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The Effect of Curcumin on Acetaminophen-Induced Toxicity on Performance and some Blood Parameters of Japanese Quail from 0-37 Days of Age

Research Article

M. Emadi[1], A. Hadavi[2], J. Ameri[2] and H. Kermanshahi[2*]

[1] Department of Animal Science, Faculty of Agriculture, Payame Noor University, Tehran, Iran
[2] Department of Animal Science, Faculty of Agriculture, Ferdowsi University of Mashhad, Mashhad, Iran

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*Correspondence E-mail: kermansh@um.ac.ir

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ABSTRACT

This study was conducted to determine the effects of supplemented curcumin (CMN), derived from plant *Curcuma longa*, extract on performance and blood parameters of acetaminophen (ACT) induced quail hepatic injury. 240 quails from 0-37 days of age were used in a completely randomized design with 4 treatments of 4 replicates each and 15 chickens per replicate. All groups received 750 mg/kg body weight oral doses of ACT at 12 days of age. Japanese quails were divided into four groups: control (no CMN), commercial diet with 20 g CMN per ton, commercial diet with 40 g CMN per ton and commercial diet with 60 g CMN per ton. Feed intake and body weight gain were recorded weekly. Blood albumin, glucose, total protein, triglyceride, aspartate aminotransferase, alanine aminotransferase, bilirubin, uric acid and creatinine were determined at 28 and 35 days of age. Adding curcumin to the diets significantly increased serum aspartate aminotransferase at 28 days of age ($P<0.05$) and decreased triglyceride and bilirubin at 35 days of age ($P<0.05$). There were no significant differences in performance and other blood parameters among the treatment groups at 28 and 35 days of age. The data indicated that curcumin is a natural antioxidant hepatoprotective agent against hepatotoxicity induced by acetaminophen model. Thus, curcumin may have a therapeutic value in drug-induced hepatotoxicity as well as in acetaminophen therapy.

KEY WORDS acetaminophen, curcumin, liver, performance, quail.

INTRODUCTION

Any organ of body is a potential target for injurious effects from chemicals but some organs are more vulnerable to adverse effects than the others. The liver is often a target organ for a number of reasons. First, most toxicants enter the body via the gastrointestinal tract and after absorption they are carried by the hepatic portal vein to the liver. Thus the liver will be exposed to the highest concentrations of these chemicals (Reed, 1994). Chemicals encountered by other routes of exposure may also reach the liver through its blood supply from the hepatic artery as well as the portal vein (Stacey *et al.* 1993; Kulkarni and Byczkowski, 1994). Second, the liver has the ability to concentrate biotransform and excrete chemicals, irrespective of routes of exposure (Plaa and Hewitt, 1982). It has high concentrations of xenobiotic metabolizing enzymes, mainly cytochrome P450, which render most toxicants less toxic, more water-soluble and thus more readily excretable (Murry, 1994). However in some cases toxicants are activated to be capable of inducing lesions as in case of paracetamol-induced hepatotoxicity. Acetaminophen is one of the most popular analgesic and antipyretic drugs and its overdose, which can cause severe damage to liver and kidneys, is one of the

most common reasons of emergency admissions. The exact mechanism of acute liver failure secondary to acetaminophen toxicity is unknown, although a presumed mechanism of hepatocellular necrosis involving the accumulation of a toxic metabolite (*N*-acetyl-*p*-benzoquinoneimine) has been postulated (Raymond *et al*. 1991).

Many plant extracts and plant products have been shown to have significant antioxidant activity (AL-Howiriny *et al.* 2005; Hussein, 2008; Hussein, 2010), which may be an important property of medicinal plants associated with the treatment of several ill fated diseases including liver toxicity.

Thus, herbal plants are considered a useful means to prevent and / or ameliorate certain disorders, such as diabetes, atherosclerosis, hepatotoxicity and other complications (AL-Howiriny *et al.* 2005; Hussein, 2008).

Among these herbal resources, curcumin, is the main yellow phenolic material present in the rhizomes of turmeric (*Curcuma longa*) and is widely used as a food coloring agent (Govindarajan, 1980). Curcumin is a ß-diketone compound which contains two ferulic acid molecules linked via a methylene bridge at the carbon atoms of the carbonyl groups (Okazaki *et al*. 2005).

Various curcumin-related phenols (curcuminoids) have also been found in edible plants, especially Zingiberaceae plants (Toda *et al.* 1985; Masuda *et al*. 1992; Masuda *et al*. 1999). Extracts of rhizomes of turmeric have been widely used in Indian medicine and they are considered to be efficacious in the treatment of liver disorders and certain pyrogenic infections.

Curcumin exhibits anti-inflammatory and antiviral effects and it is also considered as a potent scavenger of reactive oxygen and nitrogen species (Joe *et al.* 2004). *In vitro* and *in vivo* tests have been performed with curcumin to determine, for example, its antimutagenic, anticarcinogenic and anticholestatic activities (Sahu and Washington, 1992; Ahmed and Mannaa, 2004). However there are no reports on the hepatoprotective effect of curcumin against hepatotoxicity induced by acetaminophen in quail. The present study was undertaken to investigate the ability of curcumin to alleviate the adverse effects of acetaminophen on liver in Japanese quail.

MATERIALS AND METHODS

Chemicals

Acetaminophen (ACT) was provided from Iran Pharmaceutical Company. When intended to be used *in vivo* experiments, ACT was orally administrated in drinking water in dose of 750 mg/kg body weight of quails at 12 days of age. Curcumin (CMN) extracted from *Curcuma longa* was prepared from Sigma Company (Catalogue number C1386).

Animals

In this study, 240, day-old Japanese quail were allocated to four experimental diets in a completely randomized design with four replicates each and 15 chicken per replicate to evaluate the effect of CMN on ACT induced on the performance and blood parameters of quail fed the commercial, corn-soybean meal based diets for 37 days (Table 1; NRC, 1994).

Table 1 Composition of experimental diets of Japanese quail during 0-37 days of age

Ingredients (%)	0-37 days of age
Corn	37.97
Wheat	1.5
Soybean meal	37.53
Fish meal	4.32
Dicalcium phosphate	0.24
Limestone	1.21
Vitamin and mineral premix[1]	0.6
Salt	0.26
Poultry oil	2.4
Methionine	0.18
Theronine	0.27
Enzyme	0.03
Wheat bran	13.49
Calculated analysis	
Metabolizable energy (kcal/kg)	2900
Crude protein (%)	24
Available P (%)	0.30
Crude fibre (%)	4.02
Na (%)	0.5
Ca (%)	0.8
Linoleic (%)	1.81
Methionine (%)	0.5
Methinone + cystein (%)	0.96
Lysine (%)	1.38
Arginine (%)	1.55
Theronine (%)	1.02
Tryptophan (%)	0.35

[1] Supplied / kg of diet: vitamin A: 10000 IU; vitamin D_3: 9790 IU; vitamin E: 121 IU; B_{12}: 20 µg; Riboflavin: 4.4 mg; Calcium pantothenate: 40 mg; Niacin: 22 mg; Choline: 840 mg; Biotin: 30 µg; Thiamine: 4 mg; Zinc sulphate: 60 mg and Manganese oxide: 60 mg.

Treatments were 0, 20, 40 and 60 g/ton of CMN added into the feeds during experiment. Feed and water were given *ad libitum*. Body weight gain (BWG) and feed intake (FI) were recorded weekly and then adjusted for three periods (14-21 days), (22-29 days) and (30-37 days). At 28 and 35 days of age, two birds from each replicate of treatments were randomly selected and their blood sample was collected. The non-heparinized blood samples were allowed to coagulate and then centrifuged at 1000 g for 20 min. The separated sera were used for the estimation of serum activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, bilirubin, creatin, glucose, uric acid and total protein levels using appropriate laboratory kits. All the grouped data were statistically evaluated

with SAS (SAS, 1996) software. Hypothesis testing methods included one way analysis of variance (ANOVA) followed by Duncan´s new multiple range procedure. *P* values of less than 0.05 were considered to indicate statistical significance.

RESULTS AND DISCUSSION

Table 2 shows the effect of ACT as well as ACT plus CMN levels on performance in quail. The results indicated that all groups have normal growth curve and no significant differences were observed in body weight gain, feed intake and feed conversion ratio between the control and the treated groups in all periods. However addition of CMN to the ACT diet numerically improved the performance of quails in the present study. Gowda *et al*. (2008) reported that addition of 0.5% turmeric powder, containing 1.48% total curcuminoid (74 mg/kg), to the alfatoxin diet increased feed intake (906 *vs*. 858 g) and significantly improved weight gain (746 *vs*. 662 g) in chicks, suggesting antioxidant protection by turmeric.

Table 3, 4 and 5 shows the effect of ACT and ACT plus CMN treatments on serum parameters in Japanese quail. At 28 days of age aspartate aminotransferase (AST) activitiy of treated quails showed a significant increase when compared to those of the control group. Increased serum AST levels exacerbated oxidative stress and inflamative induced by acetaminophen. Serum AST and serum alanine aminotransferase (ALT) are present in the cytosol of the hepatocytes. Whenever liver hepatocytes are damaged, these enzymes are released into the blood. A significant increase in AST and ALT activities indicates the damage to the cytosol and also to mitochondria (Mathuria and Verma, 2008). Such noticed increase in AST activities could be used as an indicator of altered permeability of plasma membrane and cell damage (Mahmoud *et al*. 2012).

At 35 days of age, bilirubin treated quails (Table5) showed a highly significant decrease when compared to those of control group. The noticed increase in the bilirubin level in control group may be due to blood hemolysis that could be caused by excessive rapid destruction of erythrocytes (Hasheesh *et al*. 2002). In general, the induced alternation of liver function could be explained by the formation of lipid peroxidation which is considered as one of the molecular mechanisms for hepatic damage (Mahmoud *et al*. 2012).

Moreover, it was meaningful to correlate between the observed alternation of liver functions and the direct effect of ACT on the histological features of liver of treated quails that showed focal lymphocytic infiltration, hyperplasis of the bile ducts, and desquamation of lining ephithelial cells, proliferation of the fibrous tissue of the portal area, fatty changes and necrosis.

Previously, Emadi and Kermanshahi (2007) fed broiler chickens with turmeric powder (0.25, 0.50 and 0.75%) from hatch to 49 days of age and concluded that turmeric might have some positive effects on liver enzymes by reducing ALT and alkaline phosphatase activities that reflect a healthier liver status in the birds. Total serum protein and albumin were not significantly different between the groups. However, numerically higher in treated groups with CMN (Table 3). The noticed reduction in total protein in control group could be related to the action of ACT on nucleic acids and it may indicate a physiological adaptability of quails to compensate stress (Devi, 1981). Biosynthesis and secretion of serum protein becomes normalized as no necrotic changes were observed in histopathological study of liver of aflatoxin plus CMN treated mice (Mathuria and Verma, 2008). Serum uric acid was higher in control group compared to these of CMN treated. Creatine was also showed a numerical decrease at 35 days of age in CMN plus ACT groups. Creatine and creatine phosphate are handled differently by the kidney. Both are filtered at glomerulus. Although some additional secretion of creatinine by renal tubules might be seen, creatine is reabsorbed by the tubules at low plasma concentration. This ensures that there is little or no creatine is presented in urine (Mc Lauchlan, 1988). The heightened appearance of creatinine in the serum of ACT-fed mice indicates the increased transformation of phosphocreatine to creatinine in muscle which might be due to lesser utilization of phosphocreatine in muscular contraction.

The kidney rapidly excretes creatinine. Thus significant increase in creatinine concentration in serum could be due to increased release from muscles and / or decrease excretion from the kidney. The observed increase of serum creatinine may be attributed to renal insufficiency, urinary tract obstruction and impairment or renal function induced by ACT (Mc Lauchlan, 1998). Malik *et al*. (2004) explained the increased level of urea by the increased nitrogen retention and / or due to corrupted renal function. The increase of uric acid usually occurs due to renal failure or toxemia induced by ACT resulting in damage to the epithelium of the kidney tubules. In concurrent with the mentioned biochemical alterations, treatment with ACT induced renal degenerative changes in renal tubules, progressive infiltration, degenerative changes in renal ephithelial cells, in addition to atrophied renal corpuscles and focal interstitial nephritis (Mahmoud *et al*. 2012). Triglyceride of treated quails CMN plus with ACT showed a significant decrease (Table 3) when compared to these control in ACT treated quails.

Table 2 Effects of dietary curcumin on feed intake (FI), body weight gain (BWG) and feed conversion ratio (FCR) of Japanese quail from 14-37 days of age

Curcumin (g/ton)	BWG (g, days)				FI (g, days)				FCR (days)			
	14-21	22-29	30-37	Total	14-21	22-29	30-37	Total	14-21	22-29	30-37	Total
0	34.15	35.11	36.40	105.66	104.13	124.15	134.94	363.22	3.04	3.53	3.70	3.43
20	34.24	35.14	37.67	107.05	102.89	121.19	132.89	356.97	3.00	3.44	3.52	3.33
40	36.61	36.95	38.93	112.49	95.63	117.32	130.34	343.29	2.61	3.17	3.34	3.05
60	36.26	36.39	39.03	111.68	95.24	116.51	131.66	343.41	2.62	3.20	3.37	3.07
P-value	0.91	0.93	0.32	0.20	0.66	0. 27	0.53	0. 74	0. 78	0. 8 7	0.75	0.85

Table 3 Effects of dietary curcumin on the serum concentration of albumin (ALB), total protein (TP) and triglyceride (TG) in Japanese quail at different days of age

Curcumin (g/ton)	ALB (g dL^{-1})		TP (g dL^{-1})		TG (mg dL^{-1})	
	28 days	35 days	28 days	35 days	28 days	35 days
0	1.32	1.39	2.76	3.69	307.10	485.52[a]
20	1.41	1.32	2.72	4.53	264.23	275.75[b]
40	1.27	1.38	2.97	4.08	296.66	236.36[b]
60	1.25	1.38	3.00	4.13	265.34	210.00[b]
P-value	0.227	0.375	0.063	0.548	0.488	0.051

The means within the same columns with at least one common letter, do not have significant difference (P>0.05).

Table 4 Effects of dietary curcumin on the serum concentration of aspartate amino-transferase (AST), alanine amino-transferase (ALT) and creatinine (C) in Japanese quail at different days of age

Curcumin (g/ton)	AST (UL^{-1})		ALT (UL^{-1})		C (mg dL^{-1})	
	28 days	35 days	28 days	35 days	28 days	35 days
0	75.17[c]	133.51	21.47	22.49	60	48
20	166.50[a]	167.08	21.85	22.76	56	44
40	115.97[b]	154.95	21.45	22.67	65	44
60	118.67[b]	126.67	26.73	26.88	65	45
P-value	0.0002	0.617	0.554	0.443	0.971	0.548

The means within the same columns with at least one common letter, do not have significant difference (P>0.05).

Table 5 Effects of dietary curcumin on the activity of serum bilirubin (BIL), glucose (GLU) and uric acid (UA) in Japanes quail at different days of age

Curcumin (g/ton)	BIL (mg %)		GLU (mg dL^{-1})		UA (mg dL^{-1})	
	28 days	35 days	28 days	35 days	28 days	35 days
0	0.249	0.217[a]	137.45	148.86	4.56	4.74
20	0.133	0.106[c]	146.84	163.27	4.00	4.24
40	0.126	0.108[c]	164.85	167.55	3.97	4.18
60	0.134	0.154[b]	183.19	184.82	3.55	3.83
P-value	0.650	0.051	0.618	0.914	0.771	0.429

The means within the same columns with at least one common letter, do not have significant difference (P>0.05).

Regarding the triglyceride level, the recorded increase in serum triglycerides of quails might be due to increased lipid mobilization from liver and its decreased removal from plasma (Slotkin *et al*. 2005).

The results showed numerical changes in BWG and FCR in the birds fed ACT alone and curcumin levels slightly corrected this effect as some improvements in BWG and FCR were seen by dietary addition of curcumin and the addition of curcumin to the acetaminophen-containing diet for 3 weeks significantly fluctuated the serum AST of the quails. With respect to these fluctuations in serum AST levels of the birds, it may speculate that the birds are facing with a metabolic pressure to handle ACT and curcumin combination that was not experienced by the birds in a short time. It is not sure this effect is positive or negative, but may show the resistance / reaction of the birds by dietary addition of ACT and pure curcumin.

There is no doubt that curcumin is the active ingredient of Curcuma long, turmeric rhizome powder (TRP), but the effect of pure curcumin in comparison with the TRP might be questionable. More research is needed to clarify this effect.

CONCLUSION

Some improvements obtained in this study may contribute to a solution to the acetaminophen problem. It is concluded that curcumin may protect the liver and kidney from the damage caused by acetaminophen overdose.

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