

Research Article



Investigating the Impact of Dietary Supplementation on mRNA Expression of Growth-Related Peptides and Gut Health in Broilers

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Abstract | The use of antibiotics for non-therapeutic purposes has been prohibited in poultry production. Recent studies have suggested that turmeric could serve as a potential alternative to antibiotics in promoting growth in chickens. Therefore, this study aimed to determine the effects of turmeric supplementation on the gene expression of growth-related peptide and mucin2, an indicator of intestinal health, in broilers. We added two percentages of turmeric (0.5% and 1%) to the standard diet, categorizing them as turmeric 0.5% and turmeric 1%, and compared the results with the control group (turmeric 0.0%). Gene expression analysis was conducted anterior pituitary (APit): liver, and intestine. The results showed that body weight gain was higher in the turmeric-treated groups, and feed conversion ratio was improved significantly, indicating that turmeric is more efficient in converting feed into body mass. Analysis of gene expression by RT-qPCR revealed an increase in mucin2 gene expression in the turmeric-treated groups, suggesting an enhancement of gut health. Furthermore, the study found overexpression of the growth hormone (GH) and thyroid-stimulating hormone mRNA expression in the APit. In the liver, an increase in the mRNA expression of the GH receptor in the turmeric-treated groups could facilitate GH action on hepatocytes, leading to an increase in the gene expression of insulin-like growth factors and their binding proteins, which supports muscle cell differentiation and proliferation. Data suggested that turmeric might stimulate myoblast differentiation and satellite cell proliferation to increase muscular growth. In summary, turmeric addition promoted body growth by activating certain genes and inhibiting others. This effect could be due to an increase in the expression of genes that drive muscle cell proliferation. Finally, turmeric enhances gut health through the mucin2 gene.

Keywords | Growth hormone, TSH, Mucin2, Insulin-like growth factor, RT-PCR, Body weight

Received | October 03, 2024; **Accepted** | January 01, 2025; **Published** | February 01, 2025

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Citation | Kadhim HJ, Hasan IJ (2025). Investigating the Impact of dietary supplementation on mRNA expression of growth-related peptides and gut health in broilers. J. Anim. Health Prod. 13(1): 51-58.

DOI | <https://dx.doi.org/10.17582/journal.jahp/2025/13.1.51.58>

ISSN (Online) | 2308-2801

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INTRODUCTION

The primary determinants of animal growth can be broadly categorized into dietary and hormonal factors. Both play an essential role in influencing growth patterns, development, and health. To be more precise,

numerous genes within the somatotrophic and thyrotrophic axes are modulated by intrinsic dietary variables and metabolic interactions, influencing growth at the transcriptional level (Yoo *et al.*, 2021; Zhao *et al.*, 2004; Beccavin *et al.*, 2001). The somatotrophic axis, encompassing the interplay between growth hormone (GH) and insulin-like growth

factor I (IGF-I): is a vital mechanism in controlling animal growth, illustrating the intricate link among nutrition, metabolism, and gene expression. GH is released from somatotrophic cells of the anterior pituitary (APit) into the circulation, where it interacts with growth hormone receptors (GHR) on hepatocytes, resulting in the release of IGF-I (Vázquez-Borrego *et al.*, 2021; Gahete *et al.*, 2009). IGF-I promoted the differentiation and proliferation of bone and muscle cell, maintained skeletal muscle mass, and activated myoblast cells (Bikle *et al.*, 2015; Anh *et al.*, 2015; Clemmons, 2009; Kita *et al.*, 2002; Kuhn *et al.*, 2002). Furthermore, it has been observed that peripheral IGFs regulated GH negatively (Romero *et al.*, 2012). Additionally, the IGF system comprises an IGF-binding protein (IGFBP) that modulates IGF actions by inhibiting insulin-like effects, controlling the half-life of IGFs in circulation, redistributing IGFs between extracellular fluids in tissues, balancing positive and negative signals, and managing muscle development in birds (Kim, 2010). In addition, thyroid stimulating hormone (TSH) is an essential endocrine regulator of postnatal metabolism of broilers (Ellestad *et al.*, 2019; Decuyper and Buyse, 2005). It has been found that thyroid hormone displayed a significant relationship with body weight, suggesting the importance of in thyroid hormone in maintaining normal growth (Mullur *et al.*, 2014; Lu *et al.*, 2007).

In rapidly growing chicks, the digestive system must be efficient to meet development and maintenance demands. In particular, goblet cells produce mucus in the intestinal lumen, which is crucial for preserving a suitable environment for nutrient digestion and transportation to the underlying layers. Goblet cells in the intestine develop quickly at an early age and are affected by several variables such as dietary and ambient factors, gut microflora, and diet (Duangnumsaeng *et al.*, 2021). According to Horn *et al.* (2009), an unsuitable diet can modify mucin2 (*MUC2*) gene expression in ducks, leading to alterations in mucin secretion and eventually disruption of intestinal functions. Therefore, maintenance of well-developed mucus-secreting cells and intestinal layers is essential for growth and body weight gain.

Hormonal levels as well as intestinal health and components influence avian growth. Previously, low levels of antibiotics have been added to animal diets to enhance growth and productivity. However, these low levels of antibiotics have resulted in an antibiotic-resistant population. Consequently, the European Union has prohibited the use of antibiotics as growth promoters since 2006. Studies have also reported the effectiveness of turmeric with no adverse effects on public health (Dono, 2014). The main active compound in turmeric is curcumin, which has a variety of roles including antioxidant, anti-inflammatory, antimicrobial, and anticancer activities (Amalraj *et al.*, 2016; Aggarwal and Harikumar, 2009; Al-Sultan, 2003). Al-Kassie *et al.*

(2019) demonstrated that using turmeric powder in chicken feed decreased mortality and morbidity in fast-growing chicks. Moreover, researchers have shown that turmeric efficiently managed blood parameters and facilitated immune system functions in chicks (Ayodele *et al.*, 2021; Raja *et al.*, 2017).

According to Kumari *et al.* (2007), turmeric significantly improves broiler growth rates and body weights. The growth-promoting effects of turmeric supplementation can be attributed to stimulation of digestive enzyme secretion (Li *et al.*, 2023; Platel and Srinivasan, 1996; 2000). However, little attention has been devoted to addressing the effect of turmeric on growth performance at the molecular level. Therefore, this study aimed to investigate the role of turmeric supplementation in the growth processes of broiler chicks. Therefore, the relative mRNA expression of growth-related and intestinal-related genes was evaluated using RT-qPCR after addition of different concentrations of turmeric.

MATERIALS AND METHODS

BIRDS AND SAMPLING

Male broiler chickens (one-day-old, Cobb 500) were grown on floor pens in a controlled house. They were fed and watered *ad libitum*. The temperature was set at 34 °C for the first five days; thereafter, it reduced gradually to 23 °C until the sampling day, which was on 42 days of the age. On the first day, chicks were divided into three groups, with the last two assigned as turmeric-treated groups that received different percentages of turmeric, including 0.5% and 1% in their standard diet. The turmeric-treated groups were categorized according to the turmeric percentages as follows: turmeric 0.5% and turmeric 1%. On the other hand, the first group was fed a standard diet with no turmeric and considered the control (turmeric 0.0%). The study involved measuring body weight weekly in all groups and calculating the feed-conversion ratio (FCR) at the end through dividing total feed intake by weight gain. Birds were cervical dissected at 42 and 43 days of age. APit, liver, and intestine, were collected for growth-associated and intestinal-related genes. Changes in the mRNA levels of growth hormone (GH) and thyroid stimulating hormone (TSH) mRNA levels were evaluated in the APit. In addition, growth hormone receptor (GHR): insulin-like factors (IGF-I and IGF-II): and IGF binding protein (IGFBP) genes were assessed in hepatic tissue. Finally, the mucin (*MUC2*) gene was studied as an intestinal-related gene.

SAMPLE PREPARATION, REVERSE TRANSCRIPTION AND REAL-TIME POLYMERASE CHAIN REACTION

Total RNA was extracted from the APit, liver, and intestine using Trizol-chloroform (Kadhim *et al.*, 2020). To eliminate genomic DNA from the samples, the RNA was

Table 1: Primers' list for real time polymerase chain reaction.

Gene	GeneBank #	Primer sequences (5'-3')	Size (bp)	Annealing Tm (°C)
cGH	NM_204359	F-CACCACAGCTAGAGACCCACATC R-CCCACCGGCTCAAACCTGC	201	58
TSH	XM_025143670	F-CCACCATCTGCGCTGGAT R- GCCCGGAATCAGTGCTGTT	128	58
GHR	NM_001001293	F-CTTCAGTGCAAGCGACACAT R-GGCCATGACTCTCTGCTTTC	186	58
IGF-I	NM_001004384	F: GAGCTGGTTGATGCTCTTCAGTT R: CCAGCCTCCTCAGGTCACAAC	148	58
IGF-II	NM_001030342.5	F-GGCGGCAGGCACCATCA R-CCCGGCAGCAAAAAGTTCAAG	215	58
IGFBP2	NM_205359	F-CCAATGTCAGCCAGAGAAC R-ACAGGCAGGACACAAGAG	219	59
MUC2	XM_040673077.2	F- CAGCACCAACTTCTCAGTTCC R- TCTGCAGCCACACATTCTTT	102	58
18S	NM_204305	F: TCCCTCCCGTTACTTGGAT R: GCGCTCGTCGGCATGTA	128	59

mixed with DNase I, and the RNeasy mini kit (Qiagen) was used to purify the extracted RNA. The RNA concentration in the samples was measured using nonodrop spectrophotometry. Then, 2µg of the RNA was used for cDNA synthesis in 40 µl using Superscript® III as described in our previous publications (Kadhim *et al.*, 2021; 2019). The housekeeping gene used in the experiment was 18S (Kadhim and Kuenzel, 2022). Primer sets for these genes were listed (Table 1). For RT-PCR, samples were obtained in duplicate, and the average Ct and delta Ct values were determined for all genes. Fold changes in mRNA expression were calculated after normalization with housekeeping genes using the $2^{-\Delta\Delta Ct}$ equation (Schmittgen and Livak, 2008).

STATISTICAL ANALYSIS

The results of the experiment were analyzed using the JMP® 18.0. After validating the normal distribution, variations across groups were examined for the studied tissues, including the APit, liver, and intestine. The findings were first calculated by one-way ANOVA, followed by Tukey's HSD test to evaluate the relative variations in mRNA levels across groups for each gene. The findings are reported as the mean ± standard errors of the mean (SEM). Statistical significance was set at $p < 0.05$.

RESULTS AND DISCUSSION

TURMERIC PROMOTED BODY WEIGHT GAIN

The addition of turmeric to the diet resulted in weight gain (Table 2). As the amount of turmeric in the diet increased, bird body weight gradually increased in the turmeric-treated groups, but the total feed intake decreased significantly as well. Specifically, the turmeric 1% group

showed the greatest increase in body weight, while the feed intake was lower in the turmeric 0.5% group compared to that in the control group. Furthermore, the increase in the birds' body weight in the turmeric 1% group was associated with a decrease in total feed consumption compared with the control. Additionally, the feed conversion ratio (FCR) decreased in the turmeric-treated groups compared to the control group. Specifically, the turmeric 1% group displayed the lowest FCR.

Table 2: Effect of different turmeric percentages on the growth performance of broiler chickens.

Parameters	Control Mean±SEM	Turmeric 0.5% (Mean±SEM)	Turmeric 1% (Mean±SEM)
Starting weight (g/b)	58.56 ±1.61 ^A	56.06 ±1.51 ^A	60.125±1.80 ^A
Final Weight (g/b)	1826.25 ±6.80 ^C	1990.125±9.14 ^B	2100.124±6.47 ^A
Net weight gain (g/b)	1767.83 ±7.48 ^B	1934.81±9.19 ^A	2040.07 ±6.83 ^A
Total feed intake (g)	3998.86 ±9.06 ^A	3767.43 ±8.60 ^B	3790.16±12.26 ^B
FCR	2.19±0.21 ^A	1.95±0.12 ^B	1.86±0.17 ^B

Rows bear different letters indicating the significance ($P < 0.05$); SEM= The Standard Errors of the Mean.

GENE EXPRESSION DATA

GH AND TSH GENE EXPRESSION DATA IN THE ANTERIOR PITUITARY (APIT): Turmeric supplementation in broiler diets increased GH gene expression in the APit (Figure 1). The turmeric-treated groups showed a significant increase in GH mRNA levels compared to the control group ($P < 0.04$). The turmeric 1% groups exhibited the highest levels of GH gene expression ($P < 0.001$). Furthermore,

TSH gene expression displayed the highest mRNA levels in the turmeric 1% group ($P<0.01$).

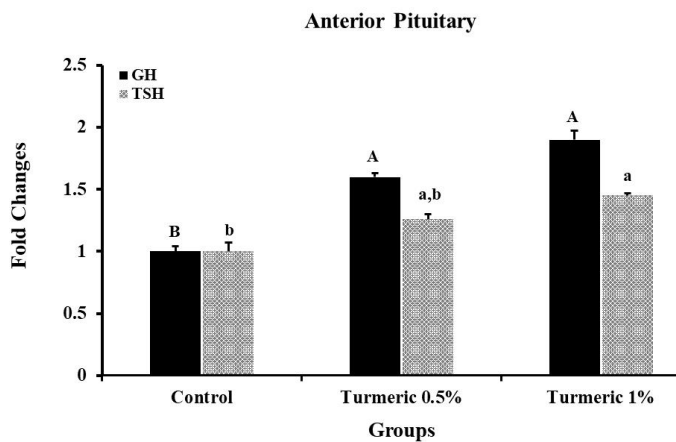


Figure 1: Growth hormone (GH) and thyroid stimulating hormone (TSH) mRNA expression in the anterior pituitary (APit). Fold changes in the mRNA expression were calculated by normalizing the results with the housekeeping gene (18S) using the $2^{-\Delta\Delta C_t}$ equation. Means $\pm$ SEM were reported for each gene in each group. A P -value less than 0.05 reflects the significant differences across groups and is indicated by a distinct letter above each histogram.

GHR, IGF-I, IGF-II AND IGFBP GENE EXPRESSION

DATA IN THE LIVER: Several genes in the hepatic tissue displayed fold changes in their mRNA expression levels (Figure 2). GHR gene expression increased significantly in the turmeric-treated groups compared with that in the control group (Figure 2A). Specifically, the turmeric 0.5% group documented the first significant increase in GHR expression ($P<0.01$); but its peak expression was in the turmeric 1% group ($P<0.001$). In the liver, IGF-I and IGF-II were significantly upregulated in the turmeric-treated groups (Figure 2B). Furthermore, the rise in IGF-I mRNA levels was more prominent and higher than that of IGF-II. Remarkably, the first significant upregulation in IGF-I and IGF-II gene expression was in the turmeric 0.5% group ($P<0.01$). Additionally, both genes showed a peak response in the turmeric 1% group ($P<0.001$). The fourth gene measured in the hepatic tissue was IGFBP, which was significantly upregulated in the turmeric-treated groups (Figure 2C, $P<0.01$). Moreover, the turmeric 1% group showed a peak increase in IGFBP mRNA levels ($P<0.001$).

MUCIN 2 GENE EXPRESSION DATA IN THE INTESTINE

Examination of mucin 2 (*MUC2*) mRNA in intestinal tissues revealed a unique pattern of expression (Figure 3). In brief, the turmeric 0.5% group showed a significant increase in *MUC2* mRNA levels compared to the control group ($P<0.01$). Remarkably, the turmeric 1% group ($P<0.001$) exhibited the greatest *MUC2* gene upregulation.

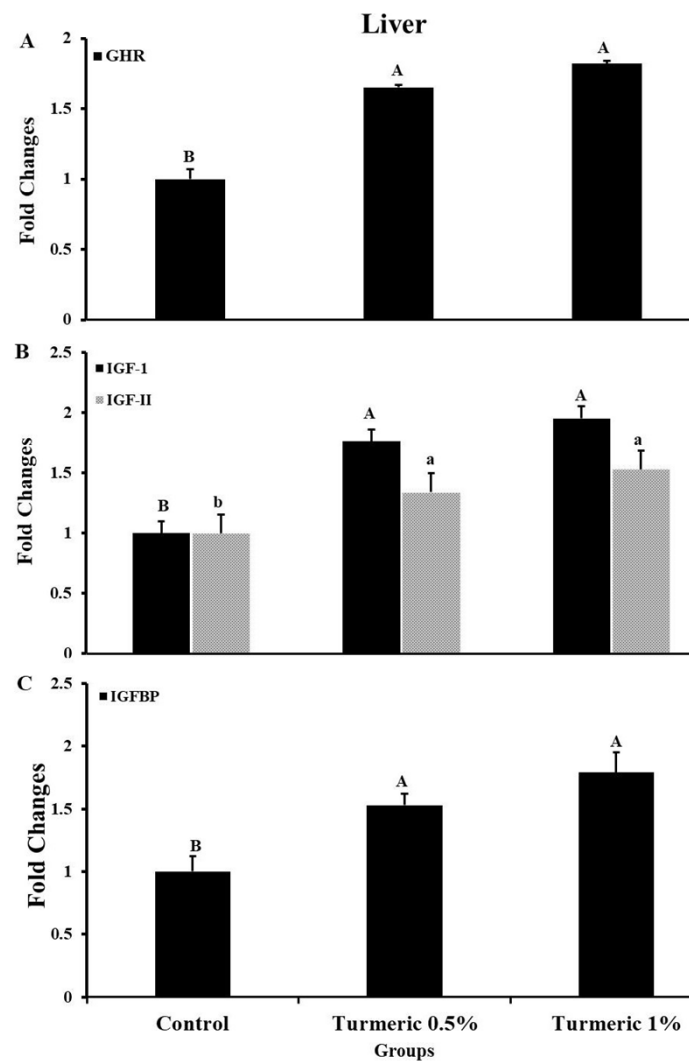


Figure 2: Growth hormone receptor (GHR): insulin-like growth factors I and II (IGF-I and IGF-II): and insulin-like growth factor binding protein (IGFBP) mRNA expression in liver tissue. Fold changes in the mRNA expression were calculated by normalizing the results with the housekeeping gene (18S) using the $2^{-\Delta\Delta C_t}$ equation. Means $\pm$ SEM were reported for each gene in each group. A P -value less than 0.05 reflects the significant differences across groups and is indicated by a distinct letter above each histogram.

This study sheds light on the molecular mechanism of the effect of turmeric on growth performance by measuring growth-related and intestinal-related genes. Body weight and feed conversion ratio were also reported. Notably, the birds' body weight increased significantly in the turmeric-treated groups as the turmeric percentages increased in their diet. Importantly, growth-promoting genes were upregulated in the turmeric-treated groups. Specifically, an increase in mRNA levels of GH, TSH, and IGFs was observed in the turmeric treated groups, indicating that turmeric may play a role in activating the somatotrophic and thyrotrophic axes. However, this was dependent on the turmeric concentration in the diet. Here, the fold changes

in the mRNA expression of several genes within the axes and intestine of broiler chicks were analyzed.

In this study, regardless of the decrease in feed consumption, the body weight of birds increased dramatically as the quantity of turmeric in the diet increased. Nevertheless, the data revealed significant variations in body weight growth in the turmeric 0.5% and turmeric 1% groups. The increase in body weight of birds in the turmeric-treated groups could be related to the presence of curcumin in the meal, which increases muscle mass. Furthermore, curcumin has been shown to increase feed utilization by promoting protein synthesis via the enzymatic system in birds (Hafez *et al.*, 2022; Al-Sultan, 2003). This resulted in improved digestion, enhanced nutrient metabolism, and, eventually, an increase in body weight (Aderemi and Alabi, 2023; Durani *et al.*, 2006). Furthermore, the increase in body weight of the treated groups was possibly due to the activation of digestive enzymes in the intestinal mucosa. In this context, digestive enzymes can enhance the synthesis of bile acids in the liver and their excretion in bile, which would beneficially affect lipid digestion and absorption (Adegoke *et al.*, 2018). In another study, chicks fed a basal diet with curcumin led to increase body weight gain by improving the secretion of endogenous digestive enzymes (Reda *et al.*, 2020; Srinivasan, 2005). However, we did not measure the digestive enzyme concentration and activity in the current study, and we plan to follow our work in the next experiment.

At the transcriptional level, curcumin induced changes in the expression of several genes linked to growth and digestive tract integrity. Specifically, an increase in GH and TSH expression within the APit was observed (Figure 1). As a result, the increase in body weight in the turmeric-treated groups might be due to activation of the GH gene in the APit. Consistent with our findings, Liczbiński *et al.* (2020) and Gupta *et al.* (2011) reported that curcumin can influence signaling molecules. Barry *et al.* (2009) demonstrated that curcumin functions in a similar way to vitamin D, modulating approximately 700 genes by inserting itself into cells.

In the liver, GH acts on the hepatic tissue via a cell membrane receptor called GHR. In the current study, GHR mRNA was upregulated in the turmeric-treated groups, allowing GH to act on hepatocytes more effectively (Figure 2A). The outcome was an increase in IGF gene expression in the liver tissue (Figure 2B). IGF overexpression may have a positive influence on muscle cell differentiation and growth via its receptors in skeletal muscle cells. In this context, studies have demonstrated that IGF-I can induce skeletal muscle growth and inhibit muscle atrophy (Yoshida and Delafontaine, 2020; Timmer *et al.*, 2018; Wen *et al.*,

2014; Lin *et al.*, 2004). IGFs, via IGFR, promote muscle cell proliferation and increase metabolism rates (Yoshida and Delafontaine, 2020; Giachetto *et al.*, 2004). This could be due to IGF activity on DNA and protein synthesis (Liu and Zhao, 2014; Duclos, 2005). The increase in the body weight of turmeric-treated groups could be attributed to curcumin activity, which increases IGF expression.

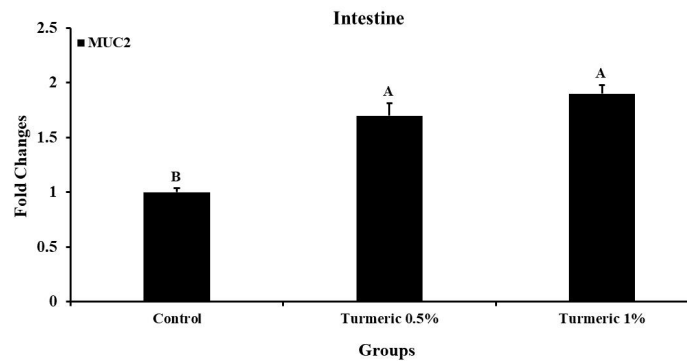


Figure 3: Mucin 2 (MUC2) mRNA expression in the intestinal tissue. Fold changes in the mRNA expression were calculated by normalizing the results with a housekeeping gene (18S) using the $2^{-\Delta\Delta C_t}$ equation. Means $\pm$ SEM were reported for each gene in each group. A *P*-value less than 0.05 states the significant differences across groups and is indicated by a distinct letter above each histogram.

IGFs are carried in the blood by a protein called IGFBP, which is essential for regulating the half-life and redistribution of IGFs between tissues and extracellular fluids (Kim, 2010). IGFBPs are sensitive to changes in dietary protein levels (Lee *et al.*, 2005). Data showed IGFBP downregulation in turmeric-treated groups, suggesting a negative relationship between IGFBP and IGFs that resulted in better body weight gain (Figure 3C). Consistent with our results, Hosnedlova *et al.* (2020) and Kita *et al.* (2005) reported a negative correlation between IGFBP and growth performance. In addition, no IGFBP-2 mRNA expression was detected in the hepatic tissues of well-fed birds. However, IGFBP-2 gene expression markedly increased after two days of food deprivation (Kita *et al.*, 2002).

In the intestine, goblet cells produce secretory mucin (MUC2): a major component of intestinal mucus that provides a physical barrier against pathogens and preserves a suitable milieu for GIT functions (Duangnumsaeng *et al.*, 2021). In the turmeric-treated groups, upregulation of MUC2 gene expression indicated that the addition of turmeric provided an appropriate milieu for digestion and absorption. Furthermore, Rajput *et al.* (2013) reported that villus area and absorption function of the small intestine of broilers were increased when turmeric was added to their diet. Eventually, growth has a positive correlation with gut health.

Dietary alterations influenced significantly on the body's performance and weight gain of broiler chickens. When turmeric was added to their standard diet, the groups that received turmeric supplementation in it demonstrated an improvement in feed conversion ratio and an increase in body weight. Data suggested that turmeric might be used as an alternative to antibiotics in the poultry sector to promote growth. These alterations occur at the transcriptional level, affecting both growth-related peptides within the somatotrophic axis and intestinal-related genes. Turmeric positively influenced body weight gain and metabolic processes by altering the expression of genes that regulate muscle cell proliferation. Finally, turmeric plays an essential role in gut health maintenance by stimulating mucus secretion, evidenced by the increased expression of the MUC2 gene in the intestinal tract.

ACKNOWLEDGMENTS

We would like to thank College of Vet. Medicine and Surgery/ Shatrah University for their help with animal husbandry during animal experimentation.

NOVELTY STATEMENTS

The study addressed the impact of turmeric on the mRNA expression of growth-related peptides and mucin 2, a biomarker for gut health. The study found that turmeric supplementation promoted body growth by activating genes linked to muscle cell proliferation and differentiation. Additionally, turmeric enhanced gut health. As a result, it is recommended to add 1% of turmeric to the standard diet of broilers.

AUTHOR'S CONTRIBUTIONS

Hakeem J. Kadhim conceptualized the study, collected the samples, conducted the study, analyzed the data, and prepared the initial draft of the manuscript. Furthermore, Hakeem J. Kadhim and Iman Jaber Hasan have contributed in the revised version. All authors have read, improved, and approved the submitted version of the manuscript.

CONFLICT OF INTEREST

We declare no conflict of interests.

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