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ACTION OF HYDROETHANOLIC LEAVES EXTRACT OF *Solenostemon Monostachyus* (LAMIACEAE) ON CARDIOVASCULAR SYSTEM OF MAMMALIANS: BLOOD PRESSURE LOWERING EFFECTS

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ABSTRACT

Arterial blood pressure assessment was performed in normotensive rabbits using Ludwig manometer and contractile response of isolated rat heart and aorta was recorded using the bath organ system. Hydroethanolic extract of Solenostemon monostachyus (Esomo) (0.6- 17.6 mg/kg b.w), induced a significant decrease in arterial blood pressure (EC_{50} = 2.5±0.15 mg/kg b.w.) in a dose dependent manner ($p<0.001$) which was partially prevented in the presence of atropine (2mg/kg b.w.). Esomo (5.8 and 17.6 mg/kg b.w) reduced high blood pressure caused by noradrenaline (5.10^{-3} mg/kg b.w.) ($p<0.01$). On contractile response of isolated heart, Esomo ($10^{-2}$and 1mg/ml) caused concentration-dependent negative inotropic and chronotropic effects which were not altered by atropine (10^{-5} mg/ml). The extract (10^{-2}-1mg/ml) inhibited aorta smooth muscle contraction evoked by noradrenaline (0.5 µM) and by KCl (100 mM) with EC_{50} values of 0.13±0.25 mg/ml and of 0.084±3.1 mg/ml respectively , suggesting calcium channel blocking action with a major inhibitory effect on L-type voltage-operated Ca^{2+} channels. However this suggestion must be deeply studied. L-NAME, methylene blue and indomethacin incubation reduced Esomo (EC_{50} = 0.13±0.25 mg/ml) relaxation from 50±0.1% to 21.31±0.8%, 24.97±0.9% and 35.79±0.78% respectively ($p<0.001$). The results obtained exibit blood pressure lowering effect of Esomo which could result from both cardiodepression and vasodilatation mechanisms. It is also important to notice the involvement of endothelium-dependent mechanism mediated by NO/cGMP and PGI_2 in this vascular activity which could clearly explain the use of Solenostemon monostachyus leaves in folk medicine for hypertension treatment.

KEYWORDS

Solenostemon monostachyus, hypertension, NO/cGMP, PGI_2, Blood pressure, aorta, heart.

INTRODUCTION

Hypertension is mankind's most common serious disease. In 2000, it was estimated that 8-12% of the Ivorian people had hypertension and this prevalence in the population is increasing (Koffi, 2007).High blood pressure is a chronic medical condition in which the blood pressure in the arteries is elevated (Messerli et al., 2007). Its persistence is one of the risk factors for strokes, heart attacks, heart failure and is the leading cause of chronic renal failure. Hypertension leads to shortened life expectancy (McMahon, 1984) and remains a public health problem. The first mean to reduce significantly blood pressure in people with hypertension is lifestyle change includes dietary change, physical exercise and weight loss (Dickinson et al., 2006). Several classes of pharmaceutical substances, referred to as antihypertensive drugs, are available for treating hypertension (Koffi, 2007). Also, it's well reported that many medicinal plants were used to treat hypertension in Africa and particularly in Cote d'Ivoire (Yomalan *et al*., 2008; Souza *et al*., 2011, Abrogoua *et al*., 2012) for their natural chemical constituents and for their low cost.

Solenostemon monostachyus P.Beauv. (Lamiaceae) is a plant widely distributed in Ivory Coast. Traditional heath practioners of this country have claimed that is a useful remedy for hypertension treatment (Koffi et al., 2009). Phytochemical investigations on *Solenostemon monostachyus* leaves have shown: water, proteins, lipids, glucids, calcium, phosphate (Buisson et al., 1965), essential oil (Mve-Mba et al., 1994) and phytoconstituents such as diterpenoids (Toshio et al. 1980), flavonoids, coumarin, polyphenol (Datte et al., 2010;N'guessan Hugues et al., 2011). This plant possesses an important antioxidant activity (Datte et al., 2010; N'guessan Hugues et al., 2011; Tebekeme Okoko and Diepreye Ere, 2012). No more pharmacological activities of *Solenostemon monostachyus* have been reported in the literature, excepted antimicrobial activities (Ekundayo and Ezeogu, 2006) and its weak toxic effect in mice (Oden Onu, 1996; Datte et al, 2010). This study aims to bring out pharmacological basis to the use of *Solenostemon monostachyus* for hypertension management in traditional medicine through its evaluation on the arterial blood pressure and its mechanism elucidation on isolated rat heart and aorta.

MATERIAL AND METHODS

Plant materials

Fresh leaves of *Solenostemon monostachyus* P.Beauv.(Lamiaceae), collected in June (rain season) from farms specialized in growing plants for medicinal purposes, was identified and authenticated by Pr Aké Assi Laurent, expert botanist. Voucher specimens number 8217 were preserved and catalogued in the Herbarium of the Centre National de Floristique (Abidjan, Cote d' Ivoire)

Preparation of the extract

The collected plant material was dried at room temperature and powdered. 75g of the fine powder was extracted with 300mL of 70% ethanol by maceration during 24 hours under magnetic shaker. The suspension was filtered. The filtrate collected was evaporated. The final extract yielded (0.5%, w/w) and was stored at 5°C for further use.

Animal experiments

Two species of animal were used for experiments: rabbits (*Oryctologus cunuculus)* (2-2.5kg) and albinos Wistar rats (*Rattus norvegicus*) (150-250g). Animals were cared for and treated according to the principles for the care and use of laboratory animals for biomedical research approved by the ethical committee for animal research of Cocody University, Abidjan. They were bred in Animal house of Nutrition and Pharmacology Department, UFR Biosciences (Abidjan, Cote d'Ivoire). Rabbits and rats were kept in temperature- controlled environment (25 ± 2°C) with a 12 h light-dark cycle and had free access to water and standard diet.

Study of the effect of the plant extract on the arterial blood pressure

This experiment was performed as described by Konan *et al.*(2006) and Souza *et al.*(2011).

The thigh and the neck of anesthetized rabbit were dissected to expose the carotid and the saphenous veins. The dose of anesthesia (ethyl carbamate 40%) used, was 1g/kg b.w. A polyethylene catheter, filled with heparinized saline and connected to a "U" tube of the Ludwig pressure gauge via a polyethylene tube, was inserted into the carotid. The "U" tube contained mercury which was surmounted by a float connected by a wire to an inscriptor stylet. The variations of arterial blood pressure transmitted to the mercury were collected by a float and registered on a kymograph. The saline solution and drugs were administered through the saphenous vein via a polyethylene canula.

Study of the effect of the plant extract in rat isolated heart

The heart of anesthetized rat maintained under artificial respiration, was quickly dissected and removed. Ethyl carbamate (20%) used as anesthesia was applied at a dose of 1g/kg b.w The isolated heart was suspended on the exit of a tap through multiple connections to bottles placed at 50cm with the top of the equipment as described in detail by Konan *et al* (2006) and Souza *et al.*(2011). The bottles contained the control and the test solutions were maintained at a temperature of 37°C and continuously aerated with air.The activity of the isolated heart was recorded on a Kymograph via an inscriptor stylet connected to the isolated heart apex.

Study of the effect of the plant extract on the isolatedaorta activity of rat

The methods were previously described (Baccelli *et al*., 2007 and Martinsen *et al*., 2009). Aortic rings (2mm length) were suspended between two hooks under a resting tension of 20 mN in 12,5ml organ baths containing Krebs physiological solution (composition (mM): NaCl, 115,3; KCl, 4,9 $CaCl_2$, 1,46; KH_2PO_4, 1,2; $NaHCO_3$, 25; MgSO4, 1,2; glucose, 11) maintained at 37°C and bubbled with gas mixture of 95% O_2 and 5% CO_2. Muscle tone was recorded with an isometric transducer. After one-hour resting period, Krebs normal solution was changed to a depolarizing 100mM KCl solution to produce a first contraction. Carbachol or acetylcholine (1µM) was added into the bath solution during the plateau phase of the contraction to test endothelium integrity. And then after 45 min resting period in Krebs normal solution, aortic rings were contracted either by replacing normal solution by depolarizing KCl solution or by using noradrenaline (0.5µM). The effect of Esomo on the contraction was evaluated either by adding cumulative concentration of the extract in the bath during the plateau phase of the contraction, or by testing the contractile response after incubating the aorta in the presence of different concentration of Esomo. The amplitude of contraction evoked in the presence of Esomo was compared to the response obtained in its absence. Inhibition of the contraction measured in the presence of extract was normalized to controls. Involvement of nitic oxide (NO), guanylate cyclase (cGMP) and prostacyclin (PGI2) in the plant extract effect was performed in the presence of the N^w-nitro-L-arginine (100µM), methylene blue (5µM) and indomethacin (10µM).

Drugs

Acetylcholine, noradrenaline, N^w-nitro-L-arginine, methylene blue, indomethacin and atropine were purchased from Sigma-Aldrich (Bornem, Belgium). Drugs were dissolved in physiological solution just before use for the tests.

Statistics

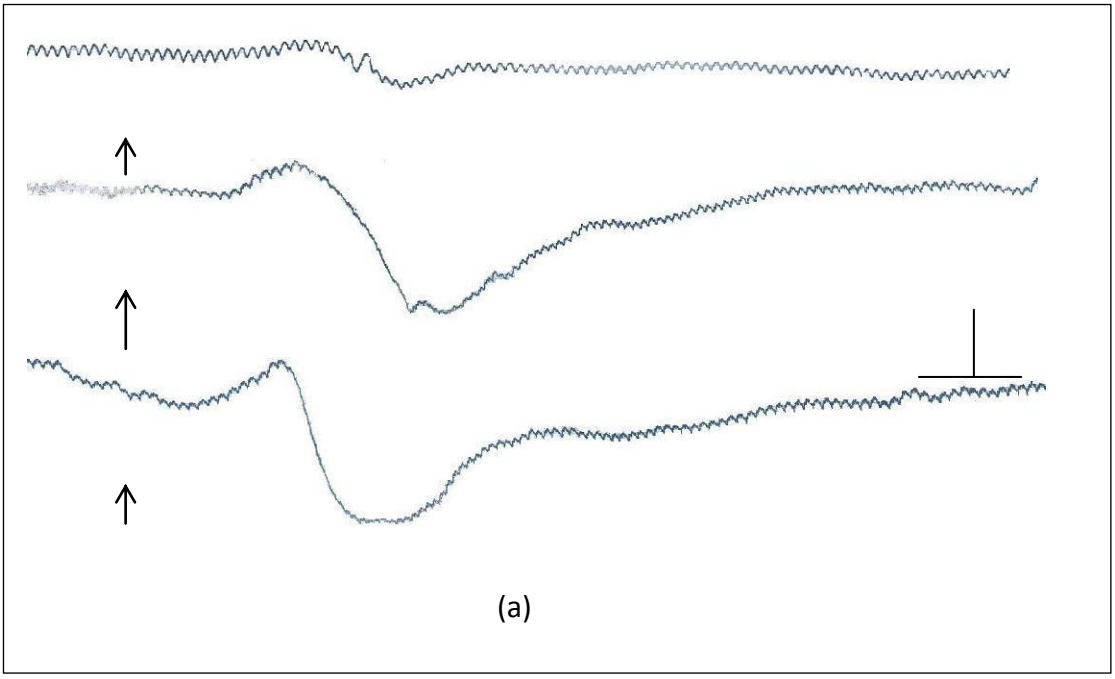
All values in the text and illustrations are presented as (mean ± SEM), with *n* representing the number of different separate experiments. Statistical significance between values was analyzed by means of an analysis of variance (ANOVA) followed by Tukey-Kramer's multiple comparison tests. P values less than 0.05 were considered as significant.

RESULTS

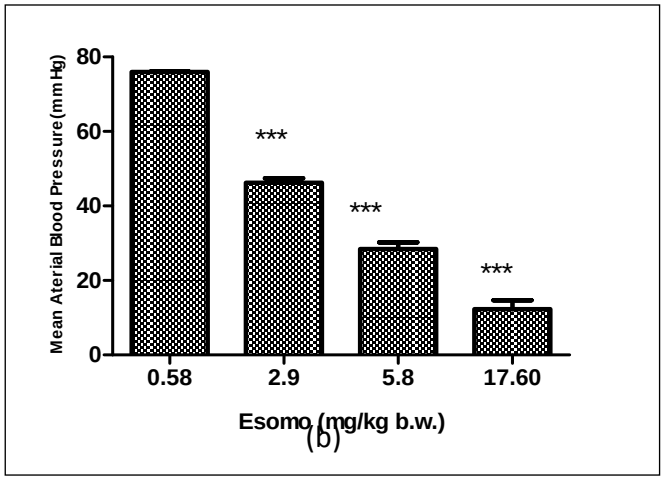
Effect of Esomo on arterial blood pressure

The hydroethanolic extract of *Solenostemon monostachyus* (Esomo) was tested on arterial blood pressure at different doses. In this experiment, the mean blood arterial pressure of anesthetized rabbits was 80.57±0.67 mmHg. The dose of 0.58mg/kg b.w. produced a slight fall in mean arterial blood pressure (MABP) from the initial level of 80.57±0.67 mmHg to 75.96±0.14 mmHg. Therefore, at doses of 2.9, 5.8 and 17.6 mg/kg b.w, Esomo induced a

significant decrease in MABP of 46.24±1.2, 28.41±1.8 and 12.3±2.4 mmHg respectively (p<0.001) in a dose dependent manner (**Figure 1a, 1b**). And the percentage of decrease ranging from 42.6±1.7 to 84.73±3.1%. Esomo and Atropine were simultaneously administered to anesthetized rabbits. As shown in **Figure 2a**, Atropine (2mg/kg b.w.) affected partially the decrease in MABP evoked by Esomo (5.8mg/kg b.w.) (p<0.05). It dropped from 54.23±6.7 to 24.56±9.2 mmHg or a drop of 54.71±0.5%. To create hypertension situation, noradrenaline was applied at a dose of 5.10^{-3} mg/kg b.w. In our experimental case, an increase in MABP of +27.36±1.03 mmHg (80.57±0.67 +27.36±1.03) induced by noradrenaline was registered, with an enhancement of 25.34±0.2%. Thus, at doses of 5.8 and 17.6 mg/kg b.w, Esomo reduced significantly the mean arterial blood pressure caused by noradrenaline of 20.32±0.4 and 25.46±1.8 % respectively (p<0.001) (**Figure 2b**).



(a)

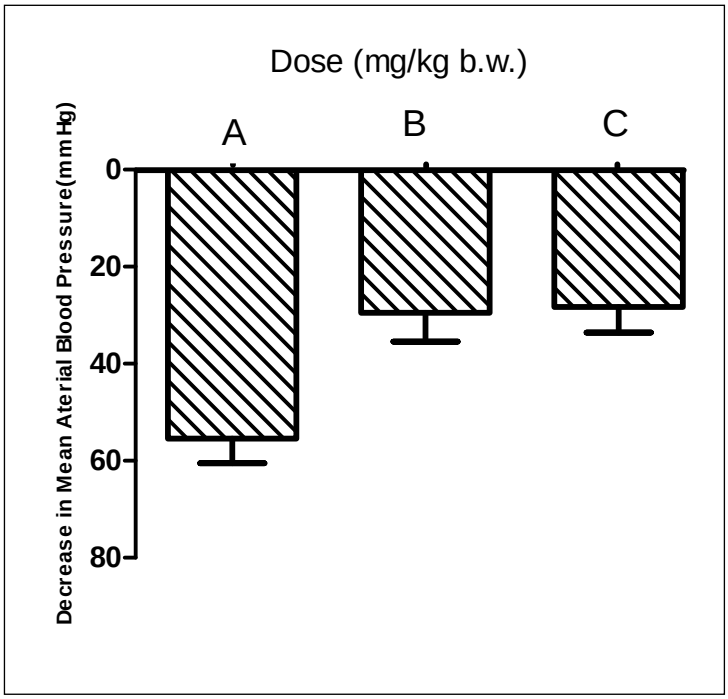


(b)

Figure 1: Blood pressure lowering effects induced by hydroethanolic extract of *Solenostemon monostachyus* P.Beauv.(a): Typical tracings from a record of the rabbit arterial blood pressure. Arrows indicate administration of Esomo (0.58 to 17.6 mg/kg b.w.). Horizontale scale: 15 sec, Vertical scale: 20mmHg.(b): Histogram

representing dose-dependent hypotension evoked by Esomo on arterial blood pressure. Values are expressed in mmHg. Each value represent the mean ±SEM (n=4).). *P< 0.05, ** P<0.01, ***P<0.001.

(a)



(b)

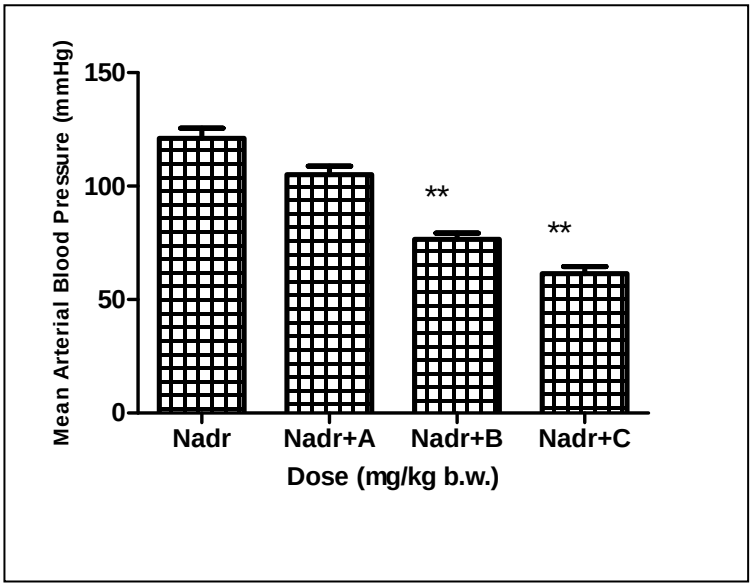


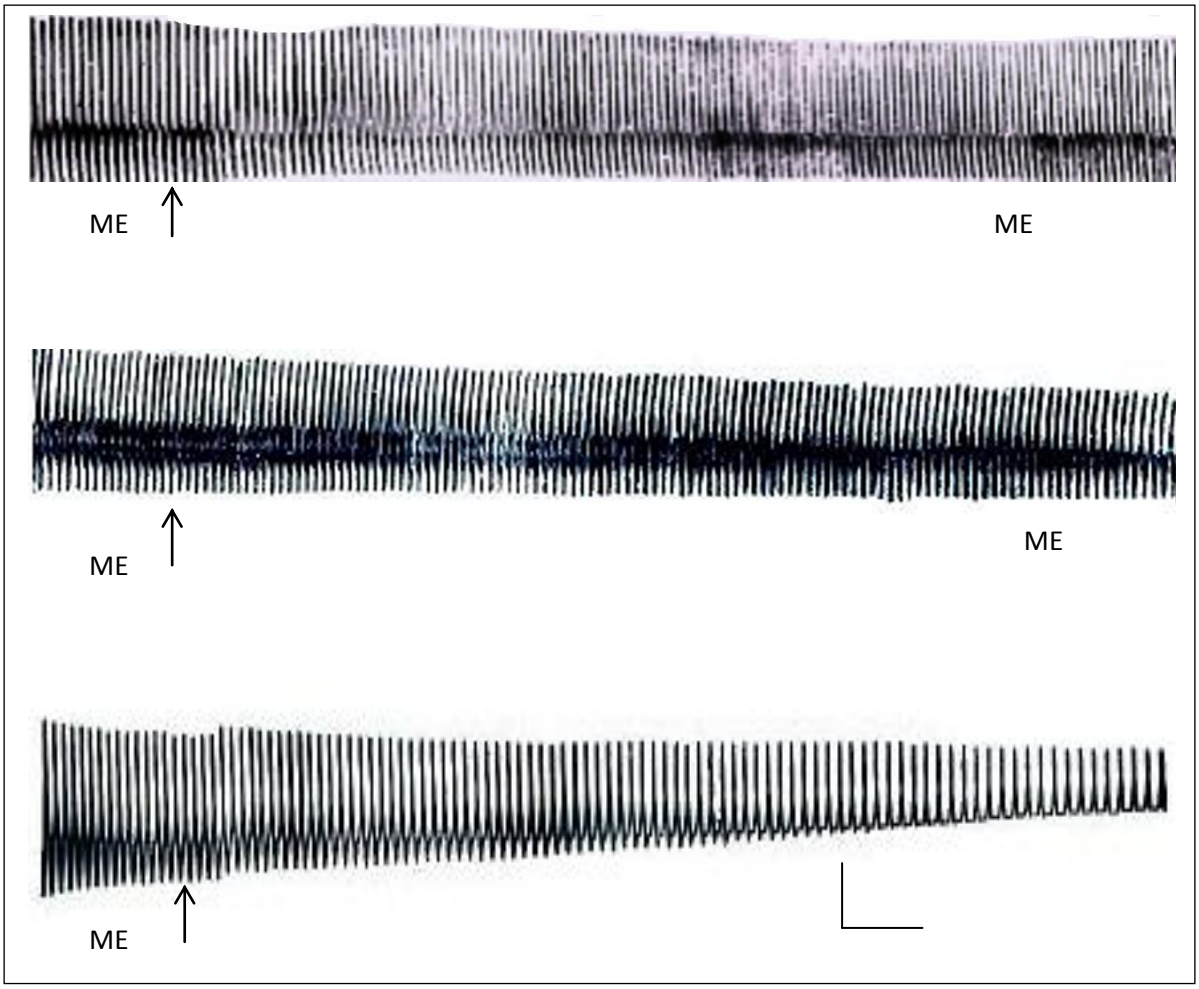
Figure 2: Effects of hydroethanolic extract of *Solenostemon monostachyus* P.Beauv. in presence of atropine and noradrenaline.

(a) Histogram representing Esomo effects in presence of atropine. Atropine (ATR) applied at 2mg/ml reduced partially Esomo-induced fall in MABP. A: Esomo (5.8mg/kg p.c.), B :ATR+Esomo, C: Esomo+ATR.

(b) Histogram representing Esomo effects on hypertension evoked by noradrenaline or adrenaline (Nadr). A: Esomo **(2.9mg/kg p.c.),** B: Esomo **(5.8mg/kg p.c.**) and C: Esomo **(17, 6 mg/kg p.c.**) administration decrease hypertension induced by noradrenaline. Mean ±SEM (n=4).). *P< 0.05, ** P<0.01, ***P<0.001.

Effect of Esomo on isolated heart and aorta

(a)



(b)

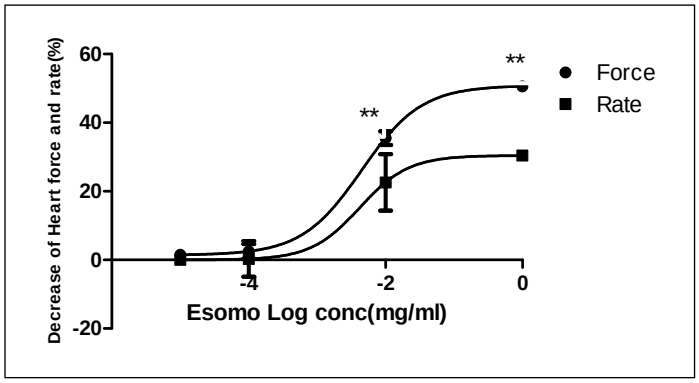


Figure 3: Negative inotropic and chronotropic effects induced by hydroethanolic extract of *Solenostemon monostachyus* P.Beauv.

(a) : Typical tracings from record mechanical activity in the rat heart. Arrows indicate administration of the extract (10^{-6} to 1mg/ml). ME : Mac Ewen used to wash the preparation. Horizontale scale: 5 sec, Vertical scale: 0.5g.

(b) : Concentration-dependent diminution evoked by Esomo (10^{-6} to 1mg/ml) on the isolated heart contractile activity. Values are expressed as a percentage of decrease. Each value represent the mean ±SEM (n=4).). *P< 0.05, ** P<0.01, ***P<0.001.

Isolated heart's rhythmic contractions occur spontaneously and the frequency of cardiac cycle is described by heart rate. Esomo application on isolated heart induced a concentration-dependent negative inotropic and chronotropic effects (**Figure 3a**). Esomo ($10^{-6}$and 10^{-4} mg/ml) did not produce significant effect on heart contraction parameters (force and rate).

However, the extract at concentrations of $10^{-2}$and 1mg/ml decrease significantly heart force contractions of, 35.3 ± 0.5 and 50.56 ± 0.8% and heart rate contractions of 22.2 ± 3.2 and 27.7 ± 0.1% respectively (**Figure 3b**) (p<0.01). **Table 1** present atropine (10^{-5} mg/ml) effects with or without Esomo.

Atropine did not affect significantly on Esomo-induced cardiodepression (decrease of force and rate contraction).

Table 1: Effects of hydroethanolic extract of *Solenostemon monostachyus* P.Beauv. in rat heart force and rate. Atropine (10^{-5} mg/ml) application did not affect Esomo-evoked cardiodepression effects

Drugs	Conc (mg/ml)	Inhibition (%)	
		Heart force	Heart rate
Esomo	10^{-2}	35±1,7	22,20±3.5
Atropine followed by Esomo	(10^{-5}+10^{-2})	31,5±2.4	20,15±0.5
Esomo followed by Atropine.	(10^{-2}+10^{-5})	32,32±3,1	19,63±5.9

Each value represent the mean ±SEM (n=4). *P< 0.05, ** P<0.01, ***P<0.001

Table 2: Effects of L-NAME, methylène blue and indomethacin on the relaxation of rat intact aortic strips induced by hydroethanolic extract of *Solenostemon monostachyus* of noradrenaline-induced precontraction. Vasorelaxation induced by Esomo (0.13 and 0.3 mg/ml) was significantly reduced in presence of L-NAME, methylène blue and indomethacin

Concentrations Esomo (mg/ml)	Relaxation (%)			
	Esomo	Esomo + L-NAME	Esomo + Methylene blue	Esomo+ Indomethacin
IC_{50}= 0,13	50±01	21,31±0,8***	24,97±0,9***	35,79±0,78**
0,3	76,60±0,6	37,31±2,8***	41,38±0,8***	50,56±0,90**

Each value represent the mean ±SEM (n=4). *P< 0.05, ** P<0.01, ***P<0.001.

Esomo was tested at different concentrations on isolated aorta rings. On aorta rings with the presence of endothelium, precontracted with noradrenaline (0.5µM), Esomo (10^{-2} - 1mg/ml) caused a concentration-dependent relaxation (EC_{50} = 0.13±0.25 mg/ml). The hydroethanolic extract of *Solenostemon monostachyus* also relaxed KCl (100mM) precontrated tissue (EC_{50} = 0.084±3.1 mg/ml). Esomo vasorelaxation was most important in rat aorta precontracted with

KCl. The concentration of 1 mg/ml provoked the maximum relaxation of 96.42±0.58% and 94.16 ± 2.1% in rat aorta rings precontracted with KCl and noradrenaline respectively (**Figure 4**).

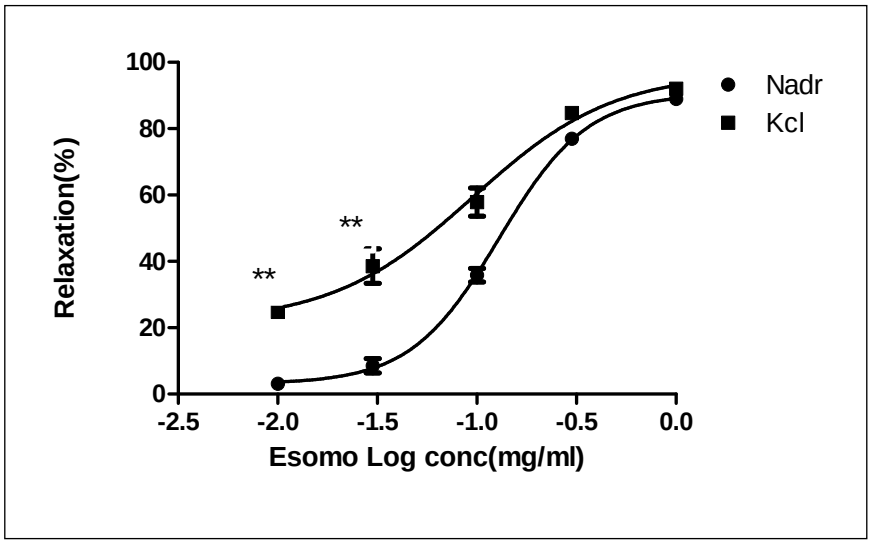


Figure 4: Concentration-dependent relaxation induced by hydroethanolic extract of *Solenostemon monostachyus* P.Beauv (10^{-2}mg/ml-1mg/ml) in rat intact aorta contraction evoked by Noradrenaline (Nadr) and Kcl. Values are expressed as a percentage. Each value represent the mean ±SEM (n=4). *P< 0.05, ** P<0.01, ***P<0.001.

Incubation of the tissue with *L*-NAME (100µM) and methylene blue (5µM), significantly reduced Esomo-induced relaxation. Esomo at concentrations of 0.13 and 0.3 mg/ml produced relaxation of 50 ± 0.1% and 76.6 ± 0.6% respectively. Incubated with *L*-NAME, methylene blue and indomethacin, Esomo relaxation decrease of 21.31± 0.8% and 37.31± 2.8% and of 24.97±0.9% and 41.38±0.8% and of 35.79±0.78% and 50,56±0,90 respectively (**Table 2**).

DISCUSSION

The major finding of the current study was that the hydroethanolic extract of *Solenostemon monostachyus* lowered blood pressure in a dose-dependent manner in normotensive rabbits. This fall in mean blood pressure observed was partially abolished in presence of atropine a muscarinic cholinergic receptors inhibitor. Also the plant extract reduced noradrenaline-induced hypertension effect. These results suggest that the active principles of *Solenostemon monostachyus* leaves could act via cholinergic mechanisms, and could also have an antihypertensive action (Abrogoua *et al*., 2012). This antihypertensive action observed, suggests the presence of other substances different of cholinomimetics substances in the extract, responsible of hypotensive effect.

To further characterize the mechanisms of the plant extract blood pressure lowering action, we tested its effect also on isolated rat hearts and aorta which are main constituent of blood pressure regulation.

The hydroethanolic extract of *Solenostemon monostachyus* produced a negative inotropic and chronotropic effect which remains unchanged by atropine. These results were in accordance with the hypothesis of the presence of other substances different of cholinomimetics substances.

The plant extract exhibited vasorelaxation activity by inhibiting the contractile response to

noradrenaline or to KCl. It inhibited KCl-evoked contraction more potently than noradrenaline-evoked contraction.

It is well reported that K^+-depolarization (KCl) induce smooth muscle contraction by activation of L-type voltage-operated Ca^{2+} channels (VOCs) leading to increase the intracellular calcium concentration (Ganitkevich and Isenberg, 1991; Karaki, 2004). Noradrenaline induce also the contraction of smooth muscle cells by binding to a specific receptor coupled to a G protein in the plasma membrane. This protein activates an intracellular signaling pathway leading to a contraction (Webb, 2003).The increase in cytosolic calcium can also result from the release of calcium from intracellular stores and from calcium entry through voltage-dependent and independent calcium channels (Webb, 2003). Thus the important relaxation noticed on KCl-evoked vasoconstriction, suggests the blockade of L-type voltage-operated Ca^{2+} channels by active principles of the plant. And the ability of the plant extract to inhibit noradrenaline-induced contraction may be due to its calcium entry blockade action, through receptor operated calcium channels (Shah AJ and Gilani AH, 2011). A class of medication (calcium antagonists) uses these mechanisms to treat hypertension (Kramoh et al., 2012). Calcium antagonists have been widely used for the treatment of hypertension as they reliably induce hypotensive effects with few adverse reactions (Savetti and Di Venanzio, 1994).

To regulate vascular hemostasis in normal and pathological conditions, vascular endothelium produces several biologically active substances (Furchgott and Vanhoutte, 1989, Si et al., 2006). Endothelial cells release endothelium-derived contracting and relaxing factors, Nitric oxide (NO) (Palmer et al., 1987) and prostacyclin (PGI_2) (Moncada et al., 1976). To investigate the involvement of nitric oxide, guanylate cyclase and prostacyclin in endothelium-dependent relaxation, vascular tissue was incubated with L-NAME a nitric oxide synthase inhibitor, methylene blue a guanylyl cyclase inhibitor and indomethacin a cyclooxygenase inhibitor respectively. Our results revealed that the hydroethanolic extract of *Solenostemon monostachyus* effect involves endothelium-dependent NO/cGMP and PGI_2-mediated vasorelaxation pathways.

It is well known that oxidative stress is one of the mechanisms involved in the pathogenesis of arterial hypertension (Touyz, 2004). The antioxidant properties of *Solenostemon monostachyus* leaves have been demonstrated by several authors (Datte et al., 2010; N'guessan Hugues et al., 2011and Tebekeme Okoko and Diepreye Ere, 2012). Thus the ability of the plant extracts to scavenge free radical maybe beneficial for hypertension management.

Many bioactive compounds such as flavonoids, terpens, referred to as antihypertensive compounds, showed vasorelaxant activity (Silvana Morello *et al*., 2005; Martinsen *et al*., 2009). Thus, the presence of flavonoids, terpens in the plant extract might be responsible of blood pressure lowering observed (Toshio *et al*., 1980, Datte *et al*., 2010; N'guessan Hugues et *al*., 2011).

CONCLUSION

The present study indicates that the hydroethanolic extract of *Solenostemon monostachyus* blood pressure lowering activity could result from both cardiac and vasodilator depressant mechanism. It is also essential to note that the plant extract promotes vasodilatation mediated by NO/cGMP and PGI_2 which could account for its use in traditional medicine for hypertension management. Further investigations must be conducted to clarify endothelium-independent pathway mediated by L-type voltage-operated Ca^{2+}

channels blockade using adapted experimentations.

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