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Original Research

Effects of *Lactobacillus rhamnosus* Supplementation on Growth Performance, Immune Function, and Antioxidant Capacity of Newborn Foals

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ABSTRACT

This study aimed to explore the effects of *Lactobacillus rhamnosus* GG (LGG) supplementation on the growth performance, immune function, and antioxidant capacity of foals. Fifteen newborn foals with similar birth weight (51.67 ± 6.07 kg) and good health were randomly assigned to three groups: control group and test groups I and II, which were supplemented with 5.0×10^9 CFU/day and 1.0×10^{10} CFU/day LGG, respectively, for 150 days. LGG intake increased the daily body height ($P < .01$) and weight ($P < .01$) gain of foals aged 120 to 150 days. The foals' IgA ($P < .05$) and IgG ($P < .01$) plasma levels increased at 30 and 150 days, respectively, and IL-6 plasma level increased at 90 days ($P < .01$). Plasma total antioxidant capacity level was significantly higher in test group I than in the control and test group II at 30 days ($P < .01$), whereas glutathione peroxidase level was significantly higher in test group II than in the control and test group I at 30 days ($P < .01$). Both test groups had significantly higher superoxide dismutase level than the control group ($P < .01$) and significantly decreased malondialdehyde plasma level at 90 and 150 days ($P < .05$). Overall, our findings indicate that dietary supplementation of LGG can improve the growth performance, immune function, and antioxidant capacity of newborn foals.

1. Introduction

In horses, the hindgut microbial community has a wide range of biological functions, including nutrient digestion, vitamin synthesis, and protection from pathogens. Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes have been detected in foal meconium, confirming that the microbial colonization of foals' gastrointestinal tract begins before birth [1,2]. However, the intestinal flora is imperfect at birth, and there is a high probability of infection leading to diarrhea and enteritis between 2 and 10 weeks of birth. Changes in diet may affect the composition of the intestinal flora and reduce the immune function of the intestinal tract [3]. Previously, the incidence of infection in foals was reported to be 11% to 2% within 2 weeks of birth, with a mortality rate of 3% to 4% [4,5]. Recently, the prevalence of diarrhea in small- and medium-sized foals on farms has been reported to be 25% to 80% [6].

Probiotics have been shown to promote the immune function of animals, improving immunity and health, and are thus a potential alternative to antibiotics [7]. Probiotics provide "colonization resistance," causing a "barrier effect" in the intestine, which can help maintain the survival of the intestinal flora and inhibit the colonization of pathogenic microorganisms invading the intestine [8,9]. In addition to competing with pathogens, probiotics can produce compounds that kill pathogens [10,11]. Tejero et al. [12] studied the in vitro effects of probiotics on the survival of *Salmonella enterica*, *Salmonella typhimurium*, and *Clostridium difficile* and found that probiotics inhibit pathogens by producing short-chain fatty acids (SCFAs), such as acetic acid, propionic acid, butyric acid, and lactic acid. [13]. In young animals, probiotics can regulate the microbial community structure in the gastrointestinal tract, increase the utilization rate of nutrients in the intestine, promote intestinal development (increasing villi length and recess depth in the small intestine), activate the intestinal immune system, and improve immune function [14]. Bogere et al. [15] showed that probiotics can replace antibiotics to prevent and treat diarrhea after weaning by regulating the immune system of piglets. Moreover, probiotics can

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increase the number of neutrophils, improve phagocytosis, and increase immunoglobulin expression [16].

Lactobacillus rhamnosus GG (LGG) is a gram-positive facultative anaerobic bacterium first extracted from the digestive tract of healthy people in 1983. It is a relatively widely studied probiotic. In animals, LGG colonizes the intestine by attaching to intestinal epithelial cells. After reaching a certain colony size, it can form a biological barrier on the digestive tract surface, thus regulating the animal's intestinal flora and improving the function of the digestive tract [17,18]. Lam et al. [19] showed that LGG could colonize the gastric mucosa and ulcer sites in mice with gastric ulcer, alleviating the symptoms of gastric ulcer and significantly reducing their size. Collado et al. [20] selected several probiotics, including LGG and *L. rhamnosus Lc705*, to compare the adhesion strength of a single probiotic and a probiotic combination to the intestinal mucosa; the results showed that the probiotic combination performed slightly better than single LGG, particularly in inhibiting the adhesion of harmful bacteria. Therefore, using a combination of probiotics might be advantageous for inhibiting harmful bacteria. Intestinal homeostasis is mediated by the dominance of obligate anaerobes, such as Firmicutes and Bifidobacteriaceae, whereas increased presence of facultative anaerobes, such as Enterobacteriaceae, is a common marker of intestinal ecological imbalance [21]. Lactic acid is the main product of carbohydrate metabolism during intestinal fermentation by Bifidobacterium [22], which can be absorbed and used for energy production by the host. Increased lactic acid content has been found in the excreta of rats treated with oral LGG, confirming that oral LGG can improve the metabolic activity of Bifidobacteria in the intestinal tract. Zhang et al. [23] selected 12-day-old calves for a supplementary feeding LGG test. The results showed that 1.0×10^{10} CFU LGG significantly increased the daily weight gain and significantly altered the rumen pH value, protease activity, and microbial protein content, thus indicating that LGG can improve digestion and growth in calves. Therefore, in this study, we supplemented newborn foals with LGG over 150 days after birth. We evaluated the growth performance, immune function, and antioxidant capacity of the foals to preliminarily explore the effects of LGG on foal growth, development, and health and provide a reference for healthy foal breeding.

2. Materials and methods

2.1. Test materials

Animal experiments were conducted in accordance with the guidelines of the institutional committee on animal use (permit number: 2018012). EU standards for the protection of animals and/or feed legislation were met.

LGG (1.0×10^{10} CFU/g) was purchased from Xi'an Wanfang Biotechnology Co, Ltd LGG capsules (body length 16.4 ± 0.4 mm, outer diameter 6.61 ± 0.03 mm) were purchased from Zhejiang Chunbao capsule Co, Ltd (protocol permit number: 2018012, July 13, 2018).

2.2. Test time and place

This study was conducted at the Zhaosu Yili Kazak Autonomous Prefecture (E80° 83′ 23″, N42° 83′ 12″) for 180 days from May 2021 to November 2021.

2.3. Experimental design and feeding management

A total of 15 healthy newborn pure blood horses with an average weight of 51.67 ± 6.07 kg were selected and randomly assigned to three groups (control and test groups I and II; 5 horses per group). All experimental foals were fed alfalfa hay and water *ad libitum* and could freely nurse. Foals in test groups I and II were supplemented with 5.0×10^9 CFU/day and 1.0×10^{10} CFU/day LGG, respectively. From 2 months of age, a concentrated supplement with the same nutritional level was fed every day. The supplement was 0.65 kg/100 kg body weight per day, divided into three administrations at 09:00, 14:00, and 18:00 hours. Its composition and nutritional level are detailed in Table 1.

Table 1
Composition and nutritional value of the concentrated supplement (based on dry matter, %).

Ingredients	Content%	Nutrient Levels[b]	Content
Corn	37.50	OM	91.64
Wheat bran	15.00	Ash	8.36
Oat	20.00	CP	17.57
Barley	10.00	NDF	13.06
Soybean meal	15.00	ADF	28.35
Limestone	1.00	Ca	0.59
Premix	1.00[a]	P	0.32
NaCl	0.50		
Total	100.00		

[a] Premix was the supplemented for each kilogram of concentrate: vitamin A 480 IU, vitamin B1 816.32 mg, vitamin B_2 333.2 mg, vitamin B_6 48.96 mg, vitamin D 70.4 IU, vitamin E 21 333.36 IU, pantothenic acid 20.46 mg, nicotinamide 484.85 mg, copper 10.58 mg, iron 35.56 mg, manganese 33.54 mg, zinc 30.92 mg, iodine 2.46 mg, selenium 5.93 mg and cobalt 1.11 mg, Organic matter (OM), Crude ash (Ash), Crude protein (CP), Neutral detergent fiber (NDF), Acid detergent fiber (ADF), Calcium (Ca), Phosphorus(P).
[b] The nutritional level is the measured value.

2.4. Sample collection and processing

2.4.1. Plasma index

On days 30, 90, and 150, fasting blood samples (5 mL) were collected from the jugular vein of animals using a disposable needle. After leaving the samples at room temperature for 1 hour, they were centrifuged at 3,500 rpm for 15 min. The supernatant was then extracted using a pipette gun, transferred into a 1.5 mL centrifuge tube, and stored at −20°C for further testing to determine immune factor and antioxidant levels in the plasma.

2.4.2. Measurement of body weight and size

Foals' weight, oblique length, height, chest circumference, and tube circumference were measured at 0, 30, 60, 90, 120, and 150 days.

2.4.3. Index determination

Immunoglobulin A (IgA), immunoglobulin G (IgG), interleukin-6 (IL-6), interleukin-1 β (IL-1β), interferon γ (IFN-γ), and tumor necrosis factor α (TNF-α) levels were detected using enzyme-linked immunosorbent assay. Plasma total antioxidant capacity (T-AOC) and superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT), and malondialdehyde (MDA) levels were determined using visible light colorimetry at the Beijing Huaying Biotechnology Research Institute.

2.5. Data processing

Data are expressed as mean and standard error, with $0.05 \leq P < .10$ indicating a significant trend, $P < .05$ a significant difference, and $P < .01$ an extremely significant difference. The obtained data were preliminarily sorted in MS Excel 2010. The ANOVA program of the SPSS 19.0 statistical software was used for one-way analysis of variance. The Duncan method was used for multiple comparisons in case of significant differences.

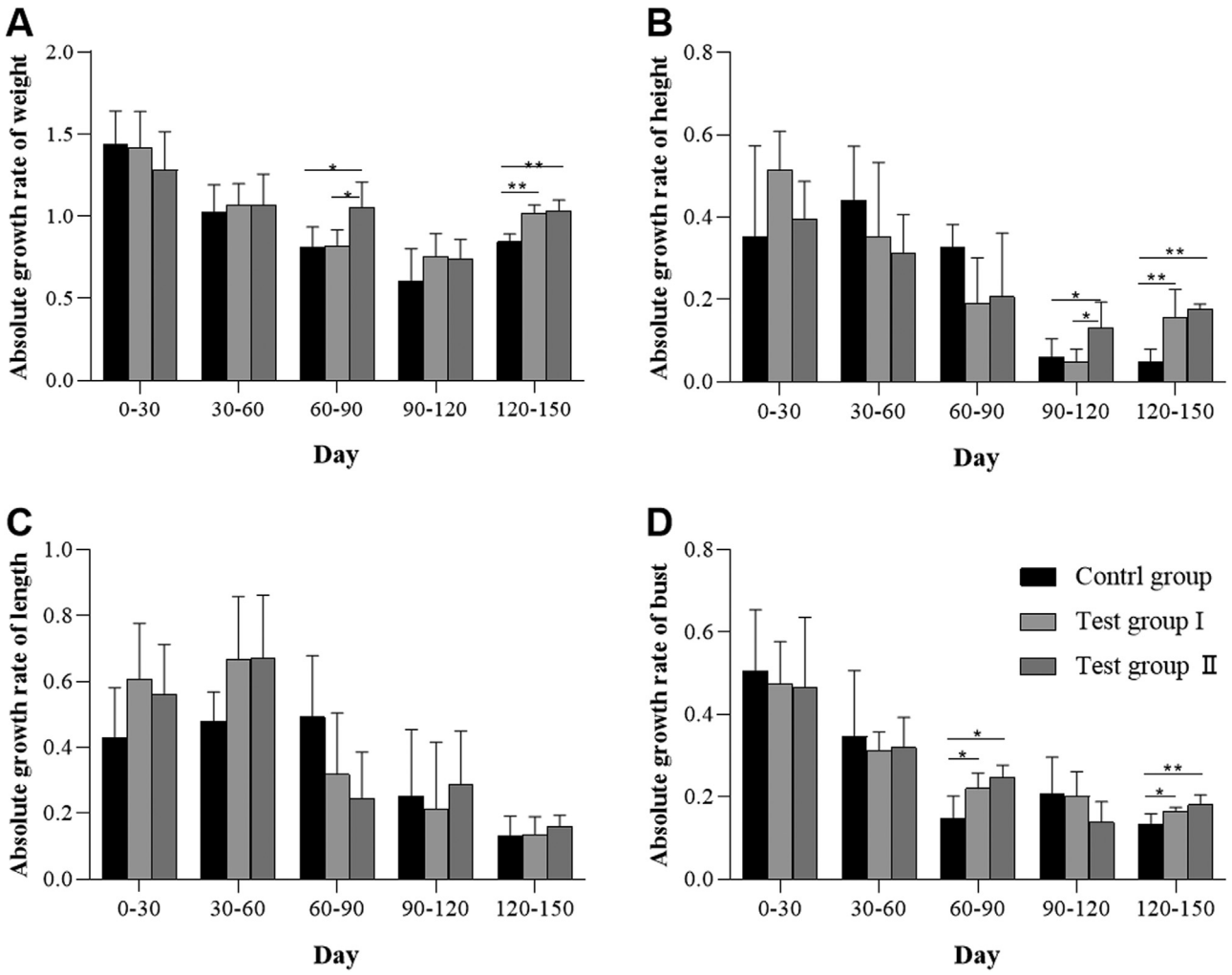

Fig. 1. Effect of supplementary LGG feeding on foal growth. (A) is the daily average body weight increase, (B) is the daily average body height increase, (C) is the daily average body length increase, and (D) is the daily average chest circumference increase. "*" and "* *"in the figure indicate significant ($P < .05$) or extremely significant ($P < .01$) difference between groups, and no mark indicates no significant difference ($P > .05$). The figure below is the same.

3. Results

3.1. Effect of supplementary LGG feeding on foals' growth performance indicators

At 60 to 90 days, the daily gain of foals in test group II was significantly greater than that of foals in test group I and the control group ($P < .05$; Fig. 1A). The daily average increase in chest circumference was significantly greater in test groups I and II than in the control group ($P < .05$; Fig. 1D). At 90 to 120 days, the daily average increase in body height was significantly greater in test group II than in test group I and the control group ($P < .05$; Fig. 1B). At 120 to 150 days, the daily body weight and height gain were significantly greater in test groups I and II than in the control group ($P < .01$; Figs. 1A and B). The daily average increase in chest circumference was significantly greater ($P < .05$) in test group I and extremely significantly greater ($P < .01$) in test group II than in the control group (Fig. 1D).

3.2. Effect of supplementary LGG feeding on foals' immunoglobulin and cytokine plasma levels

At 30 days, the IgA plasma level in test group II was significantly higher than that in test group I ($P < .05$) and was extremely significantly higher than that in the control group ($P < .01$). At 150 days, the IgA plasma level in test group I was significantly higher than that in the control group ($P < .05$; Fig. 2A). At 30 and 150 days, the IgG plasma level in test group I was significantly higher than that in the control group ($P < .05$). Particularly, at 30 days, the IgG plasma level in test group II was extremely significantly higher than that in the control group ($P < .01$); however, no significant difference was observed at 150 days (Fig. 2B). At 90 days, the IL-6 plasma level in the test groups was extremely significantly higher than that in the control group ($P < .01$; Fig. 2D). At 30 days, the IL-1β plasma level in the test groups was significantly higher than that in the control group ($P < .05$; Fig. 2C), and the TNF-α plasma level in test group I was significantly higher than that in the control group ($P < .05$; Fig. 2E). The IFN-γ plasma level did not differ significantly among groups at any time point (Fig. 2F).

3.3. Effect of supplementary LGG feeding on foals' antioxidant capacity

At 30 days, the T-AOC plasma level in test group I was significantly higher than that in the control group ($P < .05$) and tended to be higher than that in test group II ($0.05 < P < .10$). At 90 days, test group II had significantly higher T-AOC plasma level than test group I and the control group ($P < .05$). At 150 days, the T-AOC plasma level in test group II tended to be higher than that in the

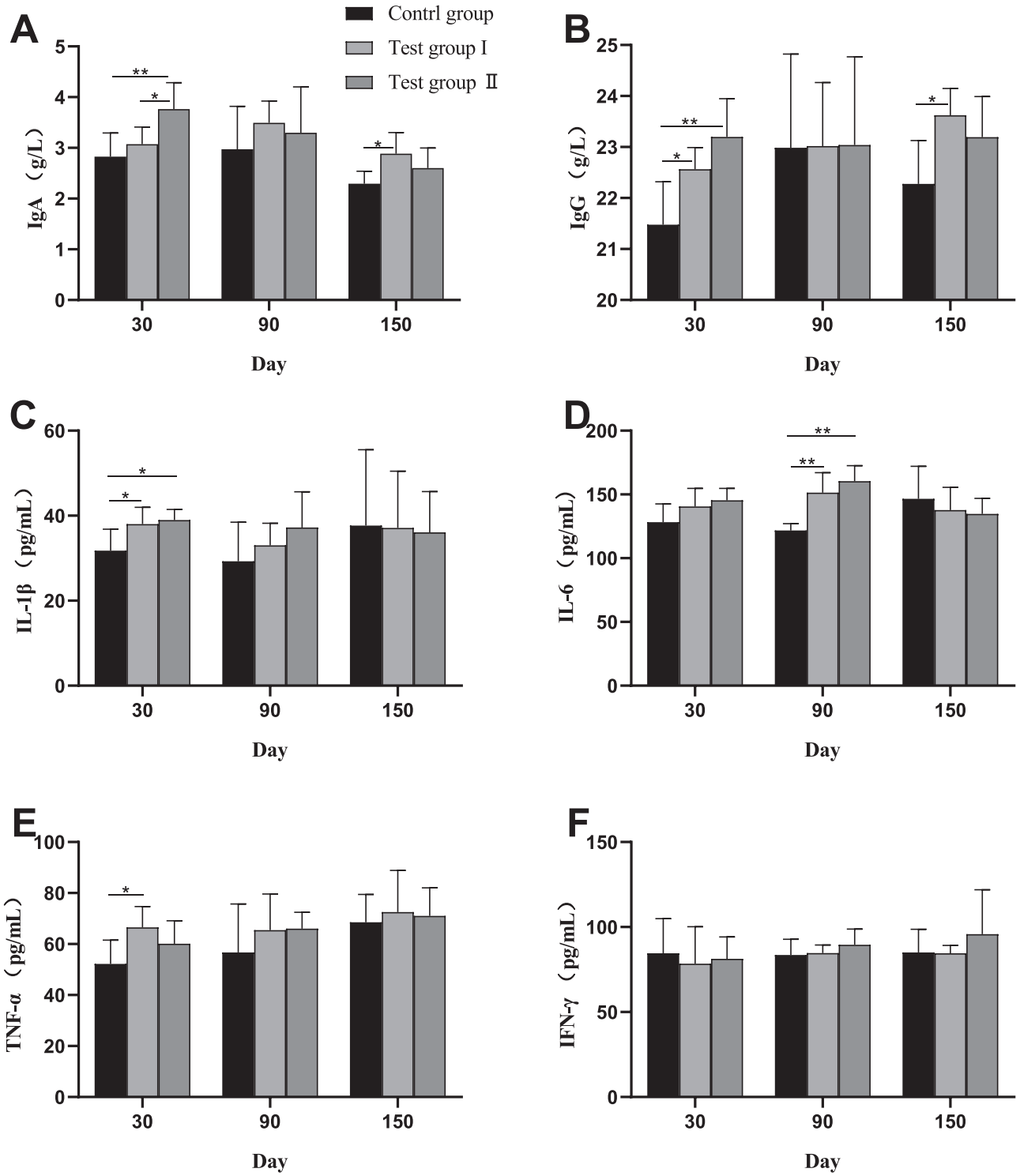

Fig. 2. Effect of supplementary LGG feeding on foals' immune function. (A) IgA plasma level, (B) IgG plasma level, (C) IL-1β plasma level, (D) IL-6 plasma level, E TNF-α plasma level, and F IFN-γ plasma level.

control group ($0.05 < P < .10$; Fig. 3A). The SOD plasma level in the test groups was extremely significantly higher than that in the control group at 30 days ($P < .01$; Fig. 3B). At that time, the CAT plasma level in test group II tended to be higher than that in the control group ($0.05 < P < .10$), but there was no significant difference among groups at each time (Fig. 3C). Similarly, at 30 days, the GSH-Px plasma level was extremely significantly higher in test group II than in test group I and the control group ($P < .01$). At 90 days, the GSH-Px plasma level in test group II was extremely significantly higher than that in the control group ($P < .01$; Fig. 3D). At 90 days, the MDA plasma level in test group II was significantly lower than that in the control group ($P < .05$). There was a decreasing trend, though not significant, in group I ($0.05 < P < .10$). At 150 days, the MDA plasma level in the test groups was significantly lower than that in the control group ($P < .05$; Fig. 3D).

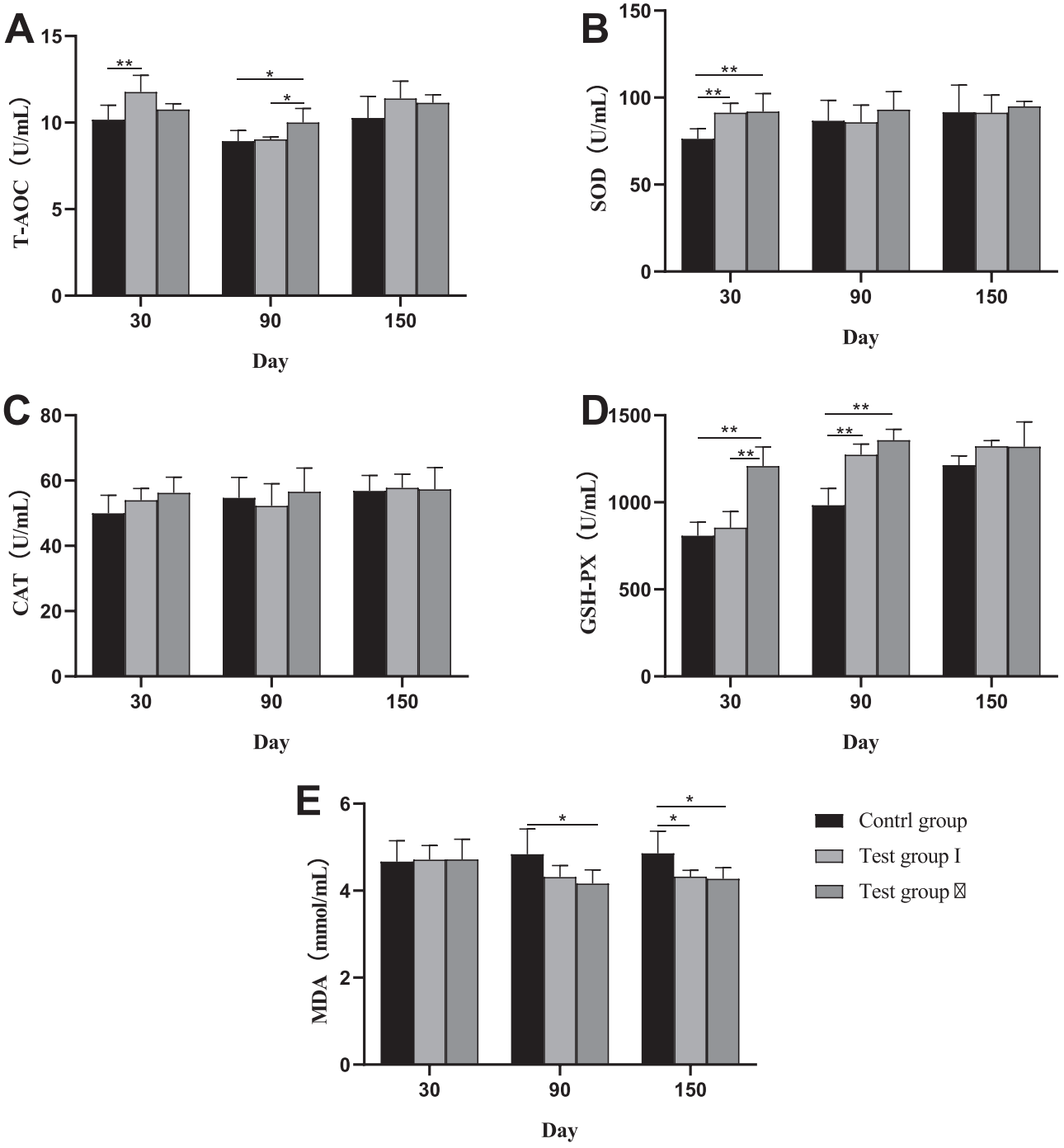

Fig. 3. Effect of supplementary LGG feeding on foals' antioxidant capacity. (A) T-AOC plasma level, (B) SOD plasma level, (C) CAT plasma level, (D) GSH-Px plasma level, and (E) MDA plasma level.

4. Discussion

Compared with other livestock, horses are herbivores with unique gastrointestinal structure. Horses are highly dependent on SCFAs produced by fibrin-degrading bacteria in the colon and cecum as energy source [2]. Shortly after birth, the gastrointestinal tract of young animals is not well developed, and a perfect flora structure does not develop in the digestive tract. Therefore, upon stimulation by external factors, stresses, such as diarrhea, can easily occur and affect their growth and development. Studies have proved that probiotic preparations can affect the colonization and structural composition of flora in the gastrointestinal tract of young animals, and some strains also produce various digestive enzymes in the process of colonization to improve the feed utilization rate of livestock and poultry and promote the growth and development of animals [24,25]. Zhang et al. [23] fed LGG to 12-day-old calves and found that 1.0×10^{10} CFU LGG significantly increased the daily weight gain in calves and significantly altered the rumen pH value, protease activity, and microbial protein content, indicating that LGG can improve the digestion and growth performance of calves. Kang et al. [26] supplemented weaned piglets with inactivated LGG. The results showed that even the inactivated LGG supplementation significantly improved the daily weight gain and reduced the incidence of diarrhea after weaning, indicating that the

bacterial structure of LGG can also enhance intestinal development in animals. In the present study, newborn foals were supplemented with LGG. LGG did not significantly alter the growth of young foals initially. However, the daily gains in weight, height, and chest circumference significantly increased with time. This finding may be attributed to the LGG count and duration of LGG colonization and function in the animals' gastrointestinal tract.

Newborn foals obtain their immunoglobulins mainly through breast milk, which contains a high concentration of IgA and IgG. Most of the IgA remains in the intestinal mucosa to strengthen its immunological barrier function, whereas IgG enters the bloodstream through the small intestinal wall to participate in humoral immunity. Studies have shown that adding LGG to infant food can effectively improve the immunoglobulin content in blood. Yan et al. [27] found that LGG gavage can effectively promote mouse growth and significantly improve IgA production. In the present study, supplementary LGG feeding could effectively increase plasma IgA and IgG levels in foals, particularly at 30 and 150 days. High dose LGG could more effectively increase IgA and IgG plasma levels and improve the humoral immunity of foals.

Grabig et al. [28] found that supplementation with probiotics can effectively increase the expression of TLR4, which activates MyD88 and NF-κB signaling to increase the expression of proinflammatory factors. Yoo et al. [29] reported that some bacteria produce SCFAs by fermenting carbohydrates to regulate host immune cells and provide a carbon source for colon cells. Studies have shown that lactic acid bacteria and their cell wall components can act on human peripheral blood mononuclear cells and promote TNF-α, IL-6, and IL-10 secretion, thereby enhancing immunity. For instance, Miettinen et al. [30] showed that LGG can act on cytokines in animal blood and promote TNF-α, IL-6, and IL-10 production, which can alleviate immune system disorders caused by the intake of pathogenic bacteria. Other studies have shown that LGG can inhibit inflammatory responses. For example, LGG can inhibit the signal transduction of lipopolysaccharide receptor TLR4, p65/NF-kB, p38/MAPK, and ERK1/2 and downregulate TNF-α and IL-6 through TLR4 and TLR9 expression to reduce the inflammatory response [31–34]. Zhang et al. [35] showed that adding LGG to the diet of weaned piglets can inhibit the increase in IL-6, IL-1β, and TNF-α expression caused by *Escherichia coli* and reduce the inflammatory response of piglets. Additionally, Pena et al. [36] cultivated intestinal mouse microorganisms in vitro and showed that LGG can act on macrophages and inhibit TNF-α secretion to alleviate and prevent intestinal inflammation; however, the effect on IL-10 was not significant, and the mechanism by which LGG acts on macrophages remains unclear. In the present study, LGG promoted the inflammatory response of foals in the early stage of the study, increasing IL-6, IL-1β, and TNF-α secretion. In later stages, LGG inhibited the expression of proinflammatory factors and upregulated IFN-γ to reduce the inflammatory damage to cells. Wu [37] proposed that probiotics may act as microbial antigens in the underdeveloped digestive tract of young animals, stimulate the regulation of intestinal mucosal immunity, promote the expression of TLRs, and stimulate the production of downstream cytokines. Wu [37] demonstrated that LGG stimulated the innate immunity of foals when they were young, improves their defense against pathogens, and inhibited the inflammatory response caused by pathogens at the age of 150 days.

Animals contain a high concentration of unsaturated fatty acids, which are susceptible to free radical damage, thus producing cytotoxic peroxides [38]. In the normal state, the free radicals in the body are balanced, but when stimulated by drugs, inflammation, and emotional tension, the level of free radicals increases markedly, causing damage to animal cell structure and organs. T-AOC reflects the body's ability to compensate for external stimuli and the strength of the body's free radical metabolism [39]. SOD eliminates the toxicity of superoxide anion, protecting cells from oxidative damage [40]. CAT can decompose hydrogen peroxide in the body and prevent the formation of free radicals. GSH-Px is an important enzyme for scavenging organic hydroperoxides that replaces catalase and scavenges hydrogen peroxide in tissues with low catalase concentration. MDA, a product of free radical-induced lipid peroxidation, exhibits cytotoxicity and genotoxicity and is a common indicator of oxidative stress in organisms [41]. Probiotics have antioxidant effects. They can enhance the cellular antioxidant capacity by secreting enzymes such as SOD, promote the production of major nonenzymatic antioxidants and GSH-Px, and increase the production of antioxidant biomolecules such as extracellular polysaccharides [42,43]. Li et al. [44] showed that the extracellular polysaccharides of LGG can scavenge 1,1-diphenyl-2-picryl hydrazine, hydroxyl radical, and superoxide anion radical after acting on intestinal epithelial cells through the Bcl-2-associated/B cell lymphoma-2 (Bcl-2) and kelch like ECH-associated protein 1/nuclear factor-erythroid 2-related factor-2 signaling pathway, reducing the cell damage caused by hydrogen peroxide and improving the expression of tight junction proteins. In this study, two LGG doses were found to improve the T-AOC plasma level of foals, effectively increasing SOD, GSH-Px, and CAT plasma levels in the early stage and reducing the MDA level in the later stage. Our findings showed that LGG can effectively eliminate free radicals in foals, reduce MDA plasma levels, and improve SOD, GSH-Px, and CAT levels, indicating that LGG can stimulate the body to produce more antioxidants and antioxidant enzymes to improve the antioxidant capacity.

5. Conclusion

Dietary supplementation of LGG improved the immune function and antioxidant capacity of foals and promoted the growth performance of 60 to 150-day-old foals, with an LGG dosage of 1.0×10^{10} CFU/day providing the best effect.

Financial disclosure

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

None of authors have any conflict of interest to declare.

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