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Safety Hepatic and Renal Concerns About Dietary Inclusion of Ginger (*Zingiber officinale*) roots in Male Japanese Quails (*Coturnix japonica*)

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Abstract

Japanese quails are an important source of animal protein. Several recent researches aimed to add natural supplements to the quails' ration to enhance growth, food conversion, or reproductivity. However, the possible adverse effects are almost neglected. This study aims to highlight the effects of Ginger roots on the histological features and functional parameters of the liver and kidney in Japanese male quails. Birds were divided randomly into three equal experimental groups. The first group (control group) was fed a commercial basal mash ration, while the second and third groups were fed on the same ration mixed with 10 and 15 grams of ginger roots/Kg feed, respectively. Supplementation with both doses of Ginger resulted in histopathological abnormalities in the liver and kidney. However, the hepatic and renal cytological deteriorations were mild to a moderate degree. Plasma aspartate aminotransferase and alanine transaminase were significantly higher in the low Ginger group than in the high Ginger and control groups. Ginger at both doses induced a significant decrease in plasma total cholesterol and uric acid levels and a significant increase in plasma malondialdehyde in Japanese male quails. Despite the observed hepatic and renal histopathological alterations in the Ginger treated groups, they are not sufficient to cause hepatic and renal dysfunction based. In conclusion, using ginger supplementation in quail could be applied at these doses and duration of intervention, however, with caution because the liver and kidney are sensitive to ginger.

Keywords: Ginger, Japanese male quail, physiology, Histopathology

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Competing interest: The authors have declared that no competing interest exists.

Introduction

Japanese quails (*Coturnix japonica*) attract much attention in the poultry industry due to their exceptional physiological characteristics including much lower space requirements, shorter life cycle, more resistance to diseases, and earlier sexual maturity compared to the other avian species (Batool *et al.,* 2021). From the breeders' point of view, they become a widespread meat source among consumers, therefore commercial quail farming is a cost-effective opportunity and the investments in this field are remarkably expanding (Santhi and Kalaikannan, 2017). Increasing growth performance and reproductive efficiency is a prerequisite approach to improving marketing opportunities. In this area of research, several studies focus on the dietary inclusion of Ginger as a promising candidate (Gholami and Ahangaran *et al.*, 2021; Herve *et al.,* 2018; Tchoffo *et al.*, 2017) without taking into account its possible adverse effects on other biological systems of quails or try to optimize an effective and a safe window of dose/duration of intervention before it becomes a part of the nutritional practice of quails. Supplementation of Ginger essential oil for 9 weeks resulted in decreased serum total cholesterol, low-density lipoprotein-cholesterol, triglycerides, transaminases, and creatinine along with decreased total protein and globulin and the antioxidant enzymes activities in comparison with the control (Herve *et al.,* 2018; Herve *et al.,* 2019). In another feeding regimen, a decrease in total cholesterol and triglycerides was observed without significant changes in glucose, total protein, albumin, and globulin following the administration of ginger powder for 5 weeks (Swain *et al.,* 2017). Although these findings confirm the improving effects of ginger on the hepatic and renal microenvironments (Herve *et al.,* 2018; Herve *et al.,* 2019; Swain *et al.,* 2017), they adopt a unidirectional look and lack of monitoring of the safety or the in situ cytological changes in these vital organs. On the other hand, aqueous extract of Ginger induced histopathological lesions in the liver and kidney of male Wistar rats such as hepatic vacuolation, glomerular degeneration and shrinkage, cellular infiltration, and vascular congestion (Ajanwachuku *et al.,* 2018). Given these contradictory data, we aimed to highlight the effects of ginger roots on the biochemical and histological features of the liver as a center of metabolism and xenobiotic detoxification and the kidney as an excretory and regulatory organ using two selected doses for 9 weeks in male Japanese quails.

Material and Methods

Characterization of phytochemical constituents of Ginger roots

It was performed by Analytical Chemistry Unit (Department of Chemistry, Faculty of Science, Assuit University, Assuit, Egypt) using GC-MS (7890A-5975B).

Birds, housing and experimental design

This experiment was carried out at the poultry research farm of the Poultry Production Department, Faculty of Agriculture, Assiut University, Assiut, Egypt. In this study, a total number of 450 one-day-old unsexed Japanese quail birds were distributed into three equal groups each with 150 birds and were housed on brooding floor pens. After gender discrimination at 4 weeks of age 120 males (40 per group) were selected and redistributed into three groups and were

transferred to individual battery cages (20 × 20 × 25 cm).

The powder of Ginger roots was purchased from an herbal store in Assiut governorate, Egypt. The administration of Ginger started at 7 days of age till the end of the experimental duration as follows: the control group was fed a commercial mash diet + 0 Ginger, the low Ginger group was fed a commercial mash diet +10 grams of Ginger/Kg feed, and the high Ginger group was fed a commercial mash diet + 15 grams of Ginger/Kg feed (Akhlaghi *et al.*, 2014; Shanoon, 2011). All procedures of the current study had been conducted following the University guidelines for the care of experimental animals. Ethical approval was obtained from the Committee of the Faculty of Veterinary Medicine, Assiut University, Egypt (aun/vet/4/0001).

Environmental conditions and experimental diets

The brooding temperature gradually reduced from 35−37°C (one day old) to 20−24°C at the 5th week of age, and the relative humidity was 65% up to the end study. The lighting program was 23h light:1h dark at the first four days, which was gradually decreased (one hour/week) to reach 17 h light: 7h dark at seven weeks of age, and light intensity was 50 lux during the study period at the head of birds. This lighting regime lasted constantly till the end of the experiment (70 days of age). Feed and water were continuously provided *ad libitum*, the starter ration contained 24% crude protein (CP) and 2800 ME Kcal/kg during the growing period and 21% (CP) and 3000 Kcal (ME)/Kg during the production period.

Sample collection

At the 10th week of age, 10 quails from each group were sacrificed by severing the jugular vein, and blood was allowed to flow freely into heparinized tubes. The blood plasma was separated by centrifugation at 3000 rpm for 15 minutes and stored at (-20°C) for further analysis. For histological evaluation, specimens from the liver and kidney were fixed in 10% neutral buffered formalin solution in dibasic anhydrous sodium phosphate and monobasic acid phosphate (pH 7.0) for 48 hours.

Histopathological examination

The tissues were dehydrated with an ascending series of alcohols and cleared by immersing in xylene and then embedded in paraffin wax (Sigma Aldrich, USA) according to the standard methodology described before (Hussein and Abdel-Maksoud, 2020). Sections were cut at 5 µm thickness using a microtome (Richert Leica RM 2125, Germany) and mounted on glass slides. The sections were deparaffinized with xylene and rehydrated through a decreasing gradient of ethanol followed by washing in distilled water. Then, the sections were stained with hematoxylin and eosin (H&E) for general histological examination and Crossmon's trichrome and Periodic Acid Schiff's (PAS). All the procedures were cited in (Suvarna *et al.*, 2018). The sections were examined for histopathological changes using an OLYMPUS BX51 microscope and photographed with an OLYMPUSDP72 camera adapted to the microscope (Department of Anatomy and Histology, Assiut University, Egypt).

Histomorphometric scoring

Each bird was assigned a score based on the tissue histopathological

examination. The samples were scored semi-quantitatively, with an assessment based on the visual field inspection of a minimum of 10 sections from each Group. Histopathological lesions were scored by a practiced veterinary pathologist who was uninformed by the experimental treatments or their information previously. The severity of each lesion was scored as follows (Gibson-Corley *et al.,* 2013): 0=no lesions; 1=minimal (1–10% of the tissue section affected); 2=mild (11–25%); 3=moderate (26–45%) and 4=severe (>45%).

Biochemical parameters

Alanine aminotransferase (ALT) (Catalog number: 264001) and aspartate aminotransferase (AST) (Catalog number: 260001) activities were measured according to the manufacturer's instructions using commercial colorimetric kits provided by Egyptian Company for Biotechnology, Cairo, Egypt. Total cholesterol (TC) was assessed based on the cholesterol oxidase phenol 4-aminoantipyrine peroxidase method following the procedure of (Roeschlau *et al.,* 1974). Urea was assessed according to the manufacturer's instructions using a commercial colorimetric kit (catalog number: 318001) provided by Egyptian Company for Biotechnology, Cairo, Egypt. Uric acid (UA) and glucose were analyzed by enzymatic colorimetric methods using kits obtained from Bio-diagnostic, Giza, Egypt (catalog number: UA2021 and GL1320, respectively). Catalase (CAT) activity was measured according to the method of (Lück, 1963) using a colorimetric kit (catalog number: CA2517, Biodiagnositic company, Egypt). Superoxide dismutase (SOD) activity was determined based on its ability to inhibit the autoxidation of epinephrine in an alkaline medium (Misra and Fridovich, 1972). Nitric oxide (NO) was measured as nitrite concentration using the method of (Ding *et al.,* 1988). Total antioxidant capacity (TAC) was measured by a commercially available kit (catalog number: TA2513, Biodiagnositic company, Egypt). It was estimated depending on the colorimetric determination of residual H_2O_2 by an enzymatic reaction following the reaction of antioxidants in the sample with exogenously provided H_2O_2 (Koracevic *et al.,* 2001). Malondialdehyde (MDA) were measured according to the procedure of (Ohkawa *et al.,* 1979) using tetramethoxypropane as an external standard.

Statistical analysis

Data were represented as mean ± standard error of the mean (SEM). The results were analyzed by one-way analysis of variance (ANOVA) followed by Duncan post-test using SPSS program version 16 (SPSS Inc., Chicago, USA). Differences of $P < 0.05$ were considered to be statistically significant.

Results

Characterization of phytochemical constituents of Ginger roots

The GC-MS revealed that cis-6-shogaol is the most prevalent compound in Ginger roots (table 1). Manganese level is 32.36 mg/kg.

Table 1. The phytochemical constituents of ginger roots

Compound	Retention time (min)	% of total	Matching factor	Molecular weight
Cis-6-shogaol	16.08	25.303	38	276
Paradol	9.931	5.562	97	194
Gingerol	16.855	4.982	95	294
(1S,2S,3S,6S)-3-hydroxy-2-(Beta-hydroxymethyl)-1,7,7-trimethyl Bicyclo(4.4.0)Decane	18.715	3.154	38	240
Zingiberene	9.307	1.008	78	204
Zingerone	14.215	0.016	50	194

Hepatic histopathological changes

The microscopic examination of the quail's liver of the control group revealed normal hepatic architectures which included, a normal central vein, hepatic cords, hepatocytes, and portal area contents (bile duct, hepatic artery, and vein) (Fig. 1A-C). Liver sections taken from the low Ginger group (10 g/kg feed) demonstrated several hepatic injuries. The central veins and hepatic arteries were dilated and engorged with blood with periportal mild fibrosis. The portal triads were bordered by threads of fibrosis and showed mononuclear inflammatory cellular infiltration. Hepatocytes revealed vacuolar degeneration and distended hepatic sinusoids in between hepatic cords (Fig. 1D-F). The sections taken from the quail's liver of the high Ginger group (15 g/kg feed) showed several areas of pathological lesions. The portal veins revealed marked dilatation and congestion and showed thickening in the wall with periportal fibrosis. Mononuclear inflammatory cellular infiltration with dissociation and disorganization of hepatic cords were also observed. Focal nodular mononuclear inflammatory cellular aggregation and focal area of fibrosis were detected. The hepatocytes showed hepatocellular necrobiotic changes (Fig. 1G-I). Based on the histopathology scoring, the severity of vascular congestion (Fig. 2A), periportal fibrosis (Fig. 2B), and hepatocellular changes (Fig. 2C) were

significantly (P< 0.05) increased by increasing the feed dosage of Ginger compared with the control group.

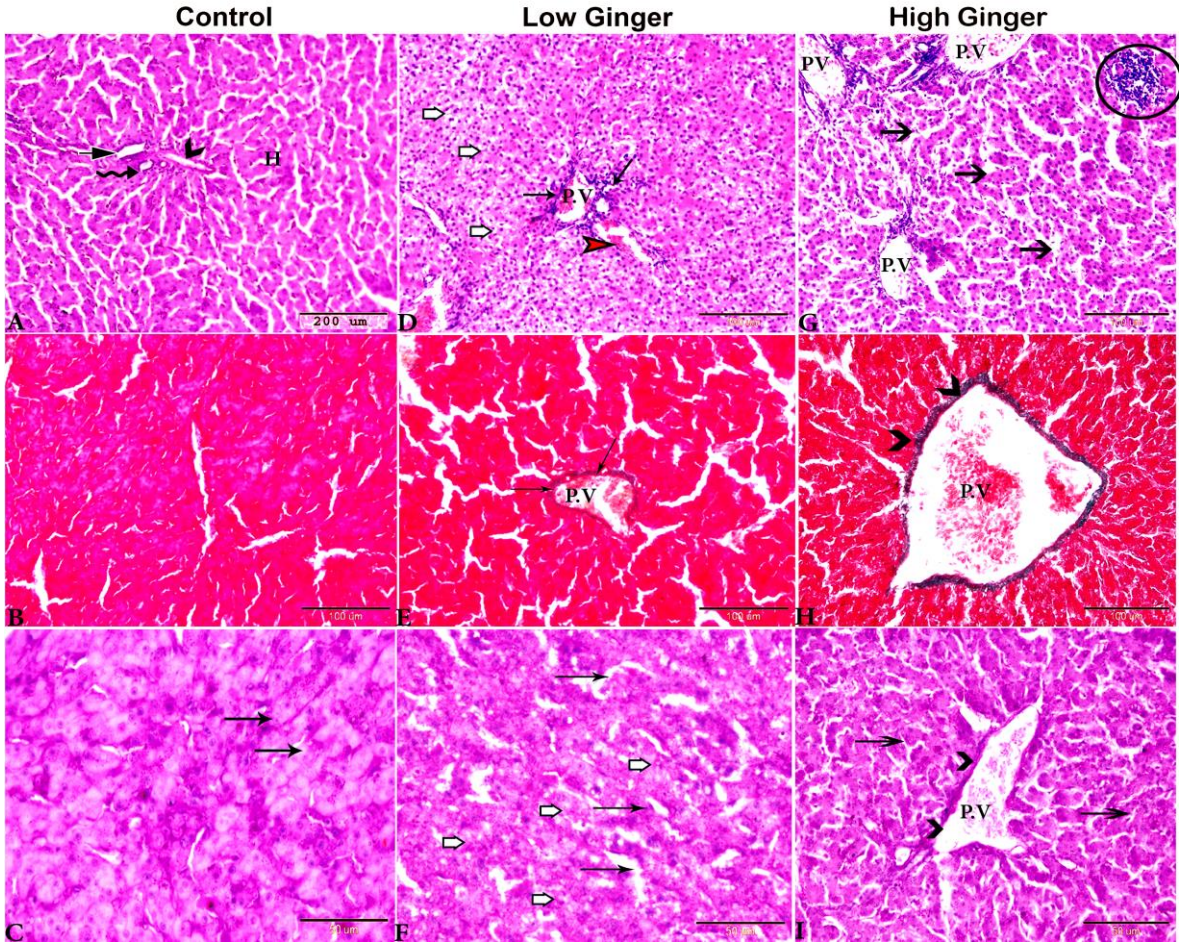

Figure 1. Photomicrograph of liver sections from the experimental groups showing: (A, B&C): liver tissue sections from the control group showed normal hepatic architectures; (A): Normal hepatic portal triad structure, normal portal vein (arrow), normal hepatic artery (arrowhead) and normal bile duct (zigzag arrow). Normal hepatocytes (H). (B): no fibrous tissue was present. (C): Hepatocytes were arranged in cords, tightly connected with the normal cellular membrane and homogenous cytoplasm (arrows). (D, E&F): Liver tissue sections from the low Ginger group showed: (D): congested portal vein (P.V) and hepatic artery (red arrowhead), the portal triad was surrounded by mild fibrous tissue infiltrated with some mononuclear inflammatory cells (arrows). Hepatocytes showed vacuolar degeneration (white arrowheads). (E): mild fibrosis (arrows) around portal vein (P.V). (F): Vacuolar degeneration of hepatocytes (white arrowheads), dilated and distended hepatic sinusoids (arrows). (G, H&I): Liver tissue sections from the high Ginger group showed: (G): marked dilatation and congestion in portal veins (P.V), surrounded by periportal fibrosis infiltrated with mononuclear inflammatory cells. Focal nodular mononuclear inflammatory cellular aggregation (circle). Dissociation of hepatic cords (arrows). (H): fibrosis (arrowheads) around portal vein (P.V). (I): thickening in the wall of the portal vein (arrowheads), necrobiotic changes in hepatocytes (arrows). (A, D&G): stained with H&E, (B, E&H): stained with Crossmon's trichrome, (C, F&I): stained with PAS. The bar size was indicated under each picture.

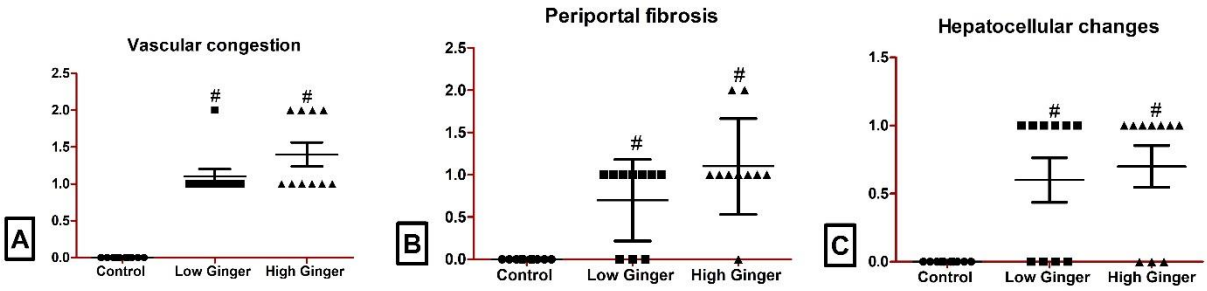

Figure 2. Histomorphometry graph showing the semi-quantitative measurements of liver alterations in quails in all experimental groups. Plots showing (A) vascular congestion, (B) periportal fibrosis, and (C) hepatocellular changes. Data were represented as mean±SEM of 10 sections per group (One-way ANOVA followed by Duncan's multiple range test). Low Ginger and high Ginger groups were fed the same commercial mash diet of the control group +10 and + 15 grams of Ginger roots/Kg feed, respectively.

Microscopic renal histopathological changes

The control group showed normal kidney architectures including renal cortical structure, glomerular corpuscle size and structure, cortical renal tubules, and renal medullary tubules (Fig. 3A-C). The quail's kidney tissue of the low Ginger group (10 g/kg feed) presented several histopathological findings compromising in atrophied glomeruli with wide Bowman's space. The interstitial tissue of the cortical area showed hemorrhage and mild inflammatory cellular infiltration. The medullary area showed cystically dilated renal medullary tubules and severe interstitial hemorrhage (Fig. 3D-F). The quail's kidney of the high Ginger group (15 g/kg feed) showed several cortical areas with severe glomerular atrophy, interstitial hemorrhage, and inflammatory cellular infiltration. The renal medullary area showed degeneration in medullary tubules, interstitial hemorrhage, and marked intertubular inflammatory cellular infiltration (Fig. 3G-I). Based on the histopathology scoring, the severity of glomerular atrophy (Fig. 4A), renal tubular degeneration (Fig. 4B), and hemorrhage (Fig. 4 C) were significantly increased by increasing the feed dosage of Ginger compared with the control group.

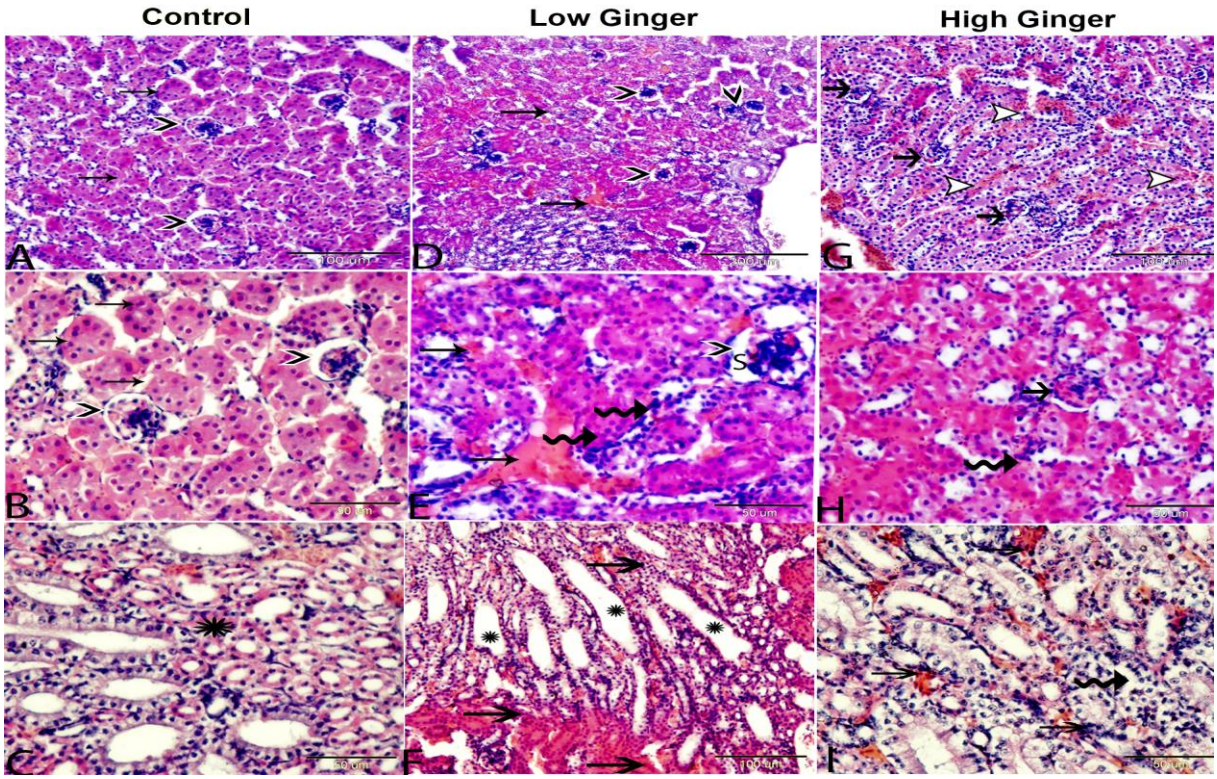

Figure 3. Photomicrograph of kidney sections from the experimental groups showing: (A, B&C): kidney tissue sections from the control group showed normal kidney architectures; (A magnified in B): Normal renal cortical structure, normal glomerular corpuscles size and structure (arrowheads), normal cortical renal tubules (arrows). (C): normal renal medullary tubules (star). (D, E&F): kidney tissue sections from the low Ginger group showed: (D magnified in E): glomerular atrophy (arrowheads), wide Bowman's space (S), interstitial hemorrhage (arrows), mild inflammatory cellular infiltration (zigzag arrows). (F): renal medullary tubules were cystically dilated (stars) with severe interstitial hemorrhage (arrows). (G, H&I): kidney tissue sections from the high Ginger group showed: (G magnified in H): Sever glomerular atrophy (arrows), severe interstitial hemorrhage (arrowheads), and inflammatory cellular infiltration (zigzag arrow). (I): renal medullary tubular degeneration with interstitial hemorrhage (zigzag arrows), severe inter-tubular inflammatory cellular infiltration (arrows). H&E stain. The bar size was indicated under the pictures.

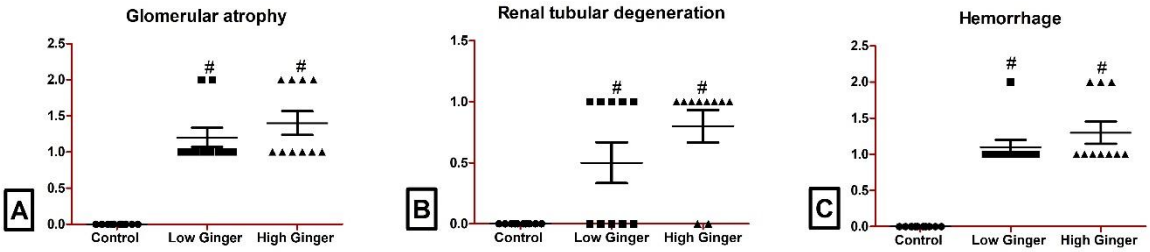

Figure 4. Histomorphometry graph showing the semiquantitative measurements of kidney alterations in quails in all experimental groups. Plots showing (A) glomerular atrophy, (B) renal tubular degeneration, and (C) hemorrhage. Data were represented as mean±SEM of 10 sections per group (One-way ANOVA followed by Duncan's multiple range test).
Low Ginger and high Ginger groups were fed the same commercial mash diet of the control group +10 and + 15 grams of Ginger roots/Kg feed, respectively.

Liver and kidney function parameters

As shown in Table (2), low Ginger group was characterized by a significant increase in the plasma AST and ALT in comparison with the Ginger II and control groups. Ginger at both doses induced hypocholesterolemia in Japanese male quails. UA was significantly decreased in quails following dietary inclusion of Ginger with both doses.

Table 2. Effect of dietary supplementation of ginger (*Zingiber officinale*) on the liver and kidney function parameters in the plasma of Japanese male quails (*Coturnix japonica*)

Group / Parameter	Control	Low Ginger	High Ginger	*P* value
AST (U/mL)	1.972±0.844	7.518±0.289$^{\#}$	2.425±0.245$^{\Phi}$	0.001
ALT (U/mL)	6.143±1.032	14.140±1.195$^{\#}$	7.178±1.134$^{\Phi}$	0.005
Glucose (mg/dL)	24.544±0.541	24.797±0.303	24.125±0.608	0.641
TC (mg/dL)	221.580±21.459	105.370±27.273$^{\#}$	132.530±4.403$^{\#}$	0.004
UA (mg/dL)	0.845±0.078	0.498±0.051$^{\#}$	0.418±0.038$^{\#}$	0.000
Urea (mg/dL)	1.357±0.137	1.231±0.326	0.828±0.048	0.200

Low Ginger and high Ginger groups were fed the same commercial mash diet of the control group +10 and + 15 grams of Ginger/Kg feed, respectively.
AST: aspartate aminotransferase; ALT: alanine aminotransferase; TC: total cholesterol; UA: uric acid.
Results are expressed as the mean±SEM of 6 Japanese male quails per group.
$^{\#}$ indicates a significant difference at $p<0.05$ in comparison with the control; $^{\Phi}$ indicates a significant difference at $p<0.05$ in comparison with Ginger I (One-way ANOVA followed by Duncan's multiple range test).

Plasma oxidant/antioxidant parameters

MDA was significantly increased in both ginger groups compared to the control group. The comparison between all experimental groups regarding TAC, CAT, SOD, and NO revealed absence of significant difference (Table 3).

Table 3. Effect of dietary supplementation of ginger (*Zingiber officinale*) on the plasma oxidant/antioxidant parameters in Japanese male quails (*Coturnix japonica*)

Group / Parameter	Control	Low Ginger	High Ginger	*P* value
MDA (nmol/mL)	3.880±0.113	7.499±0.397$^{\#}$	7.523±0.274$^{\#}$	0.000

TAC (mM/L)	0.508±0.059	0.599±0.094	0.396±0.004	0.162
CAT (U/mL)	0.361±0.003	0.343±0.010	0.357±0.025	0.692
SOD (U/mL)	15.756±1.070	11.079±1.224	11.327±1.485	0.070
NO (nmol/mL)	24.420±4.274	21.340±1.045	1.103±0.637	0.326

Low Ginger and high Ginger groups were fed the same commercial mash diet of the control group +10 and + 15 grams of Ginger/Kg feed, respectively.
LPO: lipid peroxides; TAC: total antioxidant capacity; CAT: catalase; SOD: superoxide dismutase; NO: nitric oxide.
Results are expressed as the mean±SEM of 6 Japanese male quails per group.
[#] indicates a significant difference at $p<0.05$ in comparison with the control (One-way ANOVA followed by Duncan's multiple range test).

DISCUSSION

This study is designed to evaluate the safety border of ginger roots at one of the most used doses in the avian feed practice based on the histo-architectural and functional features of hepatic and renal microenvironments. In the present study, our results revealed some adverse histopathological changes in the liver and kidney that are compatible with those found in the liver and testis of adult Wistar rats treated with Ginger (Ajanwachuku *et al.*, 2018). A closer inspection of the phytochemical constituents of ginger revealed the presence of some ingredients which could have cytotoxicity. For example, gingerol causes nuclear abnormalities (de Lima *et al.*, 2019) and induces oxidative stress by stimulating lipid peroxidation (Kiptiyah *et al.*, 2020). Shogaols trigger caspase activation and poly ADP-ribose polymerase cleavage through the endoplasmic reticulum stress-associated pathway (Hu *et al.*, 2012). Also, paradol and its derivatives evoke programmed cell death through a caspase-3-dependent mechanism (Keum *et al.*, 2002).

Although the increase in plasma AST and ALT levels in the low Ginger group indicates the escape of transaminases into the bloodstream following disruption of the hepatocyte membrane (Amacher, 1998), the therapeutic agent can continue safely with periodic enzyme checking, according to the guide rules of US Food and Drug Administration, even if ALT level rises above 3 times the upper limit of normal, especially if it is not accompanied with any signs of hepatic damage, such as a rise in bilirubin (Lewis, 2012). The liver is fully armed with effective compensatory protective mechanisms that hinder subclinical hepatocellular injury from taking a more serious form (Hall *et al.*, 2012). It should be taken into account that the statistical significance alone is not a reliable indicator of hepatic toxicity. To confirm the hepatic damage, a biologically marked alteration in other biological markers of hepatobiliary injury must be observed (e.g., gamma-glutamyl transferase, glutamate dehydrogenase, alkaline phosphatase, etc.) together with a biologically marked alteration in additional clinical pathology indicators (e.g.,

albumin, bilirubin, triglycerides, coagulation factors, etc.) (Hall et al., 2012).

The hypocholesterolemic impact of Ginger in the present investigation is in the same line with a previous finding in laying Japanese quails (Herve *et al.,* 2019) most probably owing to an increase in the activity of lipolytic effectors at the expense of the lipogenic ones (Herve *et al.,* 2019), higher excretion of fecal cholesterol (Gujral, 1978), interfering with cholesterol absorption (Srinivasan, 2019), suppression of HMG-CoA reductase, and up-regulation of low-density lipoprotein-receptors (Akash *et al.,* 2015).

A significant decrease in the plasma UA in the Ginger-supplemented quails is compatible with that found in rabbits (Abdel-Gabbar *et al.,* 2019) and streptozotocin-induced diabetic rats (Al-Attar and Zari, 2007). It was suggested that Ginger could be beneficial in removing the end products of protein metabolism from the circulation and it can be regarded as a promising natural approach to improving renal functions. Ginger possesses an amazing profile of phytochemical antioxidants that scavenge the free oxidants and prevent them from attacking the renal cells and causing inflammatory and cytotoxic burdens (Hassan Mohammed, 2015).

The adverse alterations in the hepatic and renal tissues of Ginger-fed quails, according to our histopathological examination, were of a mild to a moderate degree. The kidney is one of the most adapted organs. For instance, the glomerular filtration rate, as an index of kidney injury, must be reduced to about one-half of its normal value before plasma urea and creatinine concentration rises above the upper limit of their respective reference range (Baum *et al.,* 1975). Adaptive mechanisms including hypertrophy, as well as a decrease in vascular resistance and tubular reabsorption in the remaining nephrons, allow maintenance of internal homeostasis, even if the kidney mass is reduced to 20-25% of its normal size (Hall and Hall, 2020). Thus, we suggested that the observed histopathological lesions did not reach the alarming level to permit a loss of renal functional integrity using the current doses and duration of administration.

The ability of Ginger at both doses to trigger lipid peroxidative cascade, manifested by elevation of MDA, denotes overproduction of reactive oxygen species, but without disturbance in redox balance given insignificant changes in the antioxidants. The increase in MDA following Ginger intake is contradictory to several scholarly articles (Herve *et al.,* 2018; Ogbuewu *et al.,* 2019) reflecting the biphasic nature of nutritional antioxidants. For example, low-dose flavonoids reduce the accumulated peroxidative products and restore the activity of enzymatic antioxidants, however, high-dose flavonoids induce apoptosis via oxidative stress as evidenced by overgeneration of reactive oxidants and lipid peroxides, downregulation of enzymatic antioxidants, hampering of ATP synthesis, and impairment of mitochondrial function (Xi *et al.,* 2022). It seemed that the surplus emission of free radicals evokes a compensatory response by upregulating the antioxidant defensive tools (Chen *et al.,* 2011), signified in this study by the stabilization of plasma TAC and enzymatic antioxidants. Selective inhibition of certain antioxidants and preservation of the activities of others resulting in a still reasonable defensive action (Abd-

Elkareem *et al.,* 2022) could be proposed as an alternative explanation.

CONCLUSION

Some histological deteriorations in the liver and kidney of Japanese male quails supplemented with ginger roots at two doses (10 and 15 gm/kg feed) were found, however, they are still of a mild to a moderate degree. In light of the measured hepatic and renal functional parameters, we proposed that the histological abnormalities are not enough to induce alarming liver and kidney dysfunction. However, we recommended using hepatotonic and nephrotonic agents in parallel with the dietary administration of ginger to increase its safety window. Since the fertilized egg producing flocks remain for a long time, the effect of prolonged application of ginger (more than 90 days) still needs further investigation because the liver and kidney are sensitive to ginger.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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