Antihypertensive and Antioxidant Efficacy of Sesame Cake Extract (SCE) on Uninephrectomized DOCA-Salt Rats.

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Summary

Hypertension is one of the risk factors for cardiovascular diseases (CVD), the leading cause of death in developed countries. This study was specifically carried out to evaluate the effect of crude ethanolic extract of sesame cake on hypertensive rats. Thirty six male Wistar rats were uninephrectomized and randomly divided into six groups. Hypertension was induced by injecting DOCA-salt, 25 mg/kg BW subcutaneously, twice a week for six weeks, with NaCl 1% instead of tap water for drinking throughout the study. Blood pressure was measured every week and the toxic effect of DOCA-salt was determined using lipid peroxidative markers (thiobarbituric acid reactive substances (TBARS), lipid hydroperoxides (LOOH)). We also assessed the activity of enzymatic antioxidants superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and measured the non-enzymatic antioxidants vitamin C, vitamin E and reduced glutathione (GSH) levels in erythrocytes, plasma and tissues. The hypertensive rats showed significantly higher value of blood pressure and plasma lipid peroxides. Oral administration of SCE significantly decreased the blood pressure and enhanced antioxidant capacity in DOCA-salt hypertensive rats.

Keywords: hypertension, sesame cake extract, Deoxycorticosterone acetate, lipid peroxidation, antioxidants.

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Introduction

Hypertension is one of the most significant risk factors for cardiovascular diseases, the leading cause of death [1]. Lipid peroxidation is reported to be an important factor in pathologic conditions such as hypertension, diabetes mellitus and myocardial infarction [2-4]. An increased concentration of end products of lipid peroxidation is the evidence most frequently quoted for the involvement by toxic radicals in some diseases including hypertension [5]. A defense used by living systems against damage caused by reactive oxygen species (ROS) using enzymes to eliminate these species by means of their conversion to less-toxic compounds. Such antioxidant enzymes include superoxide dismutase converts $O_2^{\cdot}$ to H_2O_2, catalase and glutathione peroxidase [6]. Hypertension associated with sodium retention dependents on extracellular volume expansion, as well as increased sodium concentrations in vascular, cardiac, central nervous system and renal structures [7]. The prolonged administration of the DOCA-salt induces sodium salt retention, due to the presence of high salt intake; it produces a well-known volume dependent hypertension in rats [8]. This experimental model of hypertension showed increased levels of superoxide or hydrogen peroxide or both, which have many prohypertensive actions, including direct vasoconstriction, antinatriuresis and sympathetic stimulation [9].

In recent times, with a history of traditional uses sesame seeds and their by-products have demonstrated its contribution to the reduction of excessive mortality, morbidity and disability due to diseases such as hypertension, hepatotoxicity and diabetes [10]. Sesame seeds are not only rich in oil and protein, but also in vitamin E and lignans such as sesamin, sesamolin and sesaminol, etc. Sesame cake, one of the by-products, obtained from sesame seeds after pressing for oil, has been identified for some neutraceutical characteristics including antioxidant, hypocholesterolemic, and hepatoprotective effects [11]. In the present study, we have investigated the effect of sesame cake administration on hypertension and antioxidant status in uninephrectomized DOCA-salt hypertensive rats.

Materials and Methods

Preparation of sesame cake extract

Sesame seed cake was purchased from C.R oil mill at Jayankondam, Ariyalur district, Tamil Nadu, India. Commercially purchased sesame cake was dried and powered finely. Ten gram of sesame cake powder was extracted with 150 mL of 70% ethanol for 24 h. The extract was filtered by a muslin cloth and concentrated under the room temperature. The yield was approximately 1.5 g per 10 g of sesame cake. The residue was stored under refrigeration until further analysis.

Animals

Male albino Wistar rats (weighing 200-230 g) were purchased from the Central Animal House, Department of Experimental Medicine, Rajah Muthiah Medical College and Hospital, Annamalai University, and maintained in an air-conditioned room (25 ± 1ºC)

with a 12 h light/12 h dark cycle. Feed and water were provided *ad libitum*. The experimental study was approved by the Ethical Committee of Rajah Muthiah Medical College and Hospital (Reg No.160/1999/CPCSEA, Proposal No.613), Annamalai University, Annamalainagar.

Chemicals

DOCA was obtained from Sigma-Aldrich Company (St. Louis, Missouri, USA). All other chemicals used were of analytical grade obtained from E. Merck or HIMEDIA, Mumbai, India.

Uninephrectomized animals

Animals were anesthetized by an intraperitonial injection of ketamine (75 mg/kg BW). A small patch of skin above the left kidney was shaved, cleaned and applied with iodine based antiseptic. Toothed forceps and scissors were alcohol-sterilized; two 1-cm incisions were made at midscapular region, one on the skin and other on the body cavity, respectively. The kidney was freed from the surrounding tissues and pulled out gently. The adrenal glands, which is attached loosely to the anterior pole of the kidney by connective tissue and fat, was gently freed by tearing the attachments, and was put back into the abdominal cavity. The renal artery and ureter were tied by silk thread, and then the kidney was removed. The muscle and skin layers were closed separately by using a chromic sterile absorbable suture.

Experimental induction of hypertension

Animals were given, weekly twice, subcutaneous injections of DOCA (25 mg/kg BW) in dimethyl formamide (vehicle) solution, and salt was administered by substitution of 1% NaCl solution for drinking water *ad libitum* throughout the experimental period.

Experimental design

The rats were randomly divided into six groups of six rats each. Group one served as sham-operated control and group two served as sham-operated control treated with 400 mg/kg BW of sesame cake extract. Group III as DOCA-salt hypertension control, groups IV and V were hypertensive rats which received different doses of SCE, 200 and 400 mg/kg BW and group VI received nifedipine 20 mg/kg BW. SCE or nifedipine were administered orally once daily for 6 weeks between 9:00 a.m. and 10:00 a.m.

Group I : Sham-operated control

Group II : Sham-operated control + 400mg/kg BW SCE + 1% NaCl

Group III : DOCA-salt + 1% NaCl

Group IV : DOCA-salt + 1% NaCl + 200mg/kg BW SCE

Group V : DOCA-salt + 1% NaCl + 400mg/kg BW SCE

Group VI : DOCA-salt+ 1% NaCl + Nifedipine (20 mg/kg BW)

After 6 weeks, the animals were anaesthetized between 8:00 a.m. and 9:00 a.m. using ketamine (24 mg/kg BW, intramuscular injection), and sacrificed by cervical dislocation. Blood was collected in tubes with a mixture of potassium oxalate and sodium fluoride (1:3) for various biochemical estimations.

Blood pressure measurements

Systolic and diastolic blood pressure was determined by the tail-cuff method (IITC, model 31, Woodland Hills, CA, USA) from 0^{th} day to 6 weeks. The tail cuff approach to determine arterial blood pressure requires certain precautions such as reduction of stress of the animals, appropriate training of rats over multiple days and adequate prewarming to dilate the tail artery. The animals were placed in a heated chamber at an ambient temperature of 30–34°C for 15 min, and from each animal, 1–9 blood pressure values were recorded. The lowest three readings averaged to obtain a mean blood pressure. All recordings and data analyses were done using a computerized data acquisition system and software (*IITC* Inc. /Life Science Instruments, USA).

Biochemical analysis

TBARS and LOOH were estimated by the methods of Niehaus and Samuelson [12] and Jiang et al.[13], respectively. The activities of SOD, CAT and GPx were measured by the method of Kakkar et al. [14], Sinha [15], and Rotruck et al. [16], respectively. The non-enzymic antioxidants GSH, vitamin C and vitamin E were estimated by the method of Ellman [17], Roe and Kuether [18], and Bakker et al. [19], respectively.

Statistical analysis

Statistical evaluation was done using one-way analysis of variance (ANOVA) followed by Duncan's Multiple Range Test (DMRT) by using the statistical package of social sciences (SPSS) 10.0 for Windows. The significance level was set at $p \leq 0.05$

Results

Table 1 shows the effect of SCE on systolic and diastolic pressure on uninephrectomized DOCA-salt hypertensive rats. DOCA–salt administration six weeks, compared with sham-operated control the blood pressure significantly increased. Oral administration of SCE and nifedipine significantly prevented the blood pressure increase in DOCA-salt rats.

Table 1. Effect of SCE on the systolic and diastolic blood pressure in uninephrectomized DOCA-salt hypertensive rats.

Name of the group	Systolic blood pressure (mm Hg)		Diastolic blood pressure (mm Hg)	
	0 week	6th week	0 week	6th week
Sham-operated control	123.05 ± 5.95	128.67 ± 4.34[a]	83.03 ±5.67	90.42 ± 3.98[a]
Sham-operated + SCE (400 mg/kg BW)	120.10 ± 3.90	126.06 ± 7.13[a]	84.00 ± 6.92	86.47 ± 4.84[a]
DOCA + 1% NaCl	118. 39 ± 4.14	215.35 ± 5.51[b]	87.35 ±7.56	151.21 ± 4.89[b]
DOCA + 1% NaCl + SCE (200 mg/kg BW)	119.66 ± 4.02	133.39 ± 6.25[c]	84.75 ± 6.98	106.69 ± 5.31[c]
DOCA + 1% NaCl + SCE (400 mg/kg BW)	115.33 ± 4.74	190.67 ± 5.98[d]	89.07 ±6.23	153.90 ± 5.08[b]
DOCA + 1% NaCl + nifedipine (20 mg/kg BW)	117.39 ± 5.01	130.03 ± 4.50[e,c]	86.33 ±6.65	97.81± 4.91[d]

Values are means ± SD for six rats
Values not sharing a common superscript differ significantly at $p < 0.05$ (DMRT)

Tables 2 & 3 show the effect of SCE on lipid peroxidation in plasma and tissues of DOCA-salt hypertensive rats. A significant increase in the levels of TBARS and LOOH were observed when compared with sham-operated control rats. SCE treatment produced a reduction of these values in plasma and tissues.

Table 2. Effect of SCE on TBARS in the plasma and tissues of uninephrectomized DOCA salt hypertensive rats.

Name of the group	Plasma (mmol/dL)	TBARS (mmol/100 g wet tissue)		
		Liver	Kidney	Heart
Sham-operated control	0.15 ± 0.01[a]	0.84 ± 0.08[a]	1.46 ± 0.13[a]	0.50 ± 0.04[a]
Sham-operated + SCE (400 mg/kg BW)	0.14 ± 0.01[a]	0.84 ± 0.07[a]	1.46 ± 0.12[a]	0.47 ± 0.04[a]
DOCA + 1% NaCl	0.41 ± 0.04[b]	2.44 ± 0.21[b]	3.94 ± 0.25[b]	3.19 ± 0.22[b]
DOCA + 1% NaCl + SCE (200 mg/kg BW)	0.17 ± 0.01[c.a]	0.97 ± 0.08[c,a]	1.59 ± 0.14[c,a]	0.65 ± 0.05[c]
DOCA + 1% NaCl + SCE (400 mg/kg BW)	0.37 ± 0.03[d]	1.76 ± 0.10[d]	2.32 ± 0.16[d]	1.80 ± 0.17[d]
DOCA + 1% NaCl + nifedipine (20 mg/kg BW)	0.18 ± 0.01[e,c]	1.11 ± 0.09[e]	1.805 ± 0.17[e]	0.81 ± 0.06[e]

Table 3. Effect of SCE on lipid hydropeoxides in the plasma and tissues of uninephrectomized DOCA-salt hypertensive rats.

Name of the group	Plasma (mmol/dL)	LOOH (mmol/100 g wet tissue)		
		Liver	Kidney	Heart
Sham-operated control	8.90 ± 0.73[a]	76.93 ± 6.8[a]	64.37 ± 6.30[a]	66.85 ± 5.7[a]
Sham-operated + SCE (400 mg/kg BW)	8.35 ± 0.67[a]	74.39 ± 6.9[a,c]	63.09 ± 5.8[a]	65.65 ± 5.53[a]
DOCA + 1% NaCl	20.52 ± 1.89[b]	111.92 ± 9.95[b]	168.22 ± 16.6[b]	139.88 ± 11.38[b]
DOCA + 1% NaCl + SCE (200 mg/kg BW)	10.99 ± 0.99[c]	85.13 ± 8.34[c,e]	73.51 ± 6.53[c,e]	74.2 ± 6.64[c]
DOCA + 1% NaCl + SCE (400 mg/kg BW)	18.50 ±1.46[d]	101.84 ± 9.96[d]	148.8 ± 10.01[d]	120.83 ± 11.6[d]
DOCA + 1% NaCl + nifedipine (20 mg/kg BW)	11.84 ± 1.01[c,e]	87.93 ± 8.6[e]	77.46 ± 6.86[e]	76.12 ± 6.75[e]

Values are means ± SD for six rats
Values not sharing a common superscript differ significantly at $p < 0.05$ (DMRT)

Tables 4, 5 & 6 show the activities of SOD, CAT and GPx in the erythrocyte and tissues of DOCA-salt hypertensive rats. DOCA-salt rats had decreased activities of SOD, CAT, and GPx in the erythrocyte and tissues and treatment with SCE brought these parameters towards normalcy.

Table 4. Effect of SCE on SOD activity in the plasma and tissues of normal, uninephrectomized DOCA-salt hypertensive rats.

Name of the group	Erythrocyte (U^{α}/mg Hb)	SOD (U^{α}/mg protein)		
		Liver	Kidney	Heart
Sham-operated control	7.59 ± 0.67[a]	7.98 ± 0.75[a]	15.23 ± 1.48[a]	5.65 ± 0.53[a]
Sham-operated + SCE (400 mg/kg BW)	7.67 ± 0.38[a]	8.23 ± 0.32[a]	15.54 ± 1.38[a]	5.90 ± 0.47[a]
DOCA + 1% NaCl	3.43 ± 0.23[b]	4.20 ± 0.29[b]	8.36 ± 0.70[b]	3.20± 0.32[b]
DOCA + 1% NaCl + SCE (200 mg/kg BW)	6.89 ± 0.67[c]	6.92 ± 0.58[c]	12.95 ± 1.20[c]	4.72 ± 0.46[c]
DOCA + 1% NaCl + SCE (400 mg/kg BW)	4.83 ± 0.44[d]	4.89 ± 0.45[d]	9.67 ± 0.66[d]	3.65 ± 0.25[d]
DOCA-salt + 1% NaCl + nifedipine (20 mg/kg BW)	6.20 ± 0.48[e]	5.53 ± 0.55[e]	11.40 ± 1.03[e]	4.14 ± 0.42[e,c]

Table 4. Effect of SCE on CAT activity in the plasma and tissues of uninephrectomized DOCA-salt hypertensive rats.

Name of the group	Erythrocyte (U^{β}/mg Hb)	CAT (U^{β}/mg protein)		
		Liver	Kidney	Heart
Sham-operated control	168.97 ± 8.72[a]	74.13 ± 7.37[a,c]	31.57 ± 2.77[a]	50.26 ± 4.71[a]
Sham-operated + SCE (400 mg/kg BW)	171.36 ± 6.99[a]	76.95 ± 7.75[a]	33.29 ± 2.99[a]	51.25 ± 4.42[a]
DOCA + 1% NaCl	92.71 ± 5.37[b]	55.24 ± 4.76[b]	16.98 ± 1.38[b]	25.23 ± 1.95[b]
DOCA + 1% NaCl + SCE (200 mg/kg BW)	155.50 ± 12.31[c]	70.12 ± 7.61[c,a]	27.32 ± 2.22[c]	45.9 ± 4.14[c,a]
DOCA + 1% NaCl + SCE (400 mg/kg BW)	115.84 ± 10.42[d]	58.89 ± 3.88[d]	19.80 ± 1.46[d]	34.55 ± 2.7[d]
DOCA-salt + 1% NaCl + nifedipine (20 mg/kg BW)	150.00 ± 13.28[e,c]	68.38 ± 3.48[e]	23.15 ± 2.20[e]	40.04 ± 3.15[e]

Table 5. Effect of SCE on GPx activity in the plasma and tissues of uninephrectomized DOCA-salt hypertensive rats.

Name of the group	Erythrocyte (U^{γ}/mg Hb)	GPx (U^{γ}/mg protein)		
		Liver	Kidney	Heart
Sham-operated control	14.99 ± 1.24[a]	8.25 ± 0.78[a]	9.11± 0.86[a]	7.97 ± 0.63[a]
Sham-operated + SCE (400 mg/kg BW)	15.44 ± 1.27[a]	8.79 ± 0.81[a]	9.52 ± 0.91[a]	8.28 ± 0.71[a]
DOCA + 1% NaCl	5.95 ± 0.38[b]	4.60 ± 0.37[b]	3.16 ± 0.22[b]	3.34 ± 0.21[b]
DOCA + 1% NaCl + SCE (200 mg/kg BW)	12.77 ± 1.11[c]	6.90 ± 0.54[c]	7.05 ± 0.65[c]	6.08 ± 0.51[c]
DOCA + 1% NaCl + SCE (400 mg/kg BW)	8.89 ± 0.79[d]	4.42 ± 0.49[d]	5.23 ± 0.43[d]	4.64 ± 0.38[d]
DOCA + 1% NaCl + nifedipine (20 mg/kg BW)	10.45 ± 0.94[e]	6.34 ± 0.54[e,c]	6.56 ± 0.44[e,c]	5.65 ± 0.49[e]

Values are means ± SD for six rats
Values not sharing a common superscript differ significantly at $p < 0.05$ (DMRT)

IU^{α}- enzyme concentration required to inhibit the NBT to 50% in one minute
IU^{β}- µmol of H_2O_2 consumed per minute
IU^{γ}- µg of GSH utilized per minute

The levels of plasma vitamin C, vitamin E and reduced glutathione in DOCA-salt hypertensive rats and sham-operated control are shown in tables 7, 8 & 9. The levels of these non-enzymic antioxidants were significantly depleted in hypertensive rats when compared with the control. Treatment with SCE showed a significant increase in the levels of non-enzymatic antioxidants.

Table 6. Effect of SCE on vitamin C level in the plasma and tissues of uninephrectomized DOCA-salt hypertensive rats.

Name of the group	Plasma (mg/dL)	Vitamin C (μg/mg protein)		
		Liver	Kidney	Heart
Sham-operated control	2.105 ± 0.15^{a}	0.79 ± 0.06^{a}	0.7 ± 0.096^{a}	0.58 ± 0.04^{a}
Sham-operated + SCE (400 mg/kg BW)	2.12 ± 0.15^{a}	0.84 ± 0.04^{a}	0.73 ± 0.06^{a}	0.61 ± 0.05^{a}
DOCA + 1% NaCl	0.93 ± 0.08^{b}	0.51 ± 0.05^{b}	0.35 ± 0.02^{b}	0.28 ± 0.01^{b}
DOCA + 1% NaCl + SCE (200 mg/kg BW)	1.94 ± 0.10^{c}	0.69 ± 0.06^{c}	0.58 ± 0.04^{c}	0.47 ± 0.04^{c}
DOCA + 1% NaCl + SCE (400 mg/kg BW)	1.43 ± 0.14^{d}	0.59 ± 0.02^{d}	0.45 ± 0.04^{d}	0.33 ± 0.02^{d}
DOCA + 1% NaCl + nifedipine (20 mg/kg BW)	1.78 ± 0.109^{e}	$0.66 \pm 0.05^{c,e}$	0.54 ± 0.05^{e}	0.43 ± 0.04^{e}

Table 7. Effect of SCE on vitamin E level in the plasma and tissues of uninephrectomized DOCA-salt hypertensive rats.

Name of the group	Plasma (mg/dL)	Vitamin E (μg/mg protein)		
		Liver	Kidney	Heart
Sham-operated control	1.90 ± 0.16^{a}	6.14 ± 0.56^{a}	$4.09 \pm 0.27^{a,c}$	4.07 ± 0.36^{a}
Sham-operated + SCE (400 mg/kg BW)	1.96 ± 0.18^{a}	6.17 ± 0.57^{a}	4.14 ± 0.28^{a}	4.13 ± 0.40^{a}
DOCA + 1% NaCl	1.17 ± 0.11^{b}	3.74 ± 0.32^{b}	1.63 ± 0.08^{b}	2.01 ± 0.15^{b}
DOCA + 1% NaCl + SCE (200 mg/kg BW)	1.73 ± 0.15^{c}	$5.72 \pm 0.49^{c,a}$	3.82 ± 0.27^{c}	3.55 ± 0.32^{c}
DOCA + 1% NaCl + SCE (400 mg/kg BW)	1.36 ± 0.11^{d}	4.37 ± 0.39^{d}	2.33 ± 0.19^{d}	2.46 ± 0.19^{d}
DOCA + 1% NaCl + nifedipine (20 mg/kg BW)	1.56 ± 0.11^{e}	$4.90 \pm 0.46^{c,e}$	3.07 ± 0.22^{e}	2.95 ± 0.18^{e}

Table 8. Effect of SCE on GSH level in the plasma and tissues of uninephrectomized DOCA-salt hypertensive rats.

Name of the group	Plasma (mg/dL)	GSH (μg/mg protein)		
		Liver	Kidney	Heart
Sham-operated control	36.11 ± 3.29^{a}	11.74 ± 1.09^{a}	10.04 ± 0.99^{a}	8.18 ± 0.69^{a}
Sham-operated + SCE (400 mg/kg BW)	36.97 ± 3.31^{a}	12.11 ± 1.15^{a}	10.24 ± 1.01^{a}	8.26 ± 0.70^{a}
DOCA + 1% NaCl	21.37 ± 1.67^{b}	7.97 ± 0.66^{b}	5.43 ± 0.39^{b}	5.39 ± 0.77^{b}
DOCA + 1% NaCl + SCE (200 mg/kg BW)	32.62 ± 2.82^{c}	10.03 ± 0.99^{c}	$8.97 \pm 0.85^{c,a}$	$7.97 \pm 0.67^{c,a}$
DOCA + 1% NaCl + SCE (400 mg/kg BW)	25.03 ± 1.89^{d}	8.10 ± 0.69^{d}	6.53 ± 0.53^{d}	5.98 ± 0.45^{d}
DOCA + 1% NaCl + nifedipine (20 mg/kg BW)	$30.86 \pm 2.21^{c,e}$	9.31 ± 0.76^{e}	$8.44 \pm 0.73^{e,c}$	$7.69 \pm 0.6^{e,c}$

Values are means ± SD for six rats
Values not sharing a common superscript differ significantly at $p < 0.05$ (DMRT)

Discussion

In DOCA-salt administered rats, sodium (Na^+) and water are absorbed in the kidney, which increases circulating blood volume and it produces well known volume dependent type of hypertension [20] which was observed in our study. Earlier reports have noted that increased vascular superoxide production and imbalance in liver antioxidant status associated with an increase in lipid peroxidation occur in DOCA-salt hypertension [21], suggesting that oxidative stress might be closely related to the pathogenesis of this type of hypertension. Natural antioxidants and polyunsaturated fatty acids show protective function against hypertension [22]. A good free radical scavenging capacity of antioxidants from sesame cake extract has been reported and the presence of lignans such as sesamin, sesamolin, sesaminol, sesangolin and others [23]. Alternatively, sesamin may reduce the vascular O_2^- production by inhibiting the activity of an NADPH oxidase, an enzyme which is known to be a main source of O_2^- production [24], and is increased in the vascular tissues of DOCA-salt hypertensive rats [25]. In addition, there was a positive correlation between blood pressure and vascular O_2^- production thereby indicating a close relationship between sesamin induced decrease in vascular O_2^- production and its antihypertensive effects.

Increased lipid peroxidation is considered to be a consequence of oxidative stress that occurs when the dynamic balance between pro-oxidant and antioxidant mechanisms are impaired. Lipid peroxidation, arising from the reaction of free radicals with lipids, is thought to be an important feature of cellular injury brought about by free-radical attacks [26]. Oxidative stress has been implicated in the pathogenesis of hypertension [27], which is responsible for higher levels of TBARS and LOOH in hypertensive rats compared to sham-operated control. A pronounced decrease of lipid peroxidation was observed in SCE treated rats. The reduction may be due to the excessive availability of antioxidants in SCE. It has been reported that sesamolin, a lignin present in SCE, reduces lipid peroxidation in rats [28]. The lignans (sesamin, sesamolin and sesaminol) may potentiate the effect of vitamin E and themselves act as antioxidants that may also be responsible for the reduction in lipid peroxidation [29].

Free-radical-scavenging enzymes, such as SOD, CAT and GPx are the first line of defense against injury and are involved in the disposal of superoxide anions and hydrogen peroxide. We observed decreased activities of SOD, CAT, and GPx in the erythrocytes of DOCA-salt hypertensive rats, which may be an important factor in limiting the antioxidant capacity that is due to increased lipid peroxidation. The increased production of a superoxide radical in vascular tissues leads to the attenuation of endothelium-dependent vasorelaxation, probably by means of the inactivation of endothelin-derived nitric oxide. Therefore, endothelium-dependent vasorelaxation is enhanced by the SOD enzyme [30]. The selenium-containing enzyme GPx detoxifies H_2O_2 by utilizing GSH and H_2O_2 as substrates to yield H_2O and oxidized glutathione [31]. Catalase removes H_2O_2 by breaking it down directly to O_2. The increased activities of SOD, CAT and GPx could be the result of decreased utilization being that the lipid peroxidation was low in the extract-treated groups, which might be due to the presence of lignans.

Numerous studies have suggested an inverse association between dietary intake and plasma concentration of antioxidants and vitamins and cardiovascular disease [32-33]. The decrease in the levels of vitamin C, and vitamin E may be the result of their increased utilization to entrap the ROS in DOCA-salt hypertensive rats compared to the sham-operated control rats in our study. Our results showed that treatment with the extract increases concentrations of vitamin E, and Vitamin C in hypertensive rats. It has been reported that vitamin E treatment has lower blood pressure and increased membrane fluidity in rats [34]. The major cellular endogenous antioxidant, GSH, plays the role of a sulfhydryl group provider for direct scavenging reaction catalyzed by GPx and as a scavenger of vitamin C and vitamin E radicals. It has been reported that treatment with an SCE can cause an increased generation of glutathione in the liver of rats. By increasing the generation of glutathione and by decreasing lipid peroxidation, the extract may enhance resistance of cells membrane to free-radical-mediated injuries.

In conclusion, these results suggest that administration of SCE possesses potent antihypertensive and antioxidant activity in DOCA-salt hypertensive rats.

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