Journal of Research in Pharmacy

Research Article

www.jrespharm.com

Resveratrol and regular exercise can restore hepatic alterations induced by hypertension in rats

Nur Banu BAL[1] *, Emine DEMİREL-YILMAZ[2]

[1] Gazi University, Faculty of Pharmacy, Department of Pharmacology, Etiler 06330, Ankara, Turkey.
[2] Ankara University, Faculty of Medicine, Department of Medical Pharmacology, Sihhiye 06100, Ankara, Turkey

* Corresponding Author. E-mail: nurbanubal@gazi.edu.tr (N.B.B); Tel. +90-312-202 31 23.

Received: 14 March 2023 / Revised: 23 May 2023 / Accepted: 05 July 2023

ABSTRACT: Hypertension is a common disease that affects many organs including heart, vessel, and kidney. Moreover, chronic hypertension can lead to hepatic impairments accompanied by oxidative and inflammatory disturbances. In present study, the effects of regular exercise and resveratrol on hepatic alterations caused by hypertension were comparatively examined. Hypertension was produced by deoxycorticosterone-acetate and salt application in male Wistar rats for twelve weeks. In the last six weeks, resveratrol was given in the drinking water and, the exercise training was applied on a rat treadmill at 20 m/min, 5 days a week, for 45 minutes. At the end of the treatment, blood and liver samples were collected for molecular and biochemical analysis. Regular exercise reduced the elevation in liver weight, liver weight/body weight ratio and plasma lipid levels, while resveratrol only improved elevated plasma triglyceride and LDL cholesterol in hypertensive rats. Both treatments enhanced the hepatic total antioxidant capacity of hypertensive animals. Resveratrol repressed hypertension-triggered NLRP3 inflammasome activation by reversing the increase in hepatic Nod-like receptor protein 3 (NLRP3), nuclear factor- κB (NF-κB), p-NF-κB, tumor necrosis factor-α (TNF-α) expression and the cleaved-caspase-1/procaspase-1 ratio. Similarly, regular exercise inhibited stimulation of NLRP3 inflammasome in hypertensive liver by suppressing the elevation of NLRP3, p-NF-κB, NF-κB expression and the mature-IL-1β/pro-IL-1β ratio. Both interventions prevented the reduction in the mitophagic biomarker PTEN-induced putative kinase 1 (PINK1) level in the hypertensive groups. These findings revealed that resveratrol supplementation and regular exercise have beneficial effect on hypertension-induced hepatic changes by regulating antioxidant status, NLRP3 inflammasome-induced inflammation and mitophagy.

KEYWORDS: Hypertension; exercise; resveratrol; antioxidant capacity; mitophagy; NLRP3 inflammasome; liver.

1. INTRODUCTION

Hypertension, one of the most common cardiovascular diseases, is an important public health challenge with high morbidity and mortality worldwide [1,2]. According to the guideline of World Health Organization (WHO), approximately 1.4 billion people worldwide suffer from high blood pressure [3]. Chronic hypertension notably increases the risk of heart, vessel, and kidney disorders [4]. In addition to cardiovascular and renal changes, studies using different experimental models have shown that hypertension can also cause hepatic alterations [5-8]. However, the mechanisms underlying the causal link between hypertension and hepatic impairments are not completely understood.

The liver is responsible for the production of systemic antioxidant molecules (glutathione etc.,) and thus is considered the most crucial organ involved in the regulation of redox metabolism [9]. Therefore, the hepatic antioxidant defense system contributes to the systemic redox state. Excessive increase of reactive oxygen species (ROS) and/or decline of antioxidant defense systems trigger oxidative stress, which plays an influential role in the pathogenesis of hypertension and hypertension-related organ damage [10]. It is well known that the increase in vascular ROS production and the decrease in nitric oxide bioavailability is an essential mechanism leading to endothelial dysfunction and elevated blood pressure. Hypertension has been demonstrated to enhance vascular ROS production as well as alter the hepatic redox balance [11,12]. It can be thought that the disturbance in the hepatic redox system affects the vascular redox regulation and contributes to the pathogenesis of hypertension.

Bal NB, Demirel-Yılmaz E. Resveratrol and regular exercise can restore hepatic alterations induced by hypertension. J Res Pharm. 2024; 28(1): 29-39.

ISSN: 2630-6344

http://dx.doi.org/10.29228/jrp.669

Overproduction of ROS leads to organ damage by activating inflammatory signaling pathways. It is shown that low-level chronic inflammation plays an influential role in the pathogenesis of hypertension [13].

Recent investigations have indicated that Nod-like receptor protein 3 (NLRP3) inflammasome-mediated inflammatory response contributes to the progression of hypertension and development of hypertensive end-organ injury [14,15]. NLRP3, apoptosis-associated speck-like protein (ASC) and caspase-1 proteins constitute this inflammasome complex. Activation of the NLRP3 inflammasome complex mediates cleavage and activation of caspase-1, which causes the maturation and release of the proinflammatory cytokines IL-18 and IL-1β. These cytokines exacerbate the inflammatory response through stimulation of the proinflammatory transcription factor NF-κB [16]. In addition, disruption of redox balance results in mitochondrial dysfunction. A particular type of autophagy called mitophagy eliminates damaged mitochondria thereby preserving mitochondrial function and homeostasis [17]. Evidence have demonstrated that the removal of dysfunctional mitochondria by mitophagy and the decrease of ROS overproduction can reduce both NLRP3 inflammasome-induced inflammation and tissue damage [18,19]. Previous research using the DOCA-salt model have revealed that the development of hypertension and its associated cardiac and renal inflammation are partly due to the stimulation of the NLRP3 inflammasome complex and failure of mitophagy [20-22]. Although it has been reported that inflammatory pathways are triggered in the liver in hypertensive state [8], it is not known whether NLRP3 inflammasome activation and mitophagy contributes to this process.

It is recognized that lifestyle modifications (such as regular exercise, dietary supplements), which are considered as non-pharmacological interventions, have positive effects in the prevention or management of numerous diseases [23]. Resveratrol supplementation and regular exercise training have been displayed to have antioxidant and anti-inflammatory effects in different pathologies [24,25]. These favorable effects have been also accompanied by suppression of NLRP3 inflammasome activation and regulation of mitophagic deterioration [22,26,27]. However, the effects of resveratrol and regular exercise on the hepatic antioxidant status, NLRP3 inflammasome-mediated inflammation and mitophagy have not examined in hypertensive state. In the present study, the effects regular exercise and of resveratrol administration on liver function enzymes, plasma lipid profile, hepatic antioxidant status, and expression of NLRP3 inflammasome and mitophagy-related marker proteins were comparatively evaluated in the DOCA-salt hypertensive rats.

2. RESULTS

Systolic blood pressure markedly enhanced in the hypertensive rats when compared to the control animals (Control group 120,47±4,90 mmHg; DOCA-salt group 218,50±4,96 mmHg, $p < 0.05$). Regular exercise and resveratrol administration significantly reduced the systolic blood pressure of hypertensive rats (DOCA + Resveratol group 150,10±4,42 mmHg; DOCA + Exercise group 142,81±2,78 mmHg, $p < 0.05$), but did not alter the normotensive groups (Resveratrol group 115,33±2,28 mmHg; Exercise group 111,14±2,98 mmHg, $p > 0.05$), as shown in our earlier study [22]. The last body weight of the hypertensive rats was smaller than the those of control animals (Control group 478,4±11,9 g; DOCA-salt group 409,4±26,8 g). However, this decrease was not seen in the exercise and resveratrol-treated groups (DOCA + Resveratrol group 448,8±21,0 g; DOCA + Exercise group 419,7±9,7 g; Resveratrol group 494,3±13,5 g; Exercise group 441,4±12,9 g, $p > 0.05$), as displayed in our previous study [22].

The liver weight of DOCA-salt animals was notably higher than those of the control group. While regular exercise training diminished liver weight only in the hypertensive group, resveratrol administration did not change the liver weight in either group (Figure 1a). The ratio of liver weight/body weight of hypertensive rats was greater than that of control rats. While resveratrol supplementation did not alter this ratio, regular exercise declined it in hypertensive rats (Figure 1b).

Journal of Research in Pharmacy
Research Article

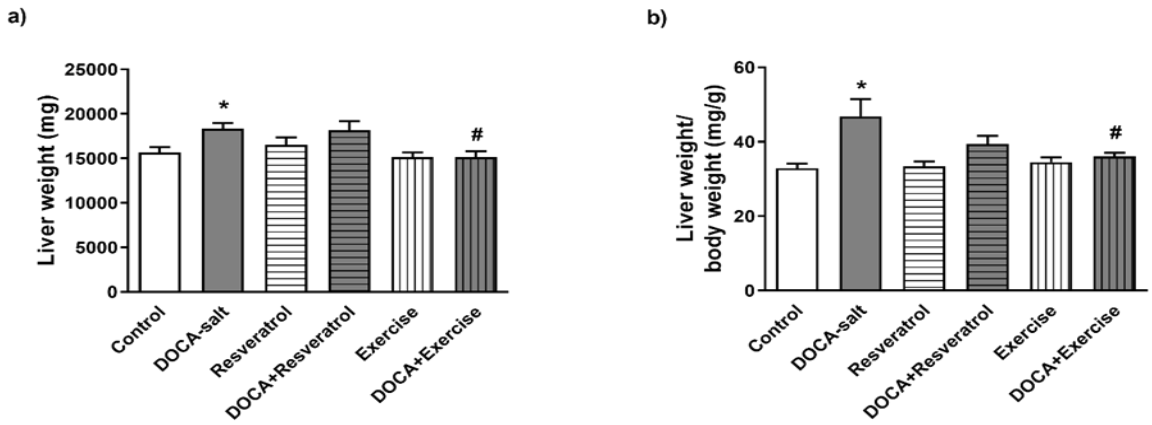

Figure 1. The effect of resveratrol supplementation and regular exercise training on liver weight and ratio of liver weight/body weight ratio in rats. Regular exercise reduced the increased liver weight and liver weight/body weight ratio of hypertensive animals *Differences from control group and #differences from DOCA-salt group, p <0.05, (n = 7–8).

Plasma ALT level was greater in hypertensive rats compared to control group and, regular exercise alleviated ALT level in normotensive rats (Figure 2a). While plasma AST was similar in all groups, LDH level was lower only in the exercise-treated normotensive group (Figure 2b and 2c).

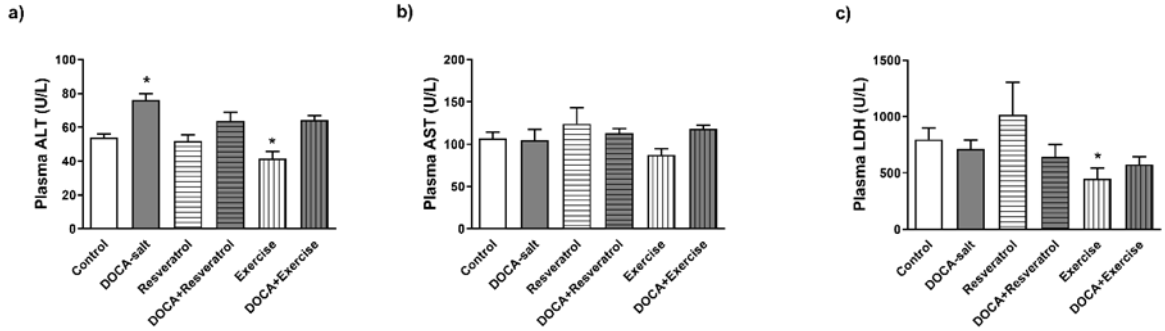

Figure 2. The effect of resveratrol supplementation and regular exercise training on plasma ALT, AST and LDH levels. Plasma ALT increased in the hypertensive group, and plasma AST and LDH decreased in the exercise-treated normotensive group. *Differences from control group, p <0.05, (n = 6–7).

Plasma triglyceride, low density lipoprotein (LDL), and total cholesterol levels significantly elevated in DOCA-salt hypertensive rats. Regular exercise training attenuated all plasma lipids, while resveratrol supplementation declined triglyceride and LDL cholesterol levels (Figure 3).

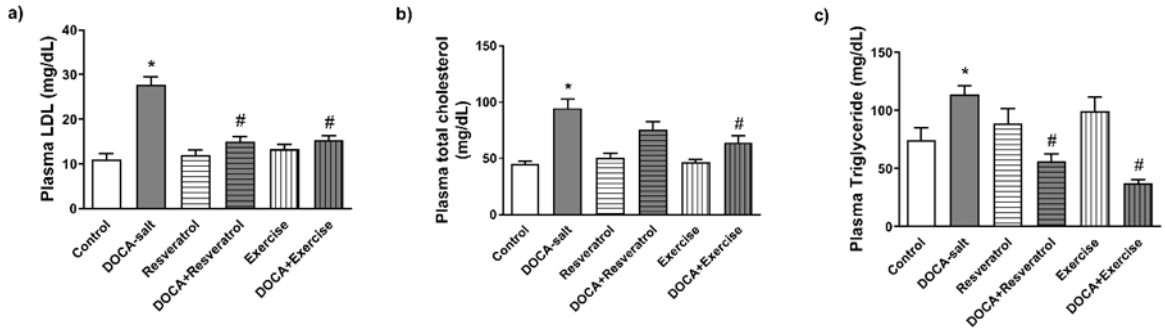

Figure 3. The effect of resveratrol supplementation and regular exercise training on plasma triglyceride, LDL, and total cholesterol levels. Resveratrol and regular exercise treatments improved the elevated plasma lipid levels of hypertensive rats. *Differences from control group and #differences from DOCA-salt group, p <0.05, (n = 6–7).

Total antioxidant capacity (TAC) level of liver tissue was unchanged in the DOCA-salt hypertension model. However, both treatments significantly enhanced hepatic TAC levels in hypertensive animals (Figure 4).

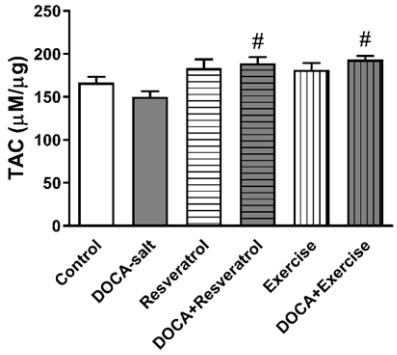

Figure 4. The effect of resveratrol supplementation and regular exercise training on hepatic TAC levels. Resveratrol administration and regular exercise training markedly enhanced hepatic TAC levels. #Differences from DOCA-salt group, $p < 0.05$, (n = 6–7).

NLRP3 protein expression, cleaved-caspase-1/pro-caspase-1 ratio and mature-IL- 1β/pro-IL-1β ratio were greater in the DOCA-salt animals than in the control animals. Both treatments alleviated hepatic NLRP3 protein levels. In hypertensive groups, regular exercise training restored the with ratio of mature-IL-1β/p-IL-1β and, resveratrol supplementation improved the ratio of cleaved-caspase-1/pro-caspase-1. ASC protein expression was not different between the groups (Figure 5).

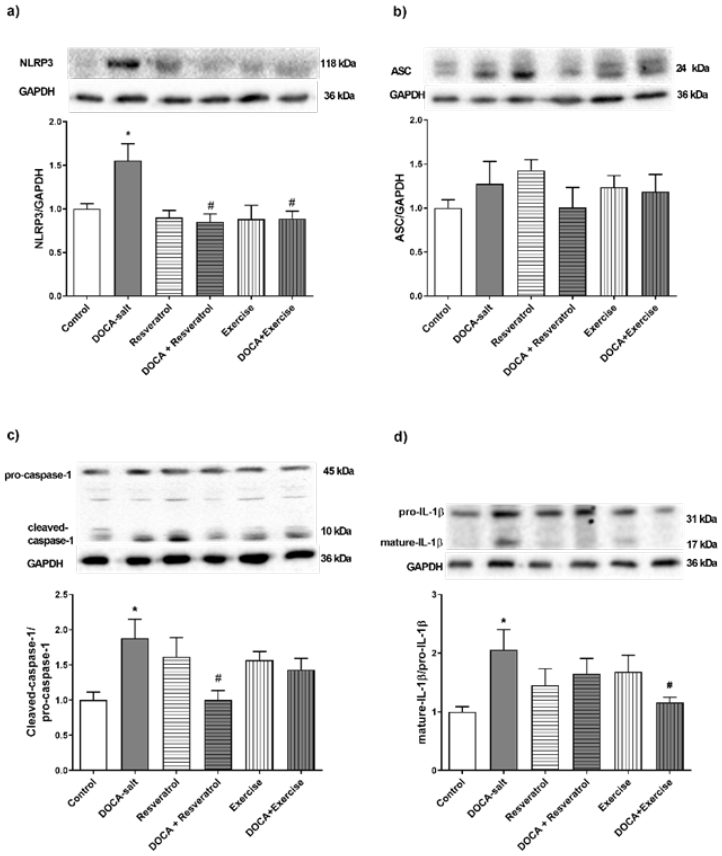

Figure 5. The effect of resveratrol supplementation and regular exercise training on NLRP3, ASC, Caspase-1 and IL-1β protein expressions. In hypertensive liver tissue, resveratrol and regular exercise applications reduced NLRP3 inflammasome-related marker protein expressions except ASC. *Differences from control group and #differences from DOCA-salt group, $p < 0.05$, (n = 5–7).

NF-κB, p-NF-κB and TNF-α protein levels remarkably increased in the hypertensive liver tissue. Exercise training reversed all these alterations, while resveratrol diminished expression of NF-κB and p-NF-κB. The reduction in hepatic PINK1 protein expression caused by hypertension was prevented by both application (Figure 6).

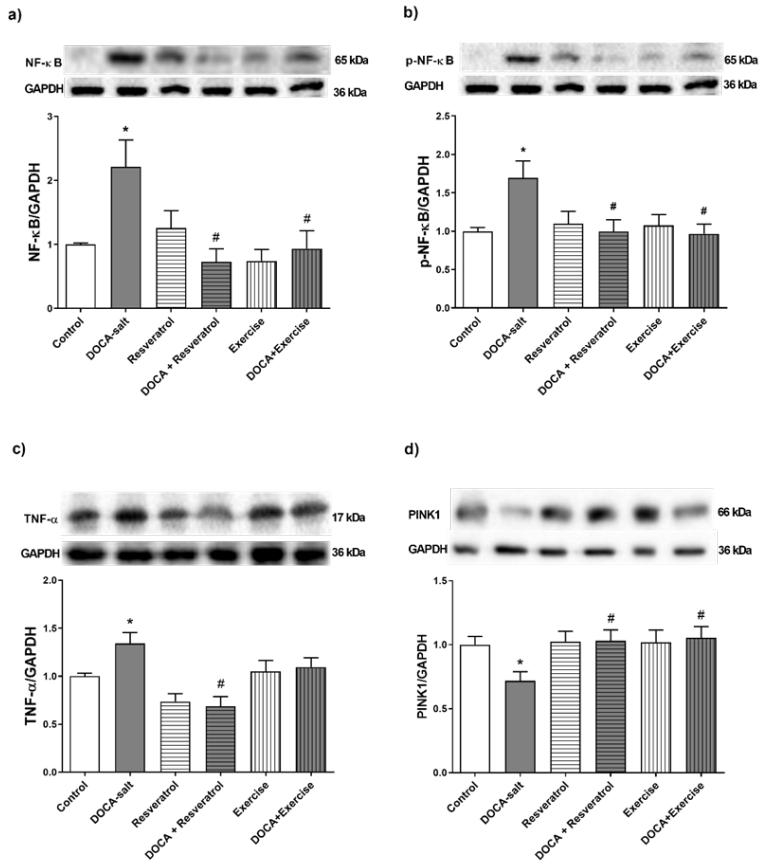

Figure 6. The effect of resveratrol supplementation and regular exercise training on NF-κB, p-NF-κB, TNF-α and PINK1 protein expressions. Resveratrol and regular exercise prevented the increase in p-NF-κB, NF-κB and TNF-α expression and the decrease in PINK1 expression in hypertensive groups. *Differences from control group and #differences from DOCA-salt group, $p < 0.05$, (n = 5–7).

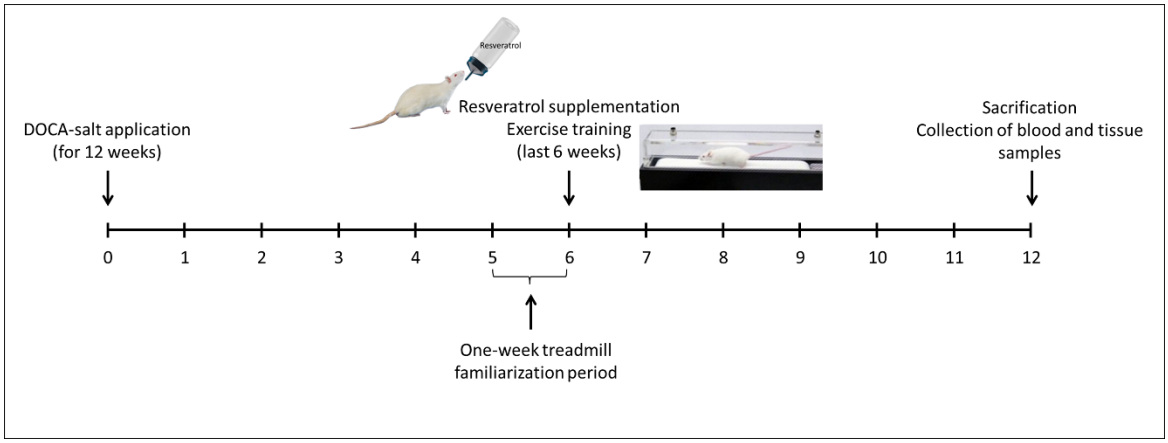

Figure 7. The schematic representation of the experimental protocol.

3. DISCUSSION

The findings of current study demonstrated that DOCA-salt hypertension leads to an increment in liver weight, liver weight/body weight ratio, plasma ALT and lipid levels and hepatic expression of some inflammatory molecules (NLRP3, cleaved-caspase-1, IL-1β, p-NF-κB, NF-κB, TNF-α) and a decrease in expression of mitophagic marker PINK1, accompanied by unchanged hepatic TAC levels. Regular exercise reduced plasma lipids, elevated hepatic TAC levels, and improved hepatic inflammatory and mitophagic changes in hypertensive rats. Also, exercise training diminished plasma ALT and LDH level in normotensive animals. While resveratrol supplementation did not affect liver function enzymes, it decreased plasma

triglyceride and LDL concentrations, increased hepatic TAC levels, and restored hepatic inflammatory and mitophagic alterations in the hypertensive group.

Hypertension is a common serious public health challenge and is a progressive disease. It has been reported that chronic hypertension causes hepatic changes as well as cardiovascular, renal, and cerebral alterations [5-8]. Lifestyle modifications such as alteration of dietary habits and regular exercise, known as non-pharmacological interventions, are seen as beneficial approach in the management and delay of hypertension and hypertension-related pathologies. Although resveratrol supplementation and regular exercise are described to have positive effects in hypertension due to their antioxidant and anti-inflammatory properties [33,34], their effects on hepatic changes in the hypertensive state have not been comparatively examined.

The liver is the main organ responsible for systemic redox balance and lipid metabolism. Plasma levels of biochemical markers involving ALT, AST and LDH are used routinely for assessing liver function [35]. An elevation in liver function enzyme levels have been shown in different hypertension models [36-38]. In this study, only the plasma level of ALT, which is primarily produced in the liver and catalyzes the transfer of amino groups, was elevated in DOCA-salt hypertensive rats. Moreover, previous studies have indicated that the hypertensive liver resembles the early phase of hepatic steatosis [6-8]. In our study, plasma triglyceride, LDL and total cholesterol levels were markedly augmented in hypertensive rats. In parallel to our results, the undesired changes in plasma lipids and liver functions have been observed in same hypertension model [8,39,40]. These alterations showed that there are irregularities in liver functions and lipid metabolism in the hypertensive state. While resveratrol and regular exercise applications did not affect liver function tests in hypertensive animals, both treatments reversed the increase in plasma lipid levels. These interventions, which are recognized to have a hepatoprotective effect, may have ameliorated the deterioration in the plasma lipid profile that occurs earlier in the hypertensive state, but may not have been sufficient to prevent the elevation in plasma ALT levels of hypertensive rats. This also may be due to the protocol of resveratrol administration (dose and duration) and exercise (exercise intensity, period, and frequency) used in present study.

Antioxidants are powerful defense system that limit toxicity and tissue damage associated with free radicals and the failure of these defense mechanisms contributes to the pathogenesis of several diseases. TAC level is considered a general indicator of antioxidant status. Previous studies have shown that hypertension alters hepatic redox status [11,12]. Although there was a tendency to decrease in hepatic TAC level in hypertensive rats, it was not statistically significant. It is well known that resveratrol administration and regular exercise training have a positive effect on many pathologies by affecting antioxidant enzymes and mechanisms [22,24,25]. Accordingly, both applications markedly enhanced hepatic TAC levels of hypertensive rats.

Accumulating evidence have revealed that the inflammation is implicated in the pathogenesis of hypertension and accompanying organ dysfunctions [13,22,41]. Lately, it has been demonstrated that the NLRP3 inflammasome-associated inflammatory response prompted by danger signals such as mitochondria-derived excessive ROS production plays an influental role in the development of hypertensive organ injury as well as hepatic disorders [20,21,42-44]. When NLRP3 is stimulated, NLRP3 interacts with pro-caspase-1 and ASC to activate caspase-1 and then active caspase-1 leads to maturation and release of proinflammatory cytokines IL-18 and IL-1β, thereby aggravating inflammation through the activation of the NF-κB pathway [16]. NLRP3 inflammasome stimulation also leads to caspase-1-dependent mitochondrial impairment and mitophagy blockade [45]. Mitophagy, a mitochondria-specific form of autophagy, is mainly regulated by the PINK1–Parkin pathway and decrease or loss of PINK1 causes damaged mitophagy [17]. Disruption of mitophagy may result in the accumulation of impaired and ROS-producing mitochondria, thereby promoting NLRP3 inflammasome activation. Our previous research has demonstrated that hypertension causes inflammatory and fibrotic changes in the liver [7,8]. In this study, NLRP3, p-NF-κB, NF-κB, TNF-α protein expression and the cleaved-caspase-1/procaspase-1 and the mature-IL-1β/pro-IL-1β ratio increased and mitophagic marker PINK expression decreased in hypertensive liver. Our study results shown for the first time that activation of NLRP3 inflammasome and suppression of mitophagy may contribute to hepatic alterations induced by hypertension. Considering the above results, it can be suggested that excessive ROS production in hypertension may lead to activation of NLRP3 inflammasome and caspase-1-mediated impaired mitophagy. On the other hand, it can also propose that decreased mitophagy may cause increased ROS production due to the disturbance of mitochondrial oxidant/antioxidant balance and, subsequently activation of NLRP3 inflammasome in hypertensive liver. Consequently, ROS overproduction, NLRP3 inflammasome and defective mitophagy, which trigger each other, could be implicated in hepatic damage induced by hypertension. Resveratrol supplementation and regular exercise training have positive effects on both NLRP3 inflammasome activation and impaired mitophagy in different pathologies [22,26,27]. Consistent with these studies, both treatments ameliorated NLRP3 inflammasome-induced inflammation and damaged mitophagy

caused by hypertension in current study. These results indicate that the hepatoprotective effects of resveratrol and regular exercise in hypertension could be mediated by the regulation of NLRP3 inflammasome and mitophagic process.

4. CONCLUSION

This study revealed that resveratrol and regular exercise decreased plasma lipid levels and only exercise training diminished liver weight and liver weight/body weight ratio in hypertensive animals. These favorable impacts on the hepatic parameters might be associated to the regulation of the antioxidant system and mitophagy and the suppression of NLRP3 inflammasome-mediated inflammation. In conclusion, our data indicate that resveratrol supplementation and regular exercise training, recognized as non-pharmacological interventions, have positive effects on the hepatic changes induced by hypertension, in addition to other known beneficial outcomes on cardiovascular, renal, and central disorders.

5. MATERIALS AND METHODS

5.1. Animals and DOCA-salt hypertension model

The experimental protocols of this study were performed according to the principles of Local Ethics Committee for Animal Experiments of Gazi University (G.Ü.ET-23.003) and Guide for the Care and Use of Laboratory Animals (NIH).

Male Wistar albino rats (eight weeks old) were housed in a temperature-controlled room with a 12:12 h light/dark cycle with free access to standard chow and tap water throughout the experimental period. After a one-week adaptation period, animals were randomly separated following groups: Control (n = 7), Resveratrol (n = 7), Exercise (n = 7), DOCA-salt (n = 8), DOCA + Resveratrol (n = 8), and DOCA + Exercise (n = 8). Since there is a risk of death in approximately 10-20% of the rats during the 12-week experimental period in the DOCA-salt hypertension model, the number of rats in the hypertensive groups was set to 8 for the current study.

To induce hypertesion, the subcutaneous DOCA injection (20 mg/kg, twice weekly) and salt administration in drinking water (1% NaCl and 0.2% KCl) for twelve weeks were treated to rats as recently published [22]. Systolic blood pressure of all animals was monitored with using the tail cuff technique (NIBP200A, COMMAT, Turkey).

5.2. Resveratrol and regular exercise interventions

In the last 6 weeks of the experiment, resveratrol was added to the drinking water of the rats in the resveratrol groups, at a level adequate to provide the proper dose (roughly 15 mg/kg) based on the consumption. The dose and duration of resveratrol was determined according to previous studies in which antioxidant and anti-inflammatory effects were observed [28,29]. The body weight and daily water consumption of rats were recorded. All rats in the exercise groups ran for 45 minutes at 20 m/min (0◦ incline) on a horizontal treadmill 5 days a week for the last 6 weeks, after acclimating to the rodent treadmill for one week. The treadmill exercise protocol (moderate exercise) was decided by examining previous investigations [29,30]. The schematic representation of the experimental protocol was shown in figure 7.

At the end of the study, blood samples were rapidly collected from abdominal aorta of rats under anesthesia (60 mg/kg ketamine and 10 mg/kg xylazine mixture, i.p.) and, plasma was separated for biochemical measurements. Liver was quickly removed, weighed, and stored at -80 ◦C for biochemical and molecular examinations.

5.3. Biochemical measurements

Plasma ALT, AST and LDH levels as indicators of liver function were measured by standard enzymatic techniques. Also, plasma triglyceride, LDL and total cholesterol levels were determined using colorimetric kits (Rel Assay Diagnostics kits).

For hepatic TAC measurement, the liver tissue (80-100 mg) was homogenized in assay buffer (900 µL assay buffer for 100 mg tissue). The homogenates were centrifuged at 10.000 g for 20 min, at 4 ◦C. Later, the supernatant was carefully taken and total protein concentration was determined by the Lowry method [31]. The level of TAC was spectrophotometrically measured in tissue homogenates by using trolox as antioxidant equivalent according to previous method [32]. In this assay, Cu^{+2} was reduced to Cu^{+} by the antioxidants of the tissue, and the absorbance was read at 455 nm.

5.4. Western Blot experiments

Liver tissue samples were homogenized in buffer that contained 50 mM Tris, 1 mM PMSF, 2 mM EDTA, 1% NP40 (v/v), 10% sucrose (w/v), protease and phosphatase inhibitors. After centrifugation (at 2.000g for 15 min at 4 °C), supernatants were carefully collected, and total protein concentrations was determined by using the Lowry method [31]. After the proteins were denatured in boiling water for 5 minutes, an equal amount of protein (30–40 µg) for each sample were separated by SDS-PAGE and then electroblotted PVDF membranes. The blots were blocked with 5% nonfat dried milk or 3% bovine serum albümin for 1 h, followed by incubation at 4 ◦C overnight with primary antibodies NLRP3 (PA1665, 1/500), caspase-1 (sc-56036, 1/500), IL-1β (ab9722, 1/500), ASC (sc-514414, 1/1000), TNF-α (ab6671, 1/500), NF-kB p65 (Biolegend-622602, 1:250), p-NF-kB p65 (sc-136548, 1:100), PINK1 (sc-517353, 1/1000) and GAPDH (sc-32233, 1/2000) in Tris-Buffered Saline (TBS). After being washed with TBS-T (with tween 20), membranes were subjected with horseradish peroxidase-conjugated secondary antibody (1/10000) for 1 h and proteins were visualized with enhanced chemiluminescence with ChemiDoc™ MP chemiluminescence detection system. The intensities of blotted bands were calculated with the software (ImageLab4.1 software), and normalized to GAPDH.

5.5. Data analysis

All data were given as mean ± standard error of the mean (SEM). One-way ANOVA followed by the Dunnett post-hoc test was used for all statistical comparisons. At a level of $p<0.05$, values were accepted as statistically significant. All analyses were performed using the statistical program GraphPad Prism (version 8.0, GraphPad Software, La Jolla, CA, USA).

Acknowledgements: Some antibodies used in this study were obtained with the fund of Gazi University Research Foundation (Grant No: 02/2019-10). I would like to thank Gazi University Academic Writing Application and Research Center for their support in editing this article.

Author contributions: Concept – N.B.B., E.D.Y.; Design – N.B.B., E.D.Y.; Supervision – N.B.B., E.D.Y.; Resources – N.B.B., E.D.Y.; Materials – N.B.B., E.D.Y.; Data Collection and/or Processing – N.B.B., E.D.Y.; Analysis and/or Interpretation – N.B.B., E.D.Y.; Literature Search – N.B.B., E.D.Y.; Writing – N.B.B., E.D.Y.; Critical Reviews – N.B.B., E.D.Y.

Conflict of interest statement: The authors declared no conflict of interest.

REFERENCES

[1] Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, He J. Global disparities of hypertension prevalence and control: A systematic analysis of population-based studies from 90 countries. Circulation. 2016;134(6):441-450. https://doi.org/10.1161%2FCIRCULATIONAHA.115.018912

[2] Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, Ahmed M, Aksut B, Alam T, Alam K, Alla F, Alvis-Guzman N, Amrock S, Ansari H, Ärnlöv J, Asayesh H, Atey TM, Avila-Burgos L, Awasthi A, Banerjee A, Barac A, Bärnighausen T, Barregard L, Bedi N, Belay Ketema E, Bennett D, Berhe G, Bhutta Z, Bitew S, Carapetis J, Carrero JJ, Malta DC, Castañeda-Orjuela CA, Castillo-Rivas J, Catalá-López F, Choi JY, Christensen H, Cirillo M, Cooper L Jr, Criqui M, Cundiff D, Damasceno A, Dandona L, Dandona R, Davletov K, Dharmaratne S, Dorairaj P, Dubey M, Ehrenkranz R, El Sayed Zaki M, Faraon EJA, Esteghamati A, Farid T, Farvid M, Feigin V, Ding EL, Fowkes G, Gebrehiwot T, Gillum R, Gold A, Gona P, Gupta R, Habtewold TD, Hafezi-Nejad N, Hailu T, Hailu GB, Hankey G, Hassen HY, Abate KH, Havmoeller R, Hay SI, Horino M, Hotez PJ, Jacobsen K, James S, Javanbakht M, Jeemon P, John D, Jonas J, Kalkonde Y, Karimkhani C, Kasaeian A, Khader Y, Khan A, Khang YH, Khera S, Khoja AT, Khubchandani J, Kim D, Kolte D, Kosen S, Krohn KJ, Kumar GA, Kwan GF, Lal DK, Larsson A, Linn S, Lopez A, Lotufo PA, El Razek HMA, Malekzadeh R, Mazidi M, Meier T, Meles KG, Mensah G, Meretoja A, Mezgebe H, Miller T, Mirrakhimov E, Mohammed S, Moran AE, Musa KI, Narula J, Neal B, Ngalesoni F, Nguyen G, Obermeyer CM, Owolabi M, Patton G, Pedro J, Qato D, Qorbani M, Rahimi K, Rai RK, Rawaf S, Ribeiro A, Safiri S, Salomon JA, Santos I, Santric Milicevic M, Sartorius B, Schutte A, Sepanlou S, Shaikh MA, Shin MJ, Shishehbor M, Shore H, Silva DAS,

Sobngwi E, Stranges S, Swaminathan S, Tabarés-Seisdedos R, Tadele Atnafu N, Tesfay F, Thakur JS, Thrift A, Topor-Madry R, Truelsen T, Tyrovolas S, Ukwaja KN, Uthman O, Vasankari T, Vlassov V, Vollset SE, Wakayo T, Watkins D, Weintraub R, Werdecker A, Westerman R, Wiysonge CS, Wolfe C, Workicho A, Xu G, Yano Y, Yip P, Yonemoto N, Younis M, Yu C, Vos T, Naghavi M, Murray C. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol. 2017;70(1):1-25. http://dx.doi.org/10.1016/j.jacc.2017.04.052.

[3] Al-Makki A, DiPette D, Whelton PK, Murad MH, Mustafa RA, Acharya S, Beheiry HM, Champagne B, Connell K, Cooney MT, Ezeigwe N, Gaziano TA, Gidio A, Lopez-Jaramillo P, Khan UI, Kumarapeli V, Moran AE, Silwimba MM, Rayner B, Sukonthasan A, Yu J, Saraffzadegan N, Reddy KS, Khan T. Hypertension Pharmacological Treatment in Adults: A World Health Organization Guideline Executive Summary. Hypertension. 2022; 79(1):293-301. http://dx.doi.org/10.1161/HYPERTENSIONAHA.121.18192.

[4] Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, Alexander L, Estep K, Hassen Abate K, Akinyemiju TF, Ali R, Alvis-Guzman N, Azzopardi P, Banerjee A, Bärnighausen T, Basu A, Bekele T, Bennett DA, Biadgilign S, Catalá-López F, Feigin VL, Fernandes JC, Fischer F, Gebru AA, Gona P, Gupta R, Hankey GJ, Jonas JB, Judd SE, Khang YH, Khosravi A, Kim YJ, Kimokoti RW, Kokubo Y, Kolte D, Lopez A, Lotufo PA, Malekzadeh R, Melaku YA, Mensah GA, Misganaw A, Mokdad AH, Moran AE, Nawaz H, Neal B, Ngalesoni FN, Ohkubo T, Pourmalek F, Rafay A, Rai RK, Rojas-Rueda D, Sampson UK, Santos IS, Sawhney M, Schutte AE, Sepanlou SG, Shifa GT, Shiue I, Tedla BA, Thrift AG, Tonelli M, Truelsen T, Tsilimparis N, Ukwaja KN, Uthman OA, Vasankari T, Venketasubramanian N, Vlassov VV, Vos T, Westerman R, Yan LL, Yano Y, Yonemoto N, Zaki ME, Murray CJ. Global Burden of Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg, 1990-2015. JAMA. 2017; 317(2):165-182. http://dx.doi.org/10.1001/jama.2016.19043.

[5] Ikuta T, Kanno K, Arihiro K, Matsuda S, Kishikawa N, Fujita K, Tazuma S. Spontaneously hypertensive rats develop pronounced hepatic steatosis induced by choline-deficient diet: Evidence for hypertension as a potential enhancer in non-alcoholic steatohepatitis. Hepatol Res. 2012;42(3):310-320. http://dx.doi.org/10.1111/j.1872-034X.2011.00920.x.

[6] Svoboda DS, Kawaja MD. Changes in hepatic protein expression in spontaneously hypertensive rats suggest early stages of non-alcoholic fatty liver disease. J Proteomics. 2012; 75(6):1752-1763. http://dx.doi.org/10.1016/j.jprot.2011.12.011.

[7] Bal NB, Han S, Usanmaz SE, Kiremitci S, Sadi G, Uludag O, Demirel-Yilmaz E. Activation of liver X receptors by GW3965 attenuated deoxycorticosterone acetate-salt hypertension-ınduced cardiac functional and structural changes. J Cardiovasc Pharmacol. 2019; 74(2):105-117. http://dx.doi.org/10.1097/FJC.0000000000000693.

[8] Bal NB, Han S, Kiremitci S, Uludag MO, Demirel-Yilmaz E. Reversal of deleterious effect of hypertension on the liver by inhibition of endoplasmic reticulum stress. Mol Biol Rep. 2020; 47(3):2243-2252. http://dx.doi.org/10.1007/s11033-020-05329-2.

[9] Cesaratto L, Vascotto C, Calligaris S, Tell G. The importance of redox state in liver damage. Ann Hepatol. 2004; 3(3):86-92. https://doi.org/10.1016/S1665-2681(19)32099-X

[10] Guzik TJ, Touyz RM. Oxidative stress, ınflammation, and vascular aging in hypertension. Hypertension. 2017; 70(4):660-667. http://dx.doi.org/10.1161/HYPERTENSIONAHA.117.07802.

[11] Binda D, Nicod L, Viollon-Abadie C, Rodriguez S, Berthelot A, Coassolo P, Richert L. Strain difference (WKY, SPRD) in the hepatic antioxidant status in rat and effect of hypertension (SHR, DOCA). Ex vivo and in vitro data. Mol Cell Biochem. 2001; 218(1-2):139-146. http://dx.doi.org/10.1023/a:1007268825721.

[12] Cediel E, Sanz-Rosa D, Oubina MP, de las Heras N, González Pacheco FR, Vegazo O, Jiménez J, Cachofeiro V, Lahera V. Effect of AT1 receptor blockade on hepatic redox status in SHR: Possible relevance for endothelial function? Am J Physiol Regul Integr Comp Physiol. 2003; 285(3):R674-81. http://dx.doi.org/10.1152/ajpregu.00643.2002.

[13] Murray EC, Nosalski R, MacRitchie N, Tomaszewski M, Maffia P, Harrison DG, Guzik TJ. Therapeutic targeting of inflammation in hypertension: from novel mechanisms to translational perspective. Cardiovasc Res. 2021; 117(13):2589-2609. http://dx.doi.org/10.1093/cvr/cvab330.

[14] Wang Y, Liu X, Shi H, Yu Y, Yu Y, Li M, Chen R. NLRP3 inflammasome, an immune-inflammatory target in pathogenesis and treatment of cardiovascular diseases. Clin Transl Med. 2020; 10(1):91-106. http://dx.doi.org/10.1002/ctm2.13.

[15] De Miguel C, Pelegrín P, Baroja-Mazo A, Cuevas S. Emerging role of the ınflammasome and pyroptosis in hypertension. Int J Mol Sci. 2021;22(3):1064. http://dx.doi.org/10.3390/ijms22031064.

[16] Yan Z, Qi Z, Yang X, Ji N, Wang Y, Shi Q, Li M, Zhang J, Zhu Y. The NLRP3 inflammasome: Multiple activation pathways and its role in primary cells during ventricular remodeling. J Cell Physiol. 2021;236(8):5547-5563. http://dx.doi.org/10.1002/jcp.30285.

[17] Ma X, McKeen T, Zhang J, Ding WX. Role and mechanisms of mitophagy in liver diseases. Cells. 2020;9(4):837. http://dx.doi.org/10.3390/cells9040837.

[18] Mishra SR, Mahapatra KK, Behera BP, Patra S, Bhol CS, Panigrahi DP, Praharaj PP, Singh A, Patil S, Dhiman R, Bhutia SK. Mitochondrial dysfunction as a driver of NLRP3 inflammasome activation and its modulation through mitophagy for potential therapeutics. Int J Biochem Cell Biol. 2021; 136:106013. http://dx.doi.org/10.1016/j.biocel.2021.106013.

[19] Huang FR, Fang WT, Cheng ZP, Shen Y, Wang DJ, Wang YQ, Sun LN. Imatinib-induced hepatotoxicity via oxidative stress and activation of NLRP3 inflammasome: an in vitro and in vivo study. Arch Toxicol. 2022;96(4):1075-1087. http://dx.doi.org/10.1007/s00204-022-03245-x.

[20] Krishnan SM, Ling YH, Huuskes BM, Ferens DM, Saini N, Chan CT, Diep H, Kett MM, Samuel CS, Kemp-Harper BK, Robertson AAB, Cooper MA, Peter K, Latz E, Mansell AS, Sobey CG, Drummond GR, Vinh A. Pharmacological inhibition of the NLRP3 inflammasome reduces blood pressure, renal damage, and dysfunction in salt-sensitive hypertension. Cardiovasc Res. 2019;115(4):776-787. http://dx.doi.org/10.1093/cvr/cvy252.

[21] Chen Z, Wu C, Liu Y, Li H, Zhu Y, Huang C, Lin H, Qiao Q, Huang M, Zhu Q, Wang L. ELABELA attenuates deoxycorticosterone acetate/salt-induced hypertension and renal injury by inhibition of NADPH oxidase/ROS/NLRP3 inflammasome pathway. Cell Death Dis. 2020; 11(8):698. http://dx.doi.org/10.1038/s41419-020-02912-0.

[22] Bal NB, Bostanci A, Sadi G, Dönmez MO, Uludag MO, Demirel-Yilmaz E. Resveratrol and regular exercise may attenuate hypertension-induced cardiac dysfunction through modulation of cellular stress responses. Life Sci. 2022;296:120424. http://dx.doi.org/10.1016/j.lfs.2022.120424.

[23] Santos L. The impact of nutrition and lifestyle modification on health. Eur J Intern Med. 2022; 97:18-25. http://dx.doi.org/10.1016/j.ejim.2021.09.020.

[24] Zucker IH, Musch TI. Benefits of exercise training on cardiovascular dysfunction: molecular and integrative. Am J Physiol Heart Circ Physiol. 2018;315(4):H1027-H1031. http://dx.doi.org/10.1152/ajpheart.00516.2018.

[25] Cheng CK, Luo JY, Lau CW, Chen ZY, Tian XY, Huang Y. Pharmacological basis and new insights of resveratrol action in the cardiovascular system. Br J Pharmacol. 2020;177(6):1258-1277. http://dx.doi.org/10.1111/bph.14801.

[26] Rai RC, Bagul PK, Banerjee SK. NLRP3 inflammasome drives inflammation in high fructose fed diabetic rat liver: Effect of resveratrol and metformin. Life Sci. 2020; 253:117727. http://dx.doi.org/10.1016/j.lfs.2020.117727.

[27] Yang W, Liu L, Wei Y, Fang C, Liu S, Zhou F, Li Y, Zhao G, Guo Z, Luo Y, Li L. Exercise suppresses NLRP3 inflammasome activation in mice with diet-induced NASH: a plausible role of adropin. Lab Invest. 2021;101(3):369-380. http://dx.doi.org/10.1038/s41374-020-00508-y.

[28] Bhatt SR, Lokhandwala MF, Banday AA. Resveratrol prevents endothelial nitric oxide synthase uncoupling and attenuates development of hypertension in spontaneously hypertensive rats. Eur J Pharmacol. 2011 ;667(1-3):258-64. http://dx.doi.org/10.1016/j.ejphar.2011.05.026.

[29] Han S, Bal NB, Sadi G, Usanmaz SE, Uludag MO, Demirel-Yilmaz E. The effects of resveratrol and exercise on age and gender-dependent alterations of vascular functions and biomarkers. Exp Gerontol. 2018;110:191-201. http://dx.doi.org/10.1016/j.exger.2018.06.009.

[30] Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP. American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011; 43(7):1334-1359. http://dx.doi.org/10.1249/MSS.0b013e318213fefb.

[31] Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. J Biol Chem. 1951;193(1):265-275. https://doi.org/10.1016/S0021-9258(19)52451-6.

[32] Usanmaz SE, Demirel Yilmaz E. A microplate based spectrophotometric method for the determination of the total antioxidant capacity of human plasma: modified cupric reducing ability assay. Conference: Fundamental and Clinical Pharmacology 2008; 22 Suppl 2: 67.

[33] Grujić-Milanović J, Jaćević V, Miloradović Z, Jovović D, Milosavljević I, Milanović SD, Mihailović-Stanojević N. Resveratrol protects cardiac tissue in experimental malignant hypertension due to antioxidant, anti-ınflammatory, and anti-apoptotic properties. Int J Mol Sci. 2021;22(9):5006. http://dx.doi.org/10.3390/ijms22095006.

[34] Song Y, Jia H, Hua Y, Wu C, Li S, Li K, Liang Z, Wang Y. The molecular mechanism of aerobic exercise ımproving vascular remodeling in hypertension. Front Physiol. 2022 ;13:792292. http://dx.doi.org/10.3389/fphys.2022.792292.

[35] Sookoian S, Pirola CJ. Liver enzymes, metabolomics and genome-wide association studies: from systems biology to the personalized medicine. World J Gastroenterol. 2015;21(3):711-725. http://dx.doi.org/10.3748/wjg.v21.i3.711.

[36] Prahalathan P, Kumar S, Raja B. Effect of morin, a flavonoid against DOCA-salt hypertensive rats: A dose dependent study. Asian Pac J Trop Biomed. 2012;2(6):443-8. http://dx.doi.org/10.1016/S2221-1691(12)60073-2.

[37] Al-Bishri WM. Favorable effects of flaxseed supplemented diet on liver and kidney functions in hypertensive Wistar rats. J Oleo Sci. 2013;62(9):709-715. http://dx.doi.org/10.5650/jos.62.709.

[38] Vinothiya K, Ashokkumar N. Modulatory effect of vanillic acid on antioxidant status in high fat diet-induced changes in diabetic hypertensive rats. Biomed Pharmacother. 2017;87:640-652. http://dx.doi.org/10.1016/j.biopha.2016.12.134.

[39] Veeramani C, Al-Numair KS, Chandramohan G, Alsaif MA, Pugalendi KV. Antihyperlipidemic effect of Melothria maderaspatana leaf extracts on DOCA-salt induced hypertensive rats. Asian Pac J Trop Med. 2012;5(6):434-439. http://dx.doi.org/10.1016/S1995-7645(12)60074-1.

[40] Wang H, Sun J, Jia Z, Yang T, Xu L, Zhao B, Yu K, Wang R. Nitrooleic acid attenuates lipid metabolic disorders and liver steatosis in DOCA-Salt hypertensive mice. PPAR Res. 2015;2015:480348. http://dx.doi.org/10.1155/2015/480348.

[41] Krzemińska J, Wronka M, Młynarska E, Franczyk B, Rysz J. Arterial hypertension-oxidative stress and inflammation. Antioxidants (Basel). 2022;11(1):172. http://dx.doi.org/10.3390/antiox11010172.

[42] Li X, Zhang Z, Luo M, Cheng Z, Wang R, Liu Q, Lv D, Yan J, Shang F, Luo S, Xia Y. NLRP3 inflammasome contributes to endothelial dysfunction in angiotensin II-induced hypertension in mice. Microvasc Res. 2022;143:104384. http://dx.doi.org/10.1016/j.mvr.2022.104384.

[43] Wang Q, Jia F, Guo C, Wang Y, Zhang X, Cui Y, Song M, Cao Z, Li Y. PINK1/Parkin-mediated mitophagy as a protective mechanism against AFB1-induced liver injury in mice. Food Chem Toxicol. 2022;164:113043. http://dx.doi.org/10.1016/j.fct.2022.113043

[44] Zhang NP, Liu XJ, Xie L, Shen XZ, Wu J. Impaired mitophagy triggers NLRP3 inflammasome activation during the progression from nonalcoholic fatty liver to nonalcoholic steatohepatitis. Lab Invest. 2019; 99(6):749-763. http://dx.doi.org/10.1038/s41374-018-0177-6

[45] Yu J, Nagasu H, Murakami T, Hoang H, Broderick L, Hoffman HM, Horng T. Inflammasome activation leads to Caspase-1-dependent mitochondrial damage and block of mitophagy. Proc Natl Acad Sci USA. 2014 ;111(43):15514-15519. http://dx.doi.org/10.1073/pnas.1414859111.