

Original Article

Garlic Powder Supplementary Diet Prevents Pulmonary Hypertension Syndrome by Reducing Apoptosis in Broiler Chickens

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ABSTRACT

Background: Pulmonary hypertension syndrome (PHS) is a metabolic disorder presenting with cardiopulmonary symptoms. However, garlic powder (GP) is used to treat many diseases, such as heart and lung diseases.

Objectives: This study investigated the effects of GP supplementary diet on apoptosis and right ventricle hypertrophy in broiler chickens with PHS.

Methods: Ninety meat-type chickens were randomly divided into three groups: Sham, PHS and PHS+GP. The PHS was induced by triiodothyronine (T3) in broiler chickens, and GP was added to the ration after week 1 of rearing (PHS+GP). Then, lung and ventricle tissues were collected at 21 and 49 days of age. PHS was calculated at 21 and 49 days based on the ratio of the right ventricle to the total ventricles (RV/TV) weight index. Gene expression of caspase1 (*CASP1*) and caspase2 (*CASP2*) were evaluated by semi-quantitative RT-PCR in the lungs and right heart ventricles.

Results: The findings showed that right ventricular hypertrophy increased at day 49 in the PHS group compared to sham ($P < 0.001$), while garlic consumption decreased this ratio to the control level ($P < 0.05$). Also, the expression of *CASP1* and *CASP2* in the lungs elevated on day 49 ($P < 0.001$), and the GP diet prevented this increase ($P < 0.05$). Moreover, in the right ventricle tissue, PHS affected *CASP1* on days 21 and 49, although the expression of *CASP2* significantly increased just at day 49 in the PHS group ($P < 0.001$). This increase in both times was weakened by garlic consumption ($P < 0.05$).

Conclusion: Consuming garlic as a dietary supplement could prevent PHS by influencing apoptosis in the lung and heart of broilers.

Keywords: Broiler, Caspase, Garlic powder, Pulmonary hypertension syndrome (PHS), Ross 308

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Introduction

Pulmonary hypertension syndrome (PHS) results from developments in both the respiratory and cardiovascular systems (Babaahmadi Milani et al., 2020). PHS is a metabolic disorder and multifactorial syndrome caused by interactions among environmental, physiological and genetic factors (Hosseini et al., 2021). Also, PHS is defined by hypoxemia, cardiopulmonary overload, venous and cardiac obstruction, and right ventricular hypertrophy (Dimopoulos et al., 2018). Heart failure is common in modern broilers with a high growth rate and the respiratory system cannot provide efficient ventilation and gas exchange, leading to hypoxia (Majidi Abdelfaraj et al., 2023). Increased levels of blood flow, stroke volume, cardiac output, vascular pressure in the pulmonary, right ventricular hypertrophy and pressure in the pulmonary arteries and capillaries are known as the result of compensatory effects of the cardiovascular system (Yadollah et al., 2023). This condition eventually causes PHS (Hassanpour et al., 2014). Studies have shown that during this syndrome, many oxidants are produced in the affected tissues (Hassanpour et al., 2015). Also, various studies investigated the most obvious environmental factors that play a role in PHS. These factors are altitude, cold stress, lighting, air quality, ventilation, high nutrient density rations, and incubation environment (Vandana et al., 2021; Ipek & Sahan, 2006; Ghiasi et al., 2023).

PHS involves complex processes and includes pathological pathways in vascular remodeling related to inflammation, vascular fibrosis, and apoptosis (Solano-Gálvez et al., 2018). Apoptosis typically occurs during growth and aging as a hemostatic mechanism to maintain tissue cell populations. Apoptosis is a defense mechanism in immune reactions or when disease damages cells (Kiraz et al., 2017). Apoptosis is a highly conserved process with multiple pathways involved in several physiological and pathological phenomena (Redza-Dutordoir & Averill-Bates, 2016; Solano-Gálvez et al., 2018). At the molecular level, major changes in this process consist of cell shrinkage, formation of apoptotic bodies, caspase activation, chromatin condensation, and eventually DNA fragmentation (Solano-Gálvez et al., 2018). The leading players in apoptosis orchestration are caspases, the special cysteine proteases with a proteolytic function (Nicholson & Thornberry, 1997). Caspases break down other cytoplasmic proteins containing aspartic acid residues (Nicholson & Thornberry, 1997). Elevation of both caspase1 (*CASP1*) (stimulated by inflammatory agents) and caspase2 (*CASP2*) could be used as evidence for the early steps of the apoptotic process (Igney & Krammer, 2002).

On the other hand, garlic has been a food supplement since ancient times. Various studies indicated garlic has preventive and therapeutic effects on many diseases, such as heart problems, intestinal disorders, atherosclerosis, thrombosis, dementia, cancer and diabetes (Sobenin et al., 2019; Ohtani & Nishimura, 2020). In addition, several experiments have reported garlic powder's (GP) antioxidant and anti-hypertensive properties in different animal models (Puvača et al., 2015; Wei & Lau, 1998). As a potent antioxidant, it protects cells against oxidative damage, reactive oxygen species (ROS) damage, and lipid peroxidation (Oloruntola et al., 2023; Askari et al., 2021; Yang et al., 2019).

So, the purpose of the study reported is to determine the protective effect of GP on the level of *CASP1* and *CASP2*, as important apoptosis markers, in the lungs and heart ventricles of broiler chickens following the PHS induction by triiodothyronine (T3).

Materials and Methods

Study animals

Ninety fast-growing 1-day-old chickens (Ross 308) were divided randomly into three groups (Sham, PHS, and PHS+GP). Each group consisted of 30 chickens with three replicate pens per group and ten chickens per pen under the same and controlled conditions, such as humidity, ventilation, temperature, light cycle and vaccination. During the experiments, the chickens were kept according to the instructions mentioned in the care and use of laboratory animals (Clark, 1997) and the Animal Care Committee of the Deputy of Medical Sciences, Islamic Azad University approved all the experimental steps. Chickens were reared in the floor pens (wood shaving litter) for three or seven weeks under standard conditions, with ad libitum access to water and a standard basal diet in mash form. In the second week, in the PHS and PHS+GP groups, thyroid hormone, i.e. T3 (Sigma Chemical Co.), was added to the diet (1.5 mg/kg). For the GP group, GP (1%) was used as a treatment after the first week of rearing (Hassanpour et al., 2014; Arab et al., 2006).

Assessment of right ventricular hypertrophy

During the breeding period, sampling was done on days 21 and 49 for the three groups (n=15). Sampling was carried out by cutting the carotid arteries and veins. Then, the abdominal area was opened, and the arteries connected to the heart were cut. Finally, the heart was removed from the chest. After examining the appearance

and weighing of the left and right ventricles (RV), the RV was dissected free of the left ventricle and septum. The weight of the RV was measured and the ratio of the RV to the total ventricle (RV/TV) weight was calculated (Hassanpour et al., 2014; Cueva et al., 1974; Wideman, 2001).

RNA extraction of lung and RV tissues

After collecting chickens' lungs and RVs, tissues were immediately immersed in liquid nitrogen and kept at -80 °C, where they were stored until RNA extraction. Total RNA was extracted from tissues using TRIzol reagent (Invitrogen, Karlsruhe, Germany). After the homogenizing tissues, chloroform was added to the mixture and centrifuged. The total RNA was settled in the upper aqueous phase. Isopropanol was used to precipitate RNA, and the RNA pellet was washed with ethanol (75%). The extracted RNAs were resuspended in DEPC-treated water. DNase was used to remove eventual residual DNA, and the RNA concentration was then measured and qualified by spectrophotometry and gel electrophoresis (Hassanpour et al., 2014).

Semi-quantitative RT-PCR

All primers used in the current study are listed in Table 1. A cDNA synthesis kit synthesized cDNA using reverse transcriptase, Oligo (dt) and random hexamer. A reverse transcription polymerase chain reaction (RT-PCR) was run, followed by 40 cycles. Beta-actin expression was measured as an endogenous control. Finally, the *CASP1* and *CASP2* expression ratio to the β -actin (*ACBT*) was calculated using Photo-Capt Image Software, version 99. The density of bands was calculated and relative densities were expressed as *CASP1/ACBT* and *CASP2/ACBT* (Hassanpour et al., 2011; Teshfam et al., 2006).

Statistical analysis

The results of the experiments were presented as Mean \pm SEM. The statistical analysis was carried out using GraphPad Prism Software, version 6. Comparisons were made between sham, PHC and PHC+GP using the

one-way analysis of variance (ANOVA). $P < 0.05$ was considered a significant difference among groups.

Results

Effect of GP on right ventricular hypertrophy

The ratio of RV/TV as an indicator of right ventricular hypertrophy and pulmonary hypertension was measured in different groups on days 21 and 49 (Figure 1). Our data showed no significant difference between all groups on day 21 ($P \leq 0.05$). Surprisingly, this ratio increased on day 49 in the PHS group by about 1.74-fold compared to the sham group ($P < 0.001$). Also, treatment with GP decreased RV/TV to 69.18% compared to the PHS group ($P < 0.001$). Besides, an increase of about 1.2-fold was seen in the PHS+GP group compared to the sham ($P < 0.05$).

Effect of GP on the expression of *CASP1* and *CASP2* in the lungs of PHS chickens

Gene expression of *CASP1* and *CASP2* was determined by semi-quantitative RT-PCR in broiler chicken lungs of different groups, as shown in Figure 2. A one-way ANOVA analysis of *CASP1* and *CASP2* expressions in the lung showed no significant change between sham, PHS, and PHS+GP groups on day 21 ($P \leq 0.05$).

However, our result showed an increase of about 2.97 and 2.51 folds in the *CASP1* and *CASP2* expressions of PHS compared to the sham group on day 49 ($P < 0.001$). Also, consumption of GP (PHS+GP group) significantly reduced the ratio of *CASP1* and *CASP2/ACBT* to about 42.01% and 40.6% compared with PHS, respectively ($P < 0.001$). Besides, the *CASP1* expression of this group (PHS+GP) increased by about 1.25 folds compared to the sham ($P < 0.05$).

Effect of GP on the expression of *CASP1* and *CASP2* in the RVs of PHS chickens

RT-PCR determined the expression of *CASP1* and *CASP2* genes in broiler chickens' RVs in treated and untreated groups (Figure 3). On day 21, our result re-

Table 1. Primer sequences of *CASP1*, *CASP2* and *ACBT*

| Gene | 5'-primer | 3'-primer | Annealing Temperature | Size of PCR Product |
|--------------|-----------------------|------------------------|-----------------------|---------------------|
| <i>ACBT</i> | ACTGGATTCGAGCAGGAGAT | TTAGAAGCATTTCGGTGGACAA | 60 °C | 468 bp |
| <i>CASP1</i> | CGGCCAGCGCCATCTTCATT | AGGGAGCTGTACAGTGCGT | 64 °C | 347 bp |
| <i>CASP2</i> | TGGCACTGATGGCAAACCTCC | ATCGGAGCGGTAGGCAAAC | 64 °C | 238 bp |

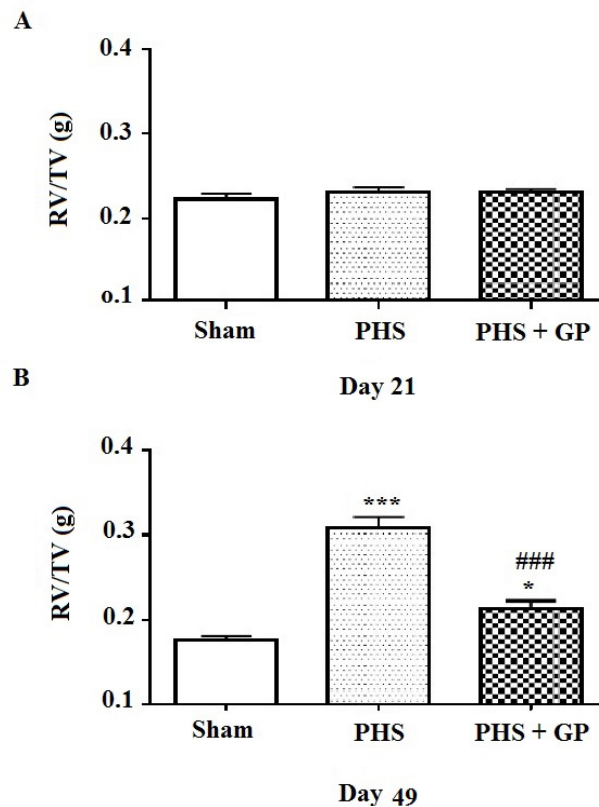


Figure 1. Effect of garlic powder on right ventricular hypertrophy of broilers

A) Effect of garlic powder on the ratio of RV/TV weight of broilers at day 21 in the broilers, B) Effect of garlic powder on the ratio of RV/TV weight of broilers at day 49 in the broilers

Notes: All data values are expressed as Mean±SEM (one-way ANOVA with Tukey's multiple comparison test). *P<0.05, ***P<0.001 compared with sham group, ###P<0.001 compared with PHS group.

vealed that the expression of *CASP1* in the PHS group increased by about 1.04 folds compared to the sham group (P<0.001). Also, this gene in the PHS+GP group was significantly decreased to 62.5% compared with the PHS group (P<0.001). At the same time, the ratio *CASP2/ACBT* did not show any significant alterations in all three groups on day 21 (P≤0.05) (Figure 3A and 3B).

Moreover, one-way ANOVA analysis of day 49 results indicated the expression of *CASP1* and *CASP2* elevated in the PHS group by about 2.25 and 1.34 folds compared to the sham group, respectively (P<0.001). Also, the consumption of GP (PHS+GP group) could decrease the ratio of *CASP1/ACBT* and *CASP2/ACBT* to about 52.0% and 44.67% when compared to the PHS group (P<0.001). Besides, the comparison of PHS+GP with sham showed an increase of about 1.19 and 1.51 folds for *CASP1* (P<0.05) and *CASP2* (P<0.01) genes, respectively (Figure 3C and 3D).

Discussion

In the present study, we evaluated the effect of GP treatment as an antioxidant during the PHS in fast-growing chickens. To propose a molecular mechanism, we assessed the anti-apoptotic effect of GP on the reduction of *CASP1* and *CASP2* gene expressions in the lung and RV of chickens.

Broilers have an innate potential to cause PHS. Consistent with the experiment of Wideman (2001), our result showed that increasing the RV/TV ratio can be detected during PHS. Studies reported a positive relation between hypertrophy of right ventricular and pulmonary arterial pressure. Based on our results, using GP as a treatment could modulate pulmonary hypertensive response and decrease hypertrophy and dilation of the heart. Allicin is an effective garlic material, and experiments have reported that allicin in garlic could prevent coronary endothelial dysfunction and RV hypertrophy (El-Sheakh et al., 2006). In addition, Sobenin et al. (2009) observed

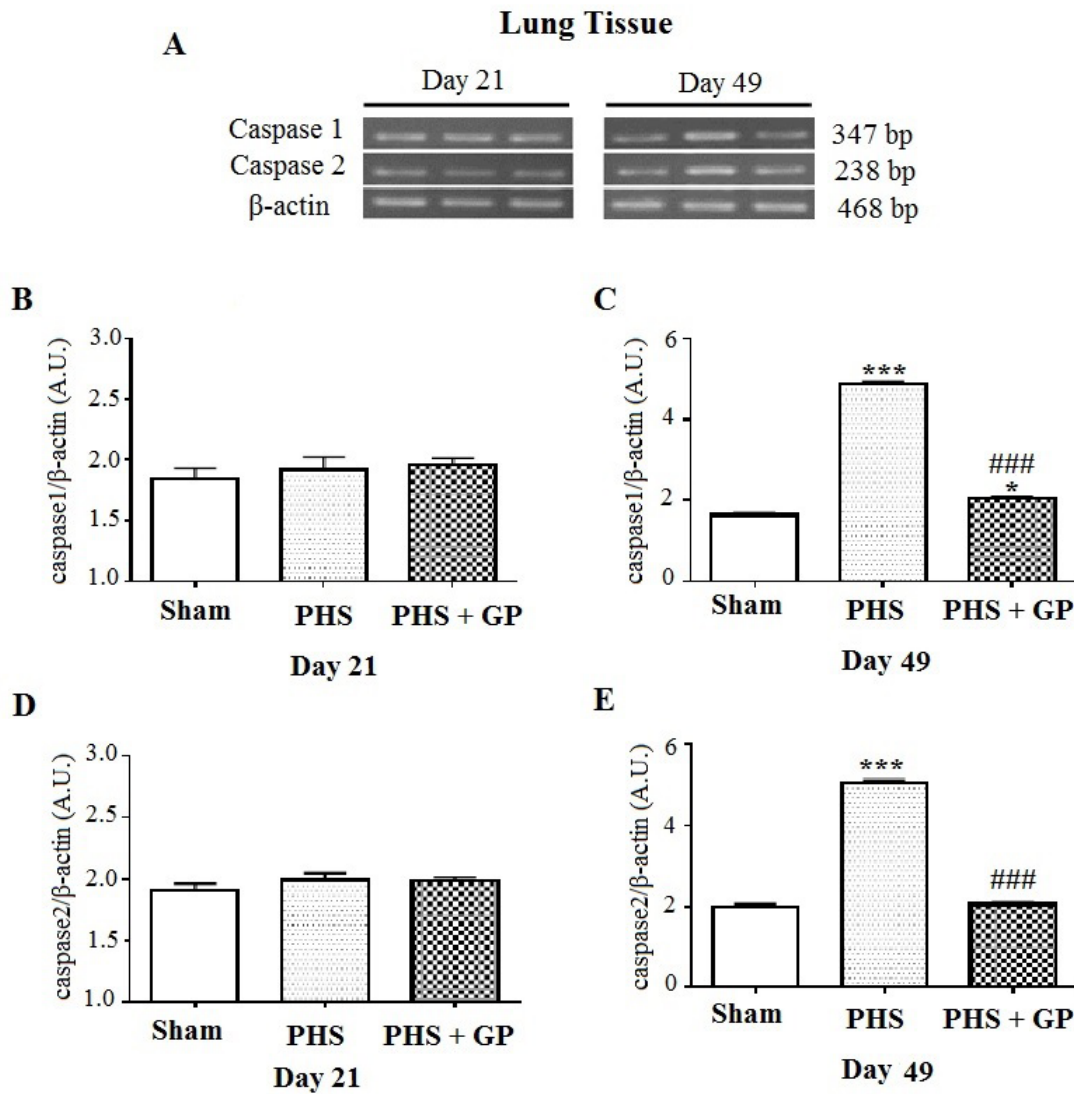


Figure 2. Effect of garlic powder on *CASP1* and *CASP2* expressions in the lung tissue of broilers at days 21 and 49

A) Effect of garlic powder on the ratio of *CASP1/ACBT* expression in the lung tissue of broilers at day 21, B) Effect of garlic powder on the ratio of *CASP1/ACBT* expression in the lung tissue of broilers at day 49, C) Effect of garlic powder on the ratio of *CASP2/ACBT* expression in the lung tissue of broilers at day 21, D) Effect of garlic powder on the ratio of *CASP2/ACBT* expression in the lung tissue of broilers at day 49

Notes: All data values are expressed as Mean±SEM (one-way ANOVA with Tukey's multiple comparison test). *P<0.05, ***P<0.001 compared with sham group, ###P<0.001 compared with PHS group.

that garlic can reduce systolic and diastolic blood pressure and may defend the heart against hypertrophy. Several mechanisms of action have been proposed for the GP effect on blood pressure, including the release of nitric oxide, a vasodilatory factor.

Apoptosis occurs in the cells during both physiological and pathological conditions. Over the past few decades, many studies have shown that apoptosis may be an essential cell death method during cardiomyopathies

in both human and animal models (Pertiwi et al., 2022; Blondeau et al., 2019). Wideman (2001) introduced a threshold for RV/TV ratio as an indicator to cause PHS, and our results did not reach the threshold at day 21 (P≤0.05). Maybe it was because we also did not see a considerable change in the apoptosis at day 21. Also, evidence demonstrated susceptibility to apoptosis in ventricle hypertrophy rises with age (Kim et al., 2005).

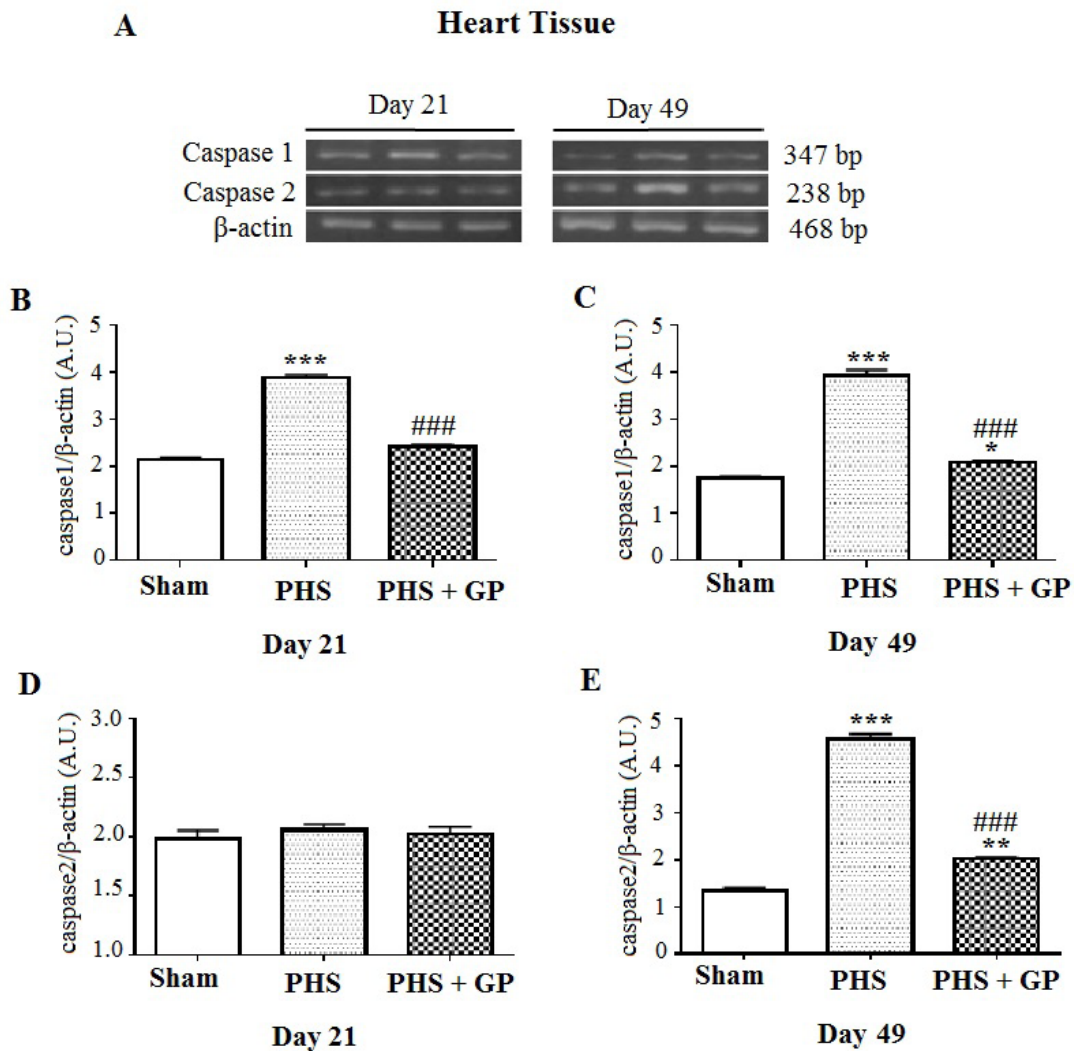


Figure 3. Effect of garlic powder on *CASP1* and *CASP2* expressions in the right ventricle tissue of broilers at days 21 and 49

A) Effect of garlic powder on the ratio of *CASP1*/*ACBT* expression in the right ventricle tissue of broilers at day 21, B) Effect of garlic powder on the ratio of *CASP1*/*ACBT* expression in the right ventricle tissue of broilers at day 49, C) Effect of garlic powder on the ratio of *CASP2*/*ACBT* expression in the right ventricle tissue of broilers at day 21, D) Effect of garlic powder on the ratio of *CASP2*/*ACBT* expression in the right ventricle tissue of broilers at day 49

Notes: All data values are expressed as Mean \pm SEM (one-way ANOVA with Tukey’s multiple comparison tests). *P<0.05, **P<0.01, ***P<0.001 compared with sham group, ###P<0.001 compared with the PHS group.

Our results showed that PHS induction during 49 days increased the expression of *CASP1* and *CASP2* genes in chickens’ lungs and RV (P<0.001). These results approved our previous work that showed apoptosis increased in the heart and lungs of broiler chickens suffering PHS at day 49 (Hassanpour et al., 2014). The release of cytochrome C from the mitochondria into the cytoplasm and the cleavage and activation of caspases initiate the onset of the apoptotic pathway. Eventually, caspase activation leads to the fragmentation of various cytoplasmic proteins and DNA (Kang & Izumo, 2000). Studies on animal experi-

mental models and human tissues have reported an essential role for *CASP1* in developing heart failure as a potent proapoptotic agent (Merkle et al., 2007). It has also been observed that due to heart failure, the expression of the *CASP2* gene is increased in the ventricle, which is a sign of apoptosis (Heinke et al., 2001).

On the other hand, progressive hypoxia occurs in the chickens’ tissues with pulmonary hypertension and can increase the free radicals and oxidant levels of affected tissues. As free radicals have been reported to be essen-

tial in activating caspases and inducing apoptosis (Solaño-Gálvez et al., 2018), using a potent antioxidant seems to be a promising treatment option for PHS.

Since ancient times, garlic has been widely used as a food additive or growth promoter and as a medicinal plant to prevent and treat many heart diseases. Our investigation revealed that it can be effective as a therapeutic supplement for PHS by reducing the RV hypertrophy and apoptosis gene expression, including *CASP1* and *CASP2*. Garlic has many bioactive ingredients such as allicin, alliin, ajoene, diallyl sulfide, dithiin and S-allyl cysteine that could target different molecular pathways and be used as a natural herbal food additive to improve the growth of broilers (Ziarlarimi et al., 2011; Khan et al., 2012). Garlic can act as a nitric oxide donor and also have a relaxing effect directly on the aortic and heart muscles (Sobenin et al., 2009). In addition, garlic affects blood pressure by inhibiting Na/K-ATPase in the kidney, which triggers diaphasic urinary and natriuretic responses. It has been reported that garlic components may increase membrane polarization through potassium ion channels that close Ca²⁺ channels, leading to cell death inhibiting (Sobenin et al., 2009). Gao et al. (2021) show that GP consumption can down-regulate the expression of caspase genes. Approving our results, Ismail et al. (2021) demonstrated that the consumption of GP as a supplementary diet positively affected performance, safety, antioxidant level, and physiological characteristics of broilers.

Conclusion

Taken together, our investigation revealed that GP can be used as a supplementary diet to prevent PHS complications, reduce RV hypertrophy, and decrease apoptosis in the hearts and lungs of broilers.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Islamic Azad University, Garmsar Branch.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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مطالعه پژوهشی

جیره مکمل پودر سیر با کاهش آپوپتوز در جوجه‌های گوشتی از سندرم پرفشاری خون ریوی جلوگیری می‌کند

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چکیده

زمینه مطالعه: سندرم پرفشاری خون ریوی (PHS) یک اختلال متابولیک با علائم قلبی ریوی است. همچنین پودر سیر (GP) یک ماده غذایی است که برای درمان بسیاری از بیماری‌ها مانند بیماری‌های قلبی و ریوی استفاده می‌شود.

هدف: این مطالعه باهدف بررسی اثرات جیره مکمل پودر سیر بر آپوپتوز و هیپرتروفی بطن راست در جوجه‌های گوشتی مبتلا به PHS انجام شد.

روش کار: در این مطالعه ۹۰ قطعه جوجه گوشتی به‌طور تصادفی در سه گروه شم، PHS و PHS+GP تقسیم شدند. PHS توسط تری‌یدوتیرونین (T3) در جوجه‌های گوشتی القا شد و GP پس از هفته اول پرورش (PHS+GP) به جیره اضافه شد. سپس بافت‌های ریه و بطن در سنین ۲۱ و ۴۹ روزگی جمع‌آوری شدند. PHS در روزهای ۲۱ و ۴۹ براساس نسبت وزن بطن راست به کل بطن (RV/TV) محاسبه شد. بیان ژن کاسپاز ۱ (CASP1) و ۲ (CASP2) با روش RT-PCR نیمه‌کمی در ریه‌ها و بطن‌های راست قلب ارزیابی شد.

نتایج: یافته‌ها نشان دادند هیپرتروفی بطن راست در روز ۴۹ در گروه PHS نسبت به شم افزایش یافت ($P < 0.001$)، درحالی‌که مصرف سیر این نسبت را به سطح شاهد کاهش داد ($P < 0.05$). همچنین، بیان CASP1 و CASP2 در ریه‌ها در روز ۴۹ افزایش یافت ($P < 0.001$) و رژیم غذایی GP از این افزایش جلوگیری کرد ($P < 0.05$). علاوه‌براین، در بافت بطن راست، PHS بیان CASP1 را در روزهای ۲۱ و ۴۹ تحت تأثیر قرار داد، اگرچه بیان CASP2 به‌طور قابل توجهی در روز ۴۹ در گروه PHS افزایش یافت ($P < 0.001$). این افزایش در هر دو زمان با مصرف سیر تضعیف شد ($P < 0.05$).

نتیجه‌گیری نهایی: بنابراین می‌توان نتیجه گرفت که مصرف سیر به‌عنوان مکمل غذایی می‌تواند با تأثیر بر آپوپتوز ریه و قلب جوجه‌های گوشتی از بروز PHS جلوگیری کند.

کلیدواژه‌ها: جوجه‌های گوشتی، کاسپاز، پودر سیر، سندرم پرفشاری خون ریوی، راس ۳۰۸

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