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SHORT COMMUNICATION

Croton grewioides Baill. (*Euphorbiaceae*) Shows Antidiarrheal Activity in Mice

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ABSTRACT

Based on chemotaxonomy, we decided to investigate the possible antidiarrheal activity in mice of a crude ethanolic extract obtained from aerial parts of *Croton grewioides* (CG-EtOH). We tested for any possible toxicity in rat erythrocytes and acute toxicity in mice. Antidiarrheal activity was assessed by determining the effect of CG-EtOH on defecation frequency, liquid stool, intestinal motility and intestinal fluid accumulation. CG-EtOH showed no *in vitro* cytotoxicity and was not orally lethal. In contrast, the extract given intraperitoneally (at 2000 mg/kg) was lethal, but only in females. CG-EtOH produced a significant and equipotent antidiarrheal activity, both in defecation frequency (ED_{50} = 106.0 ± 8.1 mg/kg) and liquid stools (ED_{50} = 105.0 ± 9.2 mg/kg). However, CG-EtOH (125 mg/kg) decreased intestinal motility by only 22.7% ±4.4%. Moreover, extract markedly inhibited the castor oil-induced intestinal contents (ED_{50} = 34.6 ± 5.4 mg/kg). We thus conclude that CG-EtOH is not orally lethal and contains active principles with antidiarrheal activity, and this effect seems to involve mostly changes in intestinal secretion.

Key words: *Croton grewioides*, Diarrheal, Intestinal fluid, Motility, Toxicity

SUMMARY

- CG-EtOH showed no *in vitro* cytotoxicity and was not orally lethal. In contrast, the extract given intraperitoneally (at 2000 mg/kg) was lethal, but only in females.
- CG-EtOH probably contains active metabolites with antidiarrheal activity.
- CG-EtOH reduced the frequency and number of liquid stools.
- Metabolites presents in the CG-EtOH act mainly by reducing intestinal fluid and, to a lesser extent, reducing intestinal motility.

Abbreviations Used: CG-EtOH: crude ethanolic extract obtained from the aerial parts of C. *grewioides*; WHO: World Health Organization; ED_{50}: dose of a drug that produces 50% of its maximum effect; E_{max}: maximum effect

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INTRODUCTION

The world's population uses different ways to treat, cure and prevent diseases, and among these tools, medicinal plants play an important part, because it has a broad and diverse application, which has been reported since the beginning of humanity.[1] Brazil has one of the richest floras on the planet, and due to different environments, it is estimated that of the 1.4 million of described organisms on the planet, around 10% occur in Brazil.[2]

Euphorbiaceae is one of the largest families of Phanerogams comprising about 300 genera and 7600 species.[3] In this family, the genus *Croton* is the second largest, with about 1200 species, distributed in tropical and subtropical regions.[4] This genus is of significant economic relevance since several species are used as a source of raw materials for the chemical and pharmaceutical industries. In addition, previous studies showed its species contain various active substances such as terpenoids, flavonoids, and alkaloids with various biological activities as, e.g., anti-inflammatory, cytotoxic, antirheumatic, antiulcer, analgesic, and antispasmodic activity.[5-10]

Croton grewioides (CG) Baill. (*Euphorbiaceae*) is known as "Canelinha" or "Canelinha-de-cheiro" in allusion to the fragrance given off by its flowers. In some regions of Northeast Brazil, the nectar of its flowers is much appreciated for its taste and aroma.[11]

The need for the discovery and research of plant compounds that act on symptoms of diarrhea and not just in regard to dehydration[12] has prompted pharmacological studies of the plant CG using a chemotaxonomic approach, since other *Croton* species have antidiarrheal properties, such as *Croton cajucara*,[13] *Croton Tiglium*,[14] and *Croton urucurana*.[15]

According to the World Health Organization, acute diarrhea is characterized by an increase in the number of stools (3 or more in a 24 h period) may be aqueous or low consistency or even an increase in stool frequency compared to what is normal for each individual.[16] It is the second leading cause of death in children under 5 years of age, with approximately 760,000 deaths/year, in addition to being a major cause of malnutrition in the same group on a global scale and reach about 1.7 billion people by year, therefore, may be a world problem.[16,17] The liquid content is the main determinant of the volume and consistency of stools, but other factors also contribute to the formation of the stool, such as the propulsion rate. In Northeast Brazil, persistent diarrhea associated with acute malnutrition remains the major cause of morbidity and mortality.[18]

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Therefore, we decided to investigate the antidiarrheal activity of a crude ethanolic extract obtained from the aerial parts of GC-EtOH in mice.

MATERIALS AND METHODS

Plant material

Aerial parts of CG were collected in the municipality of Serra Branca, State of Paraíba, in March 2007. The botanical material was identified by Professor Maria de Fatima Agra, and a voucher specimen of the plant is deposited in the Herbarium Prof. Lauro Pires Xavier (JPB), Federal University of Paraíba identified as Agra *et al.* 6987. Plant material was dried for 3–4 days at 45°C, and then pulverized in a mill. The powder of the aerial parts (2500 g) was sprayed dried and subjected to thorough maceration with 95% ethanol, in a stainless steel container for 72 h. This step was repeated 4 times. The extraction solution was concentrated by rotary evaporation under reduced pressure at a temperature of 45°C to give the crude ethanolic extract (116.28 g), yield 4.65% on dry weight of the plant.[19] The phytochemical studies of the CG aerial parts were performed by standard chromatographic methods and identified by spectroscopic methods such as infrared, mass, ^{1}H NMR, ^{13}C NMR and two-dimensional beyond compare with literature data. This phytochemical study resulted in the isolation of 13 compounds, three-first described in the literature, two isolated for the 1st time in the genus and eight-first reported in the species.[20]

Substances

Atropine (Sigma-Aldrich, USA) was used as a positive control in the experiments of transit and fluid intestinal; Cremophor® (Sigma-Aldrich, USA) as vehicle and Triton X-100 (Sigma-Aldrich, USA) as the hemolytic agent. Carboxymethyl cellulose or cellulose gum, is used as a viscosity modifier or thickener, and castor oil as stimulant laxative, both obtained from formula, Brazil. Loperamide was used as antidiarrheal standard drug (J. C. F. Ltda, Brazil), and the activated charcoal as a marker of intestinal transit obtained from Proquímios, Brazil.

Animals

Female and male Swiss mice (*Mus musculus*) and Wistar rat (*Rattus norvegicus*) from Central Animal Laboratory, Federal University of Paraíba (UFAL), weighing between 25 and 35 g, were used. All experimental procedures with CG were approved by the Ethical Committee in Research of UFAL (No. 010489/2009 15).

Toxicological evaluation: Effect of *Croton grewioides*-EtOH on rat erythrocytes

Rats (200–300 g) were fasted for a period of 12 h. Afterward, a blood sample was collected, mixed with a solution of NaCl (0.9%) and $CaCl_2$ (10 mM) and centrifuged at 5000 rpm/3 min. The extract was added to the erythrocyte suspension at various concentrations. The negative control consisted of the erythrocyte suspension in NaCl and $CaCl_2$ solution and positive control as erythrocyte suspension plus 100 mL of Triton X-100 1%. Hemolysis was quantified by spectrophotometry at 540 nm.[21]

Pharmacological behavioral screening and investigation of acute toxicity of *Croton grewioides*-EtOH

CG-EtOH was administered orally (p.o.) or intraperitoneally (i.p.) to groups of five males and females (one dose/group), which were fasted for 12 h. Simultaneously, control animals received 10 mL/kg saline plus Cremophor®. General signs and symptoms of toxicity, such as analgesia, contortions, and aggression, were recorded for (4 h). Death of animals was determined during 72 h.

Evaluation of antidiarrheal activity of the *Croton grewioides*-EtOH

Castor oil-induced diarrhea in mice

Male mice were gavaged with 10 mL/kg saline plus Cremophor® (negative control), 10 mg/kg loperamide (positive control) or CG-EtOH. After 1 h, 0.01 mL of castor oil per gram body weight was administered orally to each animal to induce diarrhea, and the counts and consistency of dung pats were determined for 4 h, classifying them according to consistency as solids or liquids.[22]

Intestinal transit in mice

Male mice were gavaged with 10 mL/kg saline plus Cremophor® (negative control), 2 mg/kg atropine (positive control) or CG-EtOH. After 30 min, 0.01 mL of activated charcoal (5%) in carboxymethyl cellulose (0.5%) was administered orally per gram body weight to each animal, which was euthanized by cervical dislocation after 30 min. The abdominal cavity was opened and the small intestine removed. The distance traveled by the marker was assessed for each animal. The results were expressed as a percentage of the distance traveled by the marker in relation to the total length.[23]

Intestinal fluid accumulation induced by castor oil in mice

Male mice (fasting for 24 h) were divided into groups: 10 mL/kg saline plus Cremophor®; 10 mg/kg loperamide and CG-EtOH. After 30 min, 2 mL of castor oil was administered to each animal. After another 30 min, the mice were euthanized, the small intestine was dissected from the pylorus throughout the cecum, and the contents were collected in a beaker to assess the volume of fluid.[24]

Statistical analysis

For all the above experiments, results were expressed as mean ± standard error of the mean statistical significance tests were performed using the Student's *t*-test or one-way ANOVA followed by Bonferroni's posttest, to multiple comparisons, and *P* values were calculated by comparison with control groups. ED_{50} (dose of a drug that produces 50% of its maximum effect) values were determined by nonlinear regression. All data were analyzed using GraphPad Prism (Software, Inc., San Diego, USA).

RESULTS AND DISCUSSION

Given the occurrence of *Croton* species with toxic effects, for example, *Croton leiophyllus*,[25] *Croton argyratus*,[25] and *C. tiglium*.[26] We investigated the toxicological potential using behavioral and pharmacological models *in vivo* of the CG-EtOH extract.

In the investigation of the cytotoxic effect of the extract (81, 243, and 500 mg/mL), we observed that it was unable to produce hemolysis in rat erythrocytes indicating that CG-EtOH had no hemolytic activity at the doses evaluated. In behavioral assessment and determination of toxicity, male mice (n = 6) showed no behavioral changes, both at doses of 2500 and 5000 mg/kg orally and doses of 1000 and 2000 mg/kg i.p., in the first 4 h of observation, nor was there any death during the 72 h following injection.

Similarly, in females (n = 6), the extract at doses of 2500 and 5000 mg/kg orally and 1000 mg/kg by i.p. did not cause behavioral changes or death. In contrast, the extract when given i.p. at a dose of 2000 mg/kg showed lethality in all animals evaluated (n = 6). Thus, in female mice was administered the extract at a dose of 1500 mg/kg i.p. Interestingly, they showed no changes or death at this dose.

These data suggest that the extract has low toxicity since only induced the death of the female at a dose of 2000 mg/kg (i.p.), possibly due to the action of hormones, present only in females, that induce changes in the metabolism or absorption of these metabolites, unlike in male mice.[27]

These results indicate that CG-EtOH is not toxic with oral (p.o.) treatment, which is an interesting result since Resolution RE 90/2004 of the Agência Nacional de Vigilância Sanitária says it should be tested via the same route proposed for the use of the product. Conversely, i.p. administration of the extract in females but only at the highest dose used (2000 mg/kg), induced behavioral changes before death, including sedation, lethargy, and drowsiness. It is also possible that the lethal dose (i.p.) may be an intermediate value between 1500 and 2000 mg/kg or simply 2000 mg/kg. Although the extract has shown lethal effect at the dose of 2000 mg/kg, this dose is much higher than the doses used in this study later in anti diarrheal test, moreover, only i.p. the extract showed this effect.

C. urucurana Baill. (600 and 800 mg/kg) has been reported that significant antidiarrheal effect[28] and several *Croton* species are used in folk medicine as anti-diarrheal, e.g. *C. cajucara*,[13] *C. tiglium*,[14] and *C. urucurana*.[15] Therefore, we decided to investigate antidiarrheal activity by castor oil-induced diarrhea model in mice, and we observed that CG-EtOH (62.5, 125, 250, and 500 mg/kg) significantly reduced the frequency of defecation in a dose-dependent manner when compared to the negative control (saline + Cremofor®), with inhibition values of 34.7 ± 5.0, 44.4 ± 5.6, 81.9 ± 7.3, and 75.0% ±3.7%, respectively (ED_{50} = 106.0 ± 8.1 mg/kg) [Figure 1a]. Similarly, in relation to liquid stools, CG-EtOH inhibited diarrhea induced by castor oil in a significant and dose-dependent manner with values of 31.8 ± 5.0, 52.2 ± 4.6, 100.0 and 88.6 ± 4.2, respectively, (ED_{50} = 105.0 ± 9.2 mg/kg) [Figure 1b]. Interestingly, this effect was more potent than observed with *C. urucurana*.[28]

The maximum effect of the extract in reducing both the frequency of defecation (E_{max} = 82.0% ±7.3%) and liquid stool (E_{max} = 100%) was observed at a dose of 250 mg/kg, similar to the standard drug, loperamide (E_{max} = 95.8 ± 1.8 and 100%, respectively). These results suggest that the extract has active metabolites with antidiarrheal activity, and these metabolites probably are in agreement with the species of this genus (flavonoids, terpenoids, and alcaloids),[29,30] since it is used in folk medicine to treat this illness. Furthermore, antidiarrheal activity has been demonstrated with some species this genus, as, e.g. *C. cajucara*,[13] *C. tiglium*,[14] and *C. urucurana*.[15]

As diarrhea often appears with signs of increased motility and/or increased secretion of the gastrointestinal mucosa in response to various stimuli,[31] we decided to evaluate the effect of CG-EtOH on motility and intestinal fluid in mice.

Similar to the atropine group, CG-EtOH only at doses of 125 and 250 mg/kg significantly reduced gastrointestinal transit by 65.1 ± 3.7 and 66.7% ±1.5%, respectively, compared to the control group. At doses of 62.5 and 500 mg/kg, the extract did not reduce gastrointestinal transit significantly [Figure 2a]. Based on these results, we suggest that the antidiarrheal effect of CG-EtOH involves changes in intestinal motility showing a maximum effect around 65%.

Oral administration of CG-EtOH (7.81, 15.62, 31.25, 62.5, 125, and 250 mg/kg) inhibited, in a significant and dose-dependent manner, the accumulation of intestinal fluid induced by castor oil, compared to the negative control. Inhibition values were 9.9 ± 3.3, 14.7 ± 3.9, 31.7 ± 7.2, 45.5 ± 6.2, 64.6 ± 2.4, 67.5% ±3.5%, respectively (ED_{50} = 34.6 ± 5.4 mg/kg) [Figure 2b].

The maximum effect of CG-EtOH to inhibit the content of intestinal fluid (E_{max} = 67.5% ±3.5%) was observed at a dose of 250 mg/kg, similar to the standard drug, loperamide (E_{max} = 70.6% ±1.0%). The results showed that CG-EtOH has an inhibitory effect on the accumulation of intestinal fluid [Figure 2b], suggesting that the antidiarrheal effect involves mainly changes in intestinal secretion. This action is the most desirable since the main manifestation common to different types of diarrhea is dehydration, and in many cases, the inhibition of intestinal transit is not desired, as it may delay or prevent the elimination of potential pathogens.[14]

The results show that the CG-EtOH probably contains active metabolites with antidiarrheal activity since it had a significant antidiarrheal effect in mice with a reduction in the frequency and number of liquid stools, and that these metabolites act mainly by reducing intestinal fluid and to a lesser extent, reducing intestinal motility.

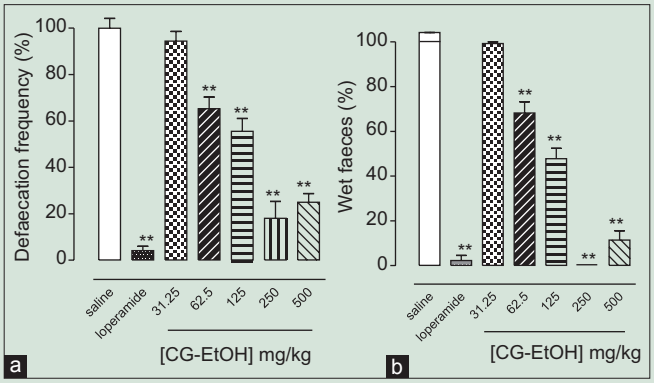

Figure 1: Antidiarrheal effect of the CH-EtOH extract in the castor oil-induced diarrhea model in mice (n = 6). (a) Percentage of defecation frequency and (b) percentage of liquid stool. Columns and vertical bars represent the percentage of the mean and standard error of the mean, respectively. One-way ANOVA followed by Bonferroni test, $^{**}P < 0.001$ (saline vs. loperamide/extract)

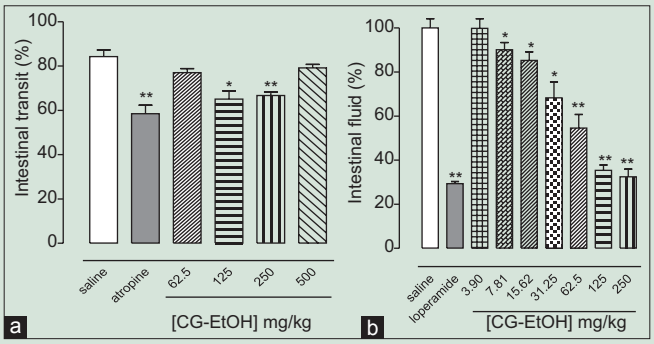

Figure 2: Effect of CH-EtOH extract on the intestinal transit (a) and fluid accumulation induced by castor oil (b) in mice (n = 6). Columns and vertical bars represent the percentage of the mean and standard error of the mean, respectively. One-way ANOVA followed by Bonferroni, $^{*}P < 0.05$ and $^{**}P < 0.001$ (saline vs. loperamide/extract)

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Conflicts of interest

There are no conflicts of interest.

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