Original article DOI: 10.2478/aiht-2023-74-3648

Protective effects of resveratrol against fumonisin B1-induced liver toxicity in mice

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[Received in April 2022; Similarity Check in April 2022; Accepted in May 2023]

The aim of this study was to investigate the effects of resveratrol against fumonisin B_1 (FB_1)-induced liver toxicity, as, to the best of our knowledge, these effects have not been investigated yet, even though the toxic effects and mechanisms of FB_1 and the antioxidative effects of resveratrol are well known. 40 BALB/c mice were divided into control, FB_1, resveratrol, and FB_1+resveratrol groups. Control received saline for 14 days. The FB_1 group received 2.25 mg/kg FB_1 every other day for 14 days. The resveratrol group received 10 mg/kg resveratrol for 14 days. The FB_1+resveratrol group received 2.25 mg/kg FB_1 every other day and 10 mg/kg resveratrol every day for 14 days. All administrations were peritoneal. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total sialic acid (TSA) levels were analysed in serum samples, while total antioxidant status (TAS) and total oxidant status (TOS) were measured in the liver. Additionally, the liver tissue was examined for histopathological changes. AST, ALT, and TSA were significantly higher in the FB_1 group than control. Resveratrol countered FB_1 effects for all parameters, including TOS and TAS. Liver histology showed FB_1-induced hyperaemia, infiltrations, and megalokaryosis in some hepatocytes. No pathological findings were detected in the control, resveratrol, or FB_1+resveratrol group. Our findings confirm resveratrol's protective effect against liver damage and oxidative stress caused by FB_1. In addition, they suggest that increased serum TSA levels can be used as a biomarker of FB_1-induced hepatotoxicity.

KEY WORDS: ALT; AST; liver damage; oxidative stress; total antioxidant status; total oxidant status; total sialic acid

Much is already known about mycotoxins and fumonisins in particular (1–3). Fumonisin B_1 (FB_1) accounts for 70–80 % of all fumonisins in food and feed products and can be found in urine, serum, and hair (1, 4). According to the International Agency for Research on Cancer (IARC), FB_1 is a Group 2B possible human carcinogen (5), and the high concentrations found in Chinese maize have been associated with human oesophageal and liver cancer in China (6, 7).

Among many harmful effects and mechanisms of fumonisin toxic action (8–11), oxidative stress stands out as it causes damage to nucleic acids, proteins, and lipids (12, 13).

The aim of our study was to see if the well-known antioxidant, resveratrol, would counter the effects of FB_1, because, to the best of our knowledge, its protective action has never been tested against this mycotoxin, even though its effects have been largely evidenced (14–18). To do that, we focused our study in mice on the protection against FB_1-induced liver injury by evaluating serum AST and ALT levels, total sialic acid level, total antioxidant, total oxidant status, and histopathological changes.

MATERIALS AND METHODS

The study included 40 (20 male and 20 female) 8–10-week-old BALB/c mice weighing 25–35 g on average, kept in cages in a 12:12-hour light/dark cycle with free access to standard pellet and water.

The mice were randomly divided into four groups of 10 (five male and five female). The first, control group, was receiving saline (10 mL/kg body weight, bw) intraperitoneally (IP) every other day for 14 days. The second, FB_1-only group was receiving an IP dose of 2.25 mg/kg bw FB_1 (Adoq Bioscience, Irvine, CA, USA) every other day for 14 days. The third, resveratrol-only group, was receiving a daily IP dose of 10 mg/kg bw resveratrol (Cayman Chemical, Ann Arbor, MI, USA) for 14 days. The fourth, FB_1+resveratrol group, received a combination of FB_1 and resveratrol as described above.

On day 15, the animals were taken blood samples by intracardiac puncture under inhalation anaesthesia (Isoflurane, Adeka Pharmaceuticals Industry and Trade Inc., Istanbul, Turkey). Later, the mice were euthanised by cervical dislocation and the liver samples were taken.

The study was approved by the Burdur Mehmet Akif Ersoy University animal experiments ethics committee (approval No. 328 of 13 September 2017).

AST and ALT measurements

Serum AST and ALT were analysed spectrophotometrically on a Randox Monaco autoanalyser (Randox Laboratories, Monaco,

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UK) with corresponding chemical kits (AS8306 and AL8304, respectively).

Total antioxidant status

Total antioxidant status (TAS) was measured in the liver with a commercial TAS kit (Rel Assay Diagnostic, Gaziantep, Turkey) (19). The method is based on the formation of the colored 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical in a colourless reduced form by the antioxidants present in the sample. This change in colour was measured spectrophotometrically at 660 nm. The method was calibrated with Trolox and data expressed as mmol Trolox eq/L.

Analysis of total oxidant status

Total oxidant status (TOS) was also measured in the liver with a commercial TOS kit (Rel Assay Diagnostic) (20). The oxidants in the sample oxidise ferric iron ions bound to the chelator. In the acidic medium, these ferric ions form a coloured complex with chromogen. Colour intensity is measured spectrophotometrically at 530 nm. The assay was calibrated with hydrogen peroxide (H_2O_2) and results are expressed as μmol H_2O_2 eq./L.

Total sialic acid measurement

As an indicator of liver damage (21, 22), total sialic acid (TSA) was determined in serum according to the method described by Sydow (23). Briefly, 0.2 mL of serum was taken into test tubes and then 1.5 mL of perchloric acid solution was added. The tubes were boiled in a water bath at 100 °C for 5 min, cooled to 4 °C, and centrifuged at 2500 *g* for 4 min. The obtained supernatants (1 mL) were transferred to clean test tubes, which were added 0.2 mL of Ehrlich reagent, and boiled in a water bath at 100 °C for 15 min. After boiling, the tubes were cooled and 1 mL of distilled water added for spectrophotometry. Optical densities (OD) were read at 525 nm and serum TSA levels determined by means of the standard curve obtained by serial dilution of *n*-acetyl neurominic acid (NANA) (Sigma-Aldrich, St. Louis, MO, USA).

Histopathological examination

Liver tissue samples collected during necropsy were fixed in a 10 % buffered formaldehyde solution and paraffin-blocked using a Leica ASP300S autotechnicon (Leica Microsystems, Wetzlar, Germany). After 4–5 hours of cooling, we cut them into 5 μm thick serial slices with a rotary microtome (Leica 2155), stained with haematoxylin-eosin (Surgipath, Deer Park, IL, USA), and covered with entellan for examination under a light microscope (Olympus CX21, Olympus Co., Tokyo, Japan). Images were taken with a digital camera (Olympus DP74) and processed using Cell Sens imaging software (Olympus Co., Tokyo, Japan).

Statistical analysis

For statistical analysis we used the Statistical Package for Social Sciences (SPSS) 16.0 (SPSS Inc., Chicago, IL, USA). Initially, the data were analysed for normality of distribution with the Shapiro-Wilk test. Since the data showed a normal distribution ($P>0.05$), comparisons between the groups were made with one-way analysis of variance (ANOVA). Pairwise differences between the groups were determined with the post hoc Tukey test. The data are shown as means ± standard error, and the significance was set to $P<0.05$.

RESULTS

Serum AST and ALT levels

Table 1 shows AST and ALT findings. Serum AST levels were significantly higher in the FB_1 than other groups ($P<0.05$). The other groups did not differ significantly from each other. The same is true for serum ALT levels.

Liver TAS and TOS and serum TSA levels

Table 2 shows that liver TAS levels were significantly lower in the FB_1 than control and resveratrol group ($P<0.05$), but not between the FB_1+resveratrol group and the rest.

Table 1 Mean (±standard error) serum AST and ALT levels in the control, resveratrol, FB_1, and FB_1+resveratrol groups receiving IP treatment for 14 days

Groups	AST (U/L)	ALT (mg/dL)
Control (saline 14 days)	89.51±7.87[a]	51.62±8.99[a]
Resveratrol (10 mg/kg)	88.30±7.75[a]	40.66±3.22[a]
FB_1 (2.25 mg/kg, qad, 14 days)	**623.62±150.52[b]**	**368.00±119.16[b]**
FB_1+resveratrol	207.99±34.93[a]	121.11±23.50[a]

[a, b] – statistically significant ($P<0.05$) differences between the groups are marked with different letters in superscript. ALT – alanine aminotransferase; AST – aspartate aminotransferase; qad – every other day

Table 2 Mean (±standard error) liver TAS in the control, resveratrol, FB_1, and FB_1+resveratrol groups receiving IP treatment for 14 days

Groups	TAS (mmol Trolox eq./L)
Control (saline 14 days)	2.58±0.33[b]
FB_1 (2.25 mg/kg qad, 14 days)	**1.53±0.07[a]**
Resveratrol (10 mg/kg)	2.69±0.25[b]
FB_1+resveratrol	2.15±0.20[ab]

[a, b] – statistically significant ($P<0.05$) differences between the groups are marked with different letters in superscript. TAS – total antioxidant status; qad – every other day

Table 3 Mean (±standard error) liver TOS in the control, resveratrol, FB_1, and FB_1+resveratrol groups receiving IP treatment for 14 days

Groups	TOS (μmol H_2O_2 eq./L)
Control (saline 14 days)	38.40±1.20[a]
FB_1 (2.25 mg/kg qad, 14 days)	**49.77±2.50[b]**
Resveratrol (10 mg/kg)	34.92±2.88[a]
FB_1+Resveratrol	40.86±2.71[ab]

[a, b] – statistically significant (P<0.05) differences between the groups are marked with different letters in superscript. TAS – total oxidant status; qad – every other day

Table 4 Mean (±standard error) serum TSA levels in the control, resveratrol, FB_1, and FB_1+resveratrol groups receiving IP treatment for 14 days

Groups	Sialic acid (mg/dL)
Control (saline 14 days)	1358.37±76.38[a]
FB_1 (2.25 mg/kg qad, 14 days)	**1594.99±33.65[b]**
Resveratrol (10 mg/kg)	1411.41±37.87[a]
FB_1+Resveratrol	1513.99±25.95[ab]

[a, b] – statistically significant (P<0.05) differences between the groups are marked with different letters in superscript. TSA – total sialic acid; qad – every other day

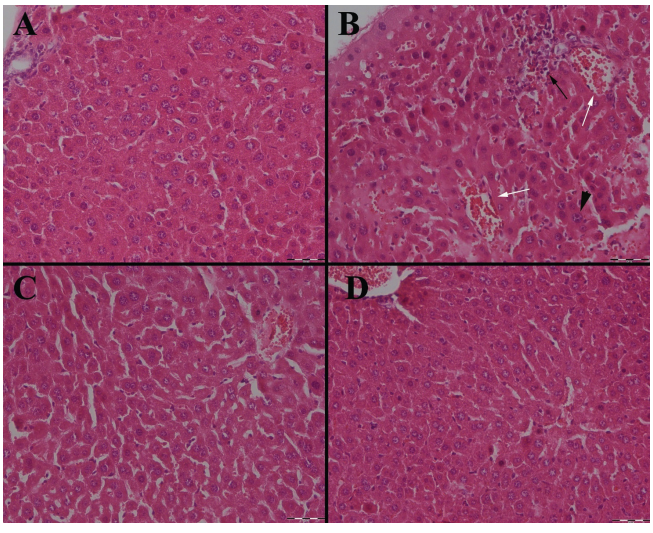

Figure 1 Comparison of liver histologies between the study groups. (A) normal liver histology in a mouse from the control group; (B) severe hyperaemia (white arrows), inflammatory cell infiltrations (black arrow), and megalokaryosis (arrow head) in a mouse from the FB_1 group; (C) normal liver histology in a mouse from the resveratrol group; (D) normal liver histology in a mouse from the FB1+resveratrol group. Scale bar=50 μm

TOS and TSA levels show the same pattern (Tables 3 and 4, respectively) in the sense that the FB_1 group differs significantly from the control and resveratrol groups, whereas the FB_1+resveratrol differs from none of the three, which points to attenuating effects of resveratrol against FB_1.

Histopathological findings

Liver samples of mice treated with FB_1 alone displayed hyperaemia, infiltrations, and large nuclei (megalokaryosis) in some hepatocytes, whereas no pathological findings were detected in the other groups (Figure 1A–D).

DISCUSSION

Our findings confirm reports of increased liver enzyme levels by the same FB_1 dose (2.25 mg/kg bw) (24–26). Administration of resveratrol in our study attenuated these effects to the levels no longer significantly higher than control. Similar protective effects of resveratrol were reported by Sehirli et al. (27) against naphthalene in BALB/c mice.

The same is true for oxidative stress parameters TAS and TOS in the liver of our mice, as resveratrol attenuated the adverse effects of FB_1. These findings confirm the reports of resveratrol protecting against fluoride-induced oxidative stress in rats by increasing TAS and decreasing TOS levels (28) or by inhibiting aflatoxin B_1-induced oxidative stress in bovine mammary epithelial cells (29). Rašić et al. (30), however, have pointed to a limited resveratrol protection against oxidative stress induced by a combination of ochratoxin A and citrinin, in the sense that resveratrol was capable of restoring glutathione levels in all tissues but had no protective effect against increased malondialdehyde levels and DNA damage. Although resveratrol is generally considered to be safe, it can also be toxic, depending on the dose and duration of exposure. At high doses it may induce oxidative stress by decreasing catalase, glutathione, and superoxide dismutase activity and increasing reactive oxygen species (ROS) and lipid peroxidation (31). In addition, Karaica et al. (32) reported that resveratrol in combination with ochratoxin A and citrinin reduced the expression of renal organic anion transporters (OATs), which led to the accumulation of OTA.

As for TSA, resveratrol lowered the FB_1-induced increase in serum sialic acid to levels not significantly higher than control, yet not significantly lower than those in the FB_1 group. Total sialic acid levels have been reported to reflect liver-related pathological conditions (21, 22) and that its levels increase with ALT/AST and liver damage (33–35). Similar was observed in the FB_1 group in our study, which supports that TSA levels can be used as a biomarker of FB_1-induced liver injury.

Our liver histology findings further support biochemistry analyses with hyperaemia and inflammatory cell infiltrations in the liver, as well as megalokaryosis in many hepatocytes of mice in the FB_1 group and no pathological changes in the remaining three

groups, the FB_1+resveratrol in particular. They are in line with an earlier study by Sehirli et al. (27), who reported that 10 mg/kg resveratrol reduced the naphthalene-induced pathological changes in the lung, liver and kidney tissues. The authors also reported that resveratrol helped tissue regeneration.

In conclusion, our biochemical and histopathological findings evidence that resveratrol has a protective effect against oxidative stress and liver damage caused by FB_1. It also confirms that total sialic acid levels in the serum can serve as a biomarker of FB_1 toxicity and liver damage.

Funding

This research was supported by the Burdur Mehmet Akif Ersoy University Scientific Research Projects Coordinatorship (project No, 0483-YL-17).

Conflicts of interest

None to declare.

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Zaštitno djelovanje resveratrola od toksičnosti fumonizina B_1 u jetri miševa

Cilj je ovog istraživanja bio utvrditi djelovanje resveratrola protiv hepatotoksičnosti izazvane fumonizinom B_1 (FB_1), budući da, koliko znamo, to djelovanje još nije istraženo, premda su toksičnost i mehanizmi djelovanja FB_1 te antioksidacijsko djelovanje resveratrola dobro poznati. U tu je svrhu 40 BALB/c miševa bilo raspodijeljeno u sljedeće skupine: kontrolu, FB_1, resveratrol te FB_1 + resveratrol. Prva je skupina primala fiziološku otopinu svaki dan 14 dana, a druga je primala FB_1 u dozi od 2,25 mg/kg svaki drugi dan 14 dana. Treća je skupina primala resveratrol u dozi od 10 mg/kg svaki dan 14 dana, a četvrta kombinaciju FB_1 (2,25 mg/kg) svaki drugi dan i resveratrola 10 mg/kg svaki dan 14 dana. Svi su spojevi davani intraperitonealno. Uzorci seruma analizirani su za alanin aminotransferaze (ALT), aspartat aminotransferaze (AST) i ukupnu količinu sijalinske kiseline (TSA), a uzorci jetrenog tkiva za ukupni antioksidacijski status (TAS), ukupni oksidacijski status (TOS) te za histopatološke promjene. AST, ALT i TSA bili su značajno viši u FB_1 skupini nego u kontroli. Resveratrol je ublažio djelovanje FB_1 na sve parametre, uključujući TOS i TAS. Histološki pregled jetre u FB_1 skupini otkrio je hiperemiju, infiltrate i abnormalno velike jezgre u pojedinim hepatocitima, a u ostalim trima skupinama nisu uočene patološke promjene. Naši rezultati potvrđuju zaštitno djelovanje resveratrola od oštećenja jetre i oksidacijskoga stresa prouzročenih FB_1. Također upućuju na to da povišene razine TSA mogu upućivati na hepatotoksičnost prouzročenu djelovanjem FB_1.

KLJUČNE RIJEČI: ALT; AST; oksidacijski stres; oštećenje jetre; ukupni antioksidacijski status; ukupni oksidacijski status; ukupna sijalinska kiselina