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Protective effects of olive cake against heart and kidney injury in dexamethasone-induced hypertensive rats

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In this study, we investigated the protective effects of olive cake (OC) from heart and kidney damage in dexamethasone-induced hypertensive (HT) rats. HT rats were divided into two groups fed standard diet supplemented (HT-OC) or not (HT) with OC at 7.5% for 28 days. A control group (C) was submitted to standard diet for the same experimental period. The results showed that serum levels of lactate dehydrogenase (LDH), creatine kinase (CK), aspartate aminotransferase (AST), urea creatinine and uric acid were significantly increased in the HT group compared with the C group. The HT group was associated with increased levels of thiobarbituric acid reactive substances, lipid hydroperoxides and protein carbonyl, while reducing glutathione concentration and glutathione peroxidase, superoxide dismutase and catalase activities in heart and kidney. OC treatment reduced systolic blood pressure, creatinine, urea, uric acid, LDH, CK and AST and increased nitric oxide in serum than the HT group. OC reduced oxidative stress biomarkers and increased antioxidants enzyme activities in heart and kidney than the HT group. In the HT group compared with C, histopathological examination of renal tissues revealed glomerular necrosis, renal tubular distortion, and increased Bowman's space, and that of the heart showed cardiac cells nuclear peripheralization, pyknosis, and congestion of myocardial blood vessels. However, OC treatment attenuated cardiac and renal damage compared with the HT group. Conclusions, in dexamethasone-induced hypertensive rats, OC protects against kidney and heart damage by reducing blood pressure, oxidative stress and improving antioxidant defense. These results could be referred to their flavonoid and polyphenol content.

KEYWORDS: Hypertension rat; dexamethasone; olive cake; antioxidant enzymes; oxidative stress.

1. INTRODUCTION

In this Hypertension is the leading cause of cardiovascular disease and premature death worldwide. It is estimated that the disease affects more than 30% of the world's population [1]. Hypertension is defined as a systolic pressure reading of 140 mmHg or more or a diastolic reading of 90 mmHg or more in persons 18 years of age and over [2]. Despite a plethora of available treatment options, a significant portion of the hypertensive population has uncontrolled blood pressure [3]. An adverse consequence of chronic hypertension is multiple target organ damage such as the brain, eyes, heart, arterial blood vessels, and kidneys [4]. A recent study reported a 70.41% prevalence of target organ damage in elderly hypertensive patients [5]. Moreover, the presence of target organ damage increases the risk of mortality and cardiovascular events [6].

The pathogenesis of target organ damage of hypertension is a multifactorial process that involves various mechanisms such as oxidative stress, inflammation, endothelial dysfunction, and hemodynamics [7, 8]. Previous study indicate that increased bioavailability of oxidative stress is one of the central mechanisms involved in this pathogenesis [9]. The heart and kidneys are the primary targets of damage caused by hypertension. The latest reports have shown overproduction of reactive oxygen species (ROS) and impaired antioxidant enzymes activities in the heart and kidney of hypertensive animal models [10, 11], leading to overproduction of ROS and reduced bioavailability of nitric oxide (NO), vasodilator [12], which in turn causes other complications related to hypertension.

Several reports had shown that the chronic administration of drugs to rats induces hypertension. Dexamethasone (Dex) is a potent synthetic glucocorticoid used in the treatment of a multitude of inflammatory and immunologic disorders. Dex therapy is associated with a variety of side effects, including hypertension, endothelial dysfunction, sarcopenia, anxiety, and organ damage [13]. Administration of Dex induces hypertension in animal models [14], develop renal and cardiac damage [15] and endothelial dysfunction [16].

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Dexamethasone administration can induce hypertension through multiple mechanisms such as increased oxidative stress, decreased antioxidant activity and nitric oxide (NO) levels [17, 18].

Successful prevention and treatment of hypertension are key in reducing disease burden and promoting longevity in the world's population [19]. In recent year, a considerable attention has been focused on natural products (herbs, diets, dietary supplements, vitamins) with antioxidant properties as a new strategy for the management of hypertension and target organ damage [16, 20]. Olive cake (OC) is the solid by-product of virgin olive oil extraction and represents nearly 45 to 80% of the weight of olives [21]. This residue has several pharmacological effects, including anti-hypercholesterolemic [22], anti-diabetic [23], anti-obesity [24], antioxidant [25] and anti-inflammatory [26]. OC is a good source of minerals, dietary fiber, proteins [27] and phenolic compounds including hydroxytyrosol, tyrosol, oleuropein, flavonoids, gallic acid, caffeic acid and ferulic acid [28]. Most of these compounds have demonstrated antioxidant and protective effects against organ damage in various experimental models [29, 30]. Indeed, OC contains a substantial amount of residual olive oil. Domínguez-Vías al. [31] reported that olive oil has a protective effect on systolic blood pressure and kidney damage.

Although the potential of olive cake to protect against organs damage associated with hypertension has not yet been explored. Therefore, this study was designed to explore the effects of olive cake on heart and kidney damage associated with dexamethasone-induced hypertension in rats.

2. RESULTS

2.1. Effect of olive cake on body weights, relative organ weights and systolic blood pressure

The effect of olive cake on body weight changes during the treatment period is shown in Fig. 1A. The growth rate of the HT group was slower than that of the C group, as indicated by the smaller body weight increase during the 28-day period. The growth curves of the hypertensive rat group treated with olive cake showed a higher growth rate than that of the rats in the HT group. Kidney and heart relative weights were increased in HT group compared to C group, which were counteracted by olive cake treatment (Fig. 1B-C). Systolic blood pressure was markedly increased in HT group compared with C group ($P<0.05$), which was significantly reduced by olive cake treatment ($P<0.05$) (Fig. 1D).

2.2. Effect of olive cake on kidney and cardiac function markers and on serum NO level

In the HT group, serum creatinine, urea and uric acid levels were increased (70%, 43%, and 71%, respectively) compared with the C group ($P< 0.05$). Treatment of hypertensive rats with olive cake significantly reduced the elevation of these values.

Similarly, serum lactate dehydrogenase and creatine kinase, aspartate aminotransferase activities, were significantly increased ($P< 0.05$) in the HT group by about 38% and 82%, respectively compared with the C group, whereas, these values were decreased by 29%, 40%, and 78% in the HT-OC group compared with the HT group ($P< 0.05$) (Table 1).

Serum nitric oxide (NO) level was decreased in the HT group compared to C group ($P< 0.05$). In hypertensive rats, OC treatment resulted in an increased of NO values compared to the HT group ($P< 0.05$).

Table 1. Effect of olive cake on kidney and cardiac function markers and on serum nitric oxide.

Parameters	C	HT	HT-OC
Creatinine (mg/dl)	0.90 ± 0.02	1.53 ± 0.16[a]	1.12 ± 0.02[b]
Uric acid (mg/dl)	2.45 ± 0.66	8.30 ± 0.98[a]	2.67 ± 0.32[b]
Urea (mg/dl)	21.33 ± 0.82	30.57 ± 2.28[a]	24.12 ± 2.07[b]
AST (UI/l)	33.17 ± 2.46	54.12 ± 2.50[a]	38.41 ± 4.93[b]
LDH (U/l)	229.49 ± 6.30	921.61 ± 46.36[a]	404.34 ± 16.59[ab]
CK (U/l)	96.70 ± 4.11	547.86 ± 9.50[a]	120.27 ± 6.43[ab]
NO (µM/l)	4.19 ± 0.34	1.73 ± 0.28 [a]	3.37± 0.12 [b]

C: Control group; HT: untreated hypertensive group; HT-GO: hypertensive rats treated with olive cake (7.5%). Results are expressed as mean ± SD. Data among groups were analyzed by two-way ANOVA followed by post-hoc test. P values: [a]<0.05 when compared with control group; [b]<0.05 when compared with HT group.

AST: Aspartate aminotransferase; CK: Creatine kinase; LDH: Lactate dehydrogenase; NO: Nitric oxide.

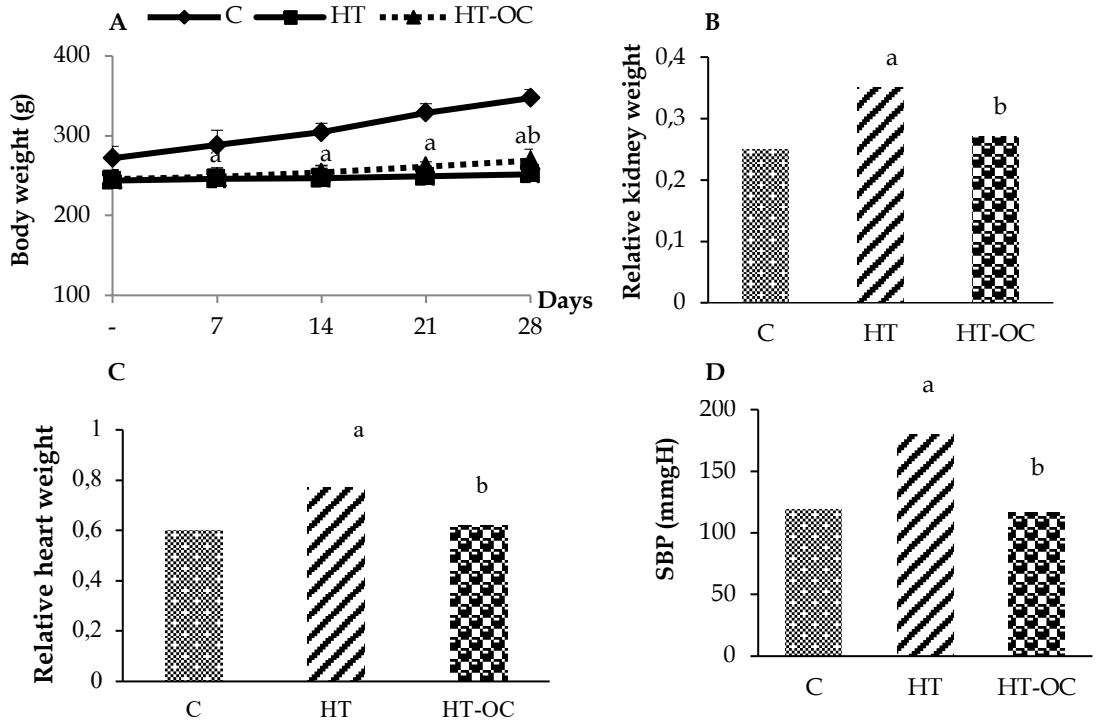

Figure 1. Effect of olive cake on body weights, relative organ weights and systolic blood pressure.

C: Control group; HT: untreated hypertensive group; HT-GO: hypertensive rats treated with olive cake (7.5%). Results are expressed as mean ± SD. Data among groups were analyzed by two-way ANOVA followed by post-hoc test. P values: [a]<0.05 when compared with control group; [b]<0.05 when compared with HT group.

2.3. Effect of olive cake on oxidative stress markers in cardiac and renal tissues

The levels of TBARS, LOOH, and PCO in cardiac and kidney tissues of the different groups are summarized in Figure 2. Untreated hypertensive rats had significantly higher levels of TBARS, LOOH, and PCO in the heart and kidney tissues compared with control rats (P<0.05). Treatment of hypertensive rats with olive cake significantly decreased oxidative stress markers in these tissues compared with untreated hypertensive rats (P<0.05).

2.4. Effects of olive cake on SOD, CAT, GSH-Px activities and GSH level in heart and kidney

Table 2 shows the SOD, CAT and, GSH-Px activities in the heart and kidney. In the HT group, compared to the C group, SOD, CAT, and GSH-Px activities were significantly reduced in all tissues (P<0.05). However, in the HT-OC group, CAT activity was increased in all tissues compared to the HT group (P<0.05). Similarly, SOD and GSH-Px activities were increased by 41% and 76%, respectively, in the hearts of rats in the HT-OC group compared with those in the HT group. In contrast, treatment of hypertensive rats with olive cake had no effect on renal GSH-Px activity.

In the HT group compared to the C group, the GSH level was significant decreased in all tissues (P<0.05). Treatment with olive cake increased the concentrations of GSH by +39% and +48% in heart and kidneys, respectively compared to the HT group.

2.5. Effects of olive cake on kidney and heart histopathology

Figure 3 illustrates the effects of OC on the histology of the kidney and heart stained with hematoxylin and eosin. The kidney of rats in the C group showed normal renal architecture with their glomeruli, Bowman's space and renal tubules (Fig. 3a). The HT group showed significant narrowing of the glomerulus with an increase in Bowman's space. There is also a glomerular necrosis, dilatation of the proximal tubules and infiltration of inflammatory cells (Fig. 3b). The kidney of the OC-treated rat showed a renal structure with a tiny glomerular degeneration and less dilated tubules (Fig. 3c).

The section of cardiac muscle from C group shows striated, parallel muscle fibers giving the appearance of a sheet. The cardiac myocytes had normal cytoplasm with centrally located oval nuclei (Fig. 3d). The HT group shows cardiomyocyte disorder with hypertrophied cardiac cells, accompanied by nuclear peripheralization and pyknosis. In addition, marked congestion and dilation of myocardial blood vessels were displayed (Fig. 3e). The HT-OC group showed marked improvement in myocardial structural disorder evidenced by the absence of pycnotic nuclei and blood vessel congestion compared with the HT group (Fig. 3f).

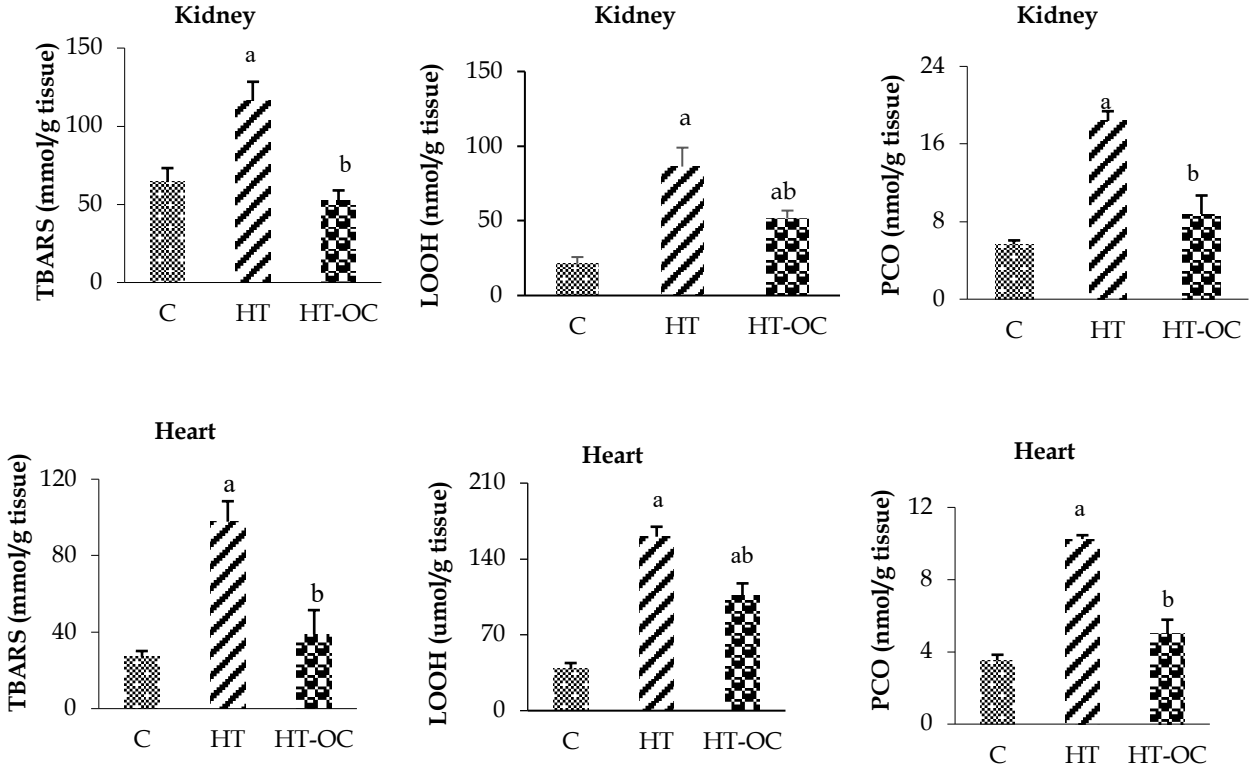

Figure 2. Effect of olive cake on TBARS, LOOH and PCO levels in heart and kidney tissues

C: Control group; HT: untreated hypertensive group; HT-GO: hypertensive rats treated with olive cake (7.5%). Results are expressed as mean ± SD. Data among groups were analyzed by two-way ANOVA followed by post-hoc test. P values: [a]<0.05 when compared with control group; [b]<0.05 when compared with HT group.

LOOH: Lipid hydroperoxides; PCO: Protein carbonyl; TBARS: Thiobarbituric acid reactive substances.

Table 2. Effect of olive cake on SOD, CAT, GSH-Px activities and GSH level in tissues.

Parameters	C	HT	HT-OC
Heart			
SOD (U/mg prot)	19.35 ± 3.02	8.62 ± 0.46[a]	14.59 ± 0.74[ab]
CAT (µM/min/g prot)	44.38 ± 1.30	19.02 ± 0.48[a]	33.52 ± 2.91[b]
GSH-Px (U/min/mg prot)	4.74 ± 0.34	1.41 ± 0.17[a]	5.77 ± 0.11[b]
GSH (nM/mg prot)	12.32 ± 0.58	6.93 ± 0.39[a]	11.78 ± 1.67
Kidney			
SOD (U/mg prot)	18.37 ± 2.12	9.85 ± 0.56[a]	16.04 ± 0.66[b]
CAT (µM/min/g prot)	43.05 ± 4.60	1.45 ± 0.01[a]	39.57 ± 1.40[b]
GSH-Px (U/min/mg prot)	8.70 ± 0.38	4.53 ± 0.21[a]	6.99 ± 0.60
GSH (nM/mg prot)	22.95 ± 1.10	14.78 ± 1.09[a]	19.28 ± 0.78

C: Control group; HT: untreated hypertensive group; HT-GO: hypertensive rats treated with olive cake (7.5%). Results are expressed as mean ± SD. Data among groups were analyzed by two-way ANOVA followed by Tukey post-hoc test. [a]P<0.05 when compared with control group; [b]P<0.05 when compared with HT group.

CAT: Catalase; GSH: Reduced glutathione; GSH-Px: Glutathione peroxidase; SOD: Superoxide dismutase.

3. DISCUSSION

In this investigation, the effect of olive cake on kidney and heart function markers as well as its influence on the redox status and damage of these tissues; were reported in dexamethasone-induced hypertensive rats.

In the present study, the induction of hypertension with dexamethasone (Dex) produced a significant elevation in systolic blood pressure (SBP) that was associated with a significant decrease in serum NO metabolites. Other studies have also shown a decrease in serum NO level, NOS activity and NOS protein expression in Dex-induced hypertensive rats [17]. Our results indicated that treatment with OC reduced SBP and increased NO value in hypertensive rats. These finding are in agreement with previous study that showed an increase in NO contents in hypertensive rats fed with pomace olive oil [43]. Suggesting; that olive cake may reduce blood pressure through an antioxidant and vasodilatory effect.

Chronic exposure to high blood pressure (BP) leads to damage of target organs, such as heart, kidney, and brain [44]. In the present study, the relative weights of kidney and heart were significantly increased in Dex-induced hypertensive rats compared with the control group. Similar results have been reported in other hypertension models [45]. In our study, the cardiac hypertrophy in Dex-induced hypertensive rats is thought to be compensatory to the chronic increase in BP, and that treatment of these HT rats with OC reduced renal and cardiac mass. In the present study, Dex-induced hypertensive rats exhibited significant increases in serum urea, creatinine, and uric acid, suggesting renal dysfunction and tubular injury. These findings were further corroborated by histological alterations observed in the kidney tissue of Dex-induced hypertensive rat. The histopathological observations of the kidney in HT rats mainly involved glomerular necrosis, renal tubular distortion, and increased Bowman space. Similar histological changes were also reported by other researchers in dexamethasone-induced oxidative stressed rats [15]. Interestingly, treatment

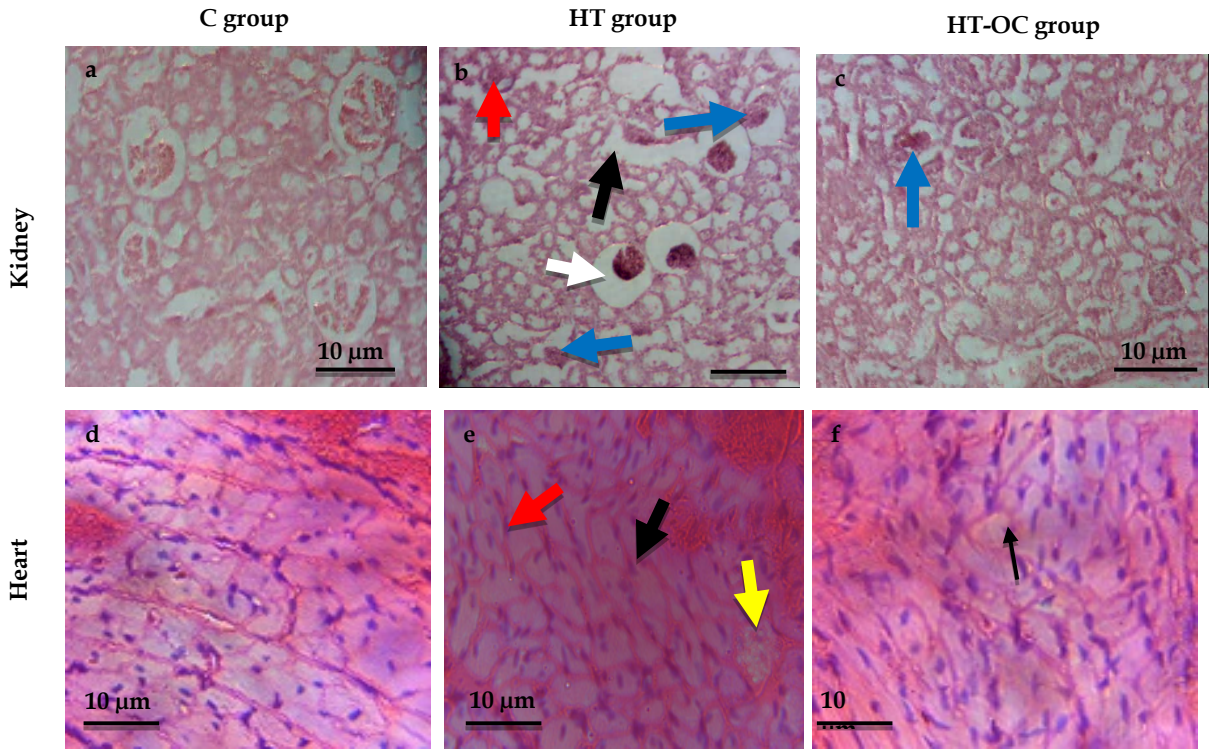

Figure 3. Representative photomicrographs showing the effect of olive cake on renal and cardiac histology.

C: Control group; HT: untreated hypertensive group; HT-GO: hypertensive rats treated with olive cake (7.5%). Sections were stained with H&E (Scale bar =10 µm). The kidney was observed at 100x, while the heart was pictured at 400x.

C group showing the normal renal architecture; HT group showing infiltration of inflammatory cells (red arrow), glomerular necrosis (blue arrow), large Bowman's space (white arrow) and tubules distortion (black arrow); HT-OC group showing normal renal architecture with less glomerular necrosis. In the section of cardiac muscle, C group showing normal cardiac muscle fibers; HT group showing hypertrophied of cardiac cells (red arrow), Pyknotic nuclei (black arrow) and congestion of blood vessels (Yellow arrow); HFD-OC group showing near normal cardiac architecture.

of HT rats with olive cake significantly reduced creatinine, urea and uric acid levels. Moreover, OC markedly alleviated the kidney tissue architecture, where it was able to get back the normal kidney histology, suggesting a renoprotective effect against dexamethasone-induced renal damage in hypertensive rats. These results are supported by our previous study showing that olive cake consumption normalizes renal function markers in streptozotocin-induced diabetic rats [23]. Kausar et al. [46] also reported that olive oil conferred protection against dexamethasone-induced renal toxicity in rats. The renoprotective mechanism of olive cake has not been elucidated. However, it is well known that blood pressure reduction is one of the most effective strategies for reducing hypertension-related target organ damage. In this study, it is worth noting that treatment with olive cake reduced systolic blood pressure. This suggests that the reduction in blood pressure may be involved in the renoprotective effect of olive cake in dexamethasone-induced hypertensive rats.

Lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and creatine kinase (CK) are cytosolic enzymes found in the heart and other tissues and serve as indicators of heart tissue damage [47, 48]. The release of such markers in the blood stream indicates impaired membrane permeability and cell death, as previously reported [49]. Various studies have reported elevated in serum AST, CK, and LDH activities during heart disease in hypertensive rats [50, 51]. Our results showed significant increase of AST, CK, and LDH activities in serum of dexamethasone induced hypertensive rats, which indicate cardiac damage in this model of hypertension. Our data are in agreement with those of Okon et al. [15], who reported high levels of LDH and AST in Dex-induced HT rats. In addition, histopathological analysis of cardiac tissues showed that our hypertensive rats had hypertrophied cardiac cells with nuclear peripheralization, pyknosis and congestion of myocardial blood vessels. Serum CK, LDH, and AST activities were significantly reduced after OC treatment. In the histopathological results, the heart tissues in the HT-OC group were healthier than those in the HT group. This means that olive cake can protect the heart from damage in dexamethasone-induced hypertensive rats. Olive cake is an excellent source of compounds with antioxidant properties such as hydroxyltyrosol, oleurapein and others that can act synergistically to neutralize free radicals, thereby reducing myocardial damage, maintaining the integrity of the myocardial membrane then improving cardiac function. Nekooeian et al. [52] reported that oleuropein offered a cardioprotective effect in rats with concurrent type 2 diabetes and renal hypertension and Nasopoulou and Zabetakis [53] also observed the same effect with polar lipids of olive cake. In this work we suggest that the ability of olive cake to protect the heart against hypertension-induced damage may be due to these different constituents.

Several studies have supported the important role of oxidative stress in the pathophysiology of hypertension and hypertension-induced target organ damage [54]. The ROS can increase kidney and heart injury in hypertensive rat [10–11]; therefore, decreasing oxidative stress may be a pivotal strategy in preventing target organ damage. Our results showed a significant increase in the end products of lipid peroxidation (TBARS, LOOH) and protein oxidation (PCO) in the kidneys and hearts of Dex-induced hypertensive rats. These results are in agreement with those of Oseni et al. [55], who reported high levels of oxidative stress markers in the plasma, liver and kidney of dexamethasone-induced HT rats. An increase in renal and cardiac oxidative stress has also been reported in other hypertension models [45] and in hypertension-associated cardiac and renal damage [9]. Treatment with OC significantly reduced the increases in TBARS, LOOH and PCO in the heart and kidney of dexamethasone-induced hypertensive rats. These results suggest that OC may counteract oxidative stress and thus reduce oxidative stress-induced cardiac and renal damage in this model of rats. This may be due to the presence of polyphenols and flavonoids in olive cake, which have been recognized as excellent free radical scavengers.

Antioxidant enzymes such as SOD, CAT, GSH-Px and non-enzymatic like GSH play an important role in protection against oxidative damage [56]. In the present study, SOD, CAT and GSH-Px activities, as well as GSH content, were decreased in the heart and kidney of dexamethasone-induced hypertensive rats. This result is consistent with other studies that have shown decreased tissue antioxidant activity in dexamethasone-induced HT rats [57]. Decreased activity of enzymatic antioxidants might be due to its inactivation by free radicals [58]. On the other hand, ROS may down-regulate the expression of genes such as the Keap/Nrf2/ ARE pathway involved in antioxidant synthesis and thus reduce antioxidant activity [59]. In the present investigation, treatment with OC significantly increased the activity of all the antioxidant enzymes (SOD, CAT and GPx) and GSH levels in the kidney and heart of dexamethasone-induced hypertensive rats. These results are in agreement with our previous studies where we found that olive cake reduces lipid peroxidation and increases antioxidant enzyme activity in several organs of diabetic rats [23]. This suggests that olive cake may protect the kidneys and heart from oxidative damage by decreasing free radical production and improving antioxidant status.

4. CONCLUSION

In dexamethasone-induced hypertensive rats, olive cake treatment reduced systolic blood pressure, oxidative stress markers, and cardiac and renal damage. In addition, olive cake improves renal and cardiac enzymatic and non-enzymatic defense systems and increased serum NO level. The histopathological examination of kidney sections from the Dex-induced hypertensive rat revealed glomerular necrosis, renal tubular distortion, and increased Bowman space. Additionally, the histopathological examination of the heart sections from the Dex-induced hypertensive rat showed hypertrophied cardiac cells with nuclear peripheralization, pyknosis and congestion of myocardial blood vessels. The structural changes seen in histological sections of heart and kidney in dexa induced hypertensive rat were markedly reduced by OC treatment. The protective effect of olive cake against kidney and heart damage could be mediated by its antioxidant properties and its ability to reduce blood pressure. Further research is still needed to elucidate the mechanisms of the antioxidant and antihypertensive effects of olive cake.

5. MATERIALS AND METHODS

5.1. Collection and preparation of olive cake

The olive cake (OC) was collected immediately after extraction of the oil in an oil mill located in Sig (Mascara, Algeria) in 2019, taken to the laboratory and dried in the dark. The dried OC was crushed to obtain a homogeneous powder and stored in airtight containers at room temperature until its use as an ingredient for the preparation of the experimental diets.

5.2. Animals

The general guidelines on the use of living animals in scientific investigations by Council of European Communities (1987) [32] were followed, and the protocol and use of rats were approved by our institutional committee on animal care and use.
Male Wistar rats (n=18), weighing 245 ± 5 g, were obtained from the animal house of the Laboratory of Clinical and Metabolic Nutrition (University Oran 1). The rats were housed in wire bottom cages and were maintained under standard laboratory conditions with a natural luminosity cycle. Tap water and standard food pellets were given ad libitum.

5.3. Induction of hypertension

Rats were divided into two groups, one (n=12) treated by intraperitoneal (i.p.) administration of dexamethasone (30 μg/kg of body weight (BW) /day) to induce hypertension and control (C) group (n=6) received NaCl at 0.9% (1 ml/kg BW/day, i.p.), for 14 days. Then, systolic blood pressure (SBP) was recorded in conscious rats using the CODA™ non-invasive blood pressure system (Kent Scientific Corporation, USA) [33]. Rats with SBP levels greater than 140 mmHg were considered hypertensive and were used in the rest of the experiment.
The dose of dexamethasone was chosen based on previous studies, which showed that this dose induces hypertension [14] and organ damage in rats [15].

5.4. Experimental design

Hypertensive (HT) rats (161.23±16.06 mmHg) were randomly divided into 2 subgroups (6 rats each) fed a standard diet concomitantly with an intraperitoneal injection of 30 ug/kg BW dexamethasone and treated (HT-OC) or not (HT) with 7.5% OC for 28 days.
Control group (C) rats continue to consume the same diet concomitantly with an intraperitoneal injection of 1 ml/kg BW of NaCl for 28 days.
During the experimental period, body weight changes of rats were recorded weekly. Systolic blood pressure of conscious rats was measured at the end of treatment using the CODA™ non-invasive blood pressure system as previously described.

At the end of the experimental period, the rats were fasted overnight and anesthetized with 3 ml/kg BW chloral hydrate (10%). Blood was drawn in dry tubes and centrifuged at 30°C, 3000 xg for 20 min and the serum was collected and stored at -40°C. The heart and kidney samples were rapidly excised, cleaned, weighed and dissected into two parts each, the first one was used for histopathological analysis and the second was homogenized (10 %, w/v) in an appropriate buffer (pH 7.4) then centrifuged at 10,000 xg for 10 min at 4°C. The supernatants were used for biochemical analyses.

5.5. Biochemical parameters

Kidney function markers including creatinine, urea and uric acid; and cardiac function marker such as aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and creatine kinase (CK) were determined using commercial kits (Biolabo, France). Serum Nitric oxide (NO) concentration were measured based on the Griess reaction [34].

5.6. Oxidative stress parameters assessments

The lipid peroxidation was evaluated by the measurement of thiobarbituric acid reactive substances (TBARS) [35] and lipid hydroperoxides (LOOH) [36]. The protein carbonyl (PCO) was determined by the method as described by Levine et al. [37].

5.7. Antioxidant enzymes assessments

Superoxide dismutase (SOD) activity was determined by the method described by Marklund and Marklund [38]. The Catalase (CAT) activity was assessed by the method of Aebi et al. [39]. Glutathione peroxidase (GSH-Px) activity was estimated by the method described by Flohe and Gunzler [40]. Reduced glutathione (GSH) level was determined by the method described by Sedlak and Lindsay [41]. Total protein level was determined by the method of Lowry *et al*. [42], using bovine serum albumin as a standard at 660 nm.

5.8. Histopathological analysis

Tissues (heart and kidney) were collected and fixed in 10% neutral buffered-formalin, dehydrated in ascending grades of alcohol and embedded in paraffin. Sections were cut at 5 mm, stained with hematoxylin and eosin (H&E). The sections were examined for pathological changes using a light microscope.

5.9. Statistical analyses

All results were expressed as the mean ± standard deviation for six rats per group. Data among groups were analyzed by two-way analysis of variances (ANOVA) followed by Tukey's honestly significant differences post-hoc test. A value of $p< 0.05$ was considered as statistically significant. All statistical analyses were performed using statistical package for the social science (SPSS) software version 25. $^{a}P<0.05$, *vs* Control (C), $^{b}P<0.05$, *vs* hypertensive (HT).

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Author contributions: Concept – SGM., BS.; Design – SGM., BS.; Supervision – BS.; Resources – SGM., BS.; Materials – SGM., BS..; Data Collection and/or Processing – SGM., BS..; Analysis and/or Interpretation – SGM.; Literature Search – SGM., BS..; Writing – SGM.; Critical Reviews – BS.

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

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