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MESTRADO EM SAÚDE E AMBIENTE

Estudo da Atividade Hipotensora das Folhas de Syzygium jambolanum D.C. (jambolão)

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Estudo da Atividade Hipotensora das folhas de *Syzygium jambolanum* D.C. (jambolão)

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RESUMO

O presente trabalho foi desenvolvido com o objetivo de avaliar o efeito das folhas de *Syzygium jambolanum* D.C. (jambolão) na pressão arterial (PA) e na reatividade da musculatura lisa vascular e não-vascular de ratos normotensos. O extrato hidroalcóolico (EH; etanol 70%) foi obtido por maceração a partir das folhas secas de *Syzygium jambolanum* D.C. para avaliação da pressão arterial de ratos conscientes e em preparações isoladas de ducto deferente ou aorta torácica de ratos. O EH foi submetido a fracionamento com solvente usando clorofórmio/água (2:1 v/v) para obtenção das frações clorofórmica (FC) e aquosa (FA) e avaliação da reatividade vascular de anéis de artéria mesentérica. A administração oral de EH (0,1 g/kg/dia ou 0,2 g/kg/dia) induziu uma significante redução da PA em ratos conscientes normotensos. Em preparações de ducto deferentes isolados de ratos, o EH 0,05; 0,1 e 0,25 mg/ml reduziu o efeito máximo (E_{max}) induzido pela noradrenalina (NE) em 22,2; 45,4 e 81,5%, respectivamente. Em ductos deferentes previamente contraídos com a $CE_{75\%}$ de noradrenalina ($3x10^{-4}$ M) o EH (0,2 a 14 mg/ml) induziu relaxamento, dependente de concentração, que atingiu 69%, com a maior concentração utilizada. Em artérias aorta torácica isoladas de ratos, o EH 0,025; 0,05 e 0,1 mg/ml deslocaram, para a direita, as curvas concentração-resposta cumulativas de cálcio (Ca^{++}) em 7,7; 2,8 e 5,2 vezes, respectivamente. Este efeito do EH foi acompanhado pela redução do E_{max} em 30,5; 56,4 e 78,4%, respectivamente. A FA (0,1; 0,25 and 0,5 mg/ml) reduziu o efeito máximo (E_{max}) da NE in 6,5; 15,7 e 51,9% deslocaram a curva para a direita em 2,0; 2,8 e 3,5 vezes, respectivamente. A FC 0,5 mg/ml reduziu o E_{max} da NE em 25,8%. A FC (0,1 e 0,25 mg/ml) reduziu o E_{max} da curva concentração-resposta cumulativa de cálcio (Ca^{++}) em 21,1 e 47,1% e deslocou para a direita em 3 e 4 vezes, respectivamente. Em adição, a FC (0,01 a 1,0 mg/ml) induziu relaxamento, dependente de concentração, em artéria mesentérica pré-contraída com cálcio ($\cong EC_{75}$), na máxima concentração (1mg/ml), na ausência ou presença do bloqueador dos canais de potássio (Tetraetilamônio -TEA), de 97,4 e 99,6%, respectivamente. Em conjunto, estes resultados sugerem que o efeito hipotensor do EH de *Syzygium jambolanum* D.C. pode estar relacionado à atividade vasorrelaxante apresentada pela FC em anéis de artéria mesentérica pré-contraídas com cálcio. Desta forma o presente trabalho contribui para a confirmação da atividade hipotensora das folhas de *Syzygium jambolanum* D.C. empregada pela população maranhense.

Palavras-chave: *Syzygium jambolanum*; jambolão; hipotensora; vasorrelaxante.

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1 INTRODUÇÃO

A hipertensão arterial é definida como a pressão diastólica mantida maior que 90 mmHg. Pode ser descrita como uma fisiopatologia de origem multifatorial, considerando-se os vários mecanismos de controle da pressão arterial envolvidos: mecanismos estruturais, neurais e hormonais; e chega a afetar vários órgãos como cérebro, olhos, coração e rins, predispondo ao aparecimento de doenças cardíacas, acidentes vasculares cerebrais e insuficiência renal, patologias que causam grande número de óbitos. Dessa forma, disfunções destes mecanismos de controle associadas a fatores genéticos, como por exemplo, alteração na produção de hormônios que modulam as funções cardiovasculares (angiotensina, noradrenalina e aldosterona) e fatores ambientais, podem desencadear o aumento da pressão arterial (PAGE, 1999).

Sabe-se que uma das variáveis envolvidas no controle da pressão arterial é a resistência vascular periférica. O aumento da reatividade vascular ou do tônus basal e alterações estruturais no músculo liso vascular podem levar ao aumento dessa resistência, condição apresentável nos modelos de hipertensão (TOSTES, 1993). As conseqüências decorrentes da hipertensão e os efeitos iatrogênicos dos fármacos comumente empregados para controlá-la, traz sérios riscos à população. Daí um interesse na pesquisa de um medicamento, de origem vegetal com menores efeitos indesejáveis, além de menor custo à população, tendo-se como pressuposto seu uso na medicina popular para hipertensão.

Desde o início da cultura humana, os recursos naturais têm sido utilizados pelo homem para sua sobrevivência, incluindo fins medicinais (SOEJARTO; SARNSWORTH, 1989). Com o tempo, o conhecimento empírico sobre o uso de ervas, substâncias animais e minerais, para a cura, foi-se cristalizando e restringindo à classe médica e farmacêutica (ANSEL,1994). O acúmulo desse conhecimento levou ao desenvolvimento de medicamentos até então utilizados pela medicina (SIMÕES, 1984).

Segundo estimativas da Organização Mundial da Saúde (OMS), 80% da população mundial usam as medicinas tradicionais para suprir as necessidades de assistência médica primária (ELISABETSKY, 1987). Com isto, a utilização de plantas

medicinais, sem respaldo científico, tem motivado o interesse da pesquisa na validação de novas drogas (MATOS, 1994).

> O estudo de uma planta inicia-se com a seleção da espécie a ser estudada, onde a escolha pode ser baseada em considerações quimiotaxonômicas, ou no seu uso etnofarmacológico. As plantas selecionadas pelo seu uso na medicina popular, em particular, têm grande chance de conter compostos biologicamente ativos (HAMBURGER; HOSTETTMANN, 1991).

O Brasil graças ao seu solo riquíssimo e ao clima tropical favorável, é dotado de uma flora variada e volumosa, constituindo uma das mais ricas biodiversidades do mundo (CYSNEIROS, 1996). Além de possuir população conhecedora das propriedades medicinais da flora e imensa maioria da população culturalmente adaptada ao uso de plantas, como medicamentos (ELISABETSKY, 1987).

A família Myrtaceae, a qual pertence a espécie em estudo, compreende centena de gêneros e cerca de 3500 espécies distribuídas por todo o mundo, preferencialmente nas zonas tropicais e subtropicais da América e Austrália (JOLY, 1979). Muitas dessas espécies são usadas pela população. Por exemplo, as folhas de *Psidium guajava* (goiaba) são usadas como agente estimulante, antiinflamatória, antibacteriano e no tratamento de infestações de vermes intestinais, hemorragias e diarréias (GUPTA, 1995). O óleo essencial das folhas de *Psidium guyanensis* e *Psidium pohlianum* (araçazeiros que ocorrem no Nordeste do Brasil) apresentam ações anticonvulsivante, analgésica e antiinflamatória em animais (SANTOS et al., 1996, 1998; TEIXEIRA et al., 1994).

Syzygium jambolanum D.C., originária da Índia, encontra-se aclimatada no Brasil, prefere climas quentes e úmidos, principalmente de regiões litorâneas. Multiplica-se por sementes, desenvolvendo-se bem em qualquer tipo de solo, porém permeáveis e profundos. Localiza-se com freqüência nos Estados do Maranhão, Bahia, Minas Gerais, Rio de Janeiro, São Paulo e Rio Grande do Sul, e frutifica fartamente no mês de Fevereiro (PIO CORRÊA, 1984).

Esta espécie é conhecida popularmente como jambolão, ameixa de caboclo, azeitona doce, jalão, jambol, jambo roxo, jambo da Índia, jambo da terra e jamelão, os quais variam de região para região do país. Esse vegetal apresenta ainda as seguintes sinonímias científicas: *Eugenia jambolana* Lam., *Calyptrantes caryophyllaefolia* D.C.,

Calyptrantes jambolana Willo., *Eugenia glomerata* Sieb., *Eugenia moorei* Müll, *Jambolifera penduculata* Hoult, *Syzygium caryofolium* D.C. e ainda, *Syzygium jambos* (L.) Alston, *Eugenia jambos* L., *Jambosa jambos* Mills., *Jambosa vulgaris* D.C., *Caryophyllus jambos* Stokes (POZETTI, 1989; MORTON, 1987) e *Syzygium cumini* (L.) Skeels (MURUGANANDAN et al., 2001).

Partes aéras de *Syzygium jambolanum* D.C. (jambolão)

Como principais constituintes químicos encontrados nesta espécie temos os glicosídeos antimielina e jambolina, óleos essenciais, resinas, ácido palmítico, esteárico e oléico, fitosterol e jambulol ($C_{16}H_8O_9$) (POZETTI, 1989). O ácido oleanóico e o ácido ursólico são alguns dos mais ricos constituintes das flores e folhas da espécie, respectivamente. Testes fitoquímicos realizados com extratos hidrofílicos e lipofílicos das folhas de *Syzygium jambolanum*, obtidos em diferentes períodos de coleta, demonstraram a presença de taninos, fenóis, flavonas, flavonóis, xantonas, catequinas e saponinas (VÉRAS, 2000). A análise fitoquímica do extrato aquoso da casca da árvore, por reações colorimétricas e cromatográficas sugerem um teor de 70% de taninos hidrolisáveis e condensados e uma pequena quantidade de saponinas (DJIPA et al., 2000).

Syzygium jambolanum tem aplicação na terapêutica homeopática na forma de tinturas (sementes) e na alopática como adstringente, anti - hemorrágico, antidiabético,

antidisentérico (sementes, casca do fruto e flores); empregado pela população em casos de leucorréia e redução de gases intestinais, sob diversas formas como as de xarope, infuso, decocto etc. (POZETTI, 1989). Ainda é utilizada como hipoglicemiante, como antibacteriano (MURUGANANDAN et al., 2001). No Maranhão é usualmente empregado pela população para redução da pressão arterial.

A tintura-mãe de *Syzygium jambolanum*, usada *in vitro*, é eficaz na hidrólise do amido, acelerando sua transformação. Além disso, diminuiu a quantidade de glicose livre levando a valores comparáveis aos alcançados com o emprego de insulina (POZETTI, 1989).

Flores et al. (1998), realizaram estudo comparativo entre medicamentos homeopáticos e alopáticos no tratamento de ratos com Diabetes mellitus induzida por aloxona, demonstrando que *Syzygium jambolanum* apresenta realmente propriedades hipoglicemiantes.

Teixeira et al. (2000), estudaram o efeito hipoglicemiante de *S. cumini* (L.) Skeels em modelo pré - clínico e clínico, com o chá das folhas de jambolão. Os resultados não foram sugestivos de que o jambolão possa apresentar efeito hipoglicemiante em pacientes com Diabetes mellitus Tipo 2.

Slowing et al. (1994), conseguiram isolar dois flavonóides glicosilados, o mircetina e quercetina 3-O-β-D-xilopiranosil (1-2) α-L-rhamnopiranosidio a partir do extrato metanólico das folhas de jambolão, e o extrato ainda demonstrou atividade antiinflamatório.

O extrato etanólico obtido das folhas de *Syzygium jambolanum*, também apresentou efeito antiinflamatório, quando administrado por via intraperitonial, em ratos e camundongos (COSTA, 1999).

Ainda constatou-se que o extrato aquoso e etanólico de *Syzygium jambolanum* não apresentaram atividade moluscicida frente aos vetores do *Schistossoma mansoni* (SOUSA et al., 1974).

Estudos realizados com extrato hidroalcóolico da casca da árvore mostraram efeito antiinflamatório, comparado ao efeito produzido pelo ácido acetilsalicílico. Esse efeito foi relacionado ao alto teor de taninos, contidos nesse extrato, que inibem a biossíntese de prostaglandinas (MURUGANANDAN et al., 2001).

Os decoctos das folhas de *Syzygium jambolanum*, além da atividade antiinflamatória, demonstraram também diminuição do trânsito intestinal e aumento do tempo de sono induzido por pentobarbital (OLAJIDI et al., 1999).

No extrato metanólico das folhas de *Syzygium jambolanum* foram recentemente encontrado dois derivados do ácido elágico: o ácido 4-θ- β- D-glucopiranosídio 3, 3', 4'- tri- θ- metilelágico e o ácido 3,3',4'- tri- θ- metilelágico (ABAD et al., 1997).

Outros estudos realizados com o extrato etanólico das folhas sugerem possível atividade antiviral para Herpes Simples Tipo I (ABAD et al., 1997). O ácido oleanóico isolado das flores do jambolão diminui a capacidade de fertilização de ratos, promovendo alteração da espermatogênese sem, contudo, afetar a morfologia das células testiculares, sugerindo um efeito contraceptivo (RAJASEKARAN et al., 1988).

Conforme Jiménez (1995), efeitos no sistema cardiovascular em cães foram observados após administração intravenosa da fração acetato de etila, obtida a partir da fração aquosa, que produziu marcado efeito hipotensor, seguido de diminuição da freqüência cardíaca.

2 OBJETIVOS

Geral

Estudar a ação hipotensora do extrato hidroalcóolico (EH) das folhas de *Syzygium jambolanum* D.C.

Específicos

- Avaliar o efeito do EH na pressão arterial;
- Estudar a ação do EH na musculatura lisa vascular e não vascular;
- Avaliar a ação das frações clorofórmica (FC) e aquosa (FA) na reatividade de anéis de artéria mesentérica.

3- ARTIGOS

Hypotensive activity of *Syzygium jambolanum* D. C.

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Abstract

The present work was developed in order to study the effect of the hydroalcoholic extract (HE) from *Syzygium jambolanum* D. C. on the arterial blood pressure (ABP) and on the smooth muscle reactivity of normotensive rats. The HE effects (ethanol 70%), obtained by maceration from leaves, were investigated on the ABP of conscious rats as well as on the deferens vas or on thoracic aorta reactivity of normotensive rats. Oral administration of HE (0.1 or 0.25 g/Kg/day, o.v.) caused a significant reduction of the ABP. Besides, the HE at 0.05; 0.1 and 0.25 mg/ml was able to significantly reduce the maximum effect (E_{max}) of noradrenalin (NE) in 22.2; 45.4 and 81.5%, respectively. In the deferens vas previously contracted with NE, HE (0.2 to 14 mg/ml) also induced relaxion of 69.4% at the highest dose (14 mg/ml) in a concentration-dependent way. In the thoracic aorta, HE at 0.025; 0.05 and 0.1 mg/ml shifted to the right, the cumulative concentration-response curve of calcium (Ca^{++}) in 7.7; 2.8 and 5.2 times, respectively. In addition, HE reduced the E_{max} in 30.5; 56.4 and 78.4%, respectively. Thus, the present work corroborates the hypothesis of a hypotensive activity of *Syzygium jambolanum* D. C. and suggests the presence of Ca^{++}- antagonistic substances in the reactions involved.

Keywords: *Syzygium jambolanum*; jambolão; hypotensive.

1 Introduction

Syzygium jambolanum D.C. (Myrtaceae) is originated from India and acclimatized in Brazil, growing well at any kind of soil and frequently found in the coastal areas of the states of Maranhão, Bahia, Minas Gerais, São Paulo, Rio de Janeiro and Rio Grande do Sul, where is commonly known as "jambolão" or sweet olive. Jambolão is a medicinal plant with application in therapeutics homeopathic in the form of dyes (seeds) and in a allopathic way as adstringent, anti-hemorrhagic, anti-inflammatory, hypoglycemic, anti-dysenteric (seeds, fruit peel and flowers). Population uses syrups, infusions and decoctions of *Syzygium jambolanum* in cases de leucorrhea and reduction of lung gases, as anti-diabetic, antimicrobial and against the HIV (Pozetti, 1989; Muruganandan, 2001). Population of Maranhão, state from Brazil, often uses the plant for reduction of the blood pressure.

From the methanolic extract of the *Syzygium jambolanum* leaves two glucosic flavonoids have been isolated: myrcetin and quercetin (3-O-β-D-xilopyranosyl (1-2) α-L-rhamnopyranosides, which present anti-inflammatory activity (Slowing et al., 1994). Phytochemical analysis of the aqueous extract of the jambolão bark by means of colorimetric and chromatographic reactions, suggests a proportion of 70% of hydrolyzed and condensed tannins and also a small aliquot of saponins (Djipa et al, 2000).

Previous pharmacological studies with various parts of the plant have confirmed the therapeutic actions of *Syzygium jambolanum* based on the oral administration in rats (Mukherjee et al., 1998; Grover et al., 2002), which led to the conclusion that the active

components present in the extract do not promote acute toxicity when orally administered.

Studies with the hydroalcoholic extract prepared from *Syzygium jambolanum* bark have demonstrated anti-inflammatory effect as compared with the acetylsalicylic acid, being such effect related to the high level of tannins in the extract, inhibiting the prostaglandins biosynthesis (Muruganandan et al., 2001). Sharma et al. (2003) have observed that the ethanol extract of *Syzygium jambolanum* seeds posses a hypolipidemic effect, since it was able to reduce the activity of the following liver enzymes: 3-hydroxy-3-methylglutaryl CoA (HMG-CoA), and therefore reducing the cholesterol and triglycerides levels in the serum.

With reference to the glycemia, the studies that were performed with seeds, fruit and bark of *Syzygium jambolanum*, following several different experimental patterns, demonstrated the hypoglycemic and anti-hyperglycemic effect (Achrekar et al., 1991; Sharma et al., 2003; Ravi et al., 2004; Sridhar, 2005; Villasenor, 2006). Nevertheless, investigations carried out in Brazil have shown that the leaves and the fruit of *Syzygium jambolanum* did not have any effect on diabetes (Teixeira et al., 1990; Teixeira et al., 1997; Teixeira et al., 2000; Pepato et al., 2005). Cardiovascular effects were observed after intravenous administration of the ethyla acetate fraction of aqueous fraction in dogs (Jiémenez, 1995).

Due to their potential as medicinal plant and popular use as hypotensive, the present work aims at the study of the hypotensive property of the hydroalcoholic extract of *Syzygium jambolanum* D. C. leaves.

2 Methodology

2.1 Plant material

Plant leaves were collected from the same specimen located at the Campus do Bacanga of Universidade Federal do Maranhão –UFMA-Brazil in 2001, May. This material was identified as *Syzygium jambolanum* D. C. (Myrtaceae) and a voucher specimen (nº 1069) is kept in the Atico Seabra Herbarium –UFMA.

2.2 Extracts preparation

Leaves were allowed to dry at room temperature and the powder directed to the Natural Products Laboratory of the Chemistry Departament of UFMA. The dried powder was macerated in 70% ethanol (1:3 v/v). After three successive washes of the solvent, the macerate was filtered and concentrated in rotaevaporator under reduced pressure and at a temperature bellow 60º C. Such concentrate was denominated hydroalcoholic extract (HE), whose final concentration was 150 mg/ml and with a yield of 16.3%.

2.4 Animals

Wistar rats from the species *Rattus norvegicus* were used in all experiments. Adult rats, ages varying from 60 up to 90 days-old, from both sexes were directly obtained from the Animal Breeding Unit of the Universidade Federal do Maranhão. Experimental protocols have been approved by the Animal Ethics Committee of the Universidade Estadual do Maranhão under approval number 06/2006.

2.5 Drugs

Salts and solvents were products with high purity from Merck Darmstadt. Norepinephrine hydrochloride and Calcium were purchased from Sigma Chemical Co. (St Louis, MO, USA).

2.6 Arterial Blood pressure (ABP) records – indirect method

ABP was measured twice weekly from the tail of pre-warmed non anesthetized rats by means of the tail-cuff technique, in which every animal has been pre-trained. The Transducer-cuff (Korotkoff sound microphone, NARCO Bio-systems) was coupled to an amplifier of a physiograph (Narcotrace 40, NARCO). An average of three readings was recorded for each animal. After a basal period of 7 days, the treated groups received, by gavage (0.1ml/100g), a daily dose of HE (100 or 250 mg/Kg) during 20 weeks. Control groups received exclusively the vehicle, in a volume corresponding to the extract (Borges et al., 1999a, 1999b).

2.7 Smooth muscle reactivity

2.7.1 Deferens vas

90 days-old rats were anesthetized with CO_2 and subsequently sacrificed for taking the deferens vas off. Organs were dissected and washed with nutritive solution for vesicle (NLV: NaCl 138 mM; KCl 5.7 mM; NaH_2PO_4 0.36 mM; $NaHCO_3$ 15 mM; $C_6H_{12}O_6$ 5.5 mM; $CaCl_2$ 1.8 mM) and quickly mounted in chamber for contraction of isolated organ, containing air full NLV and at the temperature of 30º C, adapted in a registration system (Quimiograph). After preparation stabilization (30min), cumulative concentration-response curves of noradrenalin (NE) 10^{-8} a 10^{-3} M were obtained either in the absence or presence of the HE (0.05, 0.1 and 0.25mg/ml). Ainda in preparations deferens vas, pre-contracted with noradrenaline EC_{75} (3 x 10^{-4}M), cumulative concentration-response curves of HE (0.2 to 14 mg/ml) were obtained. The widths were measured and represented in graphs after statistical analysis (VAN ROSSUM, 1963).

2.7.2 Rings isolated from thoracic aorta artery

60 days-old rats were anesthetized with CO_2 and sacrificed by section of cervical vas and the aorta was dissected, washed with fluid for aorta (Krebs, NaCl 118 mM; KCl 5 mM; $MgCl_2$ 1.2; NaH_2PO_4 1.2 mM; $NaHCO_3$ 15.5 mM; $C_6H_{12}O_6$ 11 mM; $CaCl_2$ 2 mM) and mounted in muscular chamber containing air full Krebs' liquid (95% O_2, 5%CO_2, pH 7.4; 37ºC) under tension of 1g. Preparation tension was measured with an isometric force displacement transducer (F-60, NARCO) and registered in a physiograph (NARCO). After 60 minutes of stabilization of the preparation, the nutritive liquid was substituted for depolarizing Krebs' liquid (60mM of K^+, without Ca^{2+}). After 60 minutes of successive washes, the basal tonus was recovered, becoming possible obtaining the cumulative concentration-response curves of calcium (10^{-5} to 10^{-1}M) in the absence or presence of the HE (0.05, 0.1 and 0.25mg/ml). The widths were measured and expressed in graphs after statistical analysis. (Edman; Schild., 1962).

2.8 Statistical analysis

All analyses were preformed by sigmoid non-linear regression of response-concentration curves using the software Graph Pad 3.0. Results were expressed as mean ± standard error of mean (S.E.M.) of five or six experiments. The significance of the differences was evaluated by means of analysis of variance (ANOVA). The Newmans-Keuls test for non-paired data and Student's *–t* test for paired data were also used. Differences were considered significant at the 5% level ($p \leq 0.05$).

3. Results

3.1 Effects of the HE on the arterial blood pressure (ABP) of conscious normotensive rats

The mean value of ABP was 100.5 ± 2.9 mmHg in conscious Wistar rats. Oral administration of the HE (0.1 or 0.25 g/Kg/day) was able to cause a significant concentration-independent reduction of the ABP in approximately 33% (0.1 g/Kg/day; 17 weeks) and 30.6% (0.25 g/Kg/day; 5 weeks), during the 20 weeks of treatment.

3.2 Effect of the HE on the reactivity of the non - vascular smooth muscle

Incubation of the HE at 0.05, 0.1 and 0.25 mg/ml did not alter the pD_2 of the NE. However, the same concentrations reduced in a concentration-dependent way the maximum contractions (E_{max}) induced by NE, in 22.2, 45.4 and 81.5%, respectively. Such effect of the HE was reversible after washing of the preparations with NLV, at the three doses used. (Figure 1).

EH (0.2 -14 mg/ml) caused relaxion in preparations of previously contracted deferens vas with NE EC_{75} (3×10^{-4}M) in a concentration-dependent way. The EC50 obtained for the concentration-response curves of HE was 2.9 mg/ml. Maximum relaxation obtained for the HE was 69.4%. Such effect was reversible after 30 minutes of successive washes of the preparations with NLV (Figure 2).

3.3 Effect of the HE on the reactivity of the vascular smooth muscle (Thoracic aorta artery)

HE (0.025, 0.05 and 0.1mg/ml) altered the pD_2 of the Ca^{++} of 2.1 ± 0.1 for 2.4 ± 0.2; 1.4 ± 0.2 and 1.7 ± 0.5 with consequent shift to the right in 7.7, 2.8 and 5.2 times, respectively ($p < 0.05$). The HE reduced in a concentration-dependent way the Ca^{++} induced maximum contraction in 30.5, 56.4 and 78.4%, respectively (Figure 3). This effect was reversible after successive washes of the preparation with depolarizing Krebs' fluid.

4 Discussion

The present study has shown that oral administration of 100 or 200 mg/Kg of HE from *Syzygium jambolanum* leaves in conscious normotensive rats was responsible for a significant reduction of the ABP from the second week until the end of the treatment. The hypotensive effect of the HE can possibly be attributed to its relaxant action; since the HE has produced a concentration-dependent relaxant effect in NE pre-contracted deferens vas of rats. Besides, it was able to inhibit, in a concentration-dependent and non-competitive manner, the NE-induced contractile response for the same preparation. These findings can contribute for the beneficial effects of *Syzygium jambolanum* widely reported in traditional folk medicine, in spite of the mechanisms involved in the hypotensive and relaxant effects are still not clear.

In the present study, the cumulative concentration-responses curves for the NE were shifted to the right with maximum response attenuated by HE, suggesting a non-competitive antagonism against the NE-induced contraction. In addition, HE caused relaxion in a concentration-response way in the NE-precontracted smooth muscle, indicating antagonism on the α-adrenoceptors or even other post-receptor action mechanisms. A non-competitive antagonism reduces the maximum effect and can trigger a variety of mechanisms involving the inhibition of some steps in the chain of transduction signs, such as cellular Ca^{++} influx (Gilman et al., 2001; Rang, 2001).

In order to verify whether or not the effect was result of a possible inhibition of intracellular processes associated to the Ca^{++} influx, it has been used thoracic aorta preparations depolarized with high potassium concentrations. High concentrations of K^{+} increase the Ca^{++} influx through dependent-voltage calcium channels or “operated for potentials” (VOC), where the extracellular Ca^{++}, whose concentration overcomes the intracellular one in the order of 10000 times, moves itself to the cell interior initiating

the contraction process. Membrane persistent depolarization carried out by means of successive exchanges of absent nutritional calcium liquid and high concentration of K^+, favor the return of muscle to its basal tension, exactly being depolarized (Murad, 1990; Rivaplamed, 1996), becoming possible to construct the cumulative concentration – responses curves of the calcium and to analyze the effect of the HE in the contractile process of the VSM. In depolarized aorta artery of rats, the HE (0.025, 0.05 and 0.1mg/ml) modified the CE_{50} of the Calcium control curve, causing shift to the right, and still reducing its maximum effect (Figure 3). A competitive antagonist directly binds to the agonistic receptors, being necessary an increased concentration of this agonistic for acquiring the desired effect. Consequently, there is a shift of its concentration-response curve to the right (Katsung, 1996). These results are suggestive of that *Syzygium jambolanum* presents antagonistic compounds non - competitive to calcium and compounds that seem to act directly in the calcium channels in a reversible way.

In conclusion, our results have shown that the HE of *Syzygium jambolanum* leaves can cause hypotension in conscious normotensive rats and suggest the presence of Ca^{++} - antagonistic substances. Further experiments are actually being performed in order to isolate the active principles and their possible action mechanisms. Even so, this paper contributes to corroborate the hypotensive activity of *Syzygium jambolanum* D. C.

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Figures legends

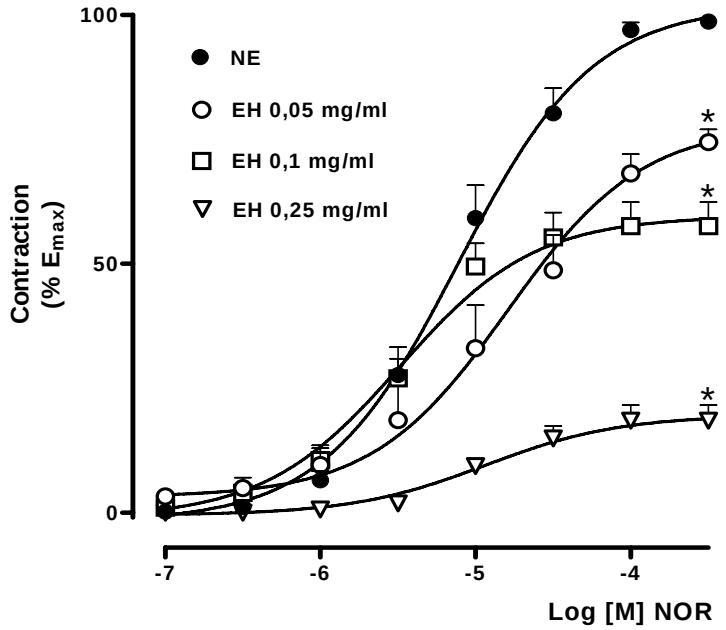

Figure 1.Cumulative concentration-response curves of NE obtained in deferens vas of rats in the absence (•) or presence (○) of HE at 0.05mg/ml, 0.1mg/ml (□) and 0.25mg/ml (▽). Points and vertical bars represent the mean ± standard error of means of 5 or 6 independent experiments, respectively. * Significant difference of the E_{max} obtained from the control curve of NE ($p \leq 0.05$, Student's *t* test).

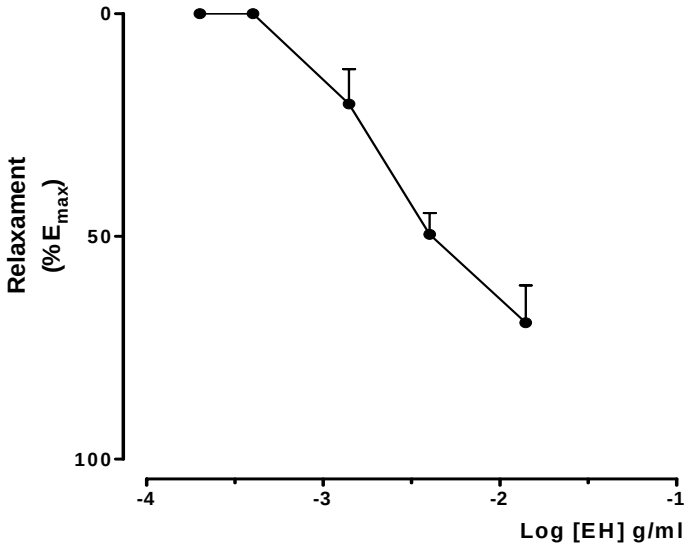

Figure 2. Cumulative concentration-response curves of NE obtained for the HE (0.02-14 mg/ml) in deferens vas of rats previously contracted with NE (EC_{75}). Points and vertical bars represent the mean ± standard error of means of 6 independent experiments, respectively.

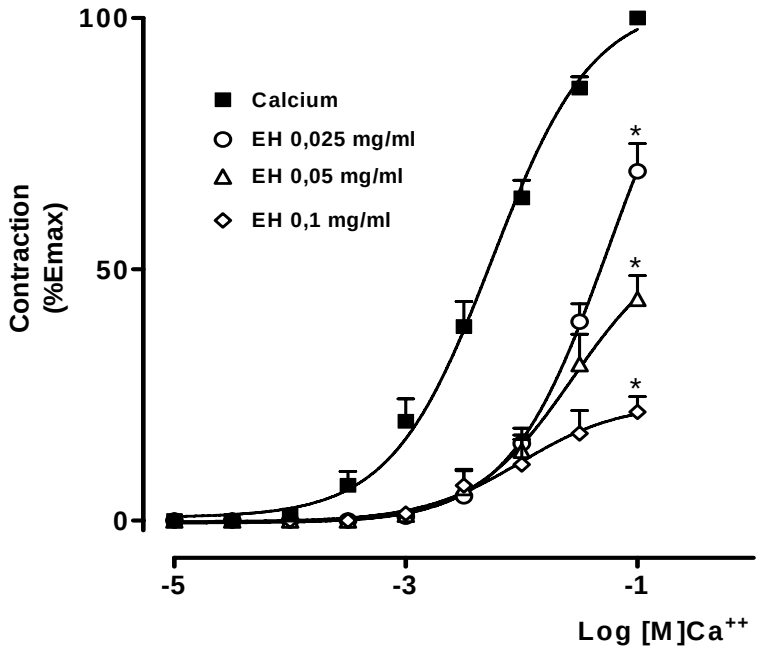

Figure 3. Cumulative concentration-response curves of Calcium obtained in depolarizing preparations of thoracic aorta artery of normotensive rats in the absence (■) or presence of HE at 0.025mg/ml (○), 0.05 mg/ml (Δ) and 0.1 mg/ml (◊). Points and vertical bars represent the mean ± standard error of means of 5 or 6 independent experiments, respectively. * Significant difference of the E_{max} obtained in the Calcium control curve ($p \leq 0.05$, Student's *t* test)

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Vasorelaxant Effect of *Syzygium jambolanum* D.C.

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Abstract

The present work was developed in order to study the effect of the fractions from the hydroalcoholic extract of *Syzygium jambolanum* D.C. (jambolão) leaves on the vascular smooth muscle (VSM) reactivity of normotensive rats. HE (ethanol 70%) was obtained by maceration of the leaves followed by fractionation with solvent using chloroform and water (2:1 v/v). It has been obtained the chloroform fractions (CF) and aqueous fractions (AF), both investigated in the mesenteric artery of rats. AF (0.1; 0.25 and 0.5 mg/ml) reduced the maximum effect (E_{max}) of noradrenalin (NE) in 6.5; 15.7 e 51.9% and shifted to the right 2.0, 2.8 e 3.5 times, respectively. The CF at 0.5 mg/ml reduced the E_{max} of NE in 25.8%. The CF (0.1 and 0.25 mg/ml) reduced the E_{max} of cumulative response-concentration curve of calcium (Ca^{++}) in 21.1 and 47.1% and shifted to the right 3 and 4 times, respectively. In addition, the CF (0.01 to 1.0 mg/ml) induced relaxation, concentration-dependent, in the mesenteric artery previously contracted with calcium ($\cong EC_{75}$), in the higher concentration (1 mg/ml), in the absence or presence of blockage of the potassium channel (Tetraethylammonium -TEA), that was 97,4 and 99,6%, respectively. These results suggest a hypotensive effect of *Syzygium jambolanum* D.C and a vasorelaxant activity in calcium-precontracted VSM.

Keywords: *Syzygium jambolanum*; jambolão; hypotensive; vasorelaxant.

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1. Introduction

Syzygium jambolanum D.C. (Myrtaceae) is originated from India and acclimatized in Brazil, growing well at any kind of soil and frequently found in the coastal areas of the states of Maranhão, Bahia, Minas Gerais, São Paulo, Rio de Janeiro and Rio Grande do Sul, where is commonly known as "jambolão" or sweet olive. Jambolão is a medicinal plant with application in therapeutics homeopathic in the form of dyes (seeds) and in a allopathic way as adstringent, anti-hemorrhagic, anti-inflammatory, hypoglycemic, anti-dysenteric (seeds, fruit peel and flowers). Population uses syrups, infusions and decoctions of *Syzygium jambolanum* in cases de leucorrhea and reduction of lung gases, as anti-diabetic, antimicrobial and against the HIV [1, 2]. Population of Maranhão, state from Brazil, often uses the plant for reduction of the blood pressure.

From the methanolic extract of the *Syzygium jambolanum* leaves two glucosic flavonoids have been isolated: myrcetin and quercetin (3-O-β-D-xilopyranosyl (1-2) α-L-rhamnopyranosides, which present anti-inflammatory activity [3]. Phytochemical analysis of the aqueous extract of the jambolão bark by means of colorimetric and chromatographic reactions, suggests a proportion of 70% of hydrolyzed and condensed tannins and also a small aliquot of saponins [4].

Previous pharmacological studies with various parts of the plant have confirmed the therapeutic actions of *Syzygium jambolanum* based on the oral administration in rats, which led to the conclusion that the active components present in the extract do not promote acute toxicity when orally administered [5, 6].

Studies with the hydroalcoholic extract prepared from *Syzygium jambolanum* bark have demonstrated anti-inflammatory effect as compared with the acetylsalicylic acid, being such effect related to the high level of tannins in the extract, inhibiting the

prostaglandins biosynthesis [2]. Sharma et al. (2003) have observed that the ethanol extract of *Syzygium jambolanum* seeds posses a hypolipidemic effect, since it was able to reduce the activity of the following liver enzymes: 3-hydroxy-3-methylglutaryl CoA (HMG-CoA), and therefore reducing the cholesterol and triglycerides levels in the serum.

With reference to the glycemia, the studies that were performed with seeds, fruit and bark of *Syzygium jambolanum*, following several different experimental patterns, demonstrated the hypoglycemic and anti-hyperglycemic effect (Achrekar et al., 1991; Sharma et al., 2003; Ravi et al., 2004; Sridhar, 2005; Villasenor, 2006). Nevertheless, investigations carried out in Brazil have shown that the leaves and the fruit of *Syzygium jambolanum* did not have any effect on diabetes (Teixeira et al., 1990; Teixeira et al., 1997; Teixeira et al., 2000; Pepato et al., 2005).

Due to the results previously obtained on the hypotensive activity of *Syzygium jambolanum*, the present work was carried out to investigate its effect on the reactivity of the mesenteric artery preparations isolated of normotensive rats, as well as to elucidate the possible action mechanism.

2. Methods

2.1 Animals

Wistar rats from the species *Rattus norvegicus* were used in all experiments. Adult rats, ages varying from 60 up to 90 days-old, from both sexes were directly obtained from the Animal Breeding Unit of the Universidade Federal do Maranhão. Experimental protocols have been approved by the Animal Ethics Committee of the Universidade Estadual do Maranhão under approval number 06/2006.

2.2 Plant material and extracts preparation

Plant leaves were collected from the same specimen located at the Campus do Bacanga of Universidade Federal do Maranhão –UFMA-Brazil in 2001, May. This material was identified as *Syzygium jambolanum* D. C. (Myrtaceae) and a voucher specimen (nº 1069) was deposited in the Atico Seabra Herbarium –UFMA.

Leaves were allowed to dry at room temperature and the powder directed to the Natural Products Laboratory of the Chemistry Department of UFMA. The dried powder was macerated in 70% ethanol (1:3 v/v). After three successive washes of the solvent, the macerate was filtered and concentrated in rotaevaporator under reduced pressure and at a temperature bellow 60º C. Such concentrate was denominated hydroalcoholic extract (HE), whose final concentration was 150 mg/ml and with a yield of 16.3%. HE was fractioned with solvent using chloroform and water (2:1 v/v), obtaining the chloroform fraction (CF) and the aqueous fraction (AF) of concentration 18 and 61mg/ml, respectively.

2.3 Effect on the mesenteric artery isolated of rats

Mesenteric artery preparations were set up as previously described [16, 17]. Rats were anaesthetized by ether inhalation followed by decapitation and the mesenteric artery was isolated. Rings (3 –5 mm) from superior mesenteric artery, without endothelium were placed between stainless steel metals (50 mm in diameter) and suspended in an organ bath chamber (5ml) containing nutritive solution (Krebs) with the following composition (mM): NaCl 118, KCl 5, $MgCl_2$ 1.2, NaH_2PO_4 1.2, 224 $NaHCO_3$ 15.5,$CaCl_2$ 2.0 and glucose 11, (pH 7.4, 37°C, equilibrated with 5% CO_2/ 95%O_2).The tension changes of the preparations were measured with an isometric force displacement transducer (F-60, NARCO) and recorded in a physiograph (NARCO).

The rings were initially equilibrated for 60 min under an optimal tension of 1.0g, washed every 10 min. After 60 min of successive washes, it were obtained cumulative concentration – response curves of NE (10^{-9} to 10^{-4}M) in the absence or in the presence of the CF (0. 25 and 0.5 mg/ml) or AF (0,1; 0,25 and 0,5 mg/ml). In another set of experiments, the nutritive liquid of the preparation was replaced by the depolarizing Krebs' liquid (60mM of K^+, without Ca^{++}). After 60 minutes of successive washes, the basal tonus was recovered, being permitted obtaining of cumulative concentration – response curves of calcium (10^{-6} to 10^{-2}M) in the absence or in the presence of the CF (0.1; 0.25 mg/ml). The tonus of this preparation was increased by the addition of the submaximum effective concentration ($\cong EC_{75}$; 3mM) of Ca^{++} and cumulative concentration – responses curves for the CF (0.01 to 1.0 mg/ml) in absence or presence of TEA (0.3 mM), were obtained in order to evaluate a possible relaxing effect of the CF in the VSM [11]. The widths were measured and expressed in graphs after statistical analysis [18].

2.4 Drugs

The salts and solvents were products with high purity from Merck Darmstadt. Acetylcholine chloride and noradrenalin hydrochloride were obtained from Sigma Chemical Co., St. Louis, MO, USA.

2.5. Statistical analysis

All analyses were preformed by sigmoid non-linear regression of response-concentration curves using the software Graph Pad 3.0. Results were expressed as mean ± standard error of mean (S.E.M.) of five or six experiments. The significance of the differences was evaluated by means of analysis of variance (ANOVA). Paired data were

analyzed by the Student's –*t* test. Differences were considered significant at the 5% level ($p \leq 0.05$) [19].

3. Results

3.1 Effect of the AF and CF fractions on the mesenteric artery isolated of the rats

The AF (0.1; 0.25 e 0.5 mg/ml) reduced the maxim effect (E_{max}) of the cumulative concentration –response curves for NE in 6.5; 15.7 e 51.9% and shifted to the right in 2.0, 2.8 e 3.5 times, respectively (Figure 1). The CF (0.5 mg/ml) reduced the E_{max} of the cumulative concentration –response curves NE in 21.6% (Figure 2). In addition, the CF (0.1 and 0.25 mg/ml) reduced the E_{max} of the cumulative concentration –response curves Ca^{++} in 21.1 and 47.1% and shifted to the right in 3.1 and 4.7 times, respectively. The cumulative additions of CF (0.01- 1.0 mg/ml) produced a dose-dependent relaxant response in mesenteric artery rings precontracted with Ca^{++} (3 mM) of the 97.4% and in the presence of TEA (0.3 mM) of the 99.6 %. (Figure 3 and Figure 4).

4. Discussion and conclusions

The hypotensive effect of *Syzygium jambolanum* D.C. can probably be attributed to its vasorelaxant action, since the CF from the ethanol extract of jambolão produced concentration-dependent relaxant effect in the mesenteric artery precontracted with Ca^{++} isolated from rat.

Ordering to evaluate the effect of the fractions of *Syzygium jambolanum* D.C. on the mesenteric reactivity, it has been used preparations of vascular smooth muscle (VSM) - rings of mesenteric artery - where AF (0.1; 0.25 and 0.5 mg/ml; Figure 1) and CF (0.5 mg/ml; Figure 2) had reduced the induced maximum contraction by the

noradrenalin. Both results suggest the presence of NE-noncompetitive substances. By contrast, FA at the three doses, produced alteration of the CE_{50} with displacement of the curve of the agonistic to the right, suggesting the presence of competitive antagonist compounds.

A competitive antagonist directly binds to the agonistic receptors, being necessary an increased concentration of this agonistic for acquiring the desired effect. Consequently, there is a shift of its concentration-response curve to the right [20]. A noncompetitive antagonism reduce of the maximum effect and is able to trigger a variety of mechanisms involving the inhibition of some steps in the chain of transduction signals, such as the Ca^{++} influx [20, 21]

It is well established that, in the rat mesenteric artery, the vasoconstriction induced by the α_1-adrenoceptor agonist (NE) involves two distinct components in the Ca^{++} -containing medium: an initial phasic component resulting from the inositol 1,4,5-triphosphate, mediating the release of Ca^{++} from intracellular stores followed by a tonic component that requires Ca^{++} input in the continuous presence of the agonist, due to Ca^{++} influx [22].

The blockage of the α_1-adrenergics receptor inhibits the induced vasoconstriction for the endogenous catecholamine, resulting in reduction of the arterial blood pressure, due to a smaller peripheral vascular resistance [20].

To verify whether or not the effect was result of a possible inhibition of intracellular processes related to the Ca^{++} influx, it has been used preparations of mesenteric artery, depolarized with high concentrations of Potassium. High concentrations of K^+ increase the influx of Ca^{++} by means of voltage-dependent Calcium channels or "operated for potentials" (VOC), where the extracellular Ca^{++}, whose concentration overcomes the intracellular one in the order of 10.000 times, moves itself

for the intracellular medium initiating the contraction process. The persistent membrane depolarization, carried out by successive exchanges of the absent nutritional calcium liquid and an increased concentration of K^+, favors the return of the muscle to the basal tension state, exactly being depolarized [23, 24], becoming possible to construct the cumulative concentration – responses curves of the calcium and to analyze the effect of the CF in the contractile process of the VSM. In depolarized mesenteric artery of rats, the CF (0.1 and 0.25 mg/ml) modified the CE_{50} of the Calcium control curve, causing shift to the right, and still reducing its maximum effect (Figure 3). These results are suggestive of that *Syzygium jambolanum* D.C. presents antagonistic compounds non - competitive to calcium and compounds that seem to act directly in the calcium channels in a reversible way.

The vasorelaxant action was decreased by CF (0.01 – 1.0 mg/ml) from *Syzygium jambolanum* D.C. in the presence of higher concentration of Ca^{++} (3 mM), i.e. by the increasing of the levels of membrane depolarization. These results suggested the involvement of hyperpolarization factors, probably bound to opened potassium channels [25]. However, the pre-treatment with TEA, did not antagonized the vasorelaxant action of the CF eliminating a possible involvement of potassium channels.

In conclusion, our results have shown that the hydroalcoholic extract of *Syzygium jambolanum* D.C. leaves can exert hypotension and vasorelaxant activity on mesenteric rings precontracted with Ca^{++} isolated from rats. Such vasorelaxant effect of the chloroform fraction can be involved in its hypotensive effect. Further experiments are actually being performed aiming at the knowledge of the active principles and their possible action mechanisms.

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Figures legends

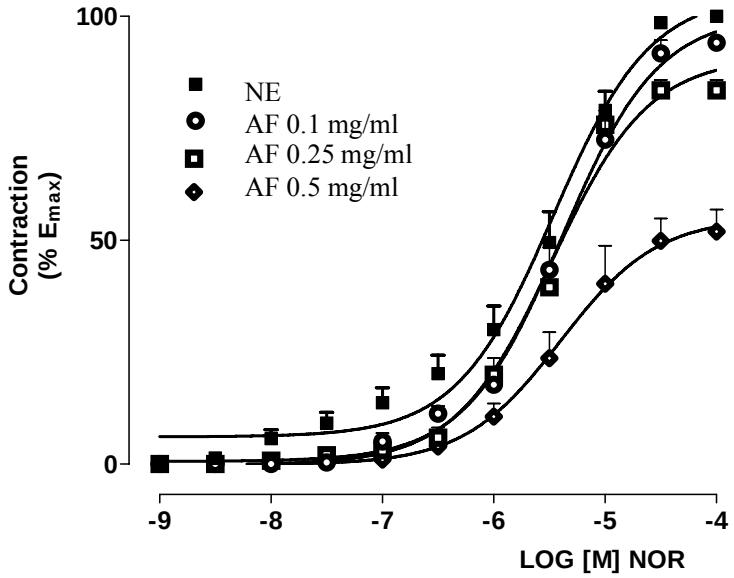

Figure 1 Cumulative concentration - response curves of noradrenaline (NE) in mesenteric artery of rats in the absence (■) or presence of the aqueous fractions (AF) at 0.1 mg/ml (O), 0.25 mg/ml (□) and 0.5 mg/ml (◊). Points and vertical bars represent, the mean ± standard error of mean (SEM), respectively, of 5 or 6 independent experiments.
*Statistically different from the E_{max} obtained in the NE control curve ($p \leq 0.05$, t test).

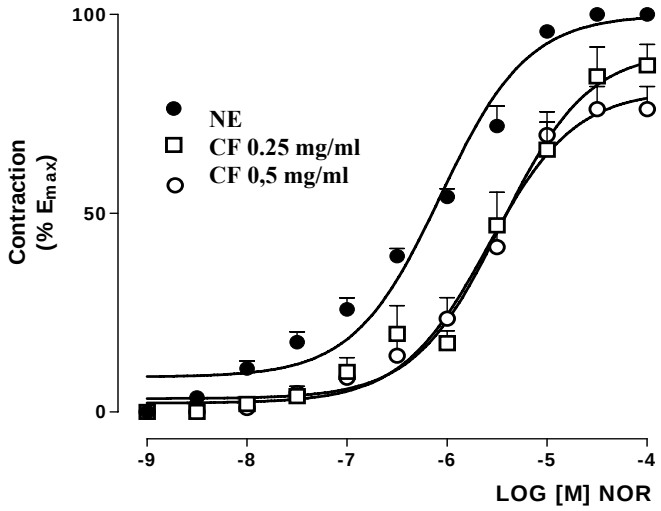

Figure 2. Cumulative concentration - response curves of the noradrenaline (NE) in the mesenteric artery of rats in the absence (■) or presence of the chloroform fraction CF at 0.25 mg/ml (□) and 0.5 mg/ml (○). Symbols and vertical bars represent the mean ± standard error of means, respectively, of 5 or 6 independent experiments.
*Statistically different from E_{max} obtained in the NE control curve ($p \leq 0.05$, Student's *t* test).

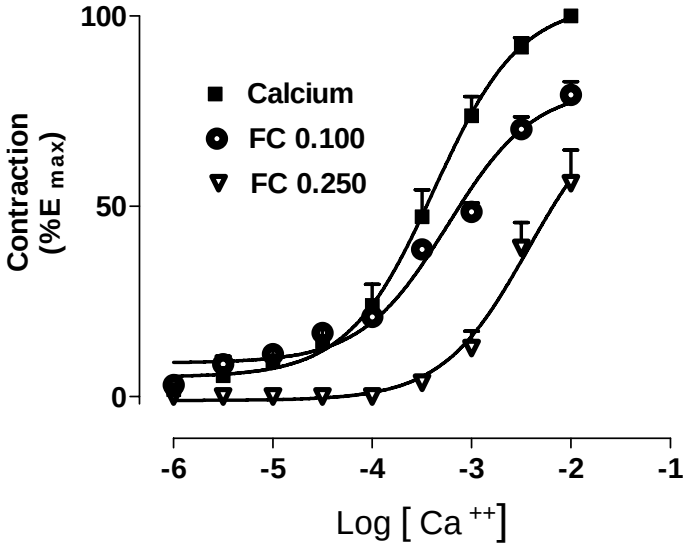

Figura 3 Cumulative concentration - response curves of the calcium (Ca^{++}) in the mesenteric artery of rats in the absence (■) or presence of the CF at 0.1 mg/ml (**O**) and 0.25 mg/ml (▽). Points and vertical bars represent, the mean ± standard error of mean (SEM), respectively, of 5 or 6 independent experiments.
*Statistically different from E_{max} obtained in the Ca^{++} control curve ($p \leq 0.05$, *t* test).

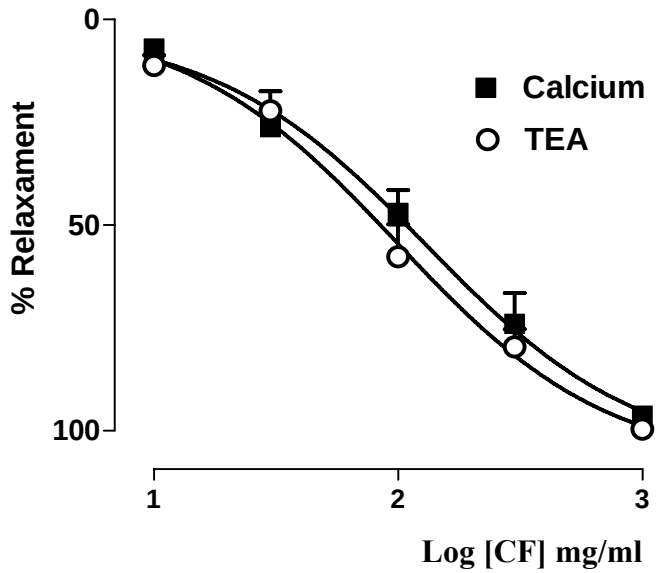

Fig. 4 Cumulative concentration - response curves in mesenteric artery of rats for the relaxation induced by the *Syzygium jambolanum* D.C. FC (0.01 a 1.0 mg/ml) in artery mesenteric pre-contracted with Ca^{++} (3mM) in absence or presence of the TEA (0.3 mM). Responses are expressed as % of the Ca^{++}-induced contraction. Vertical bars indicate the SEM values. In the abscissa, the concentrations in mg/ml of the extract were expressed as logarithms.

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4- CONCLUSÕES GERAIS

Os resultados do presente trabalho nos permite sugerir que:

- O EH das folhas de *Syzygium jambolanum* D.C. reduz a pressão arterial de ratos normotensos conscientes.

- O EH (0,05; 0,1 e 0,25 mg/ml) reduz a contração máxima produzida pela noradrenalina, no ducto deferente de rato, sugerindo a presença de substâncias que antagonizam de forma não - competitiva a noradrenalina.

- O EH (0,02 a 14 mg/ml) promove relaxamento da musculatura lisa pré - contraída confirmando o antagonismo não - competitivo observado com a noradrenalina.

- O EH (0,025; 0,05 e 0,1 mg/ml) em preparação despolarizada de aorta torácica de rato, reduz a contração máxima induzida pelo cálcio, além de antagonizar competitivamente seus efeitos, sugerindo a presença de substância(s) com atividade competitiva e não - competitiva ao cálcio.

- A FA (0,1; 0,25 e 0,5 mg/ml) em preparação de artéria mesentérica de ratos, reduz a contração máxima induzida pela noradrenalina, além de antagonizar competitivamente seus efeitos, sugerindo a presença de substância(s) com atividade competitiva e não - competitiva a noradrenalina.

- A FC (0,25 e 0,5 mg/ml) em preparação de artéria mesentérica de ratos reduz a contração máxima induzida pela noradrenalina, sugerindo a presença de substância(s) com atividade não - competitiva a noradrenalina.

- A FC (0,1 e 0,25 mg/ml) em preparação despolarizada de artéria mesentérica de ratos reduz a contração máxima induzida pelo cálcio, além de antagonizar competitivamente seus efeitos, sugerindo a presença de substância(s) com atividade competitiva e não - competitiva ao cálcio.

- A FC (0,01 e 1,0 mg/ml) promove relaxamento da musculatura lisa vascular pré - contraída com cálcio na ausência e na presença do tetraetilamônio, descartando o envolvimento de canais de potássio.

Em conjunto esses resultados demonstram que as folhas de *Syzygium jambolanum* D.C apresentam efeito hipotensor e sugerem que esta atividade possa estar relacionada o efeito vasorelaxante produzido em artéria mesentérica. Dessa forma, os artigos contribuem para confirmar a atividade hipotensora de *Syzygium jambolanum* D. C. (jambolão) empregada pela população maranhense.

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