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Short communication

Pre-clinical toxicology of garcinielliptone FC, a tautomeric pair of polyprenylated benzophenone, isolated from *Platonia insignis* Mart seeds

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ABSTRACT

Background: Garcinielliptone FC (GFC) is a tautomeric pair of polyprenylated benzophenone, which has proven to have antiepileptic, cytotoxic and antioxidant activity.
Purpose: The aim of this study was to investigate the biochemical, hematological and pathological effects of the acute toxicity study as well as to assess the locomotor activity and motor coordination in mice treated with GFC.
Methods: Swiss mice of both sexes weighing 25–30 g divided into three separate groups of five animals matched by weight and size. GFC was aseptically suspended in 0.05% Tween 80, dissolved in 0.9% saline (vehicle) and administered orally (p.o.) and intraperitoneally (i.p.) (500, 1000 and 2000 mg/kg). The acute toxicity study was performed in compliance with the Anvisa regulations.
Results: Behavioral manifestations of toxicity, such as state of consciousness, coordination, muscle tone, reflexes, the activity on the central nervous system (shake, seizures, Straub tail reaction and anesthesia) and the activity of the autonomic nervous system (lacrimation, ptosis, urination, piloerection, hypothermia, breathing and hyperemia) were not seen in any of the animals treated with doses of 500, 1000 and 2000 mg/kg. Additionally, no significant difference in body weight, food and water intake, excreta production or macroscopic changes in the organs of treated animals were detected in comparison with control group. GFC did not affect the locomotor activity and motor coordination of the animals.
Conclusion: The acute toxicity study indicated that GFC treatment, at selected doses given orally and intraperitoneally, showed relatively low risk of toxicity in all test animals, suggesting that it is safe for further investigation.

Introduction

In the hexane extract of seeds of *Platonia insignis* Mart (known as “bacuri”) has been isolated a tautomeric form polycyclic polyprenylated acylphloroglucinol called garcinielliptone FC (GFC, Fig. 1/1a). This compound is little known in the genus *Platonia* belonging to the family *Clusiaceae*, in which was observed occurrence of polyprenylated benzophenones. This class of compounds has demonstrated antidepressant activity, antifungal, cytotoxic, antiretroviral, antibacterial, antioxidant and vasorelaxant effect on mesenteric artery of rats (Costa Junior et al. 2011a; Costa Junior et al. 2011b; Costa Junior et al. 2011c and Costa Junior et al. 2013).

In spite of promising pharmacological activities, there are no studies analyzing toxicological profile of GFC in animals. In this context, this study aimed to evaluate the toxicity after administration of garcinielliptone FC at doses of 500, 1000 and 2000 mg/kg in male and female *Swiss* mice treated orally and intraperitoneally.

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; CNS, central nervous system; GFC, garcinielliptone FC; LD50, median lethal dose; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

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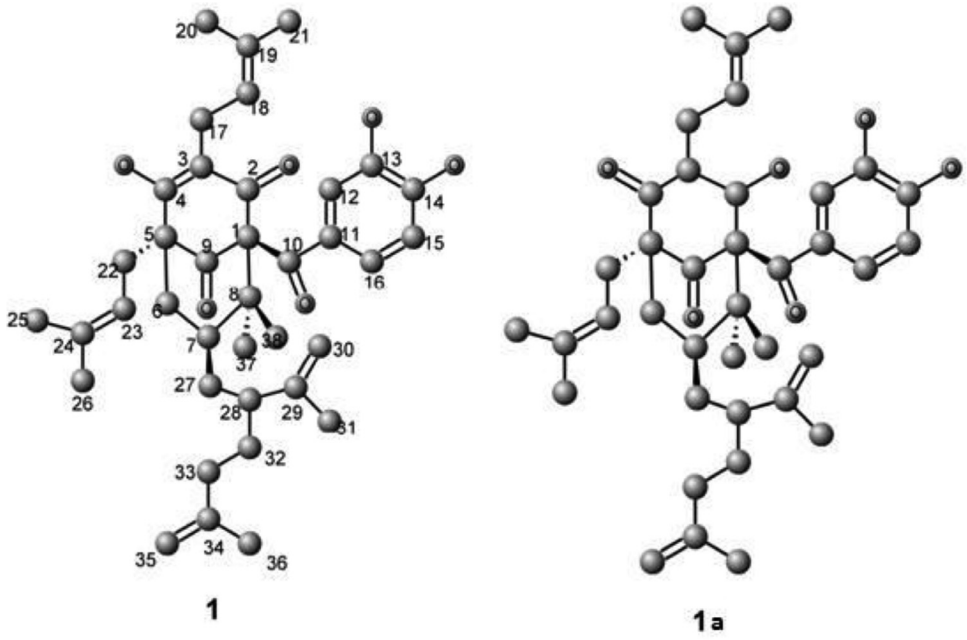

Fig. 1. Chemical structure of garcinielliptone FC (GFC). The figure shows the two isomeric forms (**1/1a**) of the substance.

Materials and methods

Plant material

The seeds were obtained from fruits of specimens located in the city of Bars, Piaui, Brazil, harvested in March 2012. After collecting one voucher specimen was stored in the Herbarium Graziella Barroso of the Federal University of Piaui (UFPI) under nº ICN TEPB 27164.

Extract preparation from P. insignis *seeds*

The seeds of *P. insignis* were dried at 55 °C and ground in order to obtain the powder. In the extraction apparatus, powder (848.2 g) was extracted with hexane (63%, v/v). The hexane extract was then subjected to saponification methylation reaction and a small (saponifiable and unsaponifiable) product of the crude extract reaction was analyzed by chromatographic methods (Costa Junior et al. 2011a).

Identification and structural determination of garcinielliptone FC (GFC)

Chemical structure was confirmed by comparing ^{1}H– and ^{13}C–nuclear magnetic resonance (NMR) data after previously analyzed and purified by chromatographic methods (column and thin layer) (Supplementary material) (Costa Junior et al. 2011a). Garcinielliptone FC (Fig. 1/1a) is a tautomeric pair of polyprenylated benzophenone with a core (diphenyl methanone) substituted by isoprenyl (s) (3-methyl-2-butenyl) and isopropenyl-2-hex-5-enyl group (s). This polyprenylated benzophenone is a yellow oil and its molecular formula and structure (*m/z* 603.3; $C_{38}H_{50}O_6$) was confirmed by ESI (+)/MS and NMR, EIMS *m/z* (%): 602 $[M]^+$ (1), 465 (6), 341 (8), 231 (10), 177 (3), 137 (20), 109 (11), 69 (100).

NMR spectra description of ^{1}H is ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H (1) 17.84 (OH-2); 6 (α 2.04 (bd, 13.5), β 2.32 (bd, 13.5)); 7 (1.46 (m)); 12 (7.02 (d, 4.5)); 13 (7.52 (OH)); 14 (7.69 (OH)); 15 (6.57 (d, 8.4)); 16 (6.99); 17 (α 2.63 (bd, 13.8), β 2.71 (bd, 13.8)); 18 (5.36 (t)); 20 (1.88 (s)); 21 ((1.73 (s)); 22 α 1.95 (15, 7.2), β 2.16 (14.5, 8.0)); 23 (4.97 (t, 7.2)); 25 (1.67 (s)); 26 (1.53 (s)); 27 (1.88 (2H, m)); 28 (2.64 (bd, 13.8)); 30 (4.30 (2H, s)); 31 (1.53 (s)); 32 (α 1.88 (m) β 1.96 (m)); 33 (1.88 (2H, m)); 35 (4.64 (s), 4.66 (s)); 36 (1.73 (s)); 37 (0.98 (s)); 38 (1.18 (s)). (1a) 17.78 (OH-2); (1H, H-3); 3.06 (1H, H-2); 3.23 (1H, H-6); 2.12 (3H, H-12′); 1.34 (3H, H-7); 1.43 (2H, H-2′); 2.47 (2H, H-10′); 1.29–1.33 (14 H, H-3′–H-9′); NMR spectra description of ^{13}C is ^{13}C NMR ($CDCl_3$, 500 MHz) δ_C–58.8 (CH, C-2); 66.1 (CH, C-3); 31.3 (CH2, C-4); 23.8 (CH2, C-5); 57.7 (CH, C-6); 16.1 (CH3, C-7); 34.8 (CH2, C-1′); 26.4 (CH2, C-2′); 30.5-30.9 (CH2, C-3′–8′); 25.0 (CH2, C-9′); 44.4 (CH2, C-10′); 212.4 (C, C-11′); 29.9 (CH3, C-12′).

Reagents and experimental protocols

GFC was prepared and emulsified in 0.05% Tween 80 (Sigma Chem. Co., St. Louis, MO, USA), diluted in 0.9% saline (vehicle) and given orally and intraperitoneally at selected doses (500, 1000, 2000 mg/kg) for acute toxicity study. For the assessment of locomotor activity and motor coordination, the animals were treated at GFC doses of 25, 50 and 75 mg/kg. Control groups were given vehicle at the same volume (10 ml/kg).

Animals and behavioral tests

Swiss mice were 2 months old of both sexes weighing 25–30 g (Central Animal Laboratory of the Federal University of Piaui). All animals were maintained under controlled temperature (26 ± 1 °C) and a 12-h light/dark cycle. Animals had free access to water and food. All behavioral tests were performed in quiet rooms under the same conditions mentioned above and isolated from external noise. All experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals, Department of Health and Human Services, Washington DC, 1985. The project was approved by the Ethics Committee for Experimental Animals from the Federal University Piaui (ECEA/UFPI # 078/2012).

Acute toxicity study

The acute toxicity study was performed in accordance with Anvisa regulations (Brazil 2013). GFC or vehicle was administered