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RESEARCH ARTICLE

Antihypertensive, vasorelaxant and antidyslipidemic effects of *Santolina africana* in rats

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Abstract

Hypertension and dyslipidemia are major causes of cardiovascular disease. Medicinal plants continue to be widely used as therapeutic options for the management of cardiovascular diseases. *Santolina africana* is a medicinal and aromatic plant of the Asteraceae family, a plant family widely recognized for its beneficial pharmacological effects, particularly in managing cardiovascular diseases. This study aimed to evaluate the antihypertensive, vasorelaxant and antidyslipidemic properties of the aqueous extract of *S. africana* in animal models of hypertension and dyslipidemia. Normotensive and L-NAME-induced hypertensive rats were orally administered the aqueous extract of *S. africana* (SAAE) at the doses of 100 and 200 mg/kg and systolic, diastolic and mean blood pressure were measured. The vasorelaxant activity of SAAE and underlying mechanism were evaluated on isolated aortic rings with and without endothelium. Additionally, the antidyslipidemic effect of SAAE (250 and 500 mg/kg) was assessed in Triton WR-1339 induced hyperlipidemic model in rats. Results showed a significant, dose-dependent reduction in blood pressure values in hypertensive rats following SAAE administration. The vasorelaxant effect appeared to be endothelium-dependent and likely mediated by nitric oxide pathway. Furthermore, in Triton WR-1339-induced hyperlipidemic rats, the SAAE significantly lowered plasma levels of total cholesterol, triglycerides and LDL-cholesterol. These findings suggest that *S. africana* possesses significant antihypertensive, vasorelaxant and antidyslipidemic properties, highlighting its potential as a promising natural therapeutic agent for managing cardiovascular and metabolic disorders.

Keywords: antidyslipidemic; antihypertensive; endothelium-dependent; NO-mediated; *Santolina africana*; vasorelaxant

Introduction

Hypertension, defined as a persistent elevation of blood pressure, affects over 1.5 billion people worldwide and remains one of the leading causes of mortality and morbidity (1). It constitutes a major risk factor for cardiovascular disease, stroke and chronic kidney disease, which are responsible for approximately 17.9 million deaths annually (WHO, 2023) (2, 3). In clinical practice, hypertensive patients are frequently treated with a combination of antihypertensive drugs with distinct mechanisms of action, aiming to achieve a more potent pharmacological effect, although effective, they are often accompanied by considerable side effects (4-6). Indeed, dyslipidemia, characterized by abnormal blood lipid levels, often co-occurs with hypertension, increasing the risk of cardiovascular complications (7). It is therefore crucial to treat hypertension and dyslipidemia simultaneously for comprehensive cardiovascular risk management (8). As an alternative approach to the treatment of arterial hypertension and the management of dyslipidemia, medicinal plants contain a variety of components targeting several mechanisms, making them promising candidates for the management of hypertension and modulating lipid levels (9).

The Asteraceae family includes a wide variety of medicinal plants that have been recognized for their pharmacological activities, particularly in the management of cardiovascular disorders. Several species within this family have demonstrated antihypertensive, vasorelaxant and antihyperlipidemic effects (10).

Santolina africana is an endemic species from North Africa (11). It is an aromatic plant, known for its strong odour, that grows spontaneously in the rocky slopes of the mountains of the Moroccan Middle and High Atlas (12, 13). It has been traditionally employed to treat dysmenorrhea, digestive disorders and hypertension (14). In Morocco, *S. africana* is primarily used in traditional medicine as a stomachic, abortifacient, emmenagogue, antidiabetic and vermifuge (13).

To the best of our knowledge, there is no scientific study that has been conducted to determine the antihypertensive and antidyslipidemic effects of *S. africana*. In this context, the current study aimed to evaluate, for the first time, the antihypertensive effect of the aqueous extract of *S. africana*, to assess its vasorelaxant activity and evaluate its antidyslipidemic effect.

Materials and Methods

Plant material and extraction procedure

The aerial parts of *S. africana* were collected during the flowering period at Tizin'talghamt mountain (GPS 32.5888, -4.5659) in May 2023. The plant specimen (Voucher no: SA5) was deposited in the herbarium of the Faculty of Sciences and Techniques, Errachidia. The aqueous extract of the plant material was prepared by decoction as previously described: 10 g of dried aerial parts of *S. africana* were powdered and mixed with 1000 mL of distilled water. The mixture was boiled for 10 min, then left to cool for 15 min. The aqueous extract obtained was then filtered, freeze-dried and stored at -8 °C until use (15).

Animals

Adult male albino rats of the Wistar strain, weighing between 150 and 250 g, were used in this study. They were maintained under controlled, standardized environmental conditions, with *ad libitum* access to food and water. All animal experiments were conducted in accordance with the local ethical guidelines for the care and use of laboratory animals established by the Pharmacological Research Committee of FSTE, Moulay Ismail University (FSTE/2015).

Chemicals and drugs

Acetylcholine chloride, epinephrine (EP), N-nitro-L-arginine methyl ester (L-NAME), indomethacin, 4-aminopyridine (4-AP), barium chloride ($BaCl_2$) and triton WR-1339 (Tyloxapol) were obtained from Sigma Chemical Company, St. Louis, MO, U.S.A. Atropine was purchased from Chem Cruz (Chem Cruz Biochemicals, USA). Diasys reagent kits for serum analysis were obtained from Diasys company (Holzheim, Germany). All other drugs were available from local sources and were of analytical quality.

Phytochemical analysis

Preliminary phytochemical screening

The aqueous extract of *S. africana* (SAAE) was subjected to preliminary analysis to identify the presence of certain bioactive molecules, notably polyphenols, flavonoids, tannins, quinones, anthraquinones, saponins, glycosides, reducing sugars, terpenoids, sterols and alkaloids. These components were identified using standard methods (16).

Quantitative analysis of total phenolic, flavonoids and tannin contents

The total content of phenolic compounds in the SAAE was assessed according to the method previously described (17). In parallel, flavonoid content was quantified using a previously known technique (18). Tannin concentration was determined using another earlier known technique (19).

Acute toxicity assessment

The acute toxicity of the SAAE was assessed in rats, in accordance with the 423 guidelines of the Organisation for Economic Co-operation and Development (OECD) (20). It consisted of two steps, each using only three animals (females), with an initial dose of 2000 mg/kg selected as the limit dose according to the OECD Acute Toxic Class Method. The animals were kept in plastic cages in a controlled environment, with ambient temperature and humidity and a 12-hr light/dark cycle. They received a standard diet and free access to tap water. Prior to the extract administration, the animals were fasted overnight and weighed. They were then randomly divided into two groups of five animals: the control group received a physiological solution, while the experimental group received a single oral dose of 2000 mg/kg of SAAE. The rats were observed for 6 hr after administration and then daily over the following 14 days, to monitor their general behaviour, detect clinical signs of toxicity and record any mortality.

Induction of hypertension

In this study, hypertension was experimentally induced in male albino Wistar rats by oral administration of 80 mg/kg/day of L-NAME, dissolved in 1.5 mL distilled water, over a period of one week. Animals with systolic blood pressure equal to or greater than 150 mm Hg were identified as hypertensive and included in the study (21).

Blood pressure measurements

For this study, normotensive and hypertensive rats were randomly divided into four separate groups, each comprising six individuals. The 1st (control) group received distilled water, the 2nd and 3rd groups were treated respectively with SAAE administered at doses of 100 mg/kg and 200 mg/kg. The 4th group was administered furosemide (reference drug) at a dose of 20 mg/kg. For the single oral administration, animals received either distilled water (control group), furosemide or SAAE, the systolic blood pressure (SBP), mean arterial pressure (MBP) and heart rate (HR) were measured before starting the experiments (t_0), then 6 hr after oral administration (t_6). For the repeated oral administration, animals were treated daily for 7 days and blood pressure parameters (SBP, MBP and HR) were monitored throughout this period. Each group consisted of 6 rats (n = 6). All measurements were performed after slight anesthesia to avoid stress due to immobilization. To estimate arterial blood pressure, animals were placed in NIBP restrainers and a suitable cuff with a sensor was attached to their tails, then warmed to approximately 35 °C for 15 to 20 min to ensure reproducible measurements (three measurements per animal per session). Blood pressure measurements were conducted using a tail cuff connected to a computer-assisted monitoring device. SBP, MBP and HR were directly measured through pulse tracing, while the diastolic blood pressure (DBP) was calculated using the following formula: DBP = (3MBP - SBP)/2. All blood pressure measurements were conducted at the same time each day during the sub-chronic test period (21).

Vasorelaxant activity and evaluation of the underlying pharmacological mechanisms involved

Male Wistar rats, weighing between 250 and 300 g, were sacrificed by stunning and exsanguination under pentobarbital sodium anesthesia. Aortas were promptly excised and placed in cold buffer, then rapidly removed and carefully cleaned of adhering fat and connective tissue. The isolated arteries were transversally sectioned into rings of 2 to 3 mm in length and suspended at a resting force of 2 g in a continuously oxygenated tissue bath (95 % O_2, 5 % CO_2) and containing 40 mL of Krebs-Henseleit solution (KH), maintained at a

temperature of 37 °C and a pH of 7.4. Length changes were measured isometrically using a lever transducer (Erma, Tokyo). The thoracic aortic rings were gently introduced between two stainless steel hooks, one attached to the base of the chamber and the other to a UF1 force transducer (LCM Systems Ltd), connected to a PowerLab/400 ADInstrument data acquisition system (Harvard, Boyer, Casablanca, Morocco) to record signals corresponding to isometric tension. The study was performed on endothelium-intact aorta. To determine the functional integrity of the endothelium, the aortic rings were precontracted with 10^{-5} M of Epinephrine (EP) followed by the addition of acetylcholine (10 µM) to induce relaxation. Aortic rings that achieved at least 60 % relaxation were considered as endothelium-intact. In some parts of the preparations, the endothelium was mechanically removed by manually rubbing the luminal surface of the aorta with a cotton swab. Aortic rings showing no relaxation or relaxation of less than 10 % by acetylcholine were defined as endothelium-denuded. The optimal tension, selected from preliminary experiments, was the one that produced a maximal response at a concentration of 10^{-5}M EP. The aortic rings were given 2 g (100 %) of initial tension and allowed to equilibrate for 1h. Thirty minutes after setting up the tissue bath, aortic rings were contracted with 10^{-5}M of EP or 80 mM potassium chloride (KCl) solution to assess their contractile responses. After exposure to EP or KCL, the tissues were washed three times with Krebs solution to restore baseline tension and this solution was renewed every 40 min. In order to determine the cumulative dose-dependent curves for SAAE-induced relaxation, aortic rings were contracted by EP (10^{-5} M) and KCl (80 mM). Once contraction reached a stable plateau, SAAE was added cumulatively (250, 375, 500 and 625 µg/mL). At each dose of SAAE, the curve was allowed to reach a stable plateau before the addition of the next dose. To determine the potential mechanistic route involved in the vasorelaxant effect of SAAE on EP-precontracted aortic rings, the following experimental protocol was performed: 20 min before the addition of EP, the aortic rings were pre-incubated for 20 min with one of the following standard drugs: 1) 10^{-4} M L-NAME, a direct inhibitor of nitric oxide (NO) synthase. 2) 10^{-5} M methylene blue (MB), a NO-cyclic guanosine monophosphate (cGMP) blocker. 3) 10^{-5} M indomethacin, a prostaglandin synthesis inhibitor. 4) 10^{-6} M atropine a muscarinic receptor antagonist. 5) 10^{-5} M nifedipine, a calcium channel blocker. 6) 10^{-5} M propranolol, a beta-blocker. 7) 10^{-5} M glibenclamide, an ATP- sensitive K+ channel blocker. 8) 10^{-4} M barium chloride ($BaCl_2$) an inhibitor of inwardly rectifying potassium channels and 9) 10^{-4} M 4-aminopyridine (4-AP) a voltage dependent K+ channel inhibitor, then the cumulative concentrations of SAAE (250, 375, 500 and 625 µg/mL) were added before and after incubation with each of the above drugs and the response curve was extrapolated (22).

Effect of SAAE on Triton WR-1339-induced hyperlipidemic rats

To study the short-term effects of SAAE on hyperlipidemic rats induced by Triton WR-1339, adult female rats weighing 160-180 g were used in this study. Triton WR-1339 (Tyloxapol), dissolved in normal saline (pH 7.4), was administered via intraperitoneal injection to induce hyperlipidemia. The animals were fasted overnight, then randomly divided into five groups, each consisting of five rats (n=5). Group 1: (normal control): rats received distilled water 30 min before intraperitoneal injection of saline (pH 7.4). Group 2: (hyperlipidemic control): Rats received distilled water 30 min before intraperitoneal injection of Triton WR-1339 (300 mg/kg). Group 3: Rats received SAAE (250 mg/kg, p.o.) 30 min before Triton WR-1339 injection. Group 4: Rats received SAAE (500 mg/kg, p.o.) 30 min before Triton WR-1339 injection. Group 5: (Standard group): Rats received simvastatin (50 mg/kg) 30 min before Triton WR-1339 injection. After 24 hr of treatment, the rats were anesthetized and blood was drawn from the retro-orbital sinus using a heparinized capillary. Blood samples were immediately centrifuged at 5000 rpm/10 min and the plasma was used for lipid analysis (23).

Data analysis and statistics

Data are expressed as mean ± SEM. Statistical analyses were performed using GraphPad Prism version 8 (GraphPad Software Inc., San Diego, CA., U.S.A). To determine statistical significance, one-way and two-way analysis of variance (ANOVA) were performed, followed by the Bonferroni test for multiple comparisons. Statistical significance was recognized as $p<0.05$.

Results

Phytochemical screening and quantitative analysis of polyphenols, tannins and flavonoid contents

The preliminary phytochemical evaluation of SAAE indicated the presence of various bioactive constituents, including polyphenolic compounds, flavonoids, tannins, alkaloids, carbohydrates, reducing sugars, anthraquinones, sterols, sesquiterpenes, terpenoids and saponins. Whereas the analysis did not detect the presence of glycosides and quinines (Table 1). The total phenolic content of SAAE was quantified at 228.54 ± 0.81 mg of gallic acid equivalents per gram of extract, utilizing gallic acid as the reference standard to construct the calibration curve. The total flavonoid content in the same extract was measured at 204.13 ± 0.65 mg of quercetin equivalents per gram of extract, with quercetin serving as the standard flavonoid for calibration purposes. The tannin content was determined to be 119.67 ± 0.34 mg of catechin equivalents per gram of extract, using catechin as the standard compound for the calibration curve.

Acute oral toxicity assessment

The acute oral toxicity study revealed normal behaviour in rats treated with SAAE (2000 mg/kg). No mortality, morbidity or clinical signs of toxicity were reported during the 14-day study. The lethal dose (LD_{50}) was therefore estimated at over 2000 mg/kg body weight.

Assessment of antihypertensive activity of SAAE

Single oral administration

The daily administration of L-NAME to male Wistar rats resulted in a significant increase in blood pressure (SBP, MBP and DPB) compared with the control group. Table 2 shows the impact of SAAE on blood pressure in normotensive and L-NAME-induced hypertensive rats after a single oral dose (6hr

Table 1. Qualitative phytochemical analysis of aqueous extract of *Santolina africana*

Phytochemicals	Test performed	Results
Polyphenols	Ferris chloride test	(+)
Flavonoids	Shinoda test	(+)
Tannins	Ferric chloride test	(+)
Saponins	Frothing test	(+)
Quinones		(-)
Sterols and terpenoids	Libermann Buchard test	(+)
Anthraquinones		(+)
Carbohydrates	Molisch's test	(+)
Glycosides	Borntrager's test	(-)
Reducing sugars	Fehling's test	(+)
Alkaloids	Mayer's test	(+)
	Wagner's test	(+)
	Dragendorff's test	(+)

- (+) Presence
- (-) Absence

post-treatment) of 100 and 200 mg/kg. In the normotensive groups, a single oral administration of SAAE at both doses (100 and 200 mg/kg) did not significantly alter blood pressure (systolic, mean and diastolic) or heart rate. Similarly, the reference drug, furosemide, showed no significant change in blood pressure or heart rate in the normotensive groups. In hypertensive rats, a single oral administration of 100 mg/kg of SAAE did not result in any significant changes in blood pressure or heart rate 6 hr post-administration. However, administration of a single dose of 200 mg/kg to hypertensive rats resulted in a considerable reduction in systolic, diastolic ($p<0.05$) and mean blood pressure ($p<0.01$), with no significant impact on heart rate. Likewise, furosemide demonstrated a notable decrease in mean ($p<0.01$), systolic and diastolic ($p<0.05$) blood pressure values 6 hr following its oral administration to L-NAME-induced hypertensive rats.

Repeated oral administration

Table 3 illustrates variations in systolic, mean and diastolic blood pressure and heart rate in normotensive and hypertensive rats following seven days of repeated oral administration of SAAE at doses of 100 and 200 mg/kg. The study findings reveal that no significant change in blood pressure parameters or heart rate was observed in normotensive rats after seven days of treatment with SAAE at doses of 100 and 200 mg/kg bw, similarly, no noticeable effect was observed in the normotensive groups receiving furosemide. For the hypertensive groups, administering SAAE at a dose of 100 mg/kg notably reduced systolic blood pressure (SBP) on days 4 and 7 ($p<0.05$ and $p<0.0001$, respectively). Furthermore, treating hypertensive rats with 200 mg/kg of SAAE significantly lowered SBP on days 2, 4 and 7 ($p<0.0001$) when compared to baseline values. In terms of mean arterial blood pressure (MBP), repeated oral administration of SAAE at a dose of 100 mg/kg resulted in a significant reduction on the 7th day ($p<0.0001$), while administering SAAE at a dose of 200 mg/kg bw led to a notable decrease in MBP at the second day ($p<0.001$), as well as at the fourth and seventh days ($p<0.0001$). For diastolic blood pressure (DBP), 100 mg/kg of SAAE administered repeatedly during the sub-chronic study period resulted in a significant decrease in DBP at the last day ($p<0.0001$). In turn, 200 mg/kg of SAAE resulted in a significant reduction in DBP on the second ($p<0.01$), fourth and seventh days ($p<0.0001$). Regarding hypertensive rats treated with furosemide, the results indicated a significant reduction in systolic blood pressure (SBP) on the 2nd, 4th and 7th days of treatment ($p<0.0001$). Additionally, furosemide caused a notable decrease in mean blood pressure (MBP) on days 4 and 7 ($p<0.0001$) compared to baseline measurements. Diastolic arterial pressure (DBP) was also significantly reduced at the 2nd, 4th and 7th days ($p<0.0001$) in

Table 2. Effect of a single oral dose of SAAE (100 and 200 mg/kg) on systolic, mean and diastolic arterial blood pressure (mm Hg) and heart rate (bpm) in anesthetized normal and L-NAME-induced hypertensive rats. Values are expressed as means ± SEM, n=6; *****p < 0.05, ******p < 0.01

Groups		SBP (mmHg)			
		Control	SAAE (mg/kg)		Furosemide
			100 mg/Kg	200 mg/Kg	
Normal	T0	132.00 ± 6.00	133± 8.00	132±5.00	120.00 ± 7.00
	T6	138.00 ± 8.00	132±6.00	133±4.00	111.00 ± 7.00
L-NAME	T0	180.00 ± 5.00	185±7.00	191±8.00	169.00 ± 7.00
	T6	175.00 ±7.00	179±4.00	165±6.00*	142.00 ± 6.00*
		MBP (mmHg)			
		Control	SAAE (mg/kg)		Furosemide
			100 mg/Kg	200 mg/Kg	
Normal	T0	111.00 ± 4.00	113±4.00	112±3.00	108.00 ± 6.00
	T6	113.00 ± 6.00	112±3.00	114±3.00	97.00 ± 2.00
L-NAME	T0	156.00 ± 6.00	154±8.00	159±5.00	150.00 ± 3.00
	T6	157.00 ± 6.00	150±5.00	135±4.00**	125.00 ± 6.00**
		DBP (mmHg)			
		Control	SAAE (mg/kg)		Furosemide
			100 mg/Kg	200 mg/Kg	
Normal	T0	106.00 ± 5.00	103±4.00	102±3.00	103.00 ± 5.00
	T6	101.00 ± 6.00	102±4.00	105±4.00	91.00 ± 4.00
L-NAME	T0	144.00 ± 7.00	139±3.00	143±5.00	152.00 ± 5.00
	T6	148.00 ± 10.00	136±4.00	120±3.00*	129.00 ± 4.00*
		HR (bpm)			
		Control	SAAE (mg/kg)		Furosemide
			100 mg/Kg	200 mg/Kg	
Normal	T0	325.00 ± 12.00	315.00 ± 14.00	310.00± 13.00	350.00 ± 18.00
	T6	300.00 ± 9.00	310.00 ± 13.00	295.00 ± 14.00	325.00 ± 10.00
L-NAME	T0	314.00 ± 14.00	323.00 ± 16.00	305.00 ± 13.00	355.00 ± 23.00
	T6	313.00 ± 10.00	312.00 ± 13.00	295.00 ± 12.00	321.00 ± 14.00

Table 3. Effect of repeated oral administration of SAAE (100 and 200 mg/kg) on systolic, mean, diastolic arterial blood pressure (mm Hg) and heart rate (bpm) in anesthetized normal and L-NAME-induced hypertensive rats. Values are expressed as means ± SEM, n=6; *p < 0.05, ** p < 0.01, ***p<0.001, ****p<0.0001

		SBP (mmHg)			
		Control	SAAE (mg/kg)		Furosemide
			100 mg/Kg	200 mg/Kg	
Normal	D0	133.00 ± 7.00	133.00 ± 8.00	134.00 ± 8.00	124.00 ± 7.00
	D2	137.00 ± 6.00	125.00 ± 4.00	129.00 ± 4.00	117.00 ± 5.00
	D4	140.00 ± 4.00	123.00 ± 6.00	123.00 ± 4.00	109.00 ± 3.00
	D7	135.00 ± 5.00	129.00 ± 5.00	120.00 ± 5.00	98.00 ± 4.00**
L-NAME	D0	183.00 ± 6.00	197.00 ± 8.00	195.00 ± 4.00	168.00 ± 7.00
	D2	177.00 ± 6.00	181.00 ± 6.00	155.00 ± 5.00****	123.00 ± 2.00****
	D4	172.00 ± 8.00	175.00 ± 6.00*	148.00 ± 7.00****	122.00 ± 4.00****
	D7	171.00 ± 7.00	162.00 ± 4.00****	138.00 ± 5.00****	110.00 ± 3.00****
		MBP (mmHg)			
		Control	SAAE (mg/kg)		Furosemide
			100 mg/Kg	200 mg/Kg	
Normal	D0	112.00 ± 5.00	113.00 ± 4.00	110.00 ± 4.00	109.00 ± 5.00
	D2	111.00 ± 6.00	112.00 ± 4.00	106.00 ± 4.00	108.00 ± 6.00
	D4	115.00 ± 5.00	109.00 ± 4.00	103.00 ± 3.00	102.00 ± 4.00
	D7	113.00 ± 3.00	110.00 ± 5.00	100.00 ± 3.00	97.00 ± 3.00
L-NAME	D0	157.00 ± 7.00	155.00 ± 4.00	156.00 ± 5.00	151.00 ± 4.00
	D2	150.00 ± 5.00	145.00 ± 2.00	127.00 ± 5.00***	149.00 ± 6.00
	D4	146.00 ± 8.00	139.00± 5.00	117.00 ± 3.00****	105.00 ± 6.00****
	D7	145.00 ± 7.00	118.00 ± 5.00****	110.00 ± 4.00****	96.00 ± 5.00****
		DBP (mmHg)			
		Control	SAAE (mg/kg)		Furosemide
			100 mg/Kg	200 mg/Kg	
Normal	D0	107.00 ± 6.00	103.00 ± 4.00	98.00 ± 6.00	104.00 ± 6.00
	D2	102.00 ± 6.00	106.00 ± 6.00	95.00 ± 4.00	99.00 ± 4.00
	D4	107.00 ± 4.00	102.00 ± 3.00	93.00 ± 6.00	98.00 ± 5.00
	D7	103.00 ± 7.00	101.00 ± 3.00	90.00 ± 5.00	97.00 ± 3.00
L-NAME	D0	145.00 ± 6.00	134.00 ± 6.00	137.00 ± 4.00	153.00 ± 6.00
	D2	136.00 ± 6.00	127.00 ± 4.00	113.00 ± 6.00**	104.00 ± 5.00****
	D4	136.00 ± 7.00	121.00 ± 3.00	102.00 ± 3.00****	101.00 ± 5.00****
	D7	137.00 ± 5.00	96.00 ±5.00****	96.00 ± 4.00****	99.00 ± 4.00****
		HR (bpm)			
		Control	SAAE (mg/kg)		Furosemide
			100 mg/Kg	200 mg/Kg	
Normal	D0	325.00 ± 12.00	298.00 ± 12.00	310.00 ± 12.00	350.00 ± 18.00
	D2	324.00 ± 13.00	305.00 ± 10.00	307.00 ± 13.00	342.00 ± 16.00
	D4	316.00 ± 14.00	296.00 ± 13.00	299.00 ± 14.00	343.00 ± 14.00
	D7	317.00 ± 10.00	298.00 ± 12.00	294.00 ± 10.00	306.00 ± 9.00
L-NAME	D0	315.00 ± 12.00	310.00 ± 14.00	307.00 ± 14.00	347.00 ± 20.00
	D2	311.00 ± 14.00	300.00 ± 12.00	303.00 ± 12.00	345.00 ± 12.00
	D4	312.00 ± 14.00	299.00 ± 13.00	296.00 ± 11.00	316.00 ± 12.00
	D7	315.00 ± 16.00	294.00 ± 11.00	300.00 ± 12.00	312.00 ± 11.00

hypertensive rats treated with the reference drug compared to baseline values. Furthermore, the heart rate (HR) of hypertensive rats remained stable after repeated oral administration of SAAE and furosemide throughout the subchronic period.

Assessment of vascular relaxation and investigation of the underlying mechanisms

Vasodilation effect of SAAE on PE- and KCl-induced contraction in aortic rings

To assess the vasorelaxant effect of SAAE on vascular smooth muscle, a series of experiments was conducted by examining the impact of cumulative doses (250, 375, 500 and 625 µg/mL) on the relaxation of aortic rings precontracted by EP and KCL. The results of the study showed that SAAE exerts a significant vasodilatory effect on aortic rings precontracted by PE (Rmax = 111.1 ± 6.75 %) (Fig. 1A). In the same way, SAAE was able to produce a significant vasorelaxant effect on aortic rings precontracted by KCl (Rmax = 94.48 ± 20.44 %) (Fig. 1B).

Role of the endothelium in SAAE-induced relaxation

As illustrated in Fig. 2, cumulative doses of SAAE (250, 375, 500 and 625 µg/mL) showed a dose-dependent vasorelaxant effect on intact aortic rings pre-contracted with EP, with a maximum response of Rmax = 111.1 ± 6.75 %. However, in endothelium-denuded aortic rings, a marked reduction in the response to SAAE was noted, characterized by a significant inhibition of vasorelaxation (Rmax = 77.45 ± 15.50 %) ($p<0.0001$).

Role of nitric Oxide, guanylate cyclase and cyclooxygenase pathways in SAAE-induced relaxation

Pretreatment of intact aortic rings with L-NAME (10^{-4} M, a non-selective NOS inhibitor) produced a significant change in response to SAAE, with significant inhibition of vasorelaxation ($p<0.001$), Rmax value decreased from Rmax =111.1 ± 6.75 % in the absence of inhibitor to 80.72 ± 7.28 % in the presence of L-NAME. While pre-incubation of aortic rings with methylene blue (MB, 10^{-5} M, a guanylate cyclase inhibitor) or indomethacin (10^{-5} M), an inhibitor of cyclooxygenase, did not significantly affect aortic responses to cumulative doses of SAAE, with Rmax of 114.3 ± 7.38 % and 123.3 ± 30.21 % respectively compared with Rmax of 111.1 ± 6.75 % for control aortic rings (Fig. 3).

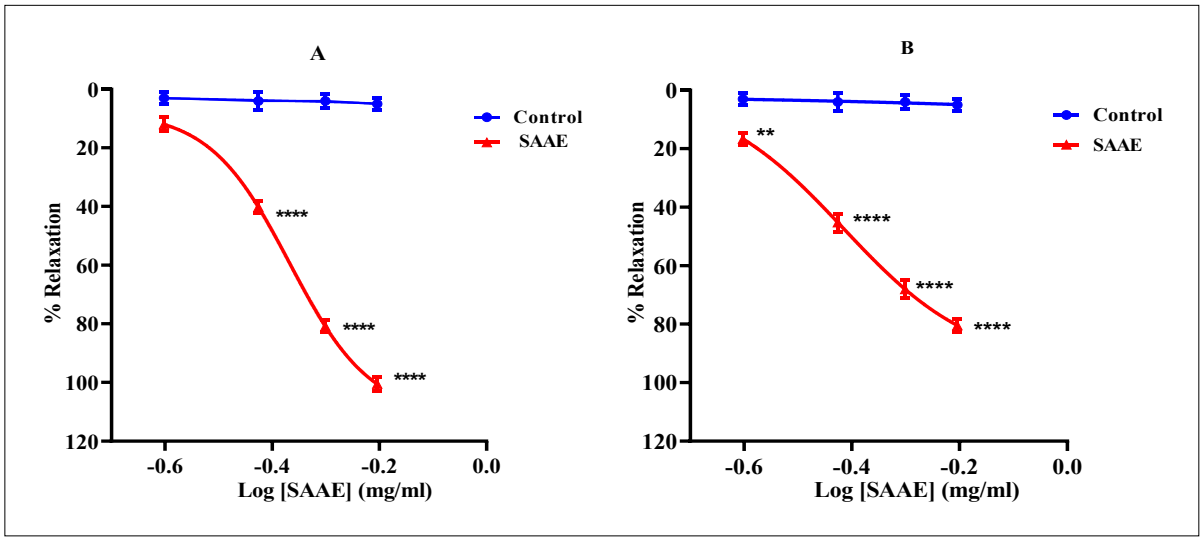

Fig. 1. Vasorelaxant effect of SAAE (250, 375, 500 and 625 µg/mL) on aortic rings precontracted with EP (10 µM) (A) or KCl (80 mM) (B). **p < 0.01, ****p < 0.0001 vs control.

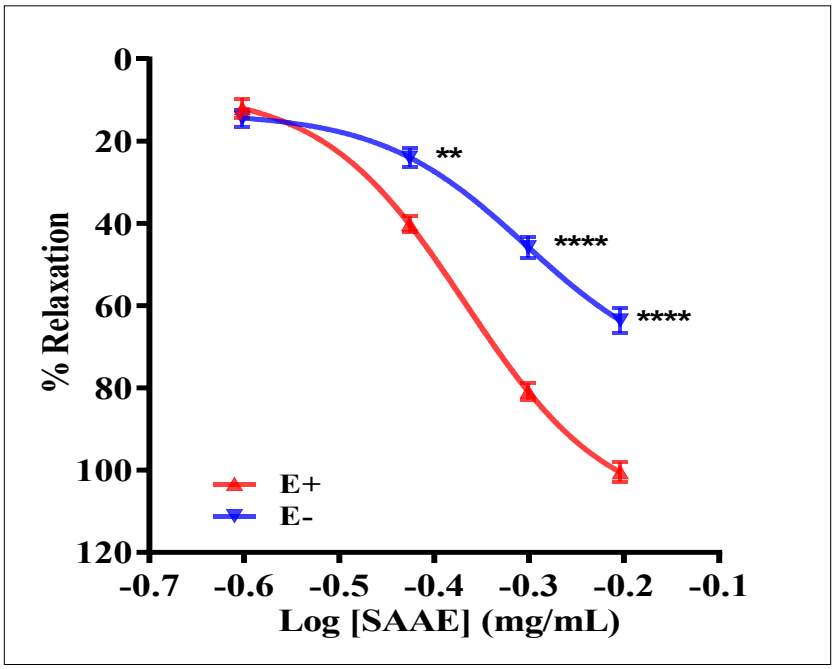

Fig. 2. Cumulative concentration-response curves of SAAE-induced vasorelaxation (250, 375, 500 and 625 µg/mL) in aortic rings pre-contracted by EP (10 µM) either with intact (E+) and denuded (E-) endothelium. **p < 0.01 and ****p < 0.0001 for E+ versus E-.

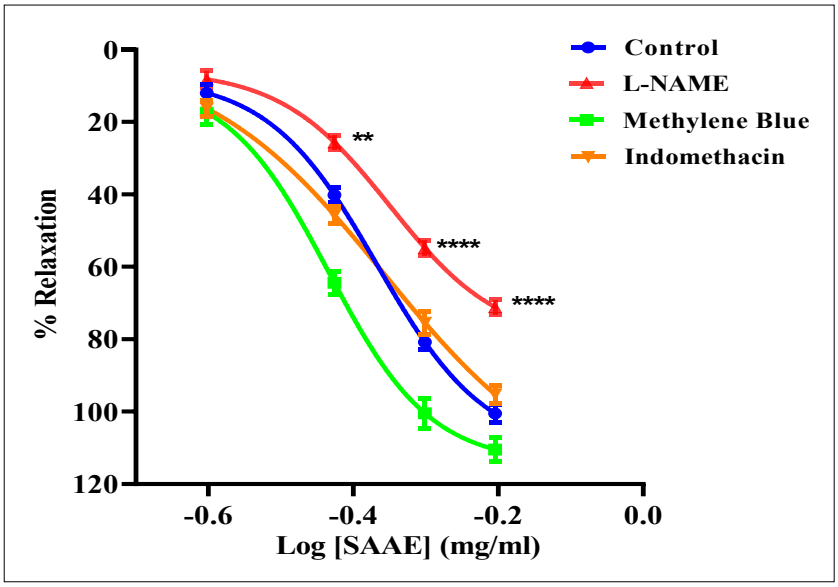

Fig. 3. Concentration-response curves for the vasorelaxant effect of SAAE on EP-precontracted aortic rings, in the presence of L-NAME (▲), methylene blue (▪) and indomethacin (▼). Values are expressed as Mean ± SEM. **p < 0.01 and **** p < 0.0001 vs control.

Vasorelaxant effect of SAAE in the presence of atropine, propranolol and nifedipine

Incubation of aortic rings precontracted with EP with atropine (10^{-6} M, muscarinic receptor blocker) and propranolol (10^{-5} M, β-adrenergic receptor antagonist) did not affect SAAE-induced vasorelaxation (SAAE: Rmax = 91.43 ± 3.59 %, SAAE + propranolol: Rmax = 115.2 ± 7.86 % and SAAE + atropine: Rmax = 110.4 ± 12.59 %). To further clarify potential mechanisms involved, the role of calcium channels in SAAE-induced vasorelaxation was explored. For this purpose, aortic rings were pretreated with nifedipine (10^{-5} M, a calcium channel blocker. Indeed, pretreatment with nifedipine had no effects on the SAAE-induced vasorelaxation; Rmax was 114.3 ± 10.65 %, compared with 111.1 ± 6.75 % for control aortic rings (Fig. 4).

Role of potassium channels in SAAE-induced relaxation of aortic rings

The vasorelaxant effect of SAAE was not significantly inhibited in the presence of glibenclamide (10^{-5} M), an ATP-sensitive potassium channels blocker, nor in the presence of barium chloride (10^{-4} M), an inhibitor of the inwardly rectilinear K+ channels, nor in the presence of in 4-aminopyridine (10^{-4} M), a voltage-gated potassium channel blocker, with Rmax of 118.7 ± 8.23 %, 112.2 ± 13.88 % and, 103.8 ± 3.72 %, respectively (Fig. 5).

Effect of SAAE on lipid profile in Triton-1339 induced dyslipidemia

Administration of Triton WR-1339 (Tyloxapol) induced a significant increase in plasma concentrations of total cholesterol (TC), triglycerides (TGs) and low-density lipoprotein cholesterol (LDL-c) compared with the normolipidemic control group. In contrast, Triton WR-1339 did not significantly influence levels of high-density lipoprotein cholesterol (HDL-c) as compared to normal control. Administration of SAAE (250 mg/kg) to hyperlipidemic rats showed no significant effect on plasma levels of TC, TGs and LDL-c, whereas treatment of hyperlipidemic rats with a dose of 500 mg/kg of SAAE significantly reduced plasma levels of TC ($p<0.05$), LDL-c ($p<0.01$) and TGs ($p<0.001$). On the other hand, treatment of rats with both doses of SAAE (250 and 500 mg/kg) did not affect plasma HDL-c levels. Similarly, simvastatin significantly reduced plasma levels of TC ($p<0.05$), LDL-c ($p<0.001$) and TGs ($p<0.0001$), without causing a notable change in plasma levels of HDL-c (Fig. 6).

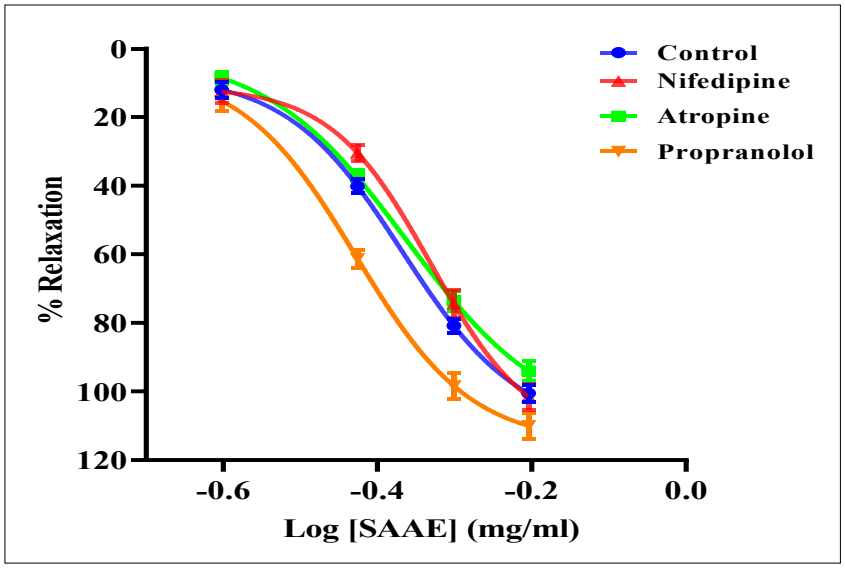

Fig. 4. Concentration-response curves for the vasorelaxant effect of SAAE on EP-precontracted aortic rings, in the presence of nifedipine (▲), atropine (▪) and propranolol (▼). Values are expressed as Mean ± SEM.

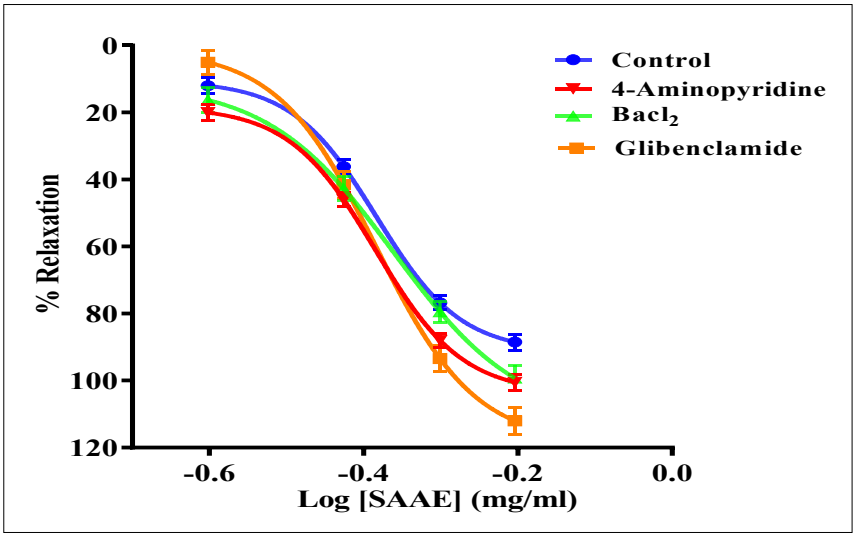

Fig. 5. Concentration-response curves for the vasorelaxant effect of SAAE on EP-precontracted aortic rings in the presence of 4-AP (▼), $BaCl_2$ (▲) and glibenclamide (▪). Values are expressed as Mean ± SEM.

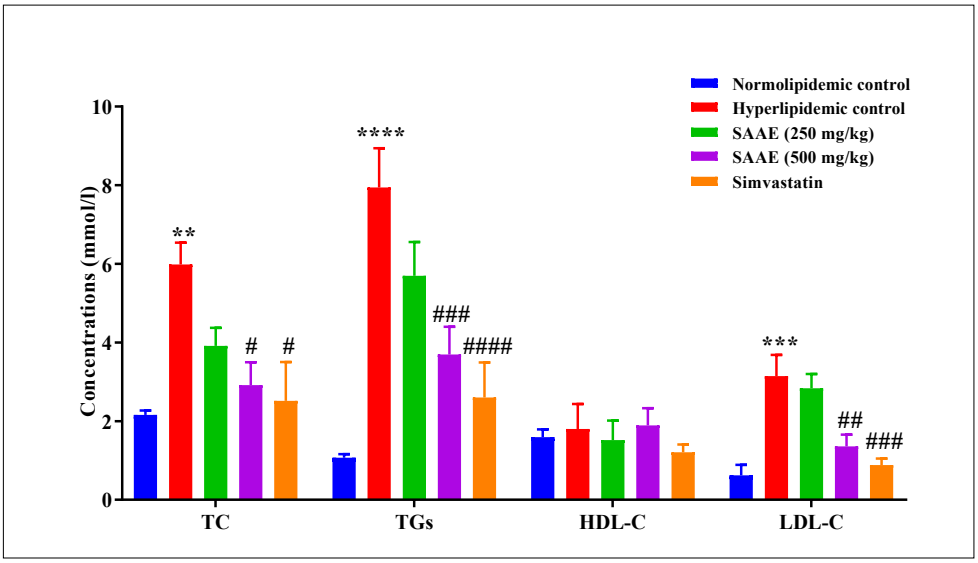

Fig. 6. Effect of SAAE (250 and 500 mg/kg) on plasma lipid profile (TC, TG, HDL-c and LDL-c) in Triton WR-1339-induced hyperlipidemic rats. Data are reported as mean±SEM. for 5 animals per group. **p < 0.01, ***p < 0.001 and ****p < 0.0001 compared to normolipidemic group, #p < 0.05, ## p < 0.01, ### p < 0,001 and #### p < 0.0001 compared to Triton WR-1339 group.

Discussion

Hypertension and dyslipidemia are major risk factors for cardiovascular diseases, which are the leading causes of morbidity and mortality worldwide (24). The objective of this study was to evaluate the antihypertensive effect of the aqueous extract of *S. africana* on normotensive and L-NAME-induced hypertensive rats, its vasorelaxant, as well as its antihyperlipidemic effects. Medicinal plants are widely regarded as safe and without adverse effects on human health (25). However, various studies have identified potential dangers associated with their inappropriate use highlighting the need to evaluate their toxicological properties to ensure safe therapeutic use (26, 27). Therefore, it was crucial to assess the safety of SAAE before investigating its pharmacological effects. Thus, a preliminary oral acute toxicity study was carried out. Accordingly, a single oral administration of SAAE at a dose of 2 g/kg showed no signs of toxicity or mortality in the animals tested, indicating that SAAE is relatively safe.

The results obtained from the present study demonstrate that the administration of SAAE (100 and 200 mg/kg) did not affect blood pressure values (SBP, MBP and DBP) and heart rate in normotensive rats, both after the acute test (6 hr) and the chronic test (7 days). Furthermore, treatment with SAAE revealed a significant antihypertensive effect in hypertensive rats in a dose-dependent manner, both after acute and repeated oral administration, characterized by a notable reduction in systolic, mean and diastolic blood pressure. However, the administration of SAAE (100 and 200 mg/kg) did not affect the heart rate of hypertensive rats in both acute and chronic studies. The lack of effect of SAAE on heart rate suggests that its antihypertensive effect is likely mediated through a vascular pathway. One of the primary mechanisms by which antihypertensive drugs function is by reducing vascular resistance through direct or indirect vasodilation (28). To investigate a potential mechanism through which SAAE exerts its antihypertensive effect, an *in vitro* study was conducted to evaluate its vasorelaxant activity on isolated rat aortic rings. The results from this study demonstrated that SAAE produced a vasorelaxant effect in intact aortic rings precontracted by EP (10 µM) and KCL (80 mM) in a concentration-dependent manner. Furthermore, the experimental results obtained demonstrate that the vasorelaxant effect of SAAE is significantly attenuated by denudation of the endothelium of the aortic rings, suggesting that SAAE exerts its vasorelaxant effects primarily via an endothelium-dependent mechanism. To explore the mechanistic pathways involved in the vasorelaxant effect of SAAE, several drugs were used in this experiment (L-NAME, indomethacin, methylene blue, propranolol, atropine, nifedipine, glibenclamide, $BaCl_2$ and 4-aminopyridine). The study findings showed that, among all these drugs tested, only pre-incubation of intact aortic rings with L-NAME, a non-selective nitric oxide synthase (NOS) inhibitor, significantly reduced SAAE-induced vasorelaxation, suggesting that the vasorelaxant effect of SAAE seems to be mainly mediated by endothelial nitric oxide (NO) production. Vascular endothelial cells, which constitute the endothelium, synthesize and secrete numerous vasoactive substances, among which nitric oxide (NO) a powerful vasodilating factor, synthesized from L-arginine by the enzyme endothelial NO synthase (eNOS) (29, 30), once synthesized, NO diffuses into vascular smooth muscle cells and activates guanylate cyclase, increasing levels of cyclic guanosine monophosphate (cGMP) which induces smooth muscle relaxation, leading to vasodilation and lowering arterial blood pressure (31). Thus, modulation of the NO synthase pathway by SAAE could be a promising therapeutic strategy for treating hypertension. Our results are comparable to previous findings reported for other Asteraceae species. *Achillea millefolium* and *Helichrysum stoechas* have demonstrated antihypertensive and vasorelaxant effects mediated by nitric oxide production. Similarly, *Artemisia herba alba* has been shown to induce endothelium-dependent vasorelaxation involving NO synthesis (32-34). Triton WR-1339, also known as Tyloxapol, is a non-ionic surfactant commonly used in animal models to induce acute dyslipidemia, it acts by inhibiting lipoprotein lipase, which is responsible for the hydrolysis of triglycerides present in plasma lipoproteins and stimulating

hydroxymethyl-glutaryl coenzyme A reductase (HMG-CoA reductase), a key enzyme in cholesterol biosynthesis (35). Interestingly, results findings from the study shows that SAAE exhibits a significant dose-dependent antihyperlipidemic effect, manifested by a reduction in plasma levels of total cholesterol, LDL-cholesterol and triglycerides of hyperlipidemic animals compared to untreated hyperlipidemic ones, suggesting that inhibition of lipid biosynthesis, might be the possible mechanism of the antihyperlipidemic effect of the SAAE. It is well established that dyslipidemia contributes to atherosclerosis, a predominant risk factor for hypertension (36, 37). High levels of total cholesterol (TC) and particularly LDL-cholesterol represent a major risk factor for coronary heart disease (38). High levels of LDL-cholesterol in plasma promote its oxidation, this oxidation alters the structure of LDL particles, allowing their uptake by receptors on macrophages, endothelial cells and smooth muscle cells. As a result, accumulation of lipid-rich foam cells, marking the onset of atherosclerotic lesions (39). This leads to narrowing of the arteries and impaired endothelial function, which results in reduced production and availability of nitric oxide (NO), essential for vasodilation (40). Therefore, improving the lipid profile could indirectly promote blood pressure reduction by decreasing arterial rigidity and reducing the development of atherosclerosis, a condition that compromises endothelial function and reduces the production of NO. Thus, by improving the lipid profile, SAAE may help maintain healthy endothelial function and promote nitric oxide (NO) production, leading to improved vasodilation, lower blood pressure and consequently better cardiovascular health. Although these findings are promising, it is necessary to evaluate the antihyperlipidemic power of this plant in another animal model and to assess its anti-atherogenic power in chronic conditions. The pharmacological activities demonstrated by SAAE may be explained by its richness in bioactive phytochemicals such as flavonoids, polyphenols, terpenoids, tannins, alkaloids and saponins, which are recognized for their antihypertensive, vasorelaxant and antihyperlipidemic effects (41, 42). Phytochemical studies conducted on the Santolina genus have shown the presence of terpenoids as the major bioactive constituent (43). Besides, studies carried out on the aerial part of *S. africana* from the Tahanaout province in Morocco revealed a particular abundance of oxygenated monoterpenes with camphor, borneol, 1,8-cineole and bornyl acetate being the main compounds (44, 45). Meanwhile, multiple studies have reported that monoterpenes could be considered as a promising agent in the prevention and treatment of cardiovascular disease, notably by promoting vasorelaxation, reducing heart rate and lowering blood pressure (46, 47). It has been demonstrated that 1,8-cineole, a monoterpene oxide present in essential oils, exerts a significant antihypertensive effect, mainly attributed to an increase in the bioavailability of nitric oxide (48-50). Likewise, (-)-borneol, a natural monoterpene found in the essential oils of many medicinal plants, possesses a powerful antihypertensive action as well as a significant vasorelaxant effect, mainly via calcium channel blockade and potassium channel activation (51-53). Furthermore, research has demonstrated that terpenoid compounds exhibit lipid-lowering potential by inhibiting the activity of hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, thereby reducing cholesterol biosynthesis (54). Finally, although *S. africana* has shown promise in the management of hypertension and dyslipidemia, the specific compounds responsible for these pharmacological effects were not isolated and characterized in this study. Thus, Identification of the active constituents of this plant, investigation of the underlying molecular mechanisms and evaluation of its long-term toxicity are required to support the development of *S. africana* as a therapeutic agent.

Conclusion

The present study is the first to demonstrate the antihypertensive, vasorelaxant and antidyslipidemic effects of the aqueous extract of *S. africana*. The results suggest that *S. africana* could be developed as a promising natural therapeutic candidate for the management of hypertension and dyslipidemia. However, further studies are required to isolate, characterize the bioactive phytocompounds of this plant and elucidate the precise molecular mechanisms involved in the observed effects.

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Authors' contributions

AQ conceived and designed the study, carried out all laboratory experiments and drafted the manuscript. IB contributed to the realization of experimental techniques and laboratory manipulations. AA[1] and AA[2] contributed to the analysis and interpretation of the data. ME supervised this work and contributed to the critical revision and correction of the manuscript. All authors read and approved the final manuscript.

[AA[1] - Ayoub Amssayef ; AA[2] -Amine Azzane]

Compliance with ethical standards

Conflict of interest: The authors declare no conflict of interest, financial or otherwise.

Ethical issues: All applicable institutional guidelines for the care and use of animals were followed according to the local committee Faculty of Sciences & Techniques Errachidia/2015.

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