Antidiabetic activity of *Croton matourensis* in alloxan-induced diabetic rats

Actividad antidiabética de *Croton matourensis* en ratas diabéticas inducido por alloxano

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Abstract

Diabetes mellitus is a chronic metabolic disorder with high prevalence worldwide. The use of medicinal plants to treat diabetes is a common practice in developing countries. Indeed, previous reports demonstrated that plants belonging to *Croton* genus have hypoglycemic potential. Nevertheless, there are limited studies related to *Croton matourensis* Aubl. Thus, this work was established to determine the hypoglycemic effect of the aqueous leaf extract from *Croton matourensis* (CMAE) in an alloxan-induced diabetic murine model. CMAE was prepared from the fresh leaves of *Croton matourensis* collected in Venezuela. The toxic and lethal effects of CMAE were determined in male Balc mice. Diabetes was induced by a single administration of alloxan in *Sprague-Dawley* rats. Then, the CMAE hypoglycemic effect was evaluated in this diabetic murine model. Our results showed that the lethal dose 50 (LD_{50}) was 3.23 g/Kg and toxic dose 50 (TD_{50}) 96 mg/Kg. Interestingly, CMAE at the dose of 48 mg/Kg (1/2 TD_{50}) produced a significant reduction in blood glucose levels in diabetics animals. Therefore, CMAE was able to reduce glucose levels in rats not treated with alloxan. Thus, the antidiabetic mechanism could be related to antioxidant effects and modulation of pathways associated with glucose metabolism and storage. Collectively, this work supports further pharmacological studies of the *Croton* genus as an alternative in diabetes mellitus treatment.

Key words: *Croton matourensis*, antidiabetic activity, cholesterol, medicinal plants.

Resumen

La diabetes mellitus es un trastorno metabólico crónico con alta prevalencia a nivel mundial. El uso de plantas medicinales para tratar la diabetes es una práctica común en países en desarrollo. De hecho, estudios anteriores demostraron que las plantas del género *Croton* tienen potencial hipoglucémico. Sin embargo, existen estudios limitados relacionados con *Croton matourensis*. Por lo tanto, este trabajo se estableció para determinar el efecto hipoglucémico del extracto acuoso de hoja de *Croton matourensis* (CMAE) en un modelo murino diabético inducido por aloxano. CMAE se preparó a partir de hojas frescas de *Croton matourensis* recolectada en Venezuela. Los efectos tóxicos y letales de CMAE se determinaron en ratones Balc. La diabetes fue inducida por la administración de aloxano en ratas *Sprague-Dawley*. Luego, se evaluó el efecto hipoglucémico de CMAE en este modelo murino diabético. Nuestros resultados muestran que la dosis letal 50 (DL_{50}) fue de 3.23 g/Kg y la dosis tóxica 50 (DT_{50}) de 96 mg/Kg. Interesantemente, CMAE, a la dosis de 48 mg/Kg (1/2 DT_{50}) redujo significativamente los niveles de glucosa en sangre en ambos grupos experimentales, ratas tratadas con aloxano (diabéticas) y ratas no diabéticas (control). El mecanismo antidiabético podría estar relacionado con los efectos antioxidantes y la modulación de las vías asociadas con el metabolismo y el almacenamiento de la glucosa. En conjunto, este trabajo respalda más estudios farmacológicos del género *Croton* como alternativa en el tratamiento de la diabetes mellitus.

Palabras clave: *Croton matourensis*, actividad antidiabética, colesterol, plantas medicinales.

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Introduction

Chronic metabolic disorders such as diabetes mellitus have a high prevalence worldwide and are associated with health problems. Diabetes is related to an imbalance in carbohydrates and lipids homeostasis, leading to cardiovascular failure. Interestingly, up to 80% of mortality by diabetes had been recorded in low- and middle-income countries (WHO, 2017). This disease requires early diagnosis, accurate treatment, and lifestyle changes to improve the patient's quality of life. Several drugs have been used in therapy to decrease blood glucose levels. Indeed, the principal hypoglycemic mechanisms are increasing insulin secretion and changing glucose metabolism (Chaudhury *et al.*, 2017). Despite significant progress in diabetes treatment, some disadvantages arose like drug resistance and side effects (Hsu *et al.*, 2009). These drawbacks had promoted a search for new anti-diabetic drugs. The use of plants to treat chronic diseases like diabetes is common practice in traditional medicine worldwide (Grover *et al.*, 2002; Trojan-Rodrigues *et al.*, 2012; Giovannini *et al.*, 2016). The main phytochemical compounds associated with the anti-diabetic effect are flavonoids, terpenes, and alkaloids. Therefore, the anti-hyperglycemic effects of these compounds are related to increasing insulin secretions or reducing intestinal glucose absorption. Some reports, however, showed that plant extracts could produce toxic effects under chronic use. The World Health Organization (WHO, 2017) has recommended scientific evaluation and validation of this ethnopharmacology knowledge (Allard *et al.*, 2013; Brima 2017; López-Gil *et al.*, 2017).

*Croton matourensis*is Aubl. is described as a medium-sized tree abundant in Brazil, Guyana, and in the south of Venezuela (Berry *et al.*, 2005; Hokche *et al.*, 2008). The species is known as "tabaquillo" and is used in folk medicine as an anti-inflammatory and analgesic (Agra *et al.*, 2008). Also, *C. matourensis* has been used to treat diabetes, diarrhea, rheumatism, and cancer (Salatino *et al.*, 2007). The phytochemical study of *Croton matourensis* showed that this plant is rich in terpenes and flavonoids (Suárez *et al.*, 2009a). The chemical constituent and cytotoxic activity of its essential oil were also reported (Compagnone *et al.*, 2010). Several species of *Croton* genus have been reported with anti-diabetic properties: *C. macrostachyus* Hochst. ex Delile (Okokon *et al.*, 2006), *C. cuneatus* Klotzsch (Torrico *et al.*, 2007), *C. pungens* Jacq. (Torrico *et al.*, 2013), *C. zambesicus* Müll.Arg. (Arika *et al.*, 2015), *C. klotzschianus* (Wight) Thwaites (Bantie and Gebeyehu, 2015), *C. lobatus* L. (Fasola *et al.*, 2016). Thus, based on the broad biological effects and the hypoglycemic properties of *Croton* genus, this research work was established to determine the effect of *Croton matourensis* in a murine model of diabetes-induced by alloxan.

Materials and methods

Plant material

Fresh leaves of C. *matourensis* Aubl. (Euphorbiaceae) were collected in Santa Elena de Uairen, Bolivar state-Venezuela. Then, Dr. Anibal Castillo carried out its botanical identification. A voucher specimen (22600) is available for inspection at the National Herbarium of Venezuela (VEN) at the Botanical Garden of Caracas, Venezuela.

Aqueous extract preparation

C. *matourensis* leaves were air-dried in shade at room temperature and then were pulverized in an electric blender. An aqueous extract was obtained by leaf decoction in distilled water (100 g/500 ml) for 30 min. The resulting solution was filtered and lyophilized. Then, the extract was reconstituted in distilled water before use.

Animals

Animals used in this study were male mice Balc strain with a weight of 18.1 ± 1.8 g; and *Sprague-Dawley* albino rats with a weight of 90-110 g. Animals were maintained in a 12 h light cycle and allowed free access to food and water. All protocols used in this study were approved by the Animal Ethical Committee of the "Facultad de Farmacia, Universidad Central de Venezuela".

Acute toxicity (TD_{50} and LD_{50})

TD_{50} was determined according to Litchfield and Wilcoxon (1949). Mice Balc 4 weeks' old were divided into 7 groups with 4 animals in each. One group was treated with vehicle and remaining groups with increasing doses (0.03 to 1.5 g/kg) of CMAE by gavage administration. Animal behavior was observed and recorded at 10, 30, 60, 90 min, 24 h, and finally, 72 h post-treatment. Toxic effects were established such as respiratory frequency changes, diarrhea, piloerection, and temperature changes. To determine LD_{50} higher doses of CMAE were administered (1.5 to 7 g/Kg). The number of animals that died at 24 h post-administration was recorded. LD_{50} and TD_{50} and the 95% confidence intervals were obtained by the Probit® method (Litchfield and Wilcoxon 1949; Irwin, 1962).

Diabetes model

Diabetes was induced experimentally in rats by single intraperitoneal administration of alloxan (Sigma-Aldrich). The dose was 140 mg/kg by body weight and the drug was delivered in citrate buffer 0.1 M, pH 4.5. The experimental animals were subjected to fasting for 24 hours before the alloxan administration (Verspohl, 2002). Glucose and cholesterol levels were determined 48 hours after alloxan administration. The animals that reach a glycemic increase above 50% were considered as diabetic.

Determination of glucose and cholesterol in serum

Male *Sprague-Dawley* rats were randomly divided into four groups with six rats in each. **Group I** was treated with vehicle; **group II** (diabetic group treated with alloxan); **group III** (½ TD_{50} CMAE), and **group IV** (alloxan plus ½ TD_{50} CMAE). CMAE was administrated by gavage every 3 days for 14 days. The extract was administrated after the animal was considered diabetic (diabetic group). Bodyweight per animal was monitored each 24 h. All experimental groups were subjected to fasting for 24 hours before serum analysis. Following, a blood sample by the tail bleeding method was extracted. Then, serum was separated by centrifugation at 4000 RPM for 10 minutes (IEC/Focuses Mp4R, International Equipment Company). Glucose and cholesterol levels in serum pre- and post-treatment were determined. Blood extraction was done every five days for two weeks. Blood glucose and cholesterol levels were measured by glucose oxidase and cholesterol oxidase (Stanbio®), using a spectrophotometer (Stat-fax, Awareness Technology Inc.).

Statistical analysis

All the reported data are expressed as mean ± S.E.M.; statistical evaluation was performed using computer software Graph Pad Instat version 7.04 followed by two way ANOVA and Tukey's multiple comparisons test. Values were considered significantly different when P-value was less than 0.05.

Results

Acute toxicity (LD_{50} and TD_{50})

The pharmacological evaluation of plant extracts should begin with establishing their toxicity profile. Thus, the acute toxicity of CMAE was determined in mice to establish a safe dosage range. A broad dosage range of CMAE was administrated and acute toxicity was determined after 24 h (**Figure 1A**). The behavior of treated or not animals was observed by a short period (4h) followed by a long period (24 h and 72 h). The main clinical-toxic effects were piloerection, diarrhea, and an increase in respiratory frequency, which were reversible and dose-dependent. Animals did not show changes in water consumption, impairment in food intake, or body temperature. These results suggest that CMAE could be used in a safe range. Only doses upper 3.2 g/Kg can produce lethal effects (**Figure 1B**). Thus, the CMAE safety dose was established below 96 mg/Kg (dose determined as TD_{50}).

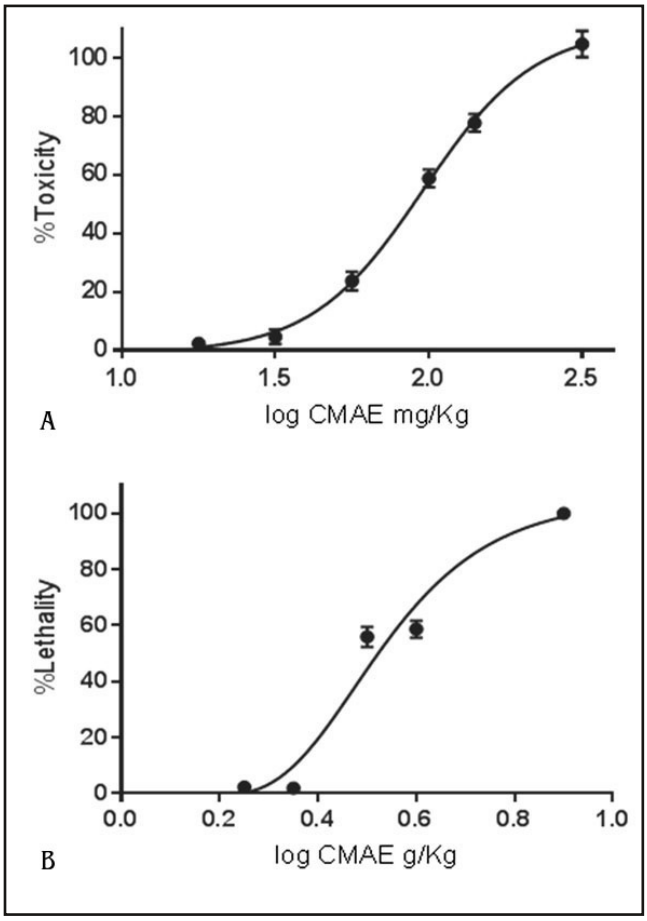

Figure 1. Toxic and lethal effects of CMAE. A) The main toxic effect developed in mice after CMAE administration was the increase in the respiratory rate. The percentage of increase in the respiratory rate was calculated in comparison with the NT control. B) Lethal effect of CMAE. The figure shows the percentage of dead animals after CMAE administration. CMAE was administrated by gavage at different dose mg/Kg (A) and g/Kg in (B). The data are expressed as the mean ± S.E.M from three experiments.

Effect of CMAE on blood glucose and cholesterol levels

Alloxan (2,4,5,6-tetraoxypyrimidine; 5,6-dioxyuracil) was used as a diabetes inductor. After the alloxan administration, animals showed a significant increase in glucose levels in comparison with control on day 9. On the other hand, chronic administration of CMAE produced a decrease in glucose levels in a time-dependent manner. These changes in glucose levels were statistically significant in comparison with the alloxan group (*$p<0.05$ y **$p<0.01$, days 9 and 13 respectively). Indeed, glucose levels reached day 13 were similar to pre-alloxan treatment, reaching values similar to control ($p=0.08$) (**Figure 2**). Moreover, CMAE

also produced a decrease in glucose levels in the group non-treated with alloxan on day 13 (**Figure 3**). Diabetes is related to an increase in cardiovascular risk and one main factor is changes in cholesterol levels. Thus, we evaluated the effect of CMAE administration on cholesterol levels. Treatment with alloxan did not alter cholesterol levels. However, the administration of CMAE and alloxan produced a significant decrease in cholesterol levels in the animals on day 9 (*p<0.05), which was reverted at the end of the study (**Figure 4**).

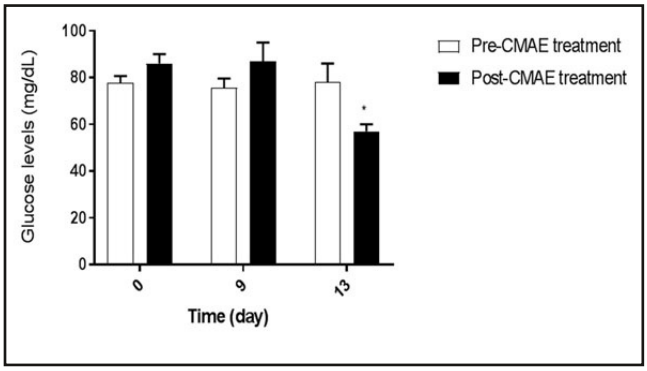

Figure 3. Effect of CMAE in the glucose levels of non-diabetic rats. The glucose levels were determined before and after CMAE administration. CMAE was administrated at a dose of 48 mg/Kg and the glucose levels were monitored at day 9 and 13 post-treatment. The glucose levels are expressed as mg/dL. The data are expressed as the mean ± S.E.M. obtained from three experiments. (*p<0.05 compared with pre-treatment group).

Discussion

Diabetes is a complex chronic disease that requires continual medical attention (American Diabetes Association, 2017; WHO, 2017). The growing prevalence of diabetes has led to a continuous search for novel antidiabetic drugs. The use of medicinal plants represents an important role in the treatment of chronic diseases like diabetes. We are interested in evaluating the hypoglycemic activity of plants from *Croton* genus. Previous studies have shown that *Croton cuneatus* (Torrico *et al.*, 2007) and *Croton* pungens (Torrico *et al.*, 2013) have hypoglycemic activity. Additionally, the *Croton* species demons-

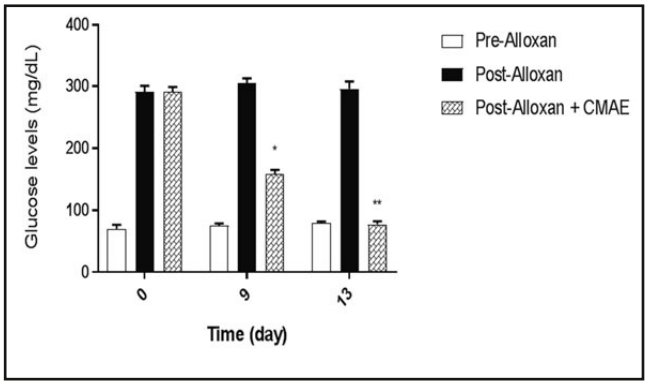

Figure 2. Effect of CMAE administration on glucose levels in diabetic rats. Diabetes was induced by alloxan administration. The glucose levels were determined before and after alloxan administration. CMAE was administrated at a dose of 48 mg/Kg and the glucose levels were monitored at day 9 and 13 post-treatment. The glucose levels are expressed as mg/dL. The data are expressed as the mean ± S.E.M. obtained from three experiments. (*p<0.05; **p<0.01 compared with post-alloxan administration group).

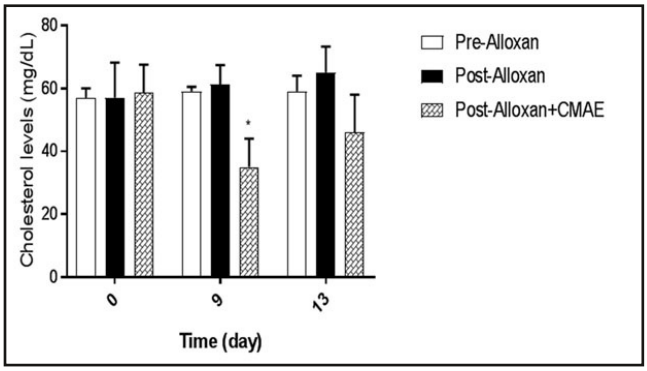

Figure 4. Effect of CMAE administration on cholesterol levels in diabetic rats. The cholesterol levels were determined before and after alloxan administration. CMAE was administrated at a dose of 48 mg/Kg and the cholesterol levels were monitored at day 9 and 13 post-treatment. The cholesterol levels are expressed as mg/dL. The data are expressed as the mean ± S.E.M. obtained from three experiments. (*p<0.05 compared with post-alloxan administration group).

trated antioxidant and anticancer activity (Suárez *et al.*, 2003, 2006, 2009a; Nath *et al.*, 2013). Thus, the goal of this work was to evaluate the toxic and hypoglycemic activities of the aqueous extract of *C. matourensis*. The dose range of CMAE was determined by calculating the TD_{50} and LD_{50}. Based on our prior experience with *Croton* genus, half of TD_{50} was established as the concentration to be evaluated in our diabetes model. This concentration is 70 times lower than the LD_{50}, having a safe therapeutic range. Interestingly, at this concentration, the CMAE produces a significant decrease in glucose levels in diabetic animals. Furthermore, the CMAE was able to reduce glycemic levels in the animal not treated with alloxan. Thus, the plant extract has hypoglycemic activity under pathological and non-pathological conditions.

Diabetes pathophysiology is related to oxidative stress (Atere *et al.*, 2016; Ullah *et al.*, 2016). Mukherjee *et al.* (2006) proposed that the hypoglycemic effects of plants are related to their antioxidant activity. Moreover, polyphenolic compounds like flavonoids are the main antioxidant agents present in plants with potential hypoglycemic activity through several molecular mechanisms (Simonovic *et al.*, 2019). The flavonoids hesperidin and naringin, as well as diterpene trans-dehydrocrotonin, were isolated as the major metabolites in *Croton matourensis* (Suárez *et al.*, 2009a,b). Thus, the hypoglycemic effect observed by CMAE could be related mainly to these compounds. Therefore, hesperidin and naringin molecular mechanisms are related to an increase in insulin, C-peptide levels, and glucokinase activity (Jung *et al.*, 2004; Babu *et al.*, 2013). In addition, these flavonoids produce a decrease in glucose-6-phosphatase and phospho-enolpyruvate carboxy kinase activity (Jung *et al.*, 2004). On the other hand, it was shown that the t-dehydro-crotonin diterpene produced a significant hypoglycemic effect in alloxan-induced diabetic rats (Farias *et al.*, 1997). Thus, the hypoglycemic effect here showed by CMAE could be related to a synergistic effect between these compounds.

Plants with hypoglycemic activity have been shown to have the potential to decrease lipid abnormalities *in vivo* (Fasola *et al.*, 2016). The effect of *Croton* genus on the homeostasis of cholesterol and triglycerides had been described. The aqueous extract from *Croton* cajucara Benth. produces a reduction in triglyceride levels in a streptozotocin-induced diabetes model (Rodrigues *et al.*, 2010). Besides, *Croton klotzschianus* (Wight) Thwaites can reduce the cholesterol and triglyceride levels in rats by increasing high-density lipoprotein (HDL) levels (Govindarajan *et al.*, 2008). In the present work, we demonstrated that CMAE produces a significant decrease in cholesterol levels, although the effect was unmaintained over time. The possible regulatory mechanism of CMAE over cholesterol levels could be related to indirect regulation of cholesterol metabolism; flavonoids present in CMAE could influence multiple functions such as HDL cholesterol content, cholesterol efflux, and their antioxidant effects (Millar *et al.*, 2017). To determine if the effect on cholesterol levels could be sustained further studies are necessary for changing administration schemes.

The rational use of plant extract is related to understanding its safety range and toxicity profile. There is a common popular conception that "If it is natural,

it is safe". However, the use of plant extracts could be associated with adverse or toxic effects such as severe allergic reactions and dangerous interactions with conventional medicines (Marinoff *et al.*, 2009). The aqueous extract from *Croton matourensis* leaves reduces glucose levels in a model of experimental diabetes without toxic effects after acute administration. In the literature has been reported that some plants belonging to the *Croton* genus can be related to some grade of liver toxicity. *Croton cajucara* had been associated with non-viral hepatitis in a rural community of the Brazilian Amazon (Soares, 2004). The toxic effect observed at TD_{50} was reversible and dose-dependent. Nevertheless, further toxicological studies are necessary to determine the effect of CMAE in the liver homeostasis after chronic administration.

Conclusions

The results reported in this work have a significant contribution to validate the ethnopharmacological knowledge and to underline *Croton matourensis* potential to treat diabetes. However, further pharmacological investigations are necessary to determine the antidiabetic mechanism of the metabolite or group of metabolites present in CMAE.

Recommendations

The use of plants to treat health problems will continue in our populations. Thus, there is a strong need to understand the main therapeutics and toxic effects associated with these preparations. We encourage the ethnopharmacological and toxicological evaluation of plants to provide safety and rational use of herbs and plants.

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Conflicts of interest

The authors declare that they have no conflicts of interest with the contents of this article.

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