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Effects of intravenous injection of glycyrrhizin on serum biochemical parameters and appetite in inflamed Arian broiler chickens

Short running title: Effects of glycyrrhizin on inflamed Arian broilers

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Abstract

Background: The broiler chicken population is currently facing a pressing issue in the form of bacterial infections, which significantly impact their growth and developmental processes. Glycyrrhizin (**GL)** a compound discovered in licorice, is a unique and versatile compound with a range of psycho-chemical properties that contribute to its diverse biological activities. It also has immunomodulatory, anti-inflammatory, antiviral, hepatoprotective, anticancer, and anti-inflammatory properties, contributing to overall poultry health.

Objectives: GL may modulate appetite and serum markers by mitigating inflammation in chickens.

Methods: The study investigated the effects of GL and LPS on broilers. 24 one-day-old male Arian broiler chickens (Simorgh Co., Mashhad, Iran) were divided into 4 groups: a control group and 3 treatment groups receiving lipopolysaccharide (**LPS**) alone or with GL at 2 different dosages. Treatments were administered intravenously on day 20, and feed intake and blood samples were monitored.

Results: LPS injection significantly reduced feed intake compared to the control group at 4.5, 5, and 6 h. after injection ($P < 0.05$). Furthermore, the co-administration of LPS+GL resulted in a dose-dependent increase in cumulative feed consumption compared to the LPS group at 4.5, 5, and 6 h. following the injection. Additionally, the groups treated with LPS and GL showed reduced activity of AST and ALT enzymes relative to the group that received only LPS, suggesting that GL may exert a hepatoprotective effect. GL was found to mitigate the negative effects of LPS and improve the A/G ratio, highlighting its potential as an anti-inflammatory agent.

Conclusion: GL positively influences appetite and liver function in inflamed Arian broilers.

Keywords: Arian broiler**,** Glycyrrhizin, Lipopolysaccharide, Appetite, Biochemical parameters

Introduction

The poultry industry has experienced significant growth and expansion over the past two decades, playing a crucial role in bridging the gap between the demand for high-quality protein and its supply for human consumption. The increasing demand for high-quality, disease-free protein sources has led to a heightened emphasis on the importance of sustainable and safe poultry production systems (Qui et al., 2024). Despite the poultry industry's efforts to address these concerns, it continues to face significant challenges in the form of various diseases, such as bacterial and viral infections, that can impact the health and well-being of both the birds and consumers (Rafiq et al., 2022; Partovi et al., 2021).

Numerous studies have been conducted on the significance of combating infections in broilers, highlighting the critical nature of this issue (Boroomand et al., 2023; Eshaghniya et al., 2024). Broiler chickens are facing an increasing challenge in the form of bacterial diseases, which significantly impede their growth and development (Gholipour-Shoshod et al., 2023; Morovati et al., 2022). Lipopolysaccharide **(LPS)**, a crucial component of the cell wall of Gram-negative bacteria, plays a pivotal role in the pathogenesis of these diseases (). LPS can induce oxidative stress and inflammation in poultry, which can compromise their antioxidant capacity and trigger the production of pro-inflammatory cytokines (Leshchinsky & Klasing, 2001). The multifaceted impact of LPS on poultry health underscores the importance of understanding its role in bacterial diseases and developing effective strategies to mitigate its effects, ultimately ensuring the sustainability of the poultry industry (Pang et al., 2023). LPS plays a crucial role in triggering cell and tissue damage, ultimately leading to the development of multiple organ dysfunction and various histopathological changes (Ding et al., 2018; Zhang et al., 2020). Studies have shown that exposure to lipopolysaccharides (LPS) leads to a decrease in antioxidant levels and the activity of antioxidant enzymes, while simultaneously elevating the levels of pro-inflammatory factors (Zheng et al., 2016).

The central nervous system is particularly affected by LPS, which can lead to changes in feeding behavior and overall nutritional status (Ghiasi et al., 2023; Yousefvand et al., 2018). The hypothalamus is recognized as the pivotal brain region governing feed intake (Yousefvand & Hamidi, 2020; Emadi et al., 2021). It assimilates signals emanating from the gastrointestinal tract, pancreas, hepatic system, adipose structures, and diverse cerebral regions (Yousefvand & Hamidi, 2022). Existing research has elucidated a significant interrelation among the immunological, neuronal, neurohumoral, endocrine, and neuroendocrine networks within the central nervous system that coordinate nutritional ingestion in the context of bacterial infections (Zendehdel et al., 2013).

LPS significantly affect nutrition and weight by causing decreased feed intake and weakness in animals. This can lead to disorders such as anorexia and fever due to its inflammatory effects. Medicinal plants are extensively studied for their various benefits such as anti-inflammatory, analgesic, and antioxidant properties (Zendehdel et al., 2012). *Glycyrrhiza glabra*, commonly known as licorice, has been utilized as a therapeutic agent for inflammation. Research has demonstrated that supplementing licorice in chicken diets can enhance their growth performance by influencing the expression of genes related to growth, lipid metabolism, and antioxidant pathways, thereby modulating the antioxidant activity in avian species (Toson et al., 2023). Licorice root extract contains up to 25% glycyrrhizin (**GL**). **GL**, the main active compound in licorice root, has been shown to have beneficial effects on inflammation (Li et al., 2014). GL and glycyrrhetinic acid have demonstrated efficacy in inhibiting the growth of gram-positive organisms, including *Bacillus subtilis* and *Staphylococcus aureus*, and gram-negative pathogens such as *Escherichia coli* and *Pseudomonas aeruginosa*. This suggests a broad-spectrum antibacterial potential for these compounds (Langer et al., 2016; Nitalikar et al., 2010). The administration of GL to broilers led to an increase in body mass and an improvement in the feed conversion ratio (FCR) compared to the control group (Ocampo et al., 2016). The precise correlation between GL intake and food consumption remains unclear in Arian broilers. The hypothesis of the current study was that the administration of GL would have positive effects on inflammation in Arian broiler chickens challenged with LPS. To address this knowledge gap, our study aimed to examine the influence of GL administration on the appetite and serum biochemical markers in Arian broiler chickens challenged with LPS..

Materials and Methods

Ethical Considerations

The research was conducted with the ethical principles and the national norms and standards for conducting medical research in Iran (IR.UM.REC.1402.221).

Reagents, animals, and experimental design

LPS (Escherichia coli 055:B5) was obtained from Sigma-Aldrich Chemical Co. (#L2880; St. Louis, MO, USA). The LPS was dissolved in a sterile 0.9% NaCl solution (1 mg LPS/mL saline). Also, GL with a purity of ≥98% was purchased from Sigma-Aldrich.

A total of 24 one-day-old male Arian broiler chickens (Simorgh Co., Iran) were randomly assigned to four treatment groups, with each group consisting of six birds, in a completely randomized design. The birds were reared in standard environmental conditions at 22 ± 1 °C, 50% relative humidity, and continuous lighting (Olanrewaju et al., 2006). The birds were provided access to mash feed and water ad libitum during the 21 days of the study. The chemical composition of the diets and additives is detailed in Table 1. The broiler chicks were randomly allocated into 4 groups: 1) Control (normal saline), 2) 1 mg/kg LPS, 3) 1 mg/kg LPS + 40 mg/kg GL, 4) 1 mg/kg LPS + 80 mg/kg GL. When the chicks reached a weight of 700 g at 20 days old, groups 2, 3, and 4 received an intravenous (IV) injection of LPS and GL, while the control group was administered a saline solution of equal volume (0.9%) as a placebo. The health condition of the animals was monitored daily throughout the study using standard diagnostic methods. In this study, all doses of GL and LPS were determined based on previous studies (Mano et al., 2023; Tan et al., 2014; Tsai et al., 1992).

Table 1. Chemical composition of the used broiler diets and additives in the diets.

Item	**Pre- starter (1 to 12 days)**	**Starter (13 to 24 days)**
Ingredients		
Corn	58.35	59.01
Soybean meal	33.02	33.00
Soy oil	1.16	2.16
Corn gluten meal	3.18	2.00
$CaHPO_4$	2.00	1.65
Limestone	1.25	1.25
Nacl	0.36	0.36
DL-Methionine	0.28	0.17
L-Lys	0.20	0.20
Vitamin premix	0.10	0.10
Mineral premix	0.10	0.10
Total	100	100
Calculated nutrient content		
ME, calculated (kcal/kg)	3000	3000
CP	21.21	21.00
Calcium	0.96	0.91
Available phosphorus	0.46	0.40
Lys	1.15	1.15
Met	0.57	0.50
TSAA	0.86	0.86
Thr	0.78	0.73
Trp	0.22	0.22

Measurement of feed intake

After the injections, chicks were deprived of food for 3 hours. Then, they were transferred to separate cages. Fresh food and water were provided, and cumulative feed intakes were recorded at 3.5, 4, 4.5, 5, and 6 hours after the injection. The body weight of the chickens was measured before they were placed in individual cages.

Serum biochemistry

Blood samples were taken from the vein under the wing eight hours after injection and placed in 5 mL Vacutainer tubes without anticoagulant. The tubes were then centrifuged at 3,000 × g for 10 minutes at 4°C, and the resulting serum was collected and stored at -80°C for further analysis. Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein (TP), albumin, globulin, and the albumin to globulin ratio (A/G) were measured using the BS-800 chemistry analyzer from Shenzhen Mindray (Bio-medical Electronics Co., China).

Body temperature

In group 2, the rectal temperature of each chick was measured before and at 1, 3, 5, and 8 hours after the injection of LPS using a digital thermometer. The tip of the thermometer was inserted at least 2 cm into the cloaca.

Statistical analysis

All data were preliminarily processed using the Excel 2016 software. Statistical analyses were performed using the statistical software SPSS 25.0, and the results are presented as mean ± SEM. Statistical analyses were performed using one-way analysis of variance (ANOVA) followed by Tukey's test. Differences were considered statistically significant at $P < 0.05$.

Results

Cumulative feed intake

The feeding response to IV injection of LPS and GL in Arian broilers is shown in Figure 2. IV injection of 1 mg/kg doses of LPS significantly reduced feed intake compared to the control group at 4.5, 5, and 6 h. after injection ($P < 0.05$). In addition, IV injections of LPS+GL (at doses of 40 and 80 mg/kg) resulted in a dose-dependent increase in cumulative feed consumption compared to the LPS group at 5 and 6 h. following the injection ($P < 0.05$). There were no notable differences observed in any of the groups compared to the control group at 3.5 and 4 hours post-injection ($P > 0.05$).

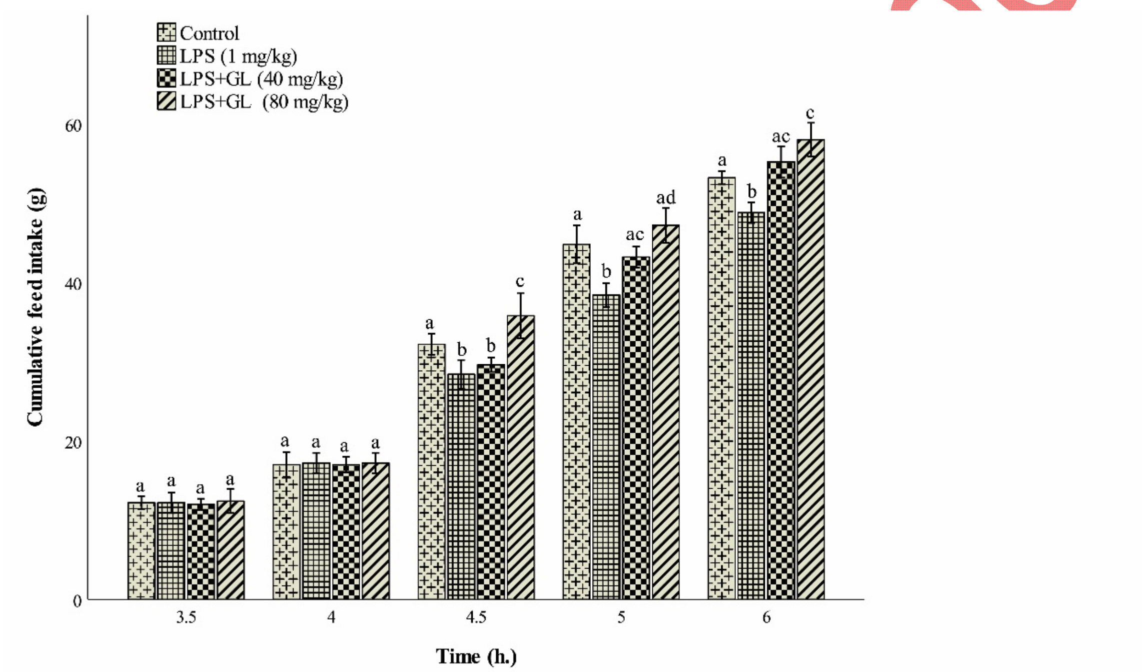

Figure 1. Effects of IV injection of control solution, lipopolysaccharides (LPS), and LPS+ glycyrrhizin (GL) on cumulative feed intake in Arian broilers. Data are expressed as the mean ±

SEM. Different letters (a, b, c, and d) indicate significant differences between treatments at each time (*P*< 0.05).

Effect of IV injection of LPS on rectal temperature

As shown in Figure 3, rectal temperature significantly changed at 1, 3, 5, and 8 hours after injection in the LPS group compared to the control group. After administering LPS, the body temperature initially dropped below the normal range and then rose above it.

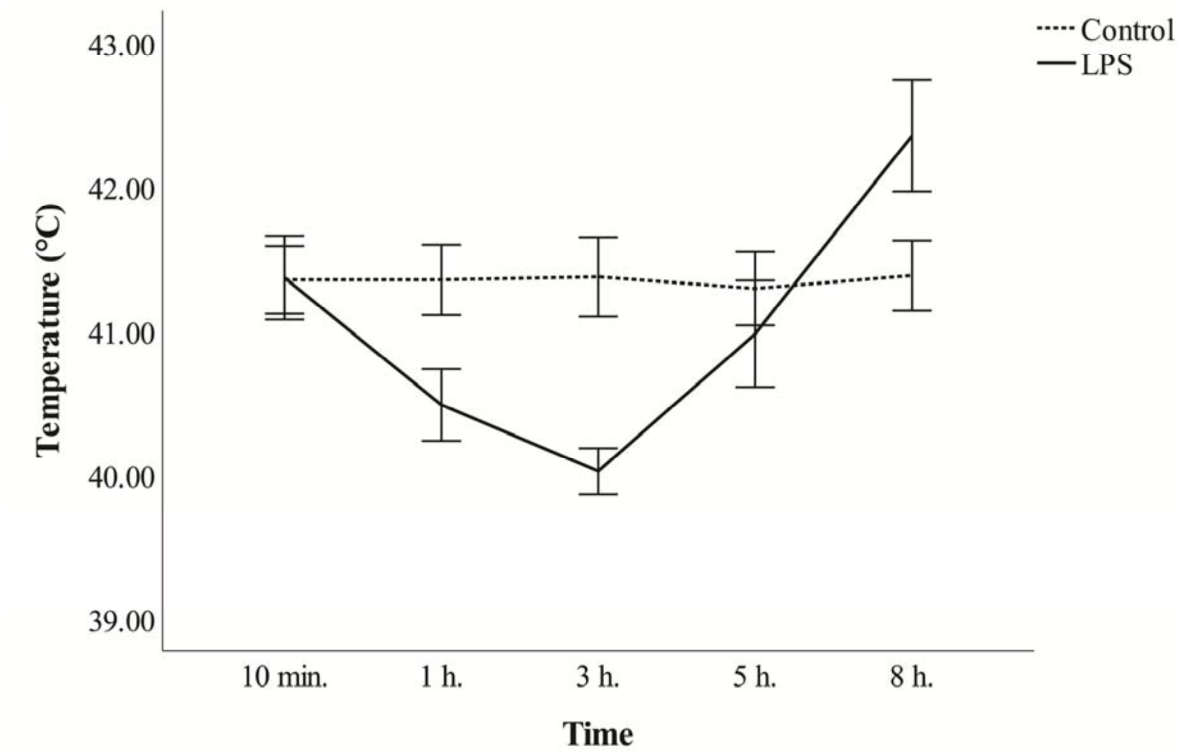

Figure 2. The effect of IV injection of LPS on rectal temperature was measured at 10 minutes before injection, 1 hour, 3 hours, 5 hours, and 8 hours after injection.

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Serum biochemical parameters

As shown in Table 2, serum biochemical indicators exhibited significant differences 8 hours after the injection. The serum biochemical indicators of AST and ALT were significantly higher in the LPS group than in the other groups ($P< 0.05$). In contrast, the GL groups displayed significantly decreased AST and ALT activity compared to the LPS group ($P< 0.05$). In this regard, the results showed that ALP indicators did not differ significantly among the four groups ($P> 0.05$). In the LPS+GL groups, the TP content was higher than that of the LPS and control groups ($P< 0.05$). Furthermore, the LPS group showed significant reductions in albumin concentrations compared to the other groups ($P< 0.05$). On the other hand, the level of globulin showed a significant increase in the LPS group compared to other groups.

Table 2. Effects of GL on some serum biochemical parameters of LPS-stimulated broilers.

Groups	ALT (U/L)	AST (U/L)	ALP (U/L)	TP (g/dL)	Albumin (g/dL)	Globulin (g/dL)	A/G
Control	3.26 ± 0.018^{a}	261 ± 4.35^{a}	18.73 ± 0.61	3.30 ± 0.038^{a}	1.99 ± 0.037^{a}	1.76 ± 0.036^{a}	1.12 ± 0.020^{a}
LPS	3.40 ± 0.043^{b}	291 ± 3.72^{b}	18.60 ± 0.52	3.31 ± 0.033^{a}	1.88 ± 0.037^{b}	2.17 ± 0.029^{b}	0.87 ± 0.023^{b}
LPS+GL (40)	3.34 ± 0.013^{bc}	275 ± 5.00^{ab}	18.36 ± 0.60	3.44± 0.062^{a}	2.10 ± 0.042^{a}	1.71 ± 0.028^{a}	1.23 ± 0.039^{ac}
LPS+GL (80)	3.24 ± 0.024^{ac}	267 ± 3.72^{ac}	18.43 ± 0.51	3.49 ± 0.038^{b}	210 ± 0.034^{a}	1.67 ± 0.015^{a}	1.25 ± 0.023^{c}

ALT = alanine transaminase; AST = spartate transaminase; ALP = alkaline phosphatase; TP = serum total protein; A: G = albumin to Globulin ratio.

Control, intravenous administration of normal saline (0.9%); LPS, intravenous administration of 1 mg/kg LPS; LPS+GL (40) (80), intravenous administration of 1 mg/kg LPS + 40 mg/kg or 80 mg/kg GLA, respectively.

Values were expressed as means ± SEM (Standard error of means).

[a,b,c]Means within rows without the same superscript are significantly different ($P < .05$).

Discussion

The growth performance of animals raised in unsanitary environments is believed to be negatively impacted by an overactive immune response, characterized by inflammation. This response is associated with decreased feed intake, reduced muscle protein synthesis, and the diversion of energy and protein resources towards defense mechanisms, ultimately leading to impaired growth (Cook, 2011; KC, 1988). The findings from our experiment indicated that IV administration of LPS led to a decrease in feed intake compared to the control group at 4.5, 5, and 6 min. post-injection. In a related investigation, researchers discovered that intracerebroventricular (ICV) and intraperitoneal (IP) injections of LPS significantly decreased feed consumption in chickens (Ghiasi et al., 2023). Our results showed a significant dose-dependent increase in cumulative feed intake in the LPS+GL groups compared to the LPS group at 4.5, 5, and 6 h. after administration. The results also indicate that the feeding response to IV injection of LPS and GL is time-dependent, with notable differences observed at specific hours post-injection. In another study, the use of GL as an additive in the drinking water of broiler chickens has been investigated as a potential strategy to enhance both production and health outcomes in the flock. Furthermore, they found that broiler chickens treated with 0.03% GL showed statistically significant improvements in weight gain (7.6% higher) and feed conversion ratio compared to non-treated controls. Additionally, the mortality rate among treated birds was reduced from 8.17% to 5.95% (Ocampo et al., 2016).

The study on the effect of IV injection of LPS on rectal temperature reveals significant changes in body temperature, initially dropping below the normal range and then rising above it. This suggests that LPS may cause a stress response in the chickens, leading to changes in body temperature. Endotoxin-induced fever has been observed across various species, including chickens (Wang et al., 2022). Consistent with our research, chickens have exhibited elevated body temperatures and a loss of appetite after injection of LPS (Johnson, 1998). Research by De

Boever et al. (2008) focused on the impact of LPS on body temperature in broiler chickens. Following the administration of a potent LPS dose, the chicken's body temperature initially decreased below normal levels before rising. This phenomenon has been corroborated by other studies that examined the effects of IV and IP injections of LPS in chickens (Uyanga et al., 2022; Xie et al., 2000).

The analysis of serum biochemical indicators in the study reveals significant differences in AST and ALT levels among the groups. The LPS group exhibited higher AST and ALT activity compared to the GL groups, indicating potential liver damage (Hong et al., 2023). In this regard, the results of other studies showed that IP injection of LPS increases ALT and AST levels (Yu et al., 2017). In contrast, the GL groups displayed decreased AST and ALT activity, suggesting a protective effect of GL on liver function. Also, GL exhibits advantageous pharmacological properties, such as anti-ulcer, anti-inflammatory, and antioxidant capabilities. It is recognized for its effectiveness as a liver-protecting agent (Orazizadeh et al., 2014). Furthermore, a study conducted by Yu et al. (2017) demonstrated that GL can reduce the activities of ALT and AST, thereby mitigating the potential damage to hepatic cells.

The ratio of albumin to globulin (A/G ratio) is a significant parameter in the assessment of the health and physiological status of broiler chickens. The A/G ratio is an important indicator of the immune status, as globulins are involved in the immune response, and a lower ratio may suggest an active immune response or inflammation (Sugiharto et al., 2024). In confirming the present study's findings, the LPS-challenged groups exhibited a significant alteration in the A/G ratio, with a marked increase in globulin levels, indicative of an inflammatory response (Pang et al., 2023). Our research findings indicate that glycyrrhizin possesses the capacity to ameliorate the adverse impacts induced by LPS while concurrently augmenting the A/G ratio. This suggests a potential therapeutic role for GL in the modulation of inflammatory responses. In line with our study, glycyrrhizin counteracts the inflammatory cascade triggered by LPS and its effect on the A/G ratio through modulation of specific signaling pathways (Chen et al., 2022).

The present study identified variations in serum protein patterns among the different groups. The results also show significant reductions in albumin concentrations in the LPS group, which could be indicative of liver damage or inflammation. Moreover, the increase in globulin levels in the LPS group may be related to the immune response to LPS. It should be emphasized that numerous pathological conditions are often associated with minor or more significant changes in serum protein profiles, including variations in the concentrations of albumin and globulins (Kaneko, 1997). The exposure of broilers to LPS triggers an immune response that compromises their growth, primarily due to the disruption of protein metabolism within the body (Nawaz et al., 2021). As a result, the nutrients that would normally support growth are redirected to combat the inflammatory response, ultimately hindering the growth performance of the broilers. In the context of the acute-phase response, serum albumin is a prominent negative acute-phase protein (APP) whose synthesis is diminished during inflammation. This phenomenon is attributed to the heightened demand for amino acids to produce positive APPs, which necessitates a reorganization of hepatic protein synthesis. In line with the current study's results, albumin production is downregulated, and amino acids are redirected towards the synthesis of positive APPs, thereby reflecting the body's adaptive response to inflammation (Abdullah, 2021).

Conclusion

In conclusion, the effects of GL on feed intake and serum biochemical parameters in inflamed Arian broiler suggest that LPS has negative effects and GL may have a positive impact on feed intake and liver function in broiler chickens under certain conditions. Further research is needed to fully understand the mechanisms underlying these effects and to explore the potential applications of GL in poultry nutrition and health management.

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تأثیر تزریق وریدی گلیسیریزین بر پارامترهای بیوشیمیایی سرم و اشتها در جوجه های گوشتی ملتهب شده آرین

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چکیده

زمینه مطالعه: جوجه های گوشتی در حال حاضر با یک چالش مهم در قالب عفونت‌های باکتریایی مواجه هستند که به طور قابل توجهی بر روند رشد و نمو آن‌ها تأثیر می‌گذارد. گلیسیریزین (GL)، یک ترکیب مهم در ریشه شیرین بیان همراه با طیف وسیعی از خواص بیوشیمیایی، با بهبود کارایی غذا و رشد اندام، عملکرد رشد جوجه‌های گوشتی را افزایش می‌دهد. همچنین دارای خواص تعدیل کننده ایمنی و ضد التهابی، ضد ویروسی، محافظت از کبد و ضد سرطان است که به سلامت کلی طیور کمک می‌کند.

هدف: گلیسیریزین ممکن است اشتها و پارامترهای سرمی را با کاهش التهاب در جوجه ها تعدیل کند.

روش کار: در این مطالعه اثرات GL و لیپوپلی ساکارید (LPS) بر جوجه های گوشتی بررسی شد. 24 جوجه گوشتی نر یک روزه نژاد آرین (کارخانه سیمرغ، مشهد، ایران) به 4 گروه تقسیم شدند: یک گروه شاهد و 3 گروه تیمار که LPS را به تنهایی یا با GLدر 2 دوز مختلف دریافت کردند. تزریق به صورت داخل وریدی در روز 20 انجام شد و مصرف خوراک و نمونه خون مورد بررسی قرار گرفت.

نتایج: تزریق LPS مصرف خوراک را در 4/5، 5 و 6 ساعت پس از تزریق نسبت به گروه کنترل کاهش داد ($P<0.05$). علاوه بر این، تجویز همزمان LPS + GL منجر به افزایش وابسته به دوز در مصرف خوراک تجمعی در مقایسه با گروه LPS در 4/5، 5 و 6 ساعت به دنبال تزریق شد. همچنین، در گروه‌های تحت درمان با LPS + GL نسبت به گروهی که فقط LPS دریافت کردند، فعالیت آنزیم‌های AST و ALT کاهش یافته است، که نشان می‌دهد GL ممکن است یک اثر محافظتی کبدی اعمال کند. مشخص شد که GL اثرات منفی LPS را کاهش می‌دهد و نسبت A/G را بهبود می‌بخشد و پتانسیل آن را به عنوان یک عامل ضد التهابی برجسته می‌کند.

نتیجه‌گیری نهایی: گلیسیریزین بر اشتها و عملکرد کبد در جوجه‌های گوشتی ملتهب شده آرین تأثیر مثبت دارد.

کلمات کلیدی: جوجه گوشتی آرین، گلیسیریزین، لیپوپلی ساکارید، اشتها، پارامترهای بیوشیمیایی