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Effects of *Jatropha gossypifolia* L. on the blood pressure and vascular reactivity of rats

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This work investigated the effects of the ethanolic extract (EEJg) of aerial parts of *Jatropha gossypifolia* L. and its aqueous (AFJg) and chloroformic (CFJg) fractions on the blood pressure and vascular reactivity (VR) in normotensive Wistar rats (NWR) and spontaneously hypertensive rats (SHR). In anaesthetized NWR, the EEJg and its fractions reduced mean blood pressure (MAP). The oral administration of EEJg (100 mg/kg/bw), for 8 weeks, did not alter MAP and heart rate in the non-anesthetized SHR. VR was determined in mesenteric artery rings, with the EEJg and fractions inhibiting the contractile responses to noradrenaline (NA, 10^{-9} to 10^{-4} M) in NWR, but not in SHR. In addition, the CFJg inhibited the contractile response to calcium (CaCl_2 , 10^{-6} to 10^{-2} M). These results suggest that *J. gossypifolia* L. has no effect on the hypertensive factors in SHR, which is a model of polygenic hypertension, but indicate the presence of substances with hypotensive activity, which act directly on the adrenoceptor and/or decrease calcium mobilization in NWR.

Key words: *Jatropha gossypifolia* L., vascular reactivity, hypertension, calcium, mesenteric artery.

INTRODUCTION

For centuries plants offered the only source of therapeutic agents for humans. At the beginning of the 19th century, with the development of pharmaceutical chemistry, plants became the main source of raw materials for the development of drugs. Currently, natural products are involved in the development of 44% of all

new drugs. Folk knowledge on the use of medicinal plants makes a very relevant contribution to the dissemination of the therapeutic benefits of plants and aids researchers in the selection of species for botanical, pharmacological and phytochemical studies. However, some factors such as adverse reactions,

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contraindications and drug interactions are often disregarded, thereby creating a risk to health. This problem reinforces the need for more extensive studies of medicinal plants to enable the public and health care professionals to use them more efficiently, safely and in as rational a way as possible (Hostettmann et al., 2003).

Jatropha gossypifolia L. (Family: Euphorbiaceae), popularly known as 'pião-roxo' and 'erva-purgante' (Pio Corrêa, 1984; Wiersema and León, 2013) is used for the treatment of hypertension and as a diuretic and anti-dysenteric. In the laboratory, substances isolated from other species in the same genus exhibit pharmacological activities. For example, Jatrophone, substance isolated from tubers of *Jatropha elliptica*, presented a non-competitive and concentration-dependent inhibition of the contractile responses to neurotransmitters, electrical stimulation, potassium (K^+) or Bay K 8644 in cardiac muscle, as well as vascular and non-vascular smooth muscle from rats, guinea pigs, rabbits and dogs (Calixto and Sant'ana, 1987; Trebien et al., 1988). The same compound exhibited a non-competitive inhibition of the contractile responses to calcium (Ca^{++}) in rat aorta or uterus, depolarized with potassium (Calixto and Sant'ana, 1990).

Meanwhile the alkaloid tetramethylpyrazine, isolated from *Jatropha podagrica* stems, presents neuromuscular blocking activity *in vitro* and a hypotensive effect in anesthetized rats and cats (Ojewole and Odebiyi, 1980). This alkaloid also inhibits the contractile responses induced by electrical stimulation or by noradrenaline (NA) in vascular and non-vascular smooth muscle from rats, guinea pigs and rabbits (Ojewole and Odebiyi, 1981).

Silva et al. (2011) have investigated the effect of *J. gossypifolia* L. aerial parts on intestinal transit velocity and on isolated. It was observed that the chloroformic fraction of *J. gossypifolia* L. ethanolic extract had a calcium-antagonist effect, whereas both chloroformic and aqueous fractions had anticholinergic effect, suggesting that the antispasmodic effect of *J. gossypifolia* L. may be due to a combination of anticholinergic and calcium-antagonist mechanisms. Another study shows that ethanol extract and the chloroformic fraction reduced the calcium-evoked contractile response of the uterine smooth muscle, promoting a rightward displacement of calcium cumulative curves, as well as reducing the maximal contractions. So the mechanisms by which they promote this effect possibly involve the impairment of Ca^{++} influx through membrane voltage-operated channels (Paes et al., 2012).

Additionally, Abreu et al. (2003) observed the hypotensive effect of the ethanolic extract (EE) from the aerial parts of *J. gossypifolia* L., which presented a significant, dose-dependent reduction, in the systolic blood pressure in non-anesthetized normotensive Wistar rats (NWR). The percentage of inhibition was 11 and 13% for groups treated orally with EE at 125 and 250 mg/kg/bw, respectively. This effect was confirmed by the

ability of the extract to produce relaxation in rat isolated mesenteric artery preparations pre-contracted with NA or $CaCl_2$, and by inhibiting, in a competitive and non-competitive, concentration-dependent manner, the contraction induced by these agonists, without demonstrating any Ca^{++} chelating property (Abreu et al., 2002). These results suggest a possible inhibitory mechanism of action on adrenoceptors and/or on the mobilization of calcium ions. Importantly, acute toxicological studies on the EE of *J. gossypifolia* L. in rats indicate a low acute oral toxicity (Mariz et al., 2008; Mariz et al., 2006).

Based on evidence from previous scientific studies on the hypotensive effects of *Jatropha*, including *J. gossypifolia* L., the present study was carried out to investigate the effects of the EE of *J. gossypifolia* L. and its fractions on the blood pressure and reactivity of smooth muscle from NWR and spontaneously hypertensive rats (SHR) resistance arteries.

MATERIALS AND METHODS

Plant

The aerial parts of *J. gossypifolia* L. (Euphorbiaceae) were collected from urban areas in São Luís, Maranhão, Brazil, in the month of August, 2011. Plant identification was done in the Atico Seabra herbarium and a voucher specimen (n° 1006) was deposited at the same herbarium for reference.

Preparation of ethanolic extract and fractions

The air-dried, powdered plant material was macerated in an ethanolic solution (95%), then concentrated in a rotary evaporator under reduced pressure, to obtain the ethanolic extract of *J. gossypifolia* L. (EEJg) with a yield of 7.6%. After this process, the EEJg was fractionated using chloroform and water as solvent, obtaining the aqueous (AFJg) and chloroformic (CFJg) fractions, with a yield of 71 and 29%, respectively (Abreu et al., 2003; Silva et al., 2011).

Experimental animals

In these experiments, adult (200 to 250 g), NWR and SHR, obtained from the Animal House of the Federal University of Maranhão, São Luís, Brazil were used. Animals were housed under conditions of controlled temperature ($25 \pm 1^\circ C$) and lighting (lights on: 06:00 to 18:00 h) and had free access to food and tap water. All procedures described in the present study were approved by the Animal Research Ethics Committee of the State University of Maranhão, Brazil (License number 05/2008).

Measurement of mean blood pressure in normotensive wistar rats – direct method

For measurement of mean blood pressure (MAP), NWR were anaesthetized with urethane 20% and nembutal 1% (1.8 g/kg/bw and 40 mg/kg/bw, respectively, i.p.). Catheters were inserted into the external iliac vein for the administration of drugs and into the

carotid artery for pressure recordings. The arterial catheter was connected to a pre-calibrated pressure transducer (P-1000B, Narco Biosystems, Inc., Houston, Texas, USA) and pressure outputs were recorded on a physiograph (Narcotrace 40, Narco BioSystems, Inc., Texas, USA). After the hemodynamics parameters had stabilized, MAP was recorded before (baselines values) and after i.v administration, of the randomized doses of ACh (1 µg/kg), EEJg (1 to 100 mg/kg/bw), AFJg (5 to 30 mg/kg/bw) and CFJg (1 to 100 mg/kg/bw), which did not exceed a volume of 0.4 ml. The successive injections were separated by a period of time sufficient to allow full recovery of baseline blood pressure (Ghayur et al., 2005).

Measurement of blood pressure and heart rate in spontaneously hypertensive rats – indirect method

Mean arterial pressure (MAP) and heart rate (HR) were measured in two groups of non-anaesthetized SHR (n = 8/group), three times a week, during a basal period of 15 days. The tail of pre-warmed (10 min, at 45°C) non-anesthetized rats was placed in a cuff coupled to an isometric force transducer (Korotkoff) for the measurement of arterial pressure. This in turn was coupled to a non-invasive blood pressure system (LE5001-Pressure Meter, LSI Letica, Panlab, Barcelona, Spain) (Queiroz-Madeira et al., 2010). After the basal period, the treated groups received, orally (0.1 ml/100g/bw), a dose of EEJg (100 mg/kg/bw), five times a week, for 8 weeks. The MAP and HR were obtained three times a week. Control groups received only the vehicle (water), in the same volume as the ethanolic extract.

Preparation of isolated rings of rat superior mesenteric artery

The superior mesenteric artery was removed carefully and placed in freshly prepared Krebs solution containing (mM): NaCl, 118; KCl, 5; MgCl₂, 1.2; NaH₂PO₄, 1.2; NaHCO₃, 15.5; C₆H₁₂O₆ (glucose), 11; CaCl₂, 2.0. Each ring (0.5 cm long) was suspended between two wire hooks and mounted in a 5.0 ml organ chamber containing Krebs solution at 37°C, pH 7.4, continuously aerated with a carbogenic mixture of 95% O₂ and 5% CO₂ under a resting tension of 1.0 g. The tissue isometric tension was recorded by a force-displacement transducer (F-60, Narco) and recorded on a polygraph (Vidrio et al., 2003).

After the stabilization period (1 h), cumulative concentration – response curves for noradrenaline (NA, 10⁻⁹ to 10⁻⁴ M) were obtained in the absence and presence of EEJg (250 µg/ml), AFJg (250 µg/ml) or CFJg (250 µg/ml) in SHR, and in the presence of AFJg (100 or 250 µg/ml) or CFJg (50, 100 or 250 µg/ml) in NWR. In some set of experiments with NWR mesenteric artery the incubation medium was replaced by depolarizing Krebs' solution (60 mM of K⁺; 63 mM of Na⁺ and without Ca⁺⁺). After the basal tonus was recovered, cumulative curves for calcium (CaCl₂, 10⁻⁶ to 10⁻² M) were obtained, in the absence or presence of AFJg (100 or 250 µg/ml) or CFJg (100 or 250 µg/ml).

EEJg, AFJg and CFJg were incubated for a period of 10 min before the addition of NA or CaCl₂, remaining in the incubation medium until the maximum contraction produced by these agonists had been recorded. The size of the contractions was measured and depicted on graphs after statistical analysis.

Drugs

Acetylcholine chloride, noradrenalin hydrochloride and urethane were purchased from Sigma Chemical Co. (St Louis, MO, USA). Nembutal (Cristália, Brasil) and all other chemicals (Merck

Darmstadt, Germany) were of high analytical grade.

Statistical analysis

Values are expressed as mean ± standard error of the mean (SEM) of n experiments. Student's t-test for blood pressure tests and One-way analyses of variance (ANOVA) followed by a Newmans-Keuls test for vascular reactivity experiments were conducted in order to evaluate the significance of differences between means. All statistical analyses were done using Graph Pad PrismTM version 5.00 software with p ≤ 0.05 considered significant.

RESULTS

Ethanolic extract (EEJg) and fractions produced important reduction on MAP of normotensive wistar rats – directed method

Anaesthetized rats, treated with EE presented an initial mean blood pressure (MAP) of 92.98 ± 7.9 mmHg. In these animals, the intravenous administration of EEJg (1 to 100 mg/kg/bw) induced dose-dependent hypotension with a variation of 3.8 to 39.4 mmHg, which represents a reduction of 4.1 to 58% (Figure 1a). In the other animals that received the fractions, AFJg and CFJg presented a baseline MAP of 84.55 ± 4.9 mmHg. The i.v administration of the AFJg (5 to 30 mg/kg/bw) induced transitory, dose-dependent hypotension with a variation of 22.1 to 35.5 mmHg, and reducing of 26 to 28% (Figure 1b); the i.v. injection CFJg (1 to 100 mg/kg/kg) induced transitory dose-dependent hypotension with a variation of 6.6 to 26.7 mmHg, which represents a fall of 5.8 to 23.1%, respectively (Figure 1c).

Ethanolic extract (EEJg) not altered the MAP and HR in non-anesthetized spontaneously hypertensive rats – indirect method

In the beginning of the study (Day 0), the values of MAP and heart rate (HR) were 144 ± 2.3 mmHg and 388 ± 2.6 bpm, respectively, an indication of established hypertension in these animals. Treatment with EEJg did not alter MAP and HR compared to the control group (Figure 2a and b). MAP of EEJg treated and control animals showed a fluctuating trend reaching 139.3 ± 9.2 and 147.2 ± 7.6 mmHg, respectively, at the end of the study (after 8 weeks), as well as HR, which reached the values of 347.8 ± 18.6 and 358.0 ± 18.2 bpm, respectively.

Ethanolic extract and fractions antagonized contractile responses in mesenteric resistance artery in NWR, but not SHR

In isolated rings of mesenteric artery from NWR, the

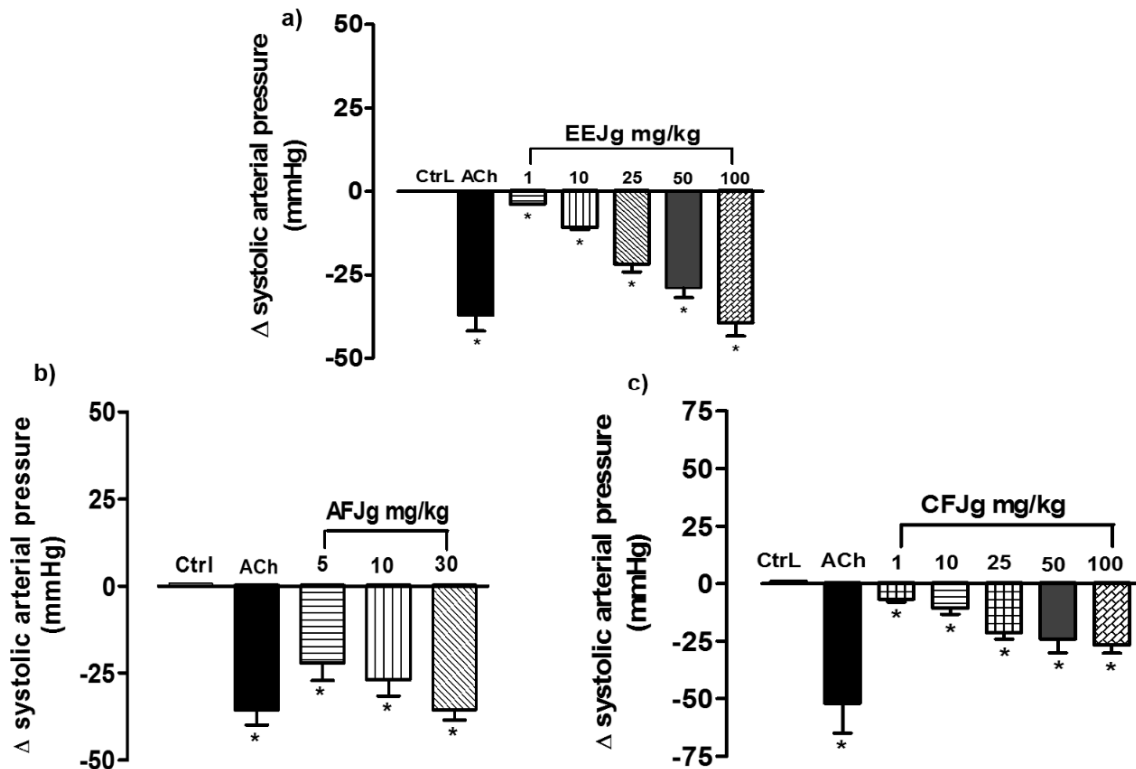


Figure 1. Ethanolic extract (EEJg) and aqueous (AFJg) and chloroformic (CFJg) fractions from *Jatropha gossypifolia* L. reduces the on mean arterial pressure of anaesthetized Normotensive Wistar Rats (NWR). The intravenous administration of EEJg (1 to 100 mg/kg/bw, a), AFJg (5 to 30 mg/kg/bw, b) or CFJg (1 to 100 mg/kg/bw, c) significantly lowered MAP in NWRs, compared to the control. Symbols expressed MAP mean $\pm$ standard error of the mean (SEM, n = 8). *p < 0.001 vs control.

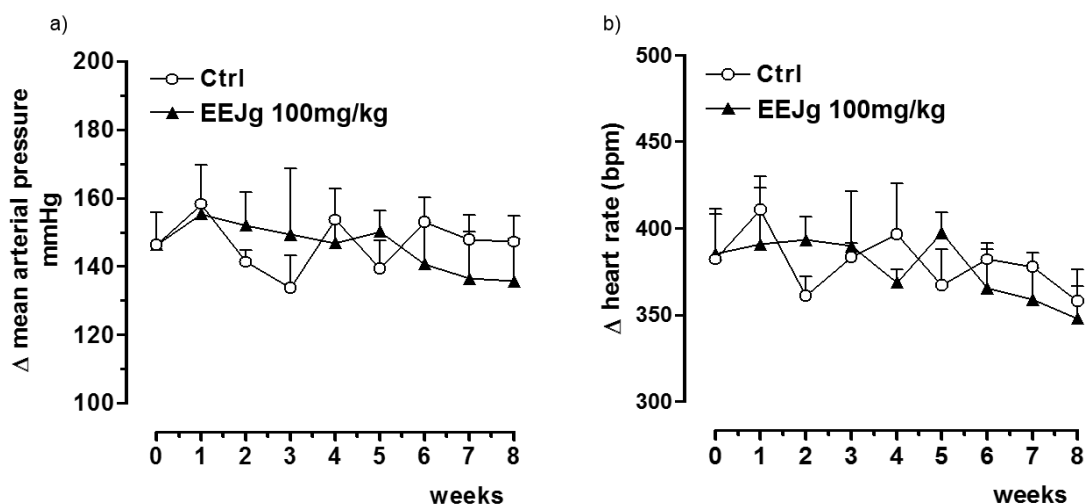


Figure 2. Ethanolic extract (EEJg) of *Jatropha gossypifolia* L. not altered BP in SHRs. (a) MAP (mmHg) values for control or EEJg treated (100 mg/kg/bw) SHRs over a period of 8 weeks. (b) HR (bpm) of SHRs in treatment groups over 8 weeks. Symbols expressed mean $\pm$ standard error of the mean (SEM, n = 8).

AFJg (100 and 250 μ g/ml) shifted the dose-response curves to the right 2.3 and 2.0 times, respectively; thus,

there was a reduction in the maximum effect (E_{max}), in the presence of AFJg (250 μ g/ml), of 31% (Figure 3a).

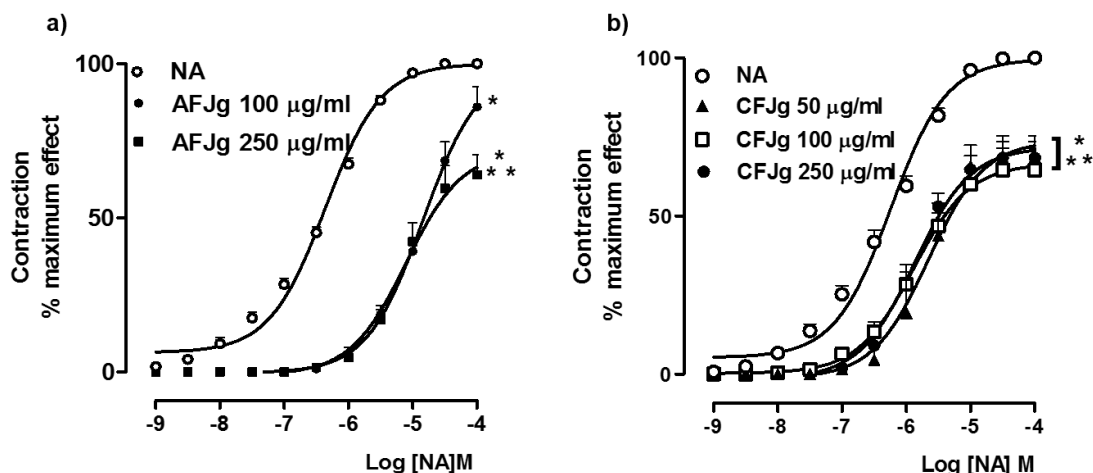


Figure 3. Aqueous (AFJg) and chloroformic (CFJg) fractions from *Jatropha gossypifolia* L. antagonized NA-induced contractile response in mesenteric artery from Normotensive Wistar Rats (NWR). * $p < 0.05$ shift to the right; ** $p < 0.05$ reduction the maximum effect vs control ($n = 5$).

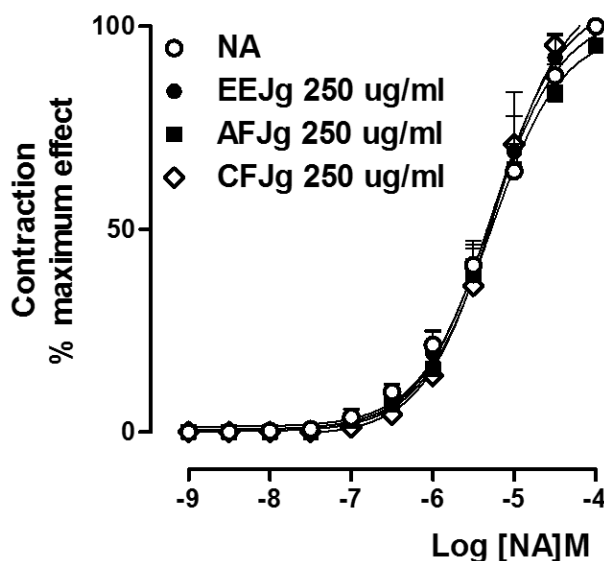


Figure 4. Ethanolic extract (EEJg) and aqueous (AFJg) and chloroformic (CFJg) fractions from *Jatropha gossypifolia* L. not altered NA-induced contractile response in mesenteric artery from Spontaneously Hypertensive Rats (SHR) ($n = 5$).

Similarly, the CFJg (50, 100 and 250 µg/ml) shifted the curves to the right 2.5, 2.5 and 3.1 times, respectively, also reducing the E_{max} by 35.4, 31.5 and 31.4%, respectively (Figure 3b). These effects were reversed after 30 min of repeated washes. By contrast, in mesenteric artery preparations from SHR, the EEJg, AFJg and CFJg did not alter the contraction induced by NA (Figure 4). The AFJg (100 or 250 µg/ml) did not alter

the contractile responses to $CaCl_2$ (Figure 5a), while the CFJg (100 and 250 µg/ml) shifted the $CaCl_2$ dose-response curves to the right by a factor of 2.2 and 3.1, respectively (Figure 5b).

DISCUSSION

In this work, we evaluated the effects of EEJg and its

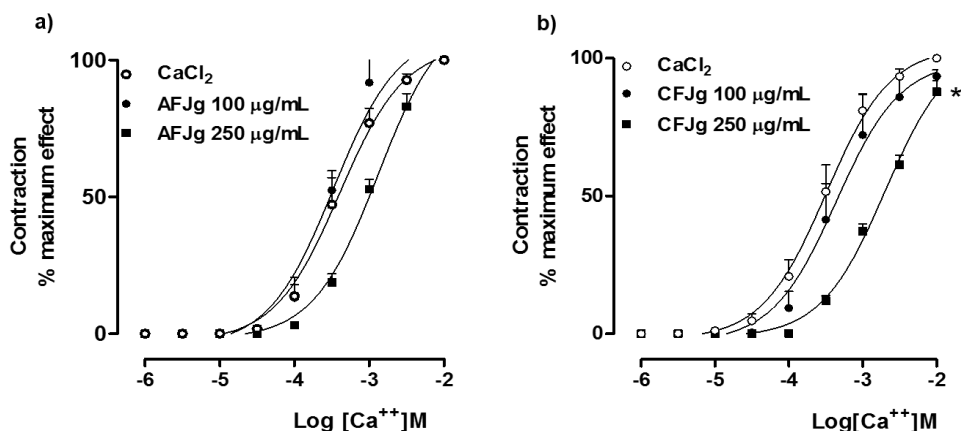


Figure 5. Effects of the aqueous (AFJg) and chloroformic (CFJg) fractions from *Jatropha gossypifolia* L. on the reactivity to Ca^{2+} ions in mesenteric artery from Normotensive Wistar Rats (NWR). Only chloroformic fraction antagonized in $CaCl_2$ -induced contractile response. * $p < 0.05$ shift to the right; ($n = 5$).

fractions on the mean blood pressure (MAP) in anaesthetized normotensive rats. Baseline MAP values were in agreement with those previously reported in other studies (Santos et al., 2007; Badzyska et al., 2014; Dantas et al., 2014), showing anesthesia and possible stress do not influence. In these animals, acute intravenous administration of EEJg, AFJg and CFJg induced significant transitory dose-dependent hypotension, with effects compatibly between the fractions at the administered doses (Figure 1). These findings are consistent with results reported by Abreu et al. (2003), where the ethanolic extract of *J. gossypifolia* L. reduced the MAP in non-anaesthetized NWR in older work. Ojewole and Odebiyi (1980) also showed that tetramethylpyrazine, isolated from *J. podagrica*, had a hypotensive effect in anaesthetized rats.

Peripheral vascular resistance mainly maintains the control of blood pressure and the major contributor is the vascular tone of several arterial beds (Santos et al., 2007). In order to verify if the hypotensive response from fractions could be due to a possible vasoconstriction reduction and consequent decrease in the peripheral vascular resistance, we performed *in vitro* experiments using rings from the isolated rat superior mesenteric artery on the reactivity to NA. In these preparations, the AFJg and CFJg inhibited, in both, a competitive and a non-competitive manner which the contractile responses induced by this agonist (Figures 3a and b).

It is known that the maintenance of smooth muscle contraction is dependent on Ca^{2+} influx from extracellular space through voltage and/or receptor operated calcium channels (VOCCs and/or ROCCs, respectively) and releases Ca^{2+} from sarcoplasmic reticulum. The high K^+ -induced contraction is inhibited by Ca^{2+} channel blockers or by removal of external Ca^{2+} and is, therefore, entirely

dependent on Ca^{2+} influx (Santos et al., 2007; Dantas et al., 2014). In order to investigate if the fractions-caused vasoconstriction reduction could be due to the decrease in the Ca^{2+} influx, we performed a concentration-response curve to $CaCl_2$ in high K^+ solution before and after incubation with fractions. In these conditions, only the CFJg fraction was capable of antagonizing, in a competitive manner, the $CaCl_2$ -induced contractions (Figure 5b).

These initial results were in agreement with the data observed by several authors that showed that ethanolic extract and fractions of *J. gossypifolia* L. antagonized, competitive and non-competitive manner, NA or $CaCl_2$ -induced contractile responses, as well as others stimulus in vascular and non-vascular smooth muscle from normotensive rats (Abreu et al., 2003; Silva et al., 2011; Paes et al., 2012), no however, formed a complex with calcium ions (Abreu et al., 2002). Other studies also shows that compounds isolated from *Jatropha* genus plants inhibited the contractions induced by several agonist in heart muscle or vascular and non-vascular smooth muscle from rats, guinea pigs and rabbits (Ojewole and Odebiyi, 1981; Calixto and Sant'ana, 1987; Trebien et al., 1988). Therefore, as reported by Chan et al. (2000), nifedipine, a L-type voltage-operated Ca^{2+} channel blocker, also inhibited the concentration-response curve to $CaCl_2$. The initial results in this work suggested that the hypotensive response induced by ethanolic extract and fractions of *J. gossypifolia* L. may be due to a direct action on the peripheral vascular resistance.

On these data, we seek to investigate if the hypotensive mechanism demonstrated by EEJg and its fractions in NWR could alter the elevation blood pressure in SHR animals, one of the most studied models in

pathophysiology of essential hypertension (Fazan Júnior et al., 2001). SHR rats show higher circulating levels of angiotensin II (Ang II), impaired vasorelaxation as well as increases in oxidative stress and inflammation, compared to normotensive rats (Jahandideh et al., 2014).

More studies indicate that renin-angiotensin-system, especially its main active agent Ang II, is critically important in control of blood pressure and regulation vascular responses in SHR. It demonstrated that (1) lower angiotensin AT₂ receptors (AT₂R) mRNA and protein expression can contribute to vasoconstriction in untreated SHR; (2) acute and chronic AT₁-blockade restored AT₂R expression and its vasodilator function in mesenteric resistance arteries and contributes to blood pressure control in SHR treated (You et al., 2005; Badzyska et al., 2014). Vasodilation induced by AT₂R stimulation has been associated with NO production by endothelial cells and cGMP production by smooth muscle cells (Hannan et al., 2004).

In mesenteric resistance arteries from SHR rats, the endothelium dysfunction too has been demonstrated in several studies. The ACh-induced endothelium-dependent vasodilator response, presumably NO, was significantly attenuated, and verifies less ACh-induced intracellular cGMP content in mesenteric arterial tree, when compared with normotensive rats. However, the concentration-response curves to NO donor sodium nitroprusside were similar in preparations from SHR and normotensive rats, indicating equal responsiveness of vascular smooth muscle cells to NO (Watt and Thurston, 1989; Rizzoni et al., 1994; Liu et al., 2002).

A activation of the sympathetic nervous system is believed to be the main mechanism that increases the peripheral vascular resistance (Fazan Júnior et al., 2001), causing a level of pressure regarded as spontaneous hypertension from the 7th week of life in SHR (Chamiot-Clerc et al., 2001). In this work, we studied the action of EEJg in SHR from the age of 8 week, which showed initial MAP and HR equal to 144 mmHg and 388 bpm, respectively, confirming high BP. We examined the effects of the EEJg on MAP and on the HR and the vascular reactivity of SHR animals. Chronic treatment with the EEJg (100 mg/kg/bw) for 8 weeks did not alter MAP or HR. In the *in vitro* tests using rings of superior mesenteric artery, the EEJg and fractions did not change the contractile responses to NA, suggesting that its substances possibly did not act through the mechanisms ACh-induced endothelium-derived relaxing or some AT₁R-blockade drug.

Taken together, the results indicate the presence of substances with hypotensive activity in the plant *J. gossypifolia* L. that can act directly on the adrenergic receptors and/or decrease the mobilization of calcium ions in normotensive animals, but did not present effects in pathophysiology factors from spontaneously hypertensive rats. However, further experiments are necessary to clearly elucidate all action mechanism.

ACKNOWLEDGEMENTS

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Conflict of interest

The authors have declared that there are no conflicts of interest.

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