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Vasoactive effects of different fractions from two Panamanians plants used in Amerindian traditional medicine

Estela I. Guerrero[a,*], Juan A. Morán-Pinzón[a], Luis Gabriel Ortíz[a], Dionisio Olmedo[c], Esther del Olmo[b], José L. López-Pérez[b], Arturo San Feliciano[b], Mahabir P. Gupta[c]

[a] Departamento de Farmacología, Facultad de Medicina, Universidad de Panamá, Panama
[b] Departamento de Química Farmacéutica, Facultad de Farmacia, Campus Miguel de Unamuno, Universidad de Salamanca, 37007 Salamanca, Spain
[c] Centro de Investigaciones Farmacognósticas, de la Flora Panameña (CIFLORPAN), Facultad de Farmacia, Universidad de Panamá, Apartado 0824-00172, Panama

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ABSTRACT

Ethnopharmacological relevance: *Cecropia obtusifolia* (Cecropiaceae) and *Psychotria poeppigiana* (Synonym: *Cephaelis elata*, Rubiaceae) are two Latin American plants broadly used in traditional Amerindian medicine. The former, together with many other species of the genus *Cecropia*, share the folk reputation of curing heart failure, cough, asthma and bronchitis. The latter is used in Panama by Kuna and Ngäbe Buglé (Guaymies) native Indians for the treatment of dyspnea.
Aim of the study: Based on screening of selected medicinal Panamanian plants by radioligand-binding techniques by Caballero-George et al. (2001), the present study was carried out in order to investigate the vasoactive effects of different fractions from both *P. poeppigiana* and *C. obtusifolia* on rat thoracic aorta and identify active fractions and their chemical constituents.
Materials and methods: Both acid and neutral methanol fractions (P-AMeOH and P-NMeOH) and acid and neutral dichlorometane fractions (P-ADCM and P-NDCM) were obtained from *P. poeppigiana* crude methanolic and dichlorometane extracts, respectively. Identical fractionation was carried out for *C. obtusifolia* (C-AMeOH, C-NMeOH, C-ADCM and C-NDCM. Vasorelaxant effect of all fractions, and their inhibition of contractile responses to angiotensin II were evaluated in isolated aortic rings.
Results: P-AMeOH, P-NMeOH and P-ADCM fractions induced a concentration-dependent relaxation ($43.9 \pm 1.8\%$, $35.3 \pm 4.7\%$ and $52.9 \pm 3.5\%$, respectively) in the endothelium-intact aorta precontracted by phenylephrine (PE, 10^{-6} M). The relaxation produced by C-AMeOH and C-NMeOH ($57.3 \pm 2.5\%$ and $53.3 \pm 3.3\%$, respectively) was greater than the effect produced by C-ADCM and C-NDCM ($42.2 \pm 3.4\%$ and $21.8 \pm 0.8\%$, respectively). Only the incubation of the aortic rings with P-AMeOH reduced the maximum contraction induced by angiotensin II at $20.08 \pm 0.55\%$.
Conclusions: The direct vasorelaxation effect observed could explain in part the ethnomedical use of these plants in Amerindian traditional medicine. The most active fractions contain phenolic and aromatic acid compounds. Furthermore, P-AMeOH, the only fraction that showed both vasorelaxant effect and inhibition of contractile responses to angiotensin II, is the most rich in aromatic acids compounds and the only one that contains scopoletin.

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1. Introduction

In our current pharmacological exploration of Panamanian medicinal plants we have examined two of the frequently used Amerindian medicinal plants, *Psychotria poeppigiana* (Synonym *Cephaelis elata:* Rubiaceae) and *Cecropia obtusifolia* (Cecropiaceae) for their pharmacological actions, in an attempt to establish a scientific basis for their ethnomedical uses.

P. poeppigiana is a plant with attractive foliage and flowers. It is a native plant widely used in Latin America for the treatment of a variety of diseases, particularly for gastrointestinal disorders, stomachaches and fever (Gupta et al., 2005). In Panama, this plant is practically localized in all national territory and used in traditional medicine by Ngäbe Buglé Amerindians for the treatment of dyspnea (Joly et al., 1987).

C. obtusifolia is a medicinal plant known in Panama and Costa Rica as "guarumo blanco". As with many other species of this genus growing in South America, it shares the reputed folk use to treat heart failure, cough, asthma and bronchitis (Andrade-Cetto and Wiedenfeld, 2001). The intravenous injection of *C. obtusifolia* crude extracts induced hypotension in both anesthetized (Vidrio et al.,

* Corresponding author. Tel.: +507 5234957; fax: +507 5234949.
E-mail address: guerrerodleon@gmail.com (E.I. Guerrero).

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1982) and conscious rats (Salas et al., 1987a,b), which is due in part to its diuretic effect (Vargas Howell and Montero, 1996). Extracts of *C. obtusifolia* have proven hypoglycemic (Román-Ramos et al., 1991), analgesic and central depressant effects (Pérez-Guerrero et al., 2001). A phytochemical study of the leaves of this plant reported the presence of alkaloids, cardiotonic glycosides, flavonoids, tannins, triterpenoid and saponin glycosides (Morton, 1981).

Both medicinal plants, *P. poeppigiana* and *C. obtusifolia*, were selected for this study because of their inhibition of angiotensin and endothelin receptors, an effect found during a broad biological screening of medicinal Panamanian plants by Caballero-George et al. (2001).

2. Experimental

2.1. Plant

Aerial parts from *C. obtusifolia* and *P. poeppigiana* were collected in Parque Nacional Soberanía (Panamá, Panamá) in February 2005 by Alex Espinosa. They were authenticated by Prof. Mireya D. Correa A., Director of the Herbarium of the University of Panama. Voucher specimens (FLORPAN no. 6608 and 6609, respectively) are deposited in the Herbarium of University of Panama (PMA).

2.2. Fractionation of plant extracts

Dried powdered aerial parts (2.8 kg) of *P. poeppigiana* were extracted with dichloromethane (5 L) at room temperature for 3 days. Evaporation of the solvent *in vacuo* yielded a crude extract (15.2 g), which was further solubilized with hot *n*-hexane (0.5 L twice) and cooled overnight at −20 °C yielding a soluble fraction (12.5 g), which was defatted successively with MeOH (0.5 L twice) and a saturated solution of urea in MeOH (0.5 L twice). The final soluble fraction (10.3 g) was partitioned with basic aqueous solution (NaOH 4%, 3 times), yielding an acidic fraction "P-ADCM" (0.15 g) and a neutral fraction "P-NDCM" (5.4 g). Another batch (2.8 kg) of the dried powdered aerial parts was extracted with MeOH (5 L) at room temperature for 3 days in order to give a methanolic extract (99.4 g) which was treated as described above and yielded 3.99 g of a defatted extract. This was partitioned (3 times) with basic aqueous solution (NaOH 4%), yielding an acidic fraction "P-AMeOH" (1.8 g) and a neutral fraction "P-NMeOH" (2.2 g). After partitioning, all the organic fractions were washed with water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to provide the final extracts for this study. Identical procedure was performed with crude dichloromethane (15.9 g) and crude methanol extracts (33.7 g) from 1.0 kg of dried powdered aerial parts of *C. obtusifolia*. Following the procedure described above, 8.6 g of defatted dichloromethane and 6.0 g of defatted methanol fractions were obtained. The partitioning with basic aqueous solution of the dichloromethane fraction gave 0.17 g of the acid fraction (C-ADCM) and 8.4 g of the neutral fraction (C-NDCM), whereas the methanolic defatted fraction allowed us to obtain 2.6 g of the acid fraction (C-AMeOH) and 3.4 of the neutral fraction (C-NMeOH) by the same procedure.

2.3. General experimental procedures

The main components of the fractions studied were identified by gas chromatography–mass spectrometry (GC–MS) using a GC 5890A Series II gas chromatograph (Hewlett Packard), equipped with capillary column HP-5MS cross-linked 5% Ph Me Silicone (30 m × 0.25 mm × 0.25 m) and coupled with a Hewlett Packard GC 5970 mass spectrometer.

The GC column temperature conditions were as follows: initial temperature of 90 °C, held for 5 min and increased at a rate of 5 °C/min to 300 °C, maintained for 10 min and finally increased to 315 °C at 3 °C/min. Helium gas flow rate was set at 1 mL/min. The interface was kept at 290 °C. Mass spectra were recorded under electron impact ionization at 70 eV electron energy, in the range from *m/z* 40 to 800. The mass spectra obtained were compared with those contained in the Wiley 275 L. Database.

2.4. Animals

Male Sprague–Dawley and Spontaneously Hypertensive Rats (SHR) (250–300 g) were obtained from our own animal facility of the University of Panama. The animals were maintained under standard laboratory conditions, with a constant 12 h light/dark cycle and controlled temperature (22 ± 2 °C). Standard pellet food and water were available *ad libitum*.

2.5. Reagents and drugs

Phenylephrine hydrochloride, acetylcholine chloride, angiotensin II and dimethylsulfoxide (DMSO) were purchased from SIGMA® (Sigma Chemical Co., St. Louis, MO, USA). Losartan was supplied by Dr. Ceferino Sánchez (MEDIPAN, S.A., Panamá). All other reagents were of the highest grade. All fractions assayed were dissolved in DMSO before performing the experiments. All other drugs and Krebs' solution were freshly prepared in bidistilled water.

2.6. Preparation of aortic rings

This study complies with the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH Publication No. 85-23, revised 1996). The descending thoracic aorta was isolated from male Sprague–Dawley rats (250–300 g) or SHR (300–350 g). The aorta was cut into ring segments of 3–4 mm in width, and the vascular rings were mounted in 15 mL organ baths containing Krebs bicarbonate buffer of the following composition (in mM): NaCl 115.5; KCl 4.6; NaH_2PO_4 1.3; $NaHCO_3$ 22; $CaCl_2$ 2.5; $MgSO_4$ 1.2; glucose 11.1. The Krebs buffer was kept at pH 7.4 by continuous bubbling with a gas mixture of oxygen/carbon dioxide (95/5%) at 37 °C. The isometric contraction was recorded with force-displacement transducers (model TRI201, LETICA) and displayed on a chart recorder (PowerLab/400 AD Instruments).

2.7. Measurement of vasorelaxation in isolated rat aorta

After the equilibration period, the presence of endothelium was confirmed by induced relaxation with acetylcholine (ACh, 1×10^{-4} M) in tissues precontracted with phenylephrine (PE, 1×10^{-6} M). A relaxation higher than 60% indicated a satisfactory endothelium activity and only these tissues were used in the experiments. After an equilibration period of 60 min the aortic preparations were precontracted by a single concentration of PE (1×10^{-6} M). Three increasing concentrations (10, 30 and 100 μg/mL) of each fraction of *P. poeppigiana* and *C. obtusifolia*, were added cumulatively to the organ bath. A set of previous experiments indicated that the contractile response produced by PE attained a maximum within 15 min and was relatively well sustained over the subsequent 60 min. One aortic ring per rat was reserved to obtain control responses in the presence of this solvent (DMSO).

2.8. Evaluation of fractions on angiotensin II-contraction on aorta isolated from SHRs

In experiments with SHR aorta the rings were allowed to equilibrate for 60 min under a resting tension of 2 g. Cumulative

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