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AQUEOUS EXTRACT OF *HIBISCUS SABDARIFFA* ALONE OR IN COMBINATION WITH VALSARTAN ATTENUATES RENOVASCULAR HYPERTENSION IN RATS

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ABSTRACT

The present study was designed to investigate the possible modulative effects of aqueous extract of *Hibiscus sabdariffa* (HS) either alone or in combination with valsartan on hypertensive male albino rats. Renovascular hypertension was induced by ligation of left renal artery for 4 weeks. HS in a dose of 250 mg/kg, valsartan in a dose of 5 mg/kg and their combination were given daily to hypertensive rats for 45 days as single oral daily dose. HS either alone or in combination with valsartan reduced blood pressure (BP) and heart rate of hypertensive rats. It also increased aortic glutathione content (GSH) and super oxide dismutase (SOD) activity. It improved lipid profile, decreased nitric oxide (NO) levels and improved the histopathological changes of aorta. Valsartan alone decreased BP more than HS, increased aortic GSH content, aortic SOD activity and NO serum level but failed to correct lipid profile. Based on this study, it can be concluded that HS alone and in combination with valsartan showed potent antihypertensive effects. This effect may be mediated via antioxidant, hypolipidemic effects and correction of lowered serum NO levels. Valsartan has more potent antihypertensive effect than HS but it was not able to correct dyslipidemia and histopathological changes associated with hypertension.

INTRODUCTION

Hypertension is a common and significant health problem with high rates of mortality and morbidity. *Hibiscus sabdariffa L.* (Malvaceae) is a plant known in many countries and is consumed as hot and cold drinks. It has been used in folk medicine to protect against hypertension [1-2], and inflammation [3]. It is used as an antibacterial, antifungal, antihypercholesterolemic, diuretic, uricosuric, mild laxative and antihypertensive substance [4].

Previous reports revealed that aqueous extract of *Hibiscus sabdariffa* relaxes pre-contracted endothelium-intact and endothelium-denuded aortic rings *in vitro* [5-6].

Tiamjan [6] reported that HS caused bradycardia and hypotension in normal rats and exhibited negative inotropic and negative chronotropic effects on isolated guinea pig atria. Administration of HS to hypertensive humans and laboratory animals caused a reduction in blood pressure [1]. HS has also been reported to significantly reduce BP in normal rats [5-6] and anesthetized cats [7].

Valsartan is a non peptide angiotensin receptor antagonist that selectively blocks the binding of angiotensin II to the angiotensin II type 1 receptor [8]. It is used in the treatment of hypertension, heart failure and post myocardial infarction. However, many drugs (like calcium channel blockers and diuretics) are used in combination with valsartan [9-10].

The present study investigated the influence of HS either alone or in combination with valsartan on some cardiovascular and biochemical changes induced by hypertension in rats.

EXPERIMENTAL

Preparation of HS

Hibiscus extract was prepared as previously described [11]. Dry calyces of Hibiscus sabdariffa were authenticated by Professor Assem El Shazly, Department of Pharmacognosy, College of Pharmacy, Zagazig University. These calyces were ground to powder, soaked in hot water (100°C), and allowed to stand for about 1 h at room temperature. The mixture was stirred vigorously and intermittently. At the end of this period, the residue was sieved off using a piece of gauze. The solution was filtered using Whatman's No. 1 filter paper at least twice and the residue was discarded. The obtained filtrate was left 1-2 days to evaporate to a pasty residue at room temperature. The pasty residue was stored in a deep freezer at -20°C until required.

Animals

Male albino rats weighing 200-250 g were obtained from the National Research Centre, Cairo, Egypt. They were housed in plastic cages (4/cage) with free access to water and rodent chow diet at constant humidity and 12h light-dark cycle. All animal procedures were performed after approval from the ethical committee of the National Research Centre Cairo, Egypt and in accordance with the recommendations for the proper care and use of laboratory animals (Canadian Council on Animal Care Guidelines, 1984).

Induction of hypertension

Male albino rats were anaesthetized using IP injection of thiopental sodium in a dose of 40 mg/Kg [12]. After shaving the hair and sterilization of the skin with topical antiseptic and alcohol, 2 cm-long incision was made at the left side just below the ribs and 0.5 cm away from the vertebral column. The left renal artery was identified then stretched with a retractor placed between the kidney

and the muscle layer; the artery was separated from the vein with a hook and dissected from the surrounding connective tissue [13]. The exposed left renal artery was completely ligated with 4-0 sterile surgical silk (instead of using clip) as close as possible to the aorta. The incision was closed by careful continuous suturing of the muscle layer of 4-0 silk with a non cutting needle; then the skin was approximated and closed with interrupted sterile surgical O-silk sutures [14]. Postoperatively, the rats were given penicillin G (100,000 units I.M per rat) for three successive days; and were allowed free access to food and water for 28 days [13].

Sham control

In this group, the effect of surgical intervention on the arterial blood pressure was evaluated. Identical surgical procedures were performed except that the ligation was placed loosely around the renal artery [14].

Experimental design

Animals were randomly divided into 3 groups. Group 1 (n = 10) served as control and given 0.5% carboxy methyl cellulose (CMC) orally; group 2, sham operated rats (n = 10) given also 0.5% CMC orally; group 3, hypertensive rats (n = 40) was subdivided into 4 equal subgroups; subgroup 1 given 0.5% CMC orally throughout the period of the study ; subgroup 2 given 250 mg/kg HS extract; subgroup 3 given 5 mg/kg valsartan suspended in 0.5 % CMC; subgroup 4 was given both HS and valsartan in the same doses stated above. All drugs were given as single daily dose orally for 45 days after induction of hypertension.

Blood pressure measurement

The rats were anaesthetized with ip urethane (ethyl carbamate) in a dose of 1.75-2.0 g/kg body weight [15]. The blood pressure of rats was determined by employing the method of Burden et al. [16]. After stabilization of anesthesia, the animal was placed on a board in the supine position. The four limbs were extended and fixed to each sides of the board. A mid line longitudinal skin incision started just below the neck and extended to the sternum was done, the skin removed and pretracheal muscles and fascia were separated. The trachea was then exposed and dissected for a suitable distance. Lateral to the trachea on the left side, the pulsation of the common carotid artery was located. The artery was separated from accompanying nerves (vagus and cervical sympathetic nerves) and internal jugular vein was carefully freed from connective tissue for a distance as long as possible. A tight ligature of the artery was applied at its distal end (cephalic end), while a loose ligature was applied around the artery at its proximal end (thoracic end). A small snip across the artery was opened by a small sharp scissors and the polyethylene arterial cannula filled with heparinized saline solution was inserted gently towards the heart, the ligature was tied around the cannula.

The right external jugular vein was exposed just under the skin at the side of the neck guided by its surface anatomy. The venous cannula with 3 way valve; fixed to tuberculin syringe, which was filled with normal saline containing 16 I.U. /ml heparin. It was inserted into the vein in the same manner as done for the artery except that the bulldog clamp was first applied proximally, and a ligature was tied a little distally while the vein was filled with blood. After fixing the cannula in position, the bulldog clamp was removed and 0.2 ml of heparinized saline solution was injected to prevent clot formation.

Blood and tissue sampling

Blood samples were collected from carotid artery after measuring the blood pressure and heart rate in the various groups. Serum was separated by centrifugation at 3500 rpm for 20 min, clear serum was obtained and divided into three aliquots, which were then stored at -20°C for determination of various biochemical parameters. The rats were sacrificed and their aortas removed, part was preserved in 10% neutral buffered formalin solution until histopathological examination and the other part was immediately immersed in liquid nitrogen and then kept at -20 for determination of aortic GSH and SOD contents.

Biochemical analysis

Serum cholesterol, triglycerides and HDL levels were determined by enzymatic methods using commercially available kits [17-19]. Serum LDL level was calculated by the use of Friedewald equation [20]. Reduced GSH and SOD were determined according to the colorimetric methods of Beutler et al. [21] and Nishikimi et al. [22] respectively using Biodiagnostic kit, Egypt. Serum calcium and nitric oxide were determined according to the colorimetric methods of Montgomery & Dymock [23] and King et al. [24] respectively using Biodiagnostic kit, Egypt. A flame photometer was used for sodium and potassium and adjusted to give a direct reading of the concentration of the ion in solution in mEq/L using prepared solutions of different concentrations of a standard solution of the particular electrolyte (sodium chloride and potassium chloride salts).

Statistical analysis

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Vol. 19, No. 2, pp, 20-29

Results were expressed as mean ± SEM. Statistical analysis was performed using one-way analysis of variance (ANOVA), and Tukey's multiple comparison tests using SPSS software version 12, SPSS Science, Chicago, Illinois, USA. Value at $P< 0.05$ was considered significant.

RESULTS

Sham operated rats

There was no difference between control and sham operated rats for all parameters measured (Table 1).

Hypertensive rats

Induction of renovascular hypertension caused a significant increase in MAP, heart rate, serum TC, TGs, LDL, and VLDL. On the other hand, it reduced serum K^+, HDL and NO levels, aortic SOD activity and GSH content. It had no significant effect on serum levels of Ca^{++} or Na^+ when compared with sham operated rats (Table 2). Histopathological examination of the aorta of hypertensive rats showed dilatation of the lumen with blood inside it and adventitial hemorrhage (Fig 1).

Treated groups

Effect on mean arterial blood pressure (MAP) and heart rate

HS, valsartan or their combination induced a significant decrease in MAP when given for 45 days after induction of hypertension compared to hypertensive rats. HS alone or in combination with valsartan also induced a significant decrease in heart rate when compared with hypertensive rats. However, valsartan alone did not induce a significant change in heart rate (Table 3).

Effect on lipid profile:

HS or HS/ valsartan combination induced a significant decrease in serum level of cholesterol, TGs, LDL and VLDL and a significant increase in serum level of HDL when given 45 days after induction of hypertension compared to hypertensive rats. Valsartan alone did not induce a significant change in all parameters of lipid profile compared to hypertensive rats (Table 4).

Effect on serum electrolytes:

HS, valsartan or combination of HS and valsartan did not alter the serum level of calcium, potassium or sodium compared to hypertensive rats (Table 5).

Effect on GSH and SOD

HS, valsartan or combination of HS and valsartan induced a significant increase in GSH and SOD compared to hypertensive rats (Fig.2, 3).

Effect on serum NO:

HS, valsartan or combination of HS and valsartan induced a significant increase in NO level compared to hypertensive rats (Fig.1).

Histopathological results:

HS either alone or in combination with valsartan normalized histopathological changes in aorta (Fig.4).

Table (1): Effect of sham operation on Mean arterial Blood pressure (MAP), heart rate and different biochemical parameters.

Parameters	Control	Sham operated
MAP (mmHg)	96.7±3.2	102.2±1.9
Heart rate (beats/min)	297.5±21	302.5±20.3
Serum Cholesterol (mg/dl)	71.9±6.7	62.3±5.5
Serum Triglycerides(TGs) (mg/dl)	19.3±1.3	21.1±0.9
Serum HDL-C (mg/dl)	37.8±2.7	40.4±1.2
Serum LDL-C (mg/dl)	27.6±1.8	21.8±2.1
Serum VLDL-C(mg/dl)	3.9±0.3	4.2±0.2
Serum Ca (mg/dl)	9.2±0.1	9.0±0.1
Serum K (mEq/L)	5.0±0.2	5.1±0.1
Serum Na (mEq/L)	140.6±3.6	139.6±0.4
Aortic GSH (nmol/gm tissue)	56.0±2.1	51.2±2.5
Aortic SOD (U/gm tissue)	62.2±1.5	57.8±1.3
Serum NO (µmol/L)	23.7±1.3	24.8±0.6

Values are presented as mean ±S.E *(n=10)*

Table (2): Effect of induction of hypertension on Mean arterial Blood pressure (MAP), heart rate and different biochemical parameters.

Parameters	Sham operated	Hypertensive rats
MAP (mmHg)	102.2±1.9	151.8@±7.5
Heart rate(beats/min)	302.5±20.3	357.5@±10.5
Serum Cholesterol (mg/dl)	62.3±5.5	110.0@±8.6
Serum TGs (mg/dl)	21.1±0.9	38.5@±2.4
Serum HDL-C (mg/dl)	40.4±1.2	16.9@±1.3
Serum LDL-C (mg/dl)	21.8±2.3	87.0@±7.7
Serum VLDL-C(mg/dl)	4.2±0.2	7.7@±0.5
Serum Ca (mg/dl)	9.0±0.1	9.2±0.1
Serum K (mEq/L)	5.1±0.1	3.9@±0.2
Serum Na (mEq/L)	139.6±0.4	132.4±3.0
Aortic GSH (nmol/gm tissue)	51.2±2.5	25.8@±1.2
Aortic SOD (U/gm tissue)	57.8±1.3	35.4@±1.3
Serum NO (µmol/L)	24.8±0.6	20.2@±0.5

Values are presented as mean ±S.E *(n=10)*, @ Significantly different from sham operated rats at $p<0.05$.

Table (3): Effect of HS (250 mg/kg/day), valsartan (5 mg/kg/day) or their combination for 45 days on mean arterial blood pressure and heart rate in hypertensive rats.

Treatment	MAP(mmHg)	Heart rate (beats/min)
Hypertensive rats	151.8±7.6	357.5±10.5
HS	72.8#α±5.3	287.5©#±20.8
Valsartan	65.0#±4.3	317.5±15.2
HS +valsartan	65.2#±5.6	305#±11.4

Values are presented as mean ±S.E (n=10), # Significantly different from hypertensive rats at $p<0.05$, © Significantly different from valsartan at $p<0.05$.

Table (4): Effect of HS (250 mg/kg/day), valsartan (5 mg/kg/day) or their combination for 45 days on serum level of cholesterol, TGs, HDL), LDL and VLDL in hypertensive rats

Treatment	Cholesterol (mg/dl)	TGs(mg/dl)	HDL (mg/dl)	LDL(mg/dl)	VLDL (mg/dl)
Hypertensive	110.0±8.6	38.5±2.4	16.9±1.3	87.0±7.7	7.7±0.5
HS	62.0©#±5.1	24.5©#±1.4	29.3©#±1.7	34.5©#±3.3	4.9©#±0.3
Valsartan	105.3±6.0	34. 8±1.9	16.6±1.0	81.8±5.7	7.0±0.4
HS +valsartan	58.7#±4.9	26.3#±1.4	30.5#±2.5	27.4#±3.4	5.3#±0.3

Values are presented as mean ±S.E *(n=10)*, # Significantly different from hypertensive rats at $p<0.05$, © Significantly different from valsartan at $p<0.05$.

Table (5): Effect of HS (250 mg/kg/day), valsartan (5 mg/kg/day) or their combination for 45 days on serum calcium, potassium and sodium in hypertensive rats.

Treatment	Serum calcium (mg/dl	Serum potassium (mEq/L)	Serum Sodium (mEq/L)
Hypertensive	9.2±1.2	3.93±0.18	132.4±3.0
HS	9.1±0.04	3.5±0.2	130.0±5.1
Valsartan	9.2±0.1	4.3±0.2	127.0±3.5
HS +valsartan	9.3±0.1	4.3±0.1	131.6±4.4

Values are presented as mean ±S.E *(n=10)*

Zagazig J. Pharm. Sci., December, 2010
Vol. 19, No. 2, pp. 20-29

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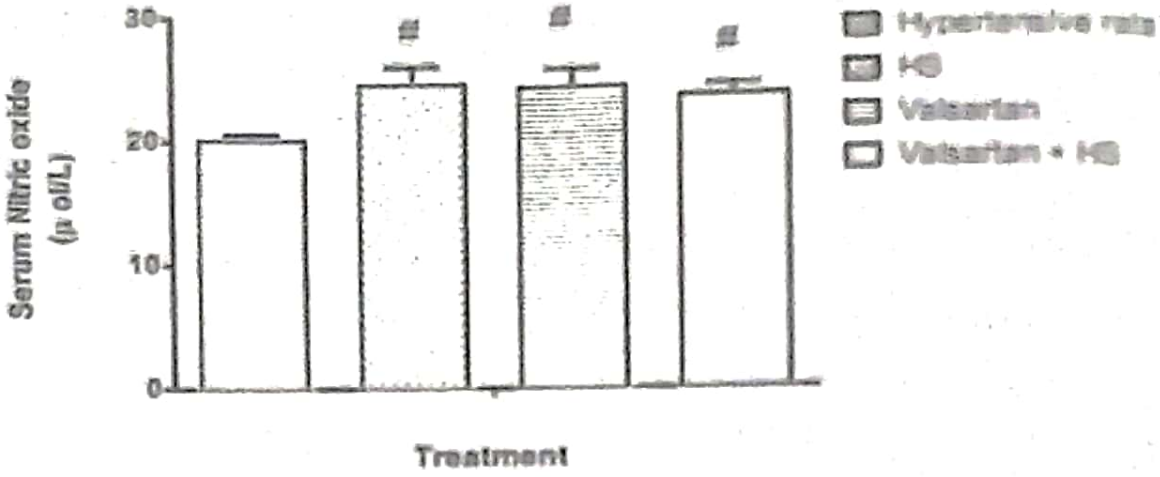

Fig. (1). Effect of HS (250 mg/kg/day), valsartan (5 mg/kg/day) or their combination for 45 days on serum nitric oxide level in hypertensive rats.
Values are presented as mean ±S.E (n=10), # Significantly different from hypertensive rats at p<0.05

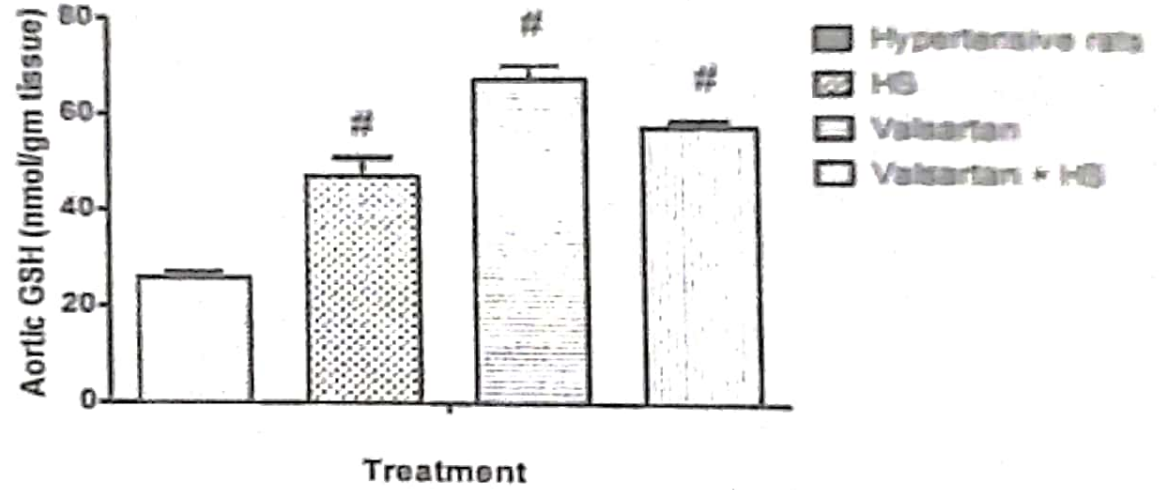

Fig. (2). Effect of HS (250 mg/kg/day), valsartan (5 mg/kg/day) or their combination for 45 days on aortic GSH content in hypertensive rats.
Values are presented as mean ±S.E (n=10), # Significantly different from hypertensive rats at p<0.05

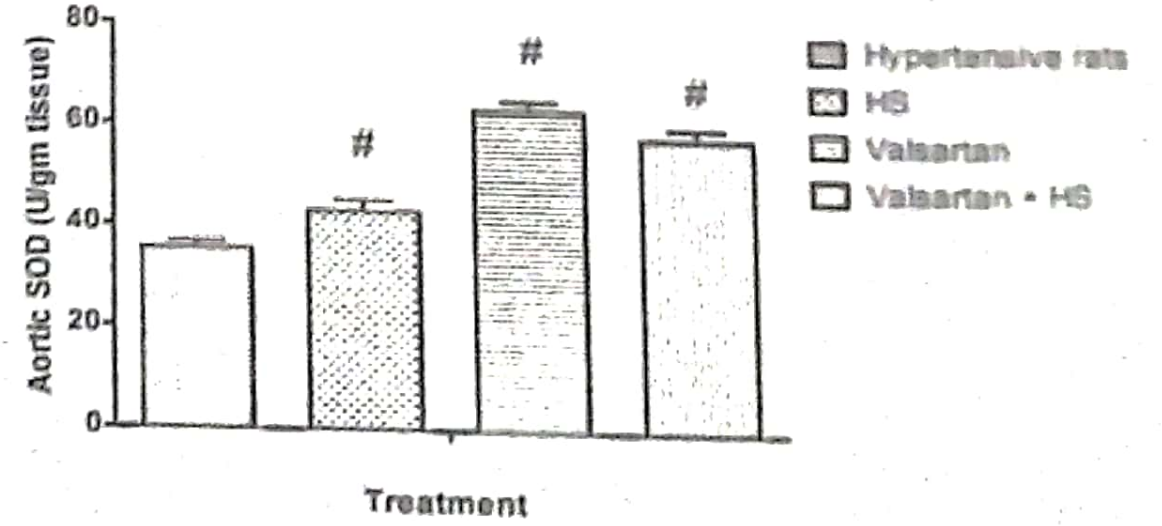

Fig. (3). Effect of HS (250 mg/kg/day), valsartan (5 mg/kg/day) or their combination for 45 days on aortic SOD content in hypertensive rats.
Values are presented as mean ±S.E (n=10), # Significantly different from hypertensive rats at p<0.05

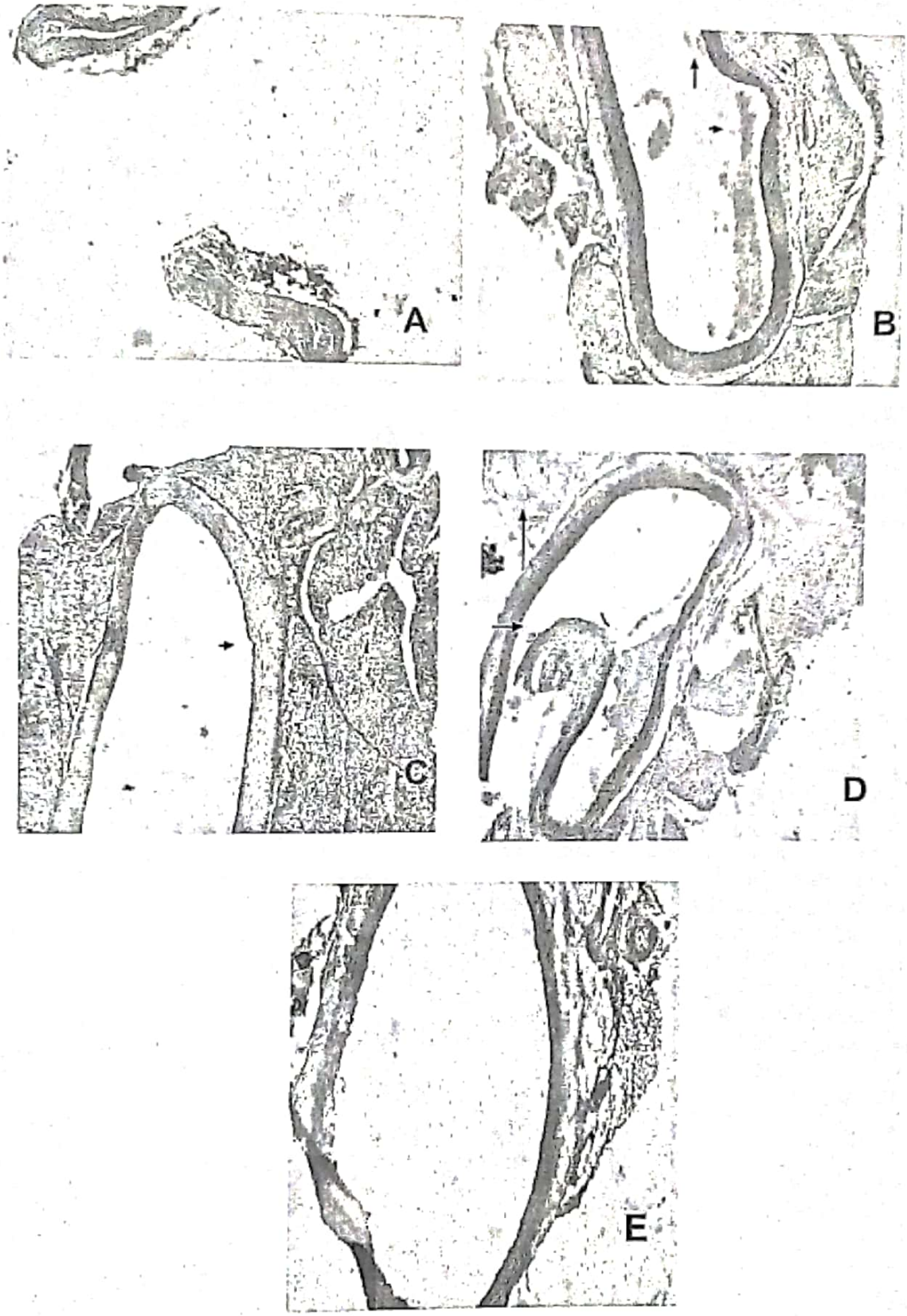

Fig. (4). A: represents the aorta of normal rat showing normal tunics. B: represents the aorta of hypertensive rat showing mild unilateral vascular dilatation (→) with little amount of blood inside its lumen. Moreover, advential hemorrhage was encountered (↑).C: represents the aorta of hypertensive rat treated with HS (250mg/kg/day) Showing normal tunics (→) and lumen D: represents aorta of hypertensive rat treated with valsartan (5mg/kg/day) showing slight aneurismal dilatation (→) with little amount of blood inside it together with stretched and edematous wall and perivascular hemorrhage (↑).E: represents the aorta of hypertensive rat treated with hs (250mg/kg/day) and valsartan (5mg/kg/day) showing a mild dilatation of lumen without blood inside it. Tunics appeared normal (H&E x120).

Zagazig J. Pharm. Sci., December, 2010
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DISCUSSION

In the present work, the 2-kidney 1-clip model was used as an animal model of hypertension. This model led to the development of hypertension within 4 weeks. It is similar to human renovascular hypertension in many aspects including endothelial dysfunction and increased oxidative stress [25].

The present study showed that hypertensive rats treated with HS, valsartan or their combination significantly lowered MAP. The antihypertensive effect of HS or its combination with valsartan was not significantly different from valsartan alone. The hypotensive effect of HS may be mediated via NO. This is confirmed in the present study by elevation of serum NO levels. It may be partly via inhibition of Ca^{2+} influx through receptor-gated channels [5-11]. However, this is not proved in the current study as HS did not change serum Ca levels. Cholinergic and histamine like mechanisms have also been implicated [5, 6]. The hypotensive effect of HS may be attributed to HS natriuretic effects or angiotensin converting enzyme (ACE) inhibition [34].

Valsartan alone did not induce any change in heart rate. On the contrary, HS or its combination with valsartan reduced heart rate to normal levels. This may be due to a negative chronotropic effect of HS [6].

Hibiscus extract and combination of HS and valsartan significantly lowered Cholesterol, TGs, LDL and VLDL. Moreover, they significantly increased the level of HDL to normal levels. The results of the present study is similar to that observed in previous studies [35-40]. These hypolipidemic effects were better than valsartan alone. It was reported that accumulation of oxidatively modified low-density lipoprotein (Ox-LDL) in the arterial wall, promotes endothelial cell (EC) dysfunction and the development of atherosclerosis [41, 42].Thus the hypolipidemic effect of HS and its combination with Valsartan may protect against endothelial dysfunction and modulate hypertension. However, valsartan alone did not change serum lipid profile when compared with non treated hypertensive rats.
of hypertension [26-28] and in studies using spontaneous hypertensive rats [29].

The decrease in serum nitric oxide observed in the present study (after ligation of renal artery) may be due to the elevation of angiotensin II (Ang II) level associated with

In the current study, the MAP and HR rose significantly in hypertensive rats after 45 days of induction of hypertension compared to normal and sham operated rats. In addition, induction of renal hypertension caused a significant increase in serum cholesterol, TGs, LDL and VLDL while the serum concentration of HDL was decreased. Also, there was a significant decrease in aortic GSH and SOD contents. The results obtained are similar to that observed in other studies using this model

renovascular hypertension. It has been shown that Ang II decreases the expression of nNOS in the brain, decreases the secretion of NO from the posterior hypothalamus [30], inhibits IL-1β-stimulated iNOS expression and decreases nitrite release in rat isolated aortic vessels [31] and cultured rat mesangial cells [32]. In rats chronically infused with doses of Ang II, the urinary nitrite concentration decreases reflecting a decrease in NO production [33]. In addition, oxidative stress associated with the reduction of aortic GSH and SOD may be responsible for NO reduction, as superoxide anion reacts with NO forming peroxynitrite anion thus reducing free NO and impairs endothelial dependent relaxation and produces more deleterious effects.

The present study showed an increase in aortic GSH content and SOD in all treated groups. Valsartan was the most potent one in this respect. The antioxidant properties of HS may be due to polyphenolic acid, flavonoids and anthocyanins contents [39, 43, 44]. Various antioxidant constituents are found in the calyx of HS, such as anthocyanin, quercetin, L-ascorbic acid and protocatechuic acid. Antioxidant effects of these constituents have been investigated in many experimental models. In a previous study, dried calyx extract of HS exerted an antioxidant effect on LDL oxidation induced by CuSO4 *in vitro* [40].

HS, valsartan and their combination in all tested groups showed a significant increase in serum NO levels. HS and valsartan showed similar potency in elevating NO levels. The increase in the serum total nitrite may be due to the increase of bradykinin, which acts on endothelial receptors to increase NO production. Anthocyanin contents of HS caused an inhibition of angiotensin converting enzyme [34] thereby reducing Ang II levels and elevating NO and serum nitrite levels. Valsartan may increase serum nitrite through partial amelioration of Ang II-mediated effects.

In the present study, induction of renovascular hypertension did not induce any change in the levels of Na^+ or Ca^{++} but caused

a significant decrease in K^+ levels when compared with control and sham operated groups. Enhanced potassium excretion is known to stimulate renal kallikrien release [45] and reduced level of kallikrien has been implicated in the pathogenesis of 2K-1C hypertension [46]. Levels of Na^+, K^+ and Ca^{++} did not change significantly in all treated groups compared with the hypertensive rats.

It has been reported that any infusion rates of valsartan did not significantly affect plasma ions in conscious spontaneous hypertensive rats [47]. In the presence of renal insufficiencies, valsartan did not raise serum K^+ to the same degree as the ACEI, lisinopril [48]. Histopathological examination of aorta showed that induction of hypertension caused dilatation of the lumen of aorta which contained blood. HS and combination of HS and valsartan showed some improvement of the aorta, while valsartan alone did not cause any improvement.

CONCLUSION

This study was the first to our knowledge in comparing valsartan with HS .We showed that HS alone and in combination with valsartan showed potent antihypertensive effects. Valsartan had a more potent antihypertensive effect than HS but failed to correct dyslipidemia and histopathological changes associated with hypertension. Further studies using lower doses of HS are required to avoid reduction of blood pressure to subnormal levels.

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Author Contribution

Mona Fouad Mahmoud designed research, followed up practical work and wrote the manuscript. Mohamad Ismail Abozaid performed the practical work. Doaa Abdullah Sourour followed up practical work. El-Maraghy, Nour El Din. Nabila followed up practical work and revised the manuscript.

Conflict of Interest:

The authors report no conflict of interest.

REFERENCES

1. Faraji M. H., Tarkhani A. H., **J. Ethnoparmacol,** 65, 231 (1999).
2. Onyenekwe P. C., Ajani E. O., Ameh D. A., Gramanil K. S., **Cell Biochem. Funct.,** 17, 199 (1999).
3. Dafallah A. A., al-Mustafa Z., **Am. J. Chin. Med.,** 24 (1), 263 (1996).
4. Farnsworth N. R., Bunyapraphatsara N. **Thai Medicinal Plants,** Prachachon Press, Bangkok, pp. 163-166 (1992).
5. Adegunloye B. J., Omoniyi J. O., Owolabi O. A., Ajagbona O. P., Sofola O. A., Coker H. A., **Afric. J. Med. Med. Sci.,** 25, 235 (1996).
6. Tiamjan R., M.Sc. Thesis. Chiang Mai University, Chiang Mai, Thailand (1999).
7. Ali M. B., Salih W. M., Mohamed A. H., Homeida A. M., **J. Ethnopharmacol.,** 31, 249 (1991).
8. Black H. R., Bailey J., Zappe D., Samuel R., **Drugs,** 69(17), 2393 (2009).
9. Flack J. M., Hilkert R., **Expert. Opin. Pharmacother.,** 10(12), 1979 (2009).
10. Destro M, Crikelair N, Yen J, Glarez R. **Vascular Health and Risk Management,** 6, 821 (2010).
11. Obiefuna P. C. M., Owolabi O. A., Adegunloye B. J., Obiefuna I. P., Sofola O. A., **Int. J. Pharmacogn.,** 32, 69 (1993).
12. Bearnes C. D., Etherington L. G., Drug dosage in laboratory animals. A handbook 2nd ed., University of California Press Barkly and Los Angeles (1964).
13. Douglas J. R., Johnson E. M., Heist J. F., Marshall G. R., Needleman P., **J. Pharmacol. Exp. Therap,** 196, 35 (1976).
14. Cangiano J. L., Rodriguez-Sargnt C., Martinez-Maldonado M., **J. Pharmacol. Exp. Ther,,** 208(2), 310 (1979).
15. Iwamoto K., Chein C., Kato E., **J. Pharmacodyn.,** 10(6), 280 (1987).
16. Burden D. T., Balber L. C., Natoff I. L., **Pharmacol. Ther.,** 5, 99 (1979).
17. Burstein M., Scholnick H. R., Morfin R., **Lipid Res.**11, 583 (1970).
18. Allain C. C., Poon L. S., Chan C. S., Richmond W., Fu P. C., **Clin. Chem.,** 20(4):470 (1974).
19. Fassati P., Prencipe L., **Clin. Chem.,** 28(10), 2077 (1982).
20. Friedewald W. T., Levy R. I., Frederickson D. S. **Clin. Chem.,** 18, 499 (1972).
21. Beutler E., Duran O., Kelly M. B., **J. Lab. Clin. Med.,** 61,882 (1963).
22. Nishikimi M., Appaji N., Yagi K., **Biochem. Bioph. Res. Common.,** 46, 849 (1972).

ISSN 1110-5089

23. Montgomery H. A. C., Dymock J. F. **Analyst.**, 86, 414 (1961).
24. King W. W., Cox C. E., Boyce W. H., **J. Urol.**, 107(5), 809 (1972).
25. Welch W. J., Mendonca M., Aslam S., Wilcox C. S., **Hypertension.** 41:692 (2003).
26. Sagar S., Kallo I. J., Kanl N., Ganguly N. D,, Sharma B. K., **Mol. Cell Biochem,** 111:103 (1992)
27. Kumar C. A., Das U. N., **Med. Sci. Monit**, 6, 901 (2000).
28. Pedro-Botet J., Covas M. I., Martin S., Rubies-Part J., **J. Hum. Hypertens.,** 14,343 (2000).
29. Newaz M. A., Nawal N. N. A., **Am. J. Hypertens.**, 11, 1480 (1998).
30. Campese V. M., Ye S., Zhong H., **Hypertension**, 39, 519 (2002).
31. Monton M., Lopez-Farre A., Mojquero J. R., De Miguell L. S., Garcia-Duran M., Sierra M. P., Bellver T., Rico L., Casado S., **Hypertension,** 30, 1191 (1997).
32. Kihara M., Yabana M., Toya Y., Kobayashi S., Fujita T., Iwamoto T., Ishigami T., Umemura S., **Kidney Int.,** 55, 1277 (1999).
33. Ortiz M. C., Sanabria E., Manrique M. C., Romero J. C., Juncos L. A. **Hypertension,** 37,505 (2001).
34. Ojeda D., Jimenez-Ferre E. , Zamipla A., Herrera-Arellano A., Tortoriello J., Alvarez L., **J. Ethnopharmacol.,** 127(1),7 (2010).
35. El-Saadany S. S., Sitohy M. Z., Labib S. M., **Die Nahrung.,** 35, 567 (1991).
36. Tseng T. H., Wang C.J., Kao E. S., Chu H. Y., **Chem. Biol. Interact.**, 101, 137 (1996).
37. Duh P. D., Yen G. C., **Food Chem. Toxicol.**, 60, 639 (1997).
38. Tseng T. H., Kao T. W., Chu C. Y., Chou F. P., Lin W. L., Wang C. J., **Biochem. Pharmacol.**, 60, 307 (2000).
39. Wang C. J., Wang J. M., Lin W. L., Chu C. Y., Chou F. P., Tseng T. H., **Food Chem. Toxicol.,** 38, 411 (2000).
40. Hirunpanich V., Utaipat A., Morales N. P., Bunyapraphatsara N., Sato H., Herunsalee A., Suthisisang C., **Biol. Pharm. Bull.,** 28, 481 (2005).
41. Aikawa M., Libby P., **Cardiovasc. Pathol.**, 13, 125 (2004).
42. Takahashi Y., Zhu H., Yoshimoto T., **Antioxid. Redox Signal.**, 7, 425 (2005).
43. Crawford R. S., Kirk E. A., Rosenfeld M. E., LeBoeuf R. C., Chait A., **Arterioscler. Thromb. Vasc. Biol.**, 18, 1506 (1998).
44. Rimm E. B., Stamfer M. J., **Med. Clin. North Am.**, 84, 239 (2000).
45. Obika L. F., Amurawaiye B. S., Etok-Akpan E., Oduleye S. O., **Pharmacol. Res. Commun.**, 20(1), 49 (1988).
46. El-Dahr SS, Dipp S, Guan S, Navar LG. **Am. J. Hypertens.**, (11), 914 (1993).
47. Chow L., De Gasparo M., Levens N., **Eur. J. Pharmacol.**, 282, 77 (1995).
48. Bakris G. L., Weir M. R., **Arch. Intern. Med.**, 160,685 (2000).

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المستخلص المائى للكركديه وحده او مجتمعا مع الفالسرتان يخفض ضغط الدم المرتفع فى الجرذان البيضاء المصابة بارتفاع ضغط الدم الكلوى

نبيلة نور الدين المراغى و منى فؤاد محمود و محمد اسماعيل ابوزيد و دعاء عبدالله سرور
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صممت هذه الدراسة للتحقيق في الآثار المحتملة للمستخلص المائي لنبات الكركديه إما وحده أو بالاشتراك مع الفالسرتان على ارتفاع ضغط الدم فى الجرذان البيضاء المصابة بارتفاع ضغط الدم ، وتم احداث ارتفاع ضغط الدم بواسطة ربط الشريان الكلوي الأيسر لمدة 4 أسابيع. أعطيت الحيوانات الكريديه بجرعة 250 ملج / كلج ، الفالسرتان بجرعة 5 مغ / كغ يوميا وكلاهما بنفس الجرعات السابقة لمدة 45 يوما جرعة واحدة يوميا عن طريق الفم.تبين عند اخذ النتائج بعد تللك المدة ان الكركديه سواء اعطى على حدة أو بالاشتراك مع الفالسرتان قد قلل ضغط الدم المرتفع ، ومعدل ضربات القلب وزاد أيضا الجلوتاثيون المخزل فى الشريان الابهر ونشاط انزيم السوبر أكسيد ديسموتاز. كما ادى الى تحسين مستوى الدهون فى الدم، وانخفاض أكسيد النيتريك وتحسين التغيرات المرضية التى ظهرت فى انسجةالشريان الأبهر نتيجة ارتفاع ضغط الدم. اما عند تجريع الجرذان الفالسرتان وحده فقد انخفض ضغط الدم الرتفع أكثر مما حدث مع الكركديه وزاد الجلوتاثيون المختزل فى الابهر ونشاط انزيم سوبر اكسيد ديسموتاز لكنه فشل في تصحيح مستوى الدهون المرتفع فى الدم. استنادا إلى هذه الدراسة ، يمكننا أن نستنتج أن الكركديه وحده ، وبالاشتراك مع الفالسرتان أكثر فعالية من الفالسرتان بمفرده فى علاج ضغط الدم المرتفع وتصحيح مستوى الدهون فى الدم بسبب تاثيره المضاد للأكسدة وتصحيح مستوى اكسيد النيتريك على الرغم من ان الفالسرتان اقوى من الكركديه فى خفض ضغط الدم المرتفع لكنه ليس قادرا على تصحيح اضطراب الدهون والتغيرات النسيجية المرتبطة بارتفاع ضغط الدم.