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Research article

The effect of curcumin on some cytokines, antioxidants and liver function tests in rats induced by Aflatoxin B1

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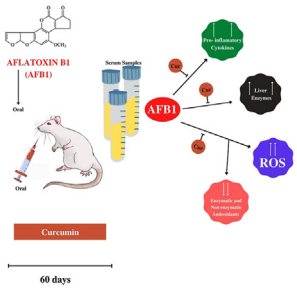
GRAPHICAL ABSTRACT



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ABSTRACT

Aflatoxins are common food contaminants threating human and animal health. Aflatoxin B1 (AFB1) toxication can lead to important health issues. Recent studies have revealed the therapeutic effect of curcumin (Cur) and have drawn attention in the pharmaceutical industry. The therapeutic efficacy of Cur on AFB1-induced oxidative stress, pro-inflammatory response, and hepatorenal damage has not been adequately studied. This study was conducted to evaluate the protective efficacy of Cur on several lipid peroxidation and antioxidant defense system enzymes, some pro-inflammatory cytokines, and liver function tests in rats suffering from chronic aflatoxicosis induced by AFB1 administered for sixty days. Rats were divided into five groups; Control (K), Dimethyl sulfoxide (D), Curcumin (Cur; 300 mg/kg/day, orally), AFB1 (AF; 250 μg/kg/day, oral) and AFB1+ Curcumin (AF + Cur). Oxidative stress caused by AFB1 caused an increase in Malondialdehyde (MDA), a lipid peroxidation product, and a decrease in glutathione (GSH) and superoxide dismutase (SOD) activities. In addition, AFB1 led to increased levels of pro-inflammatory cytokines such as tumor necrosis factor-a (TNF-a), interleukin-1b (IL-1b), and interleukin-6 (IL-6). Liver function tests after chronic exposure to AFB1 showed that this toxic substance causes liver damage. Concomitant Cur administration normalized AFB1-induced oxidative damage, inflammatory response, and liver functions. This therapeutic effect of Cur on AFB1 was thought to be related to its antioxidant and anti-inflammatory activities. Our results suggest that CUR supplementation in food as it shows beneficial effects particularly on liver impairment exerted by AFB1.

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1. Introduction

Mycotoxins are substances that cause significant health problems in both humans and animals by contaminating feed raw materials and foods in many countries of the world [1]. Among the hundreds of mycotoxins identified, aflatoxins (AFs) produced by *Aspergillus flavus* and *Aspergillus parasiticus*, which pose a significant public health problem, are considered critical food pollutants in hot and humid climates such as Central America, Asia, and Africa [2]. Aflatoxin B1 (AFB1), the most potent member of the AF family, is classified as a group 1 carcinogen by the International Agency for Research on Cancer (IARC) [3]. AFB1 also has mutagenic, genotoxic, teratogenic, immunotoxic, nephrotoxic effects [4, 5].

After AFs are taken into the body, 75% are kept in the feces, 15–20% in the urine, and 5–6% in the liver within the first 24 h, while the rest is excreted in milk as metabolites or unchanged [6, 7, 8]. AFs mainly target the liver, causing hepatocellular damage [9]. It was reported that AFB1 which is formed after being metabolized, causes damage to DNA and different cellular proteins through its toxic metabolites such as AFB1-8,9 epoxide (AFBO) [10, 11], and disrupts protein and lipid metabolism by stimulating the production of reactive oxygen species (ROS) [12]. It is unclear whether AFB1 directly stimulates lipid peroxidation through increased ROS synthesis or the increased sensitivity of tissue to peroxidation results from impaired antioxidant defense, but both mechanisms are probably involved [13] AFB1 is involved in antioxidant enzyme activity (GSH, SOD and CAT etc.) [14] decrease and in cell membrane damage by increasing the level of malondialdehyde (MDA), a product of lipid peroxidation [13].

It is unclear how aflatoxin and other mycotoxins affect immunomodulation. Mycotoxins are said to affect many different mechanisms and cause immunosuppression by inhibiting DNA, RNA, and protein synthesis [15, 16]. According to research, AFB1 modulates cytokine production to exert immunomodulatory effects [17]. Aflatoxin B1 may also be able to stop the activation of some kinases that play a role in the activation of genes that make cytokines [18, 19] (Rossano ve diğerleri, 1999; Liu ve diğerleri, 2002).

Physical, chemical, and biological means are used for the decontamination of feeds contaminated with AF. Sodium calcium aluminosilicate, activated charcoal, glucomannan, clay, zeolite, sodium bentonite, clinoptilolite, black cumin seed as an antioxidant, and amino acids containing thymoquinone, Vitamin A, C, E, and sulfhydryl groups (methionine, cysteine, N-acetyl cysteine) are frequently used to prevent aflatoxicosis [10, 20, 21].

Researchers noted that many extracts from herbs and plants can prevent AFB1 toxicity [22, 23]. Curcumin, *Curcuma longa L.*, is a popular spice and food additive widely used in South Asian and Middle Eastern countries [24]. In recent studies, it was reported that curcumin targets over one signal molecule and has potent antioxidant and anti-inflammatory properties by showing activity at the cellular level [25]. Besides, curcumin has a protective effect against various neurological, cardiovascular, and metabolic diseases thanks to its antiviral, antiallergic, anticarcinogenic, antibacterial properties [26]. Besides all these effects, it is reported that curcumin provides efficient protection against the toxicity caused by AFB1, but further studies should be done on this subject [14].

The aflatoxicosis problem remains up to date worldwide. Since this toxic substance is consumed accidently, it is taken with food by humans and animals, causing many harmful effects. This study aimed to determine the protective effect of curcumin on the oxidant/antioxidant balance, liver functions, and pro-inflammatory response, which is impaired because of AFB1 exposure.

2. Materials and methods

2.1. 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)]. Malondialdehyde (MDA, Cat. No: E0156Ra), glutathione (GSH, Cat. No: E1101Ra), superoxide dismutase (SOD, Cat. No: E0168Ra) enzyme-linked immunosorbent assay (ELISA) kits were purchased from Bioassay Technology Laboratory (Shangai, China). Tumor necrosis factor-alpha (TNF-α, Cat. No: KRC3011), interleukin-1 beta (IL1β, Cat. No: BMS630), interleukin-6 (IL-6, Cat. No: BMS625) enzyme-linked immunosorbent assay (ELISA) kits were purchased from Thermo Fisher Scientific Inc. (USA). Alanine transaminase (ALT, Cat. No: DF143), aspartate transaminase (AST, Cat. No: DF41A), alkaline phosphatase (ALP, Cat. No: DC150), and gamma-glutamyl transferase (GGT, Cat. No: DF45A) kits were obtained from Siemens Medical System (Erlangen, Germany).

2.2. 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. Before beginning the study, 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 °C were housed ad libitum.

2.3. 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 the start of 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 fed *ad libitum*; Group II (DMSO (D), n = 6) 1 ml 10% DMSO; Group III (Curcumin (Cur), n = 6) 300 mg/kg curcumin [27]; Group IV (AFB1 (AF), n = 10) 250 μg/kg AFB1 [28]; 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 groups of animals under general anesthesia (Xylazine 10 mg/kg and Ketamine 5 mg/kg). The blood was collected in serum (BD Vacutainer SSTTM II Advance-367953) tubes and centrifuged at 4500 rpm for 10 min at +4 °C (Hettich Universal 32R). Serum samples were stored at -80 °C in Eppendorf tubes until analysis.

2.4. Analysis of lipid peroxidation and antioxidant enzyme activities

The targeted MDA, GSH, and SOD levels were measured using the ELISA method, using commercial kits, following the methods specified in the product catalog [29]. Spectrophotometric measurements were performed using ELx800 (Bio-Tek Instruments, Winooski, VT, USA) at a wavelength of 450 nm.

2.5. Analysis of pro-inflammatory parameters

In serum samples, pro-inflammatory cytokines were quantified using commercial ELISA kits. TNF-α, IL-6, IL-1β levels were measured with anti-rat ELISA kits according to the manufacturer's instructions, as mentioned above [30]. The concentration units were expressed as pg/mL.

2.6. Analysis of liver enzymes

ALT, AST, ALP, and GGT levels were measured in Siemens CentaurXP Immunoassay System following the package inserts using commercial kits from sera stored at -80°C until the time of analysis.

2.7. Data analysis

The SPSS 20.00 package program was used to conduct a statistical analysis of the data gathered at the study's end and determine the significance of the differences between groups. Visual and analytical methods were used 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.

3. Results

3.1. Evaluation of MDA, GSH, and SOD levels

The results of the present study shows that the amount of MDA, which is the end product of lipid peroxidation, was significantly greater in the AF group than in the other four experimental groups (K, Cur, D, and AF + Cur) ($p < 0.05$). Following curcumin application, the MDA level obtained from the AF + Cur group was found to be statistically lower than that of the AF group, although it was statistically greater than the values obtained from the K and Cur groups ($p < 0.05$) (Figure 1).

GSH level was found to be significantly lower in the AF group compared to the Control group ($p < 0.05$). The AF + Cur group showed an increase in GSH level increased compared to the AF group and reached similar levels to the control, Cur, and D groups ($p < 0.05$) (Figure 1).

The AF group's serum SOD level was statistically lower than all other groups ($p < 0.05$). At the same time, the SOD level in the AF + Cur group was statistically lower than in the K group ($p < 0.05$), it was found to be statistically greater than in the AF ($p < 0.05$) (Figure 1).

3.2. Evaluation of pro-inflammatory cytokine levels

Results on cytokine level show that IL-1β levels were statistically greater in the AF and AF + Cur groups than in the K, Cur, and D groups ($p < 0.05$). Although it was not statistically significant, it was noted that the IL-1β level decreased in the AF + Cur group compared to the AF group ($p > 0.05$) (Figure 2).

TNF-α levels in the AF group were statistically higher than in the other four experimental groups ($p < 0.05$) TNF-α levels were found to be statistically lower in the AF + Cur group than in the AF group ($p < 0.05$), and no significant difference was identified among the other three groups (K, Cur, D) ($p > 0.05$) (Figure 2).

In terms of IL-6, the value obtained in the AF group was significantly greater than in the other four groups ($p < 0.05$) IL-6 level of the AF + Cur group was statistically lower than that of the AF group ($p < 0.05$) (Figure 2).

3.3. Evaluation of liver functions

Serum AST, ALT, ALP, and GGT levels were significantly greater in the AF group than in the other groups (K, Cur, D, AF + Cur) ($p < 0.05$). Serum AST, ALT, ALP, and GGT levels were statistically lower in the AF + Cur group than in the AF group ($p < 0.05$). When the results from the Cur and DMSO groups were compared to the K group, there was no significant difference in enzyme levels ($p > 0.05$) (Figure 3).

4. Discussion

It has been reported that aflatoxins cause inhibition of antioxidant enzymes and anti-inflammatory cytokines, lipid peroxidation, stimulation of proinflammatory cytokines and apoptosis of hepatocytes [31, 32]. It was reported that curcumin targets more than one signal molecule and has strong antioxidant and anti-inflammatory properties by showing activity at the cellular level [33, 34]. In the study investigating the protective effect of curcumin on aflatoxicosis the effects on liver function tests such as ALT, AST, ALP, and GGT, lipid peroxidation product such as MDA, antioxidant defense system members such as GSH and SOD, and pro-inflammatory cytokines such as TNF-a, IL-1β, and IL-6 were investigated.

AFB1 has been reported to induce DNA damage by oxidative stress, which occurs through the production of ROS, which indirectly attacks membrane phospholipids and releases different mutagenic aldehydes [2]. In this study, it is suggested that the increase in MDA level in the aflatoxicosis-induced group may be caused by the formation of free radicals that cannot be tolerated by the antioxidant defense system (Figure 1). The increase in MDA level can be considered as evidence of lipid peroxidation caused by the deficiency in the antioxidant defense system or the increase in free radicals [35]. The curative effect of curcumin against AFB1-induced lipid peroxidation was consistent with previous reports [36, 37]. Numerous studies have shown that curcumin is a potent scavenger of various reactive oxygen species, including hydroxyl radicals [38] and nitrogen dioxide radicals, and inhibits lipid peroxidation, which leads to cell damage and cell death in different animal models [39, 40, 41].

It is stated that antioxidant defense system members such as GSH and SOD play a significant role in the detoxification of reactive and toxic metabolites of AFs, and chronic exposure may cause a decrease in the level of these antioxidants [42, 43, 44]. In our study, it was determined that the decrease in GSH levels and in SOD activity have been improved by adding curcumin to the diet (Figure 1). There are antioxidant defense system members such as SOD, CAT, and GSH that

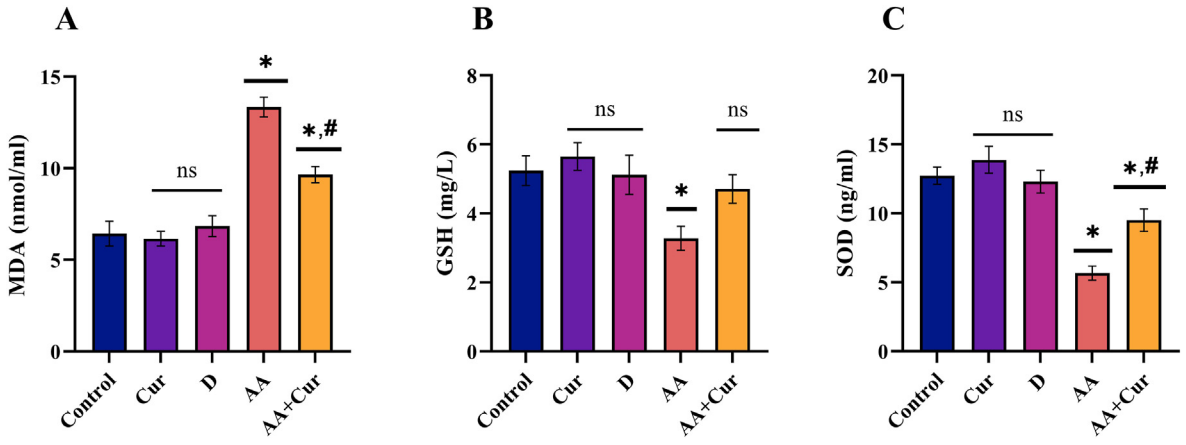

Figure 1. Effect of curcumin on serum MDA, GSH and SOD levels in rats administered orally Aflatoxin B1 (X ± SEM) (Statistically significant ($p < 0,05$) differences are indicated by * when compared to the control group, and statistically significant differences ($p < 0,05$) are indicated by # when compared with the AA group).

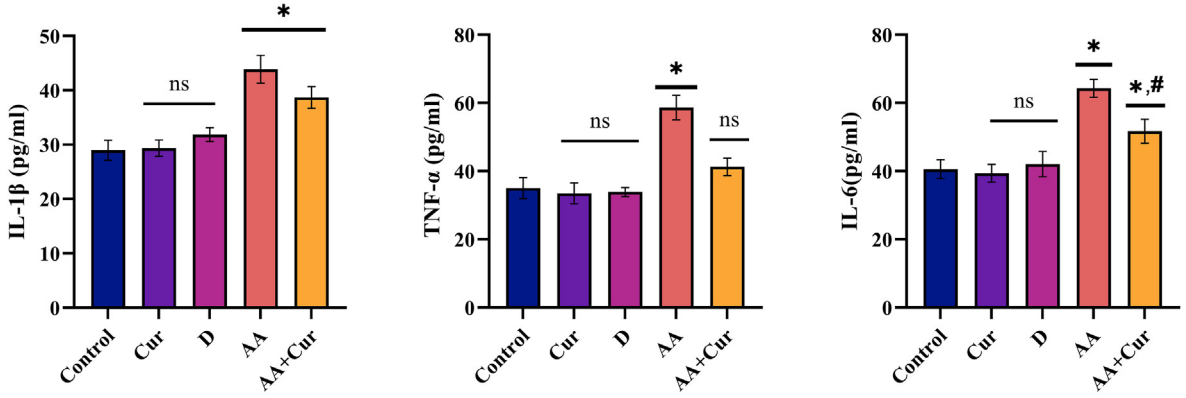

Figure 2. Effect of curcumin on serum pro-inflammatory cytokine levels in rats administered orally Aflatoxin B1 (X ± SEM) (Statistically significant ($p < 0,05$) differences are indicated by * when compared to the control group, and statistically significant differences ($p < 0,05$) are indicated by # when compared with the AA group).

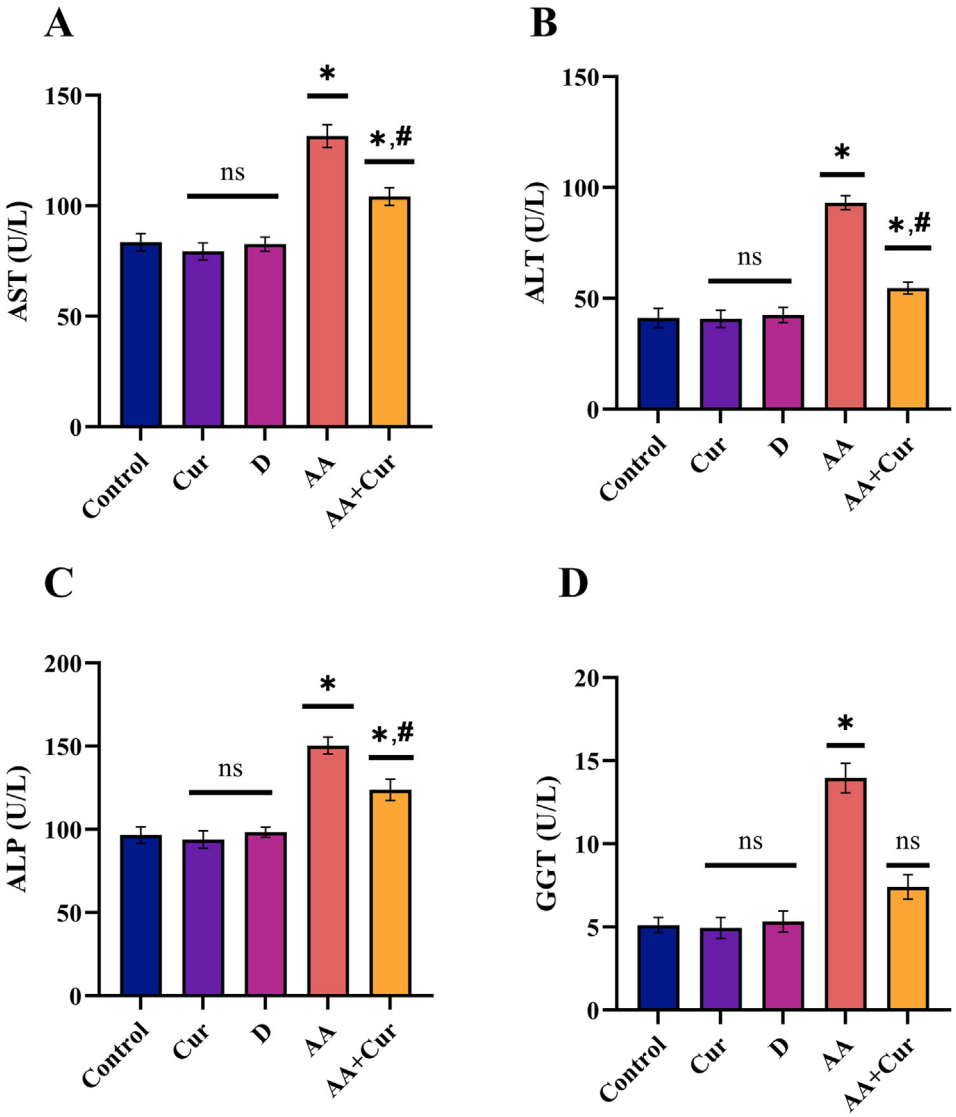

Figure 3. Effect of curcumin on serum liver enzyme levels in rats administered orally Aflatoxin B1 (X ± SEM) (Statistically significant ($p < 0,05$) differences are indicated by * when compared to the control group, and statistically significant differences ($p < 0,05$) are indicated by # when compared with the AA group).

suppress or prevent the formation of free radicals and reactive species in cells [45]. Based on the findings obtained from the present study, we concluded that curcumin can be used as a therapeutic agent to return the decreased GSH and SOD levels because of AFB1 exposure to physiological limits and to prevent the increase of lipid peroxidation products.

Inflammation and immune response are particularly important in the early response to tissue damage, and therefore a measurement of serum cytokines is used as a biomarker in routine toxicity studies [46, 47]. In parallel with other studies, in the current study, it was found that AFB1 increased IL-1β, TNF-α, and IL-6 levels [48, 49, 50] (Figure 2). This is considered as an indication that systemic inflammation is triggered [51]. It was determined that curcumin decreased TNF-α and IL-6 levels statistically significantly compared to the AF group. This decrease in IL-1B level in the AF group was not statistically significant (Figure 2). Curcumin has been reported to block pro-inflammatory cytokines through mitogen-interacting protein kinases (MAPK), signal transducer and activator of transcription 3 (STAT3), extracellular signal-regulated kinases (ERK), and NF-κB [52, 53, 54]. In our study, it was thought that the inhibition of these pathways activated by AFB1 by curcumin might have resulted in a decrease in the levels of these cytokines.

Increased serum ALT, AST, ALP and GGT activities are accepted as diagnostic indicators of liver injury. Elevated liver enzymes suggest hepatic parenchymal cell damage (ALT and AST) or degenerative changes in the bile duct (ALP). According to the findings we obtained as a result of the study, the increase in AST and ALT levels in the blood due to the loss of structural integrity of hepatocytes in the AF group indicates that a certain liver damage has occurred. Because AST and ALT, which are normally found in the cytoplasm of hepatocytes, are released into the circulatory system only when the structural integrity of the liver is affected [55]. AFB1 leads to disruption of membrane permeability and mitochondrial membrane in hepatocytes, resulting in increased levels of ALT, AST and GGT. Besides, the increase in ALP level caused by AFB1 also shows that biliary excretion is inhibited (Wang et al 2019). Abdel-Wahhab et al. (2016), report that ALT and AST levels are higher in AF group than in the control group and that curcumin treatment reduces the levels of these enzymes compared to the AFB1 group [56]. El-Agamy (2010) and El-Bahr (2015) reported that ALT, AST, and GGT levels increased significantly in rats with experimental aflatoxicosis, and that oral curcumin treatment applied to these animals resulted in significant improvement in the levels of these enzymes, similar to the current study [14, 57]. Curcumin is thought to protect the liver against oxidative damage caused by AFB1 thanks to its ability to scavenge reactive oxygen species by suppressing oxidative enzymes, normalizing antioxidant levels, and chelating metal ions [57].

5. Conclusion

AFB1 administered orally to rats had negative effects on liver functions, pro-inflammatory cytokines, and antioxidants. In our study, oral curcumin supplementation showed a hepatoprotective effect against AFB1 by supporting the antioxidant system and regulating liver functions. Curcumin supplementation also played a role in providing immunomodulation by improving pro-inflammatory cytokine levels. The development of new methods and strategies that increase the bioavailability of curcumin may provide further protection against liver damage caused by aflatoxin. Still, further research on the physiological, cellular, and molecular mechanisms involved in liver protection is needed to suggest it as a potential therapeutic agent against oxidative damage-induced liver injury because of exposure to aflatoxin.

Declarations

Author contribution statement

Durmus Hatipoglu & Ercan Keskin: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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