Research Article

Effects of Ribonucleotide Reductase Inhibitor and Curcuminoids on Growth Performance and Meat Quality in Turkey Poults

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Abstract | Ribonucleotide reductase (RNR) plays a crucial role in DNA synthesis and cellular health. When RNR is inhibited, it disrupts metabolic processes and mitochondrial function, resulting in elevated oxidative damage. Curcuminoids have antioxidants and anti-inflammatory properties making them a promising dietary supplement in broiler diet. This study examines the effects of curcuminoid supplementation on performance and meat quality particularly where RNR was restricted. The study included four treatments: control (C), curcuminoids (CU, 600 mg/kg in feed), RNR inhibitor (RI, 30mg/kg body weight/orally twice a week), or combination of both (CURI). Body weight gain remained consistent across all groups, while RI and CURI reduced feed intake during the final week. RI tended to have heavier hearts while lighter livers weight. RI lowered the percentage of breast/carcass weight, and muscle pHu, while RI and CURI increased drip loss. RI increased meat lightness while CU and CURI increased meat redness. TBARS increased for RI and CURI in the duodenum, jejunum and muscle, with the effects being stronger for RI group. Total mitochondria protein level, ATP6 and CytB expression reduced for RI and CURI in duodenum, jejunum and muscle. Villi length was shorter for both RI and CURI in duodenum, crypt depth was thicker for CURI, while villi/crypt ratio was lower for RI and CURI. In conclusion, although inhibiting RNR had no impact on growth performance, it impaired meat quality potentially by altering mitochondria function and gut health leading to increased oxidative damage, while curcuminoids partially reduced the negative impacts on the meat quality.

Keywords | Curcuminoids, Performance, Gut health, Meat quality, Mitochondrial function, Ribonucleotide reductase

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INTRODUCTION

The quality of turkey meat is a critical factor that shapes consumer perception and market competitiveness (Salgado-Pardo *et al.*, 2024). According to a market analysis by a market research group (Group, 2024), the global turkey meat industry was valued at $12.5 billion in 2024. The market is projected to grow at a compound annual growth rate of 4.9%, reaching approximately $19.3 billion by 2033. Therefore, it is essential to identify promising strategies to enhance turkey meat quality. One such approach involves targeting growth regulatory pathways, particularly Ribonucleotide Reductase enzyme (RNR), which plays a critical role in DNA synthesis and mitochondrial function. Our Previous data indicated that reduction in RNR activity play a critical role in meat

quality (Shakeri *et al*., 2024, 2025a, b).

Ribonucleotide reductase is crucial for DNA synthesis which is essential for cell proliferation, making it a key regulator of growth in the body (Wang and Liu, 2006). It has been shown that inhibition of RNR can negatively affect cellular metabolism and replication, leading to developmental delays and compromised physiological functions (Wozniak and Simmons, 2021). In poultry, reduced RNR expression has been associated with impaired mitochondrial function and increased muscle abnormalities (Shakeri *et al*., 2023, 2024). Mitochondria play a crucial role in growth by serving as the primary energy producers within cells necessary for various biological processes, including cell division, differentiation, and tissue development (Shakeri *et al*., 2025). Therefore, maintaining optimal RNR activity contributes to efficient DNA repair and mitochondria health, leading to improved growth due to optimized cellular maintenance.

Curcuminoids are a group of bioactive compounds including curcumin (the most abundant curcuminoid), demethoxycurcumin, and bisdemethoxycurcumin. The compounds exhibit strong antioxidant, anti-inflammatory, and antimicrobial properties, making them a valuable supplement to enhance growth performance in poultry (Hernández-García *et al*., 2025). Additionally, it enhances mitochondrial health by stimulating mitochondrial biogenesis, by increasing cyclic adenosine monophosphate levels and activating key signaling pathways which promote mitochondrial function (Hamidie *et al*., 2021).

There is currently no available research examining the effects of an RNR inhibitor such as Hydroxyurea in turkeys on growth and meat quality. As Hydroxyurea has never been tested *in vivo*, we first tested the inhibitor on broiler muscle cells *in vitro* (Shakeri*et al*., 2025). We found out inhibiting Hydroxyurea created similar conditions as woody breast in broiler chickens which is a major meat quality defect. Therefore, the aim of this study was to investigate the role of RNR on performance and meat quality in the first stage of the growing period of turkeys when RNR activity was restricted and birds were supplemented with curcuminoid supplementation. The first stage of bird life is crucial for their overall development and future performance.

MATERIALS AND METHODS

Experimental design

In total 160 one-day-old male turkey with an initial average body weight of 60±2g randomly assigned to 16 equally sized pens (1m×2m). Body weight, feed intake and feed conversion ratio were recorded weekly. Feed (day 1-28, CP:27.69%, ME:3020 kcal/kg) and water were provided ad-libitum throughout the trial. The temperature was maintained at 32˚C during the first three days, then gradually reduced to 23˚C on day 10 for the rest of the study. Relative humidity was maintained at an average of 60±5%. Light was provided 24 hours/day throughout the study. The dietary treatments were: (i) control (C), (ii) control with RNR inhibitor (RI, Sigma Aldrich, Hydroxyurea, 30mg/kg body weight/orally twice a week), (iii) control with curcuminoids (CU, 600 mg/kg in feed) (BulkSupplemets, Henderson, Nevada), (iv) a combination of the RNR inhibitor and curcuminoids (CURI). The curcuminoids contained ~80% curcumin, ~17% demethoxycurcumin and ~3% bisdemethoxycurcumin. The dose and frequency of Hydroxyurea administration were determined based on preliminary data and rodent model studies; however, further pharmacokinetic investigations in poultry are warranted to optimize this protocol (Marahatta *et al*., 2015; Geetha, 2018; Shakeri *et al*., 2025). Each treatment consisted of 4 replicates and 10 birds/replicate. On day 28, 16 birds/treatment were randomly selected for the analysis. The birds were fasted for 12 hours before they slaughtered. The intestine (duodenum and jejunum) and breast muscle were fixed in liquid nitrogen and transferred to -80 ˚C for further analysis. Additionally, the intestines tissues were fixed in formalin 10% for histology analysis.

Meat quality assessment

~20g of breast muscle (inner area) was suspended in a sealed box to measure drip loss (<15 minutes and 24 hours) to obtain water loss during the time. The other side of breast muscles were kept at 4˚C in sealed plastic bags for measuring meat color and pHu at 24 hours post-mortem. Internal organs weight were recorded before fixing them in liquid nitrogen or formalin.

Quantitative real-time PCR (qRT-PCR)

Total RNA was extracted using Trizol reagent and a RNeasy Mini Kit. qRT-PCR was performed based using SYBR Green reagent (Shakeri *et al*., 2025). 18S ribosomal RNA was used to normalize the data and fold change was obtained using the 2-ΔΔCt method.

Mitochondria extraction

50 mg tissue were homogenized in 5 mL isolation buffer (210 mM sucrose, 2mM EGTA, 40mM Nacl and 30 mM HEPES, pH 7.4). The homogenized samples were centrifuged for 10min at 900 xg and 4˚C. Supernatant was collected and centrifuged at 10,000 xg for 10 minutes at 4˚C. The obtained pellet was resuspended in 500 µL resuspension buffer (10mM Tris and 1mM EDTA, pH 7.4) and used for the analysis. Crude mitochondrial fraction protein was measured using protein assay (Bio-Rad).

Thiobarbituric acid reactive substances (TBARS)

TBARS was measured in the collected tissues according to a published method (Sheikhlar *et al*., 2017). Briefly, 5 g of muscle sample was homogenized in 15 mL of distilled water, 5 mL of the samples transferred into a test tube. 50 µL of butylated hydroxyanisole and 5 mL of TBA-trichloroacetic acid solution were transferred into the test tube, heated for 15 min, then centrifuged at 1000 xg for 15 minutes. Absorbance of the supernatant was read at 530 nm.

Histology

The intestinal tissues were embedded in the paraffin. The fixed tissues were cut (8µm) using microtome and then stained with H&E using a standard protocol. All images were obtained (20× magnification) using a light microscope to measure villi length and crypt depth and the ratio. Images were analyzed using Fiji image software. The distance from the tip of the villus to the villus crypt junction was measured as the villus height, and crypt depth was defined as the depth of the invagination between adjacent villi (10 images per sample).

Statistical analysis

Data was analyzed using one way ANOVA (Prism, V10.2.2). When significant effects were found, comparisons were performed using Tukey. Results were considered significant at $P<0.05$. Mean values are given as SEM.

RESULTS

Performance data are presented in Table 1. During the growing time, there were no significant differences among the groups for body weight gain and feed conversion ratio whereas both RI and CURI reduced feed intake, while CU increased feed intake during the final week of the study (P=0.01). CU tended to have a better feed intake overall among the groups (P=0.10). RI birds tended to have heavier hearts (P=0.09) and lighter livers weight (P=0.03). Skinned breast muscle/skinned carcass weight percentage was lower for RI vs CU and CURI (P=0.01) (Table 2).

Meat quality parameters were negatively impacted by the RNR inhibitor while supplementing birds with curcuminoids partially improved them. RI tended to have lower pHu (P=0.04), while increased meat lightness (P=0.007) vs other groups. Both RI and CURI increased drip loss (P=0.01), while redness tended to be higher for CU and CURI (P=0.04). No significant difference for yellowness among the groups (Table 3).

TBARS increased and total mitochondria protein reduced for both RI and CURI in duodenum (P=0.006 and P=0.01), jejunum (P=0.03 and P=0.01) and muscle (P=0.0005 and P=0.09), whereas the effects were stronger for RI. RI and CURI altered expressions of ATP6 and CytB in duodenum (both P<0.0001), jejunum (P=0.003 and P=0.02) and muscle (P=0.001 and P=0.01) (Table 4).

Table 1: Weekly gain weight, feed intake, and feed conversion ratio (FCR) of turkeys.

	C[1]	CU	RI	CURI	P values
Weight gain(g)					
Day 0-7	94.9±0.5	94.5±2.3	92.9±2.3	90.1±1.4	0.28
Day 8-14	145.5±8.4	151.6±3.7	138.2±3.4	138.6±2.1	0.24
Day 15-21	276.2±9.7	279.8±5.2	263.6±13.9	256.7±2.3	0.27
Day 22-28	534.9±12.7	562.5±9.5	519.1±25.3	564.7±34.7	0.45
Day 0-28	1052±25.9	1081±10.8	1014±40.9	1050±33.5	0.49
Feed intake (g)					
Day 0-7	101.1±3.1	101.2±3.4	101.1±2.5	98.9±2.7	0.94
Day 8-14	178.8±5.3	183.0±6.8	176.1±4.1	175.3±2.3	0.69
Day 15-21	330.1±9.6	321.9±16.3	319.6±15.3	312.6±4.7	0.79
Day 22-28	470.7±25.7[ab]	530.5±14.9[a]	443.3±20.1[b]	435.8±4.2[b]	0.01
Day 0-28	1081±40.1	1137±28.8	1040±40.9	1017±10.5	0.10
FCR					
Day 0-7	1.06±0.02	1.07±0.03	1.08±0.02	1.09±0.01	0.75
Day 8-14	1.23±0.04	1.27±0.01	1.27±0.01	1.26±0.01	0.68
Day 15-21	1.19±0.02	1.15±0.07	1.21±0.02	1.21±0.02	0.73
Day 22-28	0.87±0.02	0.94±0.03	0.85±0.02	0.77±0.04	0.26
Day 0-28	1.02±0.02	1.05±0.01	1.02±0.01	0.97±0.04	0.19

[1]C: control; CU: control + curcuminoids; RI: control + RNR inhibitor; CURI: control + curcuminoids + RNR inhibitor (n=40/treatment). [a-b] within a row with no common superscripts are different at P<0.05.

Table 2: Internal organs weight (g) and skinned carcass percentage (%) of turkeys.

	C[1]	CU	RI	CURI	P-values
Heart	3.5±0.2	3.4±0.2	4.1±0.2	3.5±0.2	0.09
Spleen	0.5±0.3	0.5±0.07	0.5±0.05	0.5±0.06	0.68
Liver	13.6±0.5[a]	14.7±0.6[a]	10.9±0.5[b]	12.8±0.5[ab]	0.03
Total small intestine	29.9±1.6	31.3±1.7	30.8±1.2	27.7±1.4	0.37
Pancreas	1.6±0.1	1.8±0.1	1.7±0.1	1.6±0.08	0.51
Breast muscle/carcass[2]	18.3±0.8[ab]	19.4±0.4[a]	16.5±0.5[b]	19.1±0.6[a]	0.01
Thigh/carcass	29.5±0.5	30.2±0.4	30.3±0.4	29.4±0.3	0.36

[1] C: control; CU: control + curcuminoids; RI: control + RNR inhibitor; CURI: control + curcuminoids + RNR inhibitor (n=16/treatment). [a-b] within a row with no common superscripts are different at P<0.05. [2] Skinned breast muscle weight/carcass weight without internal organs.

Table 3: pH, drip loss and meat color of turkey breast muscle at 24h post-mortem.

	C[1]	CU	RI	CURI	P values
pHu	5.7±0.01[a]	5.7±0.02[a]	5.6±0.01[b]	5.7±0.03[a]	0.04
Drip loss (%)	2.3±0.1[b]	2.8±0.2[ab]	3.1±0.2[a]	3.2±0.1[a]	0.01
Lightness	55.1±0.6[ab]	55.2±0.9[ab]	57.1±0.6[a]	53.3±0.6[b]	0.007
Redness	2.9±0.5[b]	4.7±0.7[a]	3.1±0.5[b]	4.4±0.3[a]	0.04
Yellowness	13.3±0.7	14.8±0.5	13.2±0.5	14.4±0.4	0.12

[1] C: control; CU: control + curcuminoids; RI: control + RNR inhibitor; CURI: control + curcuminoids + RNR inhibitor (n=16/treatment). [a-b] within a row with no common superscripts are different at P<0.05.

Table 4: Thiobarbituric Acid Reactive Substances (TBARS), crude mitochondrial fraction protein, and mitochondrial gene expression (fold change) of turkeys.

	C[1]	CU	RI	CURI	P value
TBARS (nmol/mg)					
Duodenum	4.1±0.6[ab]	2.5±0.8[b]	5.5±0.1[a]	4.8±0.2[a]	0.006
Jejunum	3.7±0.6[ab]	3.3±0.7[b]	5.4±0.1[a]	4.1±0.2[ab]	0.03
Muscle	4.3±0.2[bc]	4.2±0.1[c]	5.4±0.2[a]	5.1±0.2[ab]	0.0005
Crude mitochondrial fraction protein (mg/mL)					
Duodenum	0.33±0.05[ab]	0.37±0.09[a]	0.12±0.01[b]	0.16±0.01[ab]	0.01
Jejunum	0.29±0.07[ab]	0.43±0.08[a]	0.13±0.02[b]	0.15±0.04[b]	0.01
Muscle	0.25±0.05	0.29±0.07	0.11±0.01	0.15±0.05	0.09
ATP6[2]					
Duodenum	1.04±0.16[a]	1.06±0.15[a]	0.07±0.04[b]	0.19±0.07[b]	<0.0001
Jejunum	1.03±0.14[ab]	1.42±0.25[a]	0.21±0.12[c]	0.41±0.22[bc]	0.003
Muscle	1.01±0.11[b]	1.52±0.30[a]	0.23±0.15[b]	0.31±0.13[b]	0.001
CytB					
Duodenum	1.05±0.18[a]	0.93±0.10[a]	0.06±0.04[b]	0.07±0.03[b]	<0.0001
Jejunum	1.03±0.17[a]	0.92±0.15[ab]	0.19±0.05[b]	0.57±0.26[ab]	0.02
Muscle	1.01±0.10[a]	1.67±0.39[ab]	0.62±0.07[b]	0.70±0.03[ab]	0.01

[1]C: control; CU: control + curcuminoids; RI: control + RNR inhibitor; CURI: control + curcuminoids + RNR inhibitor (n=16/treatment). [a-c] within a row with no common superscripts are different at P<0.05. [2] Gene expression of mitochondrial genes. ATP6: mitochondrially encoded ATP synthase 6; CytB: cytochrome b. Primer's reference: (Shakeri *et al.*, 2025).

Villi length was shorter in duodenum for both RI and CURI (P<0.0001) whereas crypt depth was thicker for CURI (P<0.0001) among the groups. Villi/crypt ratio was lower for RI and CURI (P<0.0001) vs C and CU (Table 5, Figure 1). No significant changes for villi length, crypt depth and the ratio were observed in jejunum.

Table 5: Villi length, crypt depth and villi/crypt ratio of turkeys.

	C[1]	CU	RI	CURI	P-values
Villi length (µm)					
Duodenum	2017±63.3[a]	1830±55.5[a]	1536±45.6[b]	1540±86.4[b]	<0.0001
Jejunum	1223±44.6	1216±33.5	1262±17.1	1203±50.9	0.43
Crypt depth (µm)					
Duodenum	95±5.1[b]	102±3.3[b]	91±3.6[b]	122.9±5.1[a]	<0.0001
Jejunum	77±5.1	83±5.3	84±4.8	90±4.9	0.38
Villi/crypt (%)					
Duodenum	21±1.5[a]	20±1.3[ab]	16±0.7[bc]	13±0.6[c]	<0.0001
Jejunum	16±1.3	16±1.4	15±0.5	14±0.6	0.25

[1]C: control; CU: control + curcuminoids; RI: control + RNR inhibitor; CURI: control + curcuminoids + RNR inhibitor (n=16/treatment). [a-b] within a row with no common superscripts are different at P<0.05.

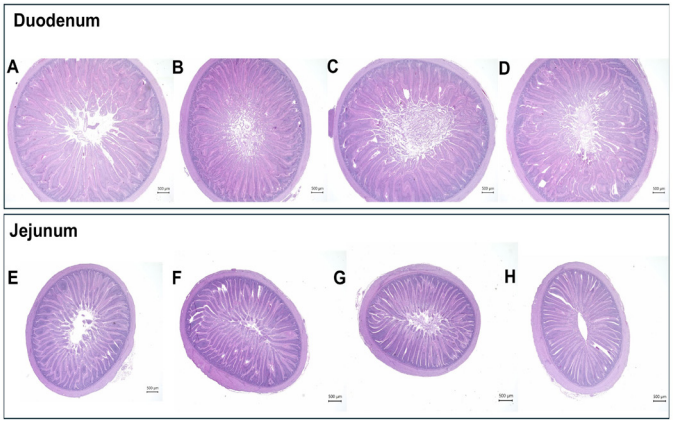

Figure 1: Photomicrographs of duodenum and jejunum of turkeys fed either control (Figures A and E), curcuminoids (600 mg/kg in feed) (Figures B and F), RNR inhibitor (30mg/kg body weight/orally twice a week) (Figures C and G), or combination of both (Figures D and H).

DISCUSSION

The current data suggests that although either the RNR inhibitor or curcuminoid had no impact on body weight gain, curcuminoid improved overall meat quality, and feed intake during the final week whereas the RNR inhibitor impaired feed intake and meat quality parameters. Interestingly, we found out in our previous works that birds with woody breast myopathy also have lower RNR activity in their muscle tissues, and similar changes were observed for most of meat quality parameters (Shakeri *et al.*, 2023, 2024). It is worth mentioning there are limited data available on how curcuminoids and Hydroxyurea interact when used in combination. Therefore, concurrent use of curcuminoid and Hydroxyurea may lead to some side effects.

Ribonucleotide reductase (RNR) is a critical enzyme that governs a fundamental step in cellular metabolism: the conversion of ribonucleotides into deoxyribonucleotides. This reaction is essential because deoxyribonucleotides serve as the building blocks for DNA synthesis and repair. Without RNR activity, cells cannot produce the deoxyribonucleotide pool required for replicating nuclear DNA during cell division or for maintaining mitochondrial DNA integrity (Nordlund and Reichard, 2006). Furthermore, RNR plays a central role in regulating the balance of nucleotide pools, which is vital for genomic stability. Its activity is tightly controlled throughout the cell cycle, particularly during the S-phase, when DNA replication is most active. In addition to its nuclear functions, RNR is also involved in mitochondrial DNA replication, making it indispensable for mitochondrial biogenesis and function. Given its pivotal role in DNA metabolism, RNR is a target for several chemotherapeutic agents, including Hydroxyurea, which inhibits its activity to suppress cell proliferation. Disruption of RNR activity can lead to impaired DNA synthesis, mitochondrial dysfunction, and compromised tissue health effects that are especially relevant in rapidly dividing cells and metabolically active tissues.

Although the current data showed no significant changes in weight gain among the groups, the administration of the RNR inhibitors reduced feed intake, and negatively impacted meat quality parameters as evidenced by increased meat lightness and drip loss. The reason for insignificant effects on growth might be related to the duration of the study; most commercial turkey breeds are fully grown and ready for harvest between 14 and 22 weeks of age. It has been reported that supplementing turkey's diets with additives such as probiotics can improve performance in turkey poults over a 13-week period (Lipiński *et al.*, 2021). In our study, feed consumption for RI and CURI decreased during the final week, which indicate potential negative impacts on later growth performance.

All the negative impacts on meat quality might be related to higher oxidative damages to tissues as TBARS level increased, while crude mitochondrial fraction protein

reduced for the birds supplemented with the RNR inhibitor. It has been shown that high oxidative damage negatively impact meat lightness, pHu and drip loss in broilers (Chen *et al*., 2022). TBARS measures the level of oxidative damage in biological samples, specifically by quantifying lipid peroxidation. Lower total mitochondrial protein content and reduced mitochondria genes expression (ATP6 and CytB in our study) can be associated with mitochondrial dysfunction. Mitochondrial dysfunction often links to reduced protein content, leading to a higher leak of electrons in the electron transport chain, resulting in increased reactive oxygen species (ROS) production (Shakeri *et al*., 2025). Excessive amounts of ROS can cause oxidative damage to lipids, DNA, and proteins (Jomova *et al*., 2023).

In our study we observed that the birds supplemented with the RNR inhibitor had lighter liver weight but heavier hearts. Our obtained data suggest that Hydroxyurea-induced inhibition of RNR activity led to liver slows DNA synthesis and cell proliferation leading to a decrease in liver weight (Odsbu and Skarstad, 2009). Reducing liver weight in broiler chickens may impair meat quality as liver is involved in managing fatty liver and nutrient metabolism (Zhang *et al*., 2024). Furthermore, our obtained data suggest that Hydroxyurea-induced inhibition of RNR activity led to compromised heart function suggests that the heart may experiencing physiological stress or altered function (Rodriguez and Singhal, 2021).

In our study, curcuminoid supplementation was largely ineffective at reversing the negative impacts of Hydroxyurea on gut morphology and mitochondrial biomarkers, despite some minor improvements in meat color. This limited efficacy may be attributed to the duration of the experiment, as a study showed growth improvements in turkey poults over a 13-week period (Lipiński *et al*., 2021). Alternatively, the dose used in this study may have been insufficient, as a study reported that birds supplemented with 400 mg/kg curcumin under stress showed no effects on growth performance (Rahmani *et al*., 2017). Previous studies showed curcuminoid improves meat quality in chickens by improving meat color and TBARS (Hernández-García *et al*., 2025). Furthermore, curcuminoid showed to have a positive impact on mitochondria function which could potentially reduce ROS production leading to lower oxidative damage to tissues such as muscle (Chen *et al*., 2025; Hamidie *et al*., 2021). In this study, supplementing the diet with curcuminoid when RNR activity was restricted helped with meat quality parameter.

The current data showed that intestinal morphology was negatively impacted when the RNR inhibitor was used while curcuminoid effects were similar to control. A study showed that there might be a link between reduced RNR and intestinal health, specifically concerning the maintenance of intestinal tissue integrity (Arnaoutov *et al*., 2020). Although curcuminoid have been shown to positively impact gut health through various mechanisms, including modulation of the gut microbiome, strengthening the intestinal barrier, and reducing inflammation (Balaji *et al*., 2025). Duration of the study potentially plays an important role in this matter as a study showed growth improvements in turkey poults over a 13-week period (Lipiński *et al*., 2021).

CONCLUSIONS

In conclusion, inhibiting RNR activity negatively impacted meat quality and intestinal health during the early developmental stages of turkeys. Dietary supplementation with curcuminoids partially alleviated these adverse effects, likely through their antioxidant and anti-inflammatory properties. Further studies are warranted to explore dose-dependent responses to RNR inhibitors and assess their influence on growth performance, meat quality traits, and the regulation of alternative growth-related pathways.

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NOVELTY STATEMENT

This is the first in-vivo avian study showing that hydroxyurea-mediated RNR inhibition impairs gut morphology, mitochondrial biomarkers, and meat quality, and that dietary curcuminoids can partially offset these defects.

AUTHOR'S CONTRIBUTION

MS: Conceptualization, funding, formal analysis, methodology, software, writing original draft, writing review, editing.
VPRK, HRK and HRRN: Methodology, funding, writing original draft, writing review, editing.
HK: Funding, investigation, writing review, editing.

Ethic statement

All procedures used in this experiment followed the guideline of Institutional Animal Care Committee of the University of Melbourne.

Generative AI and AI-assisted technology statement

No generative AI or AI-assisted tools were used in the

conception, conduct, analysis, or writing of this study.

Conflict of interest

The authors have declared no conflict of interest.

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