ORIGINAL ARTICLE

Veterinary Research Forum. 2024; 15 (3): 145 - 150
doi: 10.30466/vrf.2024.2011585.4009
Journal Homepage: vrf.iranjournals.ir

Veterinary Research Forum

Protective effect of nanocurcumin on acetaminophen-induced hepatic and renal toxicities in pigeons

Saeed Seifi[1]*, Nasser Vajdi[1], Shohreh Alian Samakkhah[2], Navideh Mirzakhani[3]

[1] Department of Clinical Sciences, Faculty of Veterinary Medicine, Amol University of Special Modern Technologies, Amol, Iran; [2] Department of Food Hygiene, Faculty of Veterinary Medicine, Amol University of Special Modern Technologies, Amol, Iran; [3] Department of Pathobiology, Faculty of Veterinary Medicine, Amol University of Special Modern Technologies, Amol, Iran.

Article Info

Article history:

Received: 14 September 2023
Accepted: 08 January 2024
Available online: 15 March 2024

Keywords:

Acetaminophen
Serum biochemistry
Nanocurcumin
Domestic pigeon

Abstract

In this study, the effects of nanocurcumin on acetaminophen-induced acute hepatorenal toxicity in domestic pigeons (*Columba livia*) were investigated. Fifteen pigeons were randomly assigned into three groups. Group I was served as a negative control group and received tap water as a placebo. Pigeons in groups II and III were administered acetaminophen at the beginning of the experiment (hr 0). Group III was further treated with nanocurcumin, at 12 hr after acetaminophen administration, being continued every 12 hr for two days. The birds were observed for clinical signs of acute drug toxicity. Blood samples were collected from the pigeons at hr 0, 12, 24 and 48 of the experiment for biochemical analysis of the serum. The results showed that acetaminophen toxicity increased the serum levels of aspartate aminotransferase, alanine aminotransferase, urea and uric acid in the pigeons. Nanocurcumin treatment of acetaminophen intoxicated pigeons attenuated increases in biomarkers of the liver and kidney functions towards control levels. Also, the consumption of nanocurcumin minimized histopathological changes in the liver and kidney. A mortality of 60.00% was seen in the acetaminophen-induced toxicity group; while, none of the birds treated with nanocurcumin died. It can be concluded that nanocurcumin alleviates the acetaminophen-induced acute toxic liver and kidney damages, which can lead to pigeon mortality.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are used in veterinary medicine to treat fever and inflammation in various animal species, including dogs, cats, horses and cattle.[1] Application of these drugs in birds is limited due to few studies, and on the other hand, most studies have been conducted in mammals.[2] Acetaminophen (N-acetyl-para-aminophenol; APAP) is the most widely used painkiller and anti-pyretic drug in the world today, and one of the reasons for this is that it is less dangerous than many painkillers. Acetaminophen intervenes in prostaglandin synthesis in the central nervous system by inhibiting the cyclooxygenase enzyme.[3] The anti-pyretic effect of APAP takes place through a direct effect on the thermoregulation center in the hypothalamus. Some of the metabolisms of this drug are carried out by the cytochrome P450 system. The cytochrome system is present everywhere in the body, but it is mostly in the liver.

Acetaminophen is converted into an active metabolite called N-acetyl-p-benzoquinone imine (NAPQI) by cytochrome P450 enzymes. In therapeutic doses, this metabolite is quickly detoxified and neutralized by glutathione. In cases of APAP poisoning, due to the reduction of liver glutathione reserves, NAPQI attacks macro-molecules in hepatocytes, leading to necrosis.[4] In general, the greatest accumulation of toxins in animals is found in the hepatic tissue. The liver performs the vital functions of the body, such as the metabolism of proteins, carbohydrates and fats, secretion of bile, storage of glycogen and vitamins, and detoxification of various drugs. The strategic location of the liver, between the gastrointestinal tract and the rest of body, is critical for the homeostasis of various micro-nutrients.[5] Also, renal failure caused by acute APAP consumption is accompanied by necrosis of renal tubules, being characterized by an increase in plasma creatinine and a decrease in glomerular filtration.[6] The mechanism of liver damage resulting from

***Correspondence:**

Saeed Seifi. DVM, DVSc
Department of Clinical Sciences, Faculty of Veterinary Medicine, Amol University of Special Modern Technologies, Amol, Iran
E-mail: s.seifi@ausmt.ac.ir

acute APAP consumption is well known, but the mechanism of kidney damage is not well documented. The process of oxidative stress can be a major reason for the fact that high doses of APAP are associated with an increase in lipid peroxidation and a decrease in intracellular glutathione in kidney tissue.[7]

Recently, large numbers of natural products and food compounds have been investigated as hepatoprotective agents. Recent studies have shown that nutritional factors play an important role in increasing the body's ability to detoxify chemicals and drugs.[8,9] Turmeric (*Curcuma longa* L.) is a perennial plant belonging to the ginger family; its rhizome is the source of turmeric powder, being used as a spice. Turmeric has several phytochemical compounds having a wide range of medicinal properties including activity against cellular tumors, hormonal disorders, inflammation, bacterial infection, oxidative stress and parasites.[10] The main active ingredient of turmeric is curcumin (diferuloylmethane; CMN), a lipophilic polyphenol being practically insoluble in water, being quite stable at the acidic pH of the stomach. The medicinal activity of turmeric is significantly dependent on the biological activity of CMN.[11] Since turmeric increases the activity of the glutathione-S-transferase enzyme, it can increase liver detoxification capacity through increasing liver glutathione reserves.[12] Poor bioavailability of CMN due to low absorption, metabolism and rapid systemic elimination from the body is an important issue in using CMN.[13] One of the suggestions to improve CMN bioavailability is the use of CMN nanoparticles, increasing oral absorption.[14] The use of CMN nanoparticles has increased its tissue distribution and half-life in rats.[15] To our knowledge, no study has been done on the effects of nanocurcumin (NCMN) on APAP poisoning in pigeons. In the present study, we aimed to investigate the therapeutic effect of NCMN on APAP-induced toxicity in domestic pigeons.

Materials and Methods

Drugs and chemicals. Acetaminophen tablets were supplied from Arya Pharmaceutical Company (Tehran, Iran). Nanocurcumin was purchased from Exir Nano Sina Company (Tehran, Iran).

Animals. In this study, 15 domestic pigeons were purchased from a local supplier and after clinical examination and health assurance, distributed randomly into three groups including group I as an untreated control, group II: Received APAP at a dose of 3,000 mg kg^{-1} body weight[16] by oral gavage at the beginning of the study (hr 0) and group III: Received APAP with previous dose and treated by oral NCMN at a dose of 50.00 mg kg^{-1} twice daily at 12 hr after APAP administration to 48 hr. The experimental protocol was approved by the Animal Care Committee of Amol University of Special Modern Technologies, Amol, Iran (Ir.ausmt.rec.1401.24).

Clinical observation. Acute drug toxicity symptoms including vomiting, diarrhea, lethargy, recumbency and death were checked four times a day in the birds.

Blood collection. Blood samples were taken from the brachial veins of all experimental groups for serum separation and rapidly transferred to the laboratory. After centrifugation (3,000 rpm for 10 min at room temperature), serum was harvested. The procedure was repeated at 12, 24 and 48 hr after administration of the APAP or water.

Serum biochemistry. The preserved sera were utilized for spectrophotometric estimation by an automated analyzer (Cobas Mira Plus; Roche, Basel, Switzerland) of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, uric acid, total protein (TP) and albumin (ALB) using commercial assay kits (Pars Azmun, Karaj, Iran).

Histopathology. At the end of the experiment, two birds from each group were euthanatized.[16] Tissue samples of 4.00 cm in length were taken from the liver and kidney. The samples were washed and fixed in 10.00% saline-formalin. Tissue was dehydrated, clarified and embedded in paraffin before cutting into 5.00-µm-thick sections using a rotary microtome (Diapath, Martinengo, Italy). After mounting on glass slides, the sections were stained with Hematoxylin and Eosin stain.

Statistical analysis. Analysis of variance (ANOVA) with the Tukey-HSD test was used to determine significant differences between uric acid, urea, AST, ALT, ALB and TP in different groups at each time point. Also, differences between the mean of these parameters in different groups along exposure times were analyzed by repeated measures ANOVA and Tukey-HSD test. All results were expressed as Mean ± SD. Statistical analyses were performed using the SPSS Software (version 26.0; IBM Corp., Armonk, USA). For all analyses, $p < 0.05$ was considered statistically significant.

Results

Clinical observations. Acute toxicity signs such as vomiting, weakness, ruffled feathers and loss of appetite were observed in birds of groups II and III after administration of APAP. Three birds (60.00%) from group II died between 36 and 48 hr post-administration (PA). No mortality was seen in the NCMN-treated group.

Blood biochemical markers. As it is shown in Table 1, there was no significant difference in tested parameters between different treatment groups at hr 0. An increase in AST, ALT and uric acid was found at 12 hr PA, being significantly higher in APAP-treated birds ($p < 0.05$). In terms of these three parameters, no significant difference was observed between the groups III and I at 24 and 48 hr PA, but both groups had a significant difference with the group II ($p < 0.05$). Regarding urea, no significant

difference was observed between the groups III and II at 24 and 48 hr PA, but both groups showed a significant difference with the untreated group ($p < 0.05$).

A decrease in ALB was found at 12 hr PA. The average ALB at hr 12, 24 and 48 was not significantly differed between the groups II and III, but both groups had a significant ($p < 0.05$) lower level of ALB than the group I.

In terms of TP, at hr 12, 24 and 48, no significant difference was observed between the groups III and I, but both groups had a significant difference with the group II ($p < 0.05$).

In the untreated group, no significant difference was seen in terms of all the investigated parameters at different hr. At hr 12, there was an increase in uric acid level, being significant in the groups II and III between hr 0 and 12. Then, the amount of uric acid in the blood decreased at hr 24 and 48 in group III, but in group II, the amount of uric acid was still high.

Regarding the trend of urea changes in the groups II and III during the studied time, a significant ($p < 0.05$) difference was observed between hr 0 and 12, and hr 24 and 48. The AST enzyme activity showed a significant ($p < 0.05$) increase in the group III at 12 hr PA compared to the other studied times, but ALT enzyme activity did not have a significant difference between the studied periods. The ALB and TP also had no significant difference between the studied times in the groups II and III.

Histopathological findings. Slides of liver and kidney tissues of experimental groups were studied and analyzed thoroughly at the end of the experiment and the photomicrographs are shown in Figures 1 and 2. The liver of the APAP-treated pigeons showed severe degeneration of hepatocytes along with intense inflammatory cell infiltration. Besides, remarkable hyperemia was observed in the hepatic tissue of this group (Fig. 1A). In the group III, remarkable reductions in the pathological processes were observed in the liver (Fig. 1B).

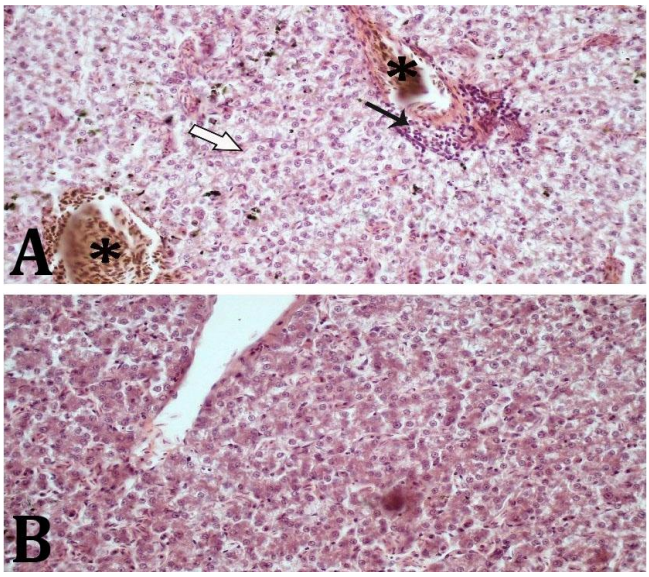

Fig. 1. Photomicrographs of hepatic tissue in experimental groups. **A)** Group II (acetaminophen) shows severe degeneration of the hepatocytes (white arrow), intense inflammatory cell infiltration (black thin arrow) and notable hyperemia (asterisks); **B)** Group III (acetaminophen and nanocurcumin) shows mild degeneration of the hepatocytes with nearly normal structure of the liver (Hematoxylin and Eosin staining, 400×).

Table 1. Effect of nanocurcumin on the serum hepatorenal function biomarkers in acetaminophen toxicity in domestic pigeons.

Parameters	Groups	Experimental period (hr)			
		0	12	24	48
Uric acid (mg dL^{-1})	I	4.06 ± 0.60^{aA}	3.83 ± 0.47^{aB}	3.56 ± 0.45^{aB}	3.86 ± 0.25^{aB}
	II	4.73 ± 1.20^{bA}	8.76 ± 0.66^{aA}	10.23 ± 0.90^{aA}	9.83 ± 0.55^{aA}
	III	3.80 ± 1.90^{bA}	7.66 ± 0.40^{aA}	4.96 ± 0.66^{abB}	4.03 ± 1.47^{abB}
Urea (mg dL^{-1})	I	5.33 ± 1.52^{aA}	5.66 ± 0.57^{aA}	6.33 ± 0.57^{aB}	6.33 ± 1.15^{aB}
	II	6.66 ± 2.51^{bA}	6.33 ± 4.50^{bA}	11.16 ± 2.75^{aA}	13.66 ± 1.52^{aA}
	III	5.00 ± 1.00^{bA}	3.33 ± 1.33^{bA}	10.00 ± 1.73^{aA}	12.66 ± 2.31^{aA}
AST (U L^{-1})	I	60.33 ± 15.50^{aA}	59.00 ± 3.60^{aA}	59.00 ± 10.53^{aB}	59.33 ± 4.04^{aB}
	II	55.66 ± 9.45^{bA}	102.33 ± 40.52^{bA}	271.33 ± 152.00^{aA}	272.66 ± 106.82^{aA}
	III	64.33 ± 8.14^{bA}	104.33 ± 24.58^{aA}	55.00 ± 11.53^{bB}	45.66 ± 16.92^{bB}
ALT (U L^{-1})	I	17.33 ± 2.51^{aA}	14.00 ± 2.00^{aA}	17.00 ± 2.00^{aB}	14.33 ± 2.08^{aB}
	II	11.00 ± 2.00^{bA}	36.33 ± 13.05^{bA}	58.66 ± 15.82^{aA}	39.33 ± 2.51^{bA}
	III	13.00 ± 5.29^{aA}	30.00 ± 12.12^{aA}	20.66 ± 8.08^{aB}	13.00 ± 3.60^{aB}
ALB (g dL^{-1})	I	1.20 ± 0.10^{aA}	1.10 ± 0.10^{aA}	1.00 ± 0.10^{aA}	1.20 ± 0.10^{aA}
	II	1.06 ± 0.21^{aA}	0.61 ± 0.23^{aB}	0.65 ± 0.12^{aB}	0.53 ± 0.06^{aB}
	III	0.93 ± 0.06^{aA}	0.74 ± 0.15^{aB}	0.81 ± 0.08^{aB}	0.82 ± 0.05^{aB}
TP (g dL^{-1})	I	2.83 ± 0.05^{aA}	2.90 ± 0.20^{aA}	2.76 ± 0.15^{aA}	3.23 ± 0.40^{aA}
	II	2.96 ± 0.51^{aA}	1.63 ± 0.40^{aB}	1.53 ± 0.05^{aB}	1.93 ± 0.05^{aB}
	III	2.83 ± 0.40^{aA}	2.43 ± 0.28^{aA}	2.20 ± 0.17^{aA}	2.70 ± 0.10^{aA}

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TP: Total protein; ALB: Albumin; Group I: Untreated control; Group II: Acetaminophen; Group III: Acetaminophen and nanocurcumin.

^{ab} The different superscript letters in the same row indicate significant differences ($p < 0.05$); ^{ABC} The different superscript letters in the same column in each parameter indicate significant differences ($p < 0.05$).

The kidney of group II presented hydropic degeneration along with epithelial cells necrosis of the proximal convoluted tubules. Besides, the epithelial cells were detached from the basal layer, and severe inflammation was observed as well. The glomeruli became shrunken in this group and the urinary space was dilated (Fig. 2A). In the group III, all the degenerative and necrotic processes in the kidney tissue were reduced notably and the tissue showed normal structure (Fig. 2B).

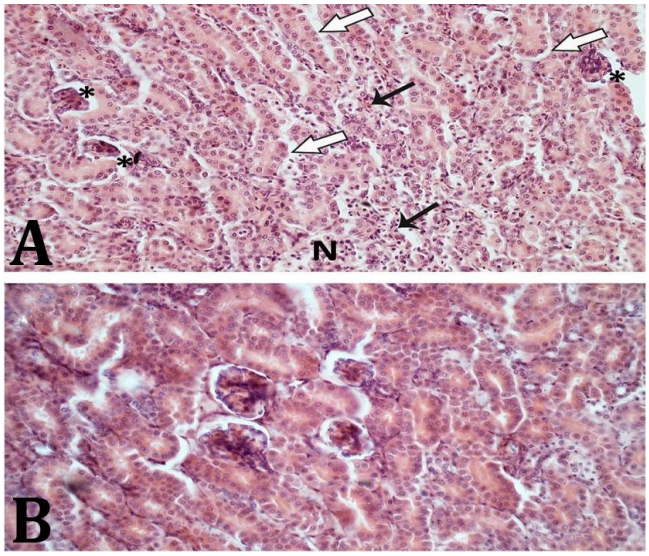

Fig. 2. Photomicrographs of renal tissue in experimental groups. **A)** Group II (acetaminophen) shows notable necrosis (N) and hydropic degeneration of the epithelial cells of proximal convoluted tubules along with detachment from basement membrane (white arrows), severe inflammatory cell infiltration (black thin arrows) and shrinkage of glomeruli (asterisks); **B)** Group III (acetaminophen and nanocurcumin) shows mild degenerative processes of epithelial cells of proximal convoluted tubules (Hematoxylin and Eosin staining, 400×).

Discussion

In avian medicine, NSAIDs are used to treat a variety of clinical conditions, such as inflammation, heat stress and beak-trimming pain. Although NSAIDs are essential to manage pain and inflammatory conditions in poultry, pet and zoo birds, their prescriptions are limited. One of the important reasons for this issue is the little research on NSAIDs usage in birds. The findings of current study showed that administration of APAP caused symptoms including vomiting, weakness, ruffled feathers and loss of appetite in groups II and III. But, it was observed that the symptoms in birds of group III (APAP + NCMN) improved after the NCMN administration; the symptoms were more stable in pigeons of group II. Also, in group II, three birds (20.00%) died; while, no death was seen in group III. Similar results were reported in a previous study investigating the protective effects of silymarin on hepatorenal toxicity caused by APAP in pigeons.[16]

In contrary, mortality was not observed in the APAP-administered broilers.[17] As shown in Table 1, hepatocyte injury markers (AST and ALT) were increased in APAP-administrated groups (II and III), but in the group III, a decrease in AST and ALT activities was recorded 48 hr PA. An increase in the ALT level as a specific liver enzyme indicates liver toxicity caused by APAP.[18] The AST is a non-specific liver enzyme being also produced in other tissues, but its increase can indicate the APAP associated hepatotoxicity. Both AST and ALT are present in the cytosol of hepatocytes and hepatocytes damage leads to an increase in cell membrane permeability, followed by cytoplasmic enzymes movement towards outside of the hepatocytes, causing their activity elevation in the serum.[19] Intra-cellular enzymes leakage prevention *via* healing of hepatic parenchyma and hepatocytes regeneration may be a potential mechanism for medicinal plants to normalize serum biomarkers of the liver.[20] In line with the present study, researchers demonstrated that administration of a single large oral dose of APAP caused apparent liver and kidney oxidative damages in rats, but pre-treatment with CMN significantly improved the altered serum biochemical parameters.[21] A decline in the ALB level was seen at 12 hr PA in both groups of pigeons received APAP. Albumin is produced mainly in parenchymal cells of the liver;[22] therefore, liver damage can change its level in the blood. Nanocurcumin treatment slightly increased ALB level in a non-significant manner. Similar findings were reported by Ihedioha *et al.*[16] and Eassawy *et al.*[19] The reduction in TP level is attributed to the initial damage to the endoplasmic reticulum, leading to the loss of cytochrome P450 enzymes, resulting in its functional failure with reduced protein synthesis and triglycerides accumulation, causing fatty liver disease.[23] Treatment of group II pigeons with NCMN could normalize APAP-induced reductions in serum TP, indicating the hepatoprotective activity.

Since birds are uricotelic and 60.00 - 80.00% of the total nitrogen excreted by birds is in the form of uric acid, it has been proposed to measure plasma uric acid concentration to assess renal function in birds.[24] An increase in uric acid and urea was seen in the APAP-treated groups 12 and 24 hr PA, respectively. Loss of appetite and vomiting in birds of these groups led to dehydration and therefore, increased the uric acid and urea levels. In addition, as shown in Figure 2, severe kidney injury was observed in group II, reducing the clearance of uric acid and urea. In kidney damage caused by chemicals and drugs, the inability to eliminate free radicals after oxidative stress leads to cell destruction. In the present study, histopathological examinations revealed the presence of inflammation, destruction and necrosis in the renal tissue. In concurrence with the present findings, increases in uric acid and urea levels were seen in pigeons being treated with APAP 12 hr PA.[16] In contrast, no adverse clinical signs and no critical change

in uric acid concentrations were observed in broilers received intra-muscular APAP injection (10.00 mg kg^{-1}).[17] These differences may be related to the experimental design and type of toxicant administration. As seen in Table 1, uric acid was decreased in the NCMN-treated group 24 hr PA. Also, the renal tissue of pigeons being treated with NCMN (group III) showed a notable reduction in the degenerative and necrotic processes and a marked decrease in the inflammatory cells population. Our outcomes were in line with earlier researches, where CMN was utilized as a nephroprotective drug, and cyclosporine A and copper were used to cause nephropathy in rats.[25,26]

In conclusion, this study demonstrated the hepatic and renal damaging effects of APAP in pigeons. In addition, treatment with NCMN effectively normalized liver and kidney functions, as well as histopathological changes caused by APAP. These results suggest that NCMN may be a useful treatment option for liver and kidney diseases in pigeons and possibly other bird species.

Acknowledgments

This research has been financially supported by a grant from the Amol University of Special Modern Technologies, Amol, Iran.

Conflict of interest

The authors do not have any potential conflict of interest to declare.

References

1. Curry SL, Cogar SM, Cook JL. Nonsteroidal anti-inflammatory drugs: a review. J Am Anim Hosp Assoc 2005; 41(5): 298-309.
2. Malik A, Valentine A. Pain in birds: a review for veterinary nurses. Vet Nurs J 2018; 33(1): 11-25.
3. Hinz B, Brune K. Paracetamol and cyclooxygenase inhibition: is there a cause for concern? Ann Rheum Dis 2012; 71(1): 20-25.
4. McGill MR, Jaeschke H. Metabolism and disposition of acetaminophen: recent advances in relation to hepatotoxicity and diagnosis. Pharm Res 2013; 30(9): 2174-2187.
5. Gu X, Manautou JE. Molecular mechanisms underlying chemical liver injury. Expert Rev Mol Med 2012; 14: e4. doi: 10.1017/S1462399411002110.
6. Blakely P, McDonald BR. Acute renal failure due to acetaminophen ingestion: a case report and review of the literature. J Am Soc Nephrol 1995; 6(1): 48-53.
7. Blantz RC. Acetaminophen: acute and chronic effects on renal function. Am J Kidney Dis 1996; 28(1 Suppl 1): S3-S6.
8. Rameshrad M, Razavi BM, Hosseinzadeh H. Protective effects of green tea and its main constituents against natural and chemical toxins: a comprehensive review. Food Chem Toxicol 2017; 100: 115-137.
9. Dorri M, Hashemitabar S, Hosseinzadeh H. Cinnamon (*Cinnamomum zeylanicum*) as an antidote or a protective agent against natural or chemical toxicities: a review. Drug Chem Toxicol 2018; 41(3): 338-351.
10. Araújo CC, Leon LL. Biological activities of *Curcuma longa* L. Mem Inst Oswaldo Cruz 2001; 96(5): 723-728.
11. Jurenka JS. Anti-inflammatory properties of curcumin, a major constituent of *Curcuma longa*: A review of preclinical and clinical research. Altern Med Rev 2009; 14(2): 141-153.
12. Sharm RA, Ireson CR, Verschoyle RD, et al. Effect of dietary curcumin on glutathione-S-transferase in rat liver. Clin Cancer Res 2001; 7(5): 1452- 1458.
13. Anand P, Kunnumakkara AB, Newman RA, et al. Bioavailability of curcumin: problems and promises. Mol Pharm 2007; 4(6): 807-818.
14. Nabavi SF, Daglia M, Moghaddam AH, et al. Curcumin and liver disease: from chemistry to medicine. Compr Rev Food Sci Food Saf 2014; 13(1): 62-77.
15. Ma Z, Shayeganpour A, Brocks DR, et al. High-performance liquid chromatography analysis of curcuminin in rat plasma: application to pharmaco-kinetics of polymeric micellar formulation of curcumin. Biomed Chromatogr 2007; 21(5): 546-552.
16. Ihedioha JI, Anyogu DC, Ogbonna ME. The effects of silymarin on acetaminophen-induced acute hepatic and renal toxicities in domestic pigeons (*Columba livia*). J Avian Med Surg 2020; 34(4): 348-357.
17. Jayakumar K, Mohan K, Swamy HDN, et al. Study of nephrotoxic potential of acetaminophen in birds. Toxicol Int 2010; 17(2): 86-89.
18. Prescott LF, Roscoe P, Wright N, et al. Plasma-paracetamol half-life and hepatic necrosis in patients with paracetamol overdosage. Lancet 1971; 1(7698): 519-522.
19. Eassawy MMT, Salem AA, Ismail AFM. Biochemical study on the protective effect of curcumin on acetaminophen and gamma-irradiation induced hepatic toxicity in rats. Environ Toxicol 2021; 36(5): 748-763.
20. Anusha M, Venkateswarlu M, Prabhakaran V, et al. Hepatoprotective activity of aqueous extract of *Portulaca oleracea* in combination with lycopene in rats. Indian J Pharmacol 2011; 43(5): 563-567.
21. El-Maddawy ZK, El-Sayed YS. Comparative analysis of the protective effects of curcumin and N-acetyl cysteine against paracetamol-induced hepatic, renal, and testicular toxicity in *Wistar* rats. Environ Sci Pollut Res Int 2018; 25(4): 3468-3479.
22. Berg JM, Tymoczko JL, Stryer L. Biochemistry. 5th ed. New York, USA: WH Freeman 2002; 231-273.
23. Topal I, Özdamar MY, Catakli T, et al. Renoprotective

effect of taxifolin in paracetamol-induced nephrontoxicity: emerging evidence from an animal model. J Clin Med 2023; 12(3): 876. doi: 10.3390/jcm12030876.
24. Ritchie BW, Harrison GJ, Harrison LR. Avian medicine: principles and application. Florida, USA: Wingers Publishing 1994; 538-544.
25. Abdul Kadhim SA, Ghafil FA, Majeed SA, et al. Nephroprotective effects of curcumin against cyclosporine A-induced nephrotoxicity in rat model. Wiad Lek 2021; 74(12): 3135-3146.
26. Hashish EA, Elgaml SA. Hepatoprotective and nephroprotective effect of curcumin against copper toxicity in rats. Indian J Clin Biochem 2016; 31(3): 270-277.