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Research Paper

Effects of diphenyl diselenide on lipid profile and hepatic oxidative stress parameters in ovariectomized female rats

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Abstract

Objectives Ovarian hormone decline after menopause is linked to many pathophysiological reactions. Female rats submitted to ovariectomy are employed as a model of postmenopausal condition. This study investigated the effects of diphenyl diselenide $(PhSe)_2$ on body weight gain, intra-abdominal fat deposition, plasma lipid profile and hepatic oxidative stress in ovariectomized rats.

Methods Female adult Wistar rats were ovariectomized (OVX rats) or sham-operated and divided into four groups: (i) sham-operated, (ii) $(PhSe)_2$, (iii) OVX and (iv) OVX + $(PhSe)_2$. $(PhSe)_2$ (5 mg/kg; 5 ml/kg, p.o.) was administered once a day for 30 days to groups (ii) and (iv). After that, rats were anaesthetized for blood sample gathering and submitted to euthanasia.

Key findings $(PhSe)_2$ (5 mg/kg) was effective in preventing the rise in body weight gain and intra-abdominal fat deposition induced in OVX rats. Although $(PhSe)_2$ was not effective in avoiding the increase in plasma total cholesterol and non-HDL levels induced in OVX rats, $(PhSe)_2$ reduced plasma triglycerides and augmented HDL levels in OVX rats. $(PhSe)_2$ also increased hepatic ascorbic acid levels, reduced glutathione content, glutathione S-transferase activity and restored catalase activity in liver of OVX rats.

Conclusions These findings suggest that $(PhSe)_2$ could be a promising alternative to minimize menopause related symptoms.

Keywords cholesterol; menopause; ovariectomy; oxidative stress; selenium

Introduction

Ovarian hormone decline after menopause is linked to many pathophysiological reactions. Dyslipidaemia is often seen in postmenopausal women and is characterized by an overall shift toward a more atherogenic lipid profile: an increase in plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL) and triglycerides, and a decrease in high-density lipoprotein cholesterol (HDL) levels.[1] The incidence of atherosclerosis in women is lower than in men of the same age group, but its incidence increases after menopause due to decreased oestrogen level, since oestrogens are involved in cholesterol metabolism by lowering LDL and increasing HDL concentrations in plasma.[2] In addition, after menopause, women gain weight and develop abdominal obesity.[1] Oestrogen has long been recognized as a major factor in regulating adipose tissue development and fat deposition in females.[3]

A clear relationship has been reported between oestrogen and malondialdehyde (MDA) levels in ovariectomized rats and that ovariectomy leads to an increase in free radical production.[4] It is well known that oestrogens, acting as free radical scavengers, break the free radical chain formation produced from membrane oxidation processes and hence inhibit lipid and protein oxidation.[5] The ovarian hormone deficiency also increases the generation of reactive oxygen species (ROS), which could result in cell damage or death. In mammalian cells, ROS are normally scavenged by three major types of primary antioxidant enzymes: copper-dependent, zinc-dependent and manganese-dependent superoxide dismutase, catalase (CAT) and glutathione peroxidase (GPx).[4] In this way, it has been shown that increased

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selenium intake induces increased GPx activity and decreased concentrations of lipid parameters, such as TC, LDL and triglycerides in blood of rabbits.[6]

Selenium is an essential trace element for normal growth and development of the mammalian species.[7] The interest in organoselenium pharmacology has increased in the last decades due to a variety of organoselenium compounds that possess biological activity. Accordingly, a number of novel pharmaceutical agents that are selenium-based or that target specific aspects of selenium metabolism are under development.[8] Diphenyl diselenide $(PhSe)_2$, an organoselenium compound, has been reported to be a good candidate for a pharmacological agent[8,9] due to its antioxidant,[10] hypoglycaemic,[11] antinociceptive,[12] anxiolytic,[13] anti-depressant-like[14,15] and hypolipidaemic activity.[16,17] It is important to point out that $(PhSe)_2$ did not display any overt sign of neurotoxicity when administered intraperitoneally, subcutaneously, orally (by gavage) and intracerebroventricularly in adult rats,[9,12,18] even when administered at high doses (500 mg/kg body weight).[19] In summary, the therapeutic potential of $(PhSe)_2$ seems to outweigh its toxic effects.[9]

Thus, considering that the use of female rats submitted to ovariectomy (bilateral removal of the ovaries) is largely employed to simulate a post-menopausal condition characterized by the absence of ovarian hormones, such as oestrogens, the novelty of this study was to investigate the effects of $(PhSe)_2$ on body weight gain, intra-abdominal fat deposition, plasma lipid profile and hepatic oxidative stress parameters in ovariectomized female rats.

Materials and Methods

Drugs

$(PhSe)_2$ was prepared and characterized in our laboratory by the method previously described by Paulmier.[20] Analysis of the ^1H NMR and ^{13}C NMR spectra showed that $(PhSe)_2$ obtained presented analytical and spectroscopic data in full agreement with its assigned structure. Yield: 96%; physical characteristics: yellow solid; ^1H NMR (200 MHz, $CDCL_3$, TMS): $\delta = 7.61–7.57$ (m, 2H), 7.25–7.21 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 132.1, 131.2, 129.4, 127.4; IR (KBr), v (cm^{-1}): 3040, 1585, 1475, 790; ^{77}Se NMR ($CDCl_3$, 76.28 MHz) $\delta = 463.1$. The chemical purity of compound (99.9%) was determined by GC/HPLC. $(PhSe)_2$ was dissolved in canola oil. All other chemicals were of analytical grade and obtained from standard commercial suppliers.

Experimental animals

Female adult Wistar rats, 200–250 g, approximately 90 days old, from our own breeding colony were used. The rats were kept on a 12-h light–dark cycle, at room temperature (22 ± 2°C), with free access to food and water. All experiments were approved by and supervised under the Committee on Care and Use of Experimental Animals Resources from the Federal University of Santa Maria, Brazil (Process number 23081.012740/2008-05) and 'The Ethic Committee for Animal and Human Experiment' according to the declaration of Helsinki 1975. All efforts were made to minimize animals' suffering and to reduce the number of animals used in the experiments.

Ovariectomy (OVX)

Rats were ovariectomized by the surgical removal of both ovaries under intraperitoneal ketamine and xylazine anaesthesia (5 : 1; 0.1 ml/100 g). Sham-operated females were only submitted to surgery without removal of the ovaries. The estrous cycle was determined by vaginal swabs during the 10 days prior to OVX, to ensure that rats were cycling normally.[21]

Treatment groups and experimental design

Female rats were assigned to one of the following groups:

Sham-operated (Control) ($n = 9$): rats non-ovariectomized received canola oil (5 ml/kg, p.o. by gavage) once a day for 30 days;

$(PhSe)_2$ ($n = 9$): rats non-ovariectomized received $(PhSe)_2$ (5 mg/kg; 5 ml/kg, p.o.)[9] once a day for 30 days;

OVX ($n = 9$): rats previously ovariectomized received canola oil (5 ml/kg, p.o.) once a day for 30 days;

OVX + $(PhSe)_2$ ($n = 9$): rats previously ovariectomized received $(PhSe)_2$ (5 mg/kg; 5 ml/kg, p.o.) once a day for 30 days.

Rats received these treatments for 30 days, beginning seven days after surgery. After that, female rats were anaesthetized for blood sample gathering and then submitted to euthanasia. The uterine atrophy was verified in all OVX female rats as an indicative of removal of both ovaries.

Body weight measurement

The body weight gain of female rats was monitored weekly during the whole course of the experiment. The body weight gain was calculated according to the following formula: final body weight–initial body weight.

Determination of intra-abdominal fat accumulation

Subsequently to blood sample collection, rats were euthanized by decapitation, and intra-abdominal fat was removed, washed in saline and weighed.

Measurement of plasma lipid values

Blood samples were collected directly from the ventricle of the heart in anaesthetized rats, using heparin as the anticoagulant, and plasma was separated by centrifugation (2400*g*) for 15 min. Plasma TC, HDL and triglycerides were determined by enzymatic colorimetric methods using commercial kits (Labtest Diagnostica, MG, Brazil). Non-HDL-cholesterol values were obtained by the difference between TC − HDL levels. Plasma lipids levels were expressed as mg/dl.

Accomplishment of liver oxidative stress parameters

After euthanasia, the liver was quickly removed and homogenized in 50 mM Tris-HCl, pH 7.4 (1/10, w/v). The homogenate was centrifuged at 2400*g* at 4°C for 15 min and a

low-speed supernatant fraction (S_1) was used for most assays, except to the determination of reduced glutathione (GSH) content.

Thiobarbituric acid reactive species

Thiobarbituric acid reactive species (TBARS), a measure of lipid peroxidation, were determined as described by Ohkawa *et al*.[22] Briefly, a sample of S1 was incubated with 0.8% thiobarbituric acid (TBA), acetic acid buffer pH 3.4 and 8.1% sodium dodecyl sulfate at 95°C for 2 h. The colour reaction was measured at 532 nm. TBARS levels were expressed as nmol MDA (malondialdehyde)/mg protein.

Non-enzymatic antioxidant defences

Ascorbic acid level

Ascorbic acid determination was performed as described by Jacques-Silva *et al*.[23] S1 was precipitated in 10 volumes of a cold 4% trichloroacetic acid solution. A portion of the sample in a final volume of 1 ml of the solution was incubated for 3 h at 38°C then 65% H_2SO_4 (v/v) was added to the medium. The reaction product was determined using colour reagent containing 4.5 mg/ml dinitrophenyl hydrazine and $CuSO_4$ (0.075 mg/ml). The colour reaction was measured spectrophotometrically at 520 nm. Ascorbic acid level was expressed as μg ascorbic acid/g tissue.

Reduced glutathione content

Reduced glutathione (GSH) content was determined fluorometrically following the method of Hissin and Hilf[24] using o-phthalaldehyde (OPA) as fluorophore. Briefly, the samples were homogenized in 0.1 M perchloric acid ($HClO_4$). Homogenates were centrifuged at 3000*g* for 10 min and the supernatants were separated for measurement of GSH. Supernatant (100 μl) was incubated with 100 μl of OPA (0.1% in methanol) and 1.8 ml of 0.1 M phosphate buffer (pH 8.0) for 15 min at room temperature in the dark. Fluorescence was measured with a fluorescence spectrophotometer at an excitation wavelength of 350 nm and an emission wavelength of 420 nm. GSH levels were expressed as nmol/g of tissue.

Antioxidant enzymatic defences

Catalase activity

CAT activity in S1 was assayed spectrophotometrically by the method of Aebi,[25] which involves monitoring the disappearance of H_2O_2 in the presence of S1 at 240 nm. A sample of S1 was added in 50 mM potassium phosphate buffer pH 7.0 and the enzymatic reaction was initiated by adding H_2O_2. One unit of enzyme was defined as the amount of enzyme required for monitoring the disappearance of H_2O_2. The enzymatic activity was expressed as Units (U)/mg protein (1 U decomposes 1 μmol H_2O_2/min at pH 7 at 25°C).

Glutathione peroxidase activity

GPx activity in S1 was assayed spectrophotometrically by the method of Wendel,[26] through the GSH/NADPH/GR system, by the dismutation of H_2O_2 at 340 nm. S1 was added in GSH/NADPH/GR system and the enzymatic reaction was initiated by adding H_2O_2. In this assay, the enzyme activity is indirectly measured by means of NADPH decay. H_2O_2 is decomposed, generating oxidized glutathione (GSSG) from GSH. GSSG is regenerated back to GSH by glutathione reductase (GR) present in the assay media at the expense of NADPH. The enzymatic activity was expressed as nmol NADPH/min/mg protein.

Glutathione S-transferase activity

Glutathione S-transferase (GST) activity was assayed spectrophotometrically at 340 nm by the method of Habig *et al*.[27] The reaction mixture contained a sample of S1, 0.1 M potassium phosphate buffer pH 7.4, 100 mM GSH and 100 mM 1-chloro-2,4-dinitrobenzene (CDNB), which was used as substrate. The enzymatic activity was expressed as nmol CDNB conjugated/min/mg protein.

Protein

Protein concentration was measured according to the method of Bradford[28] using bovine serum albumin as the standard.

Statistical analysis

The results are presented as the means ± SEM. The statistical significance between groups was calculated by means of two-way analysis of variance followed by Duncan's test when necessary. $P < 0.05$ was considered statistically significant. Main effects are presented only when the second-order interaction was not significant.

Results

Body weight measurement

The analysis of the body weight gain data yielded a significant OVX × $(PhSe)_2$ interaction ($F_{1,32} = 5.16$). Post-hoc comparisons revealed that $(PhSe)_2$ reduced the increase in the body weight induced by OVX (145%) in female rats. $(PhSe)_2$ decreased *per se* the body weight gain (0.1%) in female rats (Figure 1a).

Determination of intra-abdominal fat accumulation

The analysis of the intra-abdominal fat accumulation showed a significant OVX × $(PhSe)_2$ interaction ($F_{1,32} = 3.27$). Post-hoc comparisons revealed that $(PhSe)_2$ decreased the intra-abdominal fat accumulation induced by OVX (68%) in female rats. $(PhSe)_2$ reduced *per se* the intra-abdominal fat accumulation (30%) in female rats (Figure 1b).

Measurement of plasma lipid values

Analysis of the results presented in Table 1 shows that TC and non-HDL-cholesterol levels were significantly affected by OVX. Post-hoc comparisons demonstrated that $(PhSe)_2$ was unable to protect against the rise in plasma TC (27%) and non-HDL-cholesterol (65%) levels induced by OVX in female rats.

As revealed in Table 1, $(PhSe)_2$ exerted its main effect on HDL levels. Post-hoc comparisons showed that $(PhSe)_2$ increased HDL levels (25%) in OVX female rats.

The analysis of triglyceride levels demonstrated a significant OVX × $(PhSe)_2$ interaction. Post-hoc comparisons showed that $(PhSe)_2$ decreased triglyceride levels (29%) in OVX female rats (Table 1).

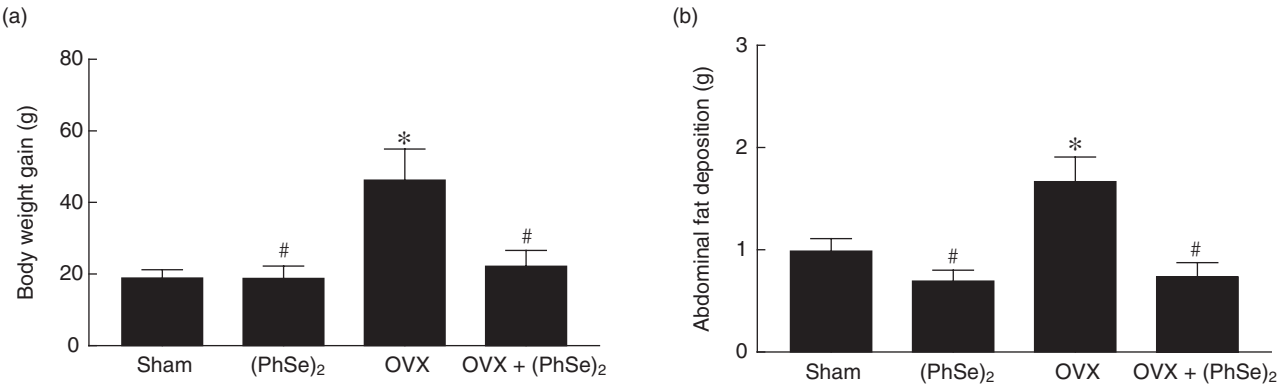

Figure 1 Effect of ovariectomization (OVX) and diphenyl diselenide $(PhSe)_2$ on body weight gain (a) and abdominal fat deposition (b) in female adult rats. Data are reported as means ± SEM for nine rats per group. *$P < 0.05$, compared with Sham-operated group; #$P < 0.05$, compared with OVX group, (two-way analysis of variance/Duncan).

Table 1 Effect of ovariectomization and diphenyl diselenide on plasma lipid values of female adult rats

	Treatment group				*F* value
	Sham	$(PhSe)_2$	OVX	OVX + $(PhSe)_2$	
Total cholesterol	66.00 ± 5.07	68.71 ± 3.03	83.80 ± 6.03*	93.11 ± 5.91*	$F_{1,32} = 17.50$
HDL	44.55 ± 2.82	47.30 ± 3.13	49.09 ± 2.49	55.81 ± 2.37*#	$F_{1,32} = 8.05$
Non-HDL	23.57 ± 3.57	26.50 ± 4.29	39.12 ± 5.21*	42.50 ± 3.94*	$F_{1,32} = 13.53$
Triglycerides	48.55 ± 4.07	48.37 ± 3.14	51.12 ± 5.33	34.50 ± 3.76*#	$F_{1,32} = 4.18$

OVX, ovariectomized; $(PhSe)_2$, diphenyl diselenide. Data are reported as means ± SEM for nine rats per group and expressed as mg/dl. *$P < 0.05$, compared with Sham-operated group; #$P < 0.05$, compared with OVX group (two-way analysis of variance/Duncan).

Table 2 Effect of ovariectomization and diphenyl diselenide on parameters of oxidative stress in liver of female adult rats

	Treatment group				*F* value
	Sham	$(PhSe)_2$	OVX	OVX + $(PhSe)_2$	
TBARS (nmol MDA/mg protein)	52.63 ± 1.02	51.98 ± 3.47	48.98 ± 2.47	54.34 ± 3.46	$F_{1,32} = 2.03$
Ascorbic acid (µg ascorbic acid/g tissue)	264.76 ± 7.64	305.84 ± 9.67*#	253.06 ± 13.16	322.30 ± 12.67*#	$F_{1,32} = 22.32$
GSH (nmol/g tissue)	17.83 ± 0.20	19.03 ± 0.37#	15.84 ± 0.78*	20.07 ± 0.61*#	$F_{1,32} = 7.61$

OVX, ovariectomized; $(PhSe)_2$, diphenyl diselenide. Data are reported as mean ± SEM for 9 rats per group. *$P < 0.05$, compared with Sham-operated group. #$P < 0.05$, compared with OVX group (two-way analysis of variance/Duncan).

Accomplishment of liver oxidative stress parameters

Thiobarbituric acid reactive species

As shown in Table 2, neither OVX nor $(PhSe)_2$ changed TBARS levels in liver of female rats.

Ascorbic acid levels

Ascorbic acid levels were significantly affected by $(PhSe)_2$. Post-hoc comparisons demonstrated that $(PhSe)_2$ increased ascorbic acid levels in liver of $(PhSe)_2$ (15%) and OVX (22%) female rats (Table 2).

Reduced glutathione content

As demonstrated in Table 2, analysis of the GSH content showed a significant OVX × $(PhSe)_2$ interaction. Post-hoc comparisons revealed that $(PhSe)_2$ increased the GSH content (12%) in OVX female rats. $(PhSe)_2$ increased *per se* the GSH content (1%) in female rats.

Catalase activity

Results presented in Table 3 show that CAT activity yielded a significant OVX × $(PhSe)_2$ interaction. Post-hoc comparisons demonstrated that $(PhSe)_2$ restored CAT activity, which was decreased in OVX female rats (18%).

Glutathione peroxidase activity

The analysis of GPx activity revealed that neither OVX nor $(PhSe)_2$ changed this parameter in liver (Table 3).

Glutathione S-transferase activity

As revealed in Table 3, GST activity was significantly affected by $(PhSe)_2$. Post-hoc comparisons showed that $(PhSe)_2$

Table 3 Effect of ovariectomization and diphenyl diselenide on antioxidant enzymatic defences in liver of female adult rats

	Treatment group				*F* value
	Sham	$(PhSe)_2$	OVX	OVX + $(PhSe)_2$	
CAT (U/mg protein)	50.84 ± 1.63	48.03 ± 2.65	41.82 ± 1.27*	46.97 ± 1.20$^{\#}$	$F_{1,32} = 4.98$
GPx (nmol NADPH/min/mg protein)	123.90 ± 11.67	112.87 ± 9.61	135.40 ± 12.10	113.25 ± 12.72	$F_{1,32} = 0.22$
GST (nmol CDNB conjugated/min/mg protein)	78.53 ± 7.53	109.78 ± 15.68*$^{\#}$	64.73 ± 3.80	116.59 ± 11.75*$^{\#}$	$F_{1,32} = 13.23$

OVX, ovariectomized; $(PhSe)_2$, diphenyl diselenide; CAT, catalase; GPx, glutathione peroxidase; GST, glutathione S-transferase. Data are reported as mean ± SEM for 9 rats per group. *$P < 0.05$, compared with Sham-operated group; $^{\#}P < 0.05$, compared with OVX group (two-way analysis of variance/Duncan).

increased GST activity (48%) in OVX female rats. $(PhSe)_2$ increased *per se* the GST activity (40%) in female rats.

Discussion

The purpose of this study was to demonstrate the beneficial effects of $(PhSe)_2$ in a mimic model for menopause. Our results showed that OVX rats presented raised plasma TC and non-HDL levels as well as reduced GSH content and CAT activity in liver. $(PhSe)_2$ treatment decreased plasma triglycerides levels and enhanced HDL levels in OVX rats. Moreover $(PhSe)_2$ was able to restrain the increase in body weight gain and abdominal fat accumulation induced by OVX. Although treatment with $(PhSe)_2$ at a dose of 5 mg/kg showed beneficial effects in OVX rats, this dose was not effective in protecting against the increase in plasma TC and non-HDL levels induced by OVX. Another important finding is that $(PhSe)_2$ increased hepatic ascorbic acid levels, GSH content, GST activity and restored CAT activity in liver of OVX rats.

Food intake and body weight regulation are influenced by estradiol in adult females.[29] OVX results in reduction in circulating oestrogen and increases daily food intake and promotes weight gain in rodents.[30] Accordingly, our results demonstrated a greater body weight gain in OVX than in sham-operated rats. $(PhSe)_2$ treatment was effective in avoiding the body weight gain in OVX rats. In agreement with this finding, previous studies have reported that chronic consumption of low doses of selenium can increase the metabolism rate and decrease body weight in men[31] and animals,[32,33] without causing overt signs of toxicity. OVX rats gain fat, specifically visceral fat.[30] Intra-abdominal adipose tissue has adipogenic, pro-atherogenic and pro-thrombotic characteristics.[29] Thus, a very important finding of this study is that $(PhSe)_2$ treatment prevented the abdominal fat deposition induced by OVX in rats.

Wakatsuki and Sagara[34] reported that low levels of endogenous oestrogens enhance plasma lipoprotein lipase activity and may lead to an elevated plasma LDL concentration in postmenopausal and bilaterally oophorectomized women. Considering that non-HDL cholesterol includes LDL and very low density lipoprotein (VLDL), our results corroborate the findings of Van Lenten *et al*.,[35] who demonstrated that OVX female rats exhibit higher TC and non-HDL levels than sham-operated ones. Accordingly, previous data from our research group showed that $(PhSe)_2$ possesses hypolipidaemic activity.[16,17] By contrast, in the present study protocol, treatment with $(PhSe)_2$ at a dose of 5 mg/kg was not enough to lower TC and non-HDL levels, although it was able to decrease triglycerides and augment HDL levels. This finding could suggest that a dose higher than 5 mg/kg might be necessary to restore plasma TC and non-HDL levels increased by OVX.

Oxidative stress, a disparity between the rates of free radical production and elimination, occurs when the antioxidant mechanisms are overwhelmed.[36–41] There is evidence that oxidative imbalance occurs in women after menopause.[42] OVX may induce variations in antioxidant/oxidant status which can be detected in rat liver.[43] Concerning the relationship between OVX and oxidative stress, the present study demonstrated that the menopause-related complications induced by OVX include a decrease in GSH content and CAT activity in liver of OVX rats. However, TBARS and ascorbic acid levels and GPx and GST activity were not altered by OVX in the present protocol.

Ha *et al*.[4] and Topçuoglu *et al*.[44] reported that MDA levels, an indicator of lipid peroxidation, in the liver total homogenate were increased in OVX rats compared with the control group. However, in the present study we did not observe any alteration in MDA levels in liver of OVX rats.

CAT, an enzyme that catalyses the conversion of hydrogen peroxide to water and molecular oxygen, is widely distributed within the living organisms. In the present study CAT activity was found to be decreased in the liver of OVX rats. These data are in accordance with Ha *et al*.,[4] which showed a reduction in CAT activity as a consequence of OVX-induced oxidative stress. In this context $(PhSe)_2$ treatment was able to restore hepatic CAT activity in OVX female rats.

The glutathione system plays a significant role in protecting cells from ROS. GSH constitutes the first line of defence against free radicals. In agreement with Oztekin *et al*.[45] and Topçuoglu *et al*.,[44] our results confirmed that OVX rats showed a decrease in hepatic GSH content, which was restored by $(PhSe)_2$ treatment. It is important to emphasize that $(PhSe)_2$ treatment enhanced *per se* the hepatic GSH content and GST activity. GST, also known as phase II enzymes, are widely distributed in the living organism catalysing and binding proteins which promote the conjugation of GSH with a variety of reactive electrophilic compounds resulting in formation of substances that are easily excreted from the body. So, the increase in GSH content and GST activity are in agreement with Luchese *et al*.,[46] who demonstrated the involvement of the glutathione system in the antioxidant effect of $(PhSe)_2$, suggesting that this organoselenium compound acts as an indirect antioxidant.

The effect of OVX on hepatic GPx activity is contradictory. Kankofer *et al*.[43] demonstrated that GPx activity tends to be high in OVX animals, but Oztekin *et al*.[45] showed that OVX reduces the activity of this enzyme.

It is well-known that ascorbic acid is a component of the first line of antioxidant defence against oxidative processes and participates in free radical scavenging. In this sense, an important finding demonstrated here was that $(PhSe)_2$ treatment enhanced *per se* the hepatic ascorbic acid levels, which could be fundamental for the antioxidant effect of $(PhSe)_2$. In accordance, Luchese *et al*.[46] showed that $(PhSe)_2$ is able to increase ascorbic acid levels, which could indicate an indirect antioxidant mechanism for $(PhSe)_2$. Data from Luchese and Nogueira[47] indicate that $(PhSe)_2$ has dehydroascorbate reductase-like activity which could increase the reduction of dehydroascorbate to ascorbic acid.

Conclusion

The data revealed that $(PhSe)_2$ treatment, at a dose of 5 mg/kg, was effective in preventing the increase in body weight gain and intra-abdominal fat deposition induced by OVX. Although $(PhSe)_2$ treatment was not effective in preventing the increase in plasma TC and non-HDL levels induced by OVX, it was able to decrease plasma triglycerides levels and to increase HDL levels in OVX rats, besides increasing hepatic ascorbic acid levels, GSH content and GST activity and restored CAT activity in liver of OVX rats. Taking together, these findings suggest that $(PhSe)_2$ could be a promising alternative to minimize menopause-related symptoms. However, further studies are warranted to improve the evidence base for clinical practice.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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