critical role in mitigating oxidative stress in poultry by chelating pro-oxidant metals like iron and calcium, stabilizing free radicals, and enhancing the activity of endogenous antioxidant enzymes. These mechanisms are supported by recent studies demonstrating the benefits of GTPs in improving poultry health, meat quality, and oxidative stability.

Synergetic activity of vitamins and tea polyphenols

Vitamins play a critical role in poultry health, influencing cellular metabolism, growth performance, and overall physiological well-being. Recent studies have highlighted the synergistic effects of tea polyphenols with vitamins such as alpha-tocopherol (*vitamin E*) and ascorbic acid (*vitamin C*) in enhancing antioxidant defense mechanisms in poultry. *Vitamin C*, a water-soluble antioxidant, directly scavenges free radicals and regenerates *vitamin E*, a lipid-soluble antioxidant, which protects cellular membranes from lipid peroxidation. These complementary roles make vitamins essential components of the antioxidant defense system. EGCG have been shown to increase the abundance of alpha-tocopherol in low-density lipoprotein (LDL) and improve serum antioxidant capacity in broiler chickens fed high-cholesterol diets (Shenoy, et al., 2022). This effect is attributed to the ability of tea polyphenols to regenerate oxidized alpha-tocopherol, thereby maintaining its antioxidant activity and reducing oxidative stress in poultry tissues (Desbruslais and Wealleans, 2022). Another critical aspect of their synergy lies in the chelation of transition metals like iron and copper, which catalyze the generation of ROS via the Fenton reaction. Tea polyphenols act as metal chelators, reducing the availability of free metal ions. Concurrently, *vitamins* enhance this effect by stabilizing redox balance and minimizing oxidative damage initiated by metal-catalyzed reactions (Surai, 2020). Additionally, tea polyphenols have been found to enhance the antioxidant status of poultry by upregulating the expression of endogenous antioxidant enzymes such as SOD and GSH-Px (Tang, et al., 2019). The antioxidant action of EGCG has been extensively studied in poultry and compared to other antioxidants such as alpha-tocopherol and ascorbic acid (Kian, et al., 2018). However, the combination of EGCG, alpha-tocopherol, and ascorbic acid has been found to produce a significantly greater antioxidant effect compared to the individual components alone. This synergistic interaction enhances the overall antioxidant capacity, providing robust protection against oxidative stress and improving growth performance in poultry (Khan and Mukhtar, 2018). The combined use of these antioxidants has been shown to enhance gut health, boost immune function, and lower the risk of metabolic disorders in poultry, highlighting their potential to improve both poultry health and production (Surai, 2020). These findings emphasize the importance of combining tea polyphenols with *vitamins* to maximize their health benefits and provide a comprehensive approach to combating oxidative damage in poultry.

Stress resistance properties of green tea EGCG

The antioxidant activity of the phytochemicals provides great hope for solving the stresses in poultry birds. GTPs, a major class of secondary metabolites widely found in many plants, are extensively utilized in specific applications due to their potent antioxidant properties (Crozier, et al., 2009). The primary component of green tea polyphenol is EGCG, which has powerful anti-inflammatory and anti-oxidant characteristics and exhibits better bioavailability than other polyphenols. The therapeutic effects of EGCG are highly dose-dependent, with varying outcomes observed at different doses. A range of studies has examined the impact of EGCG supplementation on heat stress in poultry species, including chickens, turkeys, ducks, and quail (Liu, et al., 2023; Wang, Qi and Zheng, 2022a). The optimal dose for EGCG supplementation varies between species, and determining the appropriate dose is essential to

achieving the desired benefits without causing adverse effects (Jelveh, et al., 2023). A study by Basiouni, et al. (2023), found that moderate doses of EGCG (50–100 mg/kg body weight) significantly improved antioxidant status and reduced the accumulation of ROS in the liver and muscle tissues of heat-stressed chickens. These doses also resulted in a significant increase in the expression of antioxidant enzymes such as SOD, CAT, and GPx, along with a decrease in pro-inflammatory cytokines, which are typically elevated under heat stress conditions (Kouvedaki, et al., 2024). Higher doses of EGCG (200 mg/kg or more) were found to be less effective, as they did not provide additional benefits and, in some cases, induced toxicity, leading to a decrease in feed intake and overall health (Legeay, et al., 2015). In another study was observed that chickens supplemented with 100 mg/kg of EGCG exhibited improved thermoregulation, with a significant reduction in body temperature and increased heat shock protein (HSP) expression, which is essential for cellular protection during heat stress. However, doses above 200 mg/kg resulted in adverse effects (Mangan and Siwek, 2023). In turkeys, EGCG supplementation has similarly demonstrated beneficial effects under heat stress conditions. The moderate doses of EGCG (75–150 mg/kg) helped mitigate oxidative damage and improved thermoregulation in heat-stressed turkeys. In contrast, higher doses (200 mg/kg) led to a reduction in feed intake and weight gain, suggesting a dose-dependent decline in the effectiveness of EGCG at higher concentrations (Zhao, et al., 2021). Ducks (Anas platyrhynchos) exhibit a higher natural tolerance to heat stress compared to chickens and turkeys, possibly due to their evolutionary adaptation to varying environmental conditions. However, research shown that EGCG supplementation still offers significant benefits in heat-stressed ducks. Moderate doses of EGCG (50–100 mg/kg) were found to enhance antioxidant defenses. Interestingly, ducks responded more favorably to higher doses of EGCG (up to 200 mg/kg) compared to chickens and turkeys, with no observable adverse effects at these higher doses (Tso, et al., 2021). Quail exhibits a moderate response to EGCG supplementation, with the optimal dose ranging from (50 to 100 mg/kg). In a study by (Ozercan, et al., 2008), quail supplemented with (75 mg/kg) of EGCG showed improved growth performance, enhanced antioxidant enzyme activities, and reduced oxidative damage in liver and muscle tissues. However, doses above (150 mg/kg) did not result in additional benefits and caused a decline in overall health, which was reflected in reduced feed intake and growth rates. These findings emphasize the necessity of developing species-specific supplementation strategies, taking into account both the unique physiological characteristics of each species and the intensity of heat stress conditions. Multiple studies demonstrated that green tea EGCG can reduce the extreme temperature in birds. Xue, Song, Liu, Luo, Tian and Yang (2017) found that 300-600mg/kg of EGCG supplementation in heat stress broiler feed could improve the efficiency of production, in a dose-dependent method. Luo et al., 2010 also revealed that the addition of EGCG 600 mg/kg showed the best antioxidant activity in heat-stressed broilers. According to Sahin, et al. (2010) 400mg/kg EGCG supplement showed higher antioxidant capacity in heat-stressed quails. Therefore, 400-600mg/kg might be the best dose for birds. During cellular respiration and metabolism free radicals are produced, these free radicals like the superoxide anion (O2-), hydroxyl ion (OH-), free radicals, and hydrogen peroxide (H2O2), and others are strictly involved in pathological and physiological processes in animals (Bergamini, et al., 2004; Kim, et al., 2009). Reactive oxygen species can serve as signals transduction at the low level which monitors and controls essential cellular functions such as cell proliferation and evolutionary cellular response (Lum and Roebuck, 2001). Whenever the balance of redox of the body's antioxidant process and accumulation of ROS is disturbed, it leads to oxidative stress causing various diseases and damage to cells and tissues (Mao, et al., 2017). EGCG induces the expression of antioxidant enzymes that help their cells protect against ultraviolet rays or biochemical toxins (Islam, et al., 2020). The protective effects of tea polyphenols in poultry under heat stress, as outlined in (Table 1). Moreover, the use of green tea EGCG in

Table 1
Protective role of tea polyphenols in enhancing poultry resilience to heat stress.

Tea Polyphenol	Poultry Species	Heat Stress Conditions	Protective Effects	Doses	References
EGCG	Japanese Quail	34°C for 8 hours/day	Increased Nrf2 expression, SOD, CAT, GSH-Px; decreased NF-κB expression	200/400mg/kg diet	(Sahin, Orhan, Tuzcu, Ali, Sahin and Hayirli, 2010)
EGCG	Vanadium-exposed laying hens	Heat stress with 10 mg/kg vanadium	Improved shell color, increased GST, Nrf2, HO-1 expression; decreased MDA concentration	130 mg, EGCG/kg feed	(Wang, Yuan, Zhang, Ding, Bai, Zeng, Peng and Celi, 2018a)
Tea Polyphenols	Hy-line brown laying hens	64-week-old under heat stress	Increased albumen height, improved magnum morphology	200 mg, tea polyphenols /kg feed	(Wang, et al., 2018b)
GTPs extract	Broilers	32°C for 6 hours/day	Improved feed efficiency, increased antioxidant enzyme activities, reduced lipid peroxidation	600 mg/kg feed	(Son, et al., 2023)
EGCG	Linwu laying ducks	Heat stress exposure	Enhanced egg production, improved antioxidant status, reduced oxidative stress markers	300 mg, EGCG /kg feed	(Liu, Zhang, Yao, Huang, Li, Deng, Jiang and Dai, 2023)
Green tea	Laying hens	32°C for 12 hours/day	Increased egg weight, improved yolk color	3 kg/ ton feed	(Ghanima, et al., 2021)
Tea Polyphenols	Broilers	High ambient temperature	Enhanced antioxidant capacity, induced expression of heat shock proteins (HSPs)	10 µg, tea polyphenols /mL	(Yin, et al., 2021)
Tea Polyphenols	Arbour Acres broilers	Heat stress conditions	Increased serum CAT, GPx, and SOD activities; lowered MDA levels	0 mg, 300 mg and 600 mg/ kg basel diet	(Song, et al., 2019)

laying hens can give prevention from vanadium (V) toxicity. The study confers that in the vanadium group (10mg/kg), the color of the eggshell, as well as protoporphyrin IX, were reduced relative to the normal diet, whereas green tea EGCG 130mg/kg group partially enriched eggshell color and protoporphyrin IX (Wang, et al., 2018a). Wang et al. (2018) reported that vanadium toxicity in laying hens increased cellular apoptosis and oxidative injury, reduced uterine GST, and elevated MDA levels, while EGCG significantly reduced oxidative damage by lowering MDA production. In a layered uterus, transcriptional factors such as Nrf2 and HO-1 were downregulated through vanadium usage, while dietary EGCG was capable to upregulate the transcription of Nrf2 and HO-1 gene relative to those exposed by the Vanadium group (Wang, Yuan, Zhang, Ding, Bai, Zeng, Peng and Celi, 2018a). These bioactive compounds mitigate the effects of environmental and metabolic toxins, offering therapeutic potential against oxidative damage, chronic inflammation, and toxicological impacts, as shown in (Table 2). *In vitro* studies have demonstrated that EGCG can affect cellular processes, such as preventing ROS production and triggering programmed cell death. However, these effects may not always be applicable to biological systems, as they could also harm healthy cells. EGCG has been demonstrated to influence cell membranes and regulate oxidative stress survival pathways in specific cell types, though these effects may not directly correlate with outcomes in *in vivo* systems (Zhong, et al., 2013).

The regulatory role of Nrf2 to antioxidant enzyme transcription

The regulation of transcription factors such as Nrf2, NF-κB, PPAR-γ, and MAPK significantly impacts antioxidant processes by modulating the activities of antioxidant and free-radical-producing enzymes, which are essential for stress adaptation in livestock, including poultry. Nrf2 is a well-known transcriptional factor accountable for the physiological stress controller of oxidative stress-induced signaling as the oxidoreduction-sensitive signaling molecule (G. Bardallo, et al., 2022; Singh, et al., 2010). Nrf2 has a crucial contribution to oxidative stress adaptation through stimulation of the transcription of numerous protective molecules (He, et al., 2020). Under normal conditions, Nrf2 is sequestered in the cytoplasm but translocates to the nucleus during oxidative stress, triggered by an accumulation of ROS or RNS, to initiate an antioxidant response (Ngo and Duennwald, 2022a). The Nrf2-Keap1-ARE pathway plays a pivotal role in regulating antioxidant responses, relying on the dynamic interplay between Nrf2, Keap1, the antioxidant response element (ARE), and Maf proteins. Keap1, a key

Table 2
Green tea polyphenols exhibit significant protective effects across various toxicological models.

Toxic Model System	Tea Polyphenol Assessment	Mode of Action	Protective Properties	Studies
Oxidative stress; liver injury	EGCG, ECG, EGC, Catechins	Antioxidant activity, reduction of ROS, modulation of antioxidant enzymes SOD, CAT	Protects against liver damage caused by oxidative stress, enhances antioxidant defense, reduces lipid peroxidation	(Sheng, et al., 2023; Yan, Zhong, Duan, Chen and Li, 2020)
Neurotoxicity; parkinson's disease	EGCG, ECG, Epicatechin	Reduces ROS, inhibition of α-synuclein aggregation, anti-inflammatory, mitochondrial protection	Prevents neurodegeneration, protects dopaminergic neurons, improves motor function	(Singh, et al., 2016; Wang, et al., 2022b)
Cardiovascular toxicity; atherosclerosis	EGCG, Catechins	Anti-inflammatory effects, reduction of LDL oxidation, improves endothelial function, inhibition of vascular smooth muscle proliferation	Reduces plaque formation, prevents endothelial dysfunction, lowers cholesterol levels	(Babu and Liu, 2008)
Chemical induced liver toxicity	EGCG, Green Tea Extract	Modulation of phase I and II enzymes, inhibition of hepatic stellate cell activation, reduction of fibrosis	Reduces liver enzyme levels ALT, AST, prevents liver fibrosis and necrosis, improves histopathological damage	(Laftah, et al., 2025; Mostafa-Hedeab, et al., 2022)
Heavy metal toxicity	EGCG, Green Tea Polyphenols	Chelation of metals, reduction of oxidative stress, modulation of metal-induced enzyme activities	Protects organs like liver and kidney from metal toxicity, reduces oxidative damage, improves organ function	(Ranasinghe, et al., 2023; Zwolak, 2021)
Renal toxicity; aminoglycosides, cisplatin	EGCG, Green Tea Polyphenols	Antioxidant, anti-inflammatory, inhibition of apoptosis, suppression of pro-inflammatory cytokines	Reduces kidney damage, prevents nephrotoxicity, enhances renal function	(Ayusso, et al., 2024)
Endotoxin induced; inflammation	EGCG, Green Tea Extract	Inhibition of NF-κB, reduction in pro-inflammatory cytokines like TNF-α, IL-6, enhancement of anti-inflammatory cytokines e.g., IL-10	Decreases inflammatory responses, prevents sepsis-induced organ damage	(Mokra, et al., 2022)
Skin toxicity; UV exposure	EGCG, ECG, Green Tea Extract	Inhibition of UV-induced DNA damage, antioxidant properties, modulation of inflammatory pathways	Reduces skin inflammation, prevents UV-induced erythema, photoaging, and DNA damage	(Sharma, et al., 2018)
Diabetes-induced toxicity	EGCG, Green Tea Polyphenols	Modulation of insulin signaling pathways, antioxidant effects, reduction in glucose absorption	Improves insulin sensitivity, reduces hyperglycemia, protects against diabetic complications	(Wen, et al., 2022)
Cigarette smoke induced injury	EGCG, Green Tea Extract	Anti-inflammatory, antioxidant, inhibition of NF-κB signaling, reduction in ROS	Reduces lung inflammation, oxidative damage, and lung fibrosis, prevents emphysema	(Lakshmi, et al., 2020)
Alcohol persuaded hepatotoxicity	EGCG, Green Tea Extract	Antioxidant, inhibition of pro-inflammatory cytokines, reduction of TNF-α signaling, protection of hepatocytes	Reduces liver damage caused by ethanol persuaded toxicity, restores liver function	(Han, et al., 2016)
Obesity encouraged toxicity	EGCG, Green Tea Polyphenols	Regulation of adipogenesis, anti-inflammatory, inhibition of lipogenesis, modulation of gut microbiota	Reduces weight gain, improves lipid metabolism, reduces inflammation, improves gut health	(He, et al., 2024; Meydani and Hasan, 2010)
Radiation induced injury	EGCG, Green Tea Extract	Antioxidant, DNA repair, protection against oxidative damage, inhibition of apoptosis	Protects cells from radiation-induced DNA damage, enhances cell survival, reduces apoptosis	(Singh, et al., 2011; Xie, et al., 2020)
Hyperglycemia and hyperlipidemia	EGCG, Catechins	Activation of AMPK, reduction of ROS, modulation of lipid metabolism	Lowers blood glucose and lipid levels, improves lipid profile, reduces oxidative stress	(James, et al., 2023)
Chronic inflammation	EGCG, Green Tea Extract	Inhibition of inflammatory cytokines, downregulation of COX-2 and iNOS, modulation of adipocyte signaling	Reduces systemic inflammation, improves adipocyte function, reduces risk of chronic diseases	(Tang, et al., 2021)

regulator in this pathway, features specific cysteine residues such as Cys151, Cys273, Cys288, and Cys297 that are essential for controlling Nrf2 activity (Culletta, et al., 2024). These residues regulate the interaction between Nrf2 and Keap1, ultimately dictating whether Nrf2 is stabilized or marked for degradation. Moreover, redox-sensitive cysteines in Nrf2 (e.g., Cys119, Cys235, Cys414) play a pivotal role in modulating its function and stability (Srivastava, et al., 2022). NRF2, as an anti-inflammatory regulator, can mitigate the release of MMPs by downregulation of NF-kB and TNF-α signaling (Saha, et al., 2020). Matrix metalloproteinases (MMPs-2) and (MMP-9) have been known to present a heightened activity following oxidative stress in other tissues (Timokhina, et al., 2020), making NRF2 a key mediator in the antioxidant response. NF-κB is a critical transcription factor complex that regulates genes involved in immune response, inflammation, cell survival, and stress responses. It exists in an inactive state in the cytoplasm, bound to inhibitory proteins (IκBs), and is activated by a variety of external and internal stressors, including heat stress, oxidative stress, pathogen infections, pro-inflammatory cytokines (e.g., TNF-α, IL-1β), UV radiation, and endoplasmic reticulum stress (Gilmore, 2006; Hayden and Ghosh, 2014). In poultry, for example, heat stress conditions can trigger NF-κB activation, leading to the upregulation of heat shock proteins (HSPs) and inflammatory mediators, which help mitigate cellular damage but can also impair growth and productivity if dysregulated (Liu, et al., 2017; Zhang, et al., 2017). NF-κB plays a central role in immune and inflammatory responses by upregulating cytokines, chemokines, and enzymes like COX-2 and iNOS, while also promoting cell survival through anti-apoptotic genes like Bcl-2 (Perkins, 2012; Taniguchi and Karin, 2018). Recent advances have highlighted the importance of non-canonical NF-κB signaling, involving p100 processing to p52, and its interplay with pathways like JAK-STAT and MAPK in stress and inflammation responses (Sun, 2017). The molecular mechanism of activating Nrf2 and inhibiting NF-κB described in details in (Table 3). Glutathione (GSH) is a tripeptide composed of glutamine, cysteine, and glycine, and is one of the most abundant low-molecular-weight antioxidants in cells. It plays a fundamental role in scavenging ROS and maintaining the cellular redox state. **GSH** exerts its antioxidant effects primarily through the direct neutralization of free radicals and the reduction of peroxides, particularly (H_2O_2) (Chai and Mieyal, 2023; Ngo and Duennwald, 2022b). Nrf2 activation induces the expression of key enzymes involved in GSH synthesis, including γ-glutamylcysteine synthetase, which catalyzes the rate-limiting step in GSH biosynthesis (Klaassen and Reisman, 2010). Nrf2 also upregulates the expression of glutathione peroxidase (GPx) and glutathione reductase, enzymes that facilitate the detoxification of peroxides and maintain GSH in its reduced form. Through these mechanisms, Nrf2 not only enhances GSH synthesis but also promotes the recycling of GSH, thereby enhancing cellular antioxidant capacity (Pajares, et al., 2017). In addition to promoting GSH synthesis, Nrf2 enhances the activity of several other enzymes involved in GSH utilization, including glutathione S-transferases (GSTs) and GPx. GSTs are a family of enzymes that catalyze the conjugation of GSH to electrophilic compounds, facilitating their neutralization and subsequent excretion from the cell (Mazari, et al., 2023). By upregulating GST expression, Nrf2 helps to mitigate cellular damage caused by electrophiles, such as environmental toxins and reactive metabolites. Furthermore, GPx enzymes utilize GSH to reduce peroxides, particularly hydrogen peroxide, into water, effectively protecting cellular components such as lipids, proteins, and DNA from oxidative damage (Espinosa-Diez, et al., 2015). The Trx system, is another essential antioxidant defense mechanism, interacts with the Nrf2 pathway, thereby catalyzes the reduction of disulfide bonds in proteins, and reversing oxidative damage (Yang, et al., 2024). Additionally, Nrf2 upregulates the expression of peroxiredoxins, which work in conjunction with thioredoxin to reduce hydrogen peroxide and protect cells from oxidative damage (Stancill, et al., 2022). Superoxide dismutases (SODs) are a family of enzymes that catalyze the conversion of superoxide radicals into hydrogen peroxide, a less harmful molecule. Nrf2 regulates the expression of SODs by binding to AREs in their promoter regions. For instance, SOD2, which is located in the mitochondria, is particularly important in protecting against mitochondrial oxidative damage (Rosa, et al., 2021; Wang, et al., 2018b).

The molecular mechanisms of Nrf2 activation

Nrf2 is regulated through its interaction with Kelch-like ECH-associated protein 1 (Keap1). Under normal redox conditions, Keap1 binds to Nrf2, preventing its movement into the nucleus. However, oxidation

Table 3
Molecular mechanisms of tea polyphenols in activating nrf2 and inhibiting nf-κb.

Tea Polyphenol	Target Pathway	Mechanism of Action	Biological Effect	Reference
Epigallocatechin gallate (EGCG)	Nrf2 Activation	Promotes Nrf2 movement into the nucleus by altering Keap1 cysteine residues	Increases levels of antioxidant enzymes (e.g., SOD, GSH-Px) and reduces oxidative stress	(Lv, et al., 2022)
EGCG	NF-κB Inhibition	Prevents IκBα breakdown and stops NF-κB from entering the nucleus	Lowers production of inflammatory cytokines (e.g., TNF-α, IL-6)	(Talebi, et al., 2021)
Theaflavins	Nrf2 Activation	Helps Nrf2 separate from Keap1 and boosts gene expression through ARE	Enhances antioxidant defenses and protects cells from oxidative damage	(Zhang, et al., 2019)
Theaflavins	NF-κB Inhibition	Stops NF-κB activation by blocking IKK phosphorylation	Reduces inflammation and prevents tissue damage	(O'Neill, et al., 2021)
Catechins	Nrf2 Activation	Triggers Nrf2 phosphorylation through PKC and MAPK pathways	Increases production of detoxifying enzymes	(Talebi, Talebi, Farkhondeh, Mishra, İlgün and Samarghandian, 2021)
Catechins	NF-κB Inhibition	Prevents NF-κB from binding to DNA and reduces p65 subunit phosphorylation	Reduces inflammation and oxidative stress	(Sheng, Sun, Tang, Yu, Wang, Zheng, Li and Sun, 2023)
Epicatechin (EC)	Nrf2 Activation	Stabilizes Nrf2 by preventing Keap1 from marking it for degradation	Strengthens antioxidant defenses and reduces lipid peroxidation	(Granado-Serrano, et al., 2010)
Epicatechin	NF-κB Inhibition	Reduces NF-κB activation by stopping IKK complex formation	Lowers levels of inflammatory markers (e.g., CRP, IL-1β)	(Ponnian, 2022)
Gallocatechin gallate (GCG)	Nrf2 Activation	Activates Nrf2 through ERK and PI3K/Akt signaling pathways	Boosts glutathione production and lowers ROS levels	(Pullikotil, et al., 2012)
Gallocatechin gallate	NF-κB Inhibition	Stops NF-κB activation by preventing IκBα phosphorylation	Reduces release of inflammatory cytokines and oxidative damage	(Mokra, Joskova and Mokry, 2022)
Thearubigins	Nrf2 Activation	Helps Nrf2 move into the nucleus and bind to ARE	Increases antioxidant gene expression and reduces oxidative stress	(Datta, et al., 2022)
Theasinensins	Nrf2 Activation	Boosts Nrf2 activity by stabilizing its interaction with ARE	Enhances cellular antioxidant defenses and reduces oxidative damage	(Jiang, et al., 2021)
Theasinensins	NF-κB Inhibition	Blocks NF-κB activation by inhibiting IKKβ activity	Reduces inflammation and oxidative stress in liver tissues	(Howes and Simmonds, 2014)

or covalent modification of specific cysteine residues within Keap1 can disrupt the Keap1-Nrf2 complex, stabilizing Nrf2 and facilitating its translocation to the nucleus (Kopacz, et al., 2020). These cysteine residues serve as critical sensors, detecting intracellular redox imbalances triggered by ROS or electrophiles (Dayalan Naidu and Dinkova-Kostova, 2020). Beyond this, Nrf2 activity is further modulated by post-transcriptional modifications, including phosphorylation by kinases such as protein kinase C (PKC), phosphoinositol 3-kinase (PI3K), and mitogen-activated protein kinases (MAPKs) (Gao, et al., 2025). For instance, bioactive compounds like phenethyl isothiocyanate have been shown to enhance Nrf2 phosphorylation through JNK or ERK1/2 pathways, promoting its nuclear translocation (Thiruvengadam, et al., 2021). Once inside the nucleus, Nrf2 binds to ARE or electrophile response elements (EpRE), often in collaboration with coactivators like small Maf proteins and CREB-binding protein (CBP)/p300. This interaction drives the expression of antioxidant genes, enhancing cellular defense mechanisms (Espinosa-Diez, Miguel, Mennerich, Kietzmann, Sánchez-Pérez, Cadenas and Lamas, 2015).

Enzymatic antioxidant induction regulation through EGCG by Nrf2 signaling

Preventing cells from oxidative damage is crucial, either by directly scavenging free radicals or, by enhancing the organism's antioxidant status through the activation of antioxidant gene transcription. Previous studies have demonstrated that EGCG can activate a distinct set of enzymatic antioxidants across various tissues. GTPs stimulate small intestine, liver, and lung transcription of **GPx**, catalase as well as quinone reductase in bald mice (Khan, et al., 1992). Female Japanese quail exposed to heat stress at 34°C for eight hours per day over twelve weeks, starting at five weeks of age, experienced reduced productivity and performance quality, including a 10% decline in feed intake and a 14.5% drop in egg production. Also, induced oxidative stress, evidenced by increased hepatic **MDA** concentrations and decreased hepatic enzymatic antioxidant activity, such as SOD, CAT, and GPx (Sahin, Orhan, Tuzcu, Ali, Sahin and Hayirli, 2010). Simultaneously, a decline in hepatics Nrf2 induction was also detected. In comparison, supplementation with 200 or 400 mg/kg of EGCG restored the transcriptional activity of Nrf2 affected by heat stress and improved the disruptions in the antioxidant defense network (Sahin, Orhan, Tuzcu, Ali, Sahin and Hayirli, 2010). The molecular mechanism underlying the activation of enzymatic antioxidants by EGCG or other GTPs remains a focus of extensive research. The induction of antioxidant enzyme expression by EGCG or GTPs is closely associated with the stimulation of Nrf2-ARE signaling. Gavage treatment with EGCG in wild-type mice increased the transcription of γ-glutamyltransferase 1 (GGT1), the catalytic subunit of glutamate-cysteine ligase (GCL), and heme oxygenase-1 (HO-1). However, this effect was absent in Nrf2-deficient mice (Shen, et al., 2005). It has been described that EGCG inhibits elevated liver transcription of Hsps induced via heat stress, particularly suppressing their abundance of Hsp70 and Hsp90 through inhibiting regulatory action in poultry (Orhan, et al., 2013). EGCG modulates antioxidant enzyme capacity mainly because it stimulates pathways of Nrf2. Sahin et al. (2010) reported that EGCG enhances the enzymatic antioxidant network in heat-stressed quail by activating the Nrf2 signaling pathway and Nrf2-regulated heme oxygenase-1 (HO-1). The alteration of heme to biliverdin and carbon monoxide is the responsibility of HO-1 and therefore its initiation is essential in the physiological adaptation to oxidative damage. EGCG has been shown to trigger the transcription of HO-1 in both endothelial cells and B lymphoblasts (Andreadi, et al., 2006; Wu, et al., 2006). The EGCG-dependent abundance of HO-1 is suppressed by N-Acetylcysteine (NAC), **GSH, SOD**, and **CAT**, suggesting that the EGCG-induced HO-1 expression is mediated through ROS signaling (Wu, Hsu, Hsieh, Lin, Lai and Wung, 2006). It's been demonstrated that in the polyphenolic groups, EGCG initiates auto-oxidation at regular biological pH to make dimers, induced through ROS production (Nakagawa, et al., 2004; Yang, et al., 2000). Further research has shown that metallic ions such as Cu^{2+}, which generate superoxide radicals and EGCG radicals, promote EGCG auto-oxidation within the medium (Hou, et al., 2005). Even though HO-1 has a cytoprotective role, in healthy cells, it can provide growth progress and confrontation to photodynamic therapy and chemotherapy with unusually high fundamental induction of HO-1 in human cancers (Tanaka, et al., 2003). Thus, suppressing fundamental increased HO-1 in the cancer cell is known to be suitable for the treatment of cancer. In human pulmonary adenocarcinoma cells, EGCG suppressed nuclear translocation, and ARE complexes of Nrf2 and HO-1-ARE expression level correlated with the upregulation of apoptosis in these cells. The suppression of Bach1 induction, a key transcription factor of the leucine zipper group that forms a heterodimer with small Maf proteins, was regulated by EGCG. This led to a reduced induction of HO-1, thereby suppressing the expression of enzymatic antioxidant genes (Kweon, et al., 2006). EGCG dual effect Nrf2-arbitrated ARE stimulation and the induction of the main gene seem to have been correlated in its abundance. The decreased expression of HO-1 through EGCG has been found at a comparatively high proportion whereas, at a low proportion EGCG induced HO-1 induction (Chen, Yu, Owuor and Tony Kong, 2000; Kweon, Adhami, Lee and Mukhtar, 2006). A well-adjusted proportion of **GTP** compounds, which can act as both antioxidants and pro-oxidants, seems essential for regulating Nrf2-ARE through EGCG.

Mechanism of EGCG-induced Nrf2 activation

The action potency of EGCG in initiating an antioxidant defense network lies in its ability to activate ARE-regulated antioxidant gene transcription. This process typically involves the phosphorylation of Nrf2 by protein kinases and its serine/threonine derivatives, leading to increased nuclear Nrf2 accumulation and subsequent binding to ARE. In endothelial cells, the transcription of HO-1 triggered through EGCG was regulated via induction of Akt as well as ERK1/2 (Wu, Hsu, Hsieh, Lin, Lai and Wung, 2006). Apart from Nrf2 transcriptional regulation, EGCG-regulate HO-1 stimulation also was induced via Akt and p38 MAPK sensing in B lymphoblasts (Andreadi, Howells, Atherfold and Manson, 2006). Thus, via stimulation of a recycling process of **MAPKs** liable for Nrf2 regulation, EGCG could be mediated by ARE-induced transcription of the antioxidant's gene. Modification or oxidation of cysteine thiols through ROS in Keap1 or a reactive form of EGCG produced throughout its oxidation-reduction cycling is another possible mechanism of EGCG-regulate Nrf2 stimulation. Flavonoids with significantly greater capability to develop oxidative stress and redox-cycling have also been mentioned to be the important regulator of **ARE**--induction gene transcription (Lee-Hilz, et al., 2006). It has been discovered that EGCG generates significant volumes of H_2O_2 within cultured cell circumstances (Hong, et al., 2002; Long, et al., 2000). EGCG is metabolized to form a semiquinone radical, either at the B-ring or the glucoside loop, which is then further oxidized to o-quinone (Sang, et al., 2005). Such EGCG quinones could bind with either the GSH or cysteine sulfhydryl family to build the 2″ – or 2 ″-glutathionyl EGCG or 2″ - or 2″ -cysteinyl EGCG (Joyner, 2021). Dimers are identified as biologically active molecules formed by the oxidation of EGCG. It would be meaningful to observe whether these dimeric molecules of EGCG could regulate the Nrf2-ARE molecular regulation pathway in vivo (Hong, Lu, Meng, Ryu, Hara and Yang, 2002). In this condition, up to some extent, EGCG can also perform electrophiles and pro-oxidant activity (Xu, et al., 2005). Flavonoids substantially enhanced the EpRE-regulated transcription of gene expression by reducing cellular **GSH** levels (Sang, Lambert, Hong, Tian, Lee, Stark, Ho and Yang, 2005). Therefore, EpRE-Stimulated expression of gen through EGCG is probably to be correlated by its pro-oxidants or electrophilic characteristics, which could be accomplished based on both intracellular oxidative metabolism and pH variation. Respectively, finally, we applaud the pathways through whereby Nrf2 is triggered by EGCG, contributing to increased

expression of the ARE-induced antioxidant gene (Fig. 4). It's indeed conceivable that GSH can be combined with the responsive component of EGCG, thus reducing the number of cellular GSH which can contribute to the transient redox-status degradation with consequent stimulation of Nrf2 phosphorylation-causing MAPK cascades. On the other hand, certain electrophilic sorts of EGCG can actively interact with cysteine residue that exists within Keap1, thus activating Nrf2 disintegration. Similarly, ROS produced by EGCG self-oxidation can oxidize Keap1′s cysteine thiol, which will cause Nrf2 to reduce the affinity to Keap1, thus providing the release of Nrf2 for nuclear translocation.

Potential impact of EGCG in advancing the poultry industry

EGCG's antioxidant properties enhance poultry health and productivity by improving growth performance, feed efficiency, and immune function. It also boosts product quality by reducing lipid oxidation in meat and eggs, extending shelf life, and improving nutritional profiles, such as increasing omega-3 fatty acids and lowering cholesterol levels (Abdelli, et al., 2021; Alagawany, et al., 2019). It is the most active catechin in green tea, is a potent natural antioxidant with significant potential to benefit the poultry industry. Oxidative stress, caused by an imbalance between **ROS** production and the antioxidant defense system, is a major challenge in poultry production, leading to reduced growth, impaired immunity, and poor product quality (Capasso, et al., 2025). EGCG addresses this issue through its multifaceted antioxidant mechanisms, making it a valuable tool for enhancing poultry health and productivity (Li, et al., 2024). By donating hydrogen atoms from its hydroxyl groups, EGCG neutralizes these radicals, preventing oxidative damage to lipids, proteins, and DNA. This protective effect is particularly important in high-density rearing systems, where birds are more susceptible to oxidative stress due to overcrowding, heat stress, and exposure to pathogens (Chi, et al., 2020a). EGCG perform better than other polyphenols like curcumin and quercetin in bioavailability and bioactivity, when delivered via nanoencapsulation. To address challenges like heat stress and improve poultry health and productivity, the poultry industry is increasingly prioritizing the enhancement of tea polyphenols' bioavailability and bioactivity, with a particular focus on EGCG through innovative nanoencapsulation techniques.

Conclusion

Birds exposed to heat stress produce excessive **ROS/RNS**, leading to oxidative damage. This oxidative stress appears to be the primary harmful effect of stress factors in the commercial poultry industry. Besides, heat stress declined development parameters prompted oxidative damage, depressed enzymatic antioxidant response, increased

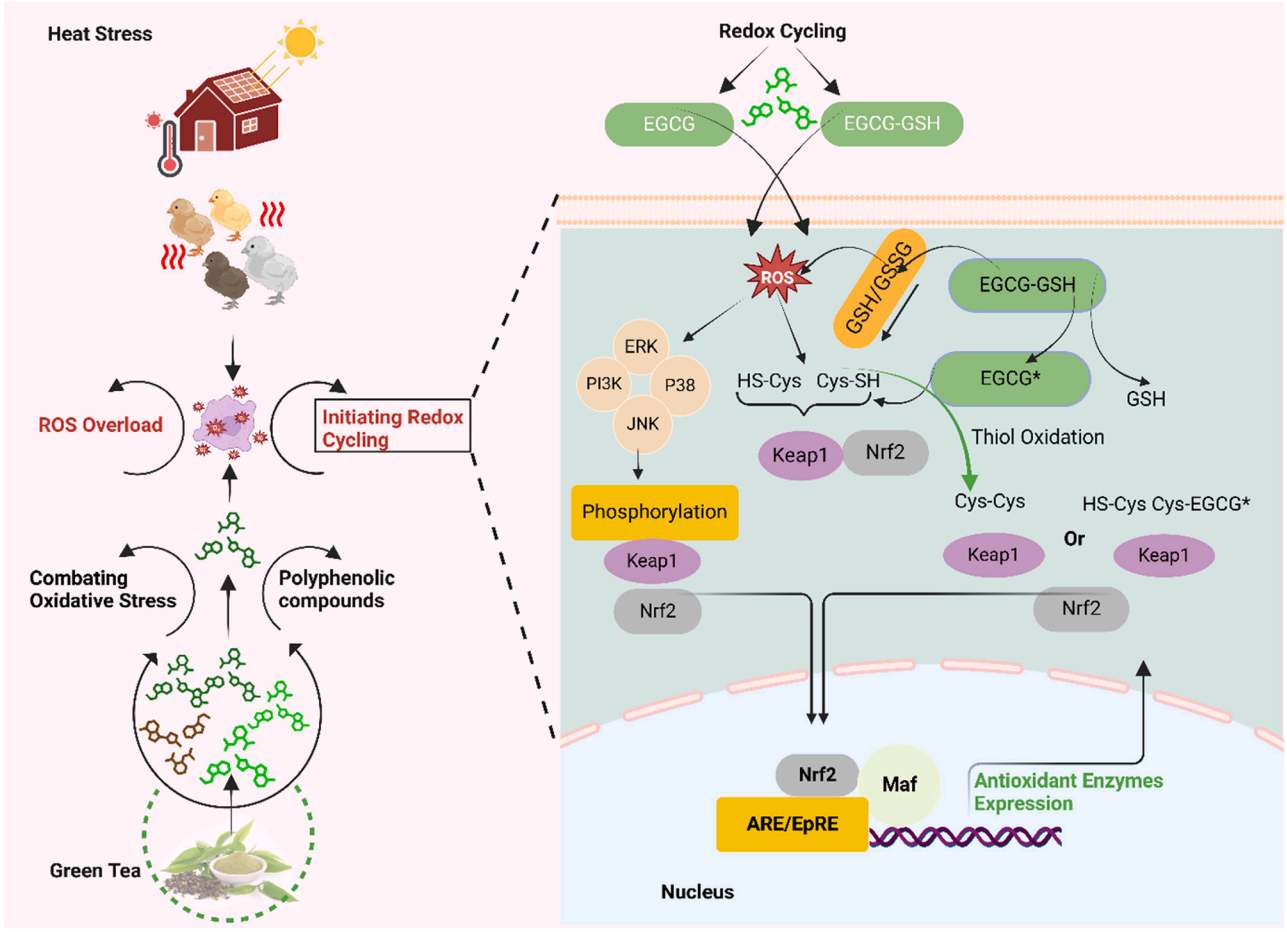

Fig. 4. The antioxidant enzyme network is upregulated through the EGCG-induced Nrf2-ARE signaling pathway. This activation stimulates the transcription of several enzymatic antioxidants via the Nrf2 transcription factor. Keap1 is an Nrf2 cytosolic suppressor that prevents the translocation of Nrf2 to the nucleus. GSH is presumed to be associated with oxidized or some other active EGCG (EGCG*) forms, therefore, reducing cells' GSH amount might cause distraction of redox status with following stimulation of upregulation kinases. Comprising PI3K, PKC, and MAPKs, such as JNK and ERK lead to Nrf2 phosphorylation activation. Otherwise, Cysteine residues exist in Keap1 and may interact directly with some reaction forms of EGCG (EGCG*), therefore upregulating Nrf2 separation. Similarly, auto-oxidation of the EGCG-generated ROS regulates the phosphatization of Nrf2 not only by stimulating induced kinases or oxidizing Keap1 cysteine thiol. Mutual action can enable the Nrf2 nuclear translocation. Finally, Nrf2 forms a heterodimer with small Maf in the nucleus that binds to ARE or EpRE to regulate the antioxidant enzyme network. The figure is generated with BioRender.com.

transcription of NF-κB, and repressed transcription of Nrf2. In HS-affected poultry, the rate of performance changes, lipid peroxidation assays, as well as transcription factors, were higher than in poultry raised under thermal neutral conditions. Through the enhancement of the antioxidant defense system, EGCG may improve cellular resilience and overall poultry performance under heat stress conditions. This suggests that EGCG could be a valuable dietary supplement for sustainable poultry farming, reducing reliance on synthetic antioxidants and promoting animal welfare. Further in vivo studies are needed to determine the optimal dosages, long-term effects, and mechanisms of Nrf2 modulation by EGCG, along with its interactions with other pathways under different conditions. Despite these promising findings, it is important to note that the current evidence is still preliminary, and many aspects of EGCG's mode of action in poultry remain speculative. While a growing body of research suggests that EGCG may activate the Nrf2 pathway, leading to increased expression of antioxidative enzymes like SOD and CAT, the underlying mechanisms need to be further clarified. Studies on the molecular interactions between EGCG and key components of the Nrf2 pathway are limited, requiring further experimental work to clarify the molecular cascade that EGCG triggers. For instance, it remains uncertain whether **EGCG's** effects on Nrf2 activation are direct or if they involve intermediary signaling molecules or transcription factors that are yet to be identified. Thus, a more in-depth mechanistic understanding of EGCG's role in antioxidant responses under heat stress is warranted. Studies investigating the pharmacokinetics of EGCG in poultry are essential to establish the effective in vivo concentrations and assess their potential for therapeutic efficacy. Also, determining the safety of long-term EGCG supplementation in poultry is of paramount importance, as high doses could potentially lead to unintended side effects such as metabolic disruptions or nutrient imbalances. **EGCG**, a key green tea polyphenol, shows promise in mitigating oxidative stress in heat-stressed poultry via the Nrf2 pathway, but further *in vivo* studies under varied heat stress conditions are needed to confirm its efficacy and clarify the underlying mechanisms. Additionally, while the activation of the **Nrf2** pathway is hypothesized to be a central mechanism, there is insufficient evidence to confirm whether **EGCG** consistently modulates this pathway under practical farming conditions. The optimal dosage, long-term safety, and potential side effects of **EGCG** in poultry also remain uncertain and must be systematically evaluated.

Future perspectives

1. The pharmacokinetics of EGCG in poultry birds should focus on systematically investigating its absorption, distribution, metabolism, and excretion (ADME) to address the current knowledge gap. Key areas include evaluating oral bioavailability and plasma concentration-time profiles, assessing tissue distribution in critical organs like the liver, kidneys, and muscles, and identifying species-specific metabolic pathways and major metabolites. Advanced analytical techniques, such as LC-MS/MS, should be employed to quantify EGCG and its metabolites in plasma and tissues.
2. Future studies need to clarify the actual concentration of **GTPs** and elucidate the existing mechanism of action for a safe range of tea absorption and health benefits.
3. Improvement of further precise and profound approaches with more illustrative prototypes along with the development of worthy prognostic biomarkers will provide a comprehensive understanding of how green tea polyphenol intermingles with the endogenous system (Transcriptional factors such as Nrf2) and other exogenous factors (Humidity, temperature, stresses).
4. Also, The Nrf2 pathway exhibited to play a crucial role in health adaptability and can become strong through specific dietary factors comprising different phytochemicals such as green tea, curcumin, resveratrol, and trace minerals such as Se, Mn, and Zn.
5. Definitive supposition regarding the beneficial effect of green tea polyphenol has to derive from well-made observational, different epidemiological and clinical studies, and intervention trials. The development of a biomarker as well as a molecular marker for green tea polyphenol utilization and its biological effects will provide future studies in this area.

Authors Contribution

Ibrar Muhammad Khan and Haji Gul: conceptualization, designing, reviewing and editing, data curation; Samiullah Khan: Visualized the study design; Nourhan Nassar: data curation, editing; Anam Khalid: data curation; Ayman Swelum, Zaigui Wang: supervision, manuscript review.

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Data availability statement

Not applicable.

Declaration of competing interest

No potential conflict of interest was reported by the author(s).

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