Effects of soy isoflavone on cardiac dysfunction in geripause-like rats: comparisons with hormone-replacement therapy

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Background
Cardiovascular diseases are a primary cause of morbidity and mortality worldwide. The prevalence of cardiovascular disease as well as inflammation in postmenopausal women is higher than premenopausal women.
Objective
The present study investigated cardiac dysfunction elicited by estrogen deprivation and aging and assessed a possible beneficial impact of isoflavones compared with estradiol-replacement therapy.
Materials and methods
Forty aged female rats were equally divided into four groups. Except for sham-operated animals in group 1 (negative control), all other rats were ovariectomized. One month after surgery, animals were assigned to groups 3 and 4. Rats in the former group were treated with 17β-estradiol, 100 μg/kg, intramuscular, every other day. Animals in group 4 were administered soy isoflavones (SIF), 40 mg/kg/day orally. Treatments continued for 1 month.
Results and conclusion
Compared with control rats, ovariectomized animals showed cardiac dysfunction and inflammation evidenced by dyslipidemia and elevated serum creatine phosphokinase and lactate dehydrogenase activity, angiotensin II, cardiac malondialdehyde and nitric oxide levels, and serum tumor necrosis factor-α and interleukin-6 levels. These impacts were concurrent with significant decreases in cardiac catalase activity and total antioxidant capacity. Treatment with SIF was more effective in mitigating inflammation and cardiac dysfunction compared with estradiol-replacement therapy. Histopathological examination of heart tissues supports these biochemical findings. SIF are a safe and well-tolerated alternative to estradiol for improving cardiac dysfunction elicited by menopause and age.

Keywords:
geripause, soy isoflavones, estradiol, cardiovascular disease, inflammation

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Introduction

Cardiovascular disease (CVD) is a primary cause of morbidity and mortality globally. In Egypt, CVD incidence is greater than 16% in people aged 40–64 [1]. Remarkable progress in medical care is evident, especially in gynecology, for early detection of diseases and their related causes. This progress has led to an increase in life expectancy of women. Eskin and Troen [2] newly defined postmenopausal stages as 'early' (age 65) and 'late' (age 85) geripause.

The occurrence of CVD among women is low before menopause and gradually increases after the its onset [3], reflecting the critical role of sex hormones in the development of CVD [4,5]. Hormone-replacement therapy (HRT) can ameliorate signs of estrogen deficiency, especially during menopause. Meanwhile, it leads to many adverse impacts such as cancer [6].

Several studies documented the postive correlation of circulating inflammatory markers and of CVD [7]. An elevation in circulating tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), proinflammatory markers, in apparently healthy individuals, is a strong risk of CVD [8,9]. Postmenopause and aging are factors that strongly induced an elevation in inflammatory markers, which are related to oxidative stress [10,11].

Soy isoflavones (SIF), a subclass of phytoestrogens, exist in many legumes and their products. The biological properties of SIF include antitumor [12], antimenopausal [13], anti-osteoporotic [14], antidyslipidemia [15], and anti-inflammatory activities [16]. Further, isoflavones exert a protective

effect against coronary heart diseases [17–19]. It might also be an effective treatment for cardiac dysfunction in ovariectomized rats. The aim of this research was to study the efficacy of such treatment on CVD following menopause against estradiol HRT.

Materials and methods

Chemicals

17β-estradiol (E_2) was purchased from Sedico Pharmaceutical Company (Giza, Egypt). E_2 was dissolved in olive oil to prepare for the administration dose of 100 μg/kg. SIF were purchased from Mepaco-Arab Company for Pharmaceuticals & Medicinal Plants (Cairo, Egypt). SIF was freshly suspended in 1 ml of Tween80 and distilled water for the administration of the dose of 40 mg/kg. Enzyme-linked immunosorbent assay (ELISA) rat serum estradiol kit was purchased from BioSource Co. Ltd. (California, USA). Serum activity of lactate dehydrogenase (LDH) and creatine phosphokinase (CK-MB) commercial kits were purchased from Reactivos GPL (Barcelona, Spain). Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) kits were purchased from Biodiagnostic (Cairo, Egypt). TNF-α, IL-6, and angiotensin II (ANG-II) ELISA kits were purchased from Cusabio (Germany). Total antioxidant capacity (TAC) commercial kit was purchased from Biodiagnostic.

Animals

All study protocols were approved by the Institutional Animal Ethics Committee at the National Organization for Drug Control and Research (approval no. 8/231/2019) and followed the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). Forty aged albino Wistar female rats, weighing 220–240 g, 12-month age, were obtained from the National Organization for Drug Control and Research. Animals were acclimated for two weeks at 25±2°C and 55±5% humidity under a 12-h light/dark cycle and allowed free access to a standard diet and water before starting the experiment.

Experimental design

The animals were randomly allocated four groups, 10 rats per group. Group 1 rats received sham operations and served as a negative-control group. Animals in groups 2–4 were ovariectomized under aseptic conditions. Rats in groups 1 and 2 received intramuscular injections of olive oil every other day. One month after surgery, animals in groups 3 and 4 were treated with intramuscular injections of E_2 dissolved in olive oil at a dose of 100 μg/kg, every other day [20], and SIF 40 mg/kg/day, orally [21], respectively. All treatments were continued for 1 month.

Ovariectomy was performed under aseptic conditions by removing bilateral ovaries under mild intravenous anesthesia with 60 mg/kg body weight thiopental [22]. Treatments were delayed for 1 month after surgery to allow for recovery.

Preparation of cardiac homogenate for biochemical assays

On day 31, rats were sacrificed by decapitation under mild intravenous anesthesia with 60 mg/kg body weight thiopental. Blood samples were collected from the retro-orbital vein of all rats using heparinized glass capillary tubes. Blood samples were centrifuged at 3000 rpm for 20 min. Hearts were immediately removed and washed in ice-cold saline. Six hearts per group were homogenized in 0.05 M ice-cold phosphate buffer (pH 7.4). Homogenates were centrifuged at 3500 rpm for 20 min at 4°C, and the supernatant was used for measurement of biochemical parameters.

Determination of serum biochemical parameters

Each of rat serum estradiol, TNF-α, IL-6, and ANG-II were evaluated according to the manufacturer's instructions of ELISA kits. Serum activity of LDH and CK-MB was assayed according to the manufacturer's instructions of kinetic assay kits. Serum TC, HDL-C, and TG were assessed according to the manufacturer's instructions of colorimetric kits. Low-density lipoprotein cholesterol (LDL-C) was calculated as LDL-C=TC-HDL-C-TG/5 [23]. Atherogenic indexes (AI) I and II were calculated as TC/HDL-C and LDL-C/HDL-C ratios, respectively [24].

Determination of antioxidant/oxidant parameters in cardiac tissues

Cardiac tissue homogenates were analyzed for several antioxidant/oxidant parameters. Catalase activity was measured spectrophotometrically by decreasing H_2O_2 concentration. Catalase-activity values were reported as U/mg protein [25]. Malondialdehyde (MDA) level was analyzed at 535 nm by thiobarbituric acid-reactive substance estimation using standard method [26], and values were expressed as nmol MDA produced/g of tissue. Total nitrite and nitrates (NO_x) were analyzed by a total reduction of nitrate

to nitrite, under acidic condition, nitrite reacts with sulfanilamide to produce a diazonium ion, which is then coupled to N-(1-naphthyl) ethylenediamine (NED) to produce a chromophore azo product, which strongly absorbs at 545 nm. Total NO_x is reported as μmol/g tissue [27]. The TAC was estimated using commercial colorimetric kits based on an enzymatic reaction that involves the conversion of 3,5,-dichloro-2-hydroxy benzensulfonate to a colored product by the residual H_2O_2 liberated from the sample, which strongly absorbs at 505 nm, the values were expressed as mmol/g tissue. The total protein level was determined in cardiac homogenates [28]. All assays were analyzed with a double-beam spectrophotometer (Unicam Helios Alpha, Postdam, Germany).

Histopathological study

After scarification, the remaining four hearts in each group were quickly dissected, cleaned with cold saline, and fixed in 10% neutral buffered formalin. Fixed tissues were dehydrated in a series of 50–100% ethanol solutions and embedded in paraffin. Serial 5-μm sections were cut and stained with hematoxylin–eosin [29].

Statistical analysis

Data are presented as means±SD. Statistical significance was assessed using one-way analysis of variance followed by Tukey's multiple-comparison test [30]. *P* value less than 0.05 was considered the threshold of significance. Data analyses utilized GraphPad Prism7 (GraphPad Software, San Diego, California, USA).

Results

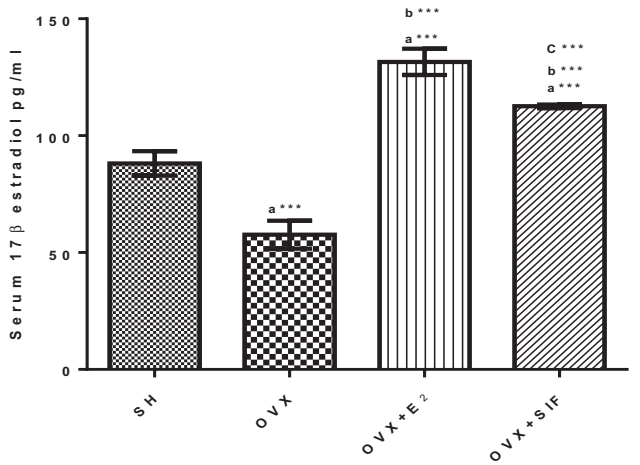
Effect of ovariectomy and treatment on serum estradiol

Ovariectomized rats showed a significant decline in serum estradiol levels (57.63±5.93, −35%) compared with SH group (88.14±5.18), *P* value less than 0.05 (Fig. 1). Groups 3 and 4 caused a significant rescue of serum E_2 levels (131.60±5.60, 128% and 112.60±0.74, 95%, respectively) compared with ovariectomized rats (57.63±5.93), *P* value less than 0.05.

Effect of ovariectomy and treatment on serum creatine phosphokinase and lactate dehydrogenase activity

A significant increase in serum CK-MB (186.5±13.82, 1581%) and LDH (2146±5.93, 888%) activities was found in ovariectomized rat animals, *P* value less than 0.05 (Fig. 2), compared with serum CK-MB and LDH in SH group (11.09±1.927 and 217.2±6.343, respectively). Administration of estradiol and SIF

Figure 1



Significant effects of ovariectomy (OVX), estradiol (OVX+E_2), and soy isoflavones (OVX+SIF) on serum estradiol level. The data are presented as the mean±SD, *n*=6. [a]Significant difference versus the sham (SH) group; [b]significant difference versus the ovariectomized (OVX) group; [c]significant difference versus estradiol treatment. **P* value less than 0.05, ***P* value less than 0.01, and****P* value less than 0.001. Analysis of variance followed by Tukey's correction for multiple comparisons.

induced a significant decline in serum CK-MB (78.62±4.86, −58% and 55.29±6.99, −70%, respectively) and serum LDH (870.80±15.92, −59% and 30.8±19.14, −80%, respectively), compared with ovariectomized animals, *P* value less than 0.05.

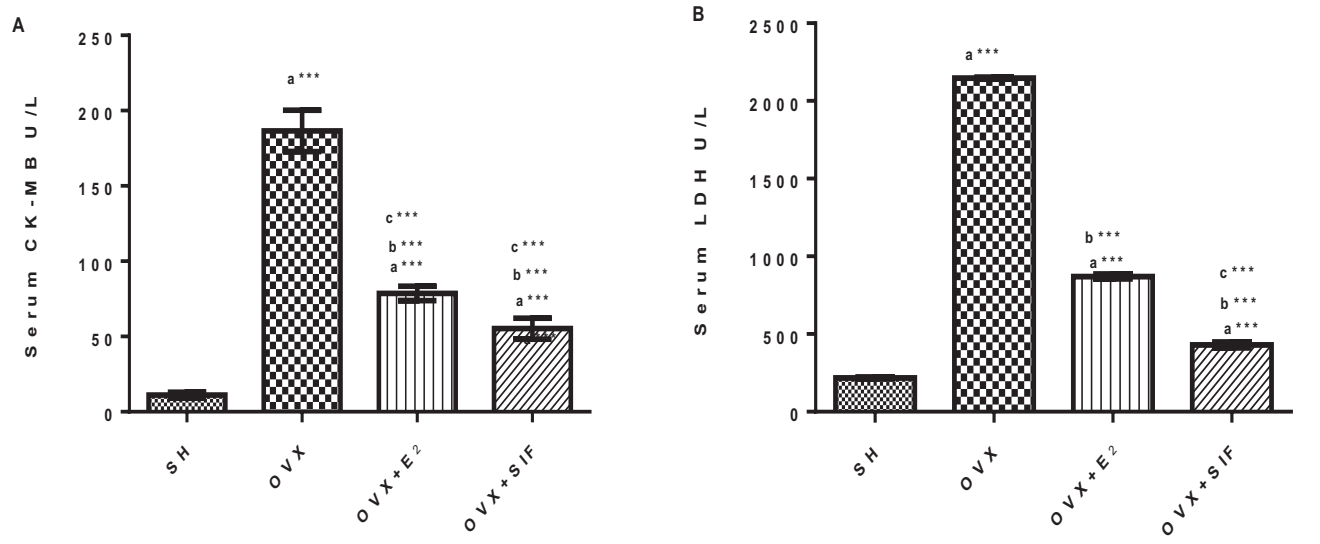
Effect of ovariectomy and different treatments on serum lipid profile

Ovariectomy induced dyslipidemia, evidenced by a significant increase in serum TC (165±26.02, 46.93%), TG (229.8±11.92, 46.74%), and LDL-C (85.18±7.33, 104.66%) and significant depletion of HDL-C (20.29±5.16, −58%), compared with SH group (112.30±7.94, 156.60±4.52, 41.62±10.45, and 48.75±8.64, respectively). SIF induced a significant depletion in serum TC (117.9±4.922, −28.55%), TG (86.63±9.19, −62.30%), and LDL-C (46.47±7.42, −45.44%), along with a significant increase in serum HDL-C (53.8±2.99, 165%). In addition, estradiol treatment exhibits a significant increase in serum TC (191.2±23.52, 15.88%), LDL-C (119.5±15.47, 40.29%), and HDL-C (31.63±7.812, 56%), with a significant depletion in serum TG (187.7±8.29, −18.32%). SIF treatment was superior to estradiol as indicated by re-establishment of normal lipid profiles (Fig. 3).

Effects of ovariectomy and treatment on atherogenic indices

Ovariectomized rats showed a significant increase in AI-I (8.69±1.54, 265.52%) and AI-II (9.41±1.54,

Figure 2



Significant effects of ovariectomy (OVX), estradiol (OVX+E_2), and soy isoflavones (OVX+SIF) on serum cardiac markers. (a) Creatine kinase (CK-MB) and (b) lactate dehydrogenase (LDH) activities. The data are presented as the mean±SD, n=6. [a]Significant difference versus the sham (SH) group; [b]significant difference versus the ovariectomized (OVX) group; [c]significant difference versus estradiol treatment. **P* value less than 0.05, ***P* value less than 0.01, and*** *P* value less than 0.001. Analysis of variance followed by Tukey's correction for multiple comparisons.

360%), compared with SH group (2.38±0.52 and 2.05 ±0.44, respectively). Treatment with SIF induced a significant decrease in AI-I (2.20±0.12, −74.75%) and AI-II (2.66±0.20, −72%). In addition, treatment with estradiol exhibited a similar approach as SIF with a lesser effect as it induced a significant depletion in AI-I (5.873±1.508, −32.43%) and AI-II (6.40±1.37, −32%), compared with OVX group (Fig. 4).

Effects of ovariectomy and treatment on antioxidant/ oxidative parameters

Significant increases in the levels of MDA (150.9 ±21.0, 101%) and total NO_x (239.8±7.9, 76%), along with significant depletion in catalase activity (0.05 ±0.02, −77%) and TAC level (7.28±1.12, −34%) in cardiac tissues of ovariectomized rats were observed, compared with SH group (74.9±5.8, 136.0±10.6, 0.21 ±0.07, and 11.1±2.32, respectively). Treatments with SIF and estradiol induced a significant depletion in MDA level (51.1±6.1, −66% and 76.8±11.6, −49%, respectively), total NO_x (131.7±8.4, −45% and 134.0 ±21.9, −44%, respectively), where they induced a significant increase in catalase activity (0.216±0.04, 341%, and 0.182±0.04, 271%, respectively), compared with OVX group. Collectively, SIF treatment was as effective as estradiol-replacement therapy for renormalizing oxidant/antioxidant balance (Table 1).

The data are presented as the mean±SD, n=10. (a) Significant difference versus the sham (SH) group; (b) significant difference versus the ovariectomized (OVX) group; (c) significant difference versus estradiol treatment. *P* value less than 0.05, *P* value less than 0.01, and *P* value less than 0.001. Analysis of variance followed by Tukey's correction for multiple comparisons.

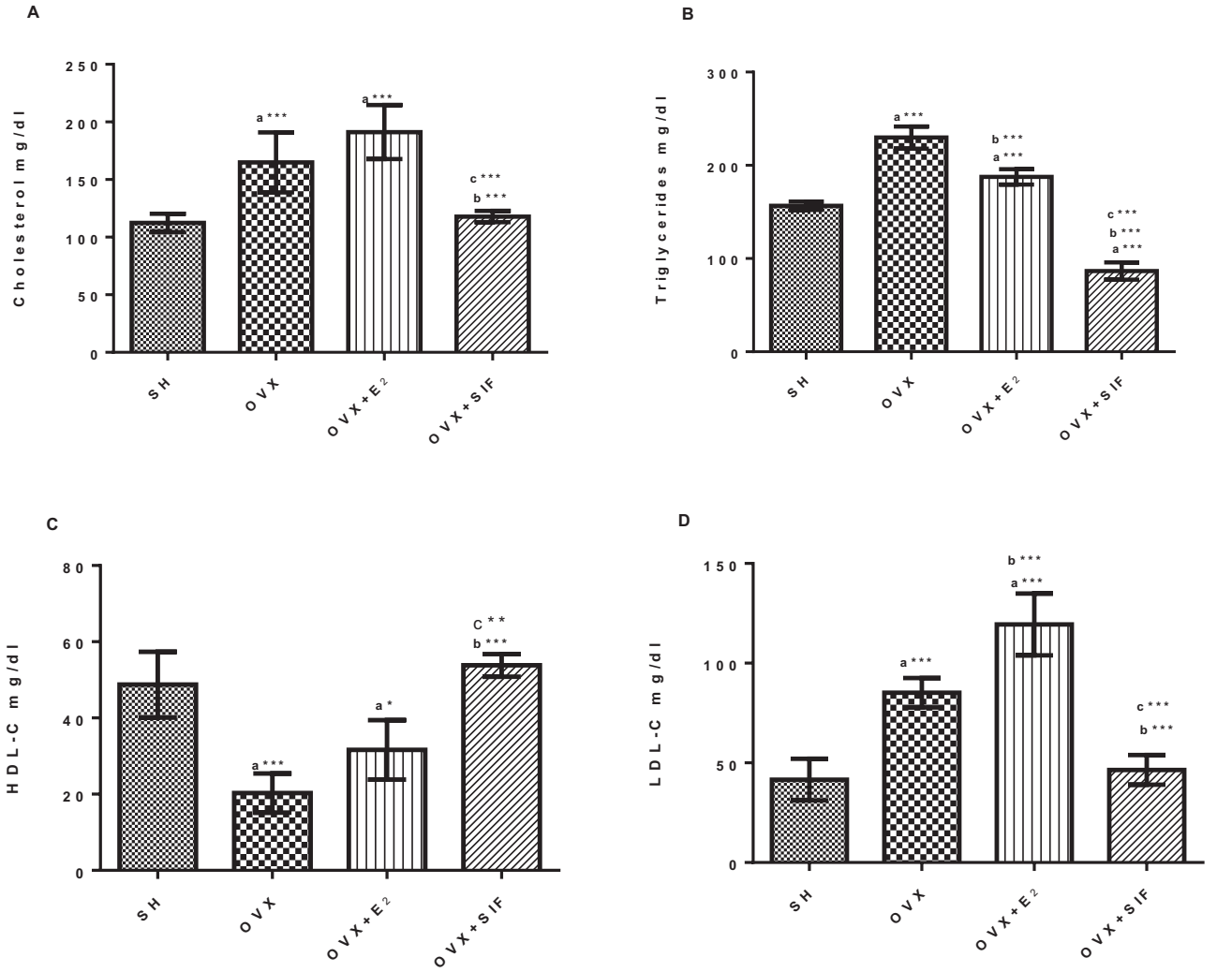
Effects of ovariectomy and treatment on serum tumor necrosis factor-α, interleukin-6 and angiotensin II

Ovariectomy induced significant inflammation in OVX rats (Fig. 5). Significant increases in serum TNF-α (91.71±8.13, 316.3%), IL-6 (80.7±7.73, 339.5%), and ANG-II (64.91±7.59, 641.8%) levels were observed following ovariectomy compared with SH group (22.03±2.41, 18.4±2.15, and 8.75±0.92, respectively). Both treatments of SIF and estradiol induced a significant depletion in serum levels of TNF-α (29.19±1.73, −68.17% and 38.77±2.1, −57.73%, respectively), IL-6 (26.15±1.773, −67.61% and 36.09±2.077, −55.30%, respectively), and ANG-II (14.88±0.895, −77.08% and 20.72±2.304, −68.08%, respectively), compared with OVX group. From the recorded result, treatment with SIF was more effective than estradiol for normalizing these serum parameters.

Histopathological investigation

No histopathological alterations were found in control animals (group 1) and normal histological structure of the myocardium was noted (Fig. 6a). Heart tissues from ovariectomized rats showed degeneration of the myocardium with congestion in the blood vessels and focal hemorrhage between myocardial bundles (Fig. 6b). SIF-treated and E_2-treated rats displayed

Figure 3



Significant effects of ovariectomy (OVX), estradiol (OVX+E_2), and soy isoflavones (OVX+SIF) on serum lipid profile. (a) Total cholesterol (TC) and (b) triglycerides (TG), (c) high-density lipoprotein cholesterol (HDL-C), (d) low-density lipoprotein (LDL-C) levels. The data are presented as the mean±SD, n=6. [a]Significant difference versus the sham (SH) group; [b]significant difference versus the ovariectomized (OVX) group; [c]significant difference versus estradiol treatment. *P value less than 0.05, **P value less than 0.01, and***P value less than 0.001. Analysis of variance followed by Tukey's correction for multiple comparisons.

no-to-mild histopathological changes in myocardial tissues (Fig. 6c and d).

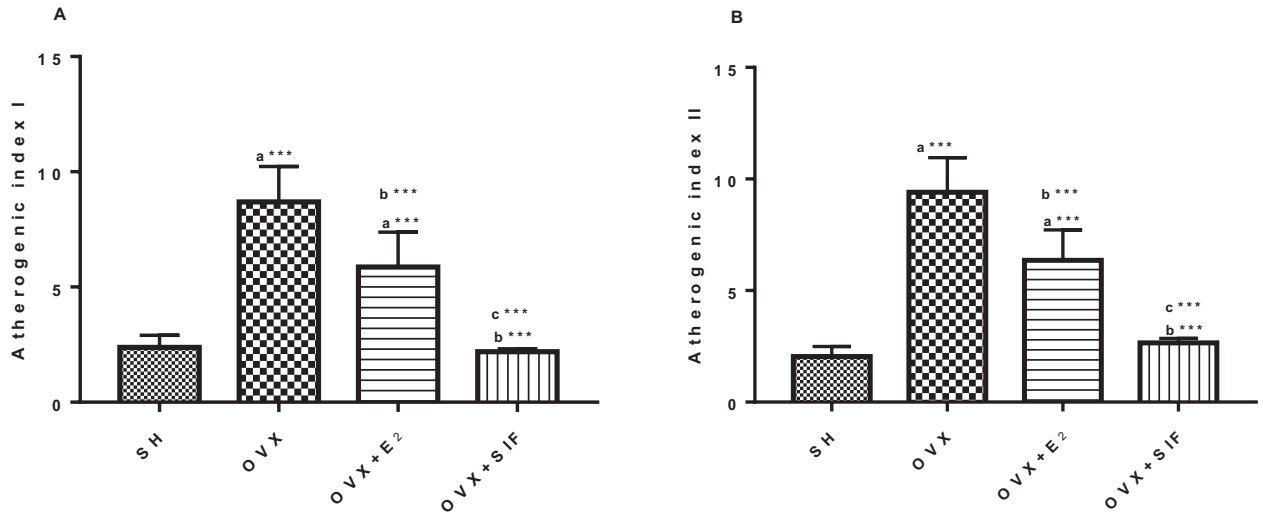
Discussion

Treatment of postmenopausal women with HRT causes several adverse impacts, such as endometriosis, breast cancer, and stroke [31,32]. SIF is a promising alternative treatment to improve cardiac dysfunction resulting from menopause and aging.

Twelve-month-old female rats were ovariectomized to induce geripause-like status and cardiac dysfunction [33]. In line with the current results, previous researches documented a significant depletion of serum estradiol following 1 month of ovariectomy [6,34]. Ovariectomy produces cardiac dysfunction, evidenced by increases in serum LDH and CK-MP activity, oxidative insult in cardiac tissues assessed by increased MDA and nitric oxide (NO) levels, and concomitant depletion in catalase activity and TAC levels. Also, significant increases in serum TNF-α and IL-6 concentrations and decreased serum estradiol levels were observed.

Plasma AIs are indicators of risk for cardiac dysfunction associated with dyslipidemia [24]. Dyslipidemia concurrent with elevated AI-I and AI-II was found in ovariectomized rats (Figs 3 and 4). Depletion in serum estradiol after menopause or ovariectomy may downregulate genes and enzymes involved in lipolysis and fatty acid metabolism and thus elicit dyslipidemia [35,36].

Figure 4



Significant effects of ovariectomy (OVX), estradiol (OVX+E_2), and soy isoflavones (OVX+SIF) on atherogenic indices. (a): Atherogenic index I, (b) atherogenic index II. The data are presented as the mean±SD, n=6. [a]Significant difference versus the sham (SH) group; [b]significant difference versus the ovariectomized (OVX) group; [c]significant difference versus estradiol treatment. *P value less than 0.05, **P value less than 0.01, and***P value less than 0.001. Analysis of variance followed by Tukey's correction for multiple comparisons.

Table 1 Effect of ovariectomy, estradiol (ovariectomy+estradiol), and soy isoflavones (ovariectomy+soy isoflavones) on cardiac malondialdehyde, nitric oxide, catalyze, and total antioxidant capacity

	MDA (μmol/g tissue)	Total NOx (μmol/g tissue)	CAT (U/mg protein)	TAC (mmol/g tissue)
SH	74.9±5.81	136.0±10.6	0.213±0.07	11.11±2.32
OVX	$150.9\pm21.0^{a*,**}$	$239.8\pm7.9^{a***}$	$0.049\pm0.02^{a***}$	$7.281\pm1.12^{a**}$
OVX+E_2	$76.8\pm11.6^{b**}$	$134.0\pm21.9^{b***}$	$0.182\pm0.04^{b**}$	$10.21\pm1.16^{b*}$
OVX+SIF	$51.1\pm6.1^{a*b***c*}$	$131.7\pm8.4^{b***}$	$0.216\pm0.04^{b***}$	$13.21\pm1.11^{b***\ c*}$

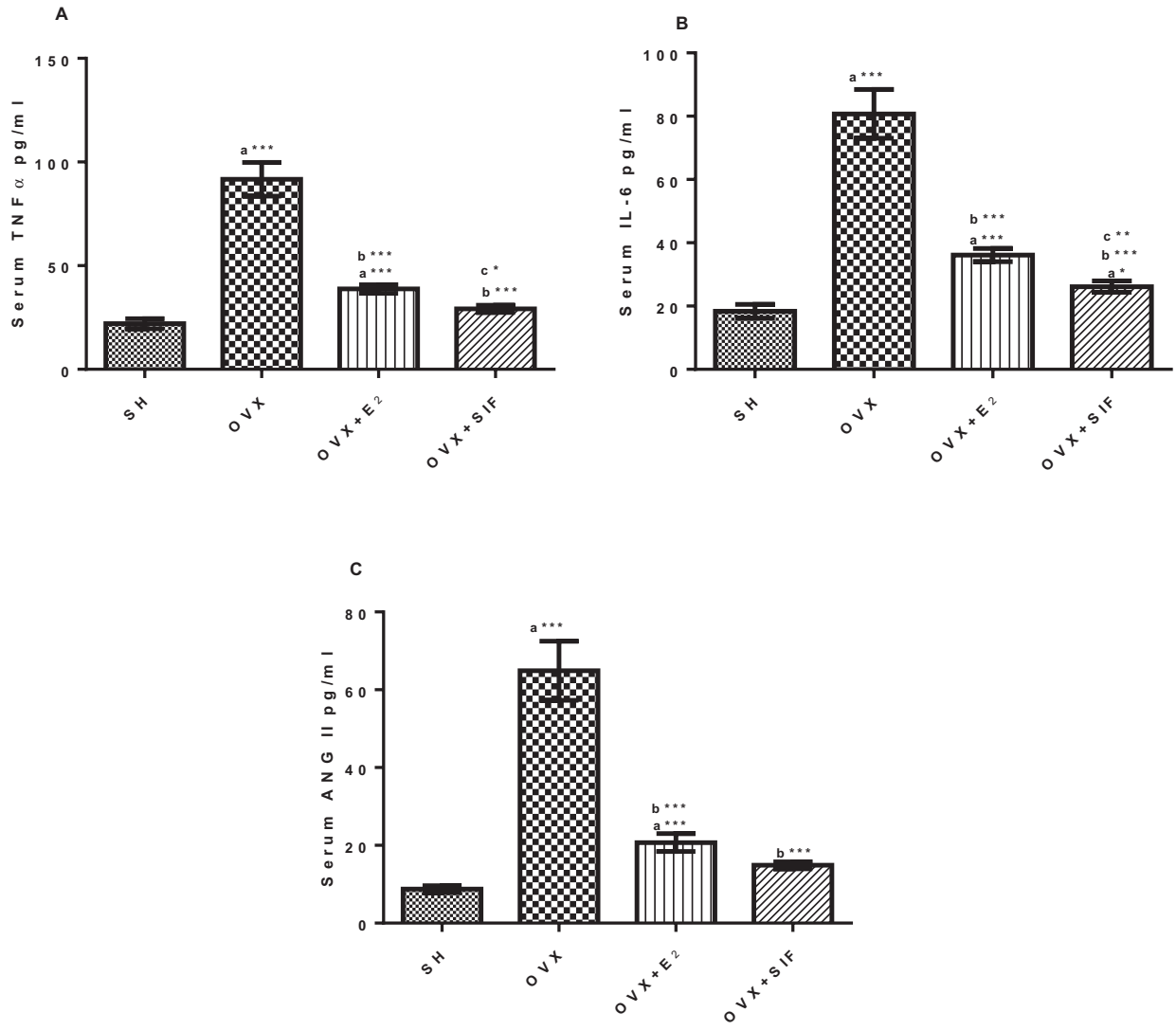
E_2, estradiol; MDA, malondialdehyde; OVX, ovariectomy; SIF, soy isoflavones; TAC, total antioxidant capacity. The data are presented as the mean ± SD, n=6. [a]Significant difference versus the sham (SH) group; [b]Significant difference versus the ovariectomized (OVX) group and [c]Significant difference versus estradiol treatment. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$. ANOVA followed by Tukey's correction for multiple comparisons.

The dose of SIF orally administered in the current study was within the range of daily intake of isoflavones for Asian populations (25–50 mg/day) [21]. Treatment with SIF renormalized the levels of serum estradiol, consistent with several researches [37,38]. Additional studies are needed to assess the mode of action for increased serum estradiol levels caused by SIF.

Ovariectomized animals treated with SIF showed renormalized lipid profiles and AIs. SIF may induce hypolipidemic effects in at least three ways. First, SIF may cause a reduction in ghrelin levels. This potent growth hormone promotes white adipose tissue lipogenesis via a hypothalamic-mediated mechanism. Second, SIF might induce an increase in bile acid degradation, which decreases intestinal absorption of cholesterol. Third, SIF may activate AMPK, which enhances fatty acid oxidation in the liver and adipocytes [39–41].

Ovariectomized rats showed oxidative insult, evidenced by a significant rise in cardiac MDA and total NO_x, concurrent with significant depletion in cardiac catalase activity and antioxidant capacity. Previous studies report dyslipidemia associated with increased free-radical production. This excess free-radical formation results in lipid peroxidation and generation of MDA. Free radicals also lead to decreasing antioxidant enzyme activity (e.g. catalase) and TAC [42–46]. NO is a free radical derived from the oxidative deamination of L-arginine nitric oxide synthase (NOS) with the reducing cofactor, tetrahydrobiopterin (BH_4). Total cardiac nitrate (NO_x) levels in ovariectomized rats could be attributed to depletion of estrogen after gonadectomy. Such depletion upregulates NOS and increases the production of NO_x [47,48]. Conversely, BH_4 is vulnerable to oxidation by ROS through activation of NADP(H) (NOX4). NOX4 upregulation promotes conversion of molecular oxygen to superoxide ions. Increased superoxide results in uncoupling of endothelial NOS (eNOS) and increased production of $ONOO^-$, along with NO production that causes

Figure 5



Significant effects of ovariectomy (OVX), estradiol (OVX+E_2), and soy isoflavones (OVX+SIF) on (a) tumor necrosis factor alpha (TNF-α); (b) interleukin-6 (IL-6); (c) angiotensin II (ANG-II). The data are presented as the mean±SD, *n*=6. [a]Significant difference versus the sham (SH) group; [b]significant difference versus the ovariectomized (OVX) group; [c]significant difference versus estradiol treatment. **P* value less than 0.05, ***P* value less than 0.01, and****P* value less than 0.001. Analysis of variance followed by Tukey's correction for multiple comparisons.

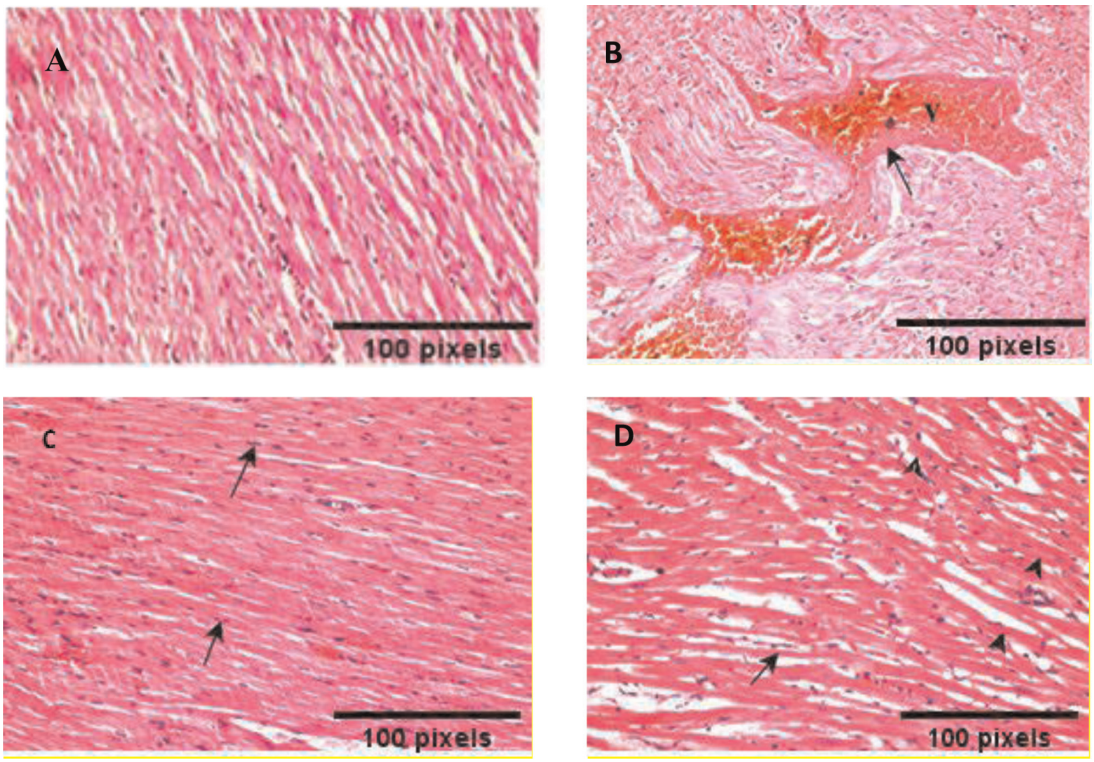
endothelial dysfunction [49]. The present study reflects an inflammatory process ovariectomized rats, shown by increases in serum inflammatory markers, TNF-α and IL-6. Inflammation may stimulate inducible NOS (iNOS) for NO metabolite production [50,51].ANG-II is a potent vasoconstrictor in vascular smooth muscle cells. AI-I acts through the liberation of ROS via NOX4. Again, excess ROS may lead to uncoupling of NOS and endothelial dysfunction [52]. Ovariectomized rats in the present study show a significant increase in ANG-II level, consistent with the findings of Jennings *et al.* [53,54].

Elevation of serum CK-MP and LDH enzymes in ovariectomized animals might be attributed to an increase in ROS in cardiac tissues following tissue injury, an increase in cell permeability, or membrane rupture. Such damage allows release of intracellular constituents into the blood [55,56]. Ovariectomy thus induces a series of oxidative insults that induce CVD-like responses and inflammation.

SIF and estradiol treatments were compared for their efficacy in attenuating biochemical changes characteristic of CVD. Several studies document the beneficial effects of 17β estradiol treatment for mitigating oxidative stress. The authors attribute this action to downregulation of NOX4, and increased SOD and catalase activity [57,58].

Treatment of ovariectomized rats with SIF in the present study mitigated oxidative insult and

Figure 6



(a) Normal histological structure of myocardium of the control group. (b) Cardiac tissue from ovariectomized rat dilated with congested blood vessel (v) with a thick hyalinized wall (arrow) (hematoxylin–eosin) (×200). (c) Cardiac tissue from ovariectomized rats treated with estradiol showing intact cardiomyocytes (arrow) (hematoxylin–eosin) (×200). (d) Cardiac tissue from ovariectomized rats treated with SIF, intact cardiomyocytes (arrow), cardiomyofibers, and hyalinized cardiomyofibers (arrow head) (hematoxylin–eosin) (×200). (hematoxylin–eosin) (×200).

protected the heart from OVX-induced damage. SIF was superior to estradiol in modulating serum ANG-II levels. These findings may reflect the superior antioxidant properties of SIF. SIF is a complex mixture of antioxidant compounds, such as α-tocopherol, glycosides and derivatives, and phenolic acids. The latter chemical group includes syringic, vanillic, caffeic, ferulic, p-coumaric, and p-hydroxybenzoic acids that are potent free-radical scavengers [59]. In addition, the antioxidant activity of SIF could be attributed to its activities as estrogen-receptor modulator in attenuating ROS production [60]. Antihyperlipidemic activity of SIF could be attributed to genistein, which is a major isoflavone component in SIF, it could decrease cholesterol synthesis by suppressing cholesterol esterification and increase LDL-receptor activity, as well as augmented sterol regulatory element-binding protein 2-regulated genes, which is a cholesterol catabolic gene [61]. The decrease of ROS production could be ascribed to antihyperlipidemic activity of SIF, that may lead to inhibition of LDL oxidation [62]. Based on previous studies and current results, the antioxidant activities of SIF may inhibit ANG-II-induced cardiovascular dysfunction [63,64]. A reduction in ROS following treatment with SIF could explain the rescue of both CK-MB and LDH enzyme levels and the attenuation of inflammation, as assessed by downregulation of IL-6 and TNF levels [57,65–67].

The above biochemical data are confirmed by histopathological findings in cardiac tissue. Histopathology induced by ovariectomy was reversed by both estradiol and SIF treatments.

Conclusion

Aged ovariectomized rats display a series of biochemical disruptions and accompanying pathohistological alterations in serum and cardiac tissues. These changes are major risk factors for cardiovascular dysfunction. SIF were used in this study as an alternative to estradiol-replacement therapy. SIF showed superior activity in mitigating oxidative insult, dyslipidemia, ANG-II, and inflammation-induced cardiovascular damage in aged ovariectomized rats.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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