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ANTIOXIDANT EFFECT OF ARRABIDEAE CHICA (CRAJIRU) EXTRACT ON OXIDATIVE STRESS IN DIABETIC RATS

EFEITO ANTIOXIDANTE DO EXTRATO DE ARRABIDEAE CHICA (CRAJIRU) NO ESTRESSE OXIDATIVO EM RATOS DIABÉTICOS

Paula Perlles Gomes Bandeira e Sousa[1], Ítalo Medeiros Azevedo[2], Aldo Cunha Medeiros[3]

1. Graduate student, Medical School, Federal University of Rio Grande do Norte (UFRN), Natal-RN, Brazil
2. PhD, Statistician, Department of Surgery, UFRN, Natal- RN, Brazil.
3. PhD, Full Professor, Chairman, Nucleus of Experimental Surgery, UFRN, Natal, RN, Brazil.

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Address for correspondence: Department of Surgery, Federal University of do Rio Grande do Norte, Ave. Nilo Peçanha 620, Natal, RN, Brazil.
E-mail: cirurgex.ufrn@gmail.com.
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ABSTRACT

Objective: This study aimed to investigate the effects of the antioxidant potential of *Arrabideae chica* (crajiru) extract on oxidative stress in diabetic rats. **Methods:** Adult Wistar rats (Rattus norvegicus), weighing 238±12g were divided into three groups of six rats each: CN normal untreated control; DIAB+NS diabetic rats treated with normal saline; and diabetic rats treated with crajiru extract, DIAB+CR. The CN and DIAB+NS groups (control groups) received normal saline solution (NS) orally (gavage); rats in the DIAB+CR group received crajiru extract (300 mg/kg) once a day by gavage for 6 weeks. Measurements of urea and creatinine in serum, and kidney tissue catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) were performed. The variables were assessed using the Tukey test, significance $p<0.05$. **Results:** All animals survived the experiments. In the CN group, compared with the DIAB+NS group, there was significant difference between the levels of glycemia on the second day of dosing and on the 10th day ($p<0.05$). No difference was observed on glycemia comparing the 2^{th} and 10^{th} day on the rats of group C+NS ($p>0.05$). Diabetic animals from DIAB+CR group had a significant reduction in glycemia on 10th day of treatment, comparing the 2nd day ($p<0.05$). There was a significant reduction in glycemia in the DIAB+CR group, comparing with the DIAB+NS group ($p<0.05$). There was an increase in urea and creatinine levels in rats DIAB+SN when compared to controls, C+SN ($p<0.001$). Rats from

the DIAB+CR group had a significant reduction in urea and creatinine, compared to the DIAB+NS group (p<0.001). There were no significant differences in urea and creatinine comparing the C+NS and DIAB+CR groups. The rats from the DIAB+NS group had significantly lower levels of CAT, GSH-px and SOD when compared to the normal control rats (p<0.001). In animals from the DIAB+SN group, the levels of these antioxidant enzymes were significantly reduced (p<0.001). The treatment of diabetics with crajiru extract caused a significant increase (p<0.001) in the levels of CAT, GSH-px and SOD, when compared to rats in the BIAB+SN group. **Conclusion:** The data of the present study confirms that the crajiru extract positively influenced the control of hyperglycemia in diabetic rats. More research is needed to provide a better understanding of the mechanisms of diabetes treatment using crajiru extract and its flavonoids.

Keywords: Diabetes; Rats; Arrabideae chica; Extract; Oxidative stress; Treatment.

RESUMO

Objetivo: Este estudo teve como objetivo investigar os efeitos do potencial antioxidante do extrato de *Arrabideae chica* (crajiru) sobre o estresse oxidativo em ratos diabéticos. **Métodos:** Ratos Wistar adultos (Rattus norvegicus), pesando 238±12g, foram divididos em três grupos de seis ratos cada. Grupo CN controle normal não tratado; Ratos diabéticos tratados com salina normal (DIAB+SN); e ratos diabéticos tratados com extrato de crajiru (DIAB+CR). Diabetes induzida com estreptozotocina. Salina e extrato de crajiru foram injetados por via oral (gavagem); o extrato de crajiru (300 mg/kg) foi usado uma vez ao dia por gavagem por 6 semanas. Foram realizadas medições de uréia e creatinina séricas, e as enzimas antioxidantes catalase (CAT), superóxido dismutase (SOD) e glutationa peroxidase (GPx) no tecido renal dos animais. As variáveis foram avaliadas pelo teste de Tukey, significância p<0,05. **Resultados:** Todos os animais sobreviveram aos experimentos. A glicemia foi significativamente mais baixa no grupo CN, em comparação com o grupo DIAB+NS, tanto no segundo quanto no 10º dia pós indução do diabetes (p<0,05). Não foi observada diferença na glicemia comparando o 2º e o 10º dia nos ratos do grupo C+NS (p>0,05). Animais diabéticos tratados com extrato de crajiru (DIAB+CR), tiveram redução significativa da glicemia, comparando o 2º dia com o 10º dia de tratamento (p<0,05). Houve redução significativa da glicemia no grupo tratado com crajiru (DIAB+CR), comparando-se o grupo DIAB+NS (p<0,05). Houve aumento dos níveis de uréia e creatinina nos ratos DIAB+SN quando comparados aos controles, C+SN (p<0,001). Ratos diabéticos do grupo DIAB+CR apresentaram redução significativa da uréia e creatinina, em comparação ao grupo DIAB+NS (p<0,001). Não houve diferenças significativas na uréia e creatinina entre os grupos C+NS e DIAB+CR. Os ratos do grupo DIAB+NS apresentaram níveis significativamente mais baixos de CAT, GSH-px e SOD quando comparados aos ratos controle normais - CN (p<0,001). O tratamento de diabéticos com extrato de crajiru causou aumento significativo (p<0,001)

nos níveis de CAT, GSH-px e SOD, quando comparados aos ratos do grupo BIAB+SN. **Conclusão:** Os dados do presente estudo confirmam que a o extrato de crajiru influenciou positivamente no controle da hiperglicemia em ratos diabéticos. Mais pesquisas são necessárias para fornecer uma melhor compreensão dos mecanismos de tratamento do diabetes usando extrato de crajiru e seus flavonóides.

Descritores: Diabetes; Ratos; *Arrabideae chica*; Extrato; Estresse oxidativo; Tratamento.

INTRODUCTION

Diabetes mellitus (DM) is one of the epidemic challenging public health problems throughout the world[1]. The prevalence rate of diabetes is increasing exponentially and the World Health Organization predicts that by the year 2030, diabetes is expected to be the seventh leading cause of death worldwide[2,3]. DM is a metabolic disorder characterized by the elevation of blood glucose due to the defects in insulin action, secretion or both (insulin is insuficient or ineficient)[4]. Type 1, type 2, and gestational diabetes are the three main types of diabetes targeting children, adults, and pregnant women, respectively[5].

The factors such as obesity, urbanization, genetic mutations, and a lack of physical activities contribute to the pathogenesis of diabetes[6]. The symptoms and signs of diabetes include polyuria (frequent urination), polyphagia (increased hunger), polydipsia (increased thirst), weight loss, and unconsciousness[7]. Diabetes could lead to deleterious complications like nephropathy, atherosclerosis, and cardiac dysfunction and target major organs in the body such as heart, nerves, kidneys, eyes, and blood vessels[8].

Oxidative stress is increased in DM, and there is often a decrease in the body's stores of ascorbic acid, which is an important dietary-derived antioxidant. Antioxidant supplementation has been suggested as a potentially beneficial adjuvant therapy[9-11]. A high intake of antioxidants in the diet can decrease oxidative stress and thus lower the risk of oxidative stress-related illnesses such as DM. In line with this, a higher intake of certain nutrients with antioxidant properties has been associated with a lower risk of DM[12,13]. Flavonoids exhibit several beneficial activities, including antibacterial, antidiabetic, antiviral, anti-inflammatory, antioxidant, anticarcinogenic, antiallergic, hepatoprotective, vasodilatory and antithrombotic activities. Some researches have focused on its antioxidant potential, due to its ability to reduce the formation of free radicals and eliminate them, leading to a therapeutic possibility of being used against diseases mediated by free radicals[14-16].

There is a growing interest in natural antioxidants present in medicinal and dietary plants that can help to mitigate oxidative damage[17]. *Arrabidaea chica* (crajiru) is is widely distributed from southern Mexico to central Brazil, mainly in the Amazon region. It has been used as an anti-inflammatory and astringent agent, as well as a

remedy for intestinal cramps, diarrhea, leukorrhea, diabetes, anemia, and leukemia. This plant is a source of anthocyanins, flavonoids, tannins and phytosterols[18-22]. A study by Siraichi et al[23] concluded that *A. chica* extract has significant antioxidant activity. This higher activity can be attributed to the presence of a mixture of compounds in the plant extract (isocutellarein, 6-hydroxyluteolin, hispidulin, scutellarein, luteolin and apigenin)[23].

Based on this knowledge, this study aimed to investigate the effects of the antioxidant potential of *A. chica* extract (crajiru) on oxidative stress in diabetic rats.

METHODS

Animals

Eighteen adult Wistar rats (Rattus norvegicus), weighing 238±12g, from the vivarium of the Centro de Ciências da Saúde-UFRN were used. During the acclimatization period, the animals were kept for 7 days before the beginning of the study, at the Experimental Surgery Center, where the study was carried out. All animals were housed in polypropylene cages, in a climate-controlled environment (22°C), 12-hour light-dark cycle and *ad libitum* access to water and food for laboratory rats (Prevence®). The protocol was in accordance with the principles of Law 11.794/08 (CONCEA) and was approved by the Ethics Committee on the Use of Animals/HUOL (Protocol nº 02/2020).

Diabetes induction by streptozotocin

A single 45 mg/kg body weight dose of freshly prepared streptozotocin (STZ) (STZ, S0130, Sigma-Aldrich) in 0.1 mol/L citrate buffer (pH 4.5) was injected intraperitoneally to the induction of diabetes. After two days of STZ treatment, diabetes was confirmed by assessing the blood glucose of blood drawn from the tail vein of overnight fasted rats. Dosing was performed using Accu-Check, Roche Diagnostics, Germany. Rats with blood glucose levels of 250 mg/dL or more were considered diabetic and were included in the study.

Experimental design

Eighteen rats were randomly allocated into three groups of six rats each: Untreated control normal CN; diabetic rats (DIAB+NS) and diabetic rats treated with crajiru, (DIAB+CR). The CN and DIAB+NS groups (control groups) received normal saline solution (NS) orally, while the rats of the DIAB+CR experimental group received crajiru extract at a dose of (300 mg/kg) once a day. 0.9% normal saline was used as a diluent to rebuild the extract, which was administered by gavage for 6 weeks. Crajiru dose (300 mg/kg) was based on the literature and on our preliminary investigation[24].

Preparation of A. chica extract (Crajiru)

The alcoholic extract was prepared by maceration of 200 g of dried *A. chica* leaves. Ethanol at a ratio of 1:3 was added to the percolation process at room temperature. The material was filtered and concentrated on a rotary evaporator at a temperature of 60°C. The extract was weighed and diluted, and an alcoholic extract at a concentration of 10% was obtained. This final extract was stored at 4°C until dosages.

At the end of treatment (6 weeks), rats were fasted overnight and intraperitoneally anesthetized the following morning with an injection of ketamine (70 mg/kg) + xylazine 7 mg/kg. Blood samples were obtained through intracardiac puncture. Whole kidneys were quickly excised from each rat, washed in buffered saline, and used for measurements of oxidative stress markers.

Biochemical analysis

Blood samples collected by cardiac puncture were centrifuged at 3000 g for 10 min at 4◦C to obtain serum and then stored at -20◦C. Urea and creatinine were measured in an autoanalyzer (Konelab, Software Version, 60i, Finland).

Examination of antioxidant enzymatic parameters

One kidney homogenate supernatants were used to examine the enzymatic antioxidant parameters catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx), using colorimetric assay kits according to the manufacturer's instructions. (ABCAM, Cambridge, MA, USA).

Statistical analysis

To test the hypothesis of difference between groups, we used: Analysis of Variance (ANOVA), followed by Tukey's multiple comparison test, with a significance level of 5%. The statistical package BioEstat 5.0, Belém, PA, Brazil was used.

RESULTS

Evolution of glycemia with treatments

In Table 1 it can be observed that in the control group, compared with the diabetes group treated with normal saline, there was significant difference between the levels of glycemia on the second day of dosing and on the 10th day ($p<0.05$). Nevertheless, no difference was observed on glycemia comparing the 2^{th} and 10^{th} day on the rats of group C+NS ($p>0.05$). When the diabetic animals were treated with crajiru extract (DIAB+CR). There was a significant reduction in glycemia, comparing the 2nd day with the 10th day of treatment ($p<0.05$). There was a significant reduction in glycemia in the group treated with crajiru, comparing the DIAB+NS and DIAB+CR groups, on the second and tenth day after diabetes induction ($p<0.05$). Data summarized in table 1.

Table 1 – Measurement of blood glucose in the 2nd day and 10th day after STZ injection in rats of the study groups.

Groups	Glycemia (mg/dL)	
	2nd DAY	**10th DAY**
C+NS	138±12.3[a]	140.3±9.6[a]
DIAB+NS	282.2±18.4[a]	278.5±15.9[a]
DIAB+CR	205.3±13.2[a]	184.8±10.4[a]

C, control; CR, Crajiru extract; DIAB, diabetes; NS, normal saline. Measures followed of the same letter in the same line differ significantly (p<0.05, Tukey test).

There was an increase in urea and creatinine levels in diabetic rats treated with normal saline (DIAB+SN) when compared to control rats treated with normal saline (C+SN). Statistically, the difference was significant (p<0.001). When diabetic rats were treated with crajiru extract (DIAB+CR), there was a significant reduction in serum levels of urea and creatinine, compared to the DIAB+NS group (p<0.001). No significant differences were observed comparing the urea and creatinine levels of the C+NS and DIAB+CR groups. Data summarized in table 2.

Table 2 – Results of renal function tests comparing groups and study.

Variables	Groups			
	Control C+NS	**DIAB+NS**	**DIAB+CR**	**p-value[1]**
Urea mg/dl)	28,2 ± 3,1[a]	49,5 ± 2,8[a]	31,5 ± 2,7[a]	<0,001
Creatinine (mg/dl)	0,8 ± 0,2[a]	2,4 ± 0,4[a]	0,9 ± 0,2[a]	<0,001

C, control; CR, Crajiru extract; DIAB, diabetes; NS, normal saline. Measures followed of the same letter in the same line differ significantly (p<0.05, Tukey test).

Table 3 – Results of statistical analysis of antioxidant enzymes in renal tissue.

Variables	Groups			
	Control C+NS	DIAB+NS	DIAB+CR	p-value
CAT (µmol/mg)	129,2 ± 11,4[a]	49,5 ± 2,2[a]	80,4 ± 5,7[a]	<0,001
GSH-px (µmol/mg)	80 ± 3,7[a]	34,6 ± 2,3[a]	62,5 ± 4,2[a]	<0,001
SOD (µmol/mg)	26,8 ± 2,5[a]	9,4 ± 0,7[a]	21,1 ± 1,7[a]	<0,001

C, control; CR, Crajiru extract; DIAB, diabetes; NS, normal saline. CAT, catalase; SOD superóxido dismutase; GPx, glutationa peroxidase. Measures followed of the same letter in the same line differ significantly (p<0.05), Tukey test.

The rats in the DIAB+NS group had significantly lower levels of CAT, GSH-px and SOD when compared to the normal control rats ($p<0.001$). In diabetic animals treated with normal saline (DIAB+SN) the levels of these antioxidant enzymes were significantly reduced, as shown in table 3 ($p<0.001$). The treatment of diabetic animals with crajiru extract caused a significant increase ($p<0.001$) in the levels of CAT, GSH-px and SOD, when compared with the values of rats in the BIAB+SN group, which confirms the antioxidant property of the extract. Data summarized in table 3.

DISCUSSION

Arrabidaea chica leaf extract has been used by Amazonian people as an anti-inflammatory and astringent agent as well as a remedy for intestinal colic, diarrhea, leucorrhea, anemia, diabetes and leukemia[18]. *A. chica* is known to be a good producer of phenolics[18]. Flavonoids are a class of secondary plant metabolites having diverse structures[25]. They are polyphenolic compounds which is very commonly found in many plants, vegetables, and flowers[26]. Many studies have have been done on determining the biological and pharmacological activities of flavonoids that are thought to have beneficial effects on human health. The flavonoids exhibit several beneficial activities, like anti-inflammatory, antibacterial, anticarcinogenic, antiviral, antioxidant, antiallergenic, vasodilating, hepatoprotective, antidiabetic and antithrombotic activities. Most research has been focused on their antioxidant potential, which is due to their ability to reduce free radicals and scavenge free radicals, leading to a therapeutic possibility of being used against free radical-mediated diseases[15-17]. There is a growing interest in natural antioxidants present in medicinal and dietary plants that might help attenuate oxidative damage[18]. Furthermore, currently an increasing economic interest is on line with natural resources such as herbal extracts that contain antioxidants.

The significant antioxidant activity of the extract obtained from *A. chica* against the 2 metabolites might be because of the synergistic effect of the two major flavonoids present in the extract, such as scutellarein and apigenin, with other flavonoids (such as isoscutellarein, 6-hydroxyluteolin, hispidulin, and luteolin) that are known to have antioxidant activity[27-30]. Study performed by Siraichi et al[23] demonstrated that the extract of *A. chica* have significant antioxidant activity. The high activity could be attributed to the presence of a mixture of compounds in the plant extract (isoscutellarein, 6-hydroxyluteolin, hispidulin, scutellarein, luteolin, and apigenin). We know that the yield of metabolites from plants is small; hence, it is economical to use the crude extract instead of the isolated metabolites. In the present study the extract of *A. chica* had significant positive effect in diabetic rats, whose diabetes was induced by STZ.

Diabetes could lead to deleterious complications like nephropathy, atherosclerosis, and cardiac dysfunction and target major organs in the body such as

heart, nerves, kidneys, eyes, and blood vessels[31,32]. Based on this, we studied the content of antioxidant enzymes in the renal tissues.

The high mortality and morbidity rate of diabetes combined with the higher risk of bacterial or viral infections or the development of cancer is a major concern of the diseases epidemic[33]. While currently there is no cure, diabetes is successfully treated by managing a healthy lifestyle combined with the administration of anti-diabetic agents and hypoglycemic drugs such as sulphonylureas, thiazolidinediones, and biguanides all of which reduce blood glucose[34]. In riverside communities in the Amazon, and in other areas where medical care is precarious, the use of herbal remedies based on crajiru extract, or even the infusion of its leaves, can be an alternative for controlling diabetes. Nutraceuticals are natural products derived from fruits and vegetables which provide multiple health benefits[35].

Scientific attention has been given over the past 20 years toward natural compounds, such as flavonoids serving as an antidiabetic agent[36]. Flavonoids are polyphenols which are ubiquitously found in daily consumed fruits, vegetables, nuts, cocoa, tea, grain seeds, and herbs[37]. They represent a large class of approximately 8000 phenolic compounds[38]. Flavonoids are considered as a class of biologically active secondary metabolites of plants known as pigment, where they serve antiviral, anti-allergic, antibacterial and anti-inflammatory functions[39]. The structure of flavonoids consists of 15 carbon skeletons and two aromatic rings (A and B) connected by a three-carbon chain which is usually an oxygenated heterocyclic C ring[40].

Six subclasses of flavonoids are defined: flavones; flavonols; flavanones; flavan-3-ols; isoflavones; and anthocyanosides[41]. Flavonoids have multiple positive health effects on metabolic disorders, such as cardiovascular disease, cancer, obesity, and diabetes[42]. The antidiabetic activity of flavonoids supports the regulation of carbohydrate digestion, insulin signaling, insulin secretion, glucose uptake, and adipose deposition[43]. As crajiru leaves are very rich in flavonoids, anthocyanins and other components, with the potential to act on diabetes, undoubtedly the data from the present work, which is one of the pioneers to demonstrate its antidiabetic effects, provides another option for control of the disease. The flavonoids target multiple molecules that are involved in the regulation of several pathways, like improving β-cell proliferation, promoting insulin secretion, reducing apoptosis, and improving hyperglycemia by regulating glucose metabolism in the liver[44].

A US study on 200,000 women and men evaluated the association between dietary intake of flavonoids subclasses and type 2 diabetes, confirming that a higher consumption of anthocyanins from apples, blueberries, and pears, controls the risk of diabetes[45]. It is hypothesized that the majority of flavonoids bioactivity occurs due to their hydroxyl group, α, and β ketones[46].

A water soluble, unoxidized, unsaturated flavonoid, anthocyanin, is present abundantly in crajiru leaves. Several studies, both in animal models and cell lines, suggested that anthocyanins may have anti-diabetic activities[43].

In conclusion, the data of the present study confirms that the crajiru extract positively influenced the control of hyperglycemia in diabetic rats. More research is needed to provide a better understanding of the mechanisms of diabetes treatment using crajiru extract and its flavonoids.

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