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Original Research Article

Antihypertensive and Cardioprotective Effects of *Salvia officinalis* (*Sage*) Leaf in N^G-Nitro-L-Arginine Methyl Ester (L-NAME) Induced-Hypertensive Wistar Rats

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ABSTRACT

Salvia officinalis (Common Sage) is a medicinal plant, used for the treatment of various disorders. The aim of this study was to evaluate the antihypertensive and cardioprotective effects of Nigerian grown Sage leaf extract in L-NAME induced hypertensive rats. Twenty- four male Wistar rats divided into four groups were used for the study. Group A served as control, while hypertension was induced in groups B-D by the administration of 40 mg/kg of L-NAME orally. Group A (Control), Group B; L-NAME (40 mg/kg/day), Group C; L-NAME (40 g/kg/day) plus Sage plant leaf extract (500 mg/kg/day) and Group D; L- arginine (100 mg/kg/day) plus L-NAME (40 mg/kg/day). They were fed with feed and water *ad-libitum* for 28 days. Blood pressure was measured by tail-cuff weekly. On 29th day, serum was collected for the determination of Lactate dehydrogenase (LDH), creatinine phosphokinase-MB isoenzyme (CK-MB), aspartate transaminase (AST), alanine transaminase (ALT), total cholesterol (Tchol) and triglycerides (TG), and were measured in an AS-120 Auto-Analyzer (E.LabBST, China: BA-88A). Group C and D resulted to decrease in the systolic blood pressure in Weeks 3 and 4 at a significant ($p < 0.05$) level compared to Group B. There was significant ($p < 0.05$) reduction in haemodynamic parameters in groups B & C in comparison with group A. There was significant ($p < 0.05$) decrease in the levels of CK-MB, LDH, AST, ALT, Tchol and TG in groups C & D compared with group B. Administration of Sage leaf extract with L-NAME possesses anti-hypertensive and cardioprotective activity in L-NAME induced hypertension in rats.

Keywords: Hypertension, L-NAME, *Sage officinalis* leaf, Biochemical parameters, Rats.

Introduction

Hypertension is a major risk factor of ischemic heart disease.[1,2] Hypertension has been defined as a chronic elevation of systolic arterial blood pressure of greater than 140/90mmHg.[3] It is an important risk factor for stroke, coronary heart diseases (myocardial infarction, heart failure and arterial aneurysm). It is also a cause of chronic kidney failure.[4-6] Essential hypertension which is mild to moderate is often asymptomatic and referred to as silent killer.[7]There are endothelial activation and alterations in vascular tone, vascular reactivity, coagulation and fibrinolytic pathways in hypertensive patients.[3] Hypertension is a great burden the world over with Africa being the most affected. Nigeria constitute a major part of this burden with her ever growing population.[8] *Salvia officinalis* (Common sage), a perennial evergreen subshrub which grows spuriously in Vom-Jos, Plateau State-Nigeria could be of a great health benefits in the treatment of various human diseases.[9] The hypoglycaemic and hypo-lipidemic activities of *Sage officinalis* has also been documented.[9-12] The potential use of *Sage officinalis* as a natural and skin friendly hand sanitizer has been suggested.[13] Also, a comprehensive medicinal perspective property of sage plant has been documented.[14] Majority of the common therapeutic drugs for the management of cardiovascular abnormalities have attendant side effects.

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The search for alternative inexpensive therapies with little or no side effects led to the evaluation of *Sage officinalis* leaf extracts as a possible antihypertensive and cardioprotective drug.

Materials and Methods

Authentication and preparation of plant extract

The Sage plant from Vom-Jos, Plateau State was identified/authenticated by a botanist (Michael, Ozioma Emmanuel). A voucher number (DELSU#134) was assigned to it and stored for future reference. The leaves were cut into small pieces, dried at a temperature of 30 -40^{o}C for 21 days. The dry leaves were pulverized to obtain a fine powder. 50 g was weighed and added to 400 ml absolute ethanol in a flask. It was shaken at regular intervals for 3 days at room temperature. The mixture was filtered using muslin cloth and concentrated by vacuum evaporator. The extract obtained was kept in an airtight sample bottle, labelled and stored in the refrigerator.

Preparation of the extract solution

Weighed quantity of ethanol extract of the *Sage officinalis* leaf (500 mg/kg) was suspended in distilled water.

The Chemical

Analytical grade of N^G-Nitro- L-arginine methyl ester (L-NAME) and L-arginine were purchased from a registered DEMEK Pharmaceutical in Nigeria for induction of hypertension.

Animal Experiment

The research was approved by the Research and Ethics Committee, Faculty of Science, Delta State University, Nigeria and given the reference number REC/FOS/20/01. Apparently healthy male Wister rats weighing between 150-250 g were used in the study. The animals

were properly housed, fed with standard growers' marsh and water *ad libitum***.**

Acute Oral toxicity study
This was performed using OECD-423[15] guideline for animal study. Female Swiss albino mice weighing 20-24 g, divided into two groups of six animals each were used. One group was given 2,000 mg/kg body weight of the Sage leaf extract while the second group received 5,000 mg/mg body weight of the Sage leaf extract orally. They were observed for symptoms of toxicity and mortality for 72 hours.

Experimental design/protocol
Twenty-four male Wister rats were randomly divided into four groups of six rats each (A, B, C and D). Blood pressure was measured by tail-cuff weekly. Group A served as control and had feeds and water only daily for 28 days while hypertension was induced in groups B, C and D by the administration of 40 mg/kg body weight of L-NAME orally.[16] Group B: L-NAME (40 mg/kg body weight/day) fed with feed and water *ad-libitum*. Group C: L-NAME (40 g/kg body weight /day) plus Sage plant leaf extract (500 mg/kg body weight /day) which was dissolved in normal saline given orally, fed with feed and water *ad-libitum*. Group D: L-NAME (40 mg/kg body weight /day) plus Sage plant leaf extract (100 mg/kg body weight /day) and fed with feed and water *ad-libitum.*
The L-NAME (40 mg/kg) and L-arginine (100 mg/kg) were administered through oral route in distilled water using oral feeding gauges daily for 28 days. The L-NAME, L-arginine and Sage plant leaf extract were made into normal saline and were given to the animals through oral route using oral gauge for the 28 days.

Sample Collection
At the end of the protocol period, blood samples were taken from the retro-orbital plexus of each animal following the last treatment dose using plain capillary tube into 5 ml blood container. The blood was allowed to cloth and centrifuged at 3000 rpm for 5 minutes for separation of serum. Separated serum was properly labelled and stored at -8^{o}C pending biochemical analysis.

Haemodynamic parameters
Fourty-eight hours post animal experiment, the rats were anaesthetized with urethane (1.25/kg). Then cannulation of the right carotid artery of each of the animals with cannula filled with heparinized saline and connected to pressure transducer for the measurement of systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and mean arterial blood pressure (MABP). At the end of stabilization, haemodynamic parameters were recorded by the eight channel Power lab recorder (AD instrument).

Biochemical parameters
Lactate dehydrogenase (LDH) by Bermeyer (1972), creatinine phosphokinase-MB isoenzyme (CK-MB) by Young (1975), aspartate transaminase (AST) and alanine transaminase (ALT) by Reitman and Frankel (1957) methods were measured using Mindray assay kits (Shenzhen China). Total cholesterol (Tchol) by Allain et al., (1974) and triglycerides (TG) by Rifai et al., (1999) methods were measured using an AS-120 Auto-Analyzer (E.LabBST, China: BA-88A). The animals were sacrificed and then cervical decapitation was conducted before laparotomy section. The liver, kidney and heart were weighed.

Statistical Analysis
Data obtained were expressed as mean ± standard error of mean (SEM) and subjected to one-way ANOVA using Dunnett's t-test. A *p-value* of less than 0.05 was considered significant.

Results and Discussion

Acute toxicity
The acute toxicity test revealed that Sage plant leaf powder extract at 2,000 and 5,000 mg/kg body weight was non-toxic to the mice.

Measured biochemical parameters
There was increased activity in the levels of CK-MB, LDH, AST and ALT in group B (L-NAME) at a significant ($p < 0.001$, $p < 0.05$) level compared with group A (Control). There was also an increase in the serum total cholesterol (Tchol) and triglycerides (TG) at a significant ($p < 0.05$) level compared with the group A-Control (Table 1). There was significant ($p < 0.05$) decrease in the activities of CK-MB, LDH, AST and ALT. There was a decrease in the levels of Tchol and TG in group C (Sage 500mg/kg b. w. + L-NAME) and in group D (L-arginine + L-NAME) at a significant ($p < 0.05$) level in comparison with group B (L-NAME only) induction (Table 1).

Non-invasive blood pressure
The L-NAME induction alone (Group B) produced an increase in the systolic blood pressure at a significant ($p < 0.001$) levels in comparison to the Weeks 2, 3 and 4 of the group A (Control). However, the addition of Sage leaf plus L-NAME in Group C resulted to decrease in the systolic blood pressure in Weeks 3 and 4 at a significant ($p < 0.05$) level compared to Group B (L-NAME only) induction. Also the addition of L-arginine plus L-NAME in the Group D equally led to the reduction of systolic blood pressure (Table 2).

Invasive blood pressure (Haemodynamic parameters)
The mean values of haemodynamic parameters at the end of the L-NAME induced hypertension in the rats are shown in Table 3. The levels of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MABP) in Group A (Control) rats were 125.10 ± 1.36 mmHg, 94.18 ± 2.16 mmHg and 120.10 ± 2.46 mmHg respectively. The SBP, DBP and MABP in Group B (L-NAME only) were 165.10 ± 1.66 mmHg, 144.80 ± 0.16 mmHg and 150.10 ± 0.68 mmHg in that order. While the SBP, DBP and MABP in Group C (Sage leaf plus L-NAME) were 1.45.10 ± 3.16 mmHg, 124.60 ± 2.16 mmHg and 130.80 ± 1.14 mmHg. Equally, the SBP, DBP and MABP in Group D (L-arginine + L-NAME) showed mean concentrations of 141.30 ± 1.65 mmHg, 121.90 ± 1.10 mmHg and 124.6 ± 1.46 mmHg respectively. From the results, while L-NAME induced hypertension is shown by the increased levels of invasive blood pressure (haemodynamic parameters), the addition of the Sage leaf extract appreciably reduced the levels of the same haemodynamic parameters indicating that the Sage leaf possesses hypotensive effect on the rats compared to the Group B which is the L-NAME alone. The Group D (L-arginine + L-NAME) equally indicated a significant reduction on the invasive blood pressure parameters in comparison with Group B. The results showed that both the Sage leaf and L-arginine administration to the rats produced a significant ($p < 0.05$) reduction of the hypertensive effect of the L-NAME in the rats.

Weight of organs
The mean weights of the Group A (Control): heart, kidney and liver were 0.32 ± 0.07, 0.31 ± 0.04 and 3.40 ± 0.14 respectively. That of Group B (L-NAME) were heart (0.84 ± 0.18), kidney (0.64 ± 0.13) and liver (7.20 ± 0.24). The Group C (Sage leaf extract 500 mg/kg body weight. + L-NAME) showed heart (0.48 ± 0.26), kidney (0.42 ± 0.19) and liver (4.80 ± o.38). L-arginine + L-NAME (Group D) had values of 0.38 ± 0.16 for heart, 0.34 ± 0.21 for kidney and 3.80 ± 0.16 g for liver (Table 4). The results revealed an increase weight of the organs in Group B compared to the Control Group A. There was a reasonable decrease in the weight of the organs both in Groups C and D which contain the administration of the Sage leaf and L-arginine respectively.
N^{G} –nitro-L-arginine methyl ester (L-NAME) is known to induce hypertension in rats. L-NAME induction of arterial hypertension is associated with its ability to cause deficiency of nitric oxide (NO) whose inhibition results to perivascular inflammation.[1] It has been reported that NO controls the coronary vascular tone and as such its decrease is responsible for coronary ischemia and infarction.[3,17,18] Endogenious biomarkers are commonly released as a result of inflammatory damage to specific organs. The increase levels of cardiac biomarkers, CK-MB and LDH along with AST and ALT in serum is due to the organ damage caused by L-NAME (Table 1). Also the deficiency of NO is involved in the alteration of lipid metabolism.

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Table 1: Effect of Sage plant leaf on biochemical parameters in rats' induced-hypertension

GROUPS	CK-MB(IU/L)	LDH(U/L)	AST(U/L)	ALT(U/L)	TCHOL(mg/dl)	TG(mg/dl)
A. CONTROL	18.00 ± 1.20	90.20 ± 12.41	120.00 ± 6.85	30.10 ± 1.20	90.27 ± 6.17	80.18 ± 2.75
B. L-NAME (40 mg/kg)	64.10 ±3.60***	220.40±10.36***	210.10±10.18***	68.40 ± 3.60***	176.90 ± 8.66***	168.43 ± 4.96**
C. Sage l (500 mg/kg + L-NAME (40 mg/kg)	42.50 ± 2.48*	180 .00 ± 12.12*	184.60 ± 3.82*	43.48 ± 2.47*	143.21 ± 10.31*	128.10 ± 3.37*
D. L-arginine (100 mg/kg) + L-NAME (40 mg/kg)	32.40 ± 2.30**	156.10 ± 10.80**	160.10 ± 8.51*	38.60 ± 2.63*	138.67 ± 12.49*	116.14 ± 3.19*

Values are expressed as mean ± SEM (n=6) ****P < 0.001* values compared to control groups. **P < 0.05*, ***P < 0.01*, values compared to L-NAME groups.

Table 2: Effect of Sage plant leaf on non-invasive blood pressure (Tail –cuff method) in rats' induced-hypertension

	Systolic blood pressure (mmHg)			
Groups'	Week 1	Week 2	Week 3	Week 4
A. CONTROL	118.20 ± 1.42	118.30 ± 1.36	118.30 ± 1.36	118.30 ± 1.36
B. L-NAME (40 mg/kg)	121.30 ± 1.54	137.10 ± 2.46**	149.00 ± 2.60**	165.30 ± 2.13**
C. Sage l (500 mg/kg + L-NAME (40 mg/kg)	125.50 ± 1.38	130.30 ± 5.10	138.10 ± 4.64*	132.10 ± 1.28*
D.L-arginine (100 mg/kg) + L-NAME (40 mg/kg)	120.20 ± 1.40	131.50 ± 5.17	127.30 ± 2.40*	118.9 ± 1.24*

Values are expressed as mean ± SEM (n=6) ***P < 0.001* values compared to control groups. **P < 0.05* values compared to L-NAME groups.

Table 3: Effect of Sage plant leaf on haemodynamic parameters in rats' induced-hypertension

	SBP(mmHg)	DBP(mmHg)	MABP(mmHg)	BPM
A. CONTROL	125.20 ± 1.36	94.18 ± 2.16	120.30 ± 2.36	310.30 ± 6.18
B. L-NAME (40 mg/kg)	165.30 ± 1.16**	144.80 ± 0.46**	150.10 ± 0.68**	390.30 ± 7.13**
C. Sage l (500 mg/kg + L-NAME (40 mg/kg)	145.10 ± 3.18*	124.30 ± 2.16*	130.10 ± 1.14*	350.10 ± 3.26*
D. L- arginine (100 mg/kg) + L-NAME (40 mg/kg)	141.20 ± 1.65*	121.90 ± 1.17*	124.60 ± 2.46*	330.9 ± 12.14*

Values are expressed as mean ± SEM (n=6) ***P < 0.01* values compared to control groups. **P < 0.05* values compared to L-NAME groups.

Table 4: Effect of Sage plant leaf on rats' organs in L-NAME induced-hypertension

GROUPS	Heart	Kidney	Liver
A. CONTROL	0.32 ± 0.07	0.31 ± 0.06	3.40 ± 0.16
B. L-NAME(40 mg/kg)	0.84 ± 0.18**	0.64 ± 0.16**	7.10 ± 0.28**
C. Sage l (500 mg/kg + L-NAME(40 mg/kg)	0.48 ± 0.28*	0.43 ± 0.16*	4.80 ± 0.38*
D. L-arginine (100 mg/kg) + L-NAME(40 mg/kg)	0.38 ± 0.15*	0.34 ± 0.21*	3.80 ± 0.16*

Values are expressed as mean ± SEM (n = 6) ***P < 0.01* values compared to control groups. **P < 0.05* values compared to L-NAME groups

This is shown in the serum total cholesterol and triglycerides increase as depicted in our work. These findings are in agreement with previous work. [1,3] where increased levels of CK-MB, LDH, AST ALT, total cholesterol and triglycerides at very high concentrations in L-NAME induced hypertensive rats were observed. In this work, the reduction of these biochemical parameters vis –a- vis the alteration of cardiovascular activities in L-NAME induced hypertension could be attributed to the presence of flavonoids and other phytochemicals in sage leaf.[19] The reduction of non-invasive blood pressure in Table 2 as well as the haemodynamic parameters in Table 3 by the administration of sage leaf portrays the anti-hypertensive and cardioprotective activity of the Sage leaf. Also the attenuative activity of DBP as shown in Group C by the administration of sage plant leaf is significantly ($p < 0.05$) reduced in comparison with L-NAME induced hypertension in Group B. Several studies on *Salvia officinalis* showed that the plant has anti-inflammatory and antinociceptive effects.[20-26] Flavonoids are active principles of hosts of antihypertensive plants extracts and affect the inflammatory process of human body.[1,27] Flavonoids are known to possess both anti-inflammatory and immunodulatory actions both outside and inside of cells.[1,27] The decrease in the concentration of MABP in Group C is significant ($p < 0.05$) compared to L-NAME in Group B. Equally there is significant ($p < 0.05$) decrease in the level of both SEP and BPM in Sage leaf administered in Group C in comparison with Group B which is the L-NAME induction. There was significant ($p < 0.05$) decrease in the weight of the heart, kidney and the liver in Sage leaf administration in Group C as well as in Group D compared with Group B (L-NAME) induced hypertension.

Conclusion

The administration of Sage leaf extract resulted in anti-hypertensive and cardioprotective activity in L-NAME induced hypertensive Wistar rats. Therefore, we wish to suggest that Sage leaf extract could be of medicinal importance in the management of hypertension in man.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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