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Anti-inflammatory and antioxidant effect of *Moringa oleifera* against bisphenol-A-induced hepatotoxicity

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Abstract

Background: Non-pharmacological exposure or pharmacological drug-induced hepatic injury is the most common cause of hepatotoxicity. This study was conducted to evaluate the effect of *Moringa oleifera* leaf extract against bisphenol-A (BPA)-induced hepatic toxicity in rats.

Methods: Rats (n=56) were randomized into 7 groups (8 rats/each). Control groups: rats received olive oil or *Moringa oleifera* (400mg/kg) orally for 42 days. Hepatotoxicity groups: rats received BPA (50mg/kg BW) orally in a 1-ml olive oil for 42 days. Reversal groups: rats received *Moringa oleifera* (200 or 400mg/kg) and BPA (50mg/kg BW) for 42 days. Preventive groups: rats received *Moringa oleifera* (200 or 400mg/kg) for 30 days followed by BPA (50mg/kg BW) for 14 days. At the end of the experiments, blood samples were collected for glucose and liver function assay, while the liver tissue samples were collected and homogenated for measuring the inflammatory/oxidant and antioxidant markers.

Results: Rats with BPA-induced hepatotoxicity have significantly increased serum aspartate transaminase (AST), alanine transaminase (ALT), and glucose; liver lysate malondialdehyde (MDA); tumor necrosis factor (TNF-α); and macrophage migrating inhibitory factor (MIF) but significantly decreased levels of liver lysate reduced glutathione (GSH) and total antioxidant capacity (TAC) levels. The administration of *Moringa oleifera* (especially 400mg/kg BW) in both reversal and preventive groups ameliorate the toxic effects of BPA in rats, as it decreased the activities of AST, ALT, glucose, MDA, TNF-α, and MIF levels and increased the antioxidant levels of GSH and TAC.

Conclusion: *Moringa oleifera* has hepatoprotective effects against BPA-induced liver damage through the regulation of antioxidants and inflammatory biomarkers.

Keywords: *Moringa oleifera* leave extract, Bisphenol-A, Hepatic toxicity

Introduction

Hepatotoxicity or injury of the liver is resulting from pharmacological or non-pharmacological agents that have a serious impact on health [1]. There are a variety of symptoms ranging from an elevation of liver enzymes without symptoms, sudden severe liver inflammation, persistent liver inflammation, and biliary obstruction to liver damage [2]. Drug-induced hepatic damage is the most common cause of hepatotoxicities such as non-steroid anti-inflammatory drugs, anti-tubercular drugs, anti-tumor drugs, hormonal, sedative and immune suppression, and neuropsychiatric drugs [1–3].

Bisphenol A (BPA) is an industrial chemical product [4] that affects humans from diet (BPA spreads from containers of food and drink during heating or washing), air, dust, water, and dental sealants [4]. High-dose exposure to BPA during pregnancy or lactation was accompanied

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by low birth weight, slow growth rate, decreased survival, and delayed puberty in offspring [5, 6]. BPA is a potential male fertility [7], and low-dose exposure to BPA was accompanied by insulin resistance in animal research [8]. There are limited epidemiological data on BPA effects in humans. In the US general population, adults are more liable to have diseases [9, 10]. BPA may be reacted with oxygen radicals, increased reactive oxygen species (ROS), H_2O_2, and lipid peroxide-oxidant malondialdehyde (MDA) productions and decreased antioxidant levels in the hepatic tissue with steatosis, liver tumors, and metabolic syndrome [5, 6, 9, 11].

A medicinal plant, *Moringa oleifera*, is a monogeneric family Moringaceae, leaf extract derived from a drumstick or horse radish or Shagara al Rauwaq tree in the Nile valley [12]. *Moringa oleifera* has an impressive range of medicinal uses with a high nutritional value containing protein, calcium, and potassium [12]. Also, rich sources of natural antioxidants such as ascorbic acid, flavonoids, phenolics, and β-carotene [12]. The extracts of *Moringa oleifera* leaves, seed, and pod have potent antidiabetic activity [13]. It plays an important role in treating an inflammatory and infectious disease affecting the heart, blood vessels, gastro-intestinal, liver, and kidney [14]. *Moringa oleifera* has a role in a regenerative and hepatoprotective activity, improved liver fibrosis in rats, reduced liver damage, decreased effect of chemical/pharmacological-induced hepatotoxicity, and reduced hepatic myeloperoxidase activity [15–19].

Therefore, the aim of this study was to evaluate the role of *Moringa oleifera* leaf extract against BPA-induced hepatotoxicity in rats.

Materials and methods

In this study, 56 male Wister adult albino rats (8 weeks of age, 150–200 g) were used and the experimental procedures were performed in the Faculty of Medicine, Menoufia University, Egypt. These experimental studies were conducted according to the ethical guidelines of the Animal Care and Use Committee of the Faculty of Medicine of Menoufia University, which followed the Guide for the Care and Use of Laboratory Animals.

Rats were kept and accommodated in standard plastic cages under controlled laboratory conditions of humidity (65%), temperature (22°C), and 12-h light/dark cycles. Rats had free access to water and were fed ad libitum on normal commercial chow. Rats were adjusted to the laboratory conditions for 10 days before conducting the experiment.

Bisphenol A (BPA) was demanded from Merck and Sigma-Aldrich Corporation (St Louis, Missouri, USA, CAS number 80-05-7). To have a concentration of 50 mg/kg body weight, BPA dissolved using 70% ethanol and then added to a 1-ml olive oil was used for oral administration [20]. Fresh green leaves of *Moringa oleifera* (2 kg) were obtained from a farm in Sadat City, Menoufia, Egypt (latitude 30.3597; longitude 30.4952) and then washed by distilled water to eject any debris and then kept till became dry at room temperature (22°C), and after that, it was ground into a powder [16]. The powder was dissolved with 70% ethanol for 2 days at 22°C and filtrated using a filter paper, then dried to form an extract powder [16, 21, 22]. The extract was autoclaved and stored in a steriled container at 4°C till it was needed. The component and compounds from *Moringa oleifera* extracts were phytochemically analyzed using liquid chromatography-mass spectrometry in our previous and other studies [16, 22].

Experimental design

Rats (n= 56) were used and randomized into 7 groups. Each group contained 8 rats in separate cages.

Control rats

Group 1: rats received a 1-ml olive oil orally for 42 days. Group 2 (*M. oleifera* group): rats received 400 mg/kg of *M. oleifera* orally in a 1-ml olive oil for 42 days [21].

Hepatotoxicity rats

Group 3 (BPA group): rats received 50 mg/kg body weight of BPA orally in a 1-ml olive oil for 42 days [20].

Reversal study

Group 4 (200 mg/kg of *Moringa oleifera* and BPA group): rats received 200 mg/kg of *Moringa oleifera* orally and 50 mg/kg of BPA orally in a 1-ml olive oil for 42 days [21]. Group 5 (400 mg/kg of *Moringa oleifera* and the BPA group): rats received 400 mg/kg of *Moringa oleifera* orally and 50 mg/kg of BPA orally in a 1-ml olive oil for 42 days.

Preventive study

Group 6 (200 mg/kg of *Moringa oleifera* followed by the BPA group): rats received 200 mg/kg of *Moringa oleifera* orally in a 1-ml olive oil for 30 days and then followed by 50 mg/kg of BPA orally in a 1-ml olive oil for 14 days. Group 7 (400 mg/kg of *Moringa oleifera* followed by the BPA group): rats received 400 mg/kg of *Moringa oleifera* orally in a 1-ml olive oil for 30 days and then followed by 50 mg/kg of BPA orally in a 1-ml olive oil for 14 days.

Blood and liver tissue analysis

Rats were given diethyl ether anesthetics. Blood samples were obtained from the orbital venous plexus of all groups on day 45. The blood was centrifuged, and the serum was collected and refrigerated at −20°C till used for blood glucose and liver function tests. The liver

tissues of rats were isolated and washed with PBS pH 7.4 and 0.16 mg/ml heparin to remove RBCs and clots. The liver tissue was homogenized in a 2-ml cold RIPA buffer (Thermo Fisher Scientific, Rockford, Illinois, USA, Catalog Number 89900) and centrifuged at 4000 rpm for 15 min at 4°C. The supernatant was obtained and refrigerated at −80 °C until used for inflammatory/oxidant and antioxidant markers.

Blood glucose and liver function tests

The blood sample for random blood glucose was assessed based on the glucose oxidase-peroxidase chromogen system using colorimetric kits (Bio-Diagnostics Ltd., Dokki, Giza, Egypt, Catalog Number GL 13 20) according to the manufacturer's procedure. Serum liver enzyme alanine aminotransferase (ALT) (EC2.6.1.2) and aspartate aminotransferase (AST) (EC2.6.1.1) [23] were assessed using colorimetric kits (Diamond Diagnostics, Cairo, Egypt) according to the manufacturer's procedure.

Hepatic inflammatory oxidant

Liver homogenate for inflammatory lipid peroxide malondialdehyde (MDA) (the production of thiobarbituric acid reactive substances, TBARS) was analyzed using colorimetric kits (Bio-Diagnostics Ltd., Dokki, Giza, Egypt, Catalog Number MD 25 29) [24, 25].

Hepatic inflammatory cytokines

Tumor necrosis factor-alpha (TNF-α) (RayBiotech Inc. Parkway, LaneSuiteNorcross, Georgia, USA, Catalog Number ELR-TNFa-1) [17] and macrophage migration inhibitory factor (MIF) (R&D system, Minneapolis, Minnesota, USA, Catalog number DY1978) [26, 27] were assessed using enzyme-linked immunosorbent assay (ELISA) kits according to manufacturer's procedure.

Hepatic antioxidants

Liver homogenate of antioxidant-reduced glutathione (GSH) was assessed using colorimetric kits (Bio-Diagnostics Ltd., Dokki, Giza, Egypt, Catalog Number GR 25 11) [17]. Also, liver homogenate of total antioxidant capacity (TAC) was measured using colorimetric kits (Bio-Diagnostics Ltd., Dokki, Giza, Egypt, Catalog Number TA 25 13) [28, 29].

Statistical analysis

All parameters were presented as mean ± standard error mean (SEM) using the statistical analysis system program (SPSS), version 20 (IBM®, USA). Data were analyzed by one-way analysis of variance (ANOVA) followed by post hoc test to determine the significant differences. $P < 0.05$ was considered significant.

Results

Effect of Moringa oleifera on liver function test in BPA-induced hepatotoxicity rats

Treatment of rats with *Moringa oleifera* resulted in a non-significant increase in serum AST concentration as compared to control rats (28.75 ± 2.76 vs 21.00 ± 2.13 U/l, $P > 0.05$). Treatment of rats with BPA resulted in a significant increase in serum AST concentration as compared to control rats (240.56 ± 24.61 vs 21.00 ± 2.13 U/l, $P < 0.001$). AST concentrations were significantly changes in reversal study with 400 mg/kg of *Moringa oleifera* (107.0 ± 21.39 U/l, $P = 0.003$) and prevention study with 400 mg/kg of *Moringa oleifera* (102.63 ± 25.23 U/l, $P = 0.002$) compared with BPA-treated rats (Fig. 1A).

Treatment of rats with *Moringa oleifera* resulted in a non-significant increase in serum ALT concentration as compared to control rats (21.28 ± 1.82 vs 17.88 ± 1.80 U/l, $P > 0.05$). Treatment of rats with BPA resulted in a significant increase in serum ALT concentration as compared to control rats (71.14 ± 6.55 vs 17.88 ± 1.80 U/l, $P < 0.001$). ALT concentrations were significantly changes in reversal study with 400 mg/kg of *Moringa oleifera* (34.33 ±12.60 U/l, $P = 0.038$) and prevention study with 400 mg/kg of *Moringa oleifera* (33.43 ± 7.11 U/l, $P = 0.025$) compared with BPA-treated rats (Fig. 1B).

Effect of Moringa oleifera on serum glucose level in BPA-induced hepatotoxicity rats

Treatment of rats with *Moringa oleifera* resulted in a non-significant increase in serum glucose concentration as compared to control rats (125.50 ± 4.63 vs 121.36 ± 5.22 mg/dl, $P > 0.05$). Treatment of rats with BPA resulted in a significant increase in serum glucose concentration as compared to control rats (243.23 ± 25.74 vs 121.36 ± 5.22 mg/dl, $P < 0.001$). Serum glucose concentrations were reduced in reversal study with 400 mg/kg of *Moringa oleifera* (175.42 ± 16.27 mg/dl, $P = 0.019$) and prevention study with 400 mg/kg of *Moringa oleifera* (176.45 ± 17.23 mg/dl, $P = 0.056$) compared with BPA-treated rats (Fig. 2A).

Effect of Moringa oleifera on liver lysate MDA level in BPA-induced hepatotoxicity rats

There was no difference in hepatic MDA concentrations between *Moringa oleifera* and control rats (2.07 ± 0.47 vs 2.19 ± 0.46 nmol/ml; $P < 0.05$). Hepatic MDA concentrations were significantly higher in BPA-treated rats compared with control rats (3.93 ± 0.50 vs 2.19 ± 0.46 nmol/ml; $P < 0.001$). Hepatic MDA concentrations were significantly reduced in reversal study with 400 mg/kg of *Moringa oleifera* (1.86 ± 0.16 nmol/ml, $P = 0.008$) and prevention study with 400 mg/kg of *Moringa oleifera*

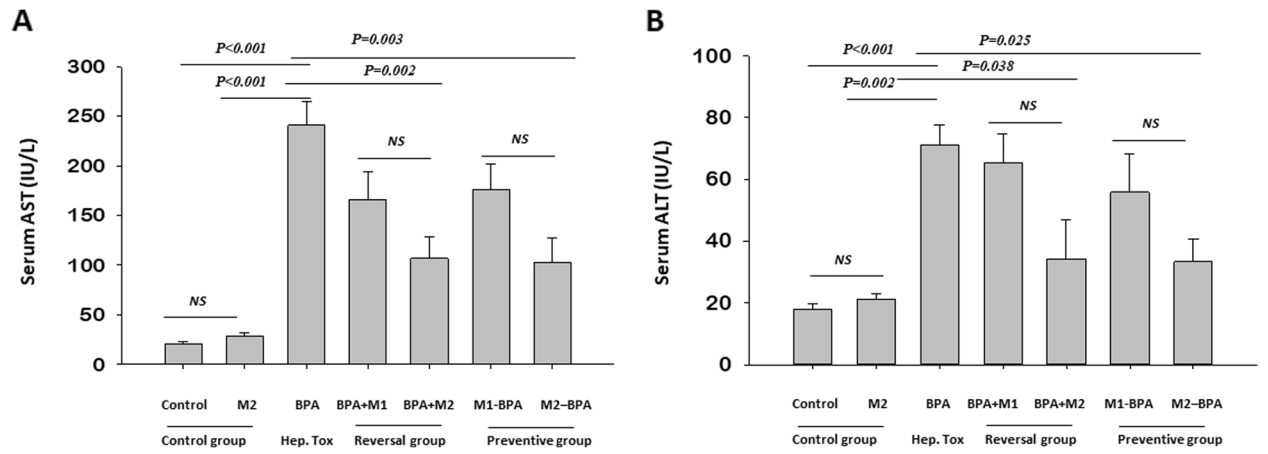

Fig. 1 Effect of *Moringa oleifera* on liver function test in BPA-induced hepatotoxicity rats. Serum aspartate transaminase (AST, **A**) and alanine transaminase (ALT, **B**) levels were assessed in all groups. All data were presented as mean ± SEM. *n*= 8 rats/group, BPA = bisphenol-A (50 mg/kg BW). M1 *Moringa oleifera* (200 mg/kg BW); M2 *Moringa oleifera* (400 mg/kg BW); $P < 0.05$ was considered significant. NS non- significant, $P > 0.05$

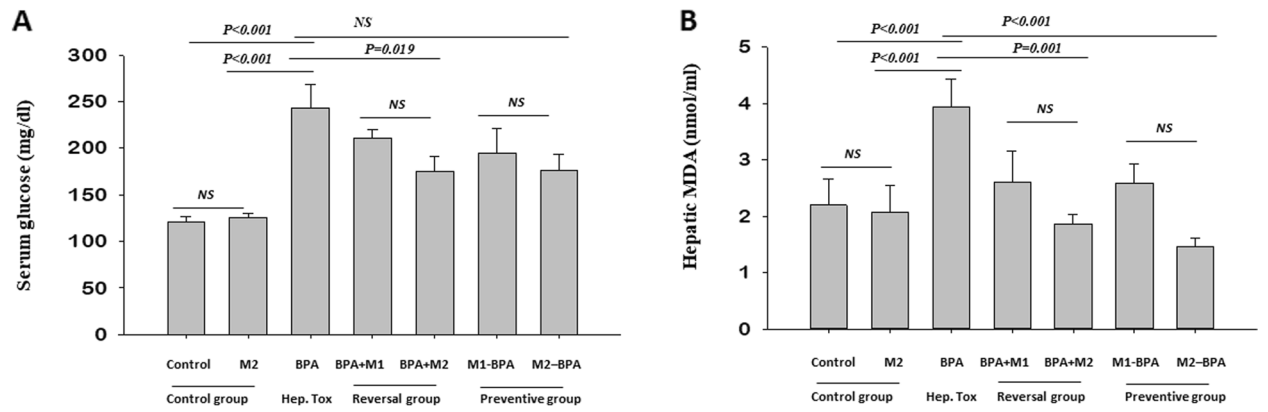

Fig. 2 Effect of *Moringa oleifera* on serum glucose level and lipid oxidant malondialdehyde in BPA-induced hepatotoxicity rats. Serum glucose (**A**) and hepatic malondialdehyde (MDA, **B**) levels were assessed in all groups. All data were presented as mean ± SEM. *n*= 8 rats/group, BPA bisphenol-A (50 mg/kg BW). M1 *Moringa oleifera* (200 mg/kg BW); M2 *Moringa oleifera* (400 mg/kg BW); $P < 0.05$ was considered significant. NS non-significant, $P > 0.05$

(1.46 ± 0.14 nmol/ml, $P = 0.001$) compared with BPA-treated rats (Fig. 2B).

Effect of Moringa oleifera on antioxidant activity of liver tissue GSH and TAC levels in BPA-induced hepatotoxicity rats

Treatment of rats with *Moringa oleifera* resulted in non-significant decrease in hepatic GSH concentration as compared to control rats (1.30 ± 0.09 *vs* 1.73 ± 0.15 mg/dl, $P > 0.05$). Hepatic GSH concentrations were non-significantly lower in BPA-treated rats compared with control rats (0.94 ± 0.13 vs 1.73 ± 0.15 mg/dl; $P = 0.062$). Hepatic GSH concentrations were increased in reversal study with 400 mg/kg of *Moringa oleifera* (1.54 ± 0.08 mg/dl, $P = 0.358$) and prevention study with 400 mg/kg of *Moringa oleifera* (2.82 ± 0.70 mg/dl, $P < 0.001$) compared with BPA-treated rats. However, treatment of rats with 400 mg/kg of *Moringa oleifera* resulted in a significant increase in hepatic GSH concentration as compared to the prevention study ($P < 0.001$) (Fig. 3A).

Treatment of rats with *Moringa oleifera* resulted in a non-significant increase in hepatic TAC concentration as compared to control rats (4.77 ± 0.33 mmol/L vs 4.58 ± 0.14 mmol/L, $P>0.05$), BPA ($P<0.001$), and reversal and prevention study ($P = 0.002$). Hepatic TAC concentrations were non-significantly lower in BPA-treated rats compared with control rats (1.98 ± 0.29 vs 4.58 ± 0.14 mmol/L; $P < 0.001$). Hepatic TAC concentrations were

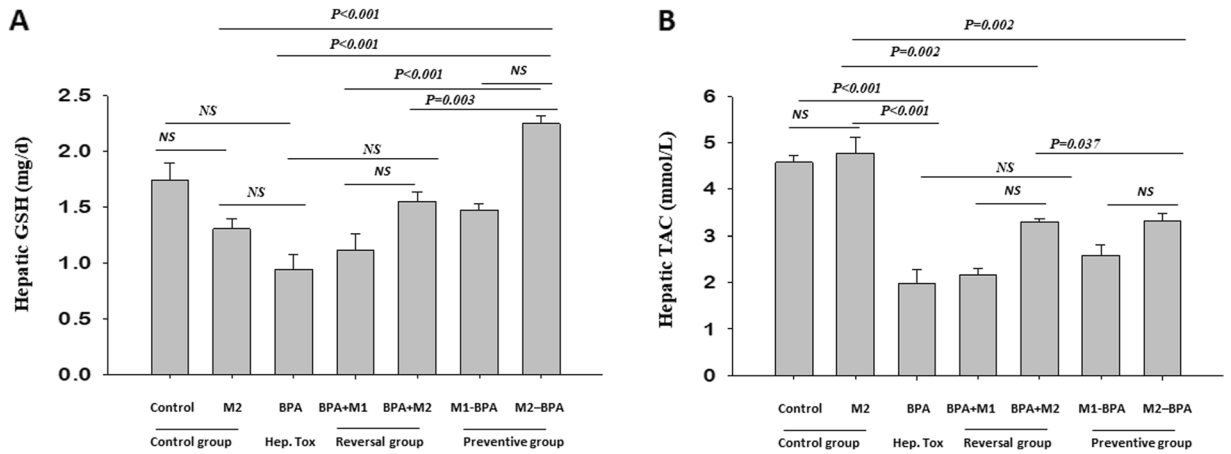

Fig. 3 Effect of *Moringa oleifera* on antioxidant activity of the liver tissue in BPA-induced hepatotoxicity rats. Hepatic-reduced glutathione (GSH, **A**) and total antioxidant capacity (TAC, **B**) levels were assessed in all groups. All data were presented as mean ± SEM. *n*= 8 rats/group, BPA bisphenol-A (50 mg/kg BW). M1 *Moringa oleifera* (200 mg/kg BW); M2 *Moringa oleifera* (400 mg/kg BW); $P < 0.05$ was considered significant. NS non-significant, $P > 0.05$

non-significantly increased in the reversal study with 400 mg/kg of *Moringa oleifera* (3.30 ± 0.05 mmol/L, $P = 0.069$) and prevention study with 400 mg/kg of *Moringa oleifera* (3.31 ± 0.16 mmol/L, P=0.10) compared with BPA-treated rats. However, treatment of rats with 400 mg/kg of *Moringa oleifera* resulted in a significant increase in hepatic TAC concentration as compared to BPA ($P < 0.001$) and both reversal and prevention studies ($P = 0.002$) (Fig. 3B).

Effect of Moringa oleifera on the inflammatory activity of liver tissue TNF-α and MIF levels in BPA-induced hepatotoxicity rats

There was no difference in hepatic TNF-α concentrations between *Moringa oleifera* and control rats (16.83 ± 0.33 vs 16.63 ± 0.23 pg/ml; $P > 0.05$). Hepatic TNF-α concentrations were significantly higher in BPA-treated rats compared with control rats (48.21 ± 2.91 vs 16.63 ± 0.23 pg/ml; $P < 0.001$). Hepatic TNF-α concentrations were significantly reduced in reversal study with 400 mg/kg of *Moringa oleifera* (24.41 ± 1.70 pg/ml, $P < 0.001$) and prevention study with 400 mg/kg of *Moringa oleifera* (22.11 ± 1.26 pg/ml, $P < 0.001$) compared with BPA-treated rats. Moreover, treatment of rats with 400 mg/kg of *Moringa oleifera* resulted in a significant decrease in hepatic TNF-α concentration as compared to BPA ($P < 0.001$) and both reversal and prevention studies ($P < 0.001$) (Fig. 4A).

There was no difference in hepatic MIF concentrations between *Moringa oleifera* and control rats (14.27 ± 0.37 vs 14.94 ± 0.47 ng/ml; $P > 0.05$). Hepatic MIF concentrations were significantly higher in BPA-treated rats compared with control rats (24.38 ± 2.29 vs 14.94 ± 0.47 ng/ml; $P < 0.001$). Hepatic MIF concentrations were significantly reduced in reversal study with 400 mg/kg of *Moringa oleifera* (17.09 ± 0.47 ng/ml, $P < 0.001$) and prevention study with 400 mg/kg of *Moringa oleifera* (12.64 ± 0.14 ng/ml, $P < 0.001$) compared with BPA-treated rats. Moreover, treatment of rats with 400 mg/kg of *Moringa oleifera* resulted in a significant decrease in hepatic MIF concentration as compared to BPA ($P < 0.001$) and reversal study ($P = 0.004$) (Fig. 4B).

Discussion

Destruction of the liver tissue by pharmacological or non-pharmacological substances causes hepatotoxicity [2, 17]. Hepatic damage by a pharmacological agent usually presents in many ways as acute or chronic hepatic disorders or cholestasis or both [30]. This may be affected by many factors such as age, sex, alcohol intake, cigarette smoking, drug intake, genetic factors, environmental factor, and other hepatic disorders [2, 30].

BPA is a chemical substance that mimics or blocks the receptors and alters hormone concentrations and its metabolism [4, 7, 8]. BPA stimulates cellular responses and affects body functions even in small concentrations [6, 9]. BPA can induce apoptosis in the hepatocytes in the hepatic sections of the BPA-treated rats [6]. The BPA induced an increase in ROS production and reduction of antioxidant activity [5, 11, 31].

Therefore, the present study was to evaluate the effect of *Moringa oleifera* leaf extract as a medicinal plant against BPA-induced liver damage in rats.

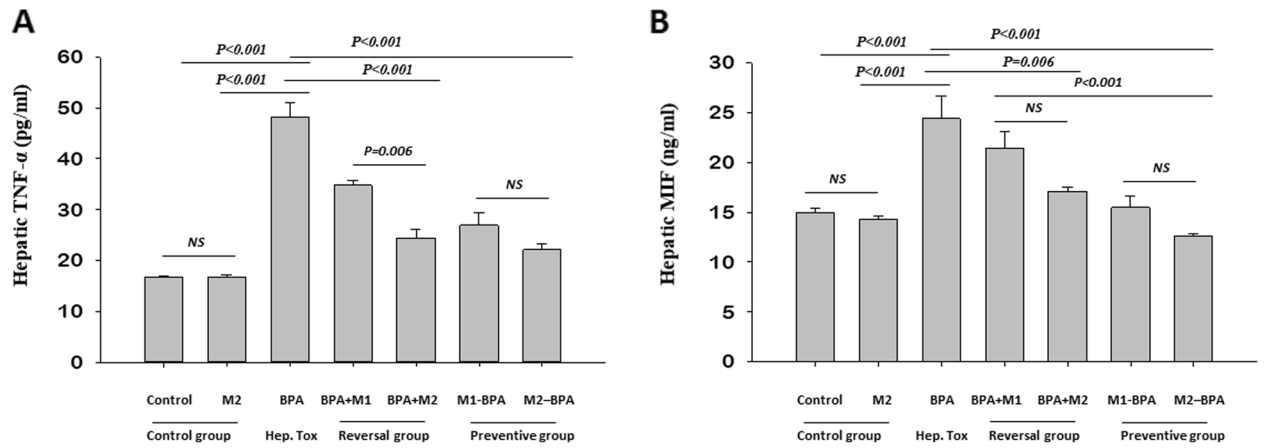

Fig. 4 Effect of *Moringa oleifera* on the inflammatory activity of the liver tissue in BPA-induced hepatotoxicity rats. Hepatic tumor necrosis factor (TNF-α, **A**) and macrophage migrating inhibitory factor (MIF, **B**) levels were assessed in all groups. All data were presented as mean ± SEM. $n = 8$ rats/group, BPA bisphenol-A (50 mg/kg BW). M1 *Moringa oleifera* (200 mg/kg BW); M2 *Moringa oleifera* (400 mg/kg BW); $P < 0.05$ was considered significant. NS non-significant, $P > 0.05$

The current study revealed that rats with BPA had hepatic toxicity and damage with significantly higher AST and ALT activities that matched with other studies [11, 32]. BPA exposure enhanced the production of ROS and inhibited the activities of antioxidant enzymes [25, 31]. This may be attributed to BPA-induced inflammatory oxidative damage to the liver and releasing hepatic enzymes into the blood [8, 32].

Moringa oleifera (200 and 400 mg/kg BW) either with BPA (reversal groups) or 1 month before BPA (preventive groups) reduced activities of serum AST and ALT. Our results agreed with other study showed that having moringa decreased the toxic effects of CCL4- on serum levels of liver enzymes [16], reported that the moringa has a part in maintaining the liver cell membrane complete and so on no leakage of enzymes into blood [16].

In the present results, there was a significantly higher serum level of blood sugar in rats that received BPA compared to the control group. This observation was similar to other studies which reported that BPA exposure led to hyperglycemia [9, 33]. BPA-induced hyperglycemia may be associated with oxidative stress [4, 33] and increased lipid peroxidation; thus, they disrupt the serum glucose regulation [34].

In the current results, there was a significant lower serum level of blood sugar in rats received by BPA with or after *Moringa oleifera* leaf extract at doses 200 and 400 mg/kg of BW. This result was matched with other study illustrated that *Moringa oleifera* leaves help glucose uptake by the liver, so reduction of serum glucose levels [35].

In our results, there was a significant elevation of lipid peroxidation biomarker (MDA) and a significant reduction of antioxidant biomarkers GSH and TAC. These findings agreed with other studies [11, 24, 31, 36]. BPA-toxic metabolites caused oxidized glutathione and reduced GSH levels [34, 37]. Moreover, MDA and 4-hydroxynonenal have the ability to change of enzymes of mitochondria and decrease the glutathione [38], which might suppress the GSH/GSSG ratio and this led to hepatocellular damage.

Our data showed the improvement effect of *Moringa oleifera* in treated and prophylactic against BPA represented by decreased MDA concentrations and increased GSH and TAC concentrations. These results are similar to other studies [18] showed the level of MDA was reduced and GSH was restored in moringa-treated animals compared to the groups induced with acetaminophen [17, 19]. *Moringa oleifera* has a cellular protection effect due to its content of phenol substances [14]. These phenol substances have protection roles against inflammation and liver cell damage [17, 39].

Our concurrent study revealed that BPA intoxication led to a significant increase in inflammatory biomarkers TNF-α and MIF. These findings agreed with other studies which demonstrated that elevation of BPA concentrations in the blood is associated with elevated concentrations of TNF-α proinflammatory cytokines [25, 33, 40, 41]. MIF is a multipotent cytokine mediator in hepatotoxic as pro-oxidant and proinflammatory and profibrotic effects [42] in thioacetamide-induced liver injury [27], ethanol-induced liver injury [26], cytotoxic-T-lymphocyte (CTL)-induced acute hepatitis [43], and acute liver injury [44].

Oral administration of *Moringa oleifera* to BPA rats decreased the level of TNF-α and MIF, and this finding

agreed with other studies [45]. Also, a perfect response after the therapy of *Moringa oleifera* leaves and in the prophylactic group showed a significant reduction in TNF-α levels [45] via antioxidant and anti-inflammatory activities [15, 16, 20–22].

Finally, taken together, *Moringa oleifera* leaves have an important value in the prevention of liver damage, oxidation, and toxicity. Furthermore, it may help in the reduction of liver enzymes to baseline concentration, decrease oxidative stress, and increase hepatic anti-oxidant/anti-inflammatory protein contents [16–18].

Conclusion

Administration of BPA can cause hepatotoxicity. These toxicities may be related to its TNF-α and MIF-mediated hepatic damage and release of aminotransferases. Also, it causes abnormalities in blood sugar and lipid profile (MDA) associated with a reduction in GSH and TAC which are antioxidants. In contrast, pre- and conjunction administration of *Moringa oleifera* with BPA toxicity altered its toxicity on liver function and protect it from damage. Thus, *Moringa oleifera* had to improve and protect the effects against BPA-induced hepatotoxicity by regulation of antioxidants and inflammatory biomarkers.

Abbreviations

ALT: Alanine transaminase; AST: Aspartate transaminase; BPA: Bisphenol-A; CCl4: Carbon tetrachloride; ELISA: Enzyme-linked immunosorbent assay; GSH: Reduced glutathione; *M. oleifera*: *Moringa oleifera*; MDA: Malondialdehyde; MIF: Macrophage migrating inhibitory factor; NSAIDs: Non-steroid anti-inflammatory drugs; ROS: Reactive oxygen species; TAC: Total antioxidant capacity; TNF-α: Tumor necrosis factor.

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Authors' contributions

YAA, IEE, MAA, EAB, MMA, and IE contributed to the study concept, design, clinical investigations, methodology, data collection, statistical analysis, and interpretation of the data. IEE, MAA, EAB, and IE contributed to the supervision and conceptualization in the study. All authors contributed to the writing of the papers and critically revised and finalized the paper. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was done on an animal model after approval of the Ethics Committee of the Faculty of Medicine, Menoufia University. ***The committee's reference number is IRB 4/2021PEDI2. The study was conducted in accordance with the Helsinki Declaration of 1964, as revised in 2013.***

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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