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GROWTH PERFORMANCE AND ANTIOXIDANT STATUS OF GROWING RABBITS FED ON DIETS SUPPLEMENTED WITH *EUCOMMIA ULMOIDES* LEAVES

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Abstract: The present study evaluated the effect of dietary *Eucommia ulmoides* leaves (EUL) on growth performance and antioxidant status of growing rabbits under heat stress condition. Four hundred and fifty weaned New Zealand male rabbits (6 wk old) were randomly divided into 3 equal groups (150 rabbits/group) and fed with a basal diet (control, digestible energy (DE): 15.92 MJ/kg and crude protein (CP): 19.24%) or the basal diet supplemented with 1 or 5 g of EUL/kg of diet (EUL1 and EUL5), in which the same quantity of barley meal was replaced. During the 21 d of experiment (43 to 63 d of age), the temperature and relative humidity of the rabbit house ranged from 27.5 to 32.5°C and from 65 to 73%, respectively. We analysed feed intake, growth performance and antioxidant status of growing rabbits. Compared with the control group, at the end of the experimental period, EUL supplementation significantly reduced the average daily feed intake (92.0, 92.8 and 100.7 g/d for EUL1, EUL5 and control, respectively; $P<0.05$), improved the feed conversion ratio (3.80, 3.81 and 4.59 for EUL1, EUL5 and control, respectively; $P<0.05$), increased the activities of glutathione peroxidase (+35.5 and +35.0% in plasma and liver of rabbits in EUL5 *vs*. control group, respectively; $P<0.05$) and reduced those of malondialdehyde (–12.0 and –46.0% in plasma and liver of rabbits in EUL5 *vs.* control group, respectively; $P<0.05$). These results suggest that inclusion of EUL in the diet of growing rabbits improved the growth performance and antioxidant status in growing rabbits.

Key Words: EUL, rabbit, growth performance, antioxidant status, heat stress condition.

INTRODUCTION

High temperature has the potential to reduce daily weight gain, meat quality and reproductive rates of rabbits, which could lead to substantial economic losses in rabbit production (Pla *et al.,* 1994; Marai *et al.,* 2002; El-Desoky *et al.,* 2017). Likewise, high temperature can cause the production of oxygen-derived free radicals, which may lead to oxidative stress (Freeman and Crapo, 1982; Bollengier-Lee *et al.,* 1998; Sahin and Kucuk, 2003). Excessive production of free radicals and their metabolites in the animal body can have a detrimental effect on biological activities of cellular macromolecules, such as sugars, DNA and protein (Halliwell *et al.,* 1989). Therefore, it is necessary to use diets enriched with natural antioxidants to remove excessive free radicals from the animal body and thus alleviate the adverse effects of high temperature on animal production (Tuzcu *et al.,* 2008; Wang *et al.,* 2008; Liu *et al.,* 2010).

In China, *Eucommia ulmoides* leaves (EUL) are rather ubiquitous as the by-product of traditional Chinese medicine EU. More importantly, EUL is rich in bioactive compounds such as polyphenol acids (such as chlorogenic acid), flavonoid compounds (such as quercetin and rutin), iridoid compounds (such as aucubin and gardenia acid), as well as other nutrients, vitamins, minerals and amino acids (Young *et al.,* 1991; Deyama *et al.,* 2001; Chen *et al.,* 2004; Takamura *et al.,* 2007). Currently, several studies have shown that the EUL has antioxidant, anti-inflammatory, antiviral and

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hepatoprotective functions (Hsieh and Yen, 2000; Yen and Hsieh, 2000; Zhang *et al.,* 2007; Zhang *et al.,* 2013). EUL is therefore expected to be a beneficial antioxidant feed additive.

Until now, there have been very few reports on the efficacy of EUL for the reduction of thermal stress in rabbits. Here, we evaluated the growth performance and antioxidant status of growing rabbits fed on diets supplemented with 1 or 5 g of EUL/kg. The main aim was to provide a theoretical basis for the use of EUL as a natural antioxidant additive for rabbit feeds.

MATERIALS AND METHODS

Ethics statement

The study was approved by the Ethics Committee of Taishan Medical University (Permit No. ECTSMU2016-016).

Experimental design

A total of 450 six-week old weaned New Zealand male rabbits, with an average live weight of 1119±39 g, were provided by the Tai'an Rabbit Industry Co., Ltd. These rabbits were randomly divided into 3 equal groups (150 rabbits per group), which received a basal diet without any supplementation (control) or supplemented with 1 or 5 g EUL/kg of diet (EUL1 and EUL5), in which the same quantity of barley meal was replaced, for 3 consecutive weeks.

The experiment was conducted in an experimental rearing room from June to July in 2016. The temperature and relative humidity of the rabbit house, respectively, ranged from 27.5 to 32.5°C and from 65 to 73%. Previous results showed that these temperature and relative humidity conditions were sufficient to induce heat stress responses in the rabbits (Cervera and Carmona, 2010; Hassan *et al.,* 2016).

Rabbit housing and diets

The rabbits were individually housed in stainless steel cages (60×40×40 cm) and exposed to 12 h light per day. All rabbits were allowed feed and water *ad libitum*, and the rearing room was cleaned and disinfected daily.

The 3 kinds of feeds (control, EUL1, and EUL5) were provided by the Tai'an Rabbit Industry Co., Ltd., and contained the appropriate nutritional and chemical composition to support optimal growth of meat rabbits (Table 1) (De Blas and Mateos, 1998; El-Gindy and Zeweil, 2017). When EUL were added, they were first mixed with 1 kg of basal diet, and additional EUL powder was gradually added during mixing to ensure a uniform distribution of EU in the basic feed, which was then pelleted to 4 mm diameter.

Growth performance and sample collection

The rabbits and feed were weighed at 7, 14 and 21 d after the beginning of the experiment and the average daily gain (ADG), average daily feed intake (ADFI) and the feed conversion ratio (FCR) were calculated, respectively. Clinical signs relating to the overall health of the rabbits were observed and the mortality rate was recorded daily. After each weighing check, 5 rabbits per group were randomly selected for the collection of 10 mL of venous ear blood. Animals were fasted for a minimum of 1 h before blood collection. Immediately, the blood samples were placed into a 20 mL coagulating vacuum blood collection tube. The samples were then centrifuged at 3000 rpm for 10 min. At 21 d, after the collection of venous ear blood, the 5 selected rabbits were euthanised to collect liver samples. The livers were removed and washed with sterile saline equilibrated to 0°C. The samples were stored at –20°C for later use.

Biochemical tests

The contents of superoxide dismutase (SOD, catalogue No. A001-1), glutathione reductase (GR, catalogue No. A002), glutathione peroxidase (GSH-Px, catalogue No. A005), total antioxidant capacity (T-AOC, catalogue No. A004-1), catalase (CAT, catalogue No. A007-1) and malondialdehyde (MDA, catalogue No. A003-1) in serum samples were tested using the testing kits developed by the Nanjing Jiancheng Bioengineering Institute. The assays were performed following the instructions from the kits.

Table 1: Ingredients and chemical composition of EUL and experimental diets[1].

Item	EUL	Control	EUL1	EUL5
Ingredients (g/kg diet)				
Dehydrated alfalfa meal		300	300	300
Wheat bran		200	200	200
Barley		170	169	165
Beet dehydrated pulp		150	150	150
Soybean seed meal		115	115	115
Molasses		20	20	20
Wheat straw		20	20	20
Vitamin-mineral premix[2]		15	15	15
Soybean oil		5	5	5
Bicalcium phosphate		5	5	5
EUL		0	1	5
Chemical composition on a dry matter basis				
Dry matter (%)	93.68	91.97	91.58	91.88
Crude ash (%)	7.78	7.30	7.75	7.69
Crude protein (%)	12.69	19.24	19.69	19.50
Crude fibre (%)	14.04			
Crude fat (%)	5.03			
Ether extract (%)		2.03	2.02	1.98
Neutral detergent fibre (%)		35.24	35.02	35.20
Acid detergent fibre (%)		20.62	20.78	20.90
Acid detergent lignin (%)		3.84	3.81	3.39
Digestible energy (MJ/kg DM)[3]		15.92	15.91	15.90

EUL: *Eucommia ulmoides* leaves; DM: dry matter.

[1]The data were provided by the Tai'an Rabbit Industry Co., Ltd.

[2]Per kg of diet: Vit. A 200 UI; α-tocopheryl acetate 16 mg; niacin 72 mg; Vit. B6 16 mg; choline 0.48 mg; DL-methionine 600 mg; Ca 500 mg; P 920 mg; K 500 mg; Na 1 g; Mg 60 mg; Mn 1.7 mg; Cu 0.6 mg.

[3]Digestible energy (DE) was estimated according to the equation DE=16.43–0.0191 ADFom–0.0208 Ash+0.0148 EE (Villamide *et al.,* 2009). ADFom, acid detergent fibre expressed exclusive of residual ash; EE, ether extract.

Statistical analysis

All data in this study were statistically analysed by one-way analysis of variance (ANOVA) using the SPSS statistical software package (version 16.0 for windows, SPSS Inc., Chicago, IL) to test the effect of EUL supplementation (3 levels: control, EUL1, EUL5 groups). Differences among groups were separated by Duncan's multiple range tests. Differences were considered statistically significant at $P<0.05$.

RESULTS

Effect of EUL on the growth performance

Effects of EUL supplementation on the growth performance are shown in Table 2. During the first experimental week, compared with the control group, the ADWG was higher in the EUL1 (+6.8 g/d; $P<0.05$), but the ADFI (–7.65 g/d; $P<0.01$) and FCR (–0.95 g/g; $P<0.05$) were significantly reduced. The ADFI (–7.76 g/d; $P<0.01$) was significantly reduced in the EUL5 compared to control group. From 8-14 d, compared to control group, in the EUL1 the ADWG was increased by 3.21 g/d, but the FCR was significantly reduced (–1.15 g/g; $P<0.05$); in the EUL5, the ADWG (+5.72 g/d; $P<0.05$) was significantly increased, but the FCR (–1.65 g/g; $P<0.05$) was significantly reduced. During the experimental period between 15-21 d, the ADFI was significantly lower in the EUL1 group than in the control group (–13.6 g/d; $P<0.05$). Over the entire experimental period (21 d), the ADWG (+2.45 g/d; $P<0.05$) was significantly

Table 2: Effect of supplementation of rabbit growing diets with EUL on feed intake and growth performance (n=5 per group).

Item	Experimental diets			SEM	P value
	Control	EUL1	EUL5		
1-7 d					
IBW (g)	1020.1	1019.8	1018.6	15.0	NS
ADWG (g/d)	26.7[a]	33.5[b]	29.8[ab]	0.7	<0.05
ADFI (g/d)	94.3[b]	86.6[a]	86.5[a]	1.3	<0.01
FCR (g/g)	3.53[b]	2.58[a]	2.90[ab]	0.12	<0.05
8-14 d					
ADWG (g/d)	16.9[a]	20.1[ab]	22.6[b]	0.8	<0.05
ADFI (g/d)	96.8	92.1	92.1	2.0	NS
FCR (g/g)	5.73[b]	4.58[a]	4.08[a]	0.22	<0.05
15-21 d					
ADWG(g/d)	20.8	18.1	20.8	0.8	NS
ADFI(g/d)	109.4[b]	95.8[a]	102.5[ab]	1.4	<0.05
FCR(g/g)	5.26	5.28	4.93	0.16	NS
1-21 d					
ADWG(g/d)	21.9[a]	24.2[ab]	24.4[b]	0.6	<0.05
ADFI(g/d)	100.7[b]	92.0[a]	92.8[b]	1.1	<0.05
FCR(g/g)	4.59[b]	3.80[a]	3.81[a]	0.13	<0.05
FBW(g)	1486.3	1566.4	1569.1	15.0	NS
Mortality (n)	10	11	9	2	NS

EUL: *Eucommia ulmoides* leaves; EUL1 or EUL5: basal diet supplemented with 1 or 5 g of EUL/kg of diet; SEM: standard error of mean; IBW: initial body weight; FBW: final body weight; FCR: feed conversion ratio; ADWG: average daily weight gain; ADFI: average daily feed intake; NS: non-significant.

[a-b]: Means in the same row with no common superscripts differ significantly (P<0.05).

increased in the EUL5, but the FCR (–0.78 g/g; P<0.05) and ADFI (–7.9 g/d; P<0.05) were significantly decreased compared with the control group. The final body weights (FBW) of the rabbits in the 2 EUL groups were increased to some extent compared with the control group (EUL1: +80.12 g; EUL5:+82.86 g). Throughout the experiment period, no difference in mortality between the three groups was observed (P>0.05).

Effects of EUL on MDA content and the activities of antioxidant enzymes

Effects of EUL on MDA contents and the activities of antioxidant enzymes are shown in tables 3 and 4. At 7 d, in the EUL1, the activities of T-AOC (+3.47 U/mL; P<0.05), SOD (+72.59 U/mL; P<0.05) and GSH-Px (+28.66 U/mL; P<0.05) were significantly increased, but the MDA content (–2.93 U/mL; P<0.05) was significantly reduced compared with the control group. Similarly, the MDA contents (–2.5 U/mL; P<0.05) were significantly decreased in the EUL5 compared with the control. At 14 d, the activities of T-AOC (+5.71 U/mL; P<0.01) and GSH-Px (+42.19 U/mL; P<0.05) were significantly increased in the EUL5, but the MDA content (–2.42 U/mL; P<0.05) was significantly reduced compared with the control group. Similarly, the activity of T-AOC (+5.3 U/mL; P<0.01) was significantly increased in the EUL1, but the MDA content (–1.99 U/mL; P<0.05) was significantly reduced compared with the control group. At 21 d, the activities of T-AOC (+3.43 U/mL; P<0.05) and GSH-Px (+41.81 U/mL; P<0.05) were significantly increased in the EUL5, but the MDA content (–0.64 U/mL; P<0.05) was significantly reduced compared with the control group. Similarly, the MDA content (–0.86 U/mL; P<0.05) was significantly reduced in the EUL1 compared with the control group. In addition, at 21 d, in terms of liver samples, the activity of GSH-Px (+56.8 U/mL; P<0.05) was significantly increased in the EUL5, but the MDA content (–5.33 U/mL; P<0.05) was significantly reduced compared with the control group. Similarly, the MDA content (–4.46 U/mL; P<0.05) in liver samples at 21 d was significantly reduced in the EUL1 compared with the control.

Table 3: Effects of EUL on total antioxidant capacity (T-AOC), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT), glutathione reductase (GR), and malondialdehyde (MDA) concentrations of serum in rabbits (n=5 per group).

	Experimental diets				
Item	Control	EUL1	EUL5	SEM	*P* value
7 Days of experiment					
T-AOC	5.02^{a}	8.49^{b}	6.95^{ab}	0.78	<0.05
SOD	214.52^{a}	287.11^{b}	256.55^{ab}	23.01	<0.05
GSH-Px	115.12^{a}	143.78^{b}	120.88^{ab}	2.96	<0.05
CAT	14.22	11.28	9.92	1.87	NS
GR	26.71	20.56	19.85	2.01	NS
MDA	7.32^{b}	4.39^{a}	4.82^{a}	0.29	<0.01
14 Days of experiment					
T-AOC	3.71^{a}	9.01^{b}	9.42^{b}	0.89	<0.01
SOD	326.12	287.26	330.81	11.21	NS
GSH-Px	127.89^{a}	148.98^{ab}	170.08^{b}	9.12	<0.05
CAT	12.02	10.82	13.29	1.62	NS
GR	19.01	19.96	20.12	3.28	NS
MDA	7.08^{b}	5.09^{a}	4.66^{a}	0.31	<0.05
21 Days of experiment					
T-AOC	4.98^{a}	4.89^{a}	8.41^{b}	0.85	<0.05
SOD	293.01	282.03	306.18	4.71	NS
GSH-Px	117.81^{a}	138.11^{ab}	159.62^{b}	5.92	<0.05
CAT	7.01	8.92	9.23	0.86	NS
GR	41.02	35.26	42.09	3.61	NS
MDA	5.02^{b}	4.16^{a}	4.38^{a}	0.18	<0.05

EUL: *Eucommia ulmoides* leaves; All parameters are expressed as U/mL. EUL1 or EUL5: basal diet supplemented with 1 or 5 g of EUL/kg of diet; SEM: standard error of mean; NS, non-significant.

$^{a-b}$: Means in the same row with no common superscripts differ significantly (*P*<0.05).

DISCUSSION

When the ambient temperature is higher than the rabbit's neutral temperature, approximately 21°C, the growth performance and feed intake of the meat rabbits decrease, as well as their feed utilisation ratio (Marai *et al.,* 2002). Many studies have found that decreases in animal growth performance as a result of thermal stress may be a consequence of damage to the intestinal mucosa and the increase in hydrolysis of muscle proteins caused by

Table 4: Effects of EUL on total antioxidant capacity (T-AOC), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT), glutathione reductase (GR), and malondialdehyde (MDA) concentrations of the rabbit livers at the end of the experimental period (n=5 per group).

	Experimental diets				
Item	Control	EUL1	EUL5	SEM	*P*-value
T-AOC	1.49	2.01	2.11	0.17	NS
SOD	418.12	457.01	459.32	13.56	NS
GSH-Px	162.16^{a}	171.83^{a}	218.96^{b}	9.78	<0.05
CAT	7.12	7.61	7.59	0.16	NS
GR	9.71	13.88	9.92	1.42	NS
MDA	11.52^{b}	7.06^{a}	6.19^{a}	0.42	<0.05

EUL: *Eucommia ulmoides* leaves; All enzyme activities are expressed as U/mg of protein. EUL1 or EUL5: basal diet supplemented with 1 or 5g of EUL/kg of diet; SEM: standard error of mean; NS: non-significant.

$^{a-b}$: Means in the same row with no common superscripts differ significantly (*P*<0.05).

temperature-induced free radicals (Hayashi *et al.,* 1994; Payne and Southern, 2005; Zhao and Shen, 2005). In this experiment, daily supplementation of a growing rabbit feed with EUL at 1 or 5% incorporation level led to an increase in the rabbits' growth performance compared with the control. Therefore, supplementation of the basal diet with EUL could favour the growth performance in rabbits under high temperature conditions. These results could be explained by the antioxidants contained in EUL, which may help maintain the health of the intestinal mucosa, thus promoting the growth of animals (Josephine *et al.,* 2008; El-Desoky *et al.,* 2017), as previously shown in poultry and growing-finishing pigs. For example, inclusion of Forsythia extract, which has antioxidant properties, in daily diet for broilers improved the growth performance under high temperature (Wang *et al.,* 2008). Dietary supplementation with 0.30% EUL powder significantly improved the daily weight gain of broilers (Wang *et al.,* 2003). Similarly, supplementation of pig feed with EUL improved production performance in growing-finishing pigs (Lee *et al.,* 2009). However, further studies are required to better characterise and define the appropriate supplementation dosages of EUL in the daily diet of growing rabbits.

Many endogenous antioxidants in the animal body can relieve the damage to tissues resulting from the presence of excessive reactive oxygen species (ROS) (Masella *et al.,* 2005). When concentrations of these molecules become high, they can potentially take away electrons from neighbouring molecules, causing a cascade of deleterious reactions (Kim *et al.,* 2006). These antioxidant enzymes are particularly important for animals exposed to high temperature conditions, as they help eliminate the oxygen free radicals resulting from excessive heat (Blokhina *et al.,* 2003; Masella *et al.,* 2005). Our results showed that feed supplementation with EUL could to some extent increase T-AOC and GSH-Px levels in blood and livers of rabbits, indicating that EUL can be used to reduce heat stress-induced oxidative damage.

Exposure to high temperatures can induce oxidative stress, which increases MDA content in the body (Halliwell and Gutteridge, 1989; Sahin and Kucuk, 2003; Hung *et al.,* 2006). In this study, our results showed that feed supplementation with EUL could to some extent reduce MDA levels in blood and livers of rabbits, supporting the theory that EUL can be used to reduce heat stress-induced oxidative damage.

CONCLUSIONS

The incorporation of EUL in the diet of growing rabbits improves growth performance, such as the feed conversion ratio (FCR) and the antioxidant status of growing rabbits, and the activities of GSH-Px and MDA in serum and livers. Further studies are required to better define the appropriate level of EUL inclusion in the diet of growing rabbits and understand the physiological mechanisms involved in these results.

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