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RESEARCH ARTICLE

SESAMOL EXERTS ANTIHYPERTENSIVE AND RENOPROTECTIVE EFFECTS IN A RAT MODEL OF DOCA-SALT-INDUCED HYPERTENSION

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ABSTRACT

This study aims to evaluate the effect of sesamol on blood pressure, and renal function markers on uninephrectomized deoxycorticosterone acetate (DOCA)-salt hypertensive rats. Hypertension was induced in surgically single-kidney-removed (left), adult male albino Wistar rats, weighing 180-200 g, by injecting DOCA (25 mg/kg BW) subcutaneously, twice a week for six weeks, with saline instead of tap water for drinking. Every week, the blood pressure was measured and documented up to six weeks for all the animals. DOCA-salt hypertensive rats showed considerably increased blood pressure, heart rate, proteinuria, renal function markers (urea, uric acid and creatinine) in plasma and sodium levels in urine. In addition, hypertensive rats showed a decreased body weight and potassium excretion. Oral administration of sesamol (50, 100 and 200 mg/kg BW) brought back all the above parameters to near normal level. The effect at a dose of 50 mg/kg BW of sesamol was more pronounced than that of the other two doses. These findings indicate that sesamol exhibits strong antihypertensive and renoprotective effects in DOCA-salt hypertensive rats.

INTRODUCTION

Hypertension is one of the most widespread cardiovascular disorders with approximately one billion people suffering from it worldwide (World Health Organization, 2003). Deoxycorticosterone acetate (DOCA)-salt (1 % NaCl) induced hypertension is salt dependent and acts by increasing blood volume and blood pressure. The DOCA-salt-induced model of hypertension is a type of pharmacologically-induced hypertension, which involves uninephrectomy (UNX), administration of a high dose of deoxycorticosterone and isotonic salt water as the sole drinking fluid. This model is easy to develop and cost effective. In DOCA-salt treated animals, sodium (Na^+) and water are absorbed in the kidney, which increases circulating blood volume and results in hypertension (Zuckerman and Yin, 1989). The role of sodium in the development of hypertension has consequently been widely studied. Salt retention is one of the characteristics of chronic human essential hypertension, which can be achieved rapidly in the mineralocorticoid hypertensive rat model (Iyer, Chan and Brown, 2010). We chose the DOCA-salt hypertensive rat model because it depicts end stage cardiac and renal damage. A large number of newer antihypertensive drugs have been introduced in the last two decades. Clinically, various antihypertensive drugs such as hypotensive diuretics, beta-receptor- blocking agents, calcium channel antagonists, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists and alpha-receptor blocking agents have been used to manage hypertension and alleviate symptoms. However, one thing that antihypertensive drugs are expensive with many adverse effects (Fatchi-hassanabad *et al.,* 2005). Therefore, there is a need for population based co-effective, adverse-effect-free hypertension control strategies. There has always been sustained research on plants as medicines. In recent years, much attention has been focused on the protective properties of exogenous antioxidants in biological systems, and on the mechanisms of their action. Sesame seeds and oil have long been categorized as traditional health food in India and other East Asian countries. It has been known for many years that sesame oil is highly resistant to oxidative deterioration as compared to other edible oils (Mohamed and Awatif, 1998), possibly due to the presence of antioxidative compounds of lignans (lowmolecular weight compounds produced by oxidative coupling of parahydroxyphenyl-propane), including sesamin and sesamolin. The lignans present in sesame oil are thought to be responsible for many of its unique chemical and physiological properties, including its antioxidant and antihypertensive properties. Sesamol is formed from decomposition of sesamolin during the processing of sesame oil. Sesamol is a phenolic derivative with a methylenedioxy group, and like vitamin E is known to be an antioxidant contained mainly in processed sesame oil (Nagata *et al.,* 1987). Several beneficial effects of sesamol, including antioxidative, chemopreventive, antimutagenic, antihepatotoxic activities, and protection of multi-organ failure have been reported (Kakkar *et al.,* 2011).

Therefore, the purpose of this study was to evaluate the effects of sesamol in the development of hypertension and renal function markers in DOCA-salt hypertensive rats.

MATERIALS AND METHODS

Animals

Albino Wistar male rats (*Rattus norvegicus*) 11-13 weeks old and weighing 180–200 g were obtained from Central Animal House, Department of Experimental Medicine, Rajah Muthiah Medical College and Hospital, Annamalai University, India and were housed in the central animal house with 12 h light and 12 h dark cycles. The animals were randomized into experimental and control groups and housed six in a polypropylene cage. The control and experimental animals were provided food and water *ad libitum*. The whole experiment was carried out according to the guidelines of the Committee for the Purpose of Control and Supervision of

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Experiments on Animals, New Delhi, India and approved by the Animal Ethics Committee of Annamalai University (Reg No: 160/1999/ CPCSEA).

Chemicals

Sesamol, DOCA and dimethyl formamide (DMF) were purchased from Sigma-Aldrich Chemical Company, St. Louis, MO. All other chemicals used in this study were of analytical grade obtained from Sisco Research Laboratories or Himedia, Mumbai, India.

Method of uninephrectomy

Rats were anesthetized by an intraperitonial injection of ketamine (75 mg/kg BW). The skin above the left kidney was shaved, cleaned and applied with iodine based antiseptic. The kidney was visualized by a left lateral abdominal incision (1 cm long), and freed from the surrounding tissues and pulled out gently. The left renal artery and ureter were tied by silk thread, and then the left kidney was removed and weighed. The muscle and skin layers were closed separately by using a chromic sterile absorbable suture. The animals were allowed to recover for 1 week.

Induction of hypertension

After the recovery period, uninephrectomized (UNX) animals were given weekly twice subcutaneous injections of DOCA-salt (25 mg/kg BW) in 0.4 mL of dimethyl formamide (vehicle) solution and salt was administered by substitution of 1% NaCl solution for drinking water *ad libitum* throughout the experimental period.

Experimental protocol

The rats were randomly divided into six groups each consisting of six rats. Sesamol was freshly solubilised in water and administered post-orally through a gavage once a day for six weeks between 9:00 am and 10:00 am.

Group 1 : UNX- control rats
Group 2 : UNX- control rats + sesamol (200 mg/kg BW)
Group 3 : DOCA-salt
Group 4 : DOCA-salt + sesamol (50 mg/kg BW)
Group 5 : DOCA-salt + sesamol (100 mg/kg BW)
Group 6 : DOCA-salt + sesamol (200 mg/kg BW)

Water intake and body weights were measured daily for all rats. At the end of the experimental period, rats were placed in metabolic cages, and 24 h urine samples were collected in sealed beakers. Protein concentration in the urine determined using the method of Bradford (1976), using bovine serum albumin as standard. After the experimental period, all the animals were anesthetized by an intramuscular injection of ketamine and sacrificed by cervical dislocation and biochemical studies were conducted on plasma, kidney and heart samples of control and experimental animals.

Blood pressure measurement

Systolic and diastolic blood pressure was measured and documented every week during the experimental period by the tail-cuff method (IITC, model 31, Woodland Hills, CA, USA). The animals were placed in a heated chamber at an ambient temperature of 30–34 ºC 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.

Biochemical estimations

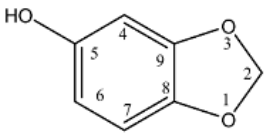
Urea in the plasma was estimated by using the diagnostic kit based on the method of Fawcett and Scott, (1960). Uric acid in the plasma was estimated by using the diagnostic kit based on the enzymic method described by Caraway, (1955). Creatinine in the plasma was estimated using the diagnostic kit based on the method of Tietz, (1987) using Jaffe's (1886) colour reaction. Sodium and potassium in urine were assayed by flame emission photometry using the method of Gowenlock (1988).

Statistical analysis

The data are expressed as means ± S.D. Statistical comparisons were performed by one-way analysis of variance (ANOVA) followed by Duncan's multiple range test (DMRT) using statistical package for the social science (SPSS) software version 11.5. The results were considered statistically significant if the *p*-values were 0.05 or less.

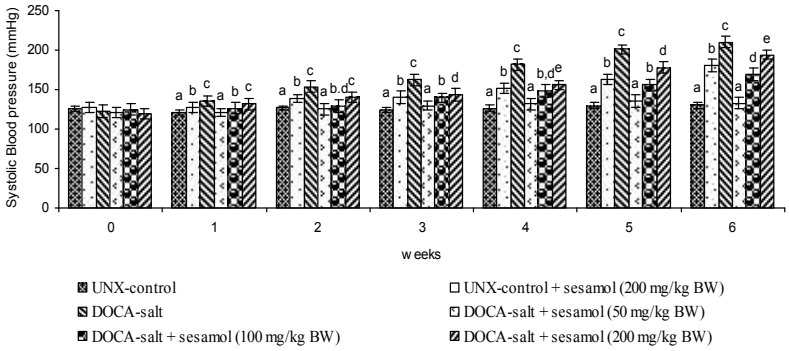
RESULTS

Figures 2, 3, 4 and 5 summarize the systolic, diastolic, mean arterial blood pressure and heart rate of DOCA-treated and UNX-control rats, respectively. The blood pressure and heart rate of DOCA-treated hypertensive rats was significantly higher than the control and administration of sesamol produced significant lowering effects on the blood pressure and heart rate, also 50 mg/kg BW dosage was better than other two doses. Figures 6 and 7 show the effect of oral administration of sesamol on body weight and water intake in UNX-control and DOCA-salt hypertensive rats, respectively. Hypertensive rats showed a decreased body weight and increased water intake and oral administration of sesamol improved the body weight and reduced the water intake.



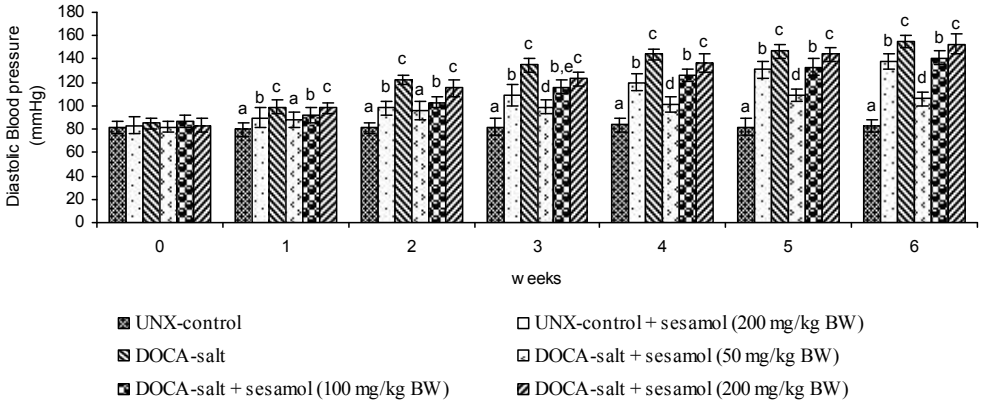
5-Hydroxy-1,3-benzodioxole

Figure 1. Structure of sesamol



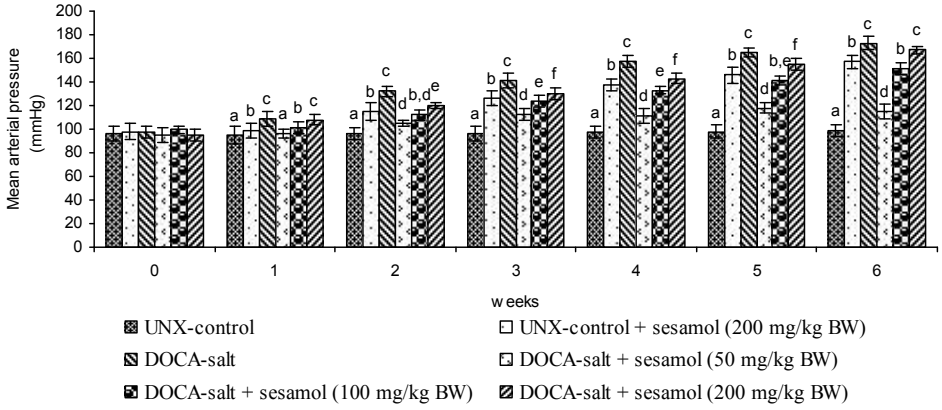
Values are means ± SD for six rats in each group
Values not sharing a common letter differ significantly at $p < 0.05$ (DMRT)

Figure 2. Effect of sesamol on systolic blood pressure in UNX-control and DOCA-salt hypertensive rats



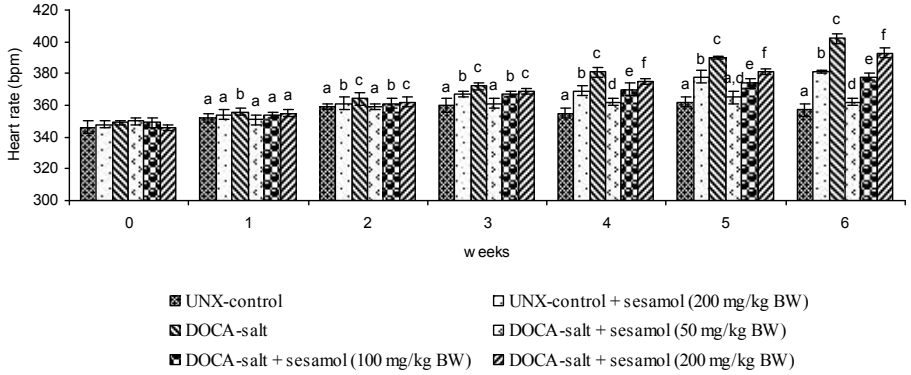
Values are means ± SD for six rats in each group
Values not sharing a common letter differ significantly at $p < 0.05$ (DMRT)

Figure 3. Effect of sesamol on diastolic blood pressure in UNX-control and DOCA-salt hypertensive rats



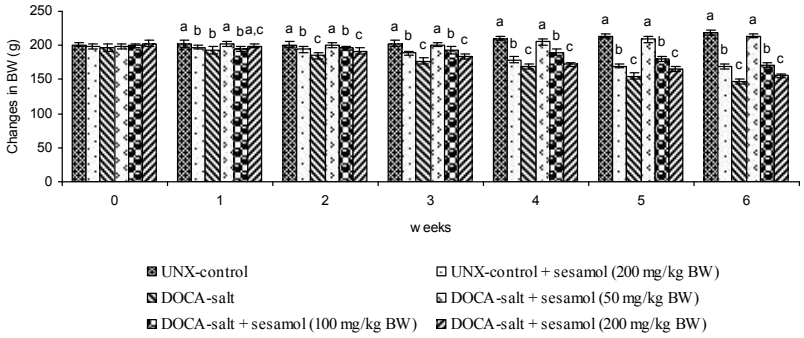
Values are means ± SD for six rats in each group
Values not sharing a common letter differ significantly at $p < 0.05$ (DMRT)

Figure 4. Effect of sesamol on mean arterial pressure in UNX-control and DOCA-salt hypertensive rats



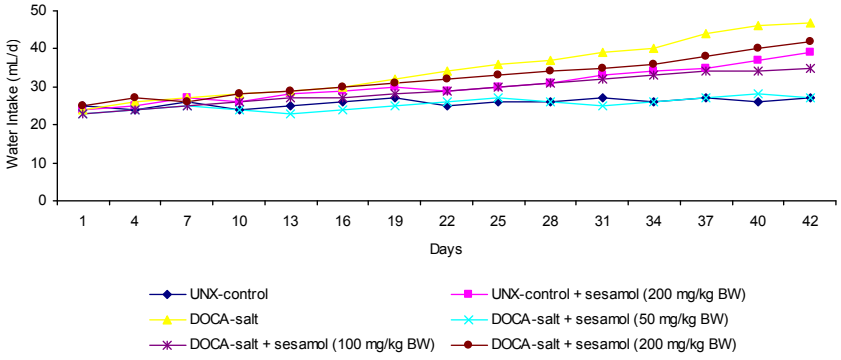
Values are means ± SD for six rats in each group
Values not sharing a common letter differ significantly at $p < 0.05$ (DMRT)

Figure 5. Effect of sesamol on heart rate in UNX-control and DOCA-salt hypertensive rats



Values are means ± SD for six rats in each group
Values not sharing a common letter differ significantly at p < 0.05 (DMRT)

Figure 6. Effect of sesamol on body weight in UNX-control and DOCA-salt hypertensive rats



Values are average of water intake for six rats in each group

Figure 7. Effect of sesamol on water intake in UNX-control and DOCA-salt hypertensive rats

Table 1. Effect of sesamol on the organ weights and proteinuria levels of UNX-control and DOCA-salt hypertensive rats

Groups	Kidney Wt. (mg)	Heart Wt.(mg)	Proteinuria (mg)
UNX- control	850.34 ± 2.32^{a}	796.90 ± 2.09^{a}	45.6 0 ± 0.72^{a}
UNX- control + sesamol (200 mg/kg BW)	1598.03 ± 5.58^{b}	1073.26 ± 5.11^{b}	66.89 ± 0.93^{b}
DOCA-salt	1869.78 ± 6.05^{c}	1249.82 ± 5.76^{c}	101.09 ± 1.14^{c}
DOCA-salt + sesamol (50 mg/kg BW)	910.02 ± 2.31^{d}	847.46 ± 3.09^{a}	50.73 ± 0.92^{a}
DOCA-salt + sesamol (100 mg/kg BW)	1241.56 ± 4.01^{e}	985.04 ± 3.11^{d}	79.43 ± 0.87^{d}
DOCA-salt + sesamol (200 mg/kg BW)	1655.45 ± 3.19^{f}	1193.78 ± 5.92^{e}	91.71 ± 1.05^{e}

Values are means ± SD for six rats in each group
Values not sharing a common letter differ significantly at p < 0.05 (DMRT)

Table 2. Effect of sesamol on the renal function markers of plasma in UNX-control and DOCA-salt hypertensive rats

Groups	Urea (mg/dL)	Uric acid (mg/dL)	Creatinine (mg/dL)
UNX- control	22.22 ± 1.44^{a}	1.42 ± 0.09^{a}	0.88 ± 0.07^{a}
UNX- control + sesamol (200 mg/kg BW)	34.16 ± 1.58^{a}	2.26 ± 0.11^{a}	1.78 ± 0.13^{a}
DOCA-salt	41.78 ± 2.05^{b}	3.52 ± 0.16^{b}	2.98 ± 0.19^{b}
DOCA-salt + sesamol (50 mg/kg BW)	24.02 ± 2.31^{c}	1.54 ± 0.09^{c}	0.97 ± 0.08^{c}
DOCA-salt + sesamol (100 mg/kg BW)	30.06 ± 2.01^{d}	1.99 ± 0.11^{d}	1.49 ± 0.08^{d}
DOCA-salt + sesamol (200 mg/kg BW)	36.45 ± 2.19^{e}	2.50 ± 0.12^{e}	2.07 ± 0.16^{e}

Values are means ± SD for six rats in each group
Values not sharing a common letter differ significantly at p < 0.05 (DMRT)

Table 3. Effect of sesamol on electrolytes level in the urine of UNX-control and DOCA-salt hypertensive rats

Groups	Sodium (µmol/mL)	Potassium (µmol/mL)
UNX- control	0.25 ± 0.03^{a}	0.04 ± 0.02^{a}
UNX- control + sesamol (200 mg/kg BW)	0.14 ± 0.01^{b}	0.20 ± 0.02^{b,e}
DOCA-salt	0.05 ± 0.01^{c}	0.29 ± 0.03^{c}
DOCA-salt + sesamol (50 mg/kg BW)	0.23 ± 0.02^{a}	0.07 ± 0.01^{d}
DOCA-salt + sesamol (100 mg/kg BW)	0.18 ± 0.02^{d}	0.16 ± 0.03^{d,e}
DOCA-salt + sesamol (200 mg/kg BW)	0.10 ± 0.01^{e}	0.23 ± 0.02^{b,c}

Values are means ± SD for six rats in each group
Values not sharing a common letter differ significantly at p < 0.05 (DMRT)

Table 1 shows the effect of sesamol on the weight of kidney and heart and proteinuria levels in UNX-control and DOCA-salt hypertensive rats. DOCA-salt rats had significantly increased kidney and heart weight and proteinuria. Treatment with sesamol significantly reduced the kidney and heart weight and protein levels in urine. The level of urea, uric acid and creatinine in the plasma of UNX-control and hypertensive rats are shown in Table 2. The levels of urea, uric acid and creatinine elevated significantly in the plasma of hypertensive rats. Hypertensive rats treated with sesamol showed these parameters towards normality. Table 3 shows the effect of sesamol on the levels of sodium and potassium in urine of control and DOCA–salt hypertensive rats. Administration of DOCA-salt for 6 weeks in UNX-rats showed a significant decrease in Na^+ excretion and increase in K^+ excretion at the end of 6 weeks as compared to UNX-control rats. Uninephrectomized rats which received sesamol for 6 weeks along with DOCA-salt showed a significant increase in Na^+ excretion and decrease in K^+ excretion as compared to DOCA-salt rats.

DISCUSSION

The present study highlights the effect of sesamol on blood pressure, urinary sodium, potassium excretion and renal function. Sesamol reduced BP, urine sodium excretion, and proteinuria and increased levels in urine K^+ excretion. This indicates that sesamol reduced the elevated BP in DOCA-salt hypertensive rats possibly through its antioxidant action. The long term administration of DOCA, a synthetic mineralocorticoid, with salt drinking water in UNX-rats has been reported to cause hypertension which is initiated in part by salt retention promoted by treatment with mineralocorticoid and uninephrectomy (Tomaschitz *et al.,* 2010). DOCA-salt hypertension is characterized by volume expansion and increased cardiac output, endothelial dysfunction, glomerulosclerosis and proteinuria. The DOCA-salt rat, a suitable model to allow the testing of natural and synthetic compounds for their effects on cardiovascular remodeling, provides opportunities for the development of new therapeutic agents (Iyer, Chan and Brown, 2010). In our study, sesamol reduced blood pressure as measured by tail cuff method, vascular reactivity changes and reversed DOCA-salt induced increase in heart rate. Administration of sesamol remarkably reduced the blood pressure. Sesamol might have reduced the vascular O_2^- production by inhibiting the activity of NADPH oxidase, an enzyme which is known to be a main source of O_2^- production (Ying *et al.,* 2011), and is increased in the vascular tissues of DOCA-salt hypertensive rats. Sustained high blood pressure is a powerful determinant of cardiac and renal hypertrophy development (Banker *et al.,* 2011). Our study revealed that the water intake and wet weights of kidney, and heart were significantly increased in DOCA-salt hypertensive rats, which are in line with previous studies (Takaoka *et al.,* 2001). Administration of sesamol reduced the water intake, kidney, and heart hypertrophy. In the present study, the significantly decreased body weight in DOCA-salt hypertensive rats might be due to the excretion of proteins by urine as reported earlier (Pinto, Paul and Ganten, 1998).

Proteinuria, which consists mainly of albuminuria, can be used as an intermediate endpoint indicating elevated intraglomerular pressure and renal damage, as well as a marker indicating treatment efficacy (de Zeeuw *et al.,* 2004). Proteinuria has also been identified as a pathway that has an independent role in the development of renal damage (Abbate *et al.,* 1998). A decline of the glomerular filtration rate (GFR) is delayed when proteinuria is decreased with antihypertensive therapy, and the protection of renal function achieved with antihypertensive therapy has been shown to be dependent on the extent of initial proteinuria (Peterson *et al.,* 1995). The significant prevention of body weight decreased in sesamol treated groups might be due to a reduced excretion of proteins in the urine. The significantly increased water intake and kidney, heart weight in DOCA-salt rats as reported earlier (Chan, Hoey and Brown, 2006) might be due to sodium and water retention. The significant reduction in water intake, renal and cardiac hypertrophy by the oral administration of sesamol might be due to its diuretic effect. The kidney plays a pivotal role in the regulation of body salt and water balance, and then disordered regulation of renal functions is liable for the altered balance of salt and water in pathophysiological states including some experimental models of hypertension (Mohring *et al.,* 1975). Kidneys maintain optimum chemical composition of body fluids by acidification of urine and removal of metabolite wastes such as urea, uric acid and creatinine. Nephrotoxicity is one of the major side effects of drug therapy in clinical practice, frequently leading to acute renal failure. Uninephrectomy before the development of hypertension markedly accelerates the progression of renal injury. On the other hand, uninephrectomy leads to adaptive functional and structural compensatory responses in the remnant kidney, resulting in increased glomerular flow and pressure (Dworkin and Feiner, 1986). The increase in urea, uric acid and creatinine concentration can be attributed to the hypertension, which is known to accelerate the decline in renal function even in people without renal disease (Matti *et al.,* 1995). Our results showed that a considerable increase in plasma urea, uric acid and creatinine levels in DOCA-salt hypertensive rats, might be due to kidney damage caused by the oxidative stress by increasing the formation of superoxide. Administration of sesamol noticeably reduced the increased kidney function marker levels, which might be due to the antioxidant activity of sesamol. The electrolytes, sodium and potassium play a vital role in the normal regulation of blood pressure (Karppanan, 1991). A number of studies suggested that intracellular sodium overload and potassium depletion may be important in the pathophysiology of hypertension (Leiba, 2005). In particular, these electrolytes have an important interrelationship in the control of arterial resistance. These electrolytes also regulate the fluid balance of the body and, hence, influence cardiac output (Blaustein, 1984). Thus, sodium excretion is central to blood pressure modulation. Decreasing sodium excretion increases fluid volume and leads to high cardiac output. Potassium can influence cell membrane stabilization and vascular smooth muscle relaxation (Das, 2000). In this study, DOCA-salt hypertensive rats showed a significant decrease in Na^+ excretion and increase in K^+ excretion when compared with UNX-control rats. Administration of sesamol elevated the sodium excretion and reduced the potassium excretion by modulating the Na^+-K^+ pump and thereby maintain the electrolytes levels in hypertensive rats.

Conclusion

In conclusion, our data shows that oral administration of sesamol reduces elevated blood pressure and renal function markers in the DOCA-salt-hypertensive model, possibly through its potent antioxidant and diuretic activity.

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Conflict of interest

There is no conflict of interest to be disclosed.

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