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Research Paper

Cardiovascular effects induced by *Cymbopogon winterianus* essential oil in rats: involvement of calcium channels and vagal pathway

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Abstract

Objectives This study has investigated the cardiovascular effects of the *Cymbopogon winterianus* essential oil (EOCW) in rats. *C. winterianus* is a plant used in folk medicine for the treatment of hypertension.

Methods For the measurement of haemodynamic and ECG parameters, male Wistar rats under anaesthesia were cannulated in the abdominal aorta and lower vena cava and electrodes were subcutaneously implanted in their paws. For an in-vitro approach, the rats were killed and the superior mesenteric artery was removed and cut into rings (1–2 mm). These rings were then mounted in organ baths containing Tyrode's solution at 37°C and gassed with carbogen.

Key findings In rats, EOCW (1–20 mg/kg, i.v.) induced dose-dependent hypotension and tachycardia. These effects were not affected by L-NAME or indometacin, but were partially reduced after atropine administration. EOCW (20 mg/kg only) also induced bradycardia-associated sinoatrial blockade, junctional rhythm, and first-degree atrioventricular block, which was abolished after atropine administration or vagotomy. In arterial rings, EOCW (0.1–3000 μg/ml) induced relaxation of phenylephrine tonus that was not affected by removal of the endothelium. These relaxations were similar to those observed in rings without endothelium precontracted with KCl 80 mM. EOCW was able to antagonize the $CaCl_2$ (30–300 μM) induced contractions in depolarizing solution (KCl 60 mM).

Conclusions These results demonstrated that EOCW induced hypotension and vasorelaxation. These effects appeared to be mainly mediated by Ca^{+2}-channel blocking. Furthermore, the higher dose of EOCW induced transient bradycardia and arrhythmias due to a cardiac muscarinic activation secondary to a vagal discharge.

Keywords calcium channel; cardiovascular effects; *Cymbopogon winterianus*; essential oil; vagal pathway

Introduction

Essential oils are natural, complex, multicomponent systems composed mainly of terpenes in addition to some other nonterpene components. These volatile substances are commonly found in aromatic plants and their therapeutic potential and cardiovascular effects have been evaluated.[1–4] Studies in animals have demonstrated beneficial properties of essential oils on the cardiovascular system such as antithrombotic, antiplatelet, endothelial protective, vasorelaxant and hypotensive activity.[2,3] Recent reports have shown that cardiovascular effects of essential oils also occur in humans, as improvements in coronary flow, and hypotensive and bradycardic effects.[5,6]

The genus *Cymbopogon* comprises approximately 140 species, which produce characteristic aromatic essential oils. In Brazil, two species of this genus, *Cymbopogon citratus* and *Cymbopogon winterianus*, are popularly known by the names 'capim-santo' and 'capim-citronela'.[7] Both plants are traditionally used in folk medicine for the treatment of hypertension.[8]

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C. winterianus Jowitt (Poaceae) is a perennial herb that grows abundantly in the northeast of Brazil. Some of its described properties include insect repellency and antifungal, antibacterial and anticonvulsant effects.[9–12] Although frequently consumed by the population for the treatment of hypertension, there have been no pharmacological studies in the literature relating to the activity of this plant on the rat cardiovascular system until now. The aim of this work was to evaluate the effects of *C. winterianus* essential oil (EOCW) on the arterial pressure, heart rate, cardiac electrical activity and vascular reactivity in rats.

Materials and Methods

Drugs

Acetylcholine, L-phenylephrine, N^{ω}-nitro-L-arginine methyl ester hydrochloride (L-NAME), atropine, indometacin and cremophor were all from Sigma (St Louis, MO, USA). Sodium thiopental was from Cristália (São Paulo, SP, Brazil) and heparin was from Ariston (São Paulo, SP, Brazil).

Animals

Male Wistar normotensive rats (200–300 g) were used in all experiments. Animals were housed under conditions of controlled temperature (25 ± 1ºC) and lighting (lights on: 06:00–18:00 h), with food and tap water freely available. All procedures described in this work were in accordance with the Animal Research Ethics Committee of the Universidade Federal de Sergipe, Brazil, and with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication 85-23, revised 1996).

Plant material and preparation of the essential oil

C. winterianus was collected in the metropolitan region of Aracaju, capital of Sergipe state, Brazil, and identified by the Biology Department at the Universidade Federal de Sergipe. A voucher specimen was deposited in the Herbarium of the Biology Department at the Universidade Federal de São Carlos, in the Brazilian state of São Paulo, under the identification code ASE 9386.

The EOCW was obtained from the fresh leaves by hydrodistillation in a Clevenger-type apparatus for 8 h and stored at 4°C. A previous gas chromatography–mass spectrometry (GC-MS) analysis of this oil performed in our laboratory demonstrated the presence of geraniol (40.06%), citronellal (27.44%) and citronellol (10.45%) as the main compounds.[12] When required, oil was dissolved in a saline/cremophor (0.1% v/v) solution, for in-vivo experiments, or distilled water/cremophor (0.1% v/v) solution, for in-vitro experiments, at the desired concentrations. Cremophor had no effect when tested in control conditions (data not shown).

Effect of EOCW on mean arterial pressure and heart rate in nonanaesthetized rats

The measurements of the mean arterial pressure (MAP) and heart rate (HR) were performed as described by Menezes *et al*.[13] Rats were anaesthetized with sodium thiopental (45 mg/kg i.p.). Polyethylene catheters were inserted into the abdominal aorta via left femoral artery for pressure recordings and into the lower vena cava via left femoral vein for the administration of drugs. Both catheters were filled with heparinized saline and led under the skin to exit between the scapulae. Twenty-four hours after surgery, rats were placed in large individual cages and experiments were performed in nonanaesthetized rats. The arterial catheter was connected to a precalibrated pressure transducer (Edwards Lifescience, Irvine, CA, USA) and pressure outputs were recorded in an amplifier-recorder (BioData, Model BD-01, PB, Brazil) connected to a personal computer equipped with an analog-to-digital converter board (BioData, PB, Brazil). For each cardiac cycle, the computer calculated systolic, diastolic and mean arterial pressures and pulse interval (referred to as heart rate).

MAP and HR were recorded before (baseline values) and after intravenous administration of doses of EOCW (1, 5, 10 and 20 mg/kg). Dose–response curves were then obtained. Successive injections were separated by a time interval sufficient to allow full recovery and stabilization of the haemodynamic parameters, which was approximately 5 min.

To check the role of muscarinic receptors, nitric oxide and metabolites of the cyclooxygenase enzyme (COX), mainly prostacyclin (PGI_2), in the responses induced by EOCW, similar records were obtained separately after administration of atropine, a muscarinic cholinergic antagonist (2 mg/kg, i.v., 15 min), L-NAME, a nitric oxide (NO) synthase inhibitor (20 mg/kg, i.v., 30 min) or indometacin (5 mg/kg, i.v. 30 min.), an inhibitor of COX, respectively.

Electrocardiogram records (ECG) and simultaneous direct blood pressure measurements in anaesthetized rats

The animals were cannulated as previously described and maintained under anaesthesia with sodium thiopental (45 mg/kg, i.v.). The cardiac electrical activity was monitored by using subcutaneous electrodes implanted in the front and back paws of the animals, which were then coupled to an ECG recorder in the DII derivation. Immediately after the surgical procedure, ECG records were obtained before (control), after a single dose of EOCW (20 mg/kg, i.v.) and after a single dose of EOCW (20 mg/kg, i.v.) plus atropine (2 mg/kg, i.v., 15 min). Furthermore, in another set of experiments, ECG records were obtained in sham-operated rats (without vagotomy), in sham-operated rats after a single dose of EOCW (20 mg/kg, i.v.) and in cervical bilateral vagotomized rats after a single dose of EOCW (20 mg/kg, i.v.).

Preparation of isolated rings of rat superior mesenteric artery

The tissue preparation was performed as described in Menezes *et al*.[13] Animals were killed by ether anaesthesia and the superior mesenteric artery was removed, cleaned from connective and fat tissues and sectioned into rings (1–2 mm). These rings were suspended by fine stainless hooks connected to a force transducer (Letica, Model TRI210; Barcelona, Spain) with cotton threads in organ baths containing 10 ml Tyrode's solution. This solution was continually gassed with carbogen and maintained at 37°C

under a resting tension of 0.75 g for 60 min (stabilization period). The isometric tension was recorded through the force transducer coupled to an amplifier-recorder (BD-01, AVS, SP, Brazil). When necessary, endothelium was removed by gently rubbing the intimal surface of the vessels with a fine stainless wire and its functionality was assessed by the ability of acetylcholine (10 μM) to induce more than 70% relaxation of L-phenylephrine (10 μM) tonus. The absence of the relaxation to acetylcholine was taken as evidence that the rings were functionally denuded of endothelium.

Effect of EOCW on L-phenylephrine (10 μM) or high concentration of K^+-induced tonus in isolated rat superior mesenteric artery rings

After a stabilization period, contractions were induced with 10 μM L-phenylephrine, in rings with or without endothelium, or with a high concentration of K^+ (KCl 80 mM) in rings without endothelium. During the tonic phase of the contraction, different concentrations of EOCW (0.1, 0.3, 1, 3, 10, 30, 100, 300, 1000 and 3000 μg/ml) were added cumulatively to the organ bath. The relaxations were measured by comparing the developed tension before and after the addition of EOCW and expressed as percentage of relaxation from induced tonus.

Effect of EOCW on concentration-response curves to $CaCl_2$ in rings without endothelium

After a stabilization period, the rings without endothelium were contracted with K^+-depolarizing solution (KCl 60 mM) and washed with normal Tyrode's solution until full recovery of initial tension was achieved. After this, the rings were incubated with nominally zero-Ca^{2+} solution for 15 min and afterwards exposed to nominally zero-Ca^{2+} solution with KCl to 60 mM for another 15 min. A first cumulative concentration–response curve to $CaCl_2$ (10^{-6}, 3×10^{-6}, 10^{-5}, 3×10^{-5}, 10^{-4}, 3×10^{-4}, 10^{-3}, 3×10^{-3} and 10^{-2} M) was then obtained. In these same preparations, concentrations of EOCW (30, 100 and 300 μg/ml) were individually pre-incubated for 15 min and a second cumulative concentration–response curve to $CaCl_2$ was obtained. This curve was compared with those obtained in the absence of EOCW and the results were expressed as percentages of the maximal response to $CaCl_2$ alone.

Statistical analysis

Values are expressed as mean ± SEM. Where appropriate the Student's *t*-test or one-way analysis of variance followed by the Bonferroni post-test were conducted to evaluate the differences between the means. All statistical analyses were done using Graph Pad Prism 3.02 (Graph Pad Prism Software Inc., San Diego, CA, USA).

Results

Effect of EOCW on mean arterial pressure and heart rate in nonanaesthetized rats

In all rats tested, MAP and HR baseline values were 117 ± 3 mmHg and 366 ± 10 beats/min, respectively. Figure 1a presents an original trace showing the effects of the EOCW (1, 5, 10 and 20 mg/kg, i.v.) on the pulsatile signal of arterial pressure of a nonanaesthetized normotensive rat. In these animals, the intravenous bolus injections of EOCW (1, 5, 10 and 20 mg/kg) induced a dose-dependent, intense and transitory hypotension (–18 ± 2, –24 ± 2, –39 ± 3 and –48 ± 2%, respectively; $n = 6$) associated with tachycardia (7 ± 1, 12 ± 2, 17 ± 2 and 25 ± 4%, respectively; $n = 6$) (Figure 2). The effects to each dose were fully recovered after 30 s (data not shown). With the 20 mg/kg dose, the EOCW induced transitory bradycardia before tachycardia (–49 ± 6%; $n = 6$). This effect is demonstrated in Figure 1a and was characterized by a fast and intensive decrease of the pulsatile signal.

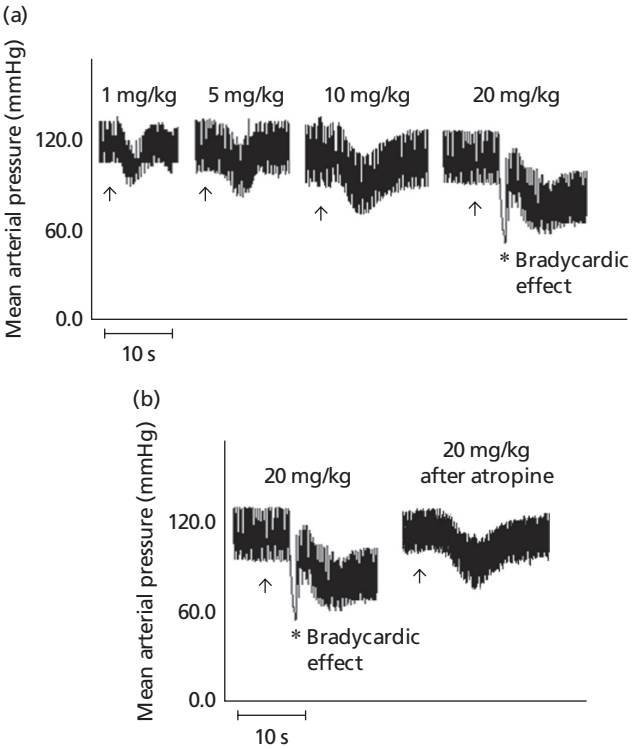

Figure 1 Original trace showing the effects of essential oil of *Cymbopogon winterianus* on mean arterial pressure of a nonanaesthetized normotensive rat. Essential oil of *C. winterianus* (EOCW) was used at 1, 5, 10 and 20 mg/kg (i.v.). (a) Control. (b) Effect of EOCW (20 mg/kg, i.v.) after atropine (2 mg/kg, 15 min, i.v.). The arrows indicate the administration point. *Bradycardic effect of EOCW is characterized by rapid and intensive decrease of pulsatile signal.

Effect of atropine, L-NAME or indometacin on EOCW-induced responses in nonanaesthetized rats

The MAP baseline values (117 ± 3 mmHg; $n = 6$) were not affected after administration of atropine (124 ± 3 mmHg) or indometacin (122 ± 1 mmHg), but were significantly increased after L-NAME (161 ± 3 mmHg; $P < 0.001$). On the other hand, baseline values of HR (366 ± 10 beats/min; $n = 6$) were significantly increased after atropine (435 ± 18 beats/min; $P < 0.05$), decreased after L-NAME (285 ± 8 beats/min;

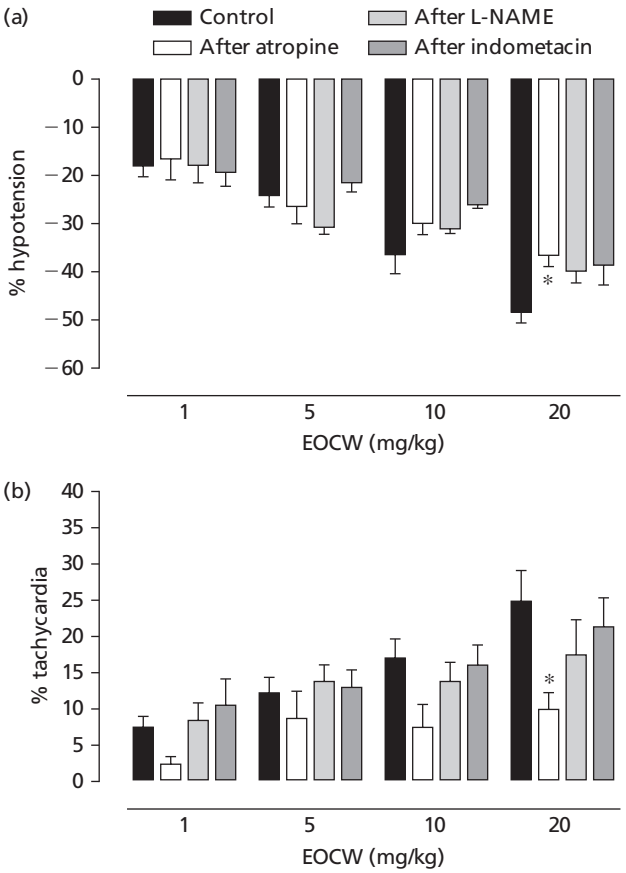

Figure 2 Hypotension (a) and tachycardia (b) induced by essential oil of *Cymbopogon winterianus* in nonanaesthetized rats before (control) and after pretreatment with atropine, L-NAME or indometacin. Essential oil of *C. winterianus* (EOCW) was used at 1, 5, 10 and 20 mg/kg (i.v.). Atropine was used at 2 mg/kg, (i.v.), L-NAME at 20 mg/kg (i.v.) and indometacin at 5 mg/kg (i.v.). Values are expressed as percentage and represent mean ± SEM of six experiments. To evaluate difference between groups, we used repeated measures two-way analysis of variance followed by Bonferroni's post-test. $^{*}P < 0.05$ vs control.

$P < 0.05$) and not changed after indometacin (354 ± 8 beats/min).

The hypotension and tachycardia induced by EOCW were not changed in rats pretreated with L-NAME or indometacin. However, in the presence of atropine, the hypotension and tachycardia induced by the 20 mg/kg dose were significantly attenuated ($P < 0.05$) (Figure 2). Furthermore, the bradycardia induced before tachycardia (–49 ± 6%; $n = 6$) was fully abolished (–1 ± 0.3%; $n = 6$). The original traces of these effects are shown in Figure 1b.

Effect of EOCW on the ECG records in anaesthetized rats

In all animals tested ($n = 4$), EOCW (20 mg/kg, i.v.) was able to induce a hypotensive effect similar to those obtained in the nonanaesthetized animals (–44 ± 3%). Furthermore, EOCW induced transitory sinoatrial blockade, junctional rhythm (Figure 3) and first-degree atrioventricular block, which was characterized by a prolongation of the PR interval (Table 1).

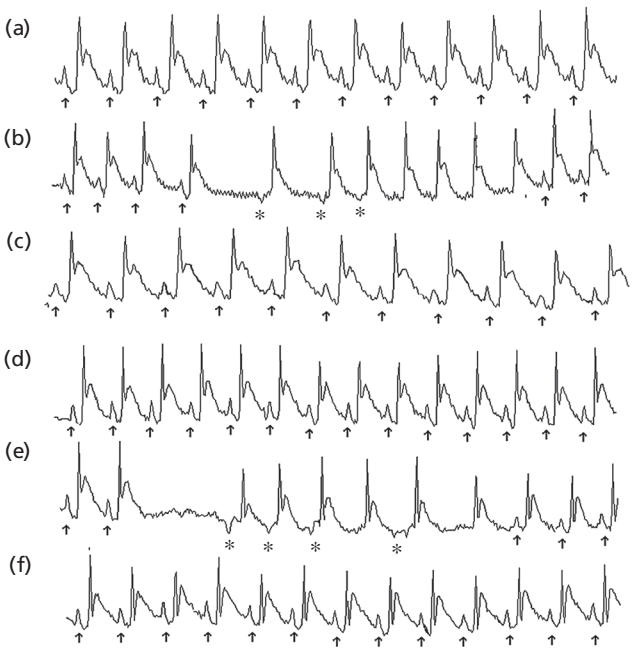

Figure 3 Original traces showing records of the electrocardiogram in anaesthetized rats. (a) Control rats. (b) After administration of essential oil of *Cymbopogon winterianus* (EOCW) (20 mg/kg; i.v.). (c) After EOCW (20 mg/kg; i.v.) plus atropine (2 mg/kg, i.v.). (d) Sham control rats. (e) After EOCW (20 mg/kg; i.v.) in sham rats. (f) After EOCW (20 mg/kg; i.v.) in vagotomized rats. The arrows indicate normal P waves, which were blocked (sinoatrial blockade) and substituted for the retrograde P waves (asterisks). These effects showed that the atrioventricular node was the origin of cardiac electrical impulse characterizing the junctional rhythm.

Table 1 Effect of essential oil of *Cymbopogon winterianus* on PR intervals in anaesthetized rats before (control and sham-operated) and after pretreatment with atropine or after cervical bilateral vagotomy

Groups	PR interval (ms)
Control	49.7 ± 0.1
EOCW 20 mg/kg	55.4 ± 0.9***
EOCW 20 mg/kg + atropine	50.8 ± 1.0
Sham	51.7 ± 1.0
Sham + EOCW 20 mg/kg	61.5 ± 2.5$^{\#}$
Vagotomized rats + EOCW 20 mg/kg	52.0 ± 0.6

Essential oil of *C. winterianus* (EOCW) was used at a dose of 20 mg/kg, i.v.). Atropine at 2 mg/kg (i.v.) was used. To evaluate the difference between curves, one-way analysis of variance followed by Bonferroni's post-test were used. $^{***}P < 0.001$ vs control and $^{\#}P < 0.05$ vs sham.

These effects were abolished after pretreatment with atropine or after cervical bilateral vagotomy.

Effect of EOCW on isolated rings of rat superior mesenteric artery

In isolated rings of the superior mesenteric artery with intact endothelium, EOCW (0.1–3000 μg/ml) induced concentration-dependent relaxations of tonus induced by 10 μM L-phenylephrine (E_{max} = 125 ± 19%, $n = 6$), which was

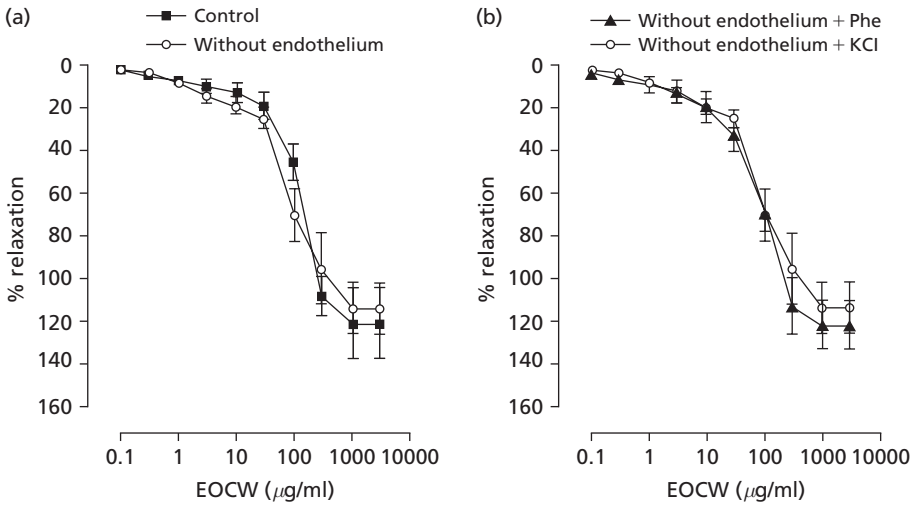

Figure 4 Vasorelaxant effect of essential oil of *Cymbopogon winterianus* in rings of rat superior mesenteric artery. Essential oil of *C. winterianus* (EOCW) was used at the following concentrations: 0.1, 0.3, 1, 3, 10, 30, 100, 300, 1000 and 3000 μg/ml, cumulatively. (a) With (control) and without endothelium precontracted with L-phenylephrine (10 μM). (b) Without endothelium precontracted with L-phenylephrine (without endothelium + Phe) or without endothelium precontracted with KCl 80 mM (without endothelium + KCl). Values are mean ± SEM of six experiments. To evaluate the difference between curves, repeated measures two-way analysis of variance followed by Bonferroni's post-test were used.

not affected after endothelium removal (E_{max} = 117 ± 13%, n = 6) (Figure 4a) or in endothelium-denuded rings precontracted with KCl 80 mM (E_{max} = 121 ± 12%, n = 6) (Figure 4b).

As shown in Figure 5, $CaCl_2$ (10^{-6}–10^{-2} M) induced contractions in denuded rings in a dose-dependent manner that were strongly inhibited after incubation with EOCW 30, 100 and 300 μg/ml (reduction of E_{max} = 24 ± 22, 90 ± 5 and 98 ± 0.6%, respectively). The curves for response to $CaCl_2$ after incubation with EOCW were shifted to the right with reduction of maximal response, suggesting a noncompetitive antagonism. The inhibitory effect of EOCW was reversed after washing for 50 min.

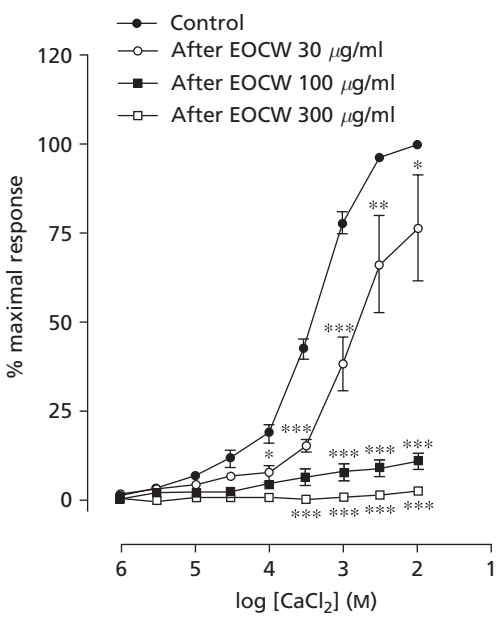

Figure 5 Concentration–response curves to $CaCl_2$ in rat superior mesenteric artery without endothelium before (control) and after pre-incubation with essential oil of *Cymbopogon winterianus* in rings of rat superior mesenteric artery. $CaCl_2$: 10^{-6}, 3×10^{-6}, 10^{-5}, 3×10^{-5}, 10^{-4}, 3×10^{-4}, 10^{-3}, 3×10^{-3} and 10^{-2} M. Essential oil of *C. winterianus* (EOCW) was used at the following concentrations: 30, 100 and 300 μg/ml, separately. Values are mean ± SEM of six experiments. To evaluate the difference between curves, repeated measures two-way analysis of variance followed by Bonferroni's post-test were used. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ compared with control.

Discussion

In Brazil, many patients with hypertension daily drink tea made from the leaves of *C. winterianus*, and this study has demonstrated the possible benefits of this plant on the cardiovascular system. Our results demonstrated that EOCW induced intense hypotension associated with tachycardia, and this oil appeared to have a calcium-blocking property as do other drugs used in the treatment of hypertension, such as nifedipine and verapamil.[14]

As well established by Mulvany & Aalkjaer[15] and White *et al.*,[16] vascular tone underlies the maintenance of peripheral resistance in circulation and it is the major contributor to the control of blood pressure. Furthermore, in most vascular beds, the activation of muscarinic receptors in endothelial cells induces vasorelaxation by release of endothelial mediators, including NO and cyclooxygenase metabolites, such as PGI_2.[17] To verify the role of muscarinic receptors and release of NO or PGI_2 in the hypotensive response induced by EOCW, we performed experiments on animals pretreated with atropine, a nonselective antagonist of these receptors, L-NAME, an inhibitor of the NO synthase, or indometacin, an inhibitor of cyclooxygenase, separately. Our results showed that atropine was unable to change the hypotensive and tachycardic responses at the three lower

doses of EOCW. However, the hypotensive and tachycardic effects induced by the higher dose (20 mg/kg) were significantly and partially reduced, suggesting the activation of muscarinic receptors, at least at this dose. It is known that drugs that induce hypotension by reducing the pheripheral vascular resistance, such as nifedipine, are also able to cause a reflex tachycardia via the baroreflex system.[14] The inhibition of the tachycardic effect by atropine appeared to be caused mainly by a decrease of the hypotensive effect and consequent reduction of the baroreflex response. L-NAME and indometacin were unable to alter EOCW-induced hypotension at any of the doses tested, suggesting that NO and prostacyclin (PGI_2) were not involved in this effect.

In a set of in-vitro experiments using rings from the rat superior mesenteric artery, we verified if the hypotensive response could be due to a decrease in peripheral vascular resistance caused by a possible vasorelaxation. In these preparations, EOCW induced vasorelaxation that was unaffected in the absence of functional endothelium. These in-vitro findings were in agreement with those obtained in our in-vivo experiments, which demonstrated that hypotension induced by the EOCW appeared not to be mediated by main endothelial mediators.

As well established by Karaki & Weiss[18] the maintenance of vascular smooth muscle contraction depends on Ca^{+2} influx through mainly voltage-gated calcium channels (CaV). Furthermore, the increase of external K^+ concentration induces smooth muscle contraction through CaV activation. 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 influx.[18] Thus, we evaluated the EOCW effect on endothelium-denuded rings precontracted with high K^+. These experiments revealed that EOCW induced vasorelaxations similar to those obtained in rings precontracted with L-phenylephrine, which suggested that EOCW could be acting through the inhibition of the Ca^{2+} influx through Ca^{2+} channels.

To check the above hypothesis, we constructed a concentration–response curve to $CaCl_2$ before and after incubation with EOCW. In this condition, EOCW shifted the concentration–response curve to the right and reduced the maximal effect in a concentration-dependent manner. This effect was characterized as a noncompetitive antagonism. Yeh *et al.*[19] demonstrated that nifedipine, an L-type voltage-operated Ca^{2+}-channel blocker, also inhibited the concentration–response curve to $CaCl_2$, strongly suggesting that EOCW could be acting, somehow, as a CaV blocker. However, further experiments are necessary to elucidate this possibility.

According to our results, the hypotensive response induced by 20 mg/kg EOCW appeared not to be due exclusively to a decrease in the peripheral vascular resistance, once the tachycardic response was preceded by a transient bradycardia. A better understanding of this effect was reached by ECG recordings during the administration of EOCW. In this experiment, the EOCW was able to induce transitory sinoatrial blockade, junctional rhythm and first-degree atrioventricular block. It is well known that disturbances of electrical atrial conduction, as it was revealed in our results, can reduce the filling volume of the ventricle and the cardiac output, and consequently decrease the blood pressure.[20]

It is established that stimulation of muscarinic receptors in cardiac muscle cells can delay or block the sinoatrial and atrioventricular nodes' conductions.[21] To evaluate the role of these receptors in the EOCW-induced responses, we performed experiments in the presence of atropine. Thus, all arrhythmias were not observed. This data, associated with the attenuation of hypotensive effect and abolishment of the bradycardic response by atropine *in vivo*, led us to suggest that EOCW-induced bradyarrhythmias could be due to an activation of muscarinic receptors in the cardiac myocytes, thereby contributing to the reduction in the blood pressure at the dose of 20 mg/kg. To analyse if EOCW could be acting either directly on muscarinic receptors or indirectly via vagal activation, we performed experiments with anaesthetized and vagotomized rats. In these animals, the responses of EOCW (20 mg/kg) were similar to those observed in animals after acute treatment with atropine, suggesting that a vagal stimulation was somehow induced by EOCW.

The main compounds of EOCW are three terpenoids (geraniol, citronellal and citronellol), which belong to a family of natural products derived from C_5 isoprene units, and which have known cardioprotective effects.[4,12] However, until this moment, no studies have been found relating the cardiovascular effects of the predominant terpenoids contained in EOCW.

On the other hand, we also found possible risks of the uncontrolled use of this plant due to its arrhythmogenic effect, mainly because various patients concomitantly use therapeutic drugs that could potentiate the risk of arrhythmias. The interaction of beta-blockers with calcium blockers increases the risk of total atrioventricular block.[22] A recent report revealed that citronellal and citronellol, constituents of EOCW, increased the intracellular accumulation of digoxin, an inotropic agent used by hypertensive patients with cardiac failure, which can induce diverse arrhythmias such as junctional rhythms, premature ventricular depolarization and ventricular fibrillation.[23,24]

Conclusions

EOCW induced hypotension associated with tachycardia in rats; however, at the dose of 20 mg/kg, EOCW induced transient bradyarrhythmias. Furthermore, EOCW induced vasodilatation in rat mesenteric artery, which appeared to be mainly mediated by an inhibition of the Ca^{2+} influx.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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