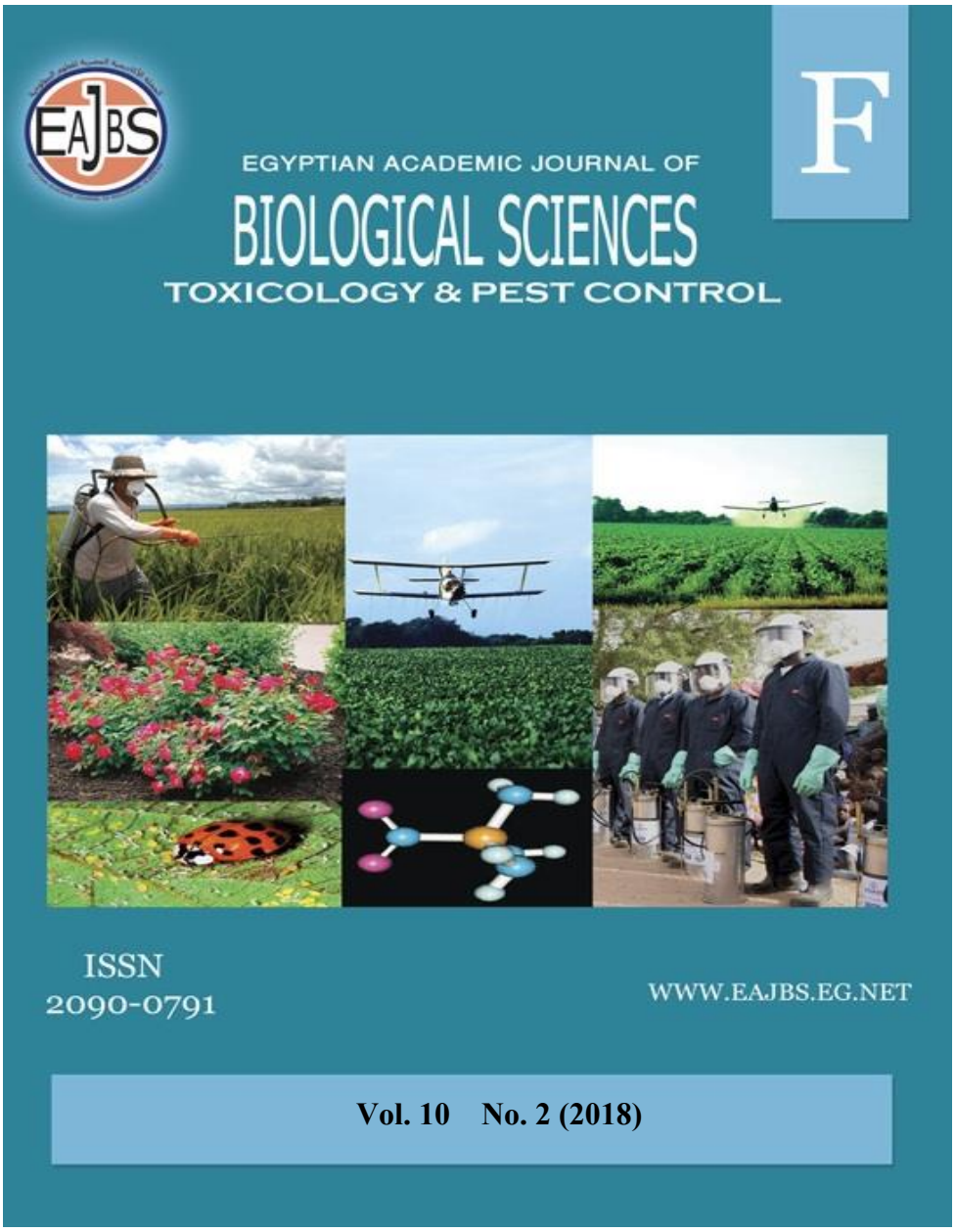

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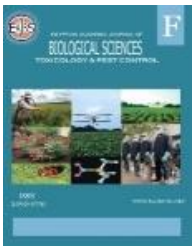
www.eajbs.eg.net

Egypt. Acad. J. Biolog. Sci., 10(2): 99– 110(2018)

Egyptian Academic Journal of Biological Sciences
F. Toxicology & Pest control
ISSN: 2090 - 0791
www.eajbs.eg.net



Effect of Dietary Curcumin on Heptorenal Afla-Toxicosis in Mice

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ARTICLE INFO

Article History
Received:19/11/2018
Accepted:25/12/2018

Keywords:
Aflatoxins, liver, kidney, curcumin

ABSTRACT

Mycotoxins contribute great adverse health concerns, especially on liver and kidney. The current study aimed to investigate the possible protective effect of dietary curcumin on hepatorenal aflatoxicosis in mice. Thirty-two male albino mice 18-20 g were divided into 4 groups. Group I, is the control group received basal diet. Group II, received a basal diet with 2% curcumin. Group III, given a basal diet with added AFs (5 µg/kg). Group IV, co-administered AFs and curcumin at the same previous doses. All treatments continued for 4 weeks. Liver and kidney weights, as well as food conversion ratio (FCR), were determined. The serum levels of Superoxide dismutase (SOD), total antioxidant capacity (TAC), Malondialdehyde (MDA) and Interleukin-6 (IL-6) were estimated. Serum alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin and creatinine were estimated. Histopathological examination to liver and kidney was performed. AFs significantly increased FCR and liver weight than control. The levels of SOD and TAC significantly reduced in-group III while MDA and IL-6 increased than control. The levels of ALP, ALT and creatinine were significantly ($P<0.05$) increased in AFs group meanwhile albumin was significantly reduced than control. Hepatic and renal tissue showed congestion, lymphocytic infiltrations and other retrogressive changes. The co-administration of curcumin with AFs significantly ameliorated the AFs induced adverse effects. Curcumin possesses antioxidant effect that ameliorated aflatoxicosis adverse effects on the kidney and liver.

INTRODUCTION

The contamination of feedstuffs with toxic materials during processing or storage have constituted a drastic problem for both animal and human health (Devendran and Balasubramanian, 2011). Among these toxic materials mycotoxins are existing which are toxins produced by fungi and contaminate feed stuffs (Glenn,

2007). The most widely spread mycotoxins are aflatoxins (AFs) that are secondary metabolites of *Aspergillus parasiticus* and *A. flavus* (Ghiasian and Maghsood, 2011). Four naturally existing AFs are distingushed; aflatoxin B1 (AFB1), B2 (AFB2), G1 (AFG1) and G2 (AFG2) with AFB1 that having the prevalent hepatotoxic effect (Clifford and Rees, 1967; Rastogi *et al.,* 2001). Also, aflatoxins can be found in edible milk, tissues and eggs produced from farm animals that consumed contaminated feed by AFs (Johanna, 1999).

Aflatoxins are incriminated in the production of several disorders in the normal physiological functions such as development, growth, metabolism, immunity and reproduction are altered. These disorders include a reduction in efficiency of feed utilization, body weight loss, reproductive capacities and immune impairments (Pestka, 2007). Moreover, liver (Rastogi *et al.,* 2001) and kidney (Al-Habib *et al.,* 2007) function impairments are recorded . All these perturbations lead to economic losses (Wu, 2006).

The excretion of AFs is primarily via hepatic biliary system as the first step followed by renal and urinary pathway (Polychronaki *et al.,* 2008). This makes the liver and kidney targets for AFs toxicity. There are sharp evidence prove that the metabolites of these toxins are excreted in human excreta and biological samples thus it makes it a necessry issue to carefully study these toxins (Jolly *et al.,* 2006). The actual mechanism by which AFs exert their toxicity is still under investigation (Li *et al.,* 2018).

Natural antioxidants have received major attention nowadays as they can eliminate free radicals produced from several metabolic processes in which intoxication by AFs is included (Abdelrazek *et al.,* 2015; Dhama et al., 2015; Vaughn *et al.,* 2016). Among these antioxidants, curcumin is existed. It is the main active ingredient of turmeric (*Curcuma longa)*. Turmeric has been used by Indians and other nations as a feed additive that adds characteristic aroma and taste to food (Hewlings and Kalman, 2017). Also turmeric have been used widely in traditional medicine as an anti-inflammatory, relieving agent for menstrual difficulties and chest pain , anti-toothache, hepatoprotective *(Menon and Sudheer, 2007).*

Curcumin is polyphenolic active ingredient of turmeric that has an antioxidant effect. It has multiple signaling pathways to alleviate toxic and inflammatory effects (Zheng *et al.,* 2018). Therefore, the current study aimed to evaluate the possible protective effect of curcumin on AFs induced hepatic and renal toxicities through estimation of some biochemical parameters and oxidative stress.

MATERIALS AND METHODS

Tested Animals and Experiment Design:

Thirty-two male albino mice weighing 18-20 g were obtained from the Organization for Biological Products and Vaccines, Helwan, Egypt. They were kept 2 weeks for accommodation prior to the onset of the experiment. Mice were kept in a ventilated room under room temperature 24±2°C, natural light/dark rhythm and humidity 49% ± 1. Mice received *ad libitum* drinking water and diet. Rats were randomly distributed to four groups; eight mice each.

Group I, is the control group received basal diet.

Group II, controls curcumin group and given a basal diet with 2% curcumin (Billerey-Larmonier et al., 2008) that was purchased from planet Ayurveda Co., India.

Group III, is AFs- reated group and given a basal diet with added AFs (5 µg/kg) based on European Community (EC) Commission Regulation (EC) (2010) to

be based on the maximum level detected in beans and rice .

Group IV, is a combination of curcumin and AFs group and given both AFs and curcumin at the same doses of groups II and III, respectively. All treatments continued for 4 weeks.

Aflatoxins (AFs):

The AFs used in the present study was a product of Animal Health Research Institute, El-Mansura, Egypt. They were obtained by inoculation toxigenic fungus strain of *Aspergillus parasiticus* NRRL 2999 to parboiled rice to be fermented. The previously mentioned procedures were done according to (Shotwell *et al.*, 1966). Fermented moldy rice was dried and ground into fine powder. The level of AFs mounted in rice powder were estimated by HPLC at Mycotoxins Central Laboratory and Food Safety of the National Research Centre, El Dokki, Giza, Egypt according to the method of Nabney and Nesbitt (1965) using AFs (B1 and B2) standards that purchased from (Biopure Referenzsubstanzen GmbH Co., Austria). The level of AFs B1 in rice was 6.8 mg/Kg, B2 was 0.09, G1 was 0.15 mg/kg and G2 was 0.16 mg/kg with total AFS contents 7.2 mg/kg.

Organs Weight and Food Conversion Ratio (FCR):

The liver and kidney of each experimental rat were excised and weighed. Experimental mice were weighed at day 1 of the experiment then weighed at the end of the experimental period. The weight gain was obtained by subtracting final weight from the initial one. Food intake was recorded all over the experimental time. FCR was calculated as follow:

FCR = (Feed consumption (g) /mice/4 weeks)/ (body weight gain (g) /mice/4 weeks). The relative kidney and liver weights were calculated in relation to body weight.

Blood and Tissue Sampling:

At the end of the experiment, the mice were anesthetized and blood samples were collected from retro-orbital venous plexus of the eye into plain tubes. The later tubes left for clotting kept in the refrigerator then sera were separated, collected and stored at -18°C. Thereafter, animals were euthanized by cervical dislocation. Liver and kidney were excised then weighed.

Antioxidants and Lipid Peroxidation:

The serum levels of Superoxide dismutase (SOD), total antioxidant capacity (TAC) and Malondialdehyde (MDA) were estimated using commercial kits purchased from Cell Biolabs. Inc. Co., USA. The procedures of the assay were followed according to manufacturers' enclosed protocol.

Interleukin-6 (IL-6) Assay:

IL-6 was assayed using specific mice ELISA commercial kits (CAUSABIO, China). The procedures were followed according to the manufacturer's protocol.

Serum Liver and Kidney Biomarkers:

The serum levels of alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin and creatinine were estimated according to enclosed pamphlet of the used commercial kits (DIACHEM LTD., Hungary).

Histopathological Examination:

Liver and kidney were immersed in 10% Formalin buffer, paraffinized in blocks and cut into 5-µm-thickness sections. These sections were stained with hematoxylin and eosin (H & E) according to Drury and Wallington (1980) and examined under the microscope.

Statistical Analysis:

Statistical analyses were performed by One-way analysis of variance (ANOVA) followed by Duncan's multiple comparison tests (SPSS v. 16.0, SPSS Inc., IL, USA). All values were represented as mean ± standard errors. A probability level of $P<0.05$ denoted significance.

RESULTS

Organs Weight and Food Conversion Ratio (FCR):

Table (1) demonstrated the effect of curcumin on FCR, food intake and weight gain. It revealed that FCR was significantly ($P<0.05$) increased in afla-intoxicated mice (group III) than the control group (group I) and other groups. The curcumin administration to afla-intoxicated mice (group IV) significantly reduced ($P<0.05$) the FCR than group III. Concerning food intake and body weight gain both were significantly reduced in control curcumin group (group II) than control. Aflatoxins (group III) significantly ($P<0.05$) decreased weight gain while increased food intake ($P<0.05$) than control (group I). Feeding curcumin to afla–intoxicated mice (group IV) significantly ($P<0.05$) reduced food intake and elevated weight gain than group III (Table 1). Relative liver weight exhibited significant increase ($P<0.05$) in-group III than control. Group IV exhibited a significantly ($P<0.05$) reduced liver weight than group III. Kidney relative weight showed non-significant alterations among groups.

Table (1): Effect of curcumin on FCR, food intake, body weight gain, relative kidney weight and relative liver weight in afla-intoxicated mice.

	Group I	Group II	Group III	Group IV
FCR	4.70 ± 0.32^{a}	4.49 ± 0.15^{a}	8.17 ± 1.01^{b}	5.68 ± 0.34^{c}
Food intake (g/ 4 weeks)	147.67 ± 3.71^{a}	124.00 ± 3.06^{b}	163.33 ± 8.82^{c}	144.67 ± 2.60^{a}
Weight gain (g/4 weeks)	31.67 ± 1.76^{a}	22.66 ± 1.20^{b}	20.33 ± 1.45^{c}	25.67 ± 1.76^{b}
Liver relative weight (%)	2.73 ± 0.15^{a}	2.7 ± 0.26^{a}	3.97 ± 0.12^{b}	3.01 ± 0.06^{c}
Kidney relative weight (%)	0.035 ± 0.11	0.027 ± 0.00	0.05 ± 0.01	0.042 ± 0.03

Different superscripts between columns are considered significant at $P<0.05$.

Antioxidants and Lipid Peroxidation:

Control curcumin group **(group II) exhibited significant promotion ($P<0.05$) in** TAC and SOD than control (group I). The TAC and SOD serum levels were significantly declined ($P<0.05$) in afla-intoxicated group **(group III)** than control. Feeding curcumin to afla-intoxicated mice resulted in significant ($P<0.05$) improvement in levels of TAC and SOD than group III. On the other hand, MDA was significantly increased ($P<0.05$) in group III than control and other groups. Group IV exhibited significant amelioration ($P<0.05$) of MDA level than group III (Table 2).

Interleukin-6 (IL-6) Assay:

Serum Il-6 was significantly increased ($P<0.05$) in group III (afla-intoxicated) than control and other groups. Group IV (AFs and curcumin group) exhibited significant amelioration ($P<0.05$) of serum Il-6 level than group III (Table 2).

Serum Liver and Kidney Biomarkers:

Serum ALP, ALT and creatinine were significantly increased ($P<0.05$) in group III (afla-intoxicated group) than control and other groups. Group IV (AFs and curcumin group) exhibited significant reduction ($P<0.05$) of serum ALP, ALT and

creatinine levels than group III (Table 2). On the other side, the serum albumin level was declined (P<0.05) in afla-intoxicated group (group III) than control. Feeding curcumin to afla-intoxicated mice resulted in significant (P<0.05) improvement in serum albumin level than group III (Table 2).

Table (2): Effect of curcumin on TAC, SOD, MDA, IL-6, Albumin, ALT, ALP and Creatinine in afla-intoxicated mice.

	Group I	Group II	Group III	Group IV
TAC (U/mL)	1.29±0.14^{a}	1.63±0.14^{ab}	0.70±0.09^{c}	0.90±0.02^{d}
SOD (U/mL)	6.54±0.05^{a}	7.36±0.32^{b}	4.36±0.35^{c}	6.1±0.38^{ab}
MDA (nmol/ mL)	0.58±0.01^{a}	0.54±0.00^{a}	1.15±0.03^{b}	0.79±0.19^{c}
IL-6 (pg/mL)	10.89±1.23^{a}	10.24±1.02^{a}	31.16±1.32^{b}	22.01±2.01^{c}
Albumin (g/dL)	4.7±2.27^{a}	5.07±0.08^{a}	1.9±0.29^{b}	3.77±0.30^{c}
ALT (U/L)	21.53±0.44^{a}	19.53±0.42^{a}	38.23±2.95^{b}	26.30±0.55^{c}
ALP (U/L)	62.36±2.30^{a}	57.71±1.97^{a}	90.47±3.72^{b}	75.91±2.96^{c}
Creatinine (mg/dL)	0.77±0.01^{a}	0.68±0.02^{a}	1.16±0.09^{b}	0.86±0.04^{c}

Different superscripts between columns are considered significant at P<0.05.

Histopathological examination

Liver of control (group I) and curcumin control (group II) are showing normal histological structure with normal central vein and hepatic cords. AFs treated group (group III) showing congested blood vessels and severe lymphocytic infiltration along with necrotic changes of some hepatocytes. Pronounced protection of curcumin-treated group (group IV) that ameliorated the AFs adverse effects. The kidney of control (group I) and curcumin control (group II) are showing normal histological structure with normal glomerulus and renal tubules. AFs treated group (group III) is showing congested blood vessels renal tubule degeneration and local lymphocytic infiltration. Pronounced protection of curcumin-treated group (group IV) is observed that ameliorated the AFs adverse effects.

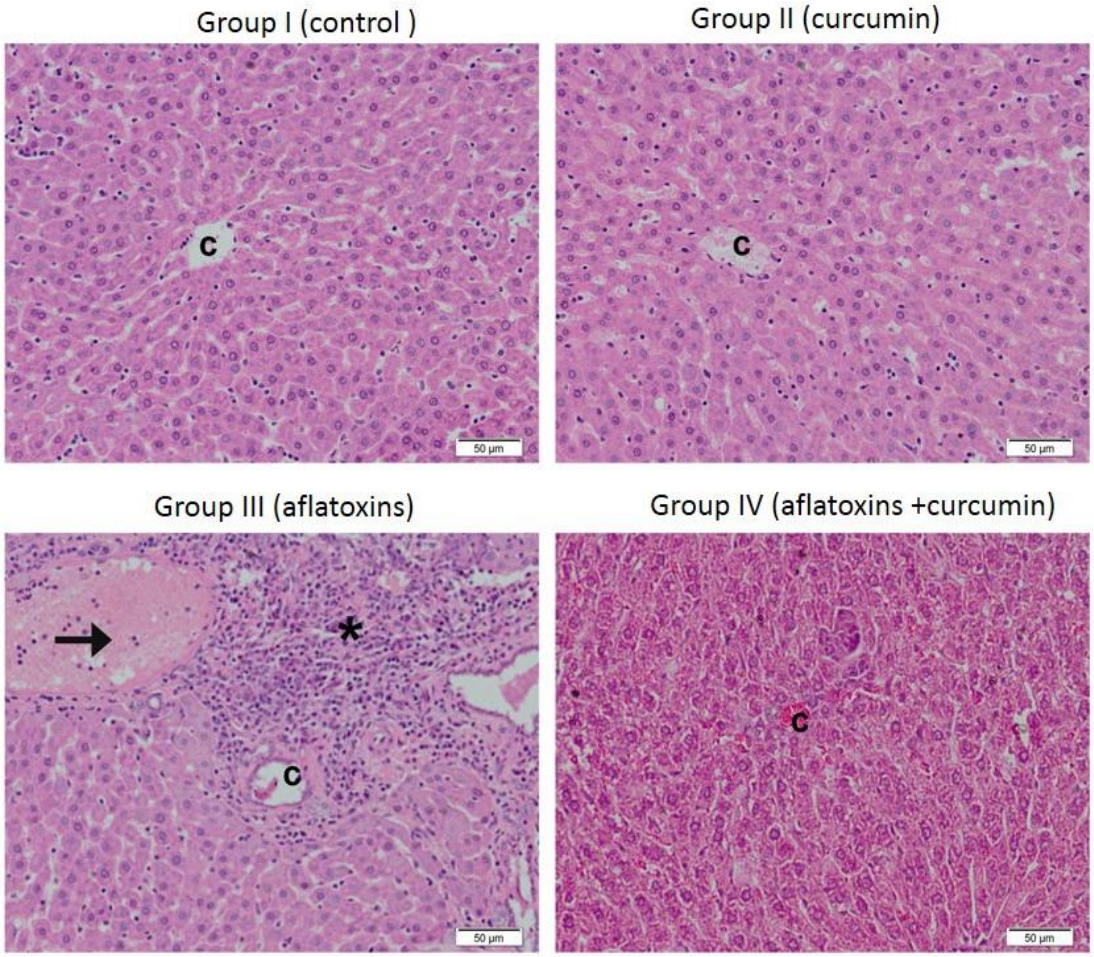

Fig.1: livers of control (group I) and curcumin control (group II) are showing normal histological structure with the normal central vein (c) and hepatic cords. AFs treated group (group III) showing congested blood vessels (arrow) and severe lymphocytic infiltration (star) along with necrotic changes of some hepatocytes. Pronounced protection of curcumin-treated group (group IV) that ameliorated the AFs adverse effects.

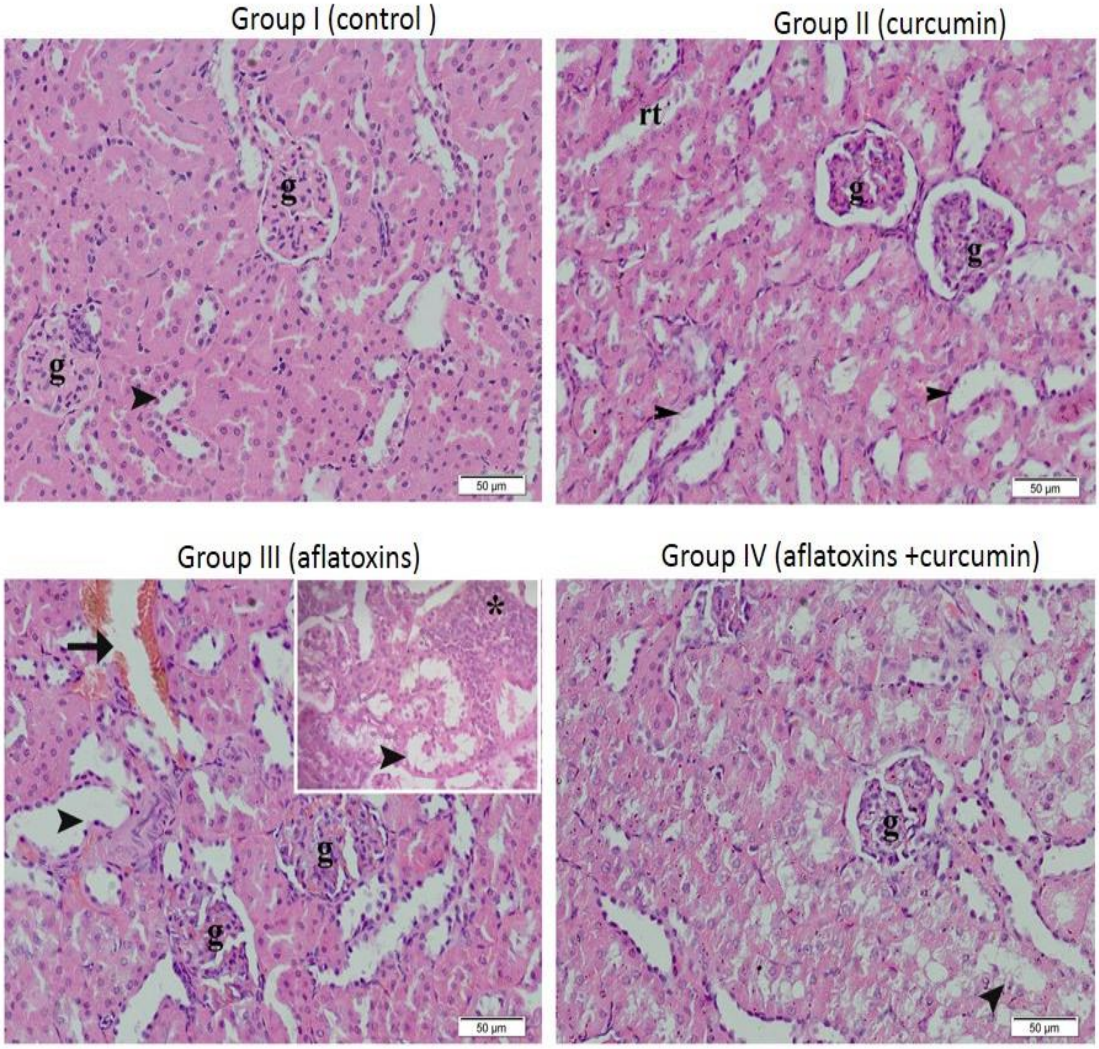

Fig.2: Kidney of control (group I) and curcumin control (group II) are showing normal histological structure with normal glomerulus (g) and renal tubules (rt). AFs treated group (group III) is showing congested blood vessels (arrows) renal tubule degeneration (arrowheads) and local lymphocytic (star) infiltration (inserted window). Pronounced protection of curcumin-treated group (group IV) is observed that ameliorated the AFs adverse effects.

DISCUSSION

There are growing interests in the effect of AFs , that are widely spread, on both human and animal health (Wild *et al.*, 2015). The use of the dietary supplement to counteract the adverse effects of such toxins is mandatory. Therefore the usage of experimental animals for detection of adverse health consequences of such toxins as well as possible protecting effects of some substances is an applicable solution to control such problem (Udomkun *et al.*, 2017). The current study investigated the effect of dietary curcumin 2% to counteract AFs in albino male mice model.

AFs in current study significantly reduced FCR and feed intake while decreased weight gain than the control group. These results were in harmony with Qian *et al.* (2016). They attributed the reduction of FCR that is closely associated with the reduced weight gain to biochemical alterations occurred by AFs. The curcumin

administration to afla-intoxicated mice significantly reduced the FCR and food intake while promoted weight gain than AFs group. This improvement could the attributed to the antioxidant effect of curcumin that improved the metabolic profile of afla-intoxicated mice (Okada *et al.,* 2001). The control curcumin group showed a significant reduction in food intake and body weight gain than control. Miyazawa *et al.* (2018) and Weisberg et al. (2008)results were in agreement with our study.The decline in mice appetite may be related to the ability of curcumin to down-regulate orexigenic leptin (Song and Choi, 2016) while promotes adiponectin (Panahi et al., 2016) that modulates energy intake (Lee and Shao, 2014).The reduction in body weight gain may be attributed to its lipolytic effect (Ejaz *et al.,* 2009). Our results were contradictory to those of Sun *et al.* (2014). The TAC and SOD serum levels were significantly declined in afla-intoxicated group while MDA was increased than control. Feeding curcumin to afla-intoxicated mice resulted in significant improvement in levels of TAC and SOD. Our results were in accordance to those of Choi *et al.,* (2011) and Abdel-Wahhab *et al.* (2016). It was clear from the results that AFs have adverse effects on mice health via their ability to induce oxidative stress that furthermore led to the promotion of lipid peroxidation. Curcumin resulted in the promotion of TAC and SOD beside amelioration of MDA than control. Also, it ameliorated the later levels in afla-toxicated mice.

Our study demonstrated that AFs increased the serum IL-6 level. This cytokine plays an important role in the immune system and inflammatory response (Debruyne and Delanghe, 2008). The elevation of this cytokine was in harmony with the obtained histopathological results. The hepatic and renal lymphocytic infiltrations as well as the congested blood vessels. There is a close association between the elevated levels of IL-6 renal (Greenberg *et al.,* 2015)and hepatic (Jin *et al.,* 2006; Othman *et al.,* 2013) injuries. Oxidative stress was an important candidate in promotion of IL-6 production as well as inflammation. The administration of curcumin significantly ameliorated the inflammatory changes of AFs in the kidney and liver as well as serum levels of IL-6. The possible attribution for this is the antioxidant potential of curcumin (Ak and Gulcin, 2008) that observed in this study by elevation of TAC and SOD activities in group II than control.

AFs also resulted in a significant increase of ALT and ALP levels while albumin level was decreased in association with increased hepatic relative weights than control. This data was in partial harmony with Sun *et al.,* (2014) who declared significant elevation in liver enzymes while albumin and relative hepatic weights were not affected. The levels of ALP, ALT and albumin had been used as valuable indicators for hepatic function (Singh *et al.,* 2013; Wang *et al.,* 2003; Wu *et al.,* 2014). The liver enzymes proposed to be bound by the cell membrane of hepatic cells inside the hepatocytes. The observed reduction in SOD and TAC as antioxidant reserves along with elevated lipid peroxidation were indicative for oxidative stress that perturbed hepatocytes integrity and liberated ALT and ALP into serum *(*de Andrade *et al., 2015;* Lu *et al., 2017*). Also increased the oxidative load on hepatocytes perturbed its synthetic function of albumin thus decreasing its serum level (Kim *et al.,* 2008). The administration of curcumin as antioxidant controlled AFs induced lipid peroxidation and oxidative stress thus restoring albumin synthetic power of liver as well as decreased liver enzymes leakage. These results were confirmed by histopathology were AFs produced some necrotic changes in hepatocytes that further ameliorated by curcumin co-administration. The increment in liver weight was in harmony with the hepatic congestion and inflammation observed in histopathology.

The serum creatinine was significantly elevated in AFs group with non-significant alteration in relative kidney weight. These results concord with those of (Li *et al.,* 2018). The oxidative stress produced by AFs could alter renal cells membrane leading to leakage of creatinine into the blood that was confirmed by renal tubules degeneration in histopathological sections.

In conclusion, the AFs have a serious effect on hepatic and renal function in albino mice as it deteriorated the hepatic and renal biomarkers through oxidative stress inducing mechanism that increased inflammatory changes in such organs. Moreover, AFs later alterations were reflected adversely on FCR, body weight gain and food intake. The co-administration of curcumin is beneficial as it alleviated oxidative stress-induced inflammatory changes. Curcumin alone could be used as appetite and weight regulator.

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ARABIC SUMMARY

تأثير الكركمين على التسمم الكبدي و الكلوى الناجم عن السموم الفطرية في الفئران

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تشكل السموم الفطرية مخاطر صحية ضارة خاصة على الكبد والكلى. يهدف البحث الحالي إلى دراسة التأثير الوقائي المحتمل للكركمين على التسمم الكبدي والكلوي الناجمين عن السموم الفطرية (الافلاتوكسين) في الفئران. تم تقسيم اثنين وثلاثين ذكرا من الفئران البيضاء والتي يتراوح وزنها من 18-20 غرام إلى 4 مجموعات. المجموعة الأولى، هي المجموعة الضابطة وتلقت نظام الغذائي اساسى. المجموعة الثانية، تلقت نظام غذائي اساسى مع 2 ٪ من الكركمين. المجموعة الثالثة، تلقت نظام غذائي أساسي مع إضافة الأفلاتوكسين (5 ميكروغرام / كيلوغرام). المجموعة الرابعة، تلقت الأفلاتوكسين مع الكركمين بنفس الجرعات السابقة. استمرت جميع العلاجات لمدة 4 أسابيع. تم تحديد أوزان الكبد والكلى وكذلك نسبة التحويل الغذائي تم تقدير مستويات فوق اكسيد الديسميوتاز والسعة الكلية المضادة للأكسدة وثنائي الدهيد المالون وانترلوكين -6 في مصل الدم. كذلك تم تقدير انزيم امين الانين الناقل وانزيم الفوسفاتيز القلوي والألبومين والكرياتينين. تم إجراء فحوص نسيجومرضية للكبد والكلى. أسفر العلاج بالأفلاتوكسين عن زيادة مئوية في معامل التحويل الغذائي ووزن الكبد عن المجموعة الضابطة. انخفضت مستويات فوق اكسيد الديسميوتاز والسعة الكلية المضادة للأكسدة بشكل معنوى في المجموعة الثالثة بينما ازداد ثنائى الدهيد المالون وانترلوكين -6 عن المجموعة الضابطة. ازدادت مستويات انزيم امين الانين الناقل وانزيم الفوسفاتيز القلوي والكرياتينين زيادة معنويه في مجموعة الأفلاتوكسين في الوقت نفسه انخفض بشكل ملحوظ مستوى الألبومين عن المجموعة الضابطة. وأظهرت القطاعات النسيجومرضيه في الكبد والكلى احتقان وتسلل ليمفاوي وبعض التغيرات التراجعية الأخرى. استخدام الكركمين مع الأفلاتوكسين حسن بشكل ملحوظ الآثار الضارة الناجمة عن الأفلاتوكسين. الكركمين له تأثير مضاد للأكسدة يخفف من الآثار الضارة الناجمة عن تسمم الأفلاتوكسين بالكلى والكبد.