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Ameliorative Effects of Curcumin on Aflatoxin B1-Induced Nephrotoxicity in Wistar-Albino Rats*

Durmuş Hatipoğlu[1,a,], Ercan Keskin[1,b]**

[1]Department of Physiology, Faculty of Veterinary Medicine, University of Selcuk, Konya, Turkey.
[a]ORCID: 0000-0003-3790-7821, [b]ORCID: 0000-0003-3839-0414

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Abstract: Mycotoxins exposed through food can lead to organ dysfunction and even failure. The number of studies on renal failure induced by aflatoxin B1 (AFB1) is limited. This trial aimed to examine the effect of AFB1 on the kidney and whether curcumin, a traditionally used and economical antioxidant, could prevent its possible harmful effect. Thirty-eight rats were divided into five groups; group I represented the control, while the others were named D, Cur, AF, and AF + Cur, respectively. Plasma samples were taken from each group after 60 days. Then, BUN, uric acid, and creatinine levels were determined by the ELISA method. Statistical analysis has done with obtained data. Bodyweight gain at the end of the study was the least in the group administered AFB1. Also, BUN, uric acid, and creatinine levels were higher in this group than in the other groups. Concomitant administration of AFB1 and curcumin improved body weight gain and BUN, uric acid, and creatinine levels. Therefore, curcumin can be considered a low-cost, high efficacy renal protective agent in preventing renal failure caused by mycotoxins, especially AFB1.
Keywords: *Aflatoxin B1, Curcumin, Kidney Injury, Rat.*

Kurkuminin Aflatoksin B1 ile İndüklenen Wistar-Albino Ratlarda Nefrotoksisite Üzerindeki İyileştirici Etkileri

Özet: Gıda yoluyla maruz kalınan mikotoksinler, organ fonksiyon bozukluğuna ve hatta yetmezliğine yol açabilir. Aflatoksin B1'in (AFB1) neden olduğu böbrek yetmezliği ile ilgili çalışmaların sayısı sınırlıdır. Bu çalışma, AFB1'in böbrek üzerindeki etkisini ve geleneksel olarak kullanılan ve ekonomik bir antioksidan olan kurkuminin olası zararlı etkisini önleyip önleyemeyeceğini incelemeyi hedeflemiştir. Otuz sekiz sıçan beş gruba ayrıldı; grup I kontrolü temsil ederken, diğerleri sırasıyla D, Kur, AF ve AF + Kur olarak adlandırıldı. Her gruptan 60 gün sonra plazma örnekleri alındı. Daha sonra BUN, ürik asit ve kreatinin düzeyleri ELISA yöntemiyle belirlendi. Elde edilen verilerle istatistiksel analiz yapıldı. Çalışmanın sonunda vücut ağırlığı artışı en az AFB1 uygulanan gruptaydı. Ayrıca bu grupta BUN, ürik asit ve kreatinin seviyeleri diğer gruplara göre daha yüksekti. AFB1 ve kurkuminin birlikte uygulanması, vücut ağırlığı artışını ve BUN, ürik asit ve kreatinin düzeylerini iyileştirdi. Bu nedenle kurkumin, mikotoksinlerin, özellikle AFB1'in neden olduğu böbrek yetmezliğini önlemede düşük maliyetli, yüksek etkili bir böbrek koruyucu ajan olarak kullanılabileceği düşünüldü.
Anahtar kelimeler: *Aflatoksin B1, Böbrek Hasarı, Kurkumin, Rat.*

Introduction

Mycotoxins are toxigenic fungal secondary metabolites produced mainly by Aspergillus, Penicillium, and Fusarium and pose a significant threat to human and animal health worldwide (Guo et al., 2021). The Food and Agriculture Organization (FAO) reports that around 25% of agricultural raw materials worldwide are contaminated with mycotoxins, causing health problems and substantial economic losses (FAO, 2013). At least 400 mycotoxin types have been identified, including aflatoxins (AF), zearalenone, deoxynivalenol, fumonisin, patulin, T-2 toxin, and ochratoxins (Cimbalo et al., 2020). AF, a mycotoxin commonly found in the environment that seriously threatens food safety and public health, are mainly fungal metabolites produced by Aspergillus flavus and Aspergillus parasiticus (Saini and Kaur, 2012). The most important of these are aflatoxin B1 (AFB1) and aflatoxin B2 (AFB2) (McLean and Dutton, 1995). Consumption of foods or indirect exposure contaminated with AFB1 causes growth retardation, suppression of the immune system, carcinogenicity, genotoxicity, and teratogenicity (Ali et al., 2021; Ates et al., 2022; Ateş and Ortatatlı, 2020; Engin and Engin, 2019; Khan et al., 2021; Wangikar et al., 2005).

It was reported that AFB1 and its metabolites cause nephrotoxicity before being removed from the body on various parts of the nephron, which are sensitive to aflatoxins. (Sharma et al., 2011). However, it is stated that increased BUN, uric acid, and creatinine levels due to aflatoxicosis indicate protein catabolism and/or renal dysfunction (Naaz et al., 2014). Abdel-Daim et al. (2021) reported that

liver enzymes, BUN, uric acid, and creatinine levels of rats exposed to AFB1 increased significantly compared to the control group. As a result, AFB1 caused hepatotoxicity and nephrotoxicity (Abdel-Daim et al., 2021).

Health organizations, researchers, manufacturers, and governments have focused on developing effective prevention, management, and decontamination technologies to minimize the toxic effects of AF (Oguz, 2011). Especially recent studies target detoxification of mycotoxins (Ates and Ortatatli, 2021; Nasrollahzadeh et al., 2022; Yavuz et al., 2017). The addition of inert and non-nutritive non-digestible binders to the diet is a current approach for solving aflatoxicosis. These substances bind aflatoxins, reducing their absorption from the gastrointestinal tract. Enzymes that cannot be absorbed from the gastrointestinal tract such as clay and zeolites are used for this purpose (Dönmez and Keskin, 2008; Oguz and Kurtoglu, 2000). Sodium calcium aluminosilicate, activated charcoal, glucomannan, clay, zeolite, sodium bentonite, clinoptilolite, polyvinylpyrrolidone (PVPP), as antioxidants Vit-A, Vit-C, Vit-E, and amino acids containing sulfhydryl groups (Methionine, Cysteine, N-acetyl cysteine) are frequently used to prevent aflatoxicosis (Dönmez et al., 2012; Oguz and Kurtoglu, 2000; Ortatatli et al., 2005).

Turmeric is a traditional spice dating back to 600 BC and used for medicine, condiment, and flavor (Gupta et al., 2013). There are about 120 known species of curcumin, also called diferuloylmethane, and they are widely found as C. Aromatica and C. Xanthorrhiza, and Curcuma longa (Sasikumar et al., 2005; Sun et al., 2017). Pharmacokinetic and bioavailability studies of curcumin have revealed its poor absorption and rapid elimination from the body, so it is safe even at very high doses (Dei Cas and Ghidoni, 2019). In addition to being used as a spice, curcumin is used as a medicinal plant due to its antioxidant, anti-inflammatory (Ak and Gülçin, 2008), anti-mutagenic, antimicrobial (Parvathy et al., 2009), and anti-carcinogenic (Allegra et al., 2017) properties. Also, Kim et al. (2018) reported that oral administration of curcumin in rats with nephrotoxicity significantly reduced serum AST, ALT, BUN, urea, and uric acid levels (Kim et al., 2018).

Many studies have documented the effects of AF on different organs, tissues, and health parameters. However, the information about the curative effect of curcumin, which is widely used among the public, on kidney damage caused by AF is insufficient. This article provides information on the impact of AF on body weight and kidney damage and the possible amelioration of these effects with curcumin administration.

Materials and Methods

Chemicals: AFB1 (≥ 99%) was supplied by Acros Organics [Gell, Belgium (Cat. No: 227340100)]. Curcumin (≥ 99%) was purchased by Sigma Aldrich [St. Louis, MO, USA (Cat. No: C1386)]. BUN (Cat. No DF21), Uric acid (Cat. No: DF77), and creatinine (Cat. No: DF33B) kits were obtained from Siemens Medical System (Erlangen, Germany).

Animals: Thirty-eight male Wistar albino rats (34-36 g) were used in the investigation. Selcuk University Experimental Application and Research Center provided the animal material. In the beginning, the animals' general health state was examined, their body weights were determined, and they were separated into five groups based on their average body weight. The rats were kept in plastic rat cages throughout the study (60 days), with 12/12 day-night light cycles and a room temperature of 23±2 ℃ were housed ad libitum.

Experimental design: This study protocol was approved by Selcuk University Experimental Medicine Research and Application Center Ethics Committee (Report no. 2018-26). Rats were weighed before starting the experiment. They were divided into five groups, with the mean body weight of each group being equal. Group I (Control (K), n=6) animals were not applied; Group II (DMSO (D), n=6) 1 ml 10% DMSO; Group III (Curcumin (Cur), n=6) 300 mg/kg curcumin (Na et al., 2013); Group IV (AFB1 (AF), n=10) 250 µg/kg AFB1 (Tang et al., 2007); Group V (AF+Cur, n=10) 250 µg/kg AFB1 + 300 mg/kg curcumin. The trial period was ended on the 60th day, and all applications were administered orally to the animals. AFB1 and curcumin were dissolved in 10% DMSO and made ready for use. At the end of the 60th day, sufficient blood was taken from the heart of all animals under general anesthesia (Xylazine 10mg/kg and Ketamine 5mg/kg). The blood was collected in serum (BD Vacutainer SSTTM II Advance-367953) tubes and centrifuged at 4500 rpm for 10 minutes at +4 °C (Hettich Universal 32R). Serum samples were stored at -80 °C in Eppendorf tubes until analysis.

Analysis of Kidney Function Test: BUN, uric acid, and creatinine levels were measured in Siemens CentaurXP Immunoassay System following the package inserts using commercial kits from sera stored at -80^{o}C until the analysis time.

Data analysis: The SPSS 20.00 package program was used to analyze the data gathered and determine the significance of the differences between groups. We used visual and analytical methods to analyze variables for normal

distribution. All variables were reported as mean and standard deviations. The groups were compared using a one-way ANOVA test. Following the determination of variance homogeneity, where the p-value was less than 0.05, pairwise post hoc comparisons (Tukey) were employed to test the significance of the groups, and Duncan's Multiple Range Test was used in the analysis of variance.

Results

Comparison of Live Weight Averages: According to the data obtained from all groups, the average body weight of the 0, 15, 30, and 60th days of the application are shown in Figure 1. The bodyweight averages at the 60th day were statistically lower in the AF group than in the other four experimental groups (C, Cur, D, and AF+Cur) ($p<0.05$). After the curcumin application, the bodyweight average of the 60th day obtained from the AF+Cur group was significantly higher than that of the AF group ($p<0.05$). At the same time,it was statistically lower than the values in the C and Cur groups ($p<0.05$) (Figure 1).

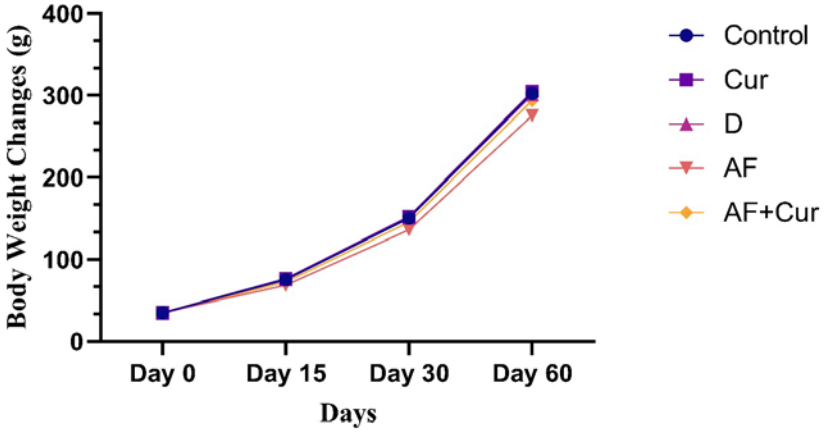

Figure 1. Intergroup average live weight changes. **C:** Control Group, **Cur:** Curcumin group, **D:** DMSO group, **AF:** Aflatoxin group, **AF+Cur:** Aflatoxin and Curcumin group

Comparison of Kidney Function Test Findings: The values of BUN, uric acid, and creatinine parameter levels obtained from all groups are shown in Figure 2. When the data obtained from the AF group were analyzed, it was observed that BUN, Uric acid, and Creatinine levels were statistically higher than the C, Cur, and D groups ($p<0.05$). Again, compared to the AF+Cur group, while no difference was observed in the creatinine level of the data obtained from the AF+Cur group compared to the AF group ($p>0.05$), it was determined that the BUN level had a decreasing trend, and the uric acid level was significantly lower ($p<0.05$). Data obtained from the Cur and D groups were similar to C. (Figure 2).

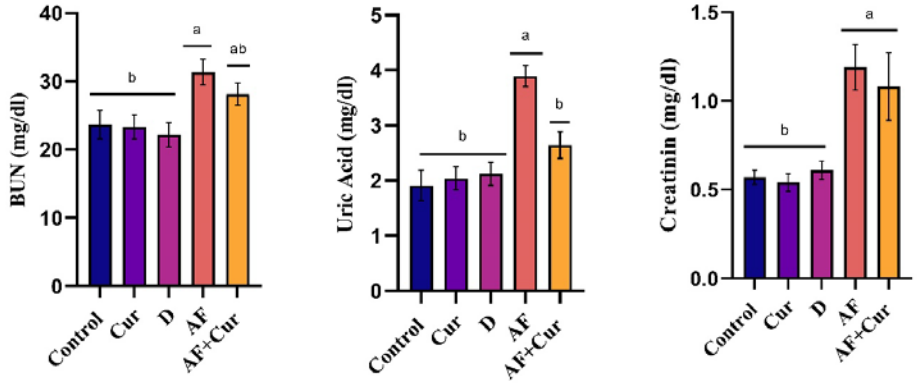

Figure 2. The effect of curcumin on renal function tests in rats administered orally Aflatoxin B_1 (X ± SEM) a,b,c; The difference between the mean values shown with different letters for the same parameter on the same graph is significant ($p<0.05$). **C:** Control Group, **Cur:** Curcumin group, **D:** DMSO group, **AF:** Aflatoxin group, **AF+Cur:** Aflatoxin and Curcumin group

Discussion

Aflatoxins are mycotoxins that cause significant economic losses due to acute-subacute and chronic toxications in farm and poultry farming and affect human health all over the world (Rai and Varma, 2010). The target organ in aflatoxicosis is the liver, followed by the kidneys. In addition to hemorrhage, cirrhosis and fatty degeneration in the liver, pancreas, gall bladder, lung and intestine are also affected (Brase et al., 2013). Removal of aflatoxin from food contaminated with aflatoxin is a critical problem. Therefore, consuming foods containing aflatoxin is still a significant public health problem for human and animal health and causes economic losses. Recently, the therapeutic effectiveness of curcumin, which is obtained from turmeric, which is readily available, easily accessible, has minimal side effects, and is a cheap therapeutic agent and widely used as a spice, has attracted attention. Curcumin has effective anti-inflammatory, antioxidant, anticarcinogenic, antimutagenic, anticoagulant, antibacterial, antiviral, and nervous system protective properties (El-Bahr, 2015; El-Mekkawy et al., 2020). Because of these properties, curcumin was preferred in this study to eliminate the damage caused by aflatoxin in the kidneys.

Urea, uric acid, and creatinine from non-protein nitrogen (NPN) fractions in the blood are used clinically to monitor kidney function (Kumar et al., 2021). It was reported that oxidative stress due to aflatoxin causes renal vasoconstriction or decreases the glomerular capillary ultrafiltration coefficient and thus leads to the formation of various vasoactive mediators that can directly affect kidney function due to reduced glomerular filtration rate (Garcia-Cohen et al., 2000).

It is known that AFB_1 causes kidney damage due to accumulation in the kidney and leads to kidney failure (Grosman et al., 1983; Karabacak et al., 2015). Oxidative stress is a significant risk factor for AFB_1-induced nephrotoxicity. AFB1 exposure increases the presence of ROS, leading to the deterioration of the antioxidant defense system and oxidative damage in the kidneys (Abdel-Hamid and Firgany, 2015; Naaz et al., 2014). In addition, AFB_1 causes an increase in the relative weight of the kidney (Quezada et al., 2000), tubular lumen obstruction and degeneration of the tubular epithelium (Asplin and Carnaghan, 1961), thickening of the glomerular basement membrane (Valdivia et al., 2001), and degenerative changes in the proximal tubule cells (Mollenhauer et al., 1989), causing structural and functional damage to the kidney. The current study observed that BUN, uric acid, and creatinine levels obtained from the AF group were statistically higher than the control groups (C, Cur, D) (Figure 2). Yu et al. (2018) reported that BUN and serum creatinine levels were higher in mice given AFB_1 than in the control group (Yu et al., 2018). Nada et al. (2010) also stated that BUN and serum creatinine levels were increased in rats given AFB1 compared to the control group. The findings obtained from this study are similar to previous studies (Eraslan et al., 2017; Nada et al., 2010; Yu et al., 2018).

According to these results, high serum creatinine level, which is an indicator of kidney toxicity and kidney damage, suggests that it may be caused by the toxic effect caused by AFB_1 (Andretta et al., 2012; Chen et al., 2014). Among the reports, the cause of high plasma urea concentrations is related to AFB_1-induced nephrotoxicity (Kubena et al., 1991). Gowda and Ledoux (2008) reported that increased urea and creatinine levels in 2–6-week-old broilers fed 3 mg/kg AFB_1 contaminated feed were associated with inflammatory and dystrophic processes in the renal tubules (Gowda et al., 2008). They suggest that higher urea and creatinine levels may indicate impaired transport function of epithelial cells of the collecting tubules and diffuse impairment of the role of the proximal tubules. It was also suggested that changes in urea and creatinine levels might be associated with necrotic changes in the kidney parenchyma (Fung and Clark, 2004). These results are accepted as an indication that AFB_1 exposure may lead to detrimental and degenerative changes in kidney tissue, leading to a decrease in the function of this organ.

Curcumin is known to have kidney protective effects against substances such as natural toxins (such as LPS) and chemical toxins (acetaminophen, cisplatin, acrylamide, gentamicin, cadmium) (García-Niño and Pedraza-Chaverrí, 2014). It is reported that curcumin significantly and dose-dependently improves creatinine and urea clearance, reducing serum creatinine and BUN levels (Hosseini and Hosseinzadeh, 2018). This study determined that BUN and creatinine levels in the AF+Cur group tended to decrease compared to the AF group.The value in this group was higher when compared to the control groups (F, Cur, D), although there was no statistical difference. It was observed that the uric acid level in the AF+Cur group was significantly lower than in the AF group. (Figure 2). Khoursandi et al. (2008) applied curcumin extract (400, 800, and 1000 mg/kg) to mice., They reported that it showed nephroprotective effects by reducing creatinine, BUN, and uric acid and lipid peroxidation levels against acetaminophen, which is used as an analgesic and antipyretic drug and causes kidney toxicity in approximately 1-2% of patients. They suggest that this effect of curcumin may be related

to its binding to acetaminophen metabolites and its decreased affinity for cellular GSH (Khoursandi and Ourazizadeh, 2008).

El-Rahman (2014) reported that curcumin administered to rats at doses of 30 and 60 mg/kg decreased serum urea and creatinine levels against cisplatin, a nephrotoxic substance, increases urea and creatinine levels (El-Rahman and Al-Jameel, 2014). It is thought that curcumin exerts its nephroprotective effect against cisplatin through its antioxidant function. Also, another study stated that a 100 mg/kg dose of curcumin decreased kidney damage by lowering MDA, serum uric acid, and creatinine levels in rats following cisplatin injection (Ugur et al., 2015). El-Bahr et al. (2015) reported that creatinine levels increased in rats given 3mg/kg AFB_1 by IP route for five weeks.The creatinine level was statistically lower in rats given 15mg/kg curcumin+3mg/kg AFB_1 orally compared to the group administered only AFB_1 for five weeks (El-Bahr, 2015). El-Mahalaway (2015) reported that serum urea, uric acid, and creatinine levels were higher in rats given AFB_1 at 250 µg/kg body weight orally five times a week for four weeks compared to the control group and that oral administration of 200 mg/kg body weight of curcumin together with AFB_1 improves the levels of these parameters (El-Mahalaway, 2015).

The data obtained in our study comply with previous studies showing that curcumin ameliorates kidney damage from exposure to AF or other toxic substances. In conclusion, curcumin is recommended to facilitate kidney damage caused by exposure to AF or other toxic substances.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Ethical Approval

This study was approved by the Ethics Committee of Selcuk University Experimental Medicine Research and Application Center with the number 2018-26.

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[*]**Yazışma Adresi:** Durmuş Hatipoğlu
Department of Physiology, Faculty of Veterinary Medicine, University of Selcuk, Konya, Turkey.
e-mail: drhatip@selcuk.edu.tr