Effects of *Cnidoscolus Quercifolius* Pohl leaves extracts on glucemia reduction in diabetic mice

Efeitos das folhas de *Cnidoscolus Quercifolius* Pohl sobre a redução da glucemia em ratos diabéticos

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ABSTRACT
Obesity, metabolic syndrome and diabetes are epidemic chronic situations in industrialized countries that are associated with the reduction of life quality and increase of patients' mortality. Before the serious epidemiological picture and the impact that the diabetes causes in the society, the use of different therapeutic interventions is priority in the scientific community. Thus, the goal of this work valued the hypoglycemic effect of the aqueous and methanolic extracts of the leaves of *Cnidoscolus quercifolius* Pohl (faveleira). The phytochemical analysis demonstrated the carbolic acids presence, flavonols, xanthone, catechin, triterpenoids, tannin and coumarins in both extracts and the liquid chromatography of high efficiency revealed the presence of the gallic acid; a powerful metabolite antioxidant. The Diabetes was induced in mice Swiss with alloxan that they did not present mortality when treated with 100, 200 mg / kg of methanolic extract and 100, 200 and 400 mg / kg of aqueous extract for 30 days. Histopathological analysis of the animal's organs (kidney, pancreas, liver) did not reveal architectural alteration. All the diabetic animals submmited to the extracts presented a higher reduction on the blood sugar level percentage than the ones which were undergone to the standard drug. It is important to highlight that the blood sugar level - of the diabetic animals undergone to 400 mg / kg of weight of the aqueous extract - presented glycemic reduction of 39,81 % after 30 days of treatment. These results are very promising because they show great potential for the use of this typical Brazilian Caatinga plant as an alternative therapeutic option to slow down or reduce the risk of hyperglycemia and oxidative stress in diabetic patients.

Keywords: diabetes mellitus, natural products, biotechnology .

ABSTRACT
Obesidade, síndrome metabólica e diabetes são situações epidémicas crónicas em países industrializados que estão associadas à redução da qualidade de vida e ao aumento da mortalidade dos doentes. Antes do grave quadro epidemiológico e do impacto que a diabetes causa na sociedade, o uso de diferentes intervenções terapêuticas é prioritário na comunidade científica. Assim, o objectivo deste trabalho valorizava o efeito hipoglicémico dos extractos aquosos e metanólicos das folhas de Cnidoscolus quercifolius Pohl (faveleira). A análise fitoquímica demonstrou a presença de ácidos carbólicos, flavonóis, xantonas, catecina, triterpenóides, tanino e cumarinas em ambos os extractos e a cromatografia líquida de alta eficiência revelou a presença do ácido gálico; um potente metabolito antioxidante. A Diabetes foi induzida em ratos suíços com aloxan que não apresentaram mortalidade quando tratados com 100, 200 mg / kg de extracto metanólico e 100, 200 e 400 mg / kg de extracto aquoso durante 30 dias. A análise

histopatológica dos órgãos do animal (rim, pâncreas, fígado) não revelou alteração arquitectónica. Todos os animais diabéticos submissos aos extractos apresentaram uma maior redução na percentagem do nível de açúcar no sangue do que os que foram submetidos ao medicamento padrão. É importante salientar que o nível de açúcar no sangue - dos animais diabéticos submetidos a 400 mg / kg de peso do extracto aquoso - apresentou uma redução glicémica de 39,81 % após 30 dias de tratamento. Estes resultados são muito promissores porque mostram um grande potencial para a utilização desta planta típica da Caatinga brasileira como uma opção terapêutica alternativa para abrandar ou reduzir o risco de hiperglicemia e stress oxidativo em pacientes diabéticos.

Palavras-chave: diabetes mellitus, produtos naturais, biotecnologia .

1 INTRODUCTION

The term Diabetes Mellitus (DM) refers to a heterogeneous group of metabolic disorders that has hyperglycemia as a common characteristic resulting from defects in secretion and / or insulin sensitivity (Brazil, 2017). This is a progressive problem of public health that occurs in parallel to aging, urbanization and changes in the population lifestyle (Casarin *et al*., 2022). It is estimated that there are approximately 415 million people living with this disease, with projection for 642 million people in the year 2040 (Idf, 2018).

Given the severe epidemiological situation and the impact that DM has on society, the use of different therapeutic interventions, particularly those that can reduce health services costs and facilitate adherence to treatments, are priorities in the scientific community (Moreira *et al*., 2021). Special attention can be given to natural substances with significant antioxidant potential that can break the cascade of events that culminate in worsening disease and patient weakness (Zeni, 2017; Dos Santos, 2019).

Cnidoscolus Quercifolius Pohl is one of the plants with a high possibility of biotechnological exploitation. It is a species of the family *Euphorbiaceae* with tuberous roots, leaves usually lobed, oval or irregularly triangular and presence of stinging trichomes. Widely used in fodder, in the production of oil for human consumption and in the manufacture of biodiesel (Oliveira, 2014; Morais *et al*., 2016).

The xerophilic character of *C. Quercifolius* allows its survival in long drought periods; this contributes to the reduction of environmental degradation and the sustainable economic exploitation of its resources by the population throughout the year (Roberto, 2016).

Folk medicine combines the use of Faveleira to fight and prevent cancer, liver problems, tumors and uterine inflammation. The stem, roots and root bark are suggested to combat hemorrhoids, kidney problems, skin problems, fractures, warts and eye cleaning (Santos, 2017). However, there are not many studies showing its hypoglycemic effect. The aim of this study was to evaluate the hypoglycemic effect of aqueous and methanolic extracts in the treatment of alloxane-induced diabetic mice.

2 MATERIALS AND METHODS

2.1 PLANT MATERIAL AND PREPARATION OF EXTRACTS

The leaves of *Cnidoscolus quercifolius Pohl* (faveleira) were collected in the city of Fortaleza-Ce and identified by a botanist from the Herbarium Prisco Bezerra (Federal University of Ceará) where a voucher specimen was deposited (No. 55753-1). The dried leaves (100g) at room temperature were boiled in water for 5 minutes. The solution was then filtered through celite and lyophilized and stored in a container at 6° C until use. In preparing the methanolic extract, the leaf material was macerated and placed separately in commercial methanol for one week. After this time, the solution was filtered and concentrated on a rotary evaporator under reduced pressure. The resulting solution from the rotoevaporation process was lyophilized and stored at 6° C until use.

2.2 PHYTOCHEMICAL ANALYSIS

The extracts were submitted to phytochemical screening following the protocols described by Matos (2007). Chemical tests were performed using specific reagents, observing color changes or formation of a precipitate, and characteristic for each class of substances. Tests were performed to detect phenols, flavonoids, flavonols, xanthones, catechins, coumarins, anthocyanidins, triterpenoids, saponins, alkaloids and tannins.

2.3 ANTIOXIDANT ACTIVITY

The *in vitro* antioxidant activity of the extracts was determined using 1,1-diphenyl-2-picrylhydrazyl (DPPH), as previously reported by Brand-Williams et al. (1995). Samples were prepared in triplicate and dissolved at 5-10,000 ppm in methanol. The solutions (0.1 mL) were mixed with 3.9 mL of DPPH-containing methanol solution (6.5 x 10−5 molL-1) for 1 h. Antioxidant activity was presented as the percentage of captured DPPH radicals that was calculated according to the equation% = [(AbsDPPH - Abssample) / Abssample] × 100, where AbsDPPH is the absorbance of the DPPH solution

and Abssample is the absorption of the extract sample. Results were expressed as IC 50 concentration where 50% inhibition of DPPH radical is obtained.

2.4 HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

High performance liquid chromatography (HPLC-DAD) was performed with a Shimadzu Prominence Auto Sampler (SIL-20A) HPLC system (Shimadzu, Kyoto, Japan), equipped with Shimadzu LC-20AT reciprocating pumps connected to a DGU 20A5 degasser with a CBM 20A. integrator, diode array detector SPD-M20A and LC software 1.22 SP1. Chromatographic analyzes were performed using a Luna C18 reverse phase column (Phenomenex®) (4.6X250mm, 5µm). Mobile phases C and D were acetonitrile and Milli-Q water, acidified to pH 2.8 with phosphoric acid, correspondingly, the solvent gradient was used as follows: 0-15 min, an isocratic elution with C: D (20: 80 v / v); 17-25min, linear variation to C: D (40:60 v / v); 25-40 min, an isocratic elution with C: D (20:80 v / v). The flow rate was 1.0 mL / min with an injection volume of 20 μ L and wavelengths 277 nm. The standard reference stock solution was prepared in HPLC methanol on a concentration scale of 0.001-0.5mg / mL for gallic acid.

Chromatographic peaks were confirmed by comparing retention time with reference standard and DAD spectrum (200 to 400nm). The calibration curve for gallic acid was Y = 3.10-8 X-0.0061 (r = 0.9997). The methanolic extract from the faveleira was analyzed by dissolving in methanol at a concentration of 50.0mg / mL. The aqueous extract was analyzed by dissolving in methanol at a concentration of 83.02 mg / mL. Samples were analyzed in triplicate and mean peak areas were measured.

2.5 ANIMALS

Sixty-four adult female (Mus musculus) Swiss mice, aged 6 to 8 weeks, weighing 25 to 40 g and coming from the Central Biottery of the Pici Campus of the Federal University of Ceará (UFC) were used. The animals were placed in polypropylene cages and the environment with a controlled temperature of 22 ° ± 2 and a 12-hour light-dark cycle. In addition, they received water and standard laboratory rodent chow (Supralab SC) ad libitum for an adaptation period of 1 week, and their body weight was monitored weekly on an analytical balance (Toledo Prix) until the end of the experiment.

The experimental protocols of the present study were submitted and accepted by the UFC Animal Research Ethics Committee (CEPA) under the number 42582992/2016

and are in accordance with the Ethical Principles on Animal Experimentation adopted by the Brazilian College of Animal Experimentation (COBEA).

2.6 INDUCTION OF DIABETES

The induction of experimental DM was done after a 24-hour fasting, with ad libitum water supply, by the administration of alloxane monohydrate, diluted in saline solution. The choice of alloxane as a DM-inducing drug was based on experimental protocols that also used this drug to induce diabetes in animals (Barbosa, *et al*. 2013). The drug was administered intraperitoneally at a single dose of 120 mg / kg weight. After 30 minutes of application, the animals were fed normally. Confirmation of DM was performed on the fifth day after induction, through blood samples taken from the infraorbital plexus of the 12-hour fasting animals. Animals that presented fasting glycemia equal to or higher than 180 mg / dL were considered diabetic (Rodrigues, 2014).

2.7 EXPERIMENTAL PROTOCOL

The animals were divided into 8 groups (n = 8): group CN-healthy mice treated with water (0.2ml of water day / animal); CP-group untreated diabetic mice; METFOR group: diabetic mice treated with the standard drug metformin at 200 mg / kg weight diluted in water. The FAV 1, FAV 2 and FAV 3 groups were diabetic mice that received aqueous extract from the *faveleira* leaves at a dose of 100, 200 and 400 mg / kg, respectively. The FAV MET 1 and FAV MET 2 groups are diabetic mice treated with methanolic extract at a dose of 200 mg / kg, respectively.

2.8 BIOCHEMICAL EVALUATION

To the determination of glucose concentration, blood was collected through the infraorbital plexus using a capillary tube on days 0, 15 and 30 days after induction. The device 23300 versions 1.7 were used, which uses the kinetic method for serum samples. In addition, serum collected after 30 days of treatment was subjected to liver function (AST and ALT), renal function (urea and creatinine) analysis by commercial kits using manufacturer's technical recommendations (Bioclins, Brazil).

2.9 HISTOPATHOLOGICAL EVALUATION

The kidneys, pancreas and liver were used for histopathological analysis. The isolated fragments were fixed in 10% neutral formaldehyde and placed in paraffin blocks

for conventional histological processing (Michalany, 1990). Slides were examined for histological changes with conventional optical microscopy (Nikon YS2, Nikon, Japan) and representative images of each organ were captured with a digital camera (Nikon Coolpix L14 7.1 megapixels, Nikon).

2.10 STATISTICAL ANALYSIS

Data were reported as mean ± SD. Statistical significance of differences between groups was assessed using one-way ANOVA, followed by Tukey test, where $p < 0.05$ was considered significant.

3 RESULTS

3.1 PHYTOCHEMICAL ANALYZES

Phytochemical analysis of aqueous and methanolic extracts of C. *quercifolius* revealed the presence of phenols, flavonols, xanthones, catechins, triterpenoids, tannins and coumarins. After performing the test to evaluate the antioxidant potential of the extracts, it was found that the methanolic extract showed IC50 = 23.01 ± 0.12 μg·mL and aqueous extract IC50 = 17.01 ± 0.38 $\mu g \mu$mL. showing the presence of metabolites capable of sequestering free radicals. Rutin was used as standard with IC50 = 13.70 ± 0.25 μg·mL.

3.2 HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

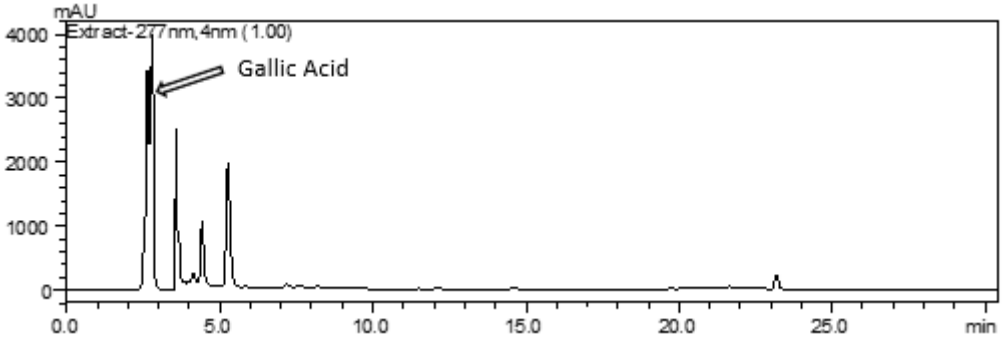
Table 1 and graphics 1 and 2 show the representative liquid chromatography of Faveleira's aqueous and methanolic extracts.

Table 1 High performance liquid chromatography representative of the aqueous and methanolic extracts of Faveleira. (t R = 3.56 min, peak 1).

	Compouds	**Gallic acid**	**Tr**
Aqueous extract	mg/g extract	2,89 ± 0,03	Min
Methanolic extract	mg/g extract	5,00 ± 0,05	Min

Own source

Graph 1- Analysis of high performance liquid chromatography of the methanolic extract of *Cnidoscolus Quercifolius Pohl* leaves



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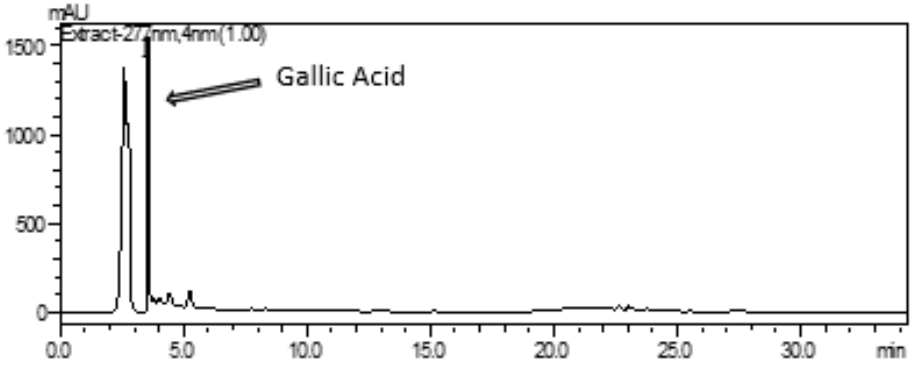
Graph 2- Analysis of high performance liquid chromatography of the aqueous extract of *Cnidoscolus Quercifolius pohl* leaves



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3.3 EFFECT OF *C. QUERCIPHOLIUS* ON BLOOD GLUCOSE IN DIABETIC ANIMALS

Table 2 presents the blood glucose values at the beginning, 15 and 30 days of treatment in the experimental groups.

Table 2 Effect of aqueous and methanolic extracts of *Cnidoscolus quercifolius Pohl* on average blood glucose of diabetic animals during 30 days of treatment.

Groups	Day 0	Day 15	Day 30	P VALUE
CN	96,68 (4,91) [a]	93,44 (3,68) [a]	96,29 (3,06) [a]	0,226
CP	308,14 (37,84) [a]	318,65 (45,42) [a]	326,22 (42,36) [a]	0,661
FAV MET 1	277,01 (26,28) [a]	205,90 (1,81) [b]	187,86 (1,93) [b]	< 0,001
FAV MET 2	325,46 (31,91) [a]	286,88 (5,26) [b]	194,45 (2,85) [c]	< 0,001
FAV 1	329,74 (30,29) [a]	297,85 (22,42) [a]	216,94 (45,43) [b]	< 0,001
FAV 2	346,00 (28,93) [a]	297,62 (19,39) [b]	197,99 (18,41) [c]	< 0,001
FAV 3	312,33 (52,32) [a]	247,24 (47,10) [b]	187,89 (2,98) [c]	< 0,001
METFOR	343,72 (74,11) [a]	290,82 (63,89) [b]	245,17 (75,11) [b]	0,038

Own source

CN- Healthy animals; PC- untreated diabetic animals; FAV MET 1- animals treated with 100mg / kg of methanolic extract weight; FAV MET 2- animals treated with 200mg / kg of methanolic extract weight; FAV1 animals treated with 100mg / kg of aqueous extract weight; FAV2 - animals treated with 200mg / kg of aqueous extract weight; FAV3 - animals treated with 400mg / kg of aqueous extract weight. METFOR- group of animals treated with the standard drug metformin. Data expressed as mean (standard deviation); £ - ANOVA test; ‡ - Kruskal-Wallis test. Tukey post-test: Different letters indicate significant difference between means. P value considered significant below 5%.

3.4 EFFECT OF *C. QUERCIPHOLIUS* ON LIPID PROFILE AND RENAL AND HEPATIC TOXICITY PARAMETERS

Table 3 presents the values of the biochemical analysis regarding liver parameters (AST / ALT), renal parameters (urea and creatinine) and lipid parameters (TGL and cholesterol) after 30 days of treatment with Faveleira extracts.

Table 3. Effect of aqueous and methanolic extracts of *Cnidoscolus Quercifolius* on biochemical parameters of diabetic animals after 30 days of treatment.

	CN	**CP**	**FAV MET 1**	**FAV MET 2**	**FAV1**	**FAV2**	**FAV3**	**METFORM**	**P VALUE**
AST (mg/dL)	30,40[a]	40,72[b]	31,79[a]	35,25[a]	25,26[c]	21,31[c]	26,27[c]	26,42[c]	<0,001
ALT (mg/dL)	29,83[a]	39,12[b]	26,84[b]	31,52[a]	22,13[c]	18,39[c]	27,05[b]	22,69[c]	<0,001
Urea (mg/dL)	101,56[a]	135,58[a]	76,68[b]	71,60[b]	71,54[b]	83,49[b]	86,03[b]	82,20[b]	<0,001
Creatinine(mg/dL)	0,72[a]	1,19[b]	0,73[a]	0,70[a]	0,75[a]	1,01[b]	0,78[a]	0,79[a]	<0,001
TGL (mg/dL)	95,44[a]	179,86[b]	120,89[c]	97,71[a]	114,50[c]	204,16[d]	211,56[d]	190,81[b]	<0,001
Cholesterol(mg/dL)	113,35[a]	138,23[b]	113,50[a]	110,46[a]	111,15[a]	133,34[b]	122,5[a]	116,38[a]	<0,001

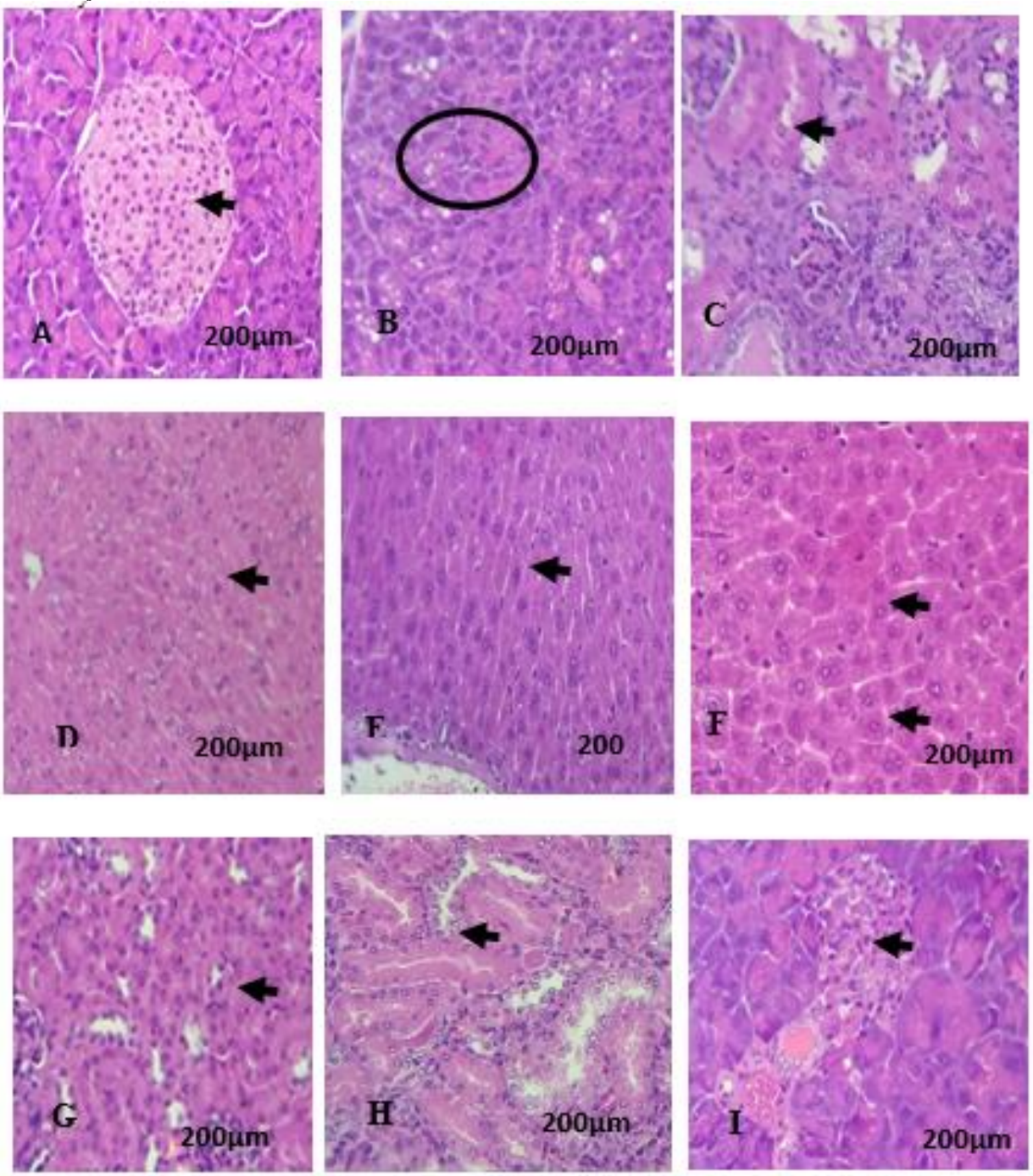
Own source

CN- Healthy animals; PC- untreated diabetic animals; FAV MET1- animals treated with 100mg / kg methanolic extract weight; FAV MET2- animals treated with 200mg / kg methanolic extract weight; FAV1 animals treated with 100mg / kg of aqueous extract weight; FAV2 - animals treated with 200mg / kg of aqueous extract weight; FAV3 - animals treated with 400mg / kg of aqueous extract weight. METFOR- animals treated with the standard drug Metformin. AST- Aspartate aminotransferase. ALT- Alanine aminotransferase. TGL - Triglycerides. Data expressed as mean £ - ANOVA test; ‡ - Kruskal-Wallis test. Tukey post-test: Different letters indicate significant difference between means. P value considered significant below 5%

3.5 HISTOPATHOLOGICAL OBSERVATION

The figures below represent the histopathological observations of the pancreas of an animal submitted to extract (A, B) Liver (D, E) and Kidney (G, H) from diabetic mice treated with Faveleira and Pancreas (C), Liver (F) extracts. and Kidney (I) from water-treated mice. Hematoxylin-eosin staining

Figure 1. Histopathological observations of Pancreas A (400mg / kg weight aqueous extract) B (200mg / kg weight methanolic extract), C untreated diabetic animal; Liver D (400mg / kg aqueous extract weight, E (200 mg / kg methanolic extract weight) and F untreated diabetic animal; Kidney G (400mg / kg aqueous extract weight), H (200 mg / kg methanolic extract weight) I untreated diabetic animal Staining with hematoxylin-eosin



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4 DISCUSSION

Phytochemical analysis of Faveleira extracts showed the presence of phenols, flavonols, xanthones, catechins, triterpenoids, tannins and coumarins. These metabolites are characteristic of the Euphorbiaceae family and are substances recognized for their

antioxidant, anti-inflammatory, antiogenic, antineoplastic and hypoglycemic capacity (Silva *et al*., 2016).

The extracts compositions found in this study agree with the study by Paredes et. al (2016) who evaluated the composition of methanolic extracts of leaf, stem bark and faveleira root. The results showed the presence of phenols, tannins, flavonols, flavones, xanthones and flavanones in all samples.

The evaluation of the ability to sequester free radicals is one of the main characteristics of antioxidant compounds. One of the most commonly used methods for determining *in vitro* antioxidant activity is radical scavenger methods such as DPPH. This method is based on the comparison between the extracts evaluated and the standard substance of the analysis (Oliveira, 2011). After analysis of the results, the extracts presented similar values to rutin, used as standard substance, proving the antioxidant capacity of the evaluated extracts.

Similar data were found in the evaluation of the antioxidant capacity of *Mormordica charantia L*. (Cucurbitaceae family), popularly known as "São Caetano melon" and already recognized for its hypoglycemic potential. The extracts of its pulp and peel evaluated by the DPPH method presented values close to the standard substance (ascorbic acid) (Maneenim, 2018).

The presence of gallic acid in the aqueous and methanolic extracts of the faveleira, presented in this study, reinforces the antioxidant character of this plant. For gallic acid is a phenolic compound that acts by retarding or inhibiting the oxidative effects of free radicals on organic molecules. In addition, its presence is believed to improve hyperglycemia by decreasing insulin resistance (Huang, 2016).

All diabetic animals submitted to treatment with Faveleira extracts presented a higher percentage of decrease in blood glucose than animals submitted to the standard drug (metformin) after 30 days of treatment (see table 2). While the glucose reduction in the metformin-treated group was 28.67%, the groups treated with 200 mg / kg aqueous extract weight were 42.77% (FAV2) and the 200 mg methanolic extract (FAVMET2) treated group was 40.25%.

Treatment of DM with plant extracts may increase treatment adherence due to decreased side effects caused by conventional drugs. Whereas patients using metformin report abdominal discomfort (Chamberlain, 2017).

The results of this study corroborate the work done by Lira (2017) who evaluated the hypoglycemic potential of three different dosages of aqueous extract of *C. quercifolius*

in diabetic animals. After 30 days there was a reduction of approximately 30% in blood glucose of animals that received 200mg / kg of the extract and showed no toxicity.

A study with *Handroanthus heptaphyllus* (Mart.), popularly known as "purple Ipe", evaluated the hypoglycemic ability of aqueous leaf extract in diabetic animals for 30 days. The animals were submitted to a daily dosage of 150mg / kg. Results indicated a significant improvement in glycemic response after the third week and a decrease in triglyceride levels after 30 days of treatment (Grochanke, 2016).

Pancreatic, hepatic and renal histopathological analyzes of diabetic animals treated with Faveleira extracts indicate that the dosages administered were safe for consumption, since no architectural alterations were observed.

Histopathological analysis of the pancreas, liver and kidney of the animals showed no foci of hemorrhage and inflammation in any of the groups studied. The pancreas of untreated diabetic animals showed a decrease in the number and size of Langerhans islets when compared to the groups treated with the extracts. No architectural changes in animal kidneys found in all groups.

Other relevant results of this research refer to the lipid parameters levels of diabetic animals treated with plant extracts. The animals submitted to methanolic extracts at two dosages (200 and 400 mg / kg weight) and the group submitted to the highest aqueous extract dosage (FAV 3) presented cholesterol levels statistically related to the healthy group after 30 days of treatment. Similar result was found in relation to triglycerides, where the FAV MET 2 group presented similar values to the healthy group.

Considering the cholesterol and triglyceride values obtained in this study, it may be suggested that treatment with aqueous and methanolic extracts decreased the likelihood of developing atherosclerotic complications that are common in diabetes.

Diabetic animals treated with both extracts presented statistically similar creatinine and urea rates to the healthy animals group ($p < 0.01$) after 30 days of treatment.

This result suggests that the use of the extracts did not cause cellular damage in these animals. Kidney damage from diabetes results from the kidney's inability to properly filter blood, making it difficult to eliminate excess salt and water from the body. Measurement of creatinine and urea levels are the best biochemical markers used in this monitoring (Vargas, 2016).

Another example of a plant recognized by the population to treat and prevent diseases is *Casearia sylvestris*. It is a common shrub in southern Brazil. Espinosa and Souza evaluated the effect of daily administration of 300 mg / kg extract on animals with

strepzotocin-induced diabetes at 45 days of treatment. The results showed a significant decrease in triglyceride and total cholesterol levels; but without any significant changes in blood glucose (Espinosa, 2015).

The use of these plant extracts can be seen as an alternative therapeutic option to slow down or reduce the risk of complications from hyperglycemia and oxidative stress in these patients.

5 FINAL CONSIDERATIONS

The present study presented promising results in all evaluated tests. The hypoglycemic capacity, the absence of signs of toxicity compared to the reference drug, prove the potential of plant extracts in combating hyperglycemia. Given this, one can infer the need for further studies that investigate and prove the popular knowledge about native plants of Caatinga and thus stimulate the development of new herbal products as an alternative in the fight against DM, lower cost and more accessible by the population.

CONFLIT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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