Original Article

Asian Pacific Journal of Tropical Biomedicine

journal homepage: www.apjtb.org

doi: 10.4103/2221-1691.333210

Impact Factor: 1.55

Gum resin extract of *Boswellia serrata* attenuates lipopolysaccharide-induced inflammation and oxidative damage in hepatic and renal tissues of rats

Narges Marefati[1], Farimah Beheshti[2,3], Poorya Etemadizadeh[1], Mahmoud Hosseini[4], Akbar Anaeigoudari[5]✉

[1]*Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*

[2]*Neuroscience Research Center, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran*

[3]*Department of Physiology, School of Paramedical Sciences, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran*

[4]*Division of Neurocognitive Sciences, Psychiatry and Behavioral Sciences Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*

[5]*Department of Physiology, School of Medicine, Jiroft University of Medical Sciences, Jiroft, Iran*

ABSTRACT

Objective: To explore the effect of ethyl acetate gum resin extract of *Boswellia serrata* on lipopolysaccharide (LPS) induced inflammation and oxidative damage in hepatic and renal tissues of rats.

Methods: The rats were divided into four groups: control, LPS, LPS+*Boswellia serrata* extracts (100 mg/kg and 200 mg/kg). LPS (1 mg/kg) and the extract (100 and 200 mg/kg, 30 min before LPS) were administered intraperitoneally for 3 weeks. The levels of liver enzymes, albumin, total protein, creatinine, blood urea nitrogen (BUN), interleukin (IL)-6, malondialdehyde (MDA), and total thiol groups and superoxide dismutase (SOD) and catalase (CAT) activities were measured.

Results: The levels of liver enzymes, creatinine, and BUN, IL-6, MDA in the LPS group were markedly increased (P<0.001) while albumin, total protein, and total thiol concentration, as well as SOD and CAT activities, were decreased compared with the control group (P<0.05 or 0.01). *Boswellia serrata* extracts diminished the levels of liver enzymes, creatinine, BUN, IL-6, and MDA (P<0.01 and P<0.001), and elevated the concentration of total protein and total thiol and SOD and CAT activities (P<0.05 or 0.01).

Conclusions: The ethyl acetate gum resin extract of *Boswellia serrata* reduces LPS-induced inflammatory reactions and oxidative damage, thus ameliorating hepatic and renal function.

KEYWORDS: *Boswellia serrata*; Lipopolysaccharide; Inflammation; Oxidative stress; Renal function; Hepatic function

1. Introduction

Inflammation and oxidative stress participate in the pathogenesis of liver[1] and kidney[2] injuries. Contact of immune cells, especially macrophages with inflammatory stimuli including bacterial endotoxins, results in excessive generation of inflammatory mediators and free radicals[3]. Tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 are inflammatory mediators causing liver and kidney destruction *via* programmed cell death[4]. It has been detected that the level of inflammatory mediators such as TNF-α remarkably increased in patients with hepatic cirrhosis associated with renal failure[5]. In addition, uncontrolled release of oxidant agents including hydrogen peroxidase and superoxide anion from the Kupffer cells has been propounded to have a central role in hepatic damages[6]. Accumulation of reactive oxygen species in the kidney tissue has been also considered as an important cause in induction of kidney injuries by triggering the inflammatory reactions and destruction of

Significance

There is no study about the effect of ethyl acetate gum resin extract of *Boswellia serrata* on LPS-stimulated hepatic and renal injuries. The findings of present study demonstrated that this extract alleviated LPS-caused hepatic and renal damage through reducing the level of IL-6 and MDA and enhancing the concentration of antioxidant indexes including total thiol groups and the activity of SOD and CAT.

✉To whom correspondence may be addressed. E-mail: Anaeiga317@gmail.com

How to cite this article: Marefati N, Beheshti F, Etemadizadeh P, Hosseini M, Anaeigoudari A. Gum resin extract of *Boswellia serrata* attenuates lipopolysaccharide-induced inflammation and oxidative damage in hepatic and renal tissues of rats. Asian Pac J Trop Biomed 2022; 12(1): 20-25.

Article history: Received 29 August 2021; Revision 22 September 2021; Accepted 12 November 2021; Available online 5 January 2022

glomerular filtration barrier[5,7].

Gram-negative bacteria cell wall possesses a toxic particle that is named lipopolysaccharide (LPS)[8]. This active bacterial endotoxin has been demonstrated to boost the release of inflammatory mediators causing oxidative stress[9]. LPS has been found to impair liver circulation and induce hepatic cell necrosis[3]. It has been reported that TNF-α released from LPS-exposed Kupffer cells disturbs normal liver function through the induction of hepatocyte apoptosis[10]. The hurtful effects of accumulation of TNF-α induced by LPS on kidney function have been also confirmed. Additionally, it has been documented that employment of anti-TNF-α antibodies could improve renal dysfunction caused by LPS[11].

Use of medicinal plants and derived compounds from them has been recognized as a beneficial strategy in reduction of destructive effects of inflammation and oxidative stress on body tissues[12]. Gum resin of *Boswellia serrata* (*B. serrata*) has been employed as an effective remedy in treatment of different ailments in traditional medicine[13]. It has been indicated that boswellic acids presented in the extract of *B. serrata* could suppress the biosynthesis of inflammatory cytokines[14]. Oleo-gum resin of *B. serrata* has been revealed to protect the liver tissue against carbon tetrachloride (CCl_4)-induced toxicity through the amplification of antioxidant capacity and suppression of inflammatory factors such as nuclear factor κB (NF-κB), IL-6, TNF-α and transforming growth factor-β (TGF-β)[15]. In addition, researchers reported that *B. serrata* extract could augment the activity of antioxidant enzymes including catalase (CAT) and superoxide dismutase (SOD). These effects were attributed to the presence of the triterpenes in the extract of this medicinal plant[14]. This study aimed to evaluate the effect of ethyl acetate gum resin extract of *B. serrata* on LPS-induced inflammation and oxidative damage in hepatic and renal tissues of rats.

2. Materials and methods

2.1. Animals and groups

A total of 32 adult male Wistar rats in the weight range of 200-250 g were procured from the animal nest of Mashhad University of Medical Sciences, Mashhad, Iran. The rats were housed in Plexiglas cages at ambient temperature at (20 ± 2)℃ and maintained on a 12-hour light/dark cycle. The rats were allowed to use adequate water and food and randomly divided into four groups (n = 8 rats per group) as follows: control group (1 mL of saline), LPS group (1 mg/kg LPS), LPS+extract (100 mg/kg) and LPS+extract (200 mg/kg). In two treatment groups, the rats were treated with 100 and 200 mg/kg of ethyl acetate gum resin extract of *B. serrata*, respectively, 30 min before LPS[12]. Treatments were executed intraperitoneally for 3 weeks. At the end of experiment, blood samples were taken from the heart of rats for measurement of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), albumin, total protein, creatinine, and blood urea nitrogen (BUN). After that, liver and kidney tissues were collected for detection of the concentration of interleukin (IL)-6, malondialdehyde (MDA), and total thiol groups and activities of SOD and CAT.

2.2. Preparation of ethyl acetate gum resin extract of B. serrata

In the current study, the gum resin of *B. serrata* was used. After identification of the plant by a botanist, a voucher specimen (E-1330 FUMH) was deposited at the Herbarium of Ferdowsi University of Mashhad, Mashhad, Iran. Preparation of ethyl acetate extract was started with comminuting and dissolving 100 g of gum resin in 400 mL of ethyl acetate. The prepared mixture was stirred at 38℃ for 48 h. After filtration, the solvent was removed completely using a rotary apparatus at 40℃. Then the extract was dissolved in dimethyl sulfoxide and saline for further experiment.

2.3. Assessment of liver and kidney function indices

For assessment of liver function indicators (ALT, AST, ALP, albumin, total protein) and kidney function markers (creatinine and BUN), the serum was isolated from blood samples by centrifuging at 3500 rpm for 15 min. Then serum samples were used for detection of liver and kidney indices.

2.4. Detection of IL–6 concentration

IL-6 concentration in the liver and kidney tissues was detected using an ELISA kit. For this purpose, filled plates of 100 μL of samples were housed at room temperature. Plates were then kept in a dark enviroment for 1 h after draining and adding biotin-antibody. After that, plates were re-incubated for 1 h in the presence of HRP-avidin. After washing 5 times, substrate-TMB was employed for 15 min and finally, the absorbance was recorded at 450 nm by an ELISA reader[16].

2.5. Evaluation of oxidative stress indices

2.5.1. MDA detection

MDA level of liver and kidney samples was assessed by thiobarbituric acid. Combination of thiobarbituric acid with MDA generated a color complex with a peak absorbance at 535 nm. In this colorimetric method, the level of MDA was presented in nanomol/g tissue[17].

2.5.2. Determination of total thiol groups

For determination of total thiol groups, 50 μL of samples, 0.5 mL of tris–EDTA buffer, and 40 μL of DTNB (10 mM) were mixed. After keeping at room temperature for 20 min, the absorbance of the color complex was calculated at 412 nm[17].

2.5.3. Determination of SOD activity

Assessment of SOD activity was implemented based on autoxidation of pyrogallol. In this colorimetric method, superoxide resulted from autoxidation of pyrogallol inhibits the reduction of

tetrazolium dye MTT to formazan. The SOD activity was measured at 570 nm[18].

2.5.4. Determination of CAT activity

For measurement of CAT activity, Aebi's method was employed. Briefly, the substrate of CAT, hydrogen peroxide (H_2O_2), was added to specimens and absorbance was computed. Decline in absorbance was considered as a sign of the decomposition of H_2O_2 into O_2 and H_2O by CAT[19].

2.6. Statistical analysis

Statistical analysis was carried out using SPSS20.0 software. The results were presented as mean ± standard deviation (SD). Analysis of data was achieved by one-way ANOVA followed by Tukey's test. $P<0.05$ was considered significantly different.

2.7. Ethical statement

The experiment complied with Recommendations of the Ethical Committee of Jiroft University of Medical Sciences (IR.JMU.REC.1400.002, 2021).

3. Results

3.1. Effect of ethyl acetate gum resin extract of B. serrata on hepatic function indicators

LPS resulted in a significant increase in the levels of ALT, AST, and ALP ($P<0.001$) and a considerable decline in serum concentration of albumin ($P<0.05$) and total protein ($P<0.01$). The levels of ALT, AST, and ALP were significantly decreased in groups treated with *B. serrata* extracts compared with the LPS group ($P<0.01$ and $P<0.001$). Moreover, *B. serrata* extract at 200 mg/kg increased the concentration of albumin ($P<0.01$) and total protein ($P<0.001$) (Figures 1 and 2).

3.2. Effect of ethyl acetate gum resin extract of B. serrata on kidney function indicators

The level of creatinine and BUN in LPS administered rats was increased compared with the control group ($P<0.001$). Pretreatment with 200 mg/kg of ethyl acetate gum resin extract of *B. serrata* significantly lowered the level of creatinine and BUN ($P<0.05$). However, there was no significant change in the level of creatinine and BUN in the group treated with 100 mg/kg of ethyl acetate gum resin extract of *B. serrata* compared with the LPS group (Figures 2C and 2D).

3.3. Effect of ethyl acetate gum resin extract of B. serrata on IL-6 in liver and kidney tissues

The level of IL-6 was increased in renal and hepatic tissues in LPS-treated rats ($P<0.001$) while it was noticeably diminished in LPS-exposed rats treated with 100 and 200 mg/kg of ethyl acetate gum resin extract of *B. serrata* ($P<0.001$). The IL-6 level in hepatic and renal tissues of the group treated with 200 mg/kg *B. serrata* extract was lower than that of the 100 mg/kg extract treated group ($P<0.01$ and $P<0.001$) (Figures 3A and 3B).

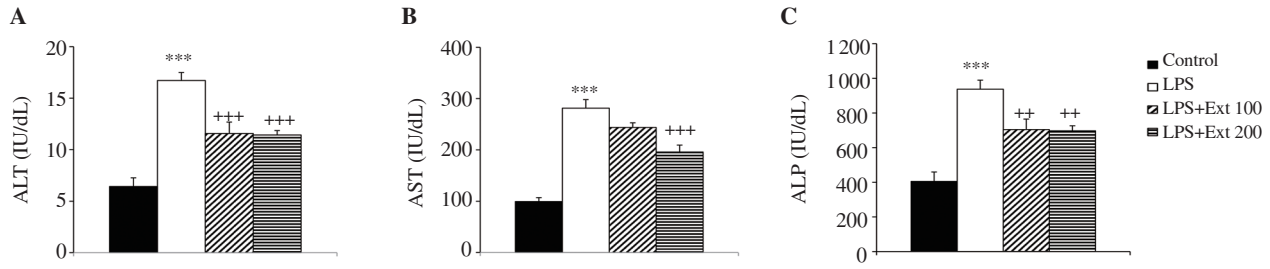

Figure 1. Serum level of alanine transaminase (ALT) (A), aspartate transaminase (AST) (B), and alkaline phosphatase (ALP) (C) in different groups. Data are indicated as mean ± SD (n= 8). $^{***}P<0.001$ versus the control group; $^{++}P<0.01$ and $^{+++}P<0.001$ versus the LPS group. Ext 100 and 200: 100 and 200 mg/kg ethyl acetate gum resin extract of *Boswellia serrata*. LPS: lipopolysaccharide.

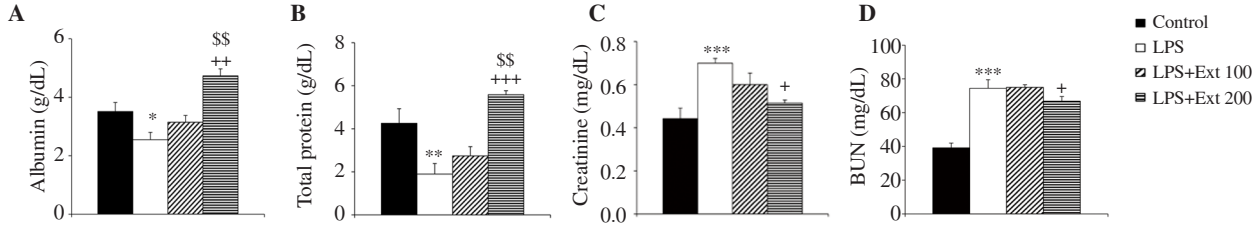

Figure 2. Serum level of albumin (A), total protein (B), creatinine (C) and BUN (D) in different groups. Data are exhibited as mean ± SD (n= 8). $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ versus the control group; $^{+}P<0.05$, $^{++}P<0.01$ and $^{+++}P<0.001$ versus the LPS group; $^{\$\$}P<0.01$ versus the LPS-Ext 100. BUN: blood urea nitrogen.

3.4. Effect of ethyl acetate gum resin extract of B. serrata on oxidative stress indicators in kidney and liver tissues

Increased MDA level was observed in hepatic and renal tissues of the LPS group (P<0.001). Administration of 200 mg/kg of ethyl acetate gum resin extract of *B. serrata* lowered the MDA level in the hepatic tissue of LPS-administered rats (P<0.001). Moreover, the MDA level was reduced by treatment of 100 and 200 mg/kg of ethyl acetate gum resin extract of *B. serrata* in the renal tissue of LPS rats (P<0.001). The 200 mg/kg of ethyl acetate gum resin extract of *B. serrata* reduced MDA level in hepatic and renal tissues of the LPS group markedly compared with 100 mg/kg *B. serrata* extract (P<0.01) (Figures 4A and 5A).

The concentration of total thiol groups in hepatic and renal tissues of the LPS group was lower than that of the control group (P<0.001). Both doses of ethyl acetate gum resin extract of *B. serrata* could reverse this change (P<0.05, P<0.01 and P<0.001). The total thiol content of hepatic (P<0.001) and renal (P<0.05) tissues in the 200 mg/kg *B. serrata* extract-treated group was higher than that of 100 mg/kg *B. serrata* extract-treated group (Figures 4B and 5B).

LPS injection also led to a noticeable decrease in SOD and CAT activities in hepatic and renal tissues (P<0.001). Administration of 100 and 200 mg/kg of ethyl acetate gum resin extract of *B. serrata* enhanced the activities of SOD and CAT in hepatic and renal tissues of rats (P<0.05 and P<0.001). Moreover, 200 mg/kg of ethyl acetate gum resin extract of *B. serrata* had more pronounced effects on

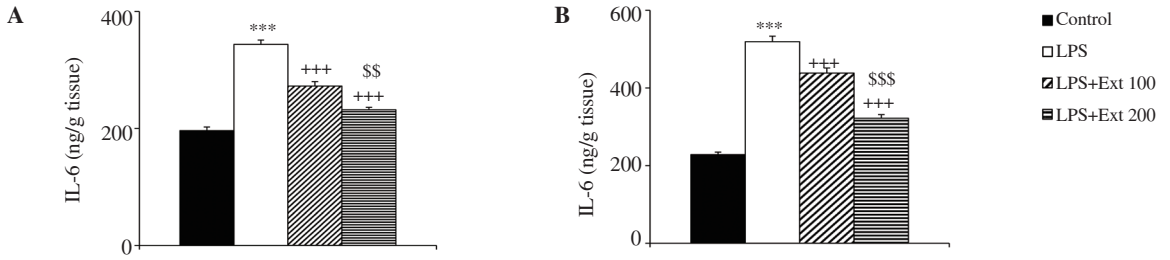

Figure 3. Concentration of IL-6 in the hepatic (A) and renal (B) tissues of different groups. Data are shown as mean ± SD (n= 8). $^{***}P$< 0.001 versus the control group; ^{+++}P< 0.001 versus the LPS group; $^{\$\$}P$<0.01 and $^{\$\$\$}P$<0.001 versus LPS-Ext 100.

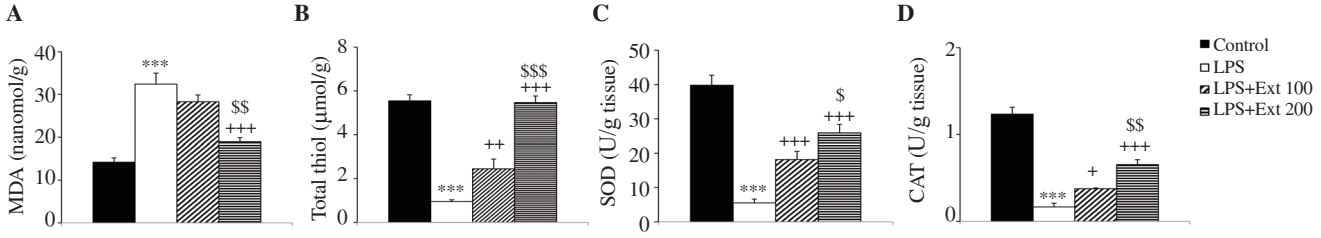

Figure 4. Effect of ethyl acetate gum resin extract of *Boswellia serrata* on oxidative stress indicators in the liver tissue of rats. (A) MDA, (B) the total thiol groups, (C) SOD, (D) CAT. Data are presented as mean ± SD (n= 8). $^{***}P$<0.001 versus the control group; ^{+}P<0.05, ^{++}P<0.01 and ^{+++}P<0.001 versus the LPS group; $^{\$}P$<0.05, $^{\$\$}P$<0.01 and $^{\$\$\$}P$<0.001 versus the LPS-Ext 100. MDA: malondialdehyde, SOD: superoxide dismutase, CAT: catalase.

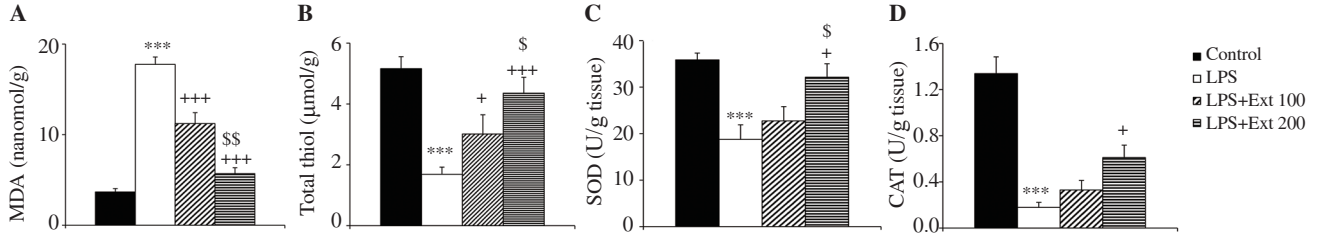

Figure 5. Effect of ethyl acetate gum resin extract of *Boswellia serrata* on oxidative stress indicators in the renal tissue of rats. (A) MDA, (B) the total thiol groups, (C) SOD, (D) CAT. Data are determined as mean ± SD (n= 8). $^{***}P$<0.001 versus the control group; ^{+}P<0.05 and ^{+++}P<0.001 versus the LPS group; $^{\$}P$<0.05 and $^{\$\$}P$<0.01 versus LPS-Ext 100.

increasing SOD and CAT activities ($P<0.05$, $P<0.01$) (Figures 4C, 4D, 5C, and 5D).

4. Discussion

In this work, as a consequence of LPS-excited liver injury, the serum levels of ALT, AST, and ALP were increased and the concentrations of albumin and total protein were reduced. In addition, LPS-induced kidney dysfunction showed enhanced levels of creatinine and BUN. These pernicious effects of LPS can be referred to as the stimulation of inflammatory reactions and the induction of oxidative damage in hepatic and renal tissues as reported in previous studies[16,20]. In agreement with previous findings, a significant increment in the level of IL-6 and MDA and a noticeable decrement in total thiol groups concentration and SOD and CAT activities were found in hepatic and renal tissues of LPS-treated rats in the current research.

Pretreatment with ethyl acetate gum resin extract of *B. serrata* effectively ameliorated the impairment of liver and kidney function resulted from LPS administration. This finding is manifested by enhancement of albumin and total protein and reduction of liver enzymes, creatinine and BUN in rats treated by *B. serrata* extracts. Gum resin of *B. serrata*, known as frankincense, is used to alleviate various ailments excited by inflammation such as ulcerative colitis, rheumatoid arthritis, asthma, and osteoarthritis[21]. Anti-inflammatory impacts of *B. serrata* are linked to the presence of constituents including *O*-acetyl-11-keto-β-boswellic acid (AKBA) and 11-keto-β-boswellic acid[22]. AKBA has been identified to inhibit the NF-κB pathway and suppress the production of TNF-α, IL-1, and IL-6 from monocytes and macrophages[23]. In addition, in ApoE-/- mice exposed to LPS, AKBA could downregulate inflammatory reactions *via* the inactivation of the NF-κB signaling pathway[21]. Reduced secretion of IL-12 and interferon-γ (IFN-γ) and elevated release of IL-4 and IL-10 in monocytes treated with *B. serrata* extract have been also detected[24]. In the current study, the ethyl acetate gum resin extract of *B. serrata* also modulated LPS-triggered inflammatory reactions in hepatic and renal tissues of rats, as evidenced by the decreased level of IL-6 in liver and kidney tissues of rats.

Alongside modulation of immune system activity, the role of *B. serrata* and its ingredients in the adjustment of oxidative status has been also understood[25]. The end product of lipid production, MDA, is checked as a key oxidative stress indicator in experimental works[26]. Boswellic acid from the gum resin of *B. serrata* has been found to reduce brain oxidative injury and ameliorate memory by lowering the MDA level and raising the glutathione concentration in rats challenged by trimethyltin[27]. Modification of lipid peroxidation followed by monosodium-urate crystals-induced inflammation has been also attributed to boswellic acid[28]. In an experimental study, the administration of oleo gum resin of *B. serrata* could improve the decreased activity of CAT resulted from CCL_4 in hepatic tissue[15]. Decline in MDA concentration and elevation of total thiol content and CAT and SOD activities were also observed in the present study in groups treated with ethyl acetate gum resin extract of *B. serrata* compared with the LPS group. Therefore, the inhibition of inflammatory reactions and modulation of oxidative stress by ethyl acetate gum resin extract of *B. serrata* may be contributed to alleviation of LPS-induced hepatic and renal damages. However, in terms of the effect of the *B. serrata* extract on improvement of LPS-induced inflammation and oxidative damage in the liver and kidney, 200 mg/kg of extract had a better effect than 100 mg/kg of extract. This finding was supported by a more markedly decreased level of IL-6 and MDA and increased concentration of total thiol and SOD and CAT activity in the group treated with 200 mg/kg of extract.

In conclusion, the ethyl acetate gum resin extract of *B. serrata* alleviated LPS-induced inflammation and oxidative stress in the liver and kidney. However, the assessment of molecular and pathological indicators can be useful to determine more precise mechanism(s) of the effect of ethyl acetate gum resin extract of *B. serrata* on LPS-induced liver and kidney malfunction, which needs further investigation in the future.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Acknowledgments

The authors would like to thank the Vice Presidency of Research of Jiroft University of Medical Sciences for their support.

Authors' contributions

NM, FB and PE performed experiments and collected data. AA and MH analyzed data. AA prepared manuscript and MH revised it.

References

[1] Beheshti F, Hosseini M, Taheri Sarvtin M, Kamali A, Anaeigoudari A. Protective effect of aminoguanidine against lipopolysaccharide-induced hepatotoxicity and liver dysfunction in rat. *Drug Chem Toxicol* 2021; **44**(2): 215-221.

[2] Hosseini M, Beheshti F, Anaeigoudari A. Improving effect of aminoguanidine on lipopolysaccharide-caused kidney dysfunction in rats. *Saudi J Kidney Dis Transpl* 2020; **31**(5): 1025-1033.

[3] Kim SJ, Kim JK, Lee DU, Kwak JH, Lee SM. Genipin protects lipopolysaccharide-induced apoptotic liver damage in *D*-galactosamine-sensitized mice. *Eur J Pharmacol* 2010; **635**(1-3): 188-193.

[4] Ni P, Liu YQ, Man JY, Li W, Xue SS, Lu TH, et al. C16, a novel

sinomenine derivatives, promoted macrophage reprogramming toward M2-like phenotype and protected mice from endotoxemia. *Int J Immunopathol Pharmacol* 2021; **35**: 20587384211026786.

[5] Chou YT, Liu TT, Yang UC, Huang CC, Liu CW, Huang SF, et al. Intestinal SIRT1 deficiency-related intestinal inflammation and dysbiosis aggravate TNFα-mediated renal dysfunction in cirrhotic ascitic mice. *Int J Mol Sci* 2021; **22**(3): 1-19.

[6] López ML, Uribe-Cruz C, Osvaldt A, Kieling CO, Simon L, Tobar S, et al. Encapsulated platelets modulate kupffer cell activation and reduce oxidative stress in a model of acute liver failure. *Liver Transpl* 2016; **22**(11): 1562-1572.

[7] Shah N, Dhar D, Mohammed FEZ, Habtesion A, Davies NA, Jover-Cobos M, et al. Prevention of acute kidney injury in a rodent model of cirrhosis following selective gut decontamination is associated with reduced renal TLR4 expression. *J Hepatol* 2012; **56**(5): 1047-1053.

[8] Chan YH, Musa NF, Chong YJ, Saat SA, Hafiz F, Shaari K, et al. 2, 4, 6-Trihydroxy-3-geranyl acetophenone suppresses vascular leakage and leukocyte infiltration in lipopolysaccharide-induced endotoxemic mice. *Pharm Biol* 2021; **59**(1): 732-740.

[9] Tsukahara T, Hara H, Haniu H, Matsuda Y. The combined effects of lysophospholipids against lipopolysaccharide-induced inflammation and oxidative stress in microglial cells. *J Oleo Sci* 2021; **70**(7): 947-954.

[10]Kawaguchi K, Kikuchi S, Hasegawa H, Maruyama H, Morita H, Kumazawa Y. Suppression of lipopolysaccharide-induced tumor necrosis factor-release and liver injury in mice by naringin. *Eur J Pharmacol* 1999; **368**(2-3): 245-250.

[11]Yura RE, Bradley SG, Ramesh G, Reeves WB, Bond JS. Meprin A metalloproteases enhance renal damage and bladder inflammation after LPS challenge. *Am J Physiol Renal Physiol* 2009; **296**(1): F135-F144.

[12]Arab Z, Hosseini M, Mashayekhi F, Anaeigoudari A. *Zataria multiflora* extract reverses lipopolysaccharide-induced anxiety and depression behaviors in rats. *Avicenna J Phytomed* 2020; **10**(1): 78-88.

[13]Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and tolerability of *Boswellia serrata* extract in treatment of osteoarthritis of knee–a randomized double blind placebo controlled trial. *Phytomedicine* 2003; **10**(1): 3-7.

[14]Montaser MM, El-Sharnouby ME, El-Noubi G, El-Shaer HM, Khalil AA, Hassanin M, et al. *Boswellia serrata* resin extract in diets of Nile tilapia, *Oreochromis niloticus*: Effects on the growth, health, immune response, and disease resistance to *Staphylococcus aureus*. *Animals* 2021; **11**(2): 446.

[15]Eltahir HM, Fawzy MA, Mohamed EM, Alrehany MA, Shehata AM, Abouzied MM. Antioxidant, anti-inflammatory and antifibrotic effects of *Boswellia serrate* gum resin in CCl_4-induced hepatotoxicity. *Exp Ther Med* 2020; **19**(2): 1313-1321.

[16]Beheshti F, Hosseini M, Arab Z, Asghari A, Anaeigoudari A. Ameliorative role of metformin on lipopolysaccharide-mediated liver malfunction through suppression of inflammation and oxidative stress in rats. *Toxin Rev* 2020. Doi: 10.1080/15569543.2020.1833037.

[17]Abareshi A, Hosseini M, Beheshti F, Norouzi F, Khazaei M, Sadeghnia HR, et al. The effects of captopril on lipopolysaccharide induced learning and memory impairments and the brain cytokine levels and oxidative damage in rats. *Life Sci* 2016; **167**: 46-56.

[18]Baghcheghi Y, Hosseini M, Beheshti F, Salmani H, Anaeigoudari A. Thymoquinone reverses learning and memory impairments and brain tissue oxidative damage in hypothyroid juvenile rats. *Arq Neuropsiquiatr* 2018; **76**(1): 32-40.

[19]Asgharzadeh F, Hosseini M, Bargi R, Soukhtanloo M, Beheshti F, Mohammady Z, et al. Effect of captopril on brain oxidative damage in pentylenetetrazole-induced seizures in mice. *Pharm Sci* 2019; **25**(3): 221-226.

[20]Jiang K, Yang J, Xue G, Dai A, Wu H. Fisetin ameliorates the inflammation and oxidative stress in lipopolysaccharide-induced endometritis. *J Inflamm Res* 2021; **14**: 2963-2978.

[21]Ammon H. Boswellic extracts and 11-keto-β-boswellic acids prevent type 1 and type 2 diabetes mellitus by suppressing the expression of proinflammatory cytokines. *Phytomedicine* 2019; **63**: 153002.

[22]Zimmermann-Klemd AM, Reinhardt JK, Nilsu T, Morath A, Falanga CM, Schamel WW, et al. *Boswellia carteri* extract and 3-*O*-acetyl-alpha-boswellic acid suppress T cell function. *Fitoterapia* 2020; **146**: 104694.

[23]Syrovets T, Büchele B, Krauss C, Laumonnier Y, Simmet T. Acetyl-boswellic acids inhibit lipopolysaccharide-mediated TNF-α induction in monocytes by direct interaction with IκB kinases. *J Immunol* 2005; **174**(1): 498-506.

[24]Gayathri B, Manjula N, Vinaykumar K, Lakshmi B, Balakrishnan A. Pure compound from *Boswellia serrata* extract exhibits anti-inflammatory property in human PBMCs and mouse macrophages through inhibition of TNFα, IL-1β, NO and MAP kinases. *Int Immunopharm* 2007; **7**(4): 473-482.

[25]Hartmann RM, Martins MIM, Tieppo J, Fillmann HS, Marroni NP. Effect of *Boswellia serrata* on antioxidant status in an experimental model of colitis rats induced by acetic acid. *Dig Dis Sci* 2012; **57**(8): 2038-2044.

[26]Ortega MA, Sánchez-Trujillo L, Bravo C, Fraile-Martinez O, García-Montero C, Saez MA, et al. Newborns of mothers with venous disease during pregnancy show increased levels of lipid peroxidation and markers of oxidative stress and hypoxia in the umbilical cord. *Antioxidants* 2021; **10**(6): 980.

[27]Ebrahimpour S, Fazeli M, Mehri S, Taherianfard M, Hosseinzadeh H. Boswellic acid improves cognitive function in a rat model through its antioxidant activity: -neuroprotective effect of boswellic acid. *J Pharmacopunct* 2017; **20**(1): 10-17.

[28]Sabina EP, Indu H, Rasool M. Efficacy of boswellic acid on lysosomal acid hydrolases, lipid peroxidation and anti–oxidant status in gouty arthritic mice. *Asian Pac J Trop Biomed* 2012; **2**(2): 128-133.