Journal of Ethnopharmacology 202 (2017) 85–91

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

Mechanisms underlying the diuretic effect of *Gomphrena celosioides* Mart. (Amaranthaceae)

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ARTICLE INFO

Keywords:
Gomphrena celosioides
Diuretic plant
Natriuresis
Aldosterone
Hypertension

ABSTRACT

Ethnopharmacological relevance: *Gomphrena celosioides* (Amaranthaceae) is a native medicinal plant found in Mato Grosso do Sul State that is used for treating urinary tract and kidney stones. This study aimed to evaluate the diuretic effects of ethanolic extract from *G. celosioides* (EEGC) on acute and extended diuresis to provide a pharmacological basis for its use in traditional medicine.

Aim of the study: To evaluate the diuretic and natriuretic activity of EEGC and its mechanism of action in an animal model.

Materials and methods: EEGC (30, 100 and 300 mg/kg) was orally administered in male *Wistar* rats, and urinary excretion was measured at intervals of up to 8 h after administration. To evaluate participation of the nitric oxide (NO), prostaglandin and bradykinin pathways in its effect, respective inhibitors were also administered together with effectives doses of EEGC and compared with control groups. A 7-day model with daily administration and urine measurement was also carried out.

Results: Oral administration of doses of 100 and 300 significantly increased urine output after 8 h compared to the control group. It was observed this effect is dependent on the NO, prostaglandin and bradykinin pathways because their inhibitors reduced the diuretic effects of EEGC. Moreover, after 7 days of treatment, the effect was sustained and a decrease in serum aldosterone was observed in the extract group.

Conclusion: According to the results, *G. celosioides* extract showed diuretic and natriuretic effects associated with more than one mechanism of action. Considering that all diuretic drugs are currently available for the treatment of volume and electrolyte disturbances, especially hypertensive status, the present results may have clinical relevance and open new possibilities for the development of new natural diuretics from *G. celosioides*.

1. Introduction

Hypertension is a predisposing factor for stroke, coronary heart disease, peripheral arterial disorders, heart failure and renal failure (Williams et al., 2004; Godfraind, 2006). Common clinical strategies to lower blood pressure include the use of agents that function by reducing arterial resistance and/or decreasing cardiac output. Diuretics are among the drugs most used to promote increased urinary sodium and urine volume output, which leads to a reduction in the volume of circulating blood, thus reducing blood pressure (Williams et al., 2004; Gallagher et al., 2006).

Gomphrena celosioides Mart. belongs to the Amaranthaceae family and is a weed up to 20 cm tall and popularly known as “perpétua”, “bachelor's button” or “prostrate globe-amaranth” (Myers et al., 2000). It is a native medicinal plant that is found and used in Mato Grosso do Sul State (Cunha and Bortolotto, 2011), where it was collected for the present study. It is also well distributed throughout South America, Asia, and East and West Africa (Takim et al., 2013). It is used in the treatment of various skin diseases and as an abortifacient in South America (Burkill, 1984). In Brazil, it has been employed to treat infectious and renal diseases as well as respiratory and gastrointestinal disorders. Gastroprotective effects were even scientifically shown (Oluwabunmi and Abiola, 2015). A decoction of the whole plant and of its related species *G. globosa* Linn. is applied to gangrenous wounds (Arenas and Azorearo, 1977). *Gomphrena* species are also employed in the treatment of bronchial disorders, diarrhoea, and fever and as an analgesic, tonic, diuretic and carminative (Vieira et al., 1994). The diuretic activity of *G. celosioides* was mentioned by Dhawan et al.

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http://dx.doi.org/10.1016/j.jep.2017.03.007
Received 4 October 2016; Received in revised form 22 February 2017; Accepted 7 March 2017
Available online 14 March 2017
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(1977) and Chauhan et al. (2009). Whole *G. celosioides* juice with *Piper nigrum* and lemon juice is taken twice a day for 10 days to prevent kidney stones and expel them (Chauhan et al., 2009). *G. celosioides* activity in urolithiasis was also demonstrated in a scientific study on rats (Goswami and Srivastava, 2015), and its effectiveness was attributed to increased diuresis and lowering of urinary concentrations of stone constituents.

An initial phytochemical study with *G. celosioides* revealed the presence of saponins, steroids, amino acids, reducing and non-reducing sugars, phenols, flavonoids, betacyanins and ketoses (Botha and Gerritsma-van der Vijver, 1986). Fractionation of the extract of the aerial parts conducted by Moura et al. (2004) led to the isolation of 4-hydroxy-benzoic acid and 4-hydroxy-3-methoxybenzoic acid (or vanillic acid), stigmasterol, sitosterol, campesterol, methyl palmitate and stigmast-6-en-3-Ob-(D-glycopyranoside).

This study aimed to experimentally evaluate the diuretic and natriuretic potential of acute and extended treatment with the ethanolic extract of *G. celosioides* (EEGC) in rats, as well as to elucidate possible mechanisms of action.

2. Material and methods

2.1. Plant material, extraction and ESI-MS/MS analysis

Aerial parts of *G. celosioides* were collected at Paranaíba, Mato Grosso do Sul, Brazil [*lat:* −19.666667 *long:* −51.183333 WGS84], in April of 1994 and 2014 and identified by Prof. Dr. Josafá Carlos de Siqueira, an expert in the family Amaranthaceae from Pontifical Catholic University of Rio de Janeiro (PUC-RJ), Brazil. A voucher specimen (SPFR-2962) was deposited in the herbarium of the Faculty of Philosophy, Sciences and Letters of Ribeirão Preto, University of São Paulo (FFCLRP/USP).

Air-dried powdered aerial parts (16.0 kg) were exhaustively extracted (maceration at room temperature) with ethanol in the proportion of plant powder mass /solvent 1:2 (w/v). The spent biomass was filtered and the solvent was removed in a rotary evaporator under reduced pressure and temperature below 40 °C, yielding 901 g of ethanolic crude extract (EEGC).

EEGC (1 mg/ml) was diluted in a solution containing 50% (v/v) chromatographic grade methanol, 50% (v/v) deionized water and 0.5% ammonium hydroxide (Merck, Darmstadt, Germany). Fingerprinting ESI-MS analyses were performed according to Salvador et al. (2011) using an UPLC-MS instrument, model ACQUITY TQD (Waters Corporation, Milford, MA, USA), and the general conditions were: source temperature of 100 °C, capillary voltage of 3.0 kV and cone voltage of 30 V. ESI-MS was performed by direct infusion using a syringe pump with a flow rate of 10 μL. min/ml. Structural analysis of single ions in the mass spectra from the extract was performed by ESI-MS/MS. Ions with *m/z* of interest were selected and submitted to 15–45 eV collisions with argon in the collision quadrupole. The collision gas pressure was optimized to produce extensive fragmentation of the ion under investigation. The compounds were identified by comparison of their ESI-MS/MS fragmentation spectra with fragmentation spectra of authentic standard samples and with literature data (Dosumu et al., 2014; Salvador et al., 2011; Moura et al., 2004).

In addition, the Sodium and Potassium content of the extract was determined by flame spectrometer and were verified 0.47 mmol/g of Sodium and 1.32 mmol/g of Potassium, concentrations that not interfere in the diuretic effect of this extract.

2.2. Animals

Male *Wistar* rats (200–250 g) were used from the animal facilities of Universidade Federal da Grande Dourados (UFGD) an were acclimated under a temperature of 23 ± 2 °C, humidity of 60–80%, and 12-h light/dark cycle; and they received food and water *ad libitum*. The animals were handled according to internationally accepted standard guidelines for animal use, and all experiments obeyed experimental protocols previously approved by the Ethics Commission on the Use of Animals from UFGD (CEUA-UFGD) under process number 01/2015.

2.3. Single-dose model of diuretic assessment

Diuretic activity was determined according to the method of Kau et al. (1984) with some modifications. Rats, after fasting overnight with water *ad libitum*, were randomly divided into five groups (n =5). Before treatment, all animals received an oral load of isotonic saline (0.9% NaCl, 50 ml/kg) to establish a uniform water and salt balance. Then, EEGC was administered by the oral route (p.o.) to animals at doses of 30, 100 and 300 mg/kg (EEGC30, EEGC100 and EEGC300). A negative control group received the same amount of vehicle, and a positive control group received 25 mg/kg of hydrochlorothiazide (HCTZ). Immediately afterwards, the animals were placed in metabolic cages. Urine was collected and measured after 1, 2, 4, 6 and 8 h. Cumulative urinary excretion was calculated relative to body weight and was expressed as ml/100 g.

2.4. Assessment of the involvement of the prostaglandin, bradykinin and NO pathways in the single-dose model

The dose of EEGC that was considered to be the best dose according to the previous assay was selected to evaluate the role of the prostaglandin, bradykinin and NO pathways on EEGC. A model similar to that above was constructed with twelve groups of animals divided into three treatment groups (vehicle, EEGC and HCTZ) for each of four pretreatments administered before the water and salt load: 1- indomethacin (prostaglandin synthesis inhibitor) 5 mg/kg, p.o.; 2- L-NAME (NO synthesis inhibitor) 60 mg/kg, p.o.; 3- HOE-140 (bradykinin antagonist) 1.5 mg/kg, i.p.; or 4- no pretreatment. Urine was collected at the same intervals as described above, and cumulative excretion was calculated.

2.5. Extended model with daily administration

The dose that was considered to be the best according to the previous assay was selected for an extended seven-day model with daily dosage. For this purpose, the experimental group vehicle, EEGC and HCTZ were placed individually in metabolic cages and received treatment orally once a day for seven days. The 24-h urine of each animal was collected, its volume was measured daily during the experiment and it was stored for biochemical analysis.

2.6. Urine and serum analysis

Urine samples were collected from each animal using metabolic cages. Blood samples were obtained at the end of the experiments by caudal puncture and immediately transferred to paediatric tubes with separating gel. Serum was obtained by centrifugation for 10 min at 4000 rpm. Urine pH was measured with a standard pH metre, and urinary density was estimated by weighing samples using a digital analytical balance. Urine and/or serum Na^+, K^+, Cl^-, calcium, urea, creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) and total proteins were quantified by a Roche® cobas Integra 400 plus automated biochemistry analyser.

2.6.1. Angiotensin converting enzyme (ACE) assay and determination of aldosterone and vasopressin

Samples were collected from rats after 7 days of treatment with EEGC (100 mg/kg) or vehicle (control). Blood was collected into glass tubes after decapitation and serum was obtained by centrifugation

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